Diabetes

1- 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021

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Abstract

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

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2- Pathophysiology of Type 2 Diabetes Mellitus

By:
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Abstract

Type 2 Diabetes Mellitus (T2DM), one of the most common metabolic disorders, is caused by a combination of two primary factors: defective insulin secretion by pancreatic beta-cells and the inability of insulin-sensitive tissues to respond appropriately to insulin. Because insulin release and activity are essential processes for glucose homeostasis, the molecular mechanisms involved in the synthesis and release of insulin, as well as in its detection are tightly regulated. Defects in any of the mechanisms involved in these processes can lead to a metabolic imbalance responsible for the development of the disease. This review analyzes the key aspects of T2DM, as well as the molecular mechanisms and pathways implicated in insulin metabolism leading to T2DM and insulin resistance. For that purpose, we summarize the data gathered up until now, focusing especially on insulin synthesis, insulin release, insulin sensing and on the downstream effects on individual insulin-sensitive organs. The review also covers the pathological conditions perpetuating T2DM such as nutritional factors, physical activity, gut dysbiosis and metabolic memory. Additionally, because T2DM is associated with accelerated atherosclerosis development, we review here some of the molecular mechanisms that link T2DM and insulin resistance (IR) as well as cardiovascular risk as one of the most important complications in T2DM.

Keywords
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type 2 diabetes mellitusinsulin resistancebeta-cellliveradipocytemusclecardiovascular diseasepathophysiology

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CORONARY-HEART-DISEASEDENSITY-LIPOPROTEIN-CHOLESTEROLHUMAN SKELETAL-MUSCLETRIGLYCERIDE-RICH LIPOPROTEINSHEPATIC INSULIN-RESISTANCEC-REACTIVE PROTEINMETABOLIC SYNDROMEBETA-CELLCARDIOVASCULAR-DISEASEOXIDATIVE STRESS

3- IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045

By:
Sun, H (Sun, Hong) [1] ; Saeedi, P (Saeedi, Pouya) [1] ; Karuranga, S (Karuranga, Suvi) [1] ; Pinkepank, M (Pinkepank, Moritz) [1] ; Ogurtsova, K (Ogurtsova, Katherine) [2] ; Duncan, BB (Duncan, Bruce B.) [3] ; Stein, C (Stein, Caroline) [3] ; Basit, A (Basit, Abdul) [4] ; Chan, JCN (Chan, Juliana C. N.) [5] , [6] ; Mbanya, JC (Mbanya, Jean Claude) [8] ;
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Abstract

Aims: To provide global, regional, and country-level estimates of diabetes prevalence and health expenditures for 2021 and projections for 2045.Methods: A total of 219 data sources meeting pre-established quality criteria reporting research conducted between 2005 and 2020 and representing 215 countries and territories were identified. For countries without data meeting quality criteria, estimates were extrap-olated from countries with similar economies, ethnicity, geography and language. Logistic regression was used to generate smoothed age-specific diabetes prevalence estimates. Diabetes-related health expenditures were estimated using an attributable fraction method. The 2021 diabetes prevalence estimates were applied to population estimates for 2045 to project future prevalence.Results: The global diabetes prevalence in 20-79 year olds in 2021 was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045. Diabetes prevalence was similar in men and women and was highest in those aged 75-79 years. Prevalence (in 2021) was estimated to be higher in urban (12.1%) than rural (8.3%) areas, and in high-income (11.1%) compared to low-income countries (5.5%). The greatest relative increase in the prevalence of diabetes between 2021 and 2045 is expected to occur in middle-income countries (21.1%) compared to high-(12.2%) and low-income (11.9%) countries. Global diabetes-related health expenditures were estimated at 966 billion USD in 2021, and are projected to reach 1,054 billion USD by 2045.Conclusions: Just over half a billion people are living with diabetes worldwide which means

that over 10.5% of the world's adult population now have this condition.(c) 2021 Published by Elsevier B.V.

Keywords
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DiabetesPrevalenceProjectionsHealth economicsEpidemiologyInternational Diabetes Federation

4- Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

By:
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Abstract

BACKGROUND
The cardiovascular effects of ertugliflozin, an inhibitor of sodium-glucose cotransporter 2, have not been established.

METHODS

In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper boundary of a 95.6% confidence interval for the hazard ratio [ertugliflozin vs. placebo] for major adverse cardiovascular events). The first key

secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

RESULTS

A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P=0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.

CONCLUSIONS

Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events.

Keywords
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EMPAGLIFLOZINMORTALITYDISEASE

5- Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

By:
Bhatt, DL (Bhatt, Deepak L.) [1] , [2] ; Szarek, M (Szarek, Michael) [3] , [4] , [5] ; Pitt, B (Pitt, Bertram) [6] ; Cannon, CP (Cannon, Christopher P.) [1] , [2] ; Leiter, LA (Leiter, Lawrence A.) [7] , [8] , [9] , [10] ; McGuire, DK (McGuire, Darren K.) [13] , [14] ; Lewis, JB (Lewis, Julia B.) [16] ; Riddle, MC (Riddle, Matthew C.) [17] ; Inzucchi, SE (Inzucchi, Silvio E.) [18] ; Kosiborod, MN (Kosiborod, Mikhail N.) [19] ;
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Abstract

