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ΔΙΑΓΝΩΣΗ

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

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Summary

Background Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.

Methods We did data-driven cluster analysis (k-means and hierarchical clustering) in patients with newly diagnosed diabetes (n=8980) from the Swedish All New Diabetics in Scania cohort. Clusters were based on six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA_{1c}, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance), and were related to prospective data from patient records on development of complications and prescription of medication. Replication was done in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485). Cox regression and logistic regression were used to compare time to medication, time to reaching the treatment goal, and risk of diabetic complications and genetic associations.

Findings We identified five replicable clusters of patients with diabetes, which had significantly different patient characteristics and risk of diabetic complications. In particular, individuals in cluster 3 (most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5, but had been prescribed similar diabetes treatment. Cluster 2 (insulin deficient) had the highest risk of retinopathy. In support of the clustering, genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

Interpretation We stratified patients into five subgroups with differing disease progression and risk of diabetic complications. This new substratification might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

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Introduction

Diabetes is the fastest increasing disease worldwide and a substantial threat to human health.[1] Existing treatment strategies have been unable to stop the progressive course of the disease and prevent development of chronic diabetic complications. One explanation for these shortcomings is that diagnosis of diabetes is based on measurement of only one metabolite, glucose, but the disease is heterogeneous with regard to clinical presentation and progression.

Diabetes classification into type 1 and type 2 diabetes relies primarily on the presence (type 1 diabetes) or absence (type 2 diabetes) of autoantibodies against pancreatic islet β-cell antigens and age at diagnosis (younger for type 1 diabetes). With this approach, 75–85% of patients are classified as having type 2 diabetes. A third subgroup, latent autoimmune diabetes in adults (LADA; affecting <10% of people with diabetes), defined by the presence of glutamic acid decarboxylase antibodies (GADA), is phenotypically indistinguishable from type 2 diabetes at diagnosis, but becomes increasingly similar to type 1 diabetes over time.[2] With the introduction of gene sequencing in clinical diagnostics, several rare monogenic forms of diabetes were described, including maturity-onset diabetes of the young and neonatal diabetes.[3,4]

Existing treatment guidelines are limited by the fact they respond to poor metabolic control when it has developed, but do not have means to predict which patients will need intensified treatment. Evidence suggests that early treatment is crucial for prevention of life-shortening complications because target tissues seem to remember poor metabolic control decades later (so-called metabolic memory).[5,6]

A refined classification could provide a powerful tool to identify at diagnosis those at greatest risk of complications and enable individualised treatment regimens in the same way as genetic diagnosis of monogenic diabetes guides clinicians to optimal treatment.[7] With this aim, we present a novel diabetes classification based on unsupervised, data-driven cluster analysis of six commonly measured variables and compare it metabolically,

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One hour post-OGTT glucose improves the early prediction of type 2 diabetes by clinical and metabolic markers

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Context
Early prediction of dysglycaemia is crucial to prevent progression to type 2 diabetes. The one-hour post-load plasma glucose (1-h PG) has been reported a better predictor of dysglycaemia than fasting plasma glucose (FPG), 2-h PG, or glycated haemoglobin (HbA1c).
Objective
To evaluate the predictive performance of clinical markers, metabolites, HbA1c, and plasma glucose (PG) and serum insulin (INS) levels during a 75-gram oral glucose tolerance test (OGTT).
Design and Setting
We measured PG and INS levels at 0, 30, 60, and 120 minutes during an OGTT in 543 individuals in the Botnia Prospective Study, 146 of whom progressed to type 2 diabetes within a 10-year follow-up period. Using combinations of variables, we evaluated 1527 predictive models for progression to type 2 diabetes.
Results

The 1-h PG outperformed every individual marker except 30-min PG or mannose, whose predictive performances were lower but not significantly worse. HbA1c performed inferior to 1-h PG according to DeLong test *p*-value but not false discovery rate. Combining the metabolic markers with PG measurements and HbA1c significantly improved the predictive models, and mannose was found to be a robust metabolic marker.
Conclusions
The 1-h PG, alone or in combination with metabolic markers, is a robust predictor for determining the future risk of type 2 diabetes outperforms the 2-h PG, and is cheaper to measure than metabolites. Metabolites add to the predictive value of PG and HbA1c measurements. Shortening the standard 75-gram OGTT to one hour improves its predictive value as well as clinical usability.

We evaluated clinical risk factors, metabolites, HbA1c and plasma glucose levels during an OGTT. The 1-hour glucose level either alone or together with metabolites robustly predicted type 2 diabetes.

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ARTICLE

New diagnostic criteria for gestational diabetes mellitus and their impact on the number of diagnoses and pregnancy outcomes

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Abstract

Aims/hypothesis Detection and management of gestational diabetes mellitus (GDM) are crucial to reduce the risk of pregnancy-related complications for both mother and child. In 2013, the WHO adopted new diagnostic criteria for GDM to improve pregnancy outcomes. However, the evidence supporting these criteria is limited. Consequently, these new criteria have not yet been endorsed in the Netherlands. The aim of this study was to determine the impact of these criteria on the number of GDM diagnoses and pregnancy outcomes.

Methods Data were available from 10,642 women who underwent a 75 g OGTT because of risk factors or signs suggestive of GDM. Women were treated if diagnosed with GDM according to the WHO 1999 criteria. Data on pregnancy outcomes were obtained from extensive chart reviews from 4,431 women and were compared between women with normal glucose tolerance (NGT) and women classified into the following groups: (1) GDM according to WHO 1999 criteria; (2) GDM according to WHO 2013 criteria; (3) GDM according to WHO 2013 fasting glucose threshold, but not WHO 1999 criteria; and (4) GDM according to WHO 1999 2 h plasma glucose threshold (2HG), but not WHO 2013 criteria.

Results Applying the new WHO 2013 criteria would have increased the number of diagnoses by 45% (32% vs 22%) in this population of women at higher risk for GDM. In comparison with women with NGT, women classified as having GDM based only on the WHO 2013 threshold for fasting glucose, who were not treated for GDM, were more likely to have been obese (46.1% vs 28.1%, $p < 0.001$) and hypertensive (3.3% vs 1.2%, $p < 0.001$) before pregnancy, and to have had higher rates of gestational hypertension (7.8% vs 4.9%, $p = 0.003$), planned Caesarean section (10.3% vs 6.5%, $p = 0.001$) and induction of labour (34.8% vs 28.0%, $p = 0.001$). In addition, their neonates were more likely to have had an Apgar score <7 at 5 min (4.4% vs 2.6%, $p = 0.015$) and to have been admitted to the Neonatology Department (15.0% vs 11.1%, $p = 0.004$). The number of large for gestational age (LGA) neonates was not significantly different between the two groups. Women potentially missed owing to the higher 2HG threshold set by WHO 2013 had similar pregnancy outcomes to women with NGT. These women were all treated for GDM with diet and 20.5% received additional insulin.

Conclusions/interpretation Applying the WHO 2013 criteria will have a major impact on the number of GDM diagnoses. Using the fasting glucose threshold set by WHO 2013 identifies a group of women with an increased risk of adverse outcomes compared with women with NGT. We therefore support the use of a lower fasting glucose threshold in the Dutch national guideline for GDM diagnosis. However, adopting the WHO 2013 criteria with a higher 2HG threshold would exclude women in whom treatment for GDM seems to be effective.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-017-4506-x) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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The impact of environmental temperature on the diagnosis of gestational diabetes mellitus

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Abstract

Objective: To investigate a probable impact of seasons on the diagnosis of GDM, as well as the specific effect of the environmental temperature on the diagnosis of this clinical entity.

