Aktuelle Entwicklungen bei chronischer Nierenerkrankung
in Verbindung mit Typ-2-Diabetes

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Für die klinische Praxis: Leitlinien, Praxisleitfäden, Übersichtsarbeiten und Metaanalysen

Combination therapy as a new standard of care in diabetic and non-diabetic chronic kidney disease

Neuen BL, Yeung EK et. al.; Nephrology Dialysis Transplantation (February 5, 2025)

A range of therapies now exists to reduce the risk of kidney failure and cardiovascular events in people with type 2 diabetes, including renin–angiotensin system blockade, sodium-glucose cotransporter 2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists. With multiple clinical trials underway, it is likely that at least some of these therapies—as well as additional agents such as endothelin receptor antagonists—will further demonstrate kidney-protective effects in people with CKD who do not have diabetes in the near future. For conditions such as IgA nephropathy, several therapies have recently been approved or are being evaluated in late phase trials. Thus combination therapy is emerging as a new standard for diabetic and non-diabetic chronic kidney disease (CKD). This approach is supported by randomized data suggesting that each therapeutic class offers independent and additive benefits in diabetic kidney disease, regardless of background therapy. Notably, the reduction in hyperkalaemia and fluid retention with SGLT2 inhibitors may enhance the tolerability and safety of other treatments. In this review, we present the rationale for combination therapy with evidence-based kidney therapies in diabetic and non-diabetic CKD. We also summarize randomized evidence supporting a multi-medicine approach, address safety considerations, review ongoing trials, and propose frameworks for implementing treatments aligned with patient risk to optimize person-centred care and reduce long-term risks of kidney failure and related complications.

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Combination therapy: an upcoming paradigm to improve kidney and cardiovascular outcomes in chronic kidney disease

Alicic RZ, Neumiller JJ, Tuttle KR; Nephrology Dialysis Transplantation (February 5, 2025)

The global burden of chronic kidney disease (CKD) increased by nearly 90% in the period spanning 1990 to 2016, mostly attributed to an increase in the prevalence of CKD in diabetes. People living with CKD have an elevated lifetime risk for cardiovascular disease (CVD) when compared with the general population, with risk increasing in parallel with albuminuria and kidney function decline. Metabolic disease, CKD and CVD share common risk factors including neurohumoral activation, systemic inflammation and oxidative stress, thus prompting the introduction of a broader construct of cardiovascular–kidney–metabolic (CKM) syndrome. An important rationale for the introduction of this concept are recent and ongoing therapeutic advancements fundamentally changing CKM management. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the non-steroidal mineralocorticoid receptor antagonist (ns-MRA) finerenone have shifted the therapeutic paradigm for patients with CKD and have emerged in rapid succession as cornerstones of guideline-directed medical therapy (GDMT). Recently completed clinical trials of aldosterone synthase inhibitors and endothelin receptor antagonists have additionally reported additive antiproteinuric effects on the background of renin–angiotensin system and SGLT2 inhibition, with acceptable safety profiles. The sum of current evidence from both preclinical and clinical studies support combination therapy in the setting of CKD to achieve additive and potentially synergistic kidney and heart protection by addressing metabolic, hemodynamic, and pro-inflammatory and pro-fibrotic mechanistic pathways. This narrative review will discuss available evidence supporting combination GDMT in CKD with diabetes and additionally discuss ongoing and future trials evaluating the efficacy and safety of combination therapies for CKD with or without diabetes.

Zur Publikation

Konsensuspapier zum Management kardiovaskulärer Erkrankungen bei chronischer Nierenerkrankung

Marx-Schütt K, Kintscher U. et al.; Die Kardiologie (January 15, 2025)

Die chronische Nierenkrankheit (CKD) ist einer der wichtigsten Risikofaktoren für Herz-Kreislauf-Erkrankungen (CVD; manifestiert durch koronare Herzkrankheit, Herzinsuffizienz, Arrhythmien und plötzlichen Herztod), und das gleichzeitige Vorliegen sowohl von CVD und CKD hat einen erheblichen Einfluss auf die Prognose der Patienten. Die diagnostischen und therapeutischen Möglichkeiten kardiovaskulärer Erkrankungen sind bei fortgeschrittener CKD häufig eingeschränkt, und für viele interventionelle und medikamentöse Therapien besteht wenig oder keine Evidenz aus großen klinischen Studien. Das vorliegende Konsensuspapier gibt einen Überblick über die Besonderheiten kardiovaskulärer Erkrankungen bei CKD und fasst die aktuelle Evidenz und Empfehlungen zur Therapie von Patienten mit CVD und CKD zusammen.