In a trial involving 10,584 patients with diabetes and chronic kidney disease, sotagliflozin resulted in fewer total deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo. Diarrhea, mycotic infections, and diabetic ketoacidosis occurred with sotagliflozin.
Background The efficacy and safety of sodium-glucose cotransporter 2 inhibitors such as sotagliflozin in preventing cardiovascular events in patients with diabetes with chronic kidney disease with or without albuminuria have not been well studied.
Methods We conducted a multicenter, double-blind trial in which patients with type 2 diabetes mellitus (glycated hemoglobin level, >= 7%), chronic kidney disease (estimated glomerular filtration rate, 25 to 60 ml per minute per 1.73 m(2) of body-surface area), and risks for cardiovascular disease were randomly assigned in a 1:1 ratio to receive sotagliflozin or placebo. The primary end point was changed during the trial to the composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. The trial ended early owing to loss of funding.
Results Of 19,188 patients screened, 10,584 were enrolled, with 5292 assigned to the sotagliflozin group and 5292 assigned to the placebo group, and followed for a median of 16 months. The rate of primary

end-point events was 5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.63 to 0.88; P<0.001). The rate of deaths from cardiovascular causes per 100 patient-years was 2.2 with sotagliflozin and 2.4 with placebo (hazard ratio, 0.90; 95% CI, 0.73 to 1.12; P=0.35). For the original coprimary end point of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, the hazard ratio was 0.84 (95% CI, 0.72 to 0.99); for the original coprimary end point of the first occurrence of death from cardiovascular causes or hospitalization for heart failure, the hazard ratio was 0.77 (95% CI, 0.66 to 0.91). Diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than with placebo.

Conclusions In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events. (Funded by Sanofi and Lexicon Pharmaceuticals; SCORED ClinicalTrials.gov number, .)

Keywords

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CARDIOVASCULAR EVENT RATESSGLT2 INHIBITORHEART-FAILUREOUTCOMESRISKOUTPATIENTSEMPAGLIFLOZINSAXAGLIPTINMORTALITYMELLITUS

6- Social Determinants of Health and Diabetes: A Scientific Review

By:
Hill-Briggs, F (Hill-Briggs, Felicia) [1] , [2] ; Adler, NE (Adler, Nancy E.) [3] ; Berkowitz, SA (Berkowitz, Seth A.) [4] ; Chin, MH (Chin, Marshall H.) [5] ; Gary-Webb, TL (Gary-Webb, Tiffany L.) [6] , [7] ; Navas-Acien, A (Navas-Acien, Ana) [8] ; Thornton, PL (Thornton, Pamela L.) [9] ; Haire-Joshu, D (Haire-Joshu, Debra) [10] , [11]
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Diabetes

7- COVID-19 and diabetes mellitus: from pathophysiology to clinical management

By:
Lim, S (Lim, Soo) [1] ; Bae, JH (Bae, Jae Hyun) [2] ; Kwon, HS (Kwon, Hyuk-Sang) [3] ; Nauck, MA (Nauck, Michael A.) [4]
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Abstract

Initial studies found increased severity of coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in patients with diabetes mellitus. Furthermore, COVID-19 might also predispose infected individuals to hyperglycaemia. Interacting with other risk factors, hyperglycaemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes. Angiotensin-converting enzyme 2 (ACE2), which is part of the renin-angiotensin-aldosterone system (RAAS), is the main entry receptor for SARS-CoV-2; although dipeptidyl peptidase 4 (DPP4) might also act as a binding target. Preliminary data, however, do not suggest a notable effect of glucose-lowering DPP4 inhibitors on SARS-CoV-2 susceptibility. Owing to their pharmacological characteristics, sodium-glucose cotransporter 2 (SGLT2) inhibitors might cause adverse effects in patients with COVID-19 and so cannot be recommended. Currently, insulin should be the main approach to the control of acute glycaemia. Most available evidence does not distinguish between the major types of diabetes mellitus and is related to type 2 diabetes mellitus owing to its high prevalence. However, some limited evidence is now available on type 1 diabetes mellitus and COVID-19. Most of these conclusions are preliminary, and further investigation of the optimal management in patients with diabetes mellitus is warranted.

Diabetes

The pathophysiology of coronavirus disease 19 (COVID-19) and diabetes mellitus are interlinked, and diabetes mellitus is associated with severe COVID-19 outcomes. This Review highlights new advances in diabetes mellitus and COVID-19, considering disease mechanisms and clinical management of patients with diabetes mellitus in the ongoing pandemic.

Keywords
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GLUCAGON-LIKE PEPTIDE-1DIPEPTIDYL PEPTIDASE-4 INHIBITORSSYNTHETIC PROTEASE INHIBITORDEEP-VEIN THROMBOSISACUTE KIDNEY INJURYBETA-CELL FUNCTIONINSULIN SENSITIVITYSARS CORONAVIRUSCYTOKINE STORMRHEUMATOID-ARTHRITIS

Diabetes

8- Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

By:
Bhatt, DL (Bhatt, Deepak L.) [1] , [2] ; Szarek, M (Szarek, Michael) [3] , [4] , [5] ; Steg, PG (Steg, P. Gabriel) [6] ; Cannon, CP (Cannon, Christopher P.) [1] , [2] ; Leiter, LA (Leiter, Lawrence A.) [9] , [10] , [11] , [12] ; McGuire, DK (McGuire, Darren K.) [14] ; Lewis, JB (Lewis, Julia B.) [16] ; Riddle, MC (Riddle, Matthew C.) [17] ; Voors, AA (Voors, Adriaan A.) [18] ; Metra, M (Metra, Marco) [19] , [20] ;
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Abstract

Patients with diabetes and recent worsening heart failure that had led to hospitalization were randomly assigned to receive sotagliflozin or placebo. At a median of 9 months, the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure was significantly lower with sotagliflozin than with placebo.

