Renal Health in T2DM

Preventing Microvascular Complication of Nephropathy

DISCLOSURES

- Speakers Bureau
- Novo Nordisk
- &
- Mannkind Corporation

Objectives

- • Identify differences in Microvascular versus Macrovascular complications of Type 2 Diabetes (T2DM)
- • Discuss and identify how to monitor and evaluate for Microvascular complication of Nephropathy
- •Epidemiology of Chronic Kidney Disease (CKD)
- • Diabetic Nephropathy Medication Interventions:
  - SGLT2i: discuss trials of SGLT2i inclusionary criteria and primary endpoints, and results
  - Mineralocorticoid Receptor Antagonists: trial((s), inclusionary criteria, primary and secondary endpoints, results
  - MOA of SGLT2i and Mineralocorticoid Receptor Antagonist
  - Dosing, safety of above medications

Background

- ***Microvascular*** Complications of T2DM:
  - Retinopathy
  - Neuropathy
  - **NEPHROPATHY**

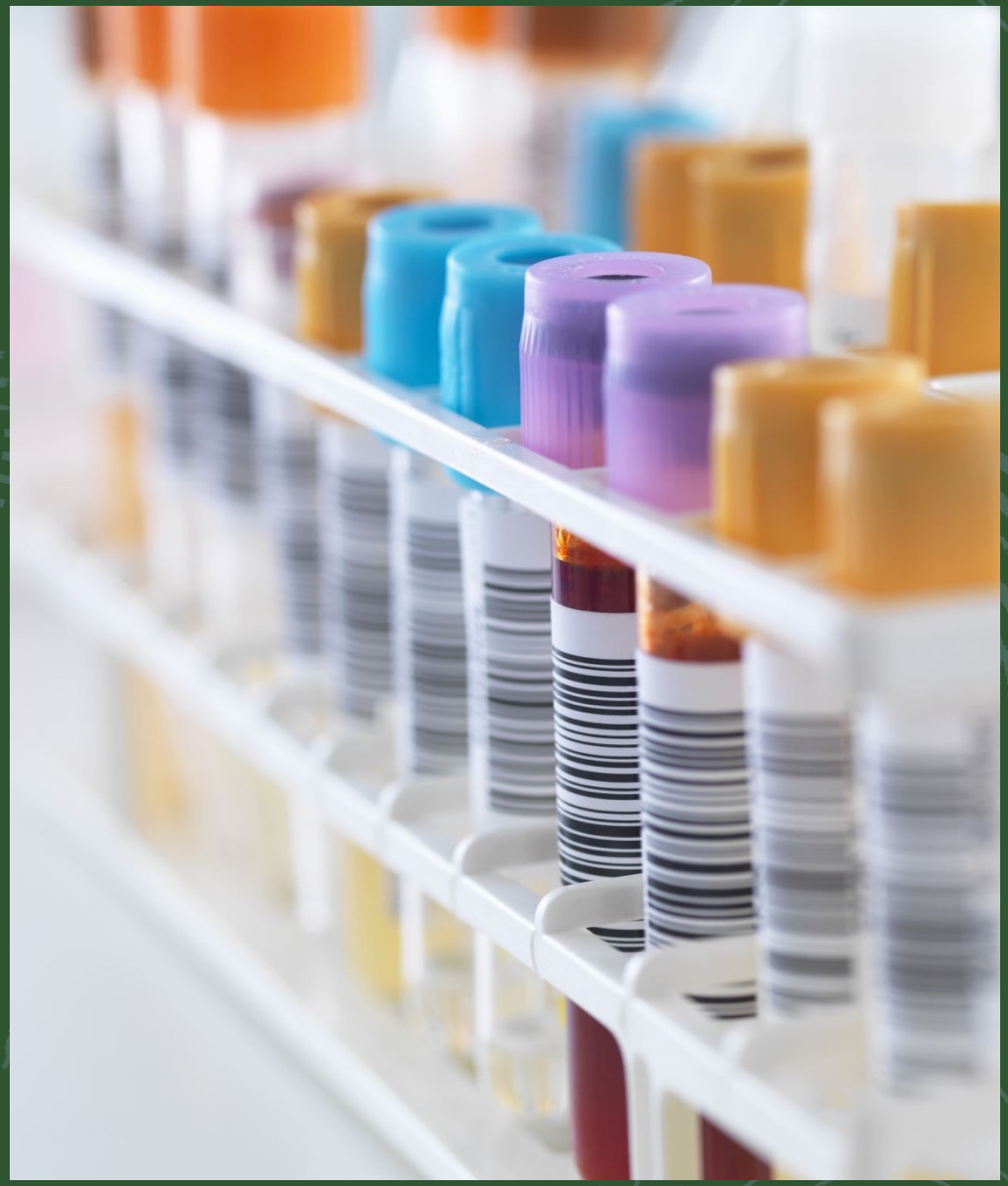
- **Diabetic Kidney Disease (DKD) can progress to CKD and accounts for 50% of cases of end stage renal failure**