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Disease Awareness in Patients with Type 2 Diabetes: Analysis of Baseline Data From the SMART-Finder Observational Study

Mueller C, Neusser T et. al.; JMIR Formative Research (February 18, 2025)

Background: Chronic kidney disease (CKD) is a common comorbidity of type 2 diabetes mellitus (T2DM). Data on the determination of CKD-related biomarkers among patients with T2DM in a real-life setting within Germany are limited.

Objective: We aimed to determine the prevalence of CKD and risk factors, availability of urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) values, treatment satisfaction, and quality of life among patients with T2DM in Germany.

Methods: SMART-Finder is a retrospective and prospective, observational, digital, patient-centered cohort study being performed as part of the routine use of an adherence-supporting app. This baseline analysis' observation period was from August to November 2023. Patients with T2DM in Germany who actively used the MyTherapy app; allowed push notifications; and documented use of diabetes medications, renin-angiotensin system inhibitors, finerenone, and/or blood glucose test strips were eligible for inclusion. Study materials (background information, electronic consent form, and laboratory and electronic questionnaires) were provided to eligible patients via app push notifications. Participants completed an electronic case report form that included questions on their blood pressure; their most recent UACR, eGFR, and glycated hemoglobin (HbA1c) values in the past 12 months; the EQ-5D-5L; and the Diabetes Treatment Satisfaction Questionnaire. The primary outcome was the proportion of patients with a UACR of ≥30 mg/g.

Results: Of 9527 invited eligible patients, 101 completed the electronic case report form (male: n=61; female: n=40; age: mean 54.2, SD 11.4 y). Of these, 1 female patient and 5 male patients reported their UACR values; 3 (all male) had a UACR of ≥30 mg/g. The remaining 95 patients reported that their health care professionals had not provided UACR measurements. Only 9 (8.9%) patients were aware of their latest eGFR values (3 patients: 15-44 mL/min/1.73 m^2; 6 patients: 45-89 mL/min/1.73 m^2), 90 provided HbA1c values (80 patients: ≥6.0%), 46 had a systolic blood pressure of ≥130 mm Hg, and 83 reported former or current nephrotoxic medication intake. The mean EQ-5D-5L index score was 0.7 (SD 0.3; range -0.1 to 1.0; 50 patients). The mean Diabetes Treatment Satisfaction Questionnaire score was 28.8 (SD 6.8; range 9.0-36.0; 49 patients).

Conclusions: Patients with T2DM who were using an adherence-supporting app in Germany lacked awareness of CKD-related biomarkers but had high knowledge of self-manageable biomarkers (eg, blood pressure, serum fasting glucose, and HbA1c values). Our results suggest that treating physicians either do not test for UACRs and eGFRs or do not inform patients about the results. Nonadherence to diagnostic testing guidelines and a lack of physician-patient communication put patients at risk. Another reason for this health literacy imbalance may be the focus on HbA1c instead of kidney comorbidity in patient education material. Future goals for diabetes management must include guideline-compliant testing of CKD-related biomarkers and open physician-patient communication.

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Nicht-steroidale Mineralokortikoidrezeptor-Antagonisten (nsMRA)

Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by diuretic use: A FIDELITY analysis

Mentz RJ, Anker SD et. al.; European Journal of Heart Failure (January 17, 2025)

Aims: This post hoc analysis aimed to assess the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist finerenone by baseline diuretic use in FIDELITY, a pre-specified pooled analysis of the phase III trials FIDELIO-DKD and FIGARO-DKD.