Background Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure or death from cardiovascular causes among patients with stable heart failure. However, the safety and efficacy of SGLT2 inhibitors when initiated soon after an episode of decompensated heart failure are unknown.

Methods We performed a multicenter, double-blind trial in which patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure were randomly assigned to receive sotagliflozin or placebo. The primary end point was the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events). The trial ended early because of loss of funding from the sponsor.

Results A total of 1222 patients underwent randomization (608 to the sotagliflozin group and 614 to the placebo group) and were followed for a median of 9.0 months; the first dose of sotagliflozin or placebo

was administered before discharge in 48.8% and a median of 2 days after discharge in 51.2%. Among these patients, 600 primary end-point events occurred (245 in the sotagliflozin group and 355 in the placebo group). The rate (the number of events per 100 patient-years) of primary end-point events was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.85; P<0.001). The rate of death from cardiovascular causes was 10.6 in the sotagliflozin group and 12.5 in the placebo group (hazard ratio, 0.84; 95% CI, 0.58 to 1.22); the rate of death from any cause was 13.5 in the sotagliflozin group and 16.3 in the placebo group (hazard ratio, 0.82; 95% CI, 0.59 to 1.14). Diarrhea was more common with sotagliflozin than with placebo (6.1% vs. 3.4%), as was severe hypoglycemia (1.5% vs. 0.3%). The percentage of patients with hypotension was similar in the sotagliflozin group and the placebo group (6.0% and 4.6%, respectively), as was the percentage with acute kidney injury (4.1% and 4.4%, respectively). The benefits of sotagliflozin were consistent in the prespecified subgroups of patients stratified according to the timing of the first dose.

Conclusions In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo. (Funded by Sanofi and Lexicon Pharmaceuticals; SOLOIST-WHF ClinicalTrials.gov number, .)

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9- 6. Glycemic Targets: Standards of Medical Care in Diabetes-2021

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Abstract

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

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10- Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

By:
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Abstract

Tirzepatide versus Semaglutide for Type 2 Diabetes This open-label, 40-week, phase 3 trial assessed the efficacy and safety of tirzepatide, a weekly dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist under development for type 2 diabetes. Tirzepatide was noninferior and superior to semaglutide with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks.
Background Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist that is under development for the treatment of type 2 diabetes. The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown. Methods In an open-label, 40-week, phase 3 trial, we randomly assigned 1879 patients, in a 1:1:1:1 ratio, to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg. At baseline, the mean glycated hemoglobin level was 8.28%, the mean age 56.6 years, and the mean weight 93.7 kg. The primary end point was the change in the glycated hemoglobin level from baseline to

40 weeks. Results The estimated mean change from baseline in the glycated hemoglobin level was -2.01 percentage points, -2.24 percentage points, and -2.30 percentage points with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and -1.86 percentage points with semaglutide; the estimated differences between the 5-mg, 10-mg, and 15-mg tirzepatide groups and the semaglutide group were -0.15 percentage points (95% confidence interval [CI], -0.28 to -0.03; P=0.02), -0.39 percentage points (95% CI, -0.51 to -0.26; P<0.001), and -0.45 percentage points (95% CI, -0.57 to -0.32; P<0.001), respectively. Tirzepatide at all doses was noninferior and superior to semaglutide. Reductions in body weight were greater with tirzepatide than with semaglutide (least-squares mean estimated treatment difference, -1.9 kg, -3.6 kg, and -5.5 kg, respectively; P<0.001 for all comparisons). The most common adverse events were gastrointestinal and were primarily mild to moderate in severity in the tirzepatide and semaglutide groups (nausea, 17 to 22% and 18%; diarrhea, 13 to 16% and 12%; and vomiting, 6 to 10% and 8%, respectively). Of the patients who received tirzepatide, hypoglycemia (blood glucose level, <54 mg per deciliter) was reported in 0.6% (5-mg group), 0.2% (10-mg group), and 1.7% (15-mg group); hypoglycemia was reported in 0.4% of those who received semaglutide. Serious adverse events were reported in 5 to 7% of the patients who received tirzepatide and in 3% of those who received semaglutide. Conclusions In patients with type 2 diabetes, tirzepatide was noninferior and superior to semaglutide with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks. (Funded by Eli Lilly; SURPASS-2 ClinicalTrials.gov number, .)

Keywords
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ONCE-WEEKLY SEMAGLUTIDEDEPENDENT INSULINOTROPIC POLYPEPTIDEOPEN-LABELPHASE 3AADD-ONEFFICACYGIPSAFETYMETFORMINGLUCAGON

11- Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

By:
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Abstract

BACKGROUND
Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has favorable effects on cardiorenal outcomes in patients with predominantly stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. The use of finerenone in patients with type 2 diabetes and a wider range of CKD is unclear.
METHODS
In this double-blind trial, we randomly assigned patients with CKD and type 2 diabetes to receive finerenone or placebo. Eligible patients had a urinary albumin-tocreatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300 and an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m(2) of body-surface area (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of at least 60 ml per minute per 1.73 m(2)

(stage 1 or 2 CKD). Patients were treated with renin-angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary outcome, assessed in a time-to-event analysis, was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The first secondary outcome was a composite of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes. Safety was assessed as investigator-reported adverse events.