CKD in Diabetes

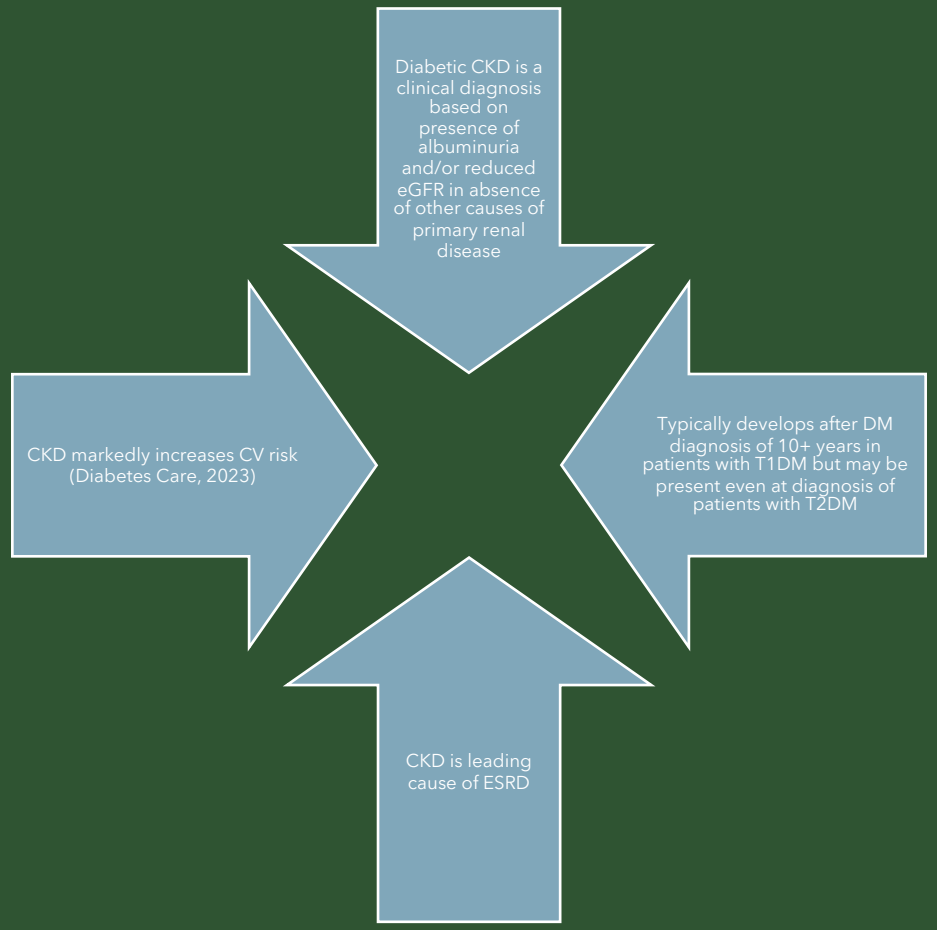
- Diagnosis: most often made by eGFR OR *by testing urine for presence of albumin or protein OR a combination of both.*
- To differentiate CKD from acute kidney injury, the standard definition includes a "chronicity criterion", i.e., that the low eGFR or elevated albumin should be detectable for at least 90 days, requiring multiple measurements over time (Kovesky, 2022)

