How Bad Pharma™ and an ambitious attorney general lead to two of the greatest therapeutic discoveries in kidney and cardiac medicine

A new era in diabetic kidney disease

Joel Topf, MD FACP
@Kidney_Boy

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Conflicts of Interest

I have an ownership stake in a few Davita run dialysis clinics and a vascular access center.

In the last two years I have participated in advisory boards for Bayer, Astra Zeneca, Cara Therapeutics, Glaxo Smith Kline, and Vifor CSL.

I am the president of NephJC, a 503c organization that supports social media in medical education. NephJC has never accepted pharmaceutical support and has not accepted any industry support since 2019.

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SorryMySlidesArentDone.com

3

I may discuss off-label indications

	Dapagliflozin:	Empagliflozin:	Canagliflozin:
	Reduce progression of **CKD** and decrease hospitalization for heart failure, and decrease CV death.	Reduce progression of **CKD** and decrease hospitalization.	Reduce progression of **CKD** and decrease hospitalization for heart failure, and decrease CV death in adults with **type 2 diabetes and albuminuria**
	Reduce the risk of cardiovascular (CV) death and hospitalization for heart failure in adults with heart failure. Reduce the risk of hospitalization for heart failure in adults with **type 2 diabetes** mellitus and either CV disease or risk factors.	Reduce the risk of cardiovascular (CV) death and hospitalization for heart failure (Both **HFrEF and HFpEF)** Reduce the risk of CV death in adults with **type 2 diabetes** mellitus and cardiovascular disease.	Reduce the risk of cardiovascular death, non-fatal MI, non-fatal stroke in adults with **type 2 diabetes** mellitus and cardiovascular disease.
	As an adjunct to diet and exercise to **improve glycemic control** in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to **improve glycemic control** in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to **improve glycemic control** in adults with type 2 diabetes mellitus

4

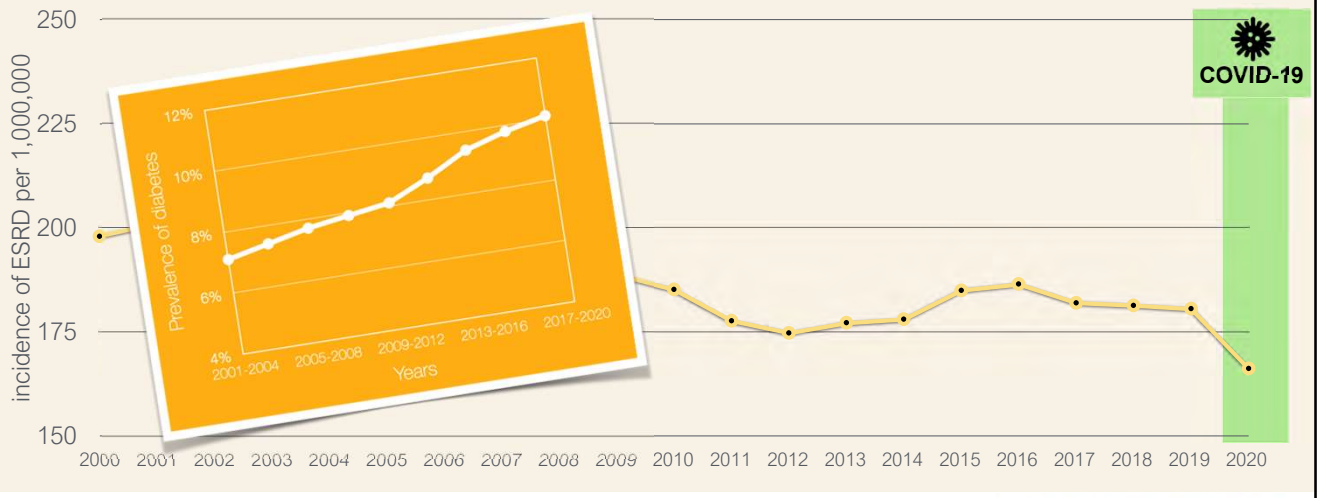
I may discuss off-label indications

	Ertugliflozin:	Sotagliflozin:	Bexagliflozin:
		Reduce the risk of cardiovascular death, hospitalization for heart failure in patients with heart failure. Reduce the risk of hospitalization for heart failure in adults with **type 2 diabetes** mellitus and either CV disease or risk factors.	
	As an adjunct to diet and exercise to **improve glycemic control** in adults with type 2 diabetes mellitus		As an adjunct to diet and exercise to **improve glycemic control** in adults with type 2 diabetes mellitus

5

Incidence of ESRD due to diabetes

adjusted for age, sex, race/ethnicity



CDC National Diabetes Statistics Report, Accessed 10/10/23
https://www.cdc.gov/diabetes/data/statistics-report/appendix.html#tabs-1-2

USRDS

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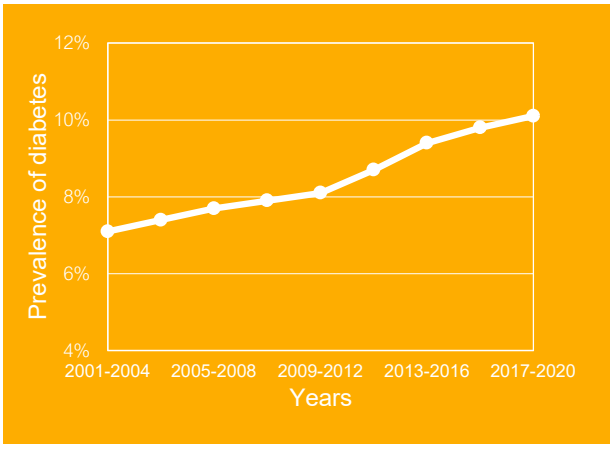

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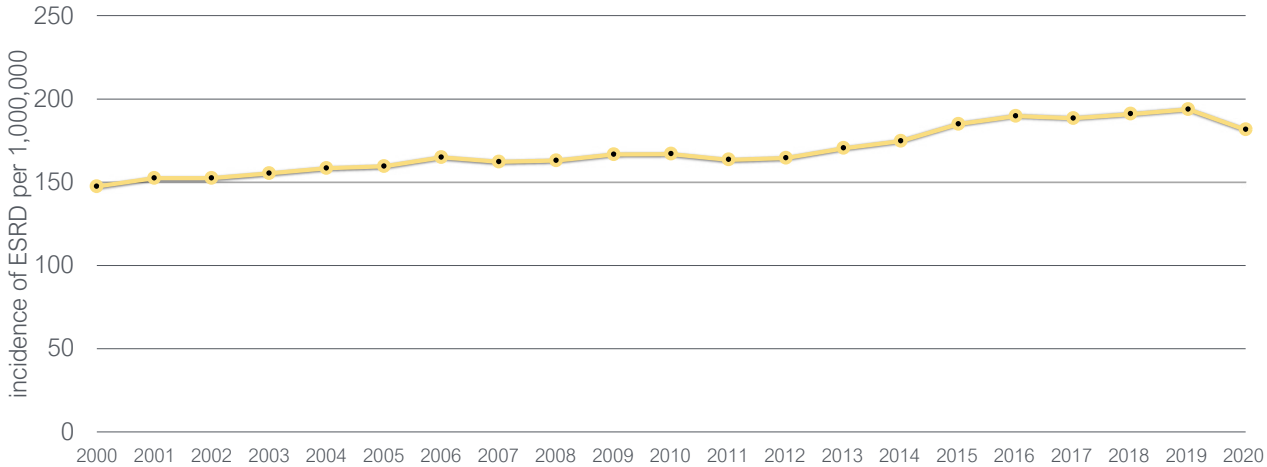
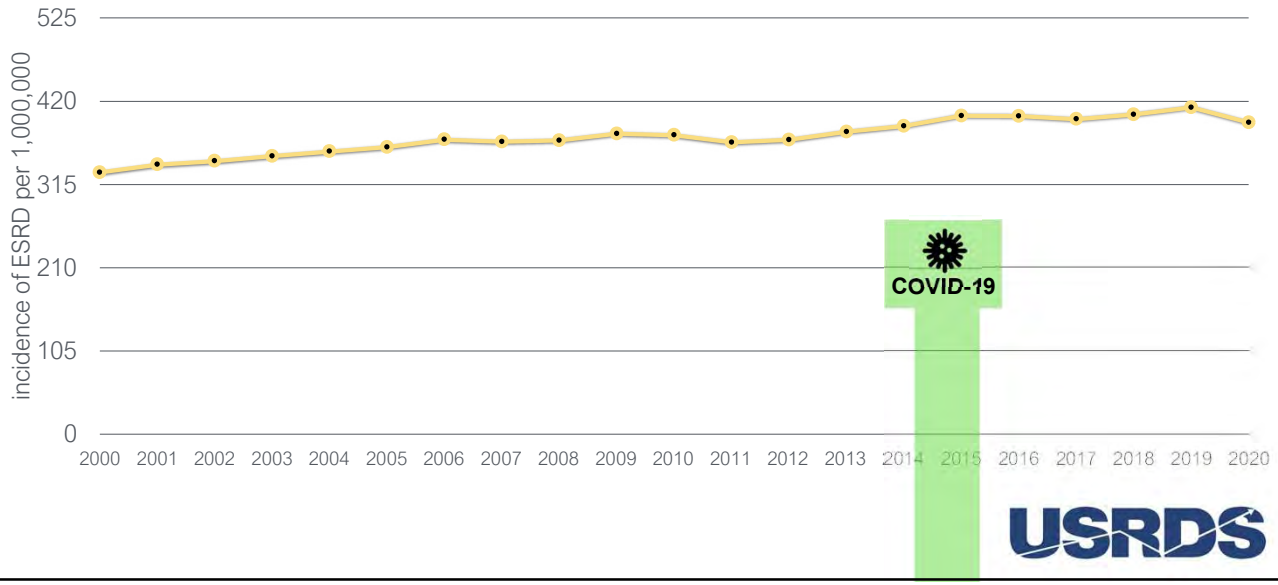
Incidence of ESRD due to diabetes