Patients and methods: Two observational studies, one retrospective and one prospective, were conducted in a referral center. Study A included retrospectively 7618 pregnant women who underwent a 3-h 100 g OGTT during the 3rd trimester of gestation. Study B prospectively included 768 pregnant women tested in the 3rd trimester of gestation with a 75 g OGTT. Temperature was recorded every day at 09:00 h.

Results: Retrospective Study A: GDM prevalence differed significantly by season: winter = 28.1%, summer = 39.2%, spring = 32.4% and autumn = 32.4% ($P < 0.0001$). The odds ratio for being diagnosed with GDM was much higher during summer 1.65 (95% CI: 1.43–1.90), with spring and autumn following with 1.23 (95% CI: 1.08–1.39) compared to winter. Glucose levels during OGTT were measured: significantly increased blood glucose values were observed at 60, 120 and 180 min in summer, which remained significant after adjustment for age, gestational age, BMI, weight gain during pregnancy and blood pressure. Prospective Study B: At temperatures above 25°C, the average glucose 60-min and 120-min levels were increased. The relative risk for abnormal glucose values at 60 min, when the environmental temperature increased over 25°C, was 2.2 (1.5–3.3).

Conclusions: GDM prevalence in Greece presents seasonal variation, with higher risk during summer due to post glucose load level variations. These variations could be attributed to differences in environmental temperature.

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Introduction

Gestational diabetes mellitus (GDM) is the type of diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes (1). GDM carries important risks for both the mother and the neonate. The results of the hyperglycemia and adverse pregnancy outcome (HAPO) study, including in total more than 25 000 multinational pregnant women, indicated strong and continuous associations of maternal glucose levels with increased fetal hyperinsulinemia and birth weight, both over the 90th percentile, as well as other adverse maternal, fetal and neonatal outcomes, such as pre-eclampsia, cesarean delivery, shoulder dystocia and neonatal hypoglycemia, even within ranges below those diagnostic of diabetes (2). These results revealed the necessity for appropriate diagnosis of GDM and proper management of these pregnant women (3).

Apart from careful consideration of the diagnostic criteria used for GDM, other parameters have also been

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ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ

ORIGINAL ARTICLE

Smoking Cessation, Weight Change, Type 2 Diabetes, and Mortality

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ABSTRACT

BACKGROUND

Whether weight gain after smoking cessation attenuates the health benefits of quitting is unclear.

METHODS

In three cohort studies involving men and women in the United States, we identified those who had reported quitting smoking and we prospectively assessed changes in smoking status and body weight. We estimated risks of type 2 diabetes, death from cardiovascular disease, and death from any cause among those who had reported quitting smoking, according to weight changes after smoking cessation.

RESULTS

The risk of type 2 diabetes was higher among recent quitters (2 to 6 years since smoking cessation) than among current smokers (hazard ratio, 1.22; 95% confidence interval [CI], 1.12 to 1.32). The risk peaked 5 to 7 years after quitting and then gradually decreased. The temporary increase in the risk of type 2 diabetes was directly proportional to weight gain, and the risk was not increased among quitters without weight gain ($P<0.001$ for interaction). In contrast, quitters did not have a temporary increase in mortality, regardless of weight change after quitting. As compared with current smokers, the hazard ratios for death from cardiovascular disease were 0.69 (95% CI, 0.54 to 0.88) among recent quitters without weight gain, 0.47 (95% CI, 0.35 to 0.63) among those with weight gain of 0.1 to 5.0 kg, 0.25 (95% CI, 0.15 to 0.42) among those with weight gain of 5.1 to 10.0 kg, 0.33 (95% CI, 0.18 to 0.60) among those with weight gain of more than 10.0 kg, and 0.50 (95% CI, 0.46 to 0.55) among longer-term quitters (>6 years since smoking cessation). Similar associations were observed for death from any cause.

CONCLUSIONS

Smoking cessation that was accompanied by substantial weight gain was associated with an increased short-term risk of type 2 diabetes but did not mitigate the benefits of quitting smoking on reducing cardiovascular and all-cause mortality. (Funded by the National Institutes of Health.)

From the Departments of Nutrition (Y.H., G.Z., G.L., W.C.W., F.B.H., Q.S.), Epidemiology (Y.H., M.W., W.C.W., J.E.M., F.B.H.), and Biostatistics (M.W., B.R.), Harvard T.H. Chan School of Public Health, and the Channing Division of Network Medicine (M.W., W.C.W., J.E.M., F.B.H., Q.S.) and the Division of Preventive Medicine (J.E.M.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School — all in Boston; and the Key Laboratory of Nutrition, Metabolism, and Food Safety, Institute of Nutrition and Health, Shanghai Institutes for Biological Sciences, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai (G.Z.), and the Department of Epidemiology and Biostatistics, Ministry of Education Key Laboratory of Environment and Health and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan (A.P.) — both in China. Address reprint requests to Dr. Sun at the Department of Nutrition, Harvard T.H. Chan School of Public Health, 665 Huntington Ave., Boston, MA 02115, or at qisun@hsph.harvard.edu.

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Impaired Sensitivity to Thyroid Hormones Is Associated With Diabetes and Metabolic Syndrome

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OBJECTIVE

Diabetes prevalence and incidence increase among individuals with hypothyroidism but also among those with hyperthyroxinemia, which seems contradictory. Both high free thyroxine (fT4) and high thyroid-stimulating hormone (TSH) are present in the resistance to thyroid hormone syndrome. A mild acquired resistance to thyroid hormone might occur in the general population and be associated with diabetes. We aimed to analyze the association of resistance to thyroid hormone indices (the Thyroid Feedback Quantile-based Index [TFQI], proposed in this work, and the previously used Thyrotroph T4 Resistance Index and TSH Index) with diabetes.

RESEARCH DESIGN AND METHODS

We calculated the aforementioned resistance to thyroid hormone indices based on a U.S. representative sample of 5,129 individuals ≥20 years of age participating in the 2007–2008 National Health and Nutrition Examination Survey (NHANES). Also, to approximate TFQI, a U.S.-referenced Parametric TFQI (PTFQI) can be calculated with the spreadsheet formula =NORM.DIST(fT4_cell_in_pmol_per_L,10.075, 2.155,TRUE)+NORM.DIST(LN(TSH_cell_in_mIU_per_L),0.4654,0.7744,TRUE)−1. Outcomes of interest were glycohemoglobin ≥6.5%, diabetes medication, diabetes-related deaths (diabetes as contributing cause of death), and additionally, in a fasting subsample, diabetes and metabolic syndrome. Logistic and Poisson regressions were adjusted for sex, age, and race/ethnicity.

RESULTS

Odd ratios for the fourth versus the first quartile of TFQI were 1.73 (95% CI 1.32, 2.27) (P_{trend} = 0.002) for positive glycohemoglobin and 1.66 (95% CI 1.31, 2.10) (P_{trend} = 0.001) for medication. Diabetes-related death rate ratio for TFQI being above versus below the median was 4.81 (95% CI 1.01, 22.94) (P_{trend} = 0.015). Further adjustment for BMI and restriction to normothyroid individuals yielded similar results. Per 1 SD in TFQI, odds increased 1.13 (95% CI 1.02, 1.25) for diabetes and 1.16 (95% CI 1.02, 1.31) for metabolic syndrome. The other resistance to thyroid hormone indices showed similar associations for diabetes-related deaths and metabolic syndrome.

CONCLUSIONS

Higher values in resistance to thyroid hormone indices are associated with obesity, metabolic syndrome, diabetes, and diabetes-related mortality. Resistance to thyroid hormone may reflect energy balance problems driving type 2 diabetes. These indices may facilitate monitoring treatments focused on energy balance.