- American Diabetes Association (ADA) 2023 *Standards of Care in Diabetes:*
  - *"CKD screening: measure urinary albumin(spot urinary albumin-to-creatinine ratio) AND eGFR should be assessed in all patients with Type 1 Diabetes (T1DM) >5 years and in all patients with Type 2 Diabetes (T2DM) regardless of treatment."*
  - *"in people with established diabetic kidney disease, urinary albumin and eGFR should be monitored 1-4x yearly depending on stage of disease"*

Epidemiology of CKD in Diabetes



Epidemiology and Diagnosis of Diabetic Kidney Disease



- Typical presentation of Diabetic Kidney Disease (DKD)includes:
  - Long standing diabetes
  - Retinopathy
  - Albuminuria without hematuria
  - Gradual loss of Egfr
  - Remember: is it rare for a patient with T1DM to develop DKD without retinopathy. However, in patients with T2DM, retinopathy is moderately sensitive and specific for DKD

Definition and Diagnosis of CKD

Clinical syndrome characterized by persistent albuminuria and progressive decline in renal fuction, ie, decrease of eGFR <60

Renal biopsy is gold standard but, in many cases, CKD is a clinical diagnosis.

If eGFR or + albuminuria, this should be confirmed on repeat testing in 3-6 month. Two elevated urine albumin tests or two eGFR <60 at least 90 days apart =+CKD

- Diagnosis in T1 and T2DM:
  - Diagnosis in T1DM: persistent, moderate or severe albuminuria OR a persistent reduction in eGFR occurring >5 years after diagnosis. In 95% of cases, patient will also have retinopathy
  - Diagnosis in T2DM: two + urine microalbumin screens at least 90 days apart OR two eGFR <60 at least 90 days apart.
    - Longer duration of T2DM and retinopathy are good pointers of CKD but unlike patients with T1DM, retinopathy is not a specific indicator of CKD

(SELBY, 2019)

Factors Affecting the Rate of DKD Onset and Progression

- **Nonmodifiable**:
  - Age at diagnosis
  - Family history
  - Level of formal education
  - Male sex
  - Type 1 versus Type 2 DM

Factors Affecting the Rate of DKD Onset and Progression

- Potentially Modifiable:
  - ETOH use
  - Hyperglycemia
  - Hyperlipidemia
  - HTN
  - Obesity
  - Physical activity
  - Social network at baseline