USRDS

8

Incidence of renal replacement therapy (all cause)



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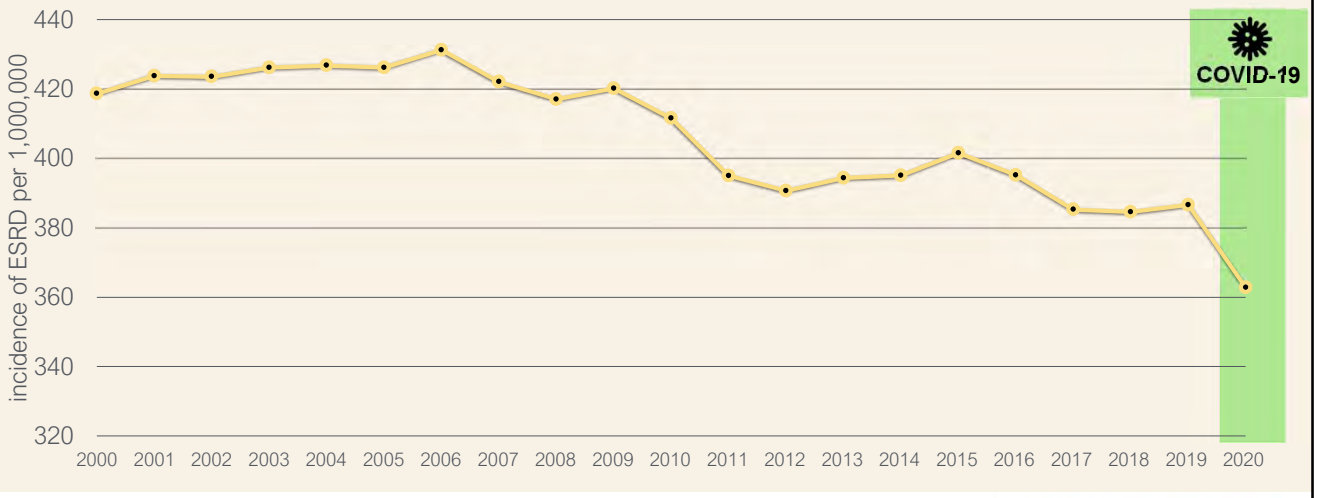
Incidence of ESRD

adjusted for age, sex, race/ethnicity



10

Glycemic control

11

1993

Hgb A1c 7 vs 9

Diabetes Control and Complications Trial

1441 Type 1 diabetics

7 years of follow up

primary outcome was decreased retinopathy and development of microalbuminuria

The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Abstract *Background.* Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Methods. A total of 1441 patients with IDDM — 726 with no retinopathy at base line (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. The patients were followed for a mean of 6.5 years, and the appearance and progression of retinopathy and other complications were assessed regularly.

Results. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe nonproliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ⩾40 mg per 24 hours) by 39 percent (95 percent confidence interval, 21 to 52 percent), that of albuminuria (urinary albumin excretion of ⩾300 mg per 24 hours) by 54 percent (95 percent confidence interval, 19 to 74 percent), and that of clinical neuropathy by 60 percent (95 percent confidence interval, 38 to 74 percent). The chief adverse event associated with intensive therapy was a two-to-threefold increase in severe hypoglycemia.

Conclusions. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM. (N Engl J Med 1993;329:977-86.)

INSULIN-dependent diabetes mellitus (IDDM) is accompanied by long-term microvascular, neurologic, and macrovascular complications. Although the daily management of IDDM is burdensome and the specter of metabolic decompensation ever-present, long-term complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease, have caused the most morbidity and mortality since the introduction of insulin therapy.[1,2] The prevention and amelioration of these complications have been major goals of recent research.

Although studies in animal models of diabetes[3-5] and epidemiologic studies[6-8] implicate hyperglycemia in the pathogenesis of long-term complications, previous clinical trials have not demonstrated a consistent or convincing beneficial effect of intensive therapy on them.[9-11] A recent publication from the Stockholm Diabetes Intervention Study demonstrated a more uniform beneficial effect of intensive therapy in patients with established complications, despite the apparent crossover of most conventionally treated patients to intensive therapy during the trial.[12]

The Diabetes Control and Complications Trial was a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of the early vascular and neurologic complications of IDDM.[13-15] The intensive-therapy regimen was designed to achieve blood glucose values as close to the normal range as possible with three or

Address reprint requests to the DCCT Research Group, Box NDIC/DCCT,

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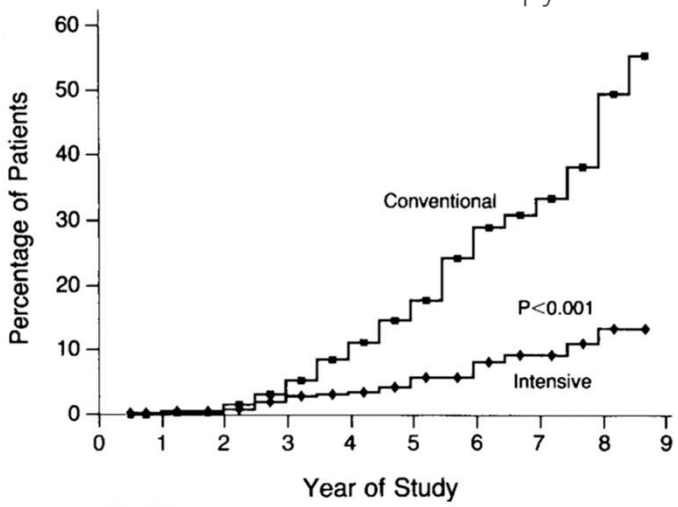
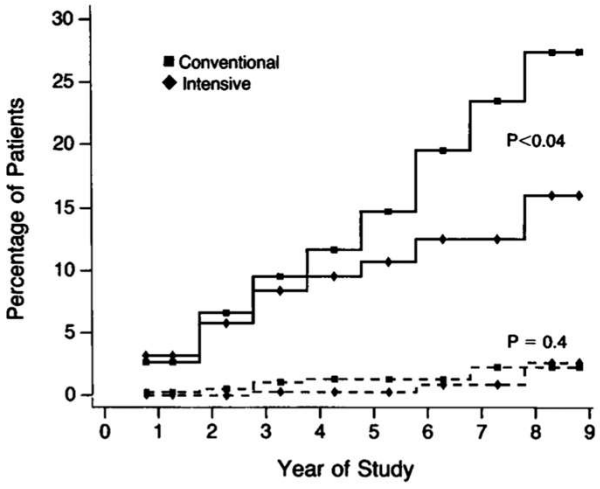
intensive therapy reduced microvascular diseased





Retinopathy: ↓76%

New onset albuminuria: ↓34%

The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. (1993). *NEJM*, *329*(14), 977–986.

13

	intensive therapy	conservative therapy
hypoglycemic episodes requiring assistance	62/100 patient years	19/100 patient years
hypoglycemic coma or seizure	16/100 patient years	5/100 patient years
hospitalizations for hypoglycemia	54 times in 40 patients	36 times in 27 patients
fatal MVA	1 (+ 1 passenger)	1