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ARTICLE

Circulating prolactin concentrations and risk of type 2 diabetes in US women

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Abstract

Aims/hypothesis Prolactin, a multifunctional hormone, is involved in regulating insulin sensitivity and glucose homeostasis in experimental studies. However, whether circulating concentrations of prolactin are associated with risk of type 2 diabetes remains uncertain.

Methods We analysed the prospective relationship between circulating prolactin concentrations and type 2 diabetes risk in the Nurses' Health Study (NHS) and NHSII with up to 22 years of follow-up. Total plasma prolactin was measured using immunoassay in 8615 women free of type 2 diabetes and cardiovascular disease at baseline blood collection (NHS 1989–1990; NHSII 1996–1999) and a subset of 998 NHS women providing a second blood sample during 2000–2002. Baseline bioactive prolactin was measured in a subset of 2478 women using the Nb2 bioassay. HRs were estimated using Cox regression.

Results A total of 699 incident type 2 diabetes cases were documented during 156,140 person-years of follow-up. Total plasma prolactin levels were inversely associated with type 2 diabetes risk; the multivariable HR comparing the highest with the lowest quartile was 0.73 (95% CI 0.55, 0.95; $p_{trend} = 0.02$). The associations were similar by menopausal status and other risk factors ($p_{interaction} > 0.70$). Additional adjustment for sex and growth hormones, adiponectin, and inflammatory and insulin markers did not significantly alter the results. The association of plasma bioactive prolactin with type 2 diabetes risk was non-significantly stronger than that of total prolactin (HR comparing extreme quartiles, 0.53 vs 0.81 among the subset of 2478 women, $p_{difference} = 0.11$). The inverse association of total prolactin with type 2 diabetes was significant during the first 9 years after blood draw but waned linearly with time, whereas for bioactive prolactin, the inverse relationship persisted for a longer follow-up time after blood draw.

Conclusions/interpretation A normally high circulating total prolactin concentration was associated with a lower type 2 diabetes risk within 9–10 years of follow-up since blood draw in US women. Our findings are consistent with experimental evidence, suggesting that among healthy women, prolactin within the biologically normal range may play a protective role in the pathogenesis of type 2 diabetes.

Keywords Hormone · Insulin · Prolactin · Type 2 diabetes

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Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis

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European Journal of Endocrinology

Abstract

Objective/Design: Menopausal transition has been associated with a derangement of glucose metabolism. However, it is not known if early menopause (EM, defined as age at menopause <45 years) or premature ovarian insufficiency (POI, defined as age at menopause <40 years) are associated with increased risk of type 2 diabetes mellitus (T2DM). To systematically investigate and meta-analyze the best evidence regarding the association of age at menopause with the risk of T2DM.

Methods: A comprehensive search was conducted in PubMed, CENTRAL and Scopus, up to January 31, 2018. Data are expressed as odds ratio (OR) with 95% confidence intervals (CI). The I^2 index was employed for heterogeneity.

Results: Thirteen studies were included in the qualitative and quantitative analysis (191 762 postmenopausal women, 21 664 cases with T2DM). Both women with EM and POI were at higher risk of T2DM compared with those of age at menopause of 45–55 years (OR: 1.15, 95% CI: 1.04–1.26, $P = 0.003$; I^2: 61%, $P < 0.002$ and OR: 1.50, 95% CI: 1.03–2.19, $P = 0.033$; I^2: 75.2%, $P < 0.003$), respectively). Similar associations emerged when women with EM and POI were compared with those of age at menopause >45 years (OR: 1.12, 95% CI: 1.01–1.20, $P < 0.02$; I^2: 78%, $P < 0.001$ and OR: 1.53, 95% CI: 1.03–2.27, $P = 0.035$; I^2: 78%, $P < 0.001$), respectively).

Conclusions: Both EM and POI are associated with increased risk of T2DM.

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Introduction

Menopause is chronically determined by the completion of 12 months after the final menstrual period. It is the consequence follicular depletion leading to estrogen deficiency (1). The average age at menopause is 50–52 years (2). However, approximately 10% of the female population enter menopause before 45 years, a condition termed 'early' or 'premature' menopause (3). About 1% of women enter menopause under the age of 40 (0.1% under the age of 30), a condition termed 'premature ovarian insufficiency' (POI) (3, 4). Except the vasomotor

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Gut microbiota and intestinal FXR mediate the clinical benefits of metformin

Lulu Sun, Cen Xie, Guang Wang, Yue Wu, Qing Wu, Xuemei Wang, Jia Liu, Yangyang Deng, Jialin Xia, Bo Chen, Songyang Zhang, Chuyu Yun, Guan Lian, Xiujuan Zhang, Heng Zhang, William H. Bisson, Jingmin Shi, Xiaoxia Gao, Pupu Ge, Cuihua Liu, Kristopher W. Krausz, Robert G. Nichols, Jingwei Cai, Bipin Rimal, Andrew D. Patterson, Xian Wang, Frank J. Gonzalez & Changtao Jiang ✉ - Show fewer authors

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Abstract

The anti-hyperglycemic effect of metformin is believed to be caused by its direct action on signaling processes in hepatocytes, leading to lower hepatic gluconeogenesis. Recently, metformin was reported to alter the gut microbiota community in humans, suggesting that the hyperglycemia-lowering action of the drug could be the result of modulating the population of gut microbiota. However, the critical microbial signaling metabolites and the host targets associated with the metabolic benefits of metformin remained elusive. Here, we performed metagenomic and metabolomic analysis of samples from individuals with newly diagnosed type 2 diabetes (T2D) naively treated with metformin for 3 d, which revealed that *Bacteroides fragilis* was decreased and the bile acid glycoursodeoxycholic acid (GUDCA) was increased in the gut. These changes were accompanied by inhibition of intestinal farnesoid X receptor (FXR) signaling. We further found that high-fat-diet (HFD)-fed mice colonized with *B. fragilis* were predisposed to more severe glucose intolerance, and the metabolic benefits of metformin treatment on glucose intolerance were abrogated. GUDCA was further identified as an intestinal FXR antagonist that improved various metabolic endpoints in mice with established obesity. Thus, we conclude that metformin acts in part through a *B. fragilis*–GUDCA–intestinal FXR axis to improve metabolic dysfunction, including hyperglycemia.

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

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ABSTRACT

BACKGROUND

The cardiovascular safety profile of dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that promotes glucosuria in patients with type 2 diabetes, is undefined.

METHODS

We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

RESULTS

We evaluated 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years. In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% confidence interval [CI], <1.3; P<0.001 for noninferiority). In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17). A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (hazard ratio, 0.93; 95% CI, 0.82 to 1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, P=0.02), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001).

CONCLUSIONS

In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure. (Funded by AstraZeneca; DECLARE–TIMI 58 ClinicalTrials.gov number, NCT01730534.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wiviott at the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, 60 Fenwood Rd., 7th Fl., Boston, MA 02115, or at swiviott@bwh.harvard.edu.

*A complete list of the DECLARE–TIMI 58 investigators and executive committee and steering committee members is provided in the Supplementary Appendix, available at NEJM.org.

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JAMA | Original Investigation

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk

The CARMELINA Randomized Clinical Trial

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IMPORTANCE Type 2 diabetes is associated with increased cardiovascular (CV) risk. Prior trials have demonstrated CV safety of 3 dipeptidyl peptidase 4 (DPP-4) inhibitors but have included limited numbers of patients with high CV risk and chronic kidney disease.

OBJECTIVE To evaluate the effect of linagliptin, a selective DPP-4 inhibitor, on CV outcomes and kidney outcomes in patients with type 2 diabetes at high risk of CV and kidney events.