Primary Prevention CKD

- 1.GLUCOSE CONTROL
- 2.BLOOD PRESSURE CONTROL

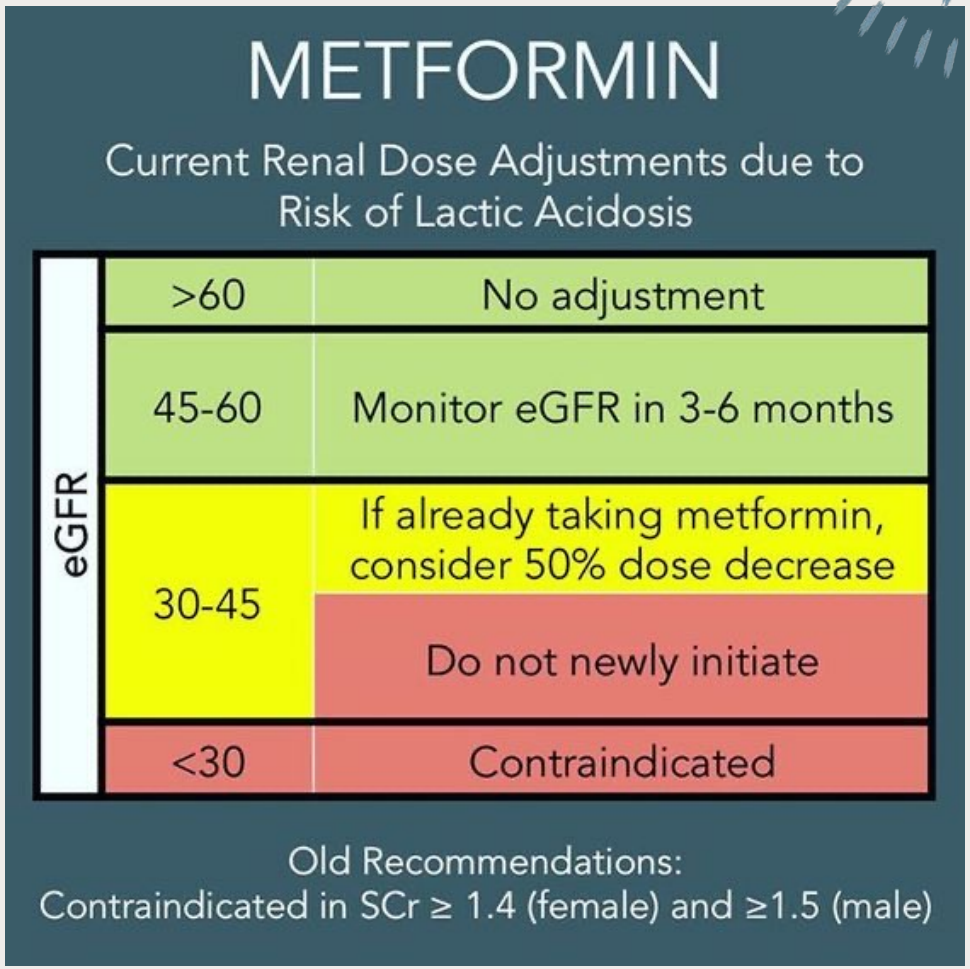
Interventions

Glucose goals

Patient	JNC-8	ACC/AHA	ADA	
Target BP for patients with DM	<140/90 mm HG	<130/80 mm HG	<140/90 mm HG	
Target BP for patients with CKD stage 3 or beyond	<140/90 mm HG	<130/80 mm HG	Not specified	
Special Populations	Patients >65 YO with CKD should still have goal <140/90 mm HG	Shared decision making for patients >65 YO with multimorbidity; risks of intensive control may outweigh the benefits	Patient with multiple risks factors may benefit from more intensive control with goal <130/80 or even <120/80 mm HG	

Medication Intervention(s)

~a word on Metformin….



Sodium-Glucose Co-transporter 2 Inhibitor(SGLT2i)

Background: SGLT2i proteins are expressed in the proximal convoluted tubule of the kidneys. These proteins are responsible for 90% of glucose reabsorption in the kidneys (Grove, 2017)

Mechanism of Action of glycosuria: reduce tubular re-absorption of glucose without stimulating insulin. These medications "off-load" glucose from bloodstream to the urine.

Lowers a1c 0.6-1% in patients with preserved renal function.

Glucose lowering in patient with renal insufficiency is lessened when Egfr is <60 and minimal, at best, when egfr is <30

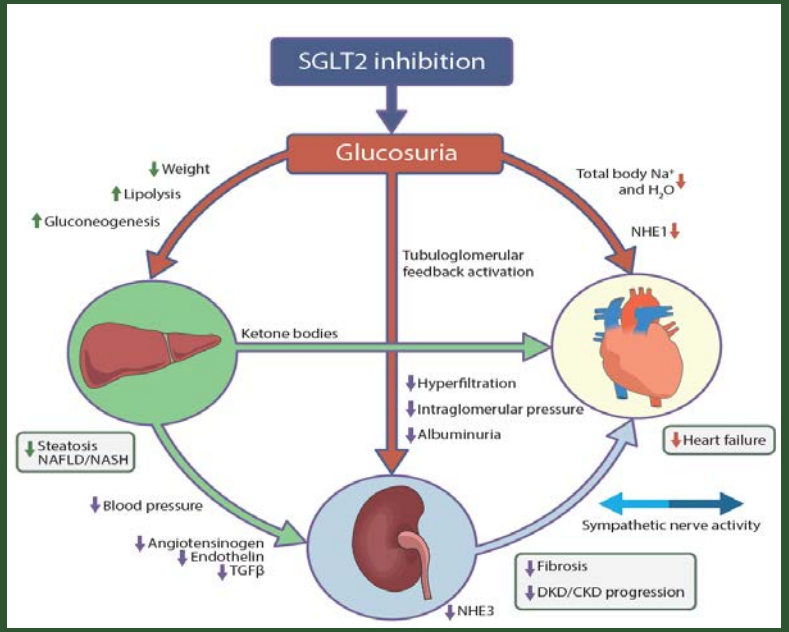
Mechanism of Action for End-Organ Protection (not mediated by glycosuria):

1. Lowers systolic b/p by 3-6mm HG and diastolic b/p by 1-2mm HG. This leads to a reduction in arterial stiffness, plasma contraction, and improvement of endothelial function
2. In patients with T2DM, SLT2is are thought to be nephroprotective by resulting in afferent vasocontriction and reduction of intraglomemerular pressure. The marker of this reduction in intraglomerular pressure is a reduction in albuminuria.