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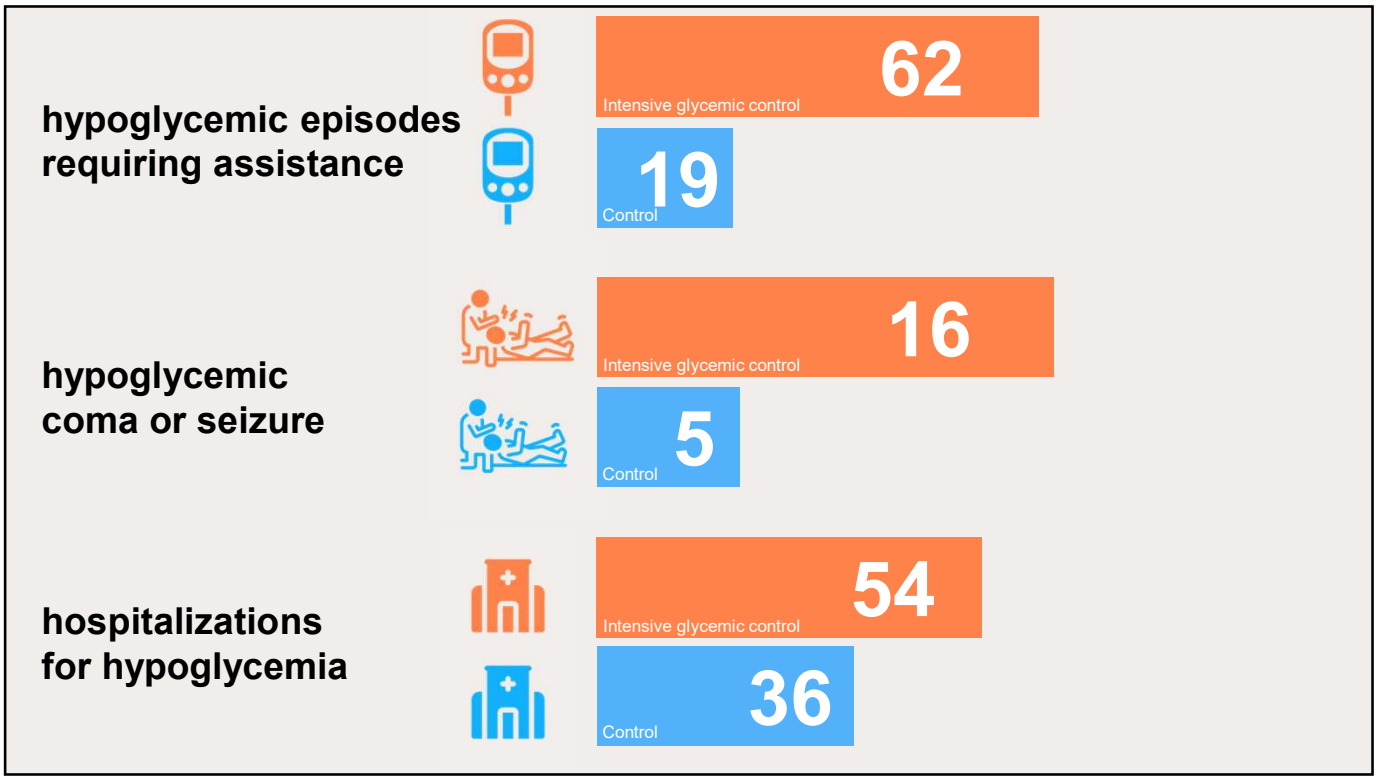
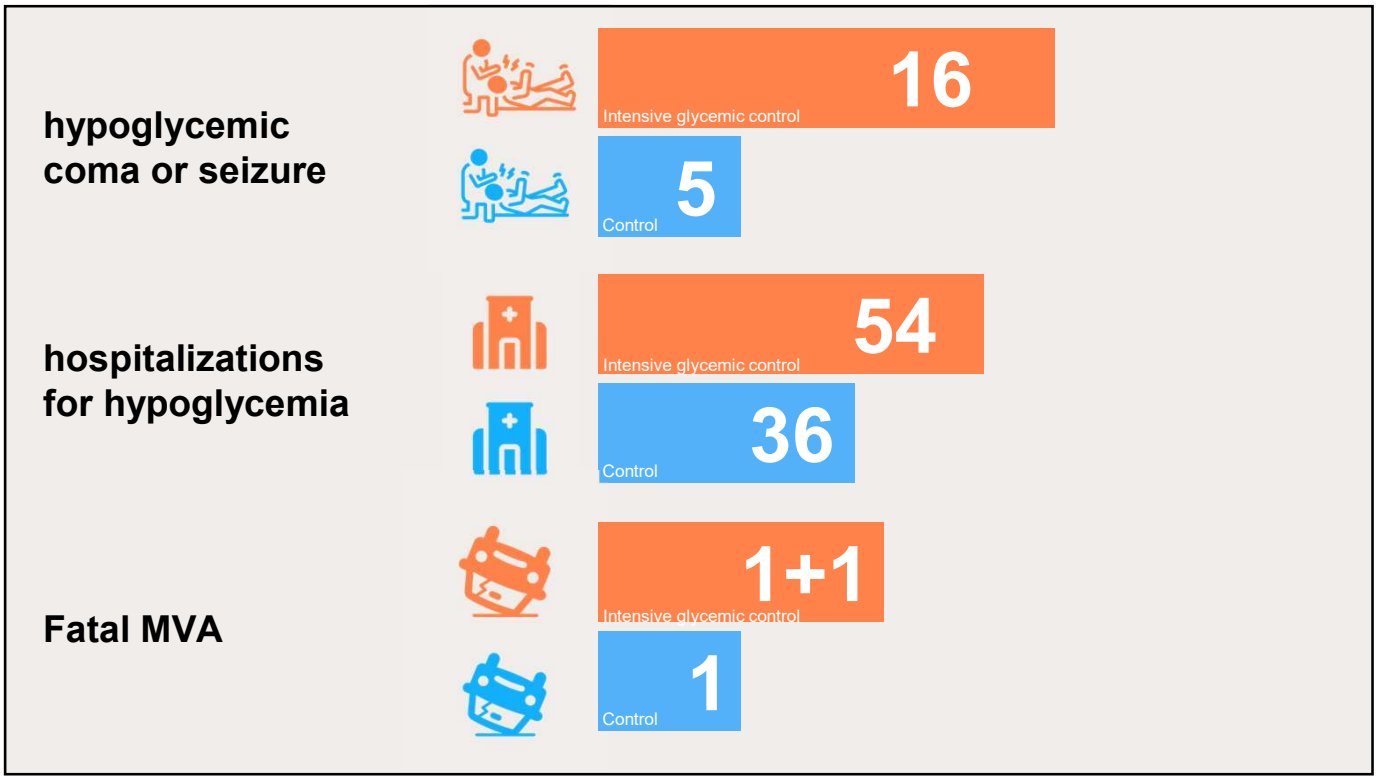

hypoglycemic episodes requiring assistance
62
Intensive glycemic control
19
Control
hypoglycemic coma or seizure
16
Intensive glycemic control
5
Control
hospitalizations for hypoglycemia
54
Intensive glycemic control
36
Control

15


hypoglycemic coma or seizure
16
Intensive glycemic control
5
Control
hospitalizations for hypoglycemia
54
Intensive glycemic control
36
Control
Fatal MVA
1+1
Intensive glycemic control
1
Control

16

DCCT long term follow up
27 years

Research

Original Investigation

Association Between 7 Years of Intensive Treatment of Type 1 Diabetes and Long-term Mortality

Writing Group for the DCCT/EDIC Research Group

Editorial page 35
Author Video Interview and JAMA Report Video at jama.com
Related article page 37
Supplemental content at jama.com

IMPORTANCE Whether mortality in type 1 diabetes mellitus is affected following intensive glycemic therapy has not been established.

OBJECTIVE To determine whether mortality differed between the original intensive and conventional treatment groups in the long-term follow-up of the Diabetes Control and Complications Trial (DCCT) cohort.

DESIGN, SETTING, AND PARTICIPANTS After the DCCT (1983-1993) ended, participants were followed up in a multisite (27 US and Canadian academic clinical centers) observational study (Epidemiology of Diabetes Control and Complications [EDIC]) until December 31, 2012. Participants were 1441 healthy volunteers with diabetes mellitus who, at baseline, were 13 to 39 years of age with 1 to 15 years of diabetes duration and no or early microvascular complications, and without hypertension, preexisting cardiovascular disease, or other potentially life-threatening disease.

INTERVENTIONS AND EXPOSURES During the clinical trial, participants were randomly assigned to receive intensive therapy (n = 711) aimed at achieving glycemia as close to the nondiabetic range as safely possible, or conventional therapy (n = 730) with the goal of avoiding symptomatic hypoglycemia and hyperglycemia. At the end of the DCCT, after a mean of 6.5 years, intensive therapy was taught and recommended to all participants and diabetes care was returned to personal physicians.

MAIN OUTCOMES AND MEASURES Total and cause-specific mortality was assessed through annual contact with family and friends and through records over 27 years' mean follow-up.

RESULTS Vital status was ascertained for 1429 (99.2%) participants. There were 107 deaths, 64 in the conventional and 43 in the intensive group. The absolute risk difference was −109 per 100 000 patient-years (95% CI, −218 to −1), with lower all-cause mortality risk in the intensive therapy group (hazard ratio [HR] = 0.67 [95% CI, 0.46-0.99]; $P = .045$). Primary causes of death were cardiovascular disease (24 deaths; 22.4%), cancer (21 deaths; 19.6%), acute diabetes complications (19 deaths; 17.8%), and accidents or suicide (18 deaths; 16.8%). Higher levels of glycated hemoglobin (HbA_{1c}) were associated with all-cause mortality (HR = 1.56 [95% CI, 1.35-1.81 per 10% relative increase in HbA_{1c}]; $P < .001$), as well as the development of albuminuria (HR = 2.20 [95% CI, 1.46-3.31]; $P < .001$).