RESULTS

A total of 7437 patients underwent randomization. Among the patients included in the analysis, during a median follow-up of 3.4 years, a primary outcome event occurred in 458 of 3686 patients (12.4%) in the finerenone group and in 519 of 3666 (14.2%) in the placebo group (hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P = 0.03), with the benefit driven primarily by a lower incidence of hospitalization for heart failure (hazard ratio, 0.71; 95% CI, 0.56 to 0.90). The secondary composite outcome occurred in 350 patients (9.5%) in the finerenone group and in 395 (10.8%) in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 1.01). The overall frequency of adverse events did not differ substantially between groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%).

CONCLUSIONS

Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo.

Keywords

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CHRONIC HEART-FAILUREMORTALITYMELLITUSOUTCOMESSAFETYRISK

12- Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

By:
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Abstract

BackgroundFinerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with chronic kidney disease (CKD) and type 2 diabetes. However, its long-term effects on kidney and cardiovascular outcomes are unknown.
MethodsIn this double-blind trial, we randomly assigned 5734 patients with CKD and type 2 diabetes in a 1:1 ratio to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml per minute per 1.73 m(2) of body-surface area, and diabetic retinopathy, or they had a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml per minute per 1.73 m(2). All the patients were treated with renin-angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome, also assessed in a time-

to-event analysis, was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.
ResultsDuring a median follow-up of 2.6 years, a primary outcome event occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P=0.001). A key secondary outcome event occurred in 367 patients (13.0%) and 420 patients (14.8%) in the respective groups (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.03). Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively).
ConclusionsIn patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. (Funded by Bayer; FIDELIO-DKD ClinicalTrials.gov number, NCT02540993.)
In this double-blind trial, patients with chronic kidney disease and type 2 diabetes were randomly assigned to receive the nonsteroidal, selective mineralocorticoid receptor antagonist finerenone or placebo. Treatment with finerenone resulted in lower risks of chronic kidney disease outcomes and cardiovascular outcomes than placebo.

Keywords
Keywords Plus
COTRANSPORTER 2 INHIBITORSBASE-LINE CHARACTERISTICSNEPHROPATHYMECHANISMSPROTECTSFAILUREINJURYDESIGN

13- Risks and burdens of incident diabetes in long COVID: a cohort study

By:
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Abstract

Background There is growing evidence suggesting that beyond the acute phase of SARS-CoV-2 infection, people with COVID-19 could experience a wide range of post-acute sequelae, including diabetes. However, the risks and burdens of diabetes in the post-acute phase of the disease have not yet been comprehensively characterised. To address this knowledge gap, we aimed to examine the post-acute risk and burden of incident diabetes in people who survived the first 30 days of SARS-CoV-2 infection.

Methods In this cohort study, we used the national databases of the US Department of Veterans Affairs to build a cohort of 181 280 participants who had a positive COVID-19 test between March 1, 2020, and Sept 30, 2021, and survived the first 30 days of COVID-19; a contemporary control (n=4 118 441) that enrolled participants between March 1, 2020, and Sept 30, 2021; and a historical control (n=4 286 911) that enrolled participants between March 1, 2018, and Sept 30, 2019. Both control groups had no evidence of SARS-CoV-2 infection. Participants in all three comparison groups were free of diabetes before cohort entry and were followed up for a median of 352 days (IQR 245-406). We used inverse probability weighted survival analyses, including predefined and algorithmically selected high dimensional variables, to estimate post-acute COVID-19 risks of incident diabetes, antihyperglycaemic use, and a composite of the two outcomes. We reported two measures of risk: hazard ratio (HR) and burden per 1000 people at 12 months.

Findings In the post-acute phase of the disease, compared with the contemporary control group, people with COVID-19 exhibited an increased risk (HR 1.40, 95% CI 1.36-1.44) and excess burden (13.46, 95% CI

12.11-14.84, per 1000 people at 12 months) of incident diabetes; and an increased risk (1.85, 1.78-1.92) and excess burden (12.35, 11.36-13.38) of incident antihyperglycaemic use. Additionally, analyses to estimate the risk of a composite endpoint of incident diabetes or antihyperglycaemic use yielded a HR of 1.46 (95% CI 1.43-1.50) and an excess burden of 18.03 (95% CI 16.59-19.51) per 1000 people at 12 months. Risks and burdens of post-acute outcomes increased in a graded fashion according to the severity of the acute phase of COVID-19 (whether patients were non-hospitalised, hospitalised, or admitted to intensive care). All the results were consistent in analyses using the historical control as the reference category.
Interpretation In the post-acute phase, we report increased risks and 12-month burdens of incident diabetes and antihyperglycaemic use in people with COVID-19 compared with a contemporary control group of people who were enrolled during the same period and had not contracted SARS-CoV-2, and a historical control group from a pre-pandemic era. Post-acute COVID-19 care should involve identification and management of diabetes.