- slow GFR loss by reducing oxidative stress thru a reduction in inflammatory mediators such as interleukin-6, nuclear factor-kB (Yau et al 2022)
- Finally, SGLT2i attenuate renal hypoxia by off loading glucose and sodium

(Diabetes Care 2023)

- **Consequences of inhibition of SGLT2 on glucose, salt and water excretion, as well as its potential metabolic impact on kidney, liver and heart function**



Wanner and Marx (2018) Diabetologia DOI 10.1007/s00125-018-4678-z

Clinical Trials

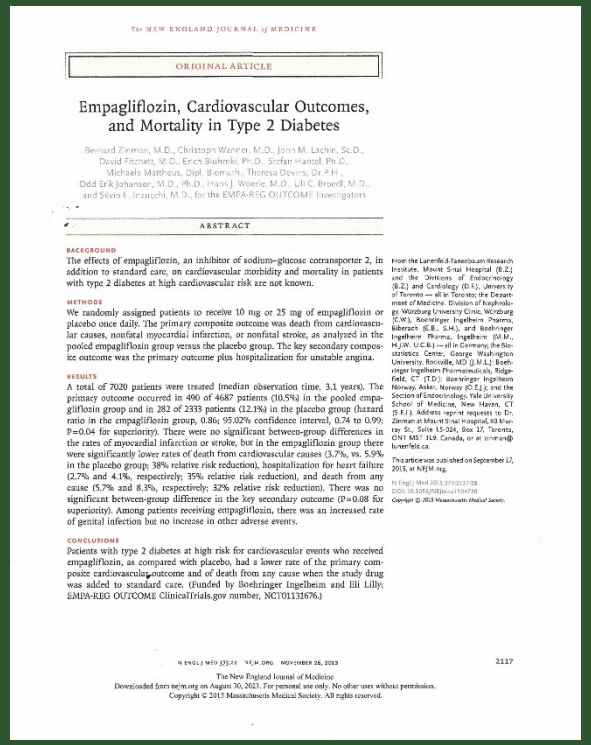
- Outcomes are variables which are monitored during the study to document the impact of the intervention.
  - *Primary* outcome is the variable most relevant to answer the research question
  - *Secondary* outcomes help interpret primary outcomes OR provide preliminary data for a larger study

Clinical Trials: SGLT2i

Trials with Renal effects as *secondary outcomes* (CVOT)

- EMPA-REG OUTCOME: Empagliflozin: compared with placebo, it reduced nephropathy or worsening nephropathy by 39% and the risk of doubling of serum creatinine (scr) accompanied by eGFR <45 by 44%
- CANVAS: canagliflozen reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD OR death from ESRD by 40%

CVOT trials: 2015 and 2017



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7% vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

CONCLUSIONS

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

From the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital (B.Z.) and the Divisions of Endocrinology (B.Z.) and Cardiology (D.F.), University of Toronto — all in Toronto; the Department of Medicine, Division of Nephrology, Würzburg University Clinic, Würzburg (C.W.), Boehringer Ingelheim Pharma, Biberach (E.B., S.H.), and Boehringer Ingelheim Pharma, Ingelheim (M.M., H.J.W., U.C.B.) — all in Germany; the Biostatistics Center, George Washington University, Rockville, MD (J.M.L.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (T.D.); Boehringer Ingelheim Norway, Asker, Norway (O.E.J.); and the Section of Endocrinology, Yale University School of Medicine, New Haven, CT (S.E.I.). Address reprint requests to Dr. Zinman at Mount Sinai Hospital, 60 Murray St., Suite 15-024, Box 37, Toronto, ONT M5T 3L9, Canada, or at bzinman@lunenfeld.ca.