CONCLUSIONS AND RELEVANCE After a mean of 27 years' follow-up of patients with type 1 diabetes, 6.5 years of initial intensive diabetes therapy was associated with a modestly lower all-cause mortality rate when compared with conventional therapy.

TRIAL REGISTRATION clinicaltrials.gov Identifiers: NCT00360815 and NCT00360893

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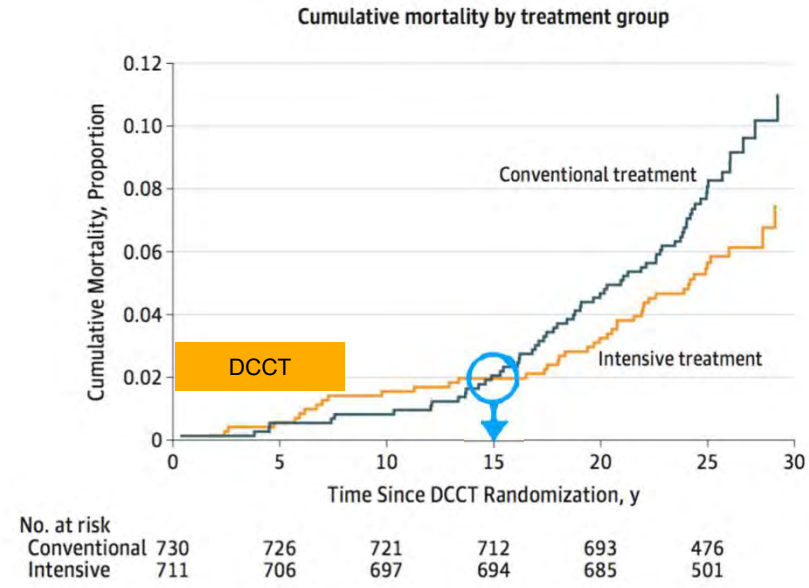

7 deaths due to diabetic kidney disease, 6 with conventional control

Orchard, T. J., Nathan, D. M., Zinman, B., Cleary, P., Brillon, D., Backlund, J.-Y. C., & Lachin, J. M. (2015). Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA*, *313*(1), 45–53.

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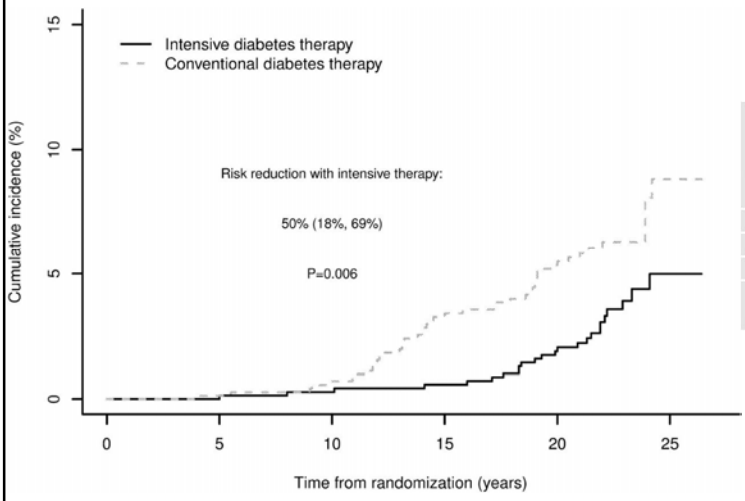
Incidence of GFR < 60



	n (events)		Relative risk	
	INT	CON	Risk reduction	*P*
Sustained estimated GFR <60 mL/min/1.73 m^2	24	46	50% (18–69%)	0.006
Estimated GFR <45 mL/min/1.73 m^2	24	39	40% (1–64%)	0.045
Estimated GFR <30 mL/min/1.73 m^2	13	23	44% (−9 to 72%)	0.088
ESRD	8	16	51% (−14 to 79%)	0.098
Combined outcome of estimated GFR <60 mL/min/1.73 m^2 or death	53	80	37% (10–55%)	0.011

De boer IH. Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):24-30.

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2008

A1c 6.4 vs 7.5

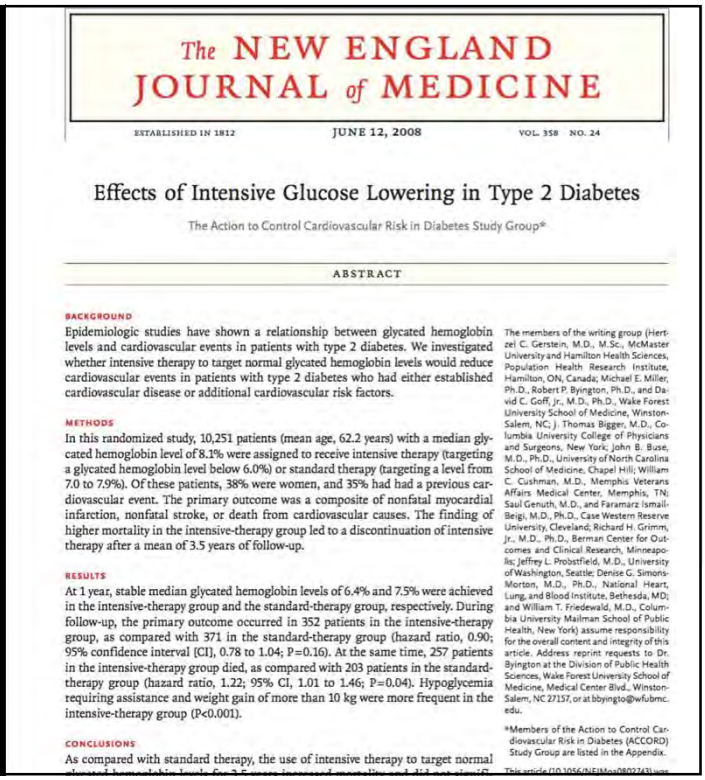
ACCORD study group

n=10,251

median follow-up 3.5 years

primary outcome:

- nonfatal myocardial infarction
- nonfatal stroke
- death from cardiovascular causes



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

ABSTRACT

BACKGROUND

Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

METHODS

In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up.

RESULTS

At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal

The members of the writing group (Hertzel C. Gerstein, M.D., M.Sc., McMaster University and Hamilton Health Sciences, Population Health Research Institute, Hamilton, ON, Canada; Michael E. Miller, Ph.D., Robert P. Byington, Ph.D., and David C. Goff, Jr., M.D., Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; J. Thomas Bigger, M.D., Columbia University College of Physicians and Surgeons, New York; John B. Buse, M.D., Ph.D., University of North Carolina School of Medicine, Chapel Hill; William C. Cushman, M.D., Memphis Veterans Affairs Medical Center, Memphis, TN; Saul Genuth, M.D., and Faramarz Ismail-Beigi, M.D., Ph.D., Case Western Reserve University, Cleveland; Richard H. Grimm, Jr., M.D., Ph.D., Berman Center for Outcomes and Clinical Research, Minneapolis; Jeffrey L. Probstfield, M.D., University of Washington, Seattle; Denise G. Simons-Morton, M.D., Ph.D., National Heart, Lung, and Blood Institute, Bethesda, MD; and William T. Friedewald, M.D., Columbia University Mailman School of Public Health, New York) assume responsibility for the overall content and integrity of this article. Address reprint requests to Dr. Byington at the Division of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, or at bbyingto@wfubmc.edu.

*Members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in the Appendix.

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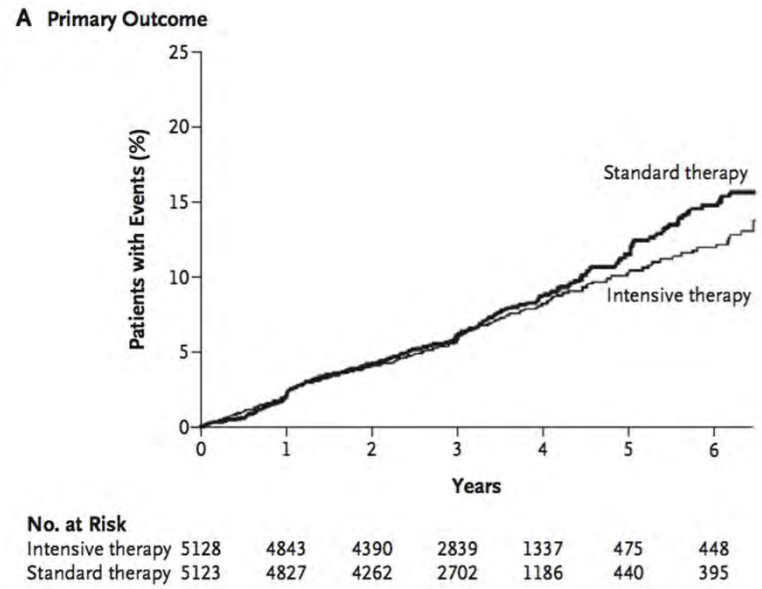
ACCORD
Primary outcome: MACE
- CV Death
- nonfatal MI
- nonfatal stroke



Action to Control Cardiovascular Risk in Diabetes Study Group. (2008). Effects of intensive glucose lowering in type 2 diabetes. *The New England Journal of Medicine*, *358*(24), 2545–2559.