Keywords
Keywords Plus
SARS-COV-2 INFECTIONCELLS

14- The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments

By:
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Abstract

Nonalcoholic fatty liver disease (NAFLD) has reached epidemic proportions worldwide. NAFLD and type 2 diabetes mellitus (T2DM) are known to frequently coexist and act synergistically to increase the risk of adverse (hepatic and extra-hepatic) clinical outcomes. T2DM is also one of the strongest risk factors for the faster progression of NAFLD to nonalcoholic steatohepatitis, advanced fibrosis or cirrhosis. However, the link between NAFLD and T2DM is more complex than previously believed. Strong evidence indicates that NAFLD is associated with an approximate twofold higher risk of developing T2DM, irrespective of obesity and other common metabolic risk factors. This risk parallels the severity of NAFLD, such that patients with more advanced stages of liver fibrosis are at increased risk of incident T2DM. In addition, the improvement or resolution of NAFLD (on ultrasonography) is associated with a reduction of T2DM risk, adding weight to causality and suggesting that liver-focused treatments might reduce the risk of developing T2DM. This Review describes the evidence of an association and causal link between NAFLD and T2DM, discusses the putative pathophysiological mechanisms linking NAFLD to T2DM and summarizes the current pharmacological treatments for NAFLD or T2DM that might benefit or adversely affect the risk of T2DM or NAFLD progression.

Keywords
Keywords Plus

Diabetes

NONALCOHOLIC FATTY LIVERHEPATIC INSULIN-RESISTANCEPLACEBO-CONTROLLED TRIALFARNESOID X RECEPTORBILE-ACIDSVITAMIN-EOBETICHOLIC ACIDFOLLOW-UPDISEASESTEATOHEPATITIS

15- 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2021

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Abstract

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Keywords
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CORONARY-ARTERY-DISEASEPRESSURE-LOWERING TREATMENTAMERICAN-HEART-ASSOCIATIONTYPE-2 DIABETES-MELLITUSSTATIN-INTOLERANT PATIENTSBASE-LINE CHARACTERISTICS14 RANDOMIZED-TRIALSLOW-DOSE ASPIRINLONG-TERM RISKBLOOD-PRESSURE

16- When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis

By:
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Abstract

Mucormycosis (MCR) has been increasingly described in patients with coronavirus disease 2019 (COVID-19) but the epidemiological factors, presentation, diagnostic certainty, and outcome of such patients are not well described. We review the published COVID-19-associated mucormycosis (CAMCR) cases (total 41) to identify risk factors, clinical features, and outcomes. CAMCR was typically seen in patients with diabetes mellitus (DM) (94%) especially the ones with poorly controlled DM (67%) and severe or critical COVID-19 (95%). Its presentation was typical of MCR seen in diabetic patients (mostly rhino-orbital and rhino-orbital-cerebral presentation). In sharp contrast to reported COVID-associated aspergillosis (CAPA) cases, nearly all CAMCR infections were proven (93%). Treating physicians should have a high suspicion for CAMCR in patients with uncontrolled diabetes mellitus and severe COVID-19 presenting with rhino-orbital or rhino-cerebral syndromes. CAMR is the convergence of two storms, one of DM and the other of COVID-19.

Keywords
Author Keywords
COVID-19diabetes mellitusmucormycosis
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KETOACIDOSISPREVALENCEINFECTION

17- A global view of the interplay between non-alcoholic fatty liver disease and diabetes

By:
Stefan, N (Stefan, Norbert) [1] , [2] , [3] ; Cusi, K (Cusi, Kenneth) [4]

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become an epidemic, much like other non-communicable diseases (NCDs), such as cancer, obesity, diabetes, and cardiovascular disease. The pathophysiology of NAFLD, particularly involving insulin resistance and subclinical inflammation, is not only closely linked to that of those NCDs but also to a severe course of the communicable disease COVID-19. Genetics alone cannot explain the large increase in the prevalence of NAFLD during the past 2 decades and the increase that is projected for the next decades. Impairment of glucose and lipid metabolic pathways, which has been propelled by the worldwide increase in the prevalence of obesity and type 2 diabetes, is most likely behind the increase in people with NAFLD. As the prevalence of NAFLD varies among subgroups of patients with diabetes and prediabetes identified by cluster analyses, stratification of people with diabetes and prediabetes by major pathological mechanistic pathways might improve the diagnosis of NAFLD and prediction of its progression. In this Review, we aim to understand how diabetes can affect the development of hepatic steatosis and its progression to advanced liver damage. First, we emphasise the extent to which NAFLD and diabetes jointly occur worldwide. Second, we address the major mechanisms that are involved in the pathogenesis of NAFLD and type 2 diabetes, and we discuss whether these mechanisms place NAFLD in an important position to better understand the pathogenesis of NCDs and communicable diseases, such as COVID-19. Third, we address whether this knowledge can be used for personalised treatment of NAFLD in the future. Finally, we discuss the current treatment strategies for people with type 2 diabetes and their effectiveness in treating the spectrum of hepatic diseases from simple steatosis to non-alcoholic steatohepatitis and hepatic fibrosis.

Diabetes

Keywords
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INTRAHEPATIC TRIGLYCERIDE CONTENTDE-NOVO LIPOGENESISAMERICAN ASSOCIATIONINSULIN-RESISTANCEPRACTICE GUIDANCEUNITED-STATESRISKFIBROSISCONSEQUENCESPIOGLITAZONE

Diabetes

18- **The Multifunctional Role of Herbal Products in the Management of Diabetes and Obesity: A Comprehensive Review**

By:
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Abstract

Obesity and diabetes are the most demanding health problems today, and their prevalence, as well as comorbidities, is on the rise all over the world. As time goes on, both are becoming big issues that have a big impact on people's lives. Diabetes is a metabolic and endocrine illness set apart by hyperglycemia and glucose narrow-mindedness because of insulin opposition. Heftiness is a typical, complex, and developing overall wellbeing worry that has for quite some time been connected to significant medical issues in individuals, all things considered. Because of the wide variety and low adverse effects, herbal products are an important hotspot for drug development. Synthetic compounds are not structurally diverse and lack drug-likeness properties. Thus, it is basic to keep on exploring herbal products as possible wellsprings of novel drugs. We conducted this review of the literature by searching Scopus, Science Direct, Elsevier, PubMed, and Web of Science databases. From 1990 until October 2021, research reports, review articles, and original research articles in English are presented. It provides top to bottom data and an examination of plant-inferred compounds that might be utilized against heftiness or potentially hostile to diabetes treatments. Our expanded comprehension of the systems of activity of phytogenic compounds, as an extra examination, could prompt the advancement of remedial methodologies for metabolic diseases. In clinical trials, a huge number of these food kinds or restorative plants, as well as their bioactive compounds, have been shown to be beneficial in the treatment of obesity.