DESIGN, SETTING, AND PARTICIPANTS Randomized, placebo-controlled, multicenter noninferiority trial conducted from August 2013 to August 2016 at 605 clinic sites in 27 countries among adults with type 2 diabetes, hemoglobin A_{1c} of 6.5% to 10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria). Participants with end-stage renal disease (ESRD) were excluded. Final follow-up occurred on January 18, 2018.

INTERVENTIONS Patients were randomized to receive linagliptin, 5 mg once daily (n = 3494), or placebo once daily (n = 3485) added to usual care. Other glucose-lowering medications or insulin could be added based on clinical need and local clinical guidelines.

MAIN OUTCOMES AND MEASURES Primary outcome was time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. Criteria for noninferiority of linagliptin vs placebo was defined by the upper limit of the 2-sided 95% CI for the hazard ratio (HR) of linagliptin relative to placebo being less than 1.3. Secondary outcome was time to first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline.

RESULTS Of 6991 enrollees, 6979 (mean age, 65.9 years; eGFR, 54.6 mL/min/1.73 m^2; 80.1% with UACR >30 mg/g) received at least 1 dose of study medication and 98.7% completed the study. During a median follow-up of 2.2 years, the primary outcome occurred in 434 of 3494 (12.4%) and 420 of 3485 (12.1%) in the linagliptin and placebo groups, respectively, (absolute incidence rate difference, 0.13 [95% CI, −0.63 to 0.90] per 100 person-years) (HR, 1.02; 95% CI, 0.89-1.17; $P < .001$ for noninferiority). The kidney outcome occurred in 327 of 3494 (9.4%) and 306 of 3485 (8.8%), respectively (absolute incidence rate difference, 0.22 [95% CI, −0.52 to 0.97] per 100 person-years) (HR, 1.04; 95% CI, 0.89-1.22; $P = .62$). Adverse events occurred in 2697 (77.2%) and 2723 (78.1%) patients in the linagliptin and placebo groups; 1036 (29.7%) and 1024 (29.4%) had 1 or more episodes of hypoglycemia; and there were 9 (0.3%) vs 5 (0.1%) events of adjudication-confirmed acute pancreatitis.

CONCLUSIONS AND RELEVANCE Among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite CV outcome over a median 2.2 years.

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Supplemental content

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Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial

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Summary

Background The results of the ELIXA trial demonstrated the cardiovascular safety of lixisenatide, a short-acting glucagon-like peptide-1 receptor agonist, in patients with type 2 diabetes and acute coronary syndrome. In this exploratory analysis of ELIXA, we investigate the effect of lixisenatide on renal outcomes.

Methods ELIXA was a randomised, double-blind, placebo-controlled trial, done at 828 sites in 49 countries. Patients with type 2 diabetes and a recent coronary artery event were randomly assigned (1:1) to a daily subcutaneous injection of lixisenatide (10–20 µg) or volume-matched placebo, in addition to usual care, until at least 844 patients had an adjudicated major adverse cardiovascular event included in the primary outcome. Patients, study staff, and individuals involved in analysis of trial data were masked to treatment assignment. The primary and secondary endpoints of this trial have been reported previously. Here, in an exploratory analysis of ELIXA, we investigated percentage change in urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) according to prespecified albuminuria status at baseline (normoalbuminuria [UACR <30 mg/g]; microalbuminuria [≥30 to ≤300 mg/g]; and macroalbuminuria [>300 mg/g]) using a mixed-effect model with repeated measures. Time to new-onset macroalbuminuria and doubling of serum creatinine were also assessed with Cox proportional hazards models. The ELIXA trial is registered with ClinicalTrials.gov, number NCT01147250, and is completed.

Findings Of 6068 patients randomly allocated between July 9, 2010, and Aug 2, 2013, baseline UACR data were available for 5978 (99%). Median follow-up time was 108 weeks. 4441 (74%; 2191 assigned to placebo and 2250 assigned to lixisenatide) had normoalbuminuria, 1148 (19%; 596 assigned to placebo and 552 assigned to lixisenatide) had microalbuminuria, and 389 (7%; 207 assigned to placebo and 182 assigned to lixisenatide) had macroalbuminuria. After 108 weeks, the placebo-adjusted least-squares mean percentage change in UACR from baseline with lixisenatide was −1·69% (95% CI −11·69 to 8·30; p=0·7398) in patients with normoalbuminuria, −21·10% (−42·25 to 0·04; p=0·0502) in patients with microalbuminuria, and −39·18% (−68·53 to −9·84; p=0·0070) in patients with macroalbuminuria. Lixisenatide was associated with a reduced risk of new-onset macroalbuminuria compared with placebo when adjusted for baseline HbA_{1c} (hazard ratio [HR] 0·808 [95% CI 0·660 to 0·991; p=0·0404]) or baseline and on-trial HbA_{1c} (HR 0·815 [0·665 to 0·999; p=0·0491]); point estimates were similar when adjusted for other traditional renal risk factors. At week 108, the largest eGFR decline from baseline was observed in the macroalbuminuric group, but no significant differences were observed between the two treatment groups. No significant differences in eGFR decline were identified between treatment groups in any UACR subgroup. In the trial safety population, doubling of serum creatinine occurred in 35 (1%) of 3032 patients in the placebo group and 41 (1%) of 3031 patients in the lixisenatide group (HR 1·163, 95% CI 0·741–1·825; p=0·5127). As previously reported in the ELIXA trial, the proportion of patients with renal adverse events was low (48 [1·6%] of 3032 patients in the placebo group *vs* 48 [1·6%] of 3031 patients in the lixisenatide group) and did not significantly differ between treatment groups.

Interpretation Lixisenatide reduces progression of UACR in macroalbuminuric patients, and is associated with a lower risk of new-onset macroalbuminuria after adjustment for baseline and on-trial HbA_{1c} and other traditional renal risk factors.

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Introduction

Diabetic kidney disease is a common and morbid long-term complication of diabetes, particularly in patients with evidence of cardiovascular disease, and has become the leading cause of chronic kidney disease in most world regions.[1] About 40% of patients with type 2 diabetes develop chronic kidney disease, which presents as albuminuria, an impaired glomerular filtration rate (GFR), or both.[1] Even mild increases in albuminuria or GFR decline are associated with a substantial increased risk of cardiovascular disease and cardiovascular death, and increased health-care costs.[2] Moreover, diabetic

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

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Summary

Background Glucagon-like peptide 1 receptor agonists differ in chemical structure, duration of action, and in their effects on clinical outcomes. The cardiovascular effects of once-weekly albiglutide in type 2 diabetes are unknown. We aimed to determine the safety and efficacy of albiglutide in preventing cardiovascular death, myocardial infarction, or stroke.

Methods We did a double-blind, randomised, placebo-controlled trial in 610 sites across 28 countries. We randomly assigned patients aged 40 years and older with type 2 diabetes and cardiovascular disease (at a 1:1 ratio) to groups that either received a subcutaneous injection of albiglutide (30–50 mg, based on glycaemic response and tolerability) or of a matched volume of placebo once a week, in addition to their standard care. Investigators used an interactive voice or web response system to obtain treatment assignment, and patients and all study investigators were masked to their treatment allocation. We hypothesised that albiglutide would be non-inferior to placebo for the primary outcome of the first occurrence of cardiovascular death, myocardial infarction, or stroke, which was assessed in the intention-to-treat population. If non-inferiority was confirmed by an upper limit of the 95% CI for a hazard ratio of less than 1·30, closed testing for superiority was prespecified. This study is registered with ClinicalTrials.gov, number NCT02465515.