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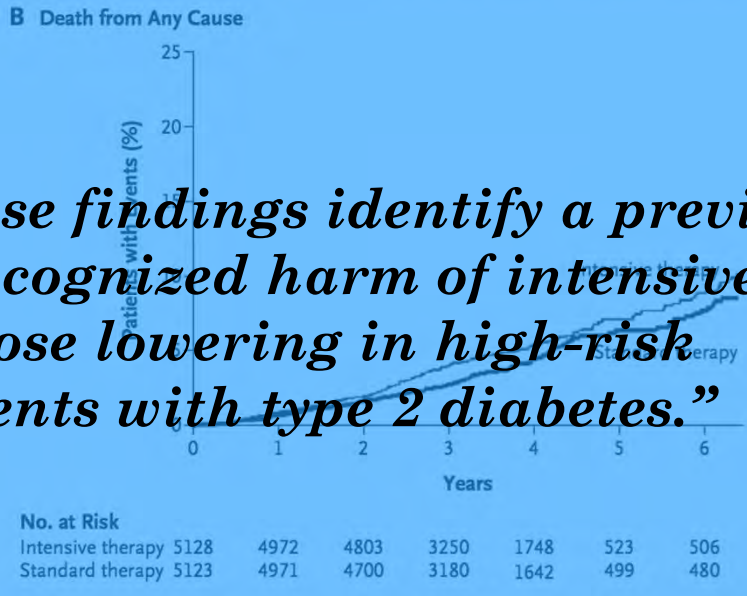
hazard ratio, 1.22; 95% CI 1.01 to 1.46; P=0.04



"These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes."

Action to Control Cardiovascular Risk in Diabetes Study Group. (2008). Effects of intensive glucose lowering in type 2 diabetes. *The New England Journal of Medicine*, *358*(24), 2545–2559.

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microvascular outcomes of ACCORD

NO DIFFERENCE	POSITIVE REDUCTION
microvascular complications	microalbuminuria HR = 0.81, CI 0.70-0.94; p = 0.005; NNT = 44
renal failure (RRT, Cr > 3.3 mg/dl) HR 0.95, p = 0.713	macroalbuminuria HR = 0.68, CI 0.54-0.86; p = 0.001; NNT = 82

Ismail-beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010;376(9739):419-30.

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Glycemic control

Some is good…a lot, not so clear

Blood pressure control

24

UKPDS randomized 1148 patients to one of two arms:

<180/105		<150/85
154/87	Achieved blood pressure	144/82

Reduced risk of

- any diabetes-related endpoint 24% p=0.005
- microvascular endpoint 37% p=0.009
- stroke 44% p=0.013

r and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* , *317*(7160), 703–713.

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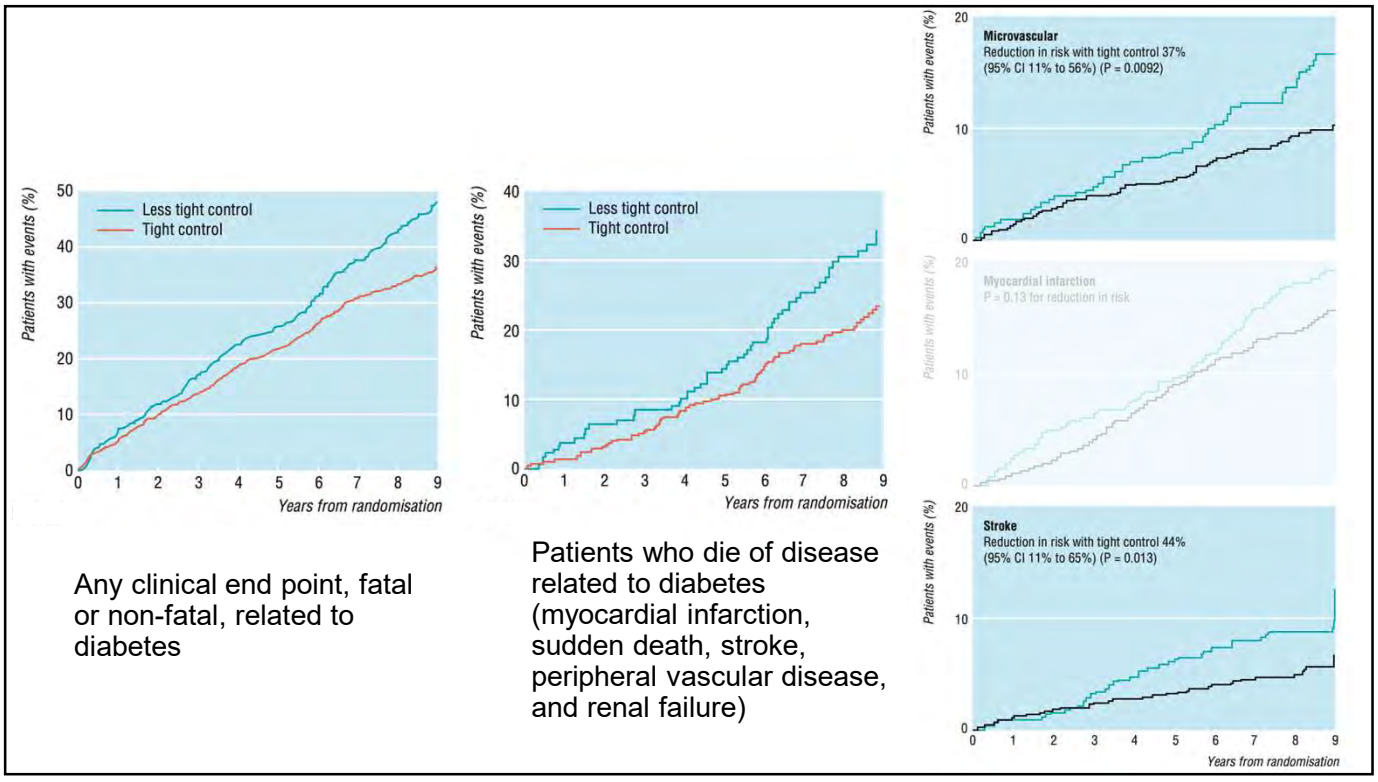

Any clinical end point, fatal or non-fatal, related to diabetes

Patients who die of disease related to diabetes (myocardial infarction, sudden death, stroke, peripheral vascular disease, and renal failure)

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ACCORD

Type 2 diabetics

Target a SBP < 120 vs. < 140

Mean follow-up: 5 years

Primary outcome: MACE

- CV death
- nonfatal MI
- nonfatal stroke

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ABSTRACT

BACKGROUND

There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events.

METHODS

A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

RESULTS

After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P=0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001).

CONCLUSIONS

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)

The members of the Writing Group (William C. Cushman, M.D., Gregory W. Evans, M.A., Robert P. Byington, Ph.D., David C. Goff, Jr., M.D., Ph.D., Richard H. Grimm, Jr., M.D., Ph.D., Jeffrey A. Cutler, M.D., M.P.H., Denise G. Simons-Morton, M.D., Ph.D., Jan N. Basile, M.D., Marshall A. Corson, M.D., Jeffrey L. Probstfield, M.D., Lois Katz, M.D., Kevin A. Peterson, M.D., William T. Friedewald, M.D., John B. Buse, M.D., Ph.D., J. Thomas Bigger, M.D., Hertzel C. Gerstein, M.D., and Faramarz Ismail-Beigi, M.D., Ph.D.) assume responsibility for the integrity of the article. Address reprint requests to Dr. Cushman at the Preventive Medicine Section (111Q), Veterans Affairs Medical Center, 1030 Jefferson Ave., Memphis, TN 38104, or at william.cushman@va.gov.

*The members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in Section 1 in Supplementary Appendix 1, available with the full text of this article at NEJM.org. The affiliations of the members of the Writing Group are listed in the Appendix.

This article (10.1056/NEJMoa1001286) was published on March 14, 2010, at NEJM.org.

N Engl J Med 2010;362:1575-85.