Methods and results: Eligible patients with type 2 diabetes (T2D) and chronic kidney disease (CKD; urine albumin-to-creatinine ratio [UACR] ≥30–<300 mg/g and estimated glomerular filtration rate [eGFR] ≥25–≤90 ml/min/1.73 m^2, or UACR ≥300–≤5000 mg/g and eGFR ≥25 ml/min/1.73 m^2) were randomized 1:1 to finerenone or placebo. Patients were analysed by baseline diuretic use (yes/no) and type of diuretic (loop or thiazide). Key efficacy outcomes included a cardiovascular composite (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) and a kidney composite (kidney failure, sustained ≥57% decrease in eGFR, or kidney-related death). Out of 12 990 patients, 51.6% were taking diuretics at baseline (21.6% loop; 24.2% thiazide diuretics). Finerenone reduced the risk of cardiovascular and kidney composite outcomes versus placebo; diuretic use did not modify this effect on the cardiovascular (p-interaction = 0.94) or kidney outcomes (p-interaction = 0.55). Hyperkalaemia incidences were similar between finerenone subgroups irrespective of diuretic use and lower with placebo versus finerenone (with diuretics: finerenone 13.7% vs. placebo 5.7%; without diuretics: 14.3% vs. 8.3%). The incidence of hyperkalaemia leading to hospitalization or study drug discontinuation was low across treatment groups irrespective of diuretic use.

Conclusion: This analysis showed that the efficacy and safety of finerenone in patients with CKD and T2D was not modified by baseline diuretic use.

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First interim results from the FINE-REAL: a prospective, non-interventional, phase 4 study providing insights into the use and safety of finerenone in a routine clinical setting

Nicholas SB, Correra-Rotter R et. al.; Journal of Nephrology (September 28, 2024)

Background: Finerenone, a selective non-steroidal mineralocorticoid receptor antagonist, improves kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D). The FINE-REAL study (NCT05348733) aims to evaluate the characteristics and treatment patterns of participants treated with finerenone in clinical practice.

Methods: FINE-REAL is a prospective, single-arm, non-interventional study of patients initiated on finerenone as part of their routine care in accordance with country-approved labels. The study, initiated in June 2022, is expected to be completed by January 2028. The cutoff for this pre-specified interim analysis was June 13, 2023.

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Results: Participants were recruited across nephrology, endocrinology, cardiology, and primary care settings. Of 556 participants enrolled in the study by the cut-off date, 504 were included in this analysis (median follow-up duration of 7 months [finerenone treatment initiation to last recorded observation]). At baseline, 76.1% of participants were in the high or very high (KDIGO) CKD risk categories. Angiotensin converting enzyme inhibitors/angiotensin receptor blockers and sodium–glucose cotransporter 2 inhibitors were prescribed to 71.8% and 46.6% of participants, respectively. Based on prescribing information, 87.9% and 12.1% of participants initiated finerenone at doses of 10 and 20 mg, respectively. Finerenone treatment was uninterrupted in 92.3% of participants after 7 months' median follow-up. Treatment-emergent adverse events occurred in 110 (21.8%) participants. Hyperkalemia occurred in 25 (5.0%) participants, with no cases leading to death, dialysis, or hospitalization.

Conclusion: At this interim analysis, finerenone was initiated in patients with CKD and T2D across various clinical practices participating in the study. Treatment discontinuation and hyperkalemia occurred infrequently.

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Low-dose spironolactone and cardiovascular outcomes in moderate stage chronic kidney disease: a randomized controlled trial

Hobbs FDR, McManus RJ et. al.; naturemedicine (September 30, 2024)

Chronic kidney disease (CKD) is associated with a substantial risk of progression to end-stage renal disease and vascular events. The nonsteroidal mineralocorticoid receptor antagonist (MRA), finerenone, offers cardiorenal protection for people with CKD and diabetes, but there is uncertainty if the steroidal MRA, spironolactone, provides the same protection. In this prospective, randomized, open, blinded endpoint trial, we assessed the effectiveness of 25 mg spironolactone in addition to usual care or usual care alone for reducing cardiovascular outcomes in stage 3b CKD among an older community cohort (mean age = 74.8 years and s.d. = 8.1). We recruited 1,434 adults from English primary care, of whom 1,372 (96%) were included in the primary analysis. The primary outcome was time from randomization until the first occurrence of death, hospitalization for heart disease, stroke, heart failure, transient ischemic attack or peripheral arterial disease, or first onset of any condition listed not present at baseline. Across 3 years of follow-up, the primary endpoint occurred in 113 of 677 participants randomized to spironolactone (16.7%) and 111 of 695 participants randomized to usual care (16.0%) with no significant difference between groups (hazard ratio = 1.05, 95% confidence interval: 0.81–1.37). Two-thirds of participants randomized to spironolactone stopped treatment within 6 months, predominantly because they met prespecified safety stop criteria. The most common reason for stopping spironolactone was a decrease in the estimated glomerular filtration rate that met prespecified stop criteria (n = 239, 35.4%), followed by participants being withdrawn due to treatment side effects (n = 128, 18.9%) and hyperkalemia (n = 54, 8.0%). In conclusion, we found that spironolactone was frequently discontinued due to safety concerns, with no evidence that it reduced cardiovascular outcomes in people with stage 3b CKD. Spironolactone should not be used for people with stage 3b CKD without another explicit treatment indication. ClinicalTrials.gov registration: ISRCTN44522369.