Findings Patients were screened between July 1, 2015, and Nov 24, 2016. 10 793 patients were screened and 9463 participants were enrolled and randomly assigned to groups: 4731 patients were assigned to receive albiglutide and 4732 patients to receive placebo. On Nov 8, 2017, it was determined that 611 primary endpoints and a median follow-up of at least 1·5 years had accrued, and participants returned for a final visit and discontinuation from study treatment; the last patient visit was on March 12, 2018. These 9463 patients, the intention-to-treat population, were evaluated for a median duration of 1·6 years and were assessed for the primary outcome. The primary composite outcome occurred in 338 (7%) of 4731 patients at an incidence rate of 4·6 events per 100 person-years in the albiglutide group and in 428 (9%) of 4732 patients at an incidence rate of 5·9 events per 100 person-years in the placebo group (hazard ratio 0·78, 95% CI 0·68–0·90), which indicated that albiglutide was superior to placebo (p<0·0001 for non-inferiority; p=0·0006 for superiority). The incidence of acute pancreatitis (ten patients in the albiglutide group and seven patients in the placebo group), pancreatic cancer (six patients in the albiglutide group and five patients in the placebo group), medullary thyroid carcinoma (zero patients in both groups), and other serious adverse events did not differ between the two groups. There were three (<1%) deaths in the placebo group that were assessed by investigators, who were masked to study drug assignment, to be treatment-related and two (<1%) deaths in the albiglutide group.

Interpretation In patients with type 2 diabetes and cardiovascular disease, albiglutide was superior to placebo with respect to major adverse cardiovascular events. Evidence-based glucagon-like peptide 1 receptor agonists should therefore be considered as part of a comprehensive strategy to reduce the risk of cardiovascular events in patients with type 2 diabetes.

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See Online for appendix 1

Introduction

The risk of fatal and non-fatal cardiovascular events is much higher in people with type 2 diabetes than in the general population.[1,2] Drugs in two classes of newer glucose-lowering therapies, the sodium-glucose co-transporter 2 (SGLT-2) inhibitors and the glucagon-like peptide 1 (GLP-1) receptor agonists, have been shown to reduce the risk of major adverse cardiovascular events, although findings regarding the GLP-1 receptor agonists have been inconsistent.[3–8] Specifically, not all tested GLP-1 receptor agonists have been shown to reduce cardiovascular events, and the effect of these treatments

Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial

Richard E Pratley, Vanita R Aroda, Ildiko Lingvay, Jörg Lüdemann, Camilla Andreassen, Andrea Navarria, Adie Viljoen, on behalf of the SUSTAIN 7 investigators

Summary

Background Despite common mechanisms of actions, glucagon-like peptide-1 receptor agonists differ in structure, pharmacokinetic profile, and clinical effects. This head-to-head trial compared semaglutide with dulaglutide in patients with inadequately controlled type 2 diabetes.

Methods This was an open-label, parallel-group, phase 3b trial done at 194 hospitals, clinical institutions or private practices in 16 countries. Eligible patients were aged 18 years or older and had type 2 diabetes with HbA_{1c} 7·0–10·5% (53·0–91·0 mmol/mol) on metformin monotherapy. Patients were randomly assigned (1:1:1:1) by use of an interactive web-response system to once a week treatment with either semaglutide 0·5 mg, dulaglutide 0·75 mg, semaglutide 1·0 mg, or dulaglutide 1·5 mg subcutaneously. The primary endpoint was change from baseline in percentage HbA_{1c}; the confirmatory secondary endpoint was change in bodyweight, both at week 40. The primary analysis population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment and before the onset of rescue medication. The safety population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment. The trial was powered for HbA_{1c} non-inferiority (margin 0·4%) and bodyweight superiority. This trial is registered with ClinicalTrials.gov, number NCT02648204.

Findings Between Jan 6, 2016, and June 22, 2016, 1201 patients were randomly assigned to treatment; of these, 301 were exposed to semaglutide 0·5 mg, 299 to dulaglutide 0·75 mg, 300 to semaglutide 1·0 mg, and 299 to dulaglutide 1·5 mg. 72 (6%) patients withdrew from the trial (22 receiving semaglutide 0·5 mg, 13 receiving dulaglutide 0·75 mg, 21 receiving semaglutide 1·0 mg, and 16 receiving dulaglutide 1·5 mg). From overall baseline mean, mean percentage HbA_{1c} was reduced by 1·5 (SE 0·06) percentage points with semaglutide 0·5 mg versus 1·1 (0·05) percentage points with dulaglutide 0·75 mg (estimated treatment difference [ETD] –0·40 percentage points [95% CI –0·55 to –0·25]; p<0·0001) and by 1·8 (0·06) percentage points with semaglutide 1·0 mg versus 1·4 (0·06) percentage points with dulaglutide 1·5 mg (ETD –0·41 percentage points [–0·57 to –0·25]; p<0·0001). From overall baseline mean, mean bodyweight was reduced by 4·6 kg (SE 0·28) with semaglutide 0·5 mg compared with 2·3 kg (0·27) with dulaglutide 0·75 mg (ETD –2·26 kg [–3·02 to –1·51]; p<0·0001) and by 6·5 kg (0·28) with semaglutide 1·0 mg compared with 3·0 kg (0·27) with dulaglutide 1·5 mg (ETD –3·55 kg [–4·32 to –2·78]; p<0·0001). Gastrointestinal disorders were the most frequently reported adverse event, occurring in 129 (43%) of 301 patients receiving semaglutide 0·5 mg, 133 (44%) of 300 patients receiving semaglutide 1·0 mg, 100 (33%) of 299 patients receiving dulaglutide 0·75 mg, and in 143 (48%) of 299 patients receiving dulaglutide 1·5 mg. Gastrointestinal disorders were also the most common reason for discontinuing treatment with semaglutide and dulaglutide. There were six fatalities: one in each semaglutide group and two in each dulaglutide group.

Interpretation At low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control and reducing bodyweight, enabling a significantly greater number of patients with type 2 diabetes to achieve clinically meaningful glycaemic targets and weight loss, with a similar safety profile.

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Introduction

Despite considerable advances in treatment options for type 2 diabetes, a significant proportion of patients do not achieve recommended glycaemic targets[1] and are, therefore, at risk of developing several chronic complications of diabetes, including cardiovascular disease.[2] Additionally, obesity, a comorbidity that affects about 85% of patients with type 2 diabetes,[3] promotes insulin resistance and is associated with poor long-term clinical outcomes.[4,5]

Glucagon-like peptide-1 receptor (GLP-1R) agonists are an established treatment option for type 2 diabetes. These drugs are effective antihyperglycaemic treatments that carry a low risk of hypoglycaemia and promote weight loss.[6] Treatments with these drugs once a week have been associated with better adherence to therapy

A 26-Week Randomized Controlled Trial of Semaglutide Once Daily Versus Liraglutide and Placebo in Patients With Type 2 Diabetes Suboptimally Controlled on Diet and Exercise With or Without Metformin

https://doi.org/10.2337/dc17-2381

Ildiko Lingvay,[1] Cyrus V. Desouza,[2] Katarina S. Lalic,[3] Ludger Rose,[4] Thomas Hansen,[5] Jeppe Zacho,[5] and Thomas R. Pieber[6]

OBJECTIVE

To investigate the efficacy and safety of once-daily semaglutide in comparison with once-daily liraglutide and placebo in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This 26-week, multicenter, double-blind trial involved patients diagnosed with type 2 diabetes with HbA_{1c} 7.0–10.0% (53–86 mmol/mol) and treated with diet and exercise with or without metformin. Patients were randomized 2:2:1 to once-daily semaglutide, liraglutide, or placebo in one of four volume-matched doses (semaglutide 0.05, 0.1, 0.2, or 0.3 mg and liraglutide 0.3, 0.6, 1.2, or 1.8 mg, with both compared within each volume-matched dose group). Primary end point was change in HbA_{1c} from baseline to week 26.