Diabetes

Keywords

Author Keywords
diabetesobesityherbal productstreatmenthyperglycemia
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ARYL-HYDROCARBON RECEPTORBODY-MASS INDEXALDOSE REDUCTASE INHIBITORSNELUMBO-NUCIFERA LEAVESADIPOSE-TISSUEINSULIN-RESISTANCENATURAL-PRODUCTSBLOOD-GLUCOSECARDIOVASCULAR-DISEASEANTIOBESITY AGENTS

19- Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes

By:
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Abstract

An open-label, first-in-human phase 1/2 study is being conducted to evaluate the safety and efficacy of pancreatic endoderm cells (PECs) implanted in non-immunoprotective macroencapsulation devices for the treatment of type 1 diabetes. We report an analysis on 1 year of data from the first cohort of 15 patients from a single trial site that received subcutaneous implantation of cell products combined with an immunosuppressive regimen. Implants were well tolerated with no teratoma formation or severe graft-related adverse events. After implantation, patients had increased fasting C-peptide levels and increased glucose-responsive C-peptide levels and developed mixed meal-stimulated C-peptide secretion. There were immunosuppression-related transient increases in circulating regulatory T cells, PD1(high) T cells, and IL17A(+)CD4(+) T cells. Explanted grafts contained cells with a mature beta cell phenotype that were immunoreactive for insulin, islet amyloid polypeptide, and MAFA. These data, and associated findings (Shapiro et al., 2021), are the first reported evidence of meal-regulated insulin secretion by differentiated stem cells in patients.

Keywords

Diabetes

Keywords Plus

ISLET TRANSPLANTATIONPROGENITOR CELLSRECENT-ONSETIN-VITROMATURATIONTHERAPYDIFFERENTIATIONCOMPLICATIONSINFECTIONADULTS

20- Investigation of interactions between COVID-19 and diabetes with hereditary traits using real data: A case study in Turkey

By:
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Abstract

In the present paper, interactions between COVID-19 and diabetes are investigated using real data from Turkey. Firstly, a fractional order pandemic model is developed both to examine the spread of COVID-19 and its relationship with diabetes. In the model, diabetes with and without complications are adopted by considering their relationship with the quarantine strategy. Then, the existence and uniqueness of solution are examined by using the fixed point theory. The dynamic behaviors of the equilibria and their stability analysis are studied. What is more, with the help of least-squares curve fitting technique (LSCFT), the fitting of the parameters is implemented to predict the direction of COVID-19 by using more accurately generated parameters. By trying to minimize the mean absolute relative error between the plotted curve for the infected class solution and the actual data of COVID-19, the optimal values of the parameters used in numerical simulations are acquired successfully. In addition, the numerical solution of the mentioned model is achieved through the Adams-Bashforth-Moulton predictor-corrector method. Meanwhile, the sensitivity analysis of the parameters according to the reproduction number is given. Moreover, numerical simulations of the model are obtained and the biological interpretations explaining the effects of model parameters are performed. Finally, in order to point out the advantages of the fractional order modeling, the memory trace and hereditary traits are taken into consideration. By doing so, the effect of the different fractional order derivatives on the COVID-19 pandemic and diabetes are investigated.

Keywords
Author Keywords

Diabetes

COVID-19 epidemic modelParameter estimationDiabetesFractional derivativeStability analysisSensitivity analysisAdams-Bashforth-Moulton schemeMemory trace

Keywords Plus

EPIDEMICCORONAVIRUSSTABILITYMODEL

Diabetes

21- Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025

By:
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Abstract

Diabetes mellitus is a leading cause of mortality and reduced life expectancy. We aim to estimate the burden of diabetes by type, year, regions, and socioeconomic status in 195 countries and territories over the past 28 years, which provide information to achieve the goal of World Health Organization Global Action Plan for the Prevention and Control of Noncommunicable Diseases in 2025. Data were obtained from the Global Burden of Disease Study 2017. Overall, the global burden of diabetes had increased significantly since 1990. Both the trend and magnitude of diabetes related diseases burden varied substantially across regions and countries. In 2017, global incidence, prevalence, death, and disability-adjusted life-years (DALYs) associated with diabetes were 22.9 million, 476.0 million, 1.37 million, and 67.9 million, with a projection to 26.6 million, 570.9 million, 1.59 million, and 79.3 million in 2025, respectively. The trend of global type 2 diabetes burden was similar to that of total diabetes (including type 1 diabetes and type 2 diabetes), while global age-standardized rate of mortality and DALYs for type 1 diabetes declined. Globally, metabolic risks (high BMI) and behavioral factors (inappropriate diet, smoking, and low physical activity) contributed the most attributable death and DALYs of diabetes. These estimations could be useful in policy-making, priority setting, and resource allocation in diabetes prevention and treatment.