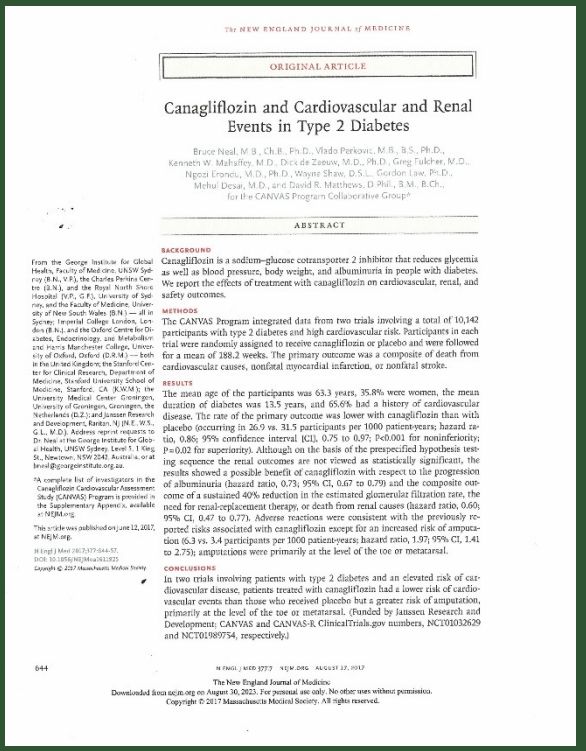
This article was published on September 17, 2015, at NEJM.org.

N Engl J Med 2015;373:2117-28.
DOI: 10.1056/NEJMoa1504720
Copyright © 2015 Massachusetts Medical Society.

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

2117

The New England Journal of Medicine
Downloaded from nejm.org on August 30, 2023. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

ABSTRACT

BACKGROUND

Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

METHODS

The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

The mean age of the participants was 63.3 years, 35.8% were women, the mean duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). Although on the basis of the prespecified hypothesis testing sequence the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). Adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.

CONCLUSIONS

In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal. (Funded by Janssen Research and Development; CANVAS and CANVAS-R ClinicalTrials.gov numbers, NCT01032629 and NCT01989754, respectively.)

644

N ENGL J MED 377;7 NEJM.ORG AUGUST 17, 2017

The New England Journal of Medicine
Downloaded from nejm.org on August 30, 2023. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

CREDENCE Trial Primary Outcome

Canagliflozen and Renal Events In Diabetes with Established Nephropathy 2019

Inclusion: 4,401 adults with T2DM, UACR >300-5,000mg/g creatinine, and eGFR range 30-90 with mean of 56

Primary endpoint: ESRD , doubling of serum creatinine or renal or CV death.

Stopped early due to positive efficacy

Showed 32% risk reduction for development of ESRD vs placebo.

Development of chronic dialysis, renal transplantation, or eGFR<15, doubling of creatinine or renal death was reduced by 30%.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

ABSTRACT

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

METHODS

In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.

RESULTS

The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.

CONCLUSIONS

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South Wales Sydney, Level 5, 1 King St., Newtown, N.S.W. 2042, Australia, or at vperkovic@georgeinstitute.org.au.

*A complete list of the CREDENCE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 14, 2019, at NEJM.org.

N Engl J Med 2019;380:2295-306.
DOI: 10.1056/NEJMoa1811744

DAPA-CKD: Primary Outcome

Dapagliflozen and Prevention of Adverse Outcomes in Chronic Kidney Disease study

Included 4,304 participants with mean egfr at baseline of 43, median URCR of 949

67.% had T2DM and CKD

33% HAD CKD without T2DM

Primary endpoint: time to first occurrence of >50% decline of eGFR, ESRD or CV or renal death.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

RESULTS

The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Heerspink at the Department of Clinical Pharmacy and Pharmacology, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands, or at h.j.lambers.heerspink@umcg.nl.

*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 24, 2020, at NEJM.org.