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Effect of finerenone across the stages of heart failure: From prevention to treatment*

Biegus J, Palazzuoli A, Greene SJ; European Journal of Heart Failure (February 17, 2025)

No abstract available.

Zur Publikation

Finerenone in the management of diabetes kidney disease

De P, Khine MT et. al.; BMC Nephrology (February 8, 2025)

People with type 2 diabetes are at risk of developing progressive diabetic kidney disease (DKD) and end stage kidney failure. Hypertension is a major, reversible risk factor in people with diabetes for development of albuminuria, impaired kidney function, end-stage kidney disease and cardiovascular disease. Slowing progression of kidney disease and reducing cardiovascular events can be achieved by a number of means including the targeting of blood pressure and the use of specific classes of drugs The use of Renin Angiotensin Aldosterone System (RAAS) blockade is effective in preventing or slowing progression of DKD and reducing cardiovascular events in people with type 2 diabetes, albeit differently according to the stage of DKD. However, emerging therapy such as non-steroidal selective mineralocorticoid antagonists (finerenone) is proven to lower blood pressure and further reduce the risk of progression of DKD and cardiovascular disease in people with type 2 diabetes. This consensus reviews current evidence and make recommendations for the use of finerenone in the management of diabetes kidney disease in the UK.

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Finerenone and new-onset diabetes in heart failure: a prespecified analysis of the FINEARTS-HF trial*

Butt JH, Jhund PS et. al.; The Lancet Diabetes & Endocrinology (February 13, 2025)

Background: Data on the effect of mineralocorticoid receptor antagonist therapy on HbA1c levels and new-onset diabetes are conflicting. We aimed to examine the effect of oral finerenone, compared with placebo, on incident diabetes in the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF) trial.

Methods: In this randomised, double-blind, placebo-controlled trial, 6001 participants with heart failure with New York Heart Association functional class II-IV, left ventricular ejection fraction 40% or higher, evidence of structural heart disease, and elevated N-terminal pro-B-type natriuretic peptide levels were randomly assigned to finerenone or placebo, administered orally. Randomisation was performed with concealed allocation. The primary outcome of the trial was the composite of cardiovascular death and total (first and recurrent) heart failure events (ie, heart failure hospitalisation or urgent heart failure visit). In the present analysis, participants with diabetes at baseline (investigator-reported history of diabetes or baseline HbA1c ≥6·5%) were excluded. New-onset diabetes was defined as a HbA1c measurement of 6·5% or higher on two consecutive follow-up visits or new initiation of glucose-lowering therapy. The full-analysis set

*Finerenon ist zugelassen zur Behandlung von chronischer Nierenerkrankung (mit Albuminurie) in Verbindung mit Typ-2-Diabetes bei Erwachsenen

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comprised all participants randomly assigned to study treatment, analysed according to their treatment assignment irrespective of the treatment received (ie, intention to treat). The safety analysis set comprised participants randomly assigned to study treatment who took at least one dose of the investigational product, analysed according to the treatment actually received. This trial is registered with ClinicalTrials.gov, NCT04435626, and is closed to new participants.