RESULTS

In total, 705 randomized patients were exposed to trial products. At week 26, a dose-dependent change in HbA_{1c} was observed with semaglutide from −1.1% (0.05 mg) to −1.9% (0.3 mg) and with liraglutide from −0.5% (0.3 mg) to −1.3% (1.8 mg) (all $P < 0.001$ in favor of volume-matched semaglutide dose). Change with pooled placebo was −0.02% ($P < 0.0001$ vs. semaglutide). Gastrointestinal (GI) disorders were the most common adverse events (AEs) with semaglutide and liraglutide, occurring in 32.8–54.0% and 21.9–41.5% of patients, respectively.

CONCLUSIONS

Once-daily semaglutide at doses up to 0.3 mg/day resulted in greater reductions in HbA_{1c} compared with liraglutide or placebo but with a higher frequency of GI AEs.

Glucagon-like peptide 1 (GLP-1) is a gut-derived peptide and a potent blood glucose (BG)-lowering hormone (1). It functions in a glucose-dependent manner and is therefore associated with a low risk of hypoglycemia (2). GLP-1 inhibits gastric emptying and reduces body weight by lowering energy intake and inducing feelings

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Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

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Summary

Background LY3298176 is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for the treatment of type 2 diabetes. We aimed to examine the efficacy and safety of co-stimulation of the GLP-1 and GIP receptors with LY3298176 compared with placebo or selective stimulation of GLP-1 receptors with dulaglutide in patients with poorly controlled type 2 diabetes.

Methods In this double-blind, randomised, phase 2 study, patients with type 2 diabetes were randomly assigned (1:1:1:1:1:1) to receive either once-weekly subcutaneous LY3298176 (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1·5 mg), or placebo for 26 weeks. Assignment was stratified by baseline glycated haemoglobin A_{1c} (HbA_{1c}), metformin use, and body-mass index (BMI). Eligible participants (aged 18–75) had type 2 diabetes for at least 6 months (HbA_{1c} 7·0–10·5%, inclusive), that was inadequately controlled with diet and exercise alone or with stable metformin therapy, and a BMI of 23–50 kg/m². The primary efficacy outcome was change in HbA_{1c} from baseline to 26 weeks in the modified intention-to-treat (mITT) population (all patients who received at least one dose of study drug and had at least one postbaseline measurement of any outcome). Secondary endpoints, measured in the mITT on treatment dataset, were change in HbA_{1c} from baseline to 12 weeks; change in mean bodyweight, fasting plasma glucose, waist circumference, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and proportion of patients reaching the HbA_{1c} target (≤6·5% and <7·0%) from baseline to weeks 12 and 26; and proportion of patients with at least 5% and 10% bodyweight loss from baseline to 26 weeks. This study is registered with ClinicalTrials.gov, number NCT03131687.

Findings Between May 24, 2017, and March 28, 2018, 555 participants were assessed for eligibility, of whom 318 were randomly assigned to one of the six treatment groups. Because two participants did not receive treatment, the modified intention-to-treat and safety populations included 316 participants. 258 (81·7%) participants completed 26 weeks of treatment, and 283 (89·6%) completed the study. At baseline, mean age was 57 years (SD 9), BMI was 32·6 kg/m² (5·9), duration from diagnosis of diabetes was 9 years (6), HbA_{1c} was 8·1% (1·0), 53% of patients were men, and 47% were women. At 26 weeks, the effect of LY3298176 on change in HbA_{1c} was dose-dependent and did not plateau. Mean changes from baseline in HbA_{1c} with LY3298176 were –1·06% for 1 mg, –1·73% for 5 mg, –1·89% for 10 mg, and –1·94% for 15 mg, compared with –0·06% for placebo (posterior mean differences [80% credible set] *vs* placebo: –1·00% [–1·22 to –0·79] for 1 mg, –1·67% [–1·88 to –1·46] for 5 mg, –1·83% [–2·04 to –1·61] for 10 mg, and –1·89% [–2·11 to –1·67] for 15 mg). Compared with dulaglutide (–1·21%) the posterior mean differences (80% credible set) for change in HbA_{1c} from baseline to 26 weeks with the LY3298176 doses were 0·15% (–0·08 to 0·38) for 1 mg, –0·52% (–0·72 to –0·31) for 5 mg, –0·67% (–0·89 to –0·46) for 10 mg, and –0·73% (–0·95 to –0·52) for 15 mg. At 26 weeks, 33–90% of patients treated with LY3298176 achieved the HbA_{1c} target of less than 7·0% (*vs* 52% with dulaglutide, 12% with placebo) and 15–82% achieved the HbA_{1c} target of at least 6·5% (*vs* 39% with dulaglutide, 2% with placebo). Changes in fasting plasma glucose ranged from –0·4 mmol/L to –3·4 mmol/L for LY3298176 (*vs* 0·9 mmol/L for placebo, –1·2 mmol/L for dulaglutide). Changes in mean bodyweight ranged from –0·9 kg to –11·3 kg for LY3298176 (*vs* –0·4 kg for placebo, –2·7 kg for dulaglutide). At 26 weeks, 14–71% of those treated with LY3298176 achieved the weight loss target of at least 5% (*vs* 22% with dulaglutide, 0% with placebo) and 6–39% achieved the weight loss target of at least 10% (*vs* 9% with dulaglutide, 0% with placebo). Changes in waist circumference ranged from –2·1 cm to –10·2 cm for LY3298176 (*vs* –1·3 cm for placebo, –2·5 cm for dulaglutide). Changes in total cholesterol ranged from 0·2 mmol/L to –0·3 mmol/L for LY3298176 (*vs* 0·3 mmol/L for placebo, –0·2 mmol/L for dulaglutide). Changes in HDL or LDL cholesterol did not differ between the LY3298176 and placebo groups. Changes in triglyceride concentration ranged from 0 mmol/L to –0·8 mmol/L for LY3298176 (*vs* 0·3 mmol/L for placebo, –0·3 mmol/L for dulaglutide). The 12-week outcomes were similar to those at 26 weeks for all secondary outcomes. 13 (4%) of 316 participants across the six treatment groups had 23 serious adverse events in total. Gastrointestinal events (nausea, diarrhoea, and vomiting) were the most common treatment-emergent adverse

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ORIGINAL ARTICLE

Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care

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ABSTRACT

BACKGROUND

In patients with diabetes, hospitalization can complicate the achievement of recommended glycemic targets. There is increasing evidence that a closed-loop delivery system (artificial pancreas) can improve glucose control in patients with type 1 diabetes. We wanted to investigate whether a closed-loop system could also improve glycemic control in patients with type 2 diabetes who were receiving noncritical care.

METHODS

In this randomized, open-label trial conducted on general wards in two tertiary hospitals located in the United Kingdom and Switzerland, we assigned 136 adults with type 2 diabetes who required subcutaneous insulin therapy to receive either closed-loop insulin delivery (70 patients) or conventional subcutaneous insulin therapy, according to local clinical practice (66 patients). The primary end point was the percentage of time that the sensor glucose measurement was within the target range of 100 to 180 mg per deciliter (5.6 to 10.0 mmol per liter) for up to 15 days or until hospital discharge.