N Engl J Med 2020;383:1436-46.
DOI: 10.1056/NEJMoa2024816

Dosing SGLT2i Recommendations CKD

eGFR	Empagliflozen	Canagliflozen	Dapagliflozen	Ertugliflozen
>60	10mg	100mg	10mg	15mg
45-60	10mg	100mg	10mg	15mg
30-45	Initiation not recommended	100mg	10mg	Not indicated
<30	Contraindicated (CL)	Initiation not recommended but may continue if uacr >300mg/g	Initiation not recommended (<25ml/min/1.73 m2)	Not indicated
DIALYSIS	CL	CL	CL	CL

Potential Adverse Effects & Interventions

A/E

1.Genital Mycotic infections and UTI

2.Ketoacidosis

3.Hypotension/syncope

4. LDL cholesterol

5. Fournier's gangrene

Interventions

1.If female and has tendency to have genital mycotic infections: use OTC topical vaginal antifungal cream, use peri-bottle, use unscented wipes to remove all urine from skin after voiding. UTI: hydration and voiding on regular basis. Urinary probiotic.

2. Hold pre-op or in times of illness or if prolonged fasting.

3. Consider decrease of other diuretics when starting SGLT2i

4. Monitor lipids

5. Monitor any complaints of redness, soreness, pain or tenderness in genital area

Key Takeaways for SGLT2i: CKD with Albuminuria

Sgkt2i with *Primary* evidence of DECREASE of CKD progression:

Canagliflozin

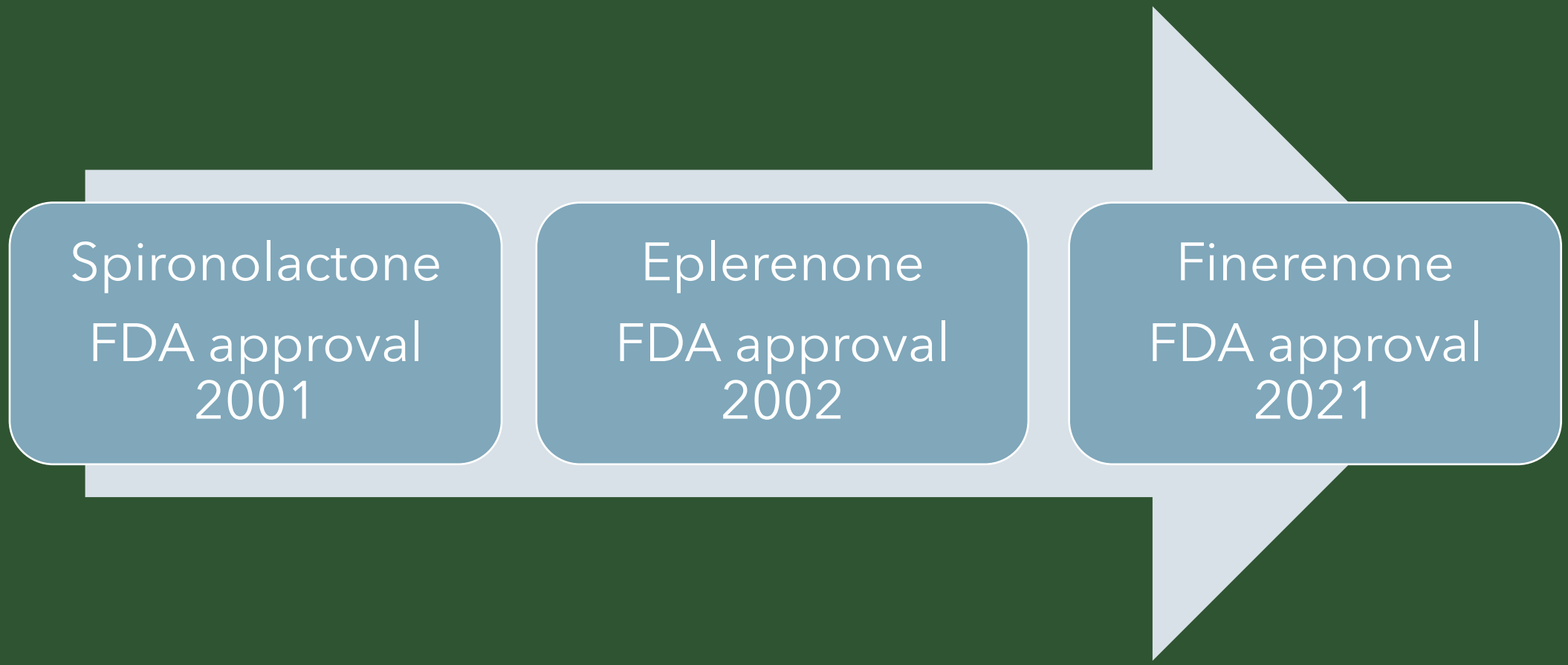
Dapagliflozin

SGLT2i with evidence of decrease of CKD protection in CVOTs

Empagliflozin (off label)

Mineralocorticoid Receptor Antagonists(MRAs)

MRAs approved by FDA



What is FINERENONE?