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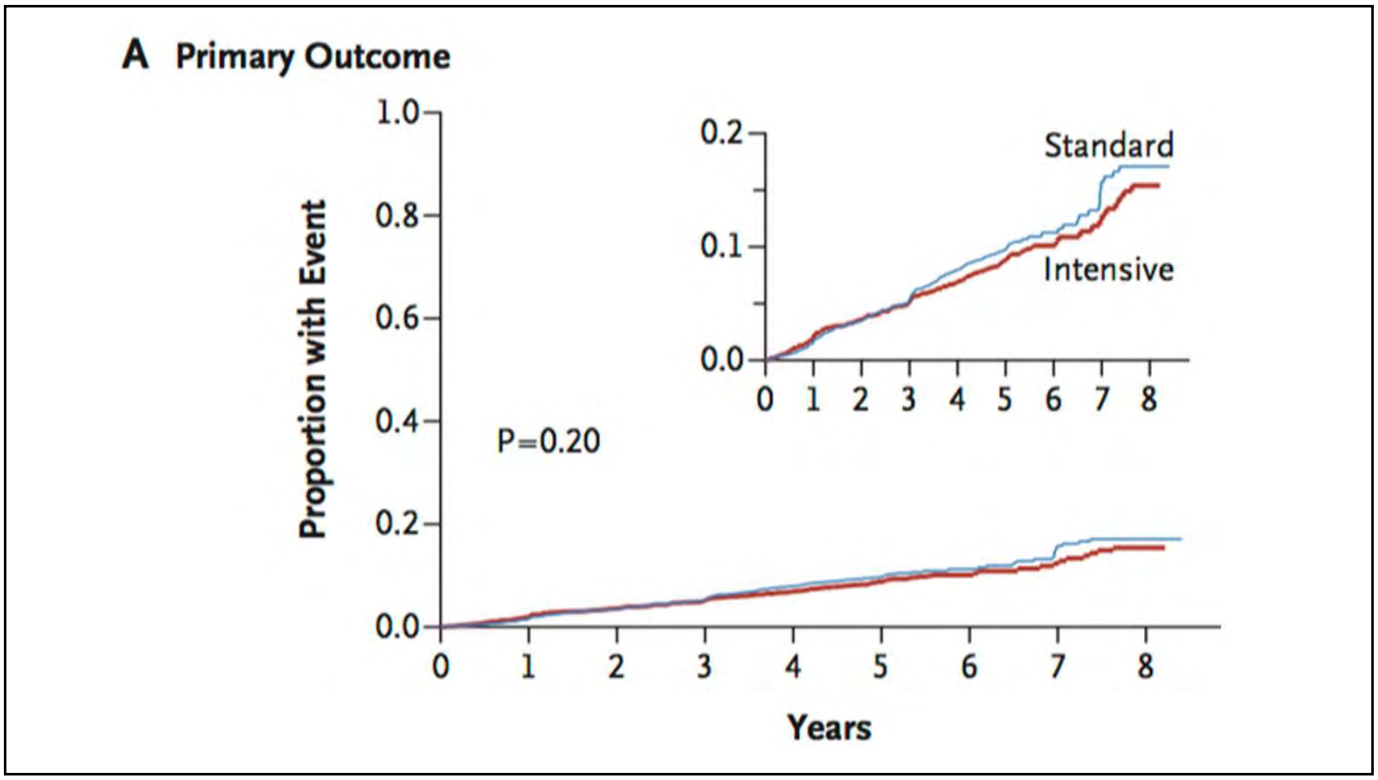

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Adverse laboratory measures — no. (%)			
Potassium <3.2 mmol/liter	49 (2.1)	27 (1.1)	0.01
Potassium >5.9 mmol/liter	73 (3.1)	72 (3.0)	0.93
Elevation in serum creatinine			
>1.5 mg/dl in men	304 (12.9)	199 (8.4)	<0.001
>1.3 mg/dl in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m²	99 (4.2)	52 (2.2)	<0.001

Twice as much hypokalemia

50% more AKI

Twice as much progression to CKD stage 4

29

Glycemic control

Some is good…a lot, not so clear

Blood pressure control

Some is good…a lot, not so clear

30

Glycemic control

Some is good…a lot, not so clear

Blood pressure control

Some is good…a lot, not so clear

RAAS inhibition

31

2001

IDNT

Irbesartan vs Amlodipine vs Placebo

n=1715 type 2 DM

Follow-up 2.6 years

Primary outcome: doubling of serum creatinine, ESRD or death

The New England Journal of Medicine

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VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D., MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S., AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*

ABSTRACT

Background It is unknown whether either the angiotensin-II–receptor blocker irbesartan or the calcium-channel blocker amlodipine slows the progression of nephropathy in patients with type 2 diabetes independently of its capacity to lower the systemic blood pressure.

Methods We randomly assigned 1715 hypertensive patients with nephropathy due to type 2 diabetes to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. The target blood pressure was 135/85 mm Hg or less in all groups. We compared the groups with regard to the time to the primary composite end point of a doubling of the base-line serum creatinine concentration, the development of end-stage renal disease, or death from any cause. We also compared them with regard to the time to a secondary, cardiovascular composite end point.

Results The mean duration of follow-up was 2.6 years. Treatment with irbesartan was associated with a risk of the primary composite end point that was 20 percent lower than that in the placebo group (P=0.02) and 23 percent lower than that in the amlodipine group (P=0.006). The risk of a doubling of the serum creatinine concentration was 33 percent lower in the irbesartan group than in the placebo group (P=0.003) and 37 percent lower in the irbesartan group than in the amlodipine group (P<0.001). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23 percent lower than that in both other groups (P=0.07 for both comparisons). These differences were not explained by differences in the blood pressures that were achieved. The serum creatinine concentration increased 24 percent more slowly in the irbesartan group than in the placebo group (P=0.008) and 21 percent more slowly than in the amlodipine group (P=0.02). There were no significant differences in the rates of death from any cause or in the cardiovascular composite end point.

Conclusions The angiotensin-II–receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood

DIABETES mellitus is increasing in prevalence worldwide and is currently estimated to affect more than 6.5 percent of the population of the United States.[1] Diabetes is the most common cause of end-stage renal disease in this country, accounting for 40 percent of cases.[2] Although the inhibition of the effects of angiotensin II has a beneficial effect in patients with nephropathy caused by type 1 diabetes,[3] no published study with definitive renal outcomes has addressed the issue of renoprotection in patients with type 2 diabetes — a population that differs substantially from patients with type 1 diabetes in terms of demographic characteristics, metabolic features, and potential mechanisms of glomerular disease.[4] Several studies have addressed the positive effects of specific antihypertensive agents on cardiovascular morbidity and mortality within this population.[5-8]

We undertook the Irbesartan Diabetic Nephropathy Trial to determine whether the use of an angiotensin-II–receptor blocker or a calcium-channel blocker would provide protection against the progression of nephropathy due to type 2 diabetes beyond that attributable to the lowering of the blood pressure. We also compared the groups assigned to different therapeutic regimens in terms of overall mortality and the rate of cardiovascular events.

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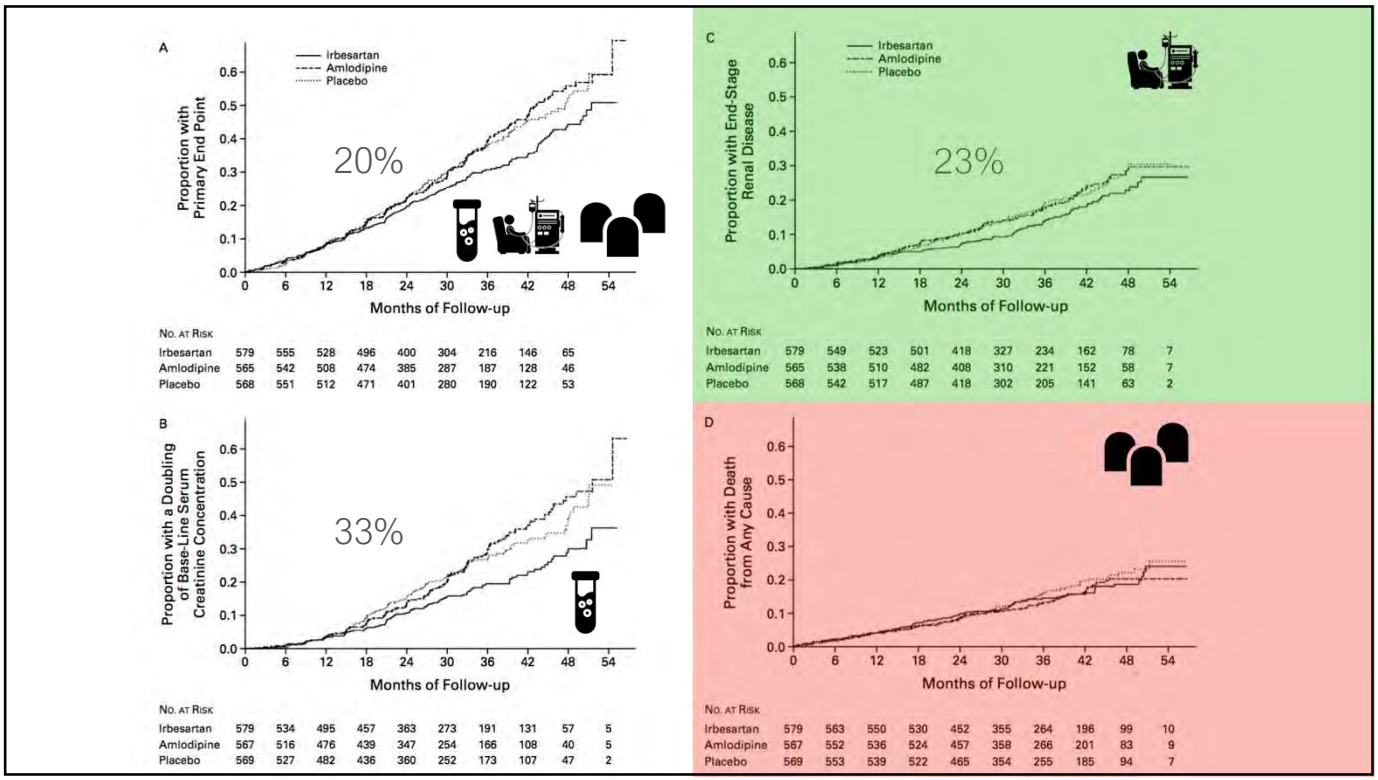