Findings: Between Sept 14, 2020, and Jan 10, 2023, 6001 participants were recruited and randomly assigned to finerenone or placebo. 3222 (53·7%) participants did not have diabetes at baseline and comprised the study population. During a median duration of follow-up of 31·3 months (IQR 21·5-36·3), 115 (7·2%) participants in the finerenone group and 147 (9·1%) in the placebo group developed new-onset diabetes, corresponding to a rate of 3·0 events per 100 person-years (95% CI 2·5-3·6) in the finerenone group and 3·9 events per 100 person-years (3·3-4·6) in the placebo group. Compared with placebo, finerenone significantly reduced the hazard of new-onset diabetes by 24% (hazard ratio [HR] 0·76 [95% CI 0·59-0·97], p=0·026). Fine-Gray competing risk analysis, accounting for the competing risk of death, yielded a similar finding (subdistribution HR 0·75 [0·59-0·96], p=0·024). Results were similar in sensitivity analyses, in which the definition of new-onset diabetes was expanded to include initiation of SGLT2 inhibitor treatment with diabetes as indication, restricted to HbA1c measurements only, and restricted to new initiation of glucose-lowering drugs only (excluding SGLT2 inhibitor treatment). Findings were similar when participants treated with glucose-lowering drugs at baseline were excluded (n=15). The effect of finerenone, compared with placebo, on new-onset diabetes was consistent across key participant subgroups. Seven participants had an adverse event of new diabetes not captured by any of the definitions above.

Interpretation: In participants with heart failure with mildly reduced or preserved ejection fraction without diabetes, oral finerenone reduced the hazard of new-onset diabetes, representing a meaningful additional clinical benefit of this treatment in these individuals.

Funding: Bayer.

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COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint (CONFIDENCE) trial: Baseline clinical characteristics

Agarwal R, Green JB et. al.; Nephrology Dialysis Transplantation (February 7, 2025)

Background and hypothesis: Finerenone, a selective nonsteroidal MRA, and SGLT2is both reduce CKD progression and improve kidney/CV outcomes. The CONFIDENCE study (NCT05254002; EudraCT 2021-003037-11) hypothesis is that early combination of finerenone and empagliflozin, a SGLT2i, is superior to either drug alone in reducing UACR over 6 months.

Methods: CONFIDENCE is an ongoing, fully enrolled, randomized, controlled, double-blind, multicentre phase 2 clinical trial in adults (≥18 years of age) with CKD and T2D, eGFR of 30 to 90 ml/min/1.73 m^2, and UACR of ≥100 to <5000 mg/g. Participants taking the clinically maximum tolerated dose of a renin–angiotensin system inhibitor for >1 month at screening were eligible. Participants were randomized 1:1:1 to once daily finerenone plus empagliflozin, finerenone plus placebo, or empagliflozin plus placebo; doses were 10 mg once daily for empagliflozin and 10 or 20 mg once daily for finerenone, depending on eGFR at baseline. Randomization was stratified by eGFR (< or ≥60 ml/min/1.73 m^2) and UACR (≤ or >850 mg/g). The primary efficacy outcome is the relative change in UACR from baseline at Day 180.

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Results: There were 818 participants randomized across 143 sites from 14 countries between July 2022 and August 2024. Mean eGFR (ml/min/1.73 m^2 [SD]) was 54.2 (17.1). Median UACR (mg/g [IQR]) was 583 (292, 1140). Mean HbA1c (% [SD]) was 7.3 (1.2). Mean systolic/diastolic BP (mmHg) was 135.2/77.3. GLP-1 RAs and insulin were used by 182 (23%) and 313 (39%) participants, respectively. Atherosclerotic CV disease, diabetic retinopathy, and a history of heart failure were present in 223 (28%), 126 (16%), and 30 (4%) participants, respectively.

Conclusions: The CONFIDENCE trial enrolled a diverse population with CKD and T2D and will determine the impact of simultaneous initiation of combination finerenone and a SGLT2i versus individual therapy on potentially mitigating the progression of CKD in people with T2D.

Trial registration number: Clinicaltrials.gov NCT05254002; EudraCT 2021-003037-11.