RESULTS

The mean (±SD) percentage of time that the sensor glucose measurement was in the target range was 65.8±16.8% in the closed-loop group and 41.5±16.9% in the control group, a difference of 24.3±2.9 percentage points (95% confidence interval [CI], 18.6 to 30.0; P<0.001); values above the target range were found in 23.6±16.6% and 49.5±22.8% of the patients, respectively, a difference of 25.9±3.4 percentage points (95% CI, 19.2 to 32.7; P<0.001). The mean glucose level was 154 mg per deciliter (8.5 mmol per liter) in the closed-loop group and 188 mg per deciliter (10.4 mmol per liter) in the control group (P<0.001). There was no significant between-group difference in the duration of hypoglycemia (as defined by a sensor glucose measurement of <54 mg per deciliter; P=0.80) or in the amount of insulin that was delivered (median dose, 44.4 U and 40.2 U, respectively; P=0.50). No episode of severe hypoglycemia or clinically significant hyperglycemia with ketonemia occurred in either trial group.

CONCLUSIONS

Among inpatients with type 2 diabetes receiving noncritical care, the use of an automated, closed-loop insulin-delivery system resulted in significantly better glycemic control than conventional subcutaneous insulin therapy, without a higher risk of hypoglycemia. (Funded by Diabetes UK and others; ClinicalTrials.gov number, NCT01774565.)

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JAMA | Original Investigation

Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin With Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and With Glycemic Control in Patients With Type 2 Diabetes

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IMPORTANCE In clinical trials of patients with type 2 diabetes, long-acting insulin analogs modestly reduced the risk of nocturnal hypoglycemia compared with human neutral protamine Hagedorn (NPH) insulin, but cost 2 to 10 times more. Outcomes in clinical practice may differ from trial results.

OBJECTIVE To compare the rates of hypoglycemia-related emergency department (ED) visits or hospital admissions associated with initiation of long-acting insulin analogs vs human NPH insulin in patients with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS A retrospective observational study using data from Kaiser Permanente of Northern California from January 1, 2006, through September 30, 2015. Patients with type 2 diabetes who initiated a long-acting insulin analog or NPH insulin were included and censored at death, loss of health plan coverage, change in insulin treatment, or study end on September 30, 2015.

EXPOSURE Initiation of basal insulin analogs (glargine or detemir) vs NPH insulin.

MAIN OUTCOMES AND MEASURES The primary outcome was the time to a hypoglycemia-related ED visit or hospital admission and the secondary outcome was the change in hemoglobin A_{1c} level within 1 year of insulin initiation.

RESULTS There were 25 489 patients with type 2 diabetes who initiated basal insulin therapy (mean age, 60.2 [SD, 11.8] years; 51.9% white; 46.8% female). During a mean follow-up of 1.7 years, there were 39 hypoglycemia-related ED visits or hospital admissions among 1928 patients who initiated insulin analogs (11.9 events [95% CI, 8.1 to 15.6] per 1000 person-years) compared with 354 hypoglycemia-related ED visits or hospital admissions among 23 561 patients who initiated NPH insulin (8.8 events [95% CI, 7.9 to 9.8] per 1000 person-years) (between-group difference, 3.1 events [95% CI, −1.5 to 7.7] per 1000 person-years; $P = .07$). Among 4428 patients matched by propensity score, the adjusted hazard ratio was 1.16 (95% CI, 0.71 to 1.78) for hypoglycemia-related ED visits or hospital admissions associated with insulin analog use. Within 1 year of insulin initiation, hemoglobin A_{1c} level decreased from 9.4% (95% CI, 9.3% to 9.5%) to 8.2% (95% CI, 8.1% to 8.2%) after initiation of insulin analogs and from 9.4% (95% CI, 9.3% to 9.5%) to 7.9% (95% CI, 7.9% to 8.0%) after initiation of NPH insulin (adjusted difference-in-differences for glycemic control, −0.22% [95% CI, −0.09% to −0.37%]).

CONCLUSIONS AND RELEVANCE Among patients with type 2 diabetes, initiation of a basal insulin analog compared with NPH insulin was not associated with a reduced risk of hypoglycemia-related ED visits or hospital admissions or with improved glycemic control. These findings suggest that the use of basal insulin analogs in usual practice settings may not be associated with clinical advantages for these outcomes.

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Editorial
Author Audio Interview

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Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

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Summary

Background Type 2 diabetes is a chronic disorder that requires lifelong treatment. We aimed to assess whether intensive weight management within routine primary care would achieve remission of type 2 diabetes.

Methods We did this open-label, cluster-randomised trial (DiRECT) at 49 primary care practices in Scotland and the Tyneside region of England. Practices were randomly assigned (1:1), via a computer-generated list, to provide either a weight management programme (intervention) or best-practice care by guidelines (control), with stratification for study site (Tyneside or Scotland) and practice list size (>5700 or ≤5700). Participants, carers, and research assistants who collected outcome data were aware of group allocation; however, allocation was concealed from the study statistician. We recruited individuals aged 20–65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body-mass index of 27–45 kg/m², and were not receiving insulin. The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance. Co-primary outcomes were weight loss of 15 kg or more, and remission of diabetes, defined as glycated haemoglobin (HbA_{1c}) of less than 6·5% (<48 mmol/mol) after at least 2 months off all antidiabetic medications, from baseline to 12 months. These outcomes were analysed hierarchically. This trial is registered with the ISRCTN registry, number 03267836.

Findings Between July 25, 2014, and Aug 5, 2017, we recruited 306 individuals from 49 intervention (n=23) and control (n=26) general practices; 149 participants per group comprised the intention-to-treat population. At 12 months, we recorded weight loss of 15 kg or more in 36 (24%) participants in the intervention group and no participants in the control group (p<0·0001). Diabetes remission was achieved in 68 (46%) participants in the intervention group and six (4%) participants in the control group (odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001). Remission varied with weight loss in the whole study population, with achievement in none of 76 participants who gained weight, six (7%) of 89 participants who maintained 0–5 kg weight loss, 19 (34%) of 56 participants with 5–10 kg loss, 16 (57%) of 28 participants with 10–15 kg loss, and 31 (86%) of 36 participants who lost 15 kg or more. Mean bodyweight fell by 10·0 kg (SD 8·0) in the intervention group and 1·0 kg (3·7) in the control group (adjusted difference −8·8 kg, 95% CI −10·3 to −7·3; p<0·0001). Quality of life, as measured by the EuroQol 5 Dimensions visual analogue scale, improved by 7·2 points (SD 21·3) in the intervention group, and decreased by 2·9 points (15·5) in the control group (adjusted difference 6·4 points, 95% CI 2·5–10·3; p=0·0012). Nine serious adverse events were reported by seven (4%) of 157 participants in the intervention group and two were reported by two (1%) participants in the control group. Two serious adverse events (biliary colic and abdominal pain), occurring in the same participant, were deemed potentially related to the intervention. No serious adverse events led to withdrawal from the study.

Interpretation Our findings show that, at 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care.

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Introduction

Type 2 diabetes affects almost one in ten adults in the UK, and 422 million adults worldwide.[1,2] Most people with type 2 diabetes have disease-related morbidity and reduced longevity. The disease is particularly devastating for the growing numbers of younger people affected, who tend to be more obese and lose more life-years through diabetes.[3] Current guidelines for management of type 2 diabetes focus heavily on multiple drug treatments to reduce blood glucose and the associated elevated risks of cardiovascular disease, but life expectancy remains substantially reduced.