A
Irbesartan
Amlodipine
Placebo
Proportion with Primary End Point
20%
Months of Follow-up
No. at Risk
Irbesartan 579 555 528 496 400 304 216 146 65
Amlodipine 565 542 508 474 385 287 187 128 46
Placebo 568 551 512 471 401 280 190 122 53
B
Proportion with a Doubling of Base-Line Serum Creatinine Concentration
33%
Months of Follow-up
No. at Risk
Irbesartan 579 534 495 457 363 273 191 131 57 5
Amlodipine 567 516 476 439 347 254 166 108 40 5
Placebo 569 527 482 436 360 252 173 107 47 2
C
Irbesartan
Amlodipine
Placebo
Proportion with End-Stage Renal Disease
23%
Months of Follow-up
No. at Risk
Irbesartan 579 549 523 501 418 327 234 162 78 7
Amlodipine 565 538 510 482 408 310 221 152 58 7
Placebo 568 542 517 487 418 302 205 141 63 2
D
Proportion with Death from Any Cause
Months of Follow-up
No. at Risk
Irbesartan 579 563 550 530 452 355 264 196 99 10
Amlodipine 567 552 536 524 457 358 266 201 83 9
Placebo 569 553 539 522 465 354 255 185 94 7

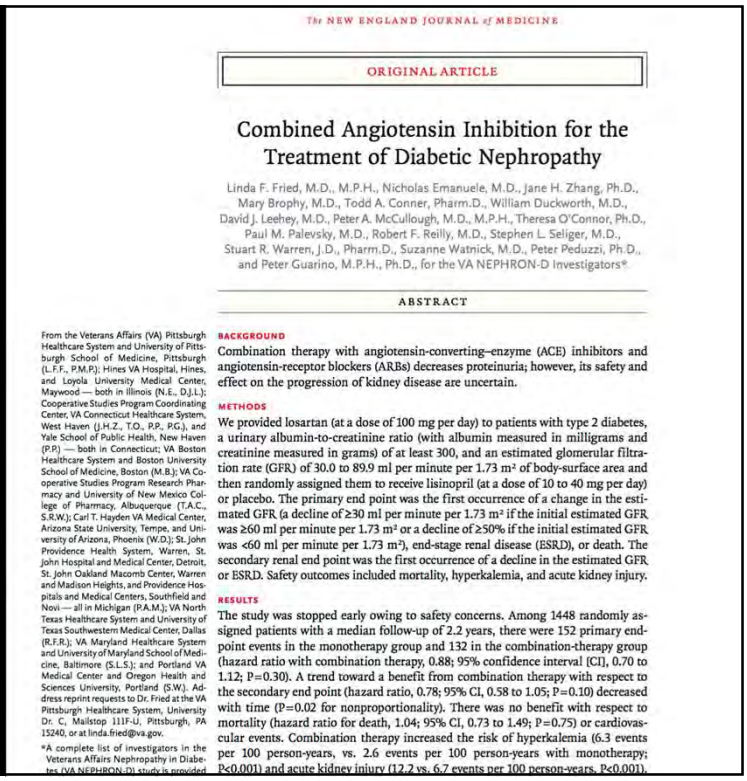
33

34

2013

VA NEPHRON-D

Losartan + placebo vs
Losartan + lisinopril
n=1448 type 2 DM
median follow-up 2.2 years
primary outcome: decline in eGFR of 30 mL/min or 50%, ESRD, death



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Linda F. Fried, M.D., M.P.H., Nicholas Emanuele, M.D., Jane H. Zhang, Ph.D., Mary Brophy, M.D., Todd A. Conner, Pharm.D., William Duckworth, M.D., David J. Leehey, M.D., Peter A. McCullough, M.D., M.P.H., Theresa O'Connor, Ph.D., Paul M. Palevsky, M.D., Robert F. Reilly, M.D., Stephen L. Seliger, M.D., Stuart R. Warren, J.D., Pharm.D., Suzanne Watnick, M.D., Peter Peduzzi, Ph.D., and Peter Guarino, M.P.H., Ph.D., for the VA NEPHRON-D Investigators*

From the Veterans Affairs (VA) Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh (L.F.F., P.M.P.); Hines VA Hospital, Hines, and Loyola University Medical Center, Maywood — both in Illinois (N.E., D.J.L.); Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven (J.H.Z., T.O., P.P., P.G.), and Yale School of Public Health, New Haven (P.P.) — both in Connecticut; VA Boston Healthcare System and Boston University School of Medicine, Boston (M.B.); VA Cooperative Studies Program Research Pharmacy and University of New Mexico College of Pharmacy, Albuquerque (T.A.C., S.R.W.); Carl T. Hayden VA Medical Center, Arizona State University, Tempe, and University of Arizona, Phoenix (W.D.); St. John Providence Health System, Warren, St. John Hospital and Medical Center, Detroit, St. John Oakland Macomb Center, Warren and Madison Heights, and Providence Hospitals and Medical Centers, Southfield and Novi — all in Michigan (P.A.M.); VA North Texas Healthcare System and University of Texas Southwestern Medical Center, Dallas (R.F.R.); VA Maryland Healthcare System and University of Maryland School of Medicine, Baltimore (S.L.S.); and Portland VA Medical Center and Oregon Health and Sciences University, Portland (S.W.). Address reprint requests to Dr. Fried at the VA Pittsburgh Healthcare System, University Dr. C, Mailstop 111F-U, Pittsburgh, PA 15240, or at linda.fried@va.gov.

*A complete list of investigators in the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study is provided

ABSTRACT

BACKGROUND

Combination therapy with angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria; however, its safety and effect on the progression of kidney disease are uncertain.

METHODS

We provided losartan (at a dose of 100 mg per day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0 to 89.9 ml per minute per 1.73 m² of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg per day) or placebo. The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m² if the initial estimated GFR was ≥60 ml per minute per 1.73 m² or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m²), end-stage renal disease (ESRD), or death. The secondary renal end point was the first occurrence of a decline in the estimated GFR or ESRD. Safety outcomes included mortality, hyperkalemia, and acute kidney injury.

RESULTS

The study was stopped early owing to safety concerns. Among 1448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end-point events in the monotherapy group and 132 in the combination-therapy group (hazard ratio with combination therapy, 0.88; 95% confidence interval [CI], 0.70 to 1.12; P=0.30). A trend toward a benefit from combination therapy with respect to the secondary end point (hazard ratio, 0.78; 95% CI, 0.58 to 1.05; P=0.10) decreased with time (P=0.02 for nonproportionality). There was no benefit with respect to mortality (hazard ratio for death, 1.04; 95% CI, 0.73 to 1.49; P=0.75) or cardiovascular events. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years, vs. 2.6 events per 100 person-years with monotherapy; P<0.001) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, P<0.001).

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Stopped early due to excess hyperkalemia (2.8x) and acute kidney injury (1.7x)

Table 3. Safety Outcomes.*

Outcome	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)	Hazard Ratio with Losartan plus Lisinopril (95% CI)	P Value
Patients with serious adverse events — no. (%)	380 (52.5)	416 (57.5)	NA	0.06
No. of serious adverse events	1274	1539†	NA	
Attribution of serious adverse events to study drugs — no. of events (%)†				0.049
Not attributed	1159 (91.0)	1365 (88.7)	NA	
Possibly attributed	104 (8.2)	146 (9.5)	NA	
Attributed	11 (0.9)	27 (1.8)	NA	
Acute kidney injury — no. of patients (%)	80 (11.0)	130 (18.0)	1.7 (1.3–2.2)	<0.001
Hyperkalemia — no. of patients (%)	32 (4.4)	72 (9.9)	2.8 (1.8–4.3)	<0.001

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Glycemic control

Some is good…a lot, not so much

Blood pressure control

Some is good…a lot, not so much

RAAS inhibition

Some is good…a lot, not so much

37

1990's	2000's	2020's
Discovery	Roll back	What's next
Blood Sugar	Not < 6.5	SGLT2i
A1c 7.0 > 7.9 👍	*A1c 6.4 vs 7.5* ☠	GLP-1ra
BP Control	Not < 120/70	
144 > 154 👍	*120 vs 140* ☠	MRA
RAASi	No ACEi+ARB	
ACEi or ARB 👍	*ACEi and ARB* ☠	