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Natrium-Glukose-Co-Transport-2-Inhibitoren (SGLT2i)

A critical review on SGLT2 inhibitors for diabetes mellitus, renal health and cardiovascular conditions

Kumar N, Kumar B et. al.; Diabetes Research and Clinical Practice (February 16, 2025)

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were originally formulated to reduce blood glucose levels in individuals with diabetes. Recent clinical trials indicate that this compound can be repurposed for other critical conditions. A literature search was performed on PubMed, Scopus, Embase, ProQuest, and Google Scholar, utilizing key terms such as SGLT2i, diabetes, and oxidative stress. SGLT2i has significant beneficial effects not only in cardiovascular disease but also in renal dysfunction. SGLT2i therapy can mitigate critical cardiovascular complications like heart attacks, strokes, mortality rates, and hospitalization duration, as well as delay the necessity for dialysis irrespective of diabetic condition. Evidence supports potential advantages of SGLT2 inhibitors for individuals with renal problems and heart failure, regardless of diabetes status. In addition to diabetic mellitus, this analysis explores the latest updates on SGLT2i and the therapeutic advantages it offers in many renal and cardiovascular diseases (CVDs).

Zur Publikation

Comparison of the Effects of SGLT-2i versus GLP-1RA on Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes Mellitus based on Baseline Renal Function

Wang Y, Xia C et. al.; Reviews in Diabetes (February 11, 2025)

There remained no head-to-head research to evaluate the cardiovascular and renal benefits of sodium-glucose cotransporter 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) in patients with type 2 diabetes mellitus (T2DM) at different baseline renal function. We performed a network meta-analysis to compare the two drugs indirectly. Systematic literature searches were conducted on PubMed, Cochrane Library, Web of Science, and Embase, covering their inception until January 7, 2025. Randomized controlled trials (RCTs) comparing the effects of SGLT-2i and GLP-1RA in T2DM with different glomerular filtration rates (eGFR) were selected. Results were reported as Risk ratios (RR) with corresponding 95% confidence intervals (CI). Finally, 10 RCTs involving 87,334 T2DM patients were included. In conclusion, In patients with eGFR > 90 mL/min/1.73m^2, GLP-1RA exhibited a superior ability to reduce the risk of all-cause death (ACD) compared to SGLT-2i (RR [95% CI]; 0.75 [0.58, 0.97]), but was less effective in reducing the risk of renal outcome (RR [95% CI]; 1.80 [1.15, 2.84]) in patients with eGFR 60-90 mL/min/1.73m^2. Conversely, in patients with eGFR 30-60 and 60-90 mL/min/1.73m^2, GLP-1RA did not show an advantage in reducing the risk of hospitalization for heart failure (HHF) (RR [95% CI]; 1.87 [1.15, 3.04] and 1.37 [1.05, 1.78], respectively).

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Identifying predictors of sodium-glucose cotransporter 2 inhibitor and glucagon-like peptide 1 receptor agonist use in hospital among adults with diabetes

Raudanskis A, Sarma S et. al.; Journal of Diabetes and its Complications (December 20, 2024)

Aims: To identify factors associated with use of novel diabetes medications among patients hospitalized under general internal medicine.

Methods: We conducted a cohort study of patients with type 2 diabetes mellitus (T2DM) hospitalized in Ontario, Canada between 2015 and 2020. We evaluated the patient- and physician-level factors associated with sodium-glucose cotransporter 2 inhibitor (SGLT2) and glucagon-like peptide 1 receptor agonist (GLP1R) use using a multivariable logistic regression model.

Results: There were 253,152 hospitalizations and 68,126 involved patients who had T2DM. Prior to discharge, 3.7% (N = 2490) of patients with T2DM received an SGLT2 and 0.2% (N = 121) received a GLP1R. The strongest predictors for receiving a novel diabetes medication were hemoglobin A1C > 9.0 % (Odds Ratio (OR) = 1.81, 95 % Confidence Interval (CI) 1.28, 2.60) and patients aged 40-60 compared with patients <40 years old (OR = 1.81, 95% CI 1.33, 2.68). The strongest predictors for not receiving a novel diabetes medication were dementia (OR = 0.47, 95% CI 0.39, 0.56) and creatinine ≥200 μmol/L (OR = 0.11, 95 % CI 0.08, 0.15). Overall, 46.8% of patients hospitalized with T2DM not receiving a novel diabetes medication would potentially benefit from an SGLT2 inhibitor.

Conclusions: Novel diabetes medications were rarely continued or initiated during hospitalization despite a high prevalence of cardiovascular disease, raising the concern for systematic under-utilization after discharge.