Keywords
Keywords Plus

Diabetes

LIFE EXPECTANCYSYSTEMATIC ANALYSISTYPE-1PREVALENCEMORTALITYRISKTHERAPYDISEASECOHORT

22- Amyloid Oligomers: A Joint Experimental/Computational Perspective on Alzheimer's Disease, Parkinson's Disease, Type II Diabetes, and Amyotrophic Lateral Sclerosis

By:
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Abstract

Protein misfolding and aggregation is observed in many amyloidogenic diseases affecting either the central nervous system or a variety of peripheral tissues. Structural and dynamic characterization of all species along the pathways from monomers to fibrils is challenging by experimental and computational means because they involve intrinsically disordered proteins in most diseases. Yet understanding how amyloid species become toxic is the challenge in developing a treatment for these diseases. Here we review what computer, in vitro, in vivo, and pharmacological experiments tell us about the accumulation and deposition of the oligomers of the (A beta, tau), alpha-synuclein, IAPP, and superoxide dismutase 1 proteins, which have been the mainstream concept underlying Alzheimer's disease (AD), Parkinson's disease (PD), type II diabetes (T2D), and amyotrophic lateral sclerosis (ALS) research, respectively, for many years.

Keywords
Keywords Plus

Diabetes

A-BETA PEPTIDECU/ZN-SUPEROXIDE-DISMUTASEHUMAN ALPHA-SYNUCLEINMOLECULAR-DYNAMICS SIMULATIONSPAIRED HELICAL FILAMENTSFREE-ENERGY LANDSCA

23- Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device

By:
Shapiro, AMJ (Shapiro, A. M. James) [1] ; Thompson, D (Thompson, David) [2] ; Donner, TW (Donner, Thomas W.) [3] ; Bellin, MD (Bellin, Melena D.) [4] ; Hsueh, W (Hsueh, Willa) [5] ; Pettus, J (Pettus, Jeremy) [6] ; Wilensky, J (Wilensky, Jon) [7] ; Daniels, M (Daniels, Mark) [8] ; Wang, RM (Wang, Richard M.) [8] ; Brandon, EP (Brandon, Eugene P.) [8] ;
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Abstract

These preliminary data from an ongoing first-in-human phase 1/2, open-label study provide proof-of-concept that pluripotent stem cell-derived pancreatic endoderm cells (PEC-01) engrafted in type 1 diabetes patients become islet cells releasing insulin in a physiologically regulated fashion. In this study of 17 subjects aged 2257 with type 1 diabetes, PEC-01 cells were implanted subcutaneously in VC-02 macroencapsulation devices, allowing for direct vascularization of the cells. Engraftment and insulin expression were observed in 63% of VC-02 units explanted from subjects at 3-12 months post-implant. Six of 17 subjects (35.3%) demonstrated positive C-peptide as early as 6 months post-implant. Most reported adverse events were related to surgical implant or explant procedures (27.9%) or to side-effects of immunosuppression (33.7%). Initial data suggest that pluripotent stem cells, which can be propagated to the desired biomass and differentiated into pancreatic islet-like tissue, may offer a scalable, renewable alternative to pancreatic islet transplants.

Keywords
Keywords Plus

Diabetes

ENDOCRINE-CELLSTRANSPLANTATIONPROGENITORSMATURATIONMARKERSISLETS

25- Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF)

By:
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Abstract

Background:
Sodium-glucose cotransporter 2 inhibitors reduce the risk of heart failure hospitalization and cardiovascular death in patients with heart failure and reduced ejection fraction (HFrEF). However, their effects on cardiac structure and function in HFrEF are uncertain.
Methods:
We designed a multicenter, randomized, double-blind, placebo-controlled trial (the SUGAR-DM-HF trial [Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure]) to investigate the cardiac effects of empagliflozin in patients in New York Heart Association functional class II to IV with a left ventricular (LV) ejection fraction <= 40% and type 2 diabetes or prediabetes. Patients were randomly assigned 1:1 to empagliflozin 10 mg once daily or placebo, stratified by age (<65 and >= 65 years) and glycemic status (diabetes or prediabetes). The coprimary outcomes were change from baseline to 36 weeks in LV end-systolic volume indexed to body surface area and LV global longitudinal strain both measured using cardiovascular magnetic resonance. Secondary efficacy outcomes included other cardiovascular magnetic resonance measures (LV end-diastolic volume index, LV ejection fraction), diuretic intensification, symptoms (Kansas City

Cardiomyopathy Questionnaire Total Symptom Score, 6-minute walk distance, B-lines on lung ultrasound, and biomarkers (including N-terminal pro-B-type natriuretic peptide).
Results:
From April 2018 to August 2019, 105 patients were randomly assigned: mean age 68.7 (SD, 11.1) years, 77 (73.3%) male, 82 (78.1%) diabetes and 23 (21.9%) prediabetes, mean LV ejection fraction 32.5% (9.8%), and 81 (77.1%) New York Heart Association II and 24 (22.9%) New York Heart Association III. Patients received standard treatment for HFrEF. In comparison with placebo, empagliflozin reduced LV end-systolic volume index by 6.0 (95% CI, -10.8 to -1.2) mL/m(2) (P=0.015). There was no difference in LV global longitudinal strain. Empagliflozin reduced LV end-diastolic volume index by 8.2 (95% CI, -13.7 to -2.6) mL/m(2) (P=0.0042) and reduced N-terminal pro-B-type natriuretic peptide by 28% (2%-47%), P=0.038. There were no between-group differences in other cardiovascular magnetic resonance measures, diuretic intensification, Kansas City Cardiomyopathy Questionnaire Total Symptom Score, 6-minute walk distance, or B-lines.
Conclusions:
The sodium-glucose cotransporter 2 inhibitor empagliflozin reduced LV volumes in patients with HFrEF and type 2 diabetes or prediabetes. Favorable reverse LV remodeling may be a mechanism by which sodium-glucose cotransporter 2 inhibitors reduce heart failure hospitalization and mortality in HFrEF.
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CARDIOVASCULAR MAGNETIC-RESONANCEGLOBAL FUNCTION INDEXCARDIAC STRUCTUREREFERENCE RANGESDYSFUNCTIONPREDICTIONMETOPROLOLMORTALITYEVENTSMARKER

26- Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials

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Abstract

Background: Hyperkalemia increases risk of cardiac arrhythmias and death and limits the use of renin-angiotensin-aldosterone system inhibitors and mineralocorticoid receptor antagonists, which improve clinical outcomes in people with chronic kidney disease or systolic heart failure. Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiorenal events in people with type 2 diabetes at high cardiovascular risk or with chronic kidney disease. However, their effect on hyperkalemia has not been systematically evaluated. Methods: A meta-analysis was conducted using individual participant data from randomized, double-blind, placebo-controlled clinical outcome trials with SGLT2 inhibitors in people with type 2 diabetes at high cardiovascular risk or with chronic kidney disease in whom serum potassium levels were routinely measured. The primary outcome was time to serious hyperkalemia, defined as central laboratory-determined serum potassium >= 6.0 mmol/L, with other outcomes including investigator-reported hyperkalemia events and hypokalemia (serum potassium <= 3.5 mmol/L). Cox regression analyses were performed to estimate treatment effects from each trial with hazards ratios and corresponding 95% CIs pooled with random-effects models to obtain summary treatment effects, overall and across key subgroups. Results: Results from 6 trials were included comprising 49 875 participants assessing 4 SGLT2 inhibitors. Of these, 1754 participants developed serious hyperkalemia, and an additional 1119 investigator-reported hyperkalemia events were recorded. SGLT2 inhibitors reduced the

risk of serious hyperkalemia (hazard ratio, 0.84 [95% CI, 0.76-0.93]), an effect consistent across studies (P-heterogeneity=0.71). The incidence of investigator-reported hyperkalemia was also lower with SGLT2 inhibitors (hazard ratio, 0.80 [95% CI, 0.68-0.93]; P-heterogeneity=0.21). Reductions in serious hyperkalemia were observed across a range of subgroups, including baseline kidney function, history of heart failure, and use of renin-angiotensin-aldosterone system inhibitor, diuretic, and mineralocorticoid receptor antagonist. SGLT2 inhibitors did not increase the risk of hypokalemia (hazard ratio, 1.04 [95% CI, 0.94-1.15]; P-heterogeneity=0.42). Conclusions: SGLT2 inhibitors reduce the risk of serious hyperkalemia in people with type 2 diabetes at high cardiovascular risk or with chronic kidney disease without increasing the risk of hypokalemia.

Keywords
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diabetes mellitustype 2heart failurehyperkalemiapotassiumrenal insufficiencychronicsodium-glucose transporter 2 inhibitors
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27- Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials

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Abstract

OBJECTIVE
To evaluate sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes at varying cardiovascular and renal risk.
DESIGN
Network meta-analysis.
DATA SOURCES Medline, Embase, and Cochrane CENTRAL up to 11 August 2020.
ELIGIBILITY CRITERIA
FOR SELECTING STUDIES Randomised controlled trials comparing SGLT-2 inhibitors or GLP-1 receptor agonists with placebo, standard care, or other glucose lowering treatment in adults with type 2 diabetes with follow up of 24 weeks or longer. Studies were screened independently by two reviewers for eligibility, extracted data, and assessed risk of bias.
MAIN OUTCOME MEASURES
Frequentist random effects network meta-analysis was carried out and GRADE (grading of recommendations assessment, development, and evaluation) used to assess evidence certainty. Results included estimated absolute effects of treatment per 1000 patients treated for five years for patients at very low risk (no cardiovascular risk factors), low risk (three or more cardiovascular risk factors), moderate

risk (cardiovascular disease), high risk (chronic kidney disease), and very high risk (cardiovascular disease and kidney disease). A guideline panel provided oversight of the systematic review.

RESULTS

764 trials including 421 346 patients proved eligible. All results refer to the addition of SGLT-2 inhibitors and GLP-1 receptor agonists to existing diabetes treatment. Both classes of drugs lowered all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure (high certainty evidence). Notable differences were found between the two agents: SGLT-2 inhibitors reduced mortality and admission to hospital for heart failure more than GLP-1 receptor agonists, and GLP-1 receptor agonists reduced non-fatal stroke more than SGLT-2 inhibitors (which appeared to have no effect). SGLT-2 inhibitors caused genital infection (high certainty), whereas GLP-1 receptor agonists might cause severe gastrointestinal events (low certainty). Low certainty evidence suggested that SGLT-2 inhibitors and GLP-1 receptor agonists might lower body weight. Little or no evidence was found for the effect of SGLT-2 inhibitors or GLP-1 receptor agonists on limb amputation, blindness, eye disease, neuropathic pain, or health related quality of life. The absolute benefits of these drugs vary substantially across patients from low to very

Keywords

Keywords Plus

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Diabetes