Type 2 diabetes is strongly related to weight gain in adult life and accumulation of excess fat within the liver and pancreas. The twin cycle hypothesis,[4] which postulated that type 2 diabetes is caused specifically by excess fat within the liver and pancreas, was tested by inducing negative energy balance with a 600–700 kcal/day diet. Liver insulin resistance and fat content normalised within 7 days, with first-phase insulin response and pancreas fat content normalising over 8 weeks.[5] In a subsequent parallel-group study,[6] the underlying changes were shown to remain stable over a 6 month period of isocaloric eating.

Fasting Glucose and All-Cause Mortality by Age in Diabetes: A Prospective Cohort Study

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OBJECTIVE

To examine associations between fasting glucose and mortality and to identify the levels associated with lowest mortality by age in diabetes.

RESEARCH DESIGN AND METHODS

A total of 359,645 Korean adults with known prevalent diabetes participated in health screening during 2001–2004 and were followed up until 2013.

RESULTS

U-curve associations were found. Fasting glucose levels associated with the lowest mortality were ~90–130 mg/dL, except for in those aged 18–44 years (~80–95 mg/dL). Multivariable-adjusted hazard ratios of fasting glucose <65, 65–74, 75–84, 140–169, 170–199, and ≥200 mg/dL were 1.46, 1.12, 1.09, 1.12, 1.31, and 1.78, respectively, compared with 85–99 mg/dL.

CONCLUSIONS

Optimal fasting glucose range for survival is higher in adults with than without known prevalent diabetes, except, perhaps, younger adults. Tight glucose control may lessen premature death in younger adults with diabetes. Hypoglycemia (<65 mg/dL) was associated with higher mortality than was fasting glucose 170–199 mg/dL, while fasting glucose 65–84 mg/dL had risks comparable with those at levels 140–169 mg/dL in diabetes.

Fasting glucose levels are a fundamental element of managing diabetes in patients to achieve good glycemic control. Precise estimates of the age-specific relative risks of death associated with fasting glucose may help determine better glucose targets for management of diabetes. However, little is known about the associations of the full range of fasting glucose with all-cause mortality and the optimal range for survival according to age in diabetes.

RESEARCH DESIGN AND METHODS

More detailed information about the Korean Metabolic Risk Factor (KOMERIT) study has previously been published (1–3). This study included 12,845,017 adults who participated in routine health screenings during 2001–2004 by the National Health Insurance Service, which provides mandatory insurance coverage for 97% of the Korean population. After exclusion of individuals with missing information or extreme anthropometric measures, 12,815,006 participants, of whom 369,645 had known prevalent diabetes, were follow up until 2013 for survival (1). This study was approved by the institutional review board of Catholic Kwandong University.

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ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

ABSTRACT

BACKGROUND

Increased intake of n–3 fatty acids has been associated with a reduced risk of cardiovascular disease in observational studies, but this finding has not been confirmed in randomized trials. It remains unclear whether n–3 (also called omega-3) fatty acid supplementation has cardiovascular benefit in patients with diabetes mellitus.

METHODS

We randomly assigned 15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules containing either n–3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. The primary outcome was a first serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization.

RESULTS

During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.08; P=0.55). The composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86 to 1.05). There were no significant between-group differences in the rates of nonfatal serious adverse events.

CONCLUSIONS

Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n–3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others; Current Controlled Trials number, ISRCTN60635500; ClinicalTrials.gov number, NCT00135226.)

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*A complete list of the members of the ASCEND Study Collaborative Group is provided in Supplementary Appendix 1, available at NEJM.org.

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ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

ABSTRACT

BACKGROUND

Diabetes mellitus is associated with an increased risk of cardiovascular events. Aspirin use reduces the risk of occlusive vascular events but increases the risk of bleeding; the balance of benefits and hazards for the prevention of first cardiovascular events in patients with diabetes is unclear.

METHODS

We randomly assigned adults who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer.

RESULTS

A total of 15,480 participants underwent randomization. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned.

CONCLUSIONS

Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard. (Funded by the British Heart Foundation and others; ASCEND Current Controlled Trials number, ISRCTN60635500; ClinicalTrials.gov number, NCT00135226.)

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*A complete list of the members of the ASCEND Study Collaborative Group is provided in Supplementary Appendix 1, available at NEJM.org.

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GUIDELINES

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the prior position statements, published in 2012 and 2015, on the management of type 2 diabetes in adults. A systematic evaluation of the literature since 2014 informed new recommendations. These include additional focus on lifestyle management and diabetes self-management education and support. For those with obesity, efforts targeting weight loss, including lifestyle, medication, and surgical interventions, are recommended. With regards to medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide 1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended. For patients with chronic kidney disease or clinical heart failure and atherosclerotic cardiovascular disease, an SGLT2 inhibitor with proven benefit is recommended. GLP-1 receptor agonists are generally recommended as the first injectable medication.

The goals of treatment for type 2 diabetes are to prevent or delay complications and maintain quality of life (Fig. 1). This requires control of glycemia and cardiovascular risk factor management, regular follow-up, and, importantly, a patient-centered approach to enhance patient engagement in self-care activities (1). Careful consideration of patient factors and preferences must inform the process of individualizing treatment goals and strategies (2,3).

This consensus report addresses the approaches to management of glycemia in adults with type 2 diabetes, with the goal of reducing complications and maintaining quality of life in the context of comprehensive cardiovascular risk management and patient-centered care. The principles of how this can be achieved are summarized in Fig. 1 and underpin the approach to management and care. These recommendations are not generally applicable to patients with monogenic diabetes, secondary diabetes, or type 1 diabetes, or to children.

Data Sources, Searches, and Study Selection

The writing group accepted the 2012 (4) and 2015 (5) editions of this position statement as a starting point. To identify newer evidence, a search was conducted on PubMed for randomized clinical trials (RCTs), systematic reviews, and meta-analyses

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This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

M.J.D. and J.B.B. were co-chairs for the Consensus Statement Writing Group. D.A.D'A., J.F., W.N.K., and D.J.W. were the writing group members for the American Diabetes Association. C.M., G.M., P.R., and A.T. were writing group members for the European Association for the Study of Diabetes.

This article is being simultaneously published in Diabetes Care *and* Diabetologia *by the American Diabetes Association and the European Association for the Study of Diabetes.*

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EXPERT CONSENSUS DECISION PATHWAY

2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

Endorsed by the American Diabetes Association

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Menopause and diabetes: EMAS clinical guide

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ABSTRACT

Introduction: Whether menopause increases the risk of type 2 diabetes mellitus (T2DM) independently of ageing has been a matter of debate. Controversy also exists about the benefits and risks of menopausal hormone therapy (MHT) in women with T2DM.

Aims: To summarise the evidence on 1) the effect of menopause on metabolic parameters and the risk of T2DM, 2) the effect of T2DM on age at menopause, 3) the effect of MHT on the risk of T2DM, and 4) the management of postmenopausal women with T2DM.

Materials and methods: Literature review and consensus of experts' opinions.

Results and conclusion: Metabolic changes during the menopausal transition include an increase in and the central redistribution of adipose tissue, as well as a decrease in energy expenditure. In addition, there is impairment of insulin secretion and insulin sensitivity and an increase in the risk of T2DM. MHT has a favourable effect on glucose metabolism, both in women with and in women without T2DM, while it may delay the onset of T2DM. MHT in women with T2DM should be administered according to their risk of cardiovascular disease (CVD). In women with T2DM and low CVD risk, oral oestrogens may be preferred, while transdermal 17β-oestradiol is preferred for women with T2DM and coexistent CVD risk factors, such as obesity. In any case, a progestogen with neutral effects on glucose metabolism should be used, such as progesterone, dydrogesterone or transdermal norethisterone. Postmenopausal women with T2DM should be managed primarily with lifestyle intervention, including diet and exercise. Most of them will eventually require pharmacological therapy. The

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