Highly selective *non-steroidal* mineralocorticoid receptor antagonist

Higher selectivity and higher affinity to MR compared to spironolactone and eplereone which are steroidal MRAs

Equal tendency to heart and kidney compared to steroidal MRAs

MOA

Inhibits the effects of aldosterone and cortisol (and activation of the MR receptor) thereby inhibiting and pro-inflammatory and pro-fibrotic factors = decrease of renal tissue damage

Eplerenone and Spironolactone have limited use in CKD associated with T2DM due to s/e hyperkalemia and gynecomastia, etc

	Spironolactone	Eplerenone	Finerenome
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal
Selectivity to MR	+	++	+++
Half-life	>20h	4-6h	2-3h
Sexual side effects	++	+	-
Effects on b/p	+++	++	+

Studies: Finerenone

- 2020, two trials : FINERENONE In Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease: FIDELIO-DKD
- Finerenone in REDUCING Cardiovascular Mortality in Diabetic Kidney Disease: FIGARO-DKD

Fidelio-DKD/Figaro DKD

- ***Primary renal outcome***:
  - ESRD
  - Sustained eGFR decrease of 40%
  - Renal death

Also had primary CV endpoint of MACE: CV death, non-fatal MI, CVA, or hospitalization for HF

N=13,000

99% on ACE/ARB

~7% on sglt2i and ~8 initiated during study

52% eGFR 25-45

87% UACR >300mg/g

Trial lasted ~2.6 yrs

Result:

31% greater reduction in UACR from baseline to month 4 was sustained throughout study

Hyperkalemia incidence was 18.3%

Hyperkalemia leading to d/c was 2.3%

Conclusion:

- **Benefits of finerenone compared with placebo on cardiorenal outcomes in patients with CKD and type 2 diabetes were observed irrespective of SGLT2i use**

Finerenone Indication

- “Kerendia is a non-steroidal mineralocorticoid receptor antagonist (MRA) indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)”

Dosing of Finerenone

Starting doses:

eGFR >60: 20mg once daily

eGFR >25-<60: 10mg once daily

eGFR <25; not recommended

K+ Monitoring

- K+: if k+ is >5mEq/L, do not start
- Check k+ four weeks after starting or sooner if K+ is 4.8-5.0 mEq/L
- Monitor throughout treatment and adjust dose as needed
- eGFR below 30%, maintain 10mg dose

	Finerenone 10mg	**Finerenone 20mg**
K+	<4.8, increase to 20mg	<4.8 maintain at 20mg
K+	>4.8-5.5 Maintain 10mg dose	>4.8-5.5 maintain at 20mg
K+	>5.5 HOLD May restart when <5.0	>5.5 HOLD May restart when <5

Key Takeaways: finerenone

Consider use in patients with T2DM at high risk for CKD and CV disease with micro or macroalbuminuria/ decrease of e GFR

Monitor K+ levels at initiation in 4 weeks then as appropriate depending on patient

Case study cont

When to refer to Nephrology

- Clinical findings inconsistent with typical DKD
- Massive proteinuria
- Rapidly declining Egfr
- Advanced CKD

- https://diabetesjournals.org/care/article/45/Supplement_1/S175/138914/11-Chronic-Kidney-Disease-and-Risk-Management

From: **11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2023**

Diabetes Care. 2022;46(Supplement_1):S191-S202. doi:10.2337/dc23-S011

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure Legend: Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal estimated GFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements dark red requires

Review

Jorge Rico-Fontalvo, Jose Cabrales, Tomás Rodriguez-Yanez, Rodrigo Daza-Arnedo,
Letter Regarding “Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations”,
Kidney International Reports,
Volume 7, Issue 11,
2022,
Pages 2545-2546,
ISSN 2468-0249,
https://doi.org/10.1016/j.ekir.2022.08.017.
(https://www.sciencedirect.com/science/article/pii/S2468024922017181)