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Effects of Sodium-Glucose Cotransporter-2 Inhibitors on Kidney Outcomes across Baseline Cardiovascular-Kidney-Metabolic Conditions - A Systematic Review and Meta-Analyses

Tariq Jamal S, David C et. al.; Journal of the American Society of Nephrology (September 4, 2024)

Key Points:

- Sodium-glucose cotransporter-2 (SGLT2) inhibitors slowed the rate of eGFR slope decline in patients with heart failure, CKD, and type 2 diabetes mellitus and in all combinations of multimorbid conditions among these diseases.
- SGLT2 inhibitors decreased kidney composite outcomes among all disease states and different combinations of multimorbidity, except in patients with heart failure with preserved ejection fraction and heart failure without type 2 diabetes mellitus.
- SGLT2 inhibitors were found to decrease the risk of kidney failure in patients with type 2 diabetes mellitus and also in those with CKD.

Background: The effects of sodium-glucose cotransporter-2 inhibitors (SGLT2is) on kidney outcomes in patients with varying combinations of heart failure, CKD, and type 2 diabetes mellitus have not been quantified.

Methods: PubMed and Scopus were queried up to December 2023 for primary and secondary analyses of placebo-controlled trials of SGLT2is in patients with heart failure, CKD, or type 2 diabetes mellitus. Outcomes of interest were composite kidney end point (combination of eGFR <15 ml/min per 1.73 m^2, sustained doubling of serum creatinine, varying percent change in eGFR, and need for KRT), rate of eGFR slope decline, and albuminuria progression. Hazard ratios (HRs) and mean differences with their 95% confidence intervals (CIs) were extracted onto an Excel sheet, and the results were then pooled using a random-effect model through Review Manager (version 5.3, Cochrane Collaboration).

Results: Eleven trials (n=80,928 patients) were included. Compared with the placebo, SGLT2is reduced the risk of the composite kidney end point by 41% (HR, 0.59; 95% CI, 0.42 to 0.83) in heart failure with reduced ejection fraction, 36% (HR, 0.64; 95% CI, 0.55 to 0.73) in CKD, and 38% (HR, 0.62; 95% CI, 0.56 to 0.69) in type 2 diabetes mellitus. A similar pattern of benefit was observed in combinations of these comorbidities and in patients without baseline heart failure, CKD, or type 2 diabetes mellitus. SGLT2is slowed the rate of eGFR slope decline and reduced the risk of sustained doubling of serum creatinine by 36% (HR, 0.64; 95% CI, 0.56 to 0.72) in the overall population, and a consistent effect on kidney outcomes was observed in most subpopulations with available data.

Conclusions: SGLT2i improved kidney outcomes in cohorts with heart failure, CKD, and type 2 diabetes mellitus, and these effects were consistent across patients with different combinations of these comorbidities.

Zur Publikation

Zur Übersicht

GLP-1-Rezeptor-Agonisten

Renal effects and safety of tirzepatide in subjects with and without diabetes: A systematic review and meta-analysis

Kamrul-Hasan A, Patra S et. al.; World Journal of Diabetes (February 15, 2025)

Background: Type 2 diabetes (T2D), as well as obesity, are risk factors for chronic kidney disease (CKD) and end-stage renal disease. The renal impacts of glucose-lowering and weight-lowering drugs and their potential benefits in preventing CKD often guide clinicians in choosing them appropriately. Only limited data based on randomized controlled trials (RCTs) is currently available on the renal effects and safety profile of tirzepatide.

Aim: To explore the renal benefits and safety of tirzepatide vs controls.

Methods: RCTs involving patients receiving tirzepatide for any indication in the intervention arm and placebo or active comparator in the control arm were searched through multiple electronic databases. The co-primary outcomes were percent change from baseline (CFB) in urine albumin-to-creatinine ratio (UACR) and absolute CFB in estimated glomerular filtration rate (eGFR; in mL/min/1.73 m^2); the secondary outcome was tirzepatide's renal safety profile. RevMan web was used to conduct meta-analysis using random-effects models. Outcomes were presented as mean differences (MD) or risk ratios with 95% confidence intervals.

Results: Fifteen RCTs (n = 14471) with mostly low risk of bias (RoB) were included. Over 26-72 weeks, tirzepatide 10 mg [MD -26.95% (-40.13, -13.76), P < 0.0001] and 15 mg [MD -18.03% (-28.58, -7.47), P = 0.0008] were superior to placebo in percent reductions of UACR. Tirzepatide, at all doses, outperformed insulin in percent reductions of UACR. Compared to the placebo, the percent UACR reduction was greater in subjects with T2D than those with obesity but without T2D (MD -33.25% vs -7.93%; P = 0.001). The CFB in eGFR with all doses of tirzepatide was comparable [5 mg: MD 0.36 (-1.41, 2.14); 10 mg: MD 1.17 (-0.22, 2.56); 15 mg: MD 1.42 (-0.04, 2.88)]; P > 0.05 for all] vs insulin. Tirzepatide (pooled and separate doses) did not increase the risks of adverse renal events, urinary tract infection, nephrolithiasis, acute kidney injury, and renal cancer compared to the placebo, insulin, and glucagon-like peptide-1 receptor agonists.

Conclusion: Short-term data from RCTs with low RoB suggests that tirzepatide positively impacts UACR without detrimental effects on eGFR in subjects with T2D and obesity without T2D, with a reassuring renal safety profile. Larger RCTs are warranted to prove the longer-term renal benefits of tirzepatide, which might also prevent eGFR decline and worsening of CKD.

Zur Publikation

Reaching the SUMMIT? Benefits and potential risks associated with the use of tirzepatide in heart failure with preserved ejection fraction

Hellenkamp K, Sato R, von Haehling S; Med (February 14, 2025)

The SUMMIT trial showed that the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist tirzepatide improves quality of life and reduces worsening heart failure (HF) events in patients with HF with preserved ejection fraction (HFpEF) and obesity. Some concerns, however, remain.

Zur Publikation

Zur Übersicht

Ausblick: Zukünftige Therapieoptionen

Targeting Krüppel-Like Factor 2 as a Novel Therapy for Glomerular Endothelial Cell Injury in Diabetic Kidney Disease

Lulin M, Yixin C et. al.; Journal of the American Society of Nephrology (October 9, 2024)

Key Points

- Krüppel-like factor 2 (KLF2) has emerged as a key endoprotective regulator by suppressing inflammatory and oxidative pathways, thrombotic activation, and angiogenesis.
- Our study now demonstrates that KLF2 protects against glomerular endothelial injury and attenuates diabetic kidney disease progression in mice.
- Compound 6 is a novel KLF2 activator that can potentially confer dual cardiorenal protection against diabetic complications.

Background: Diabetic kidney disease (DKD) is a microvascular disease, and glomerular endothelial cell injury is a key pathological event in DKD development. Through unbiased screening of glomerular transcriptomes, we previously identified Krüppel-like factor 2 (KLF2) as a highly regulated gene in diabetic kidneys. KLF2 exhibits protective effects in endothelial cells by inhibiting inflammation, thrombotic activation, and angiogenesis, all of which are protective for cardiovascular disease. We previously demonstrated that endothelial cell–specific ablation of Klf2 exacerbated diabetes-induced glomerular endothelial cell injury and DKD in mice. Therefore, in this study, we sought to assess the therapeutic potential of KLF2 activation in murine models of DKD.

Methods: We first examined the effects of endothelial cell–specific inducible overexpression of KLF2 (KLF2ov) in streptozotocin-induced diabetic mice. We developed small molecule KLF2 activators and tested whether higher KLF2 activity could impede DKD progression in type 2 diabetic db/db and BTBR ob/ob mice.

Results: Diabetic KLF2ov mice had attenuated albuminuria, glomerular endothelial cell injury, and diabetic glomerulopathy compared with control diabetic mice. A novel KLF2 activator, compound 6 (C-6), effectively induced downstream Nos3 expression and suppressed NF-kB activation in glomerular endothelial cells. The administration of C-6 improved albuminuria and glomerulopathy in db/db and BTBR ob/ob mice, which was associated with improved glomerular endothelial cell and podocyte injury.

Conclusions: These results validate KLF2 as a potential drug target and KLF2 activators, such as C-6, as a novel therapy for DKD.

Zur Publikation

KidneyintelX.dkd - An Innovation in Precision Medicine for Diabetic Kidney Disease

Coca SG, Nadkarni GN; Journal of the American Society of Nephrology (January 30, 2025)

No Abstract available.

Zur Publikation

Zur Übersicht