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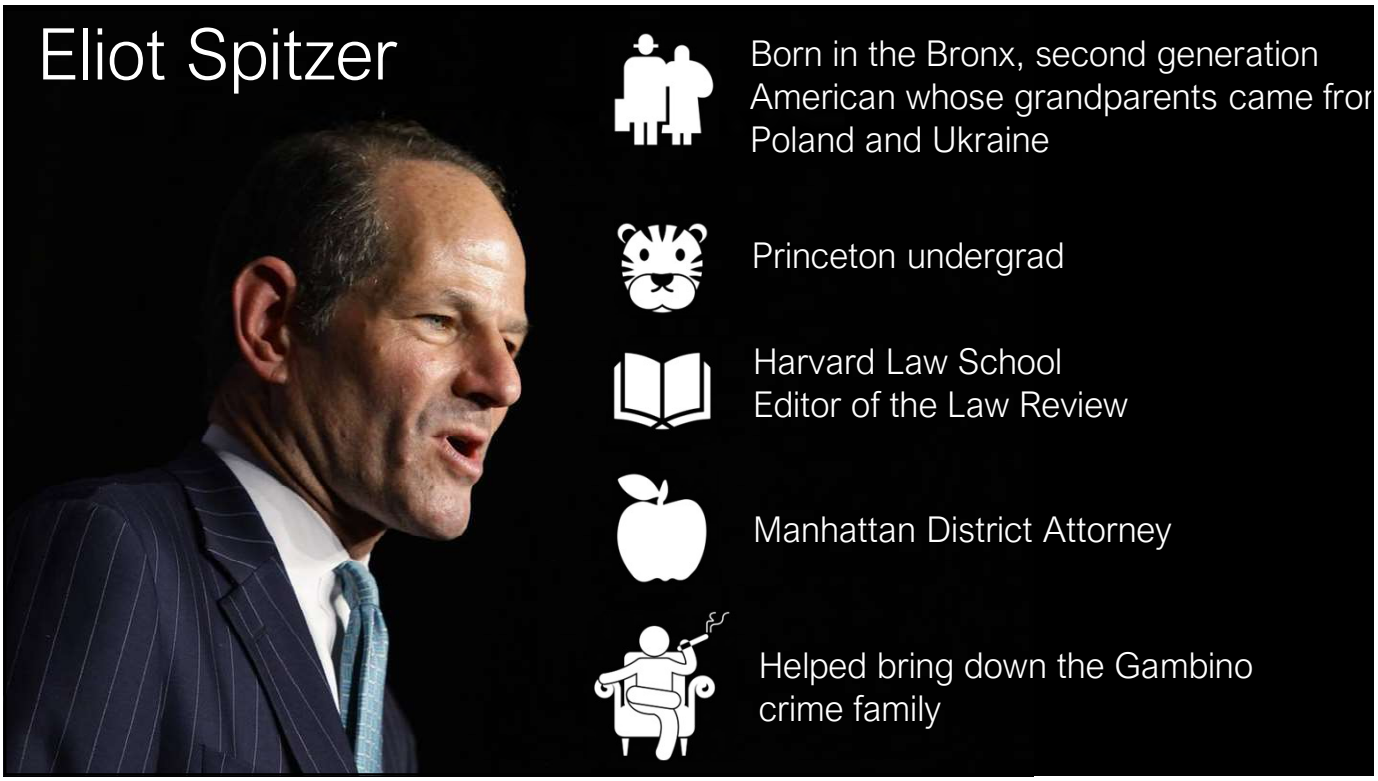
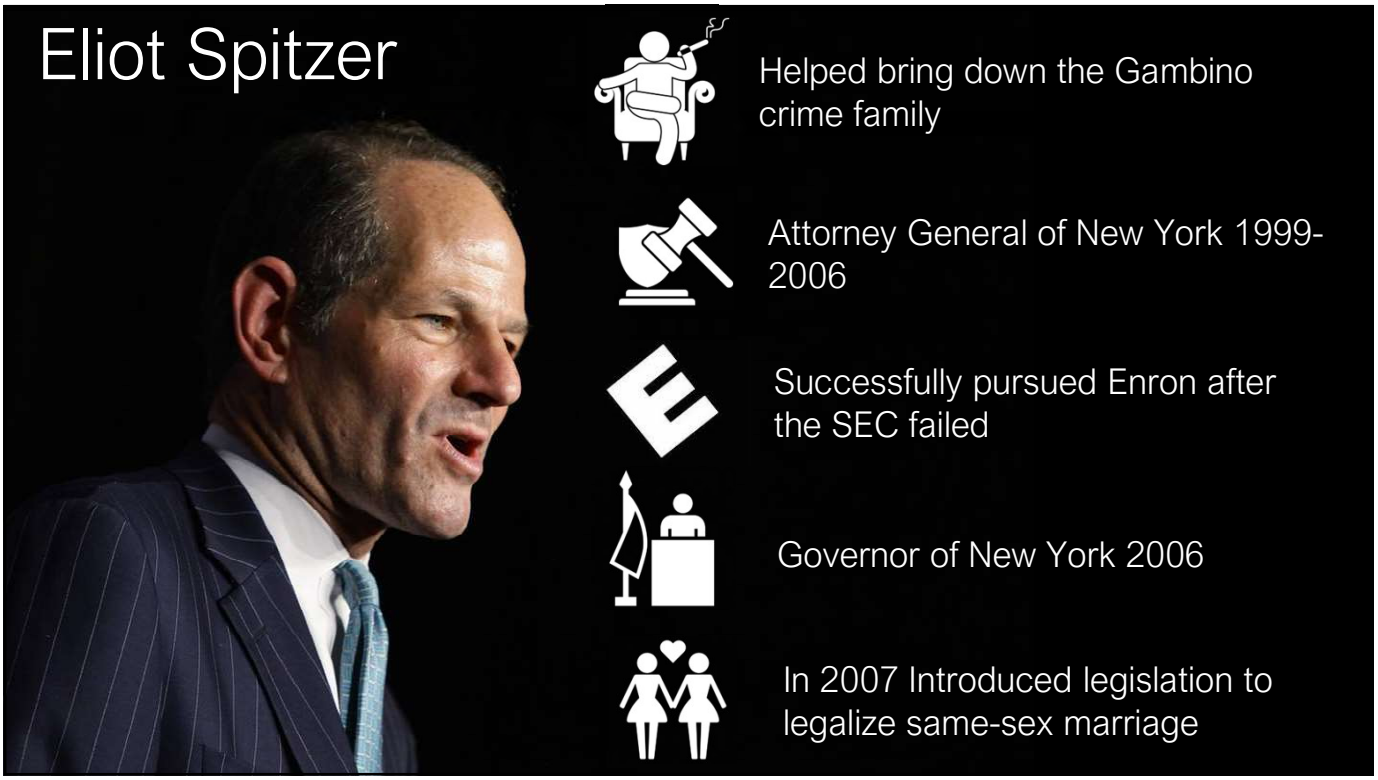
And that is without #Flozins

40


Eliot Spitzer
Born in the Bronx, second generation American whose grandparents came fror Poland and Ukraine
Princeton undergrad
Harvard Law School
Editor of the Law Review
Manhattan District Attorney
Helped bring down the Gambino crime family

41


Eliot Spitzer
Helped bring down the Gambino crime family
Attorney General of New York 1999-2006
Successfully pursued Enron after the SEC failed
Governor of New York 2006
In 2007 Introduced legislation to legalize same-sex marriage

42

43

And he was gone…

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Let's go back to 2004, as attorney general

GlaxoSmithKline

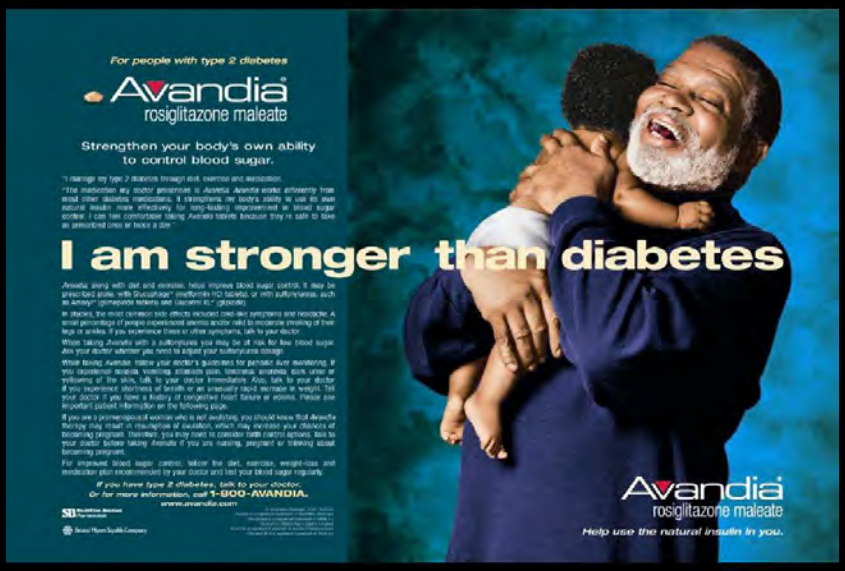
GSK was suppressing studies showing decreased effectiveness and an increased risk of suicide in young people

45

$2.5 million and release all clinical trial results

46

FDA 1999



Bristol Myers Squibb®

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Fluid retention and heart failure known problems with the glitazones

rosiglitazone

LDL ↑18%

Acute MI
HR 1.8
(0.9-3.6)

That was what was known in the published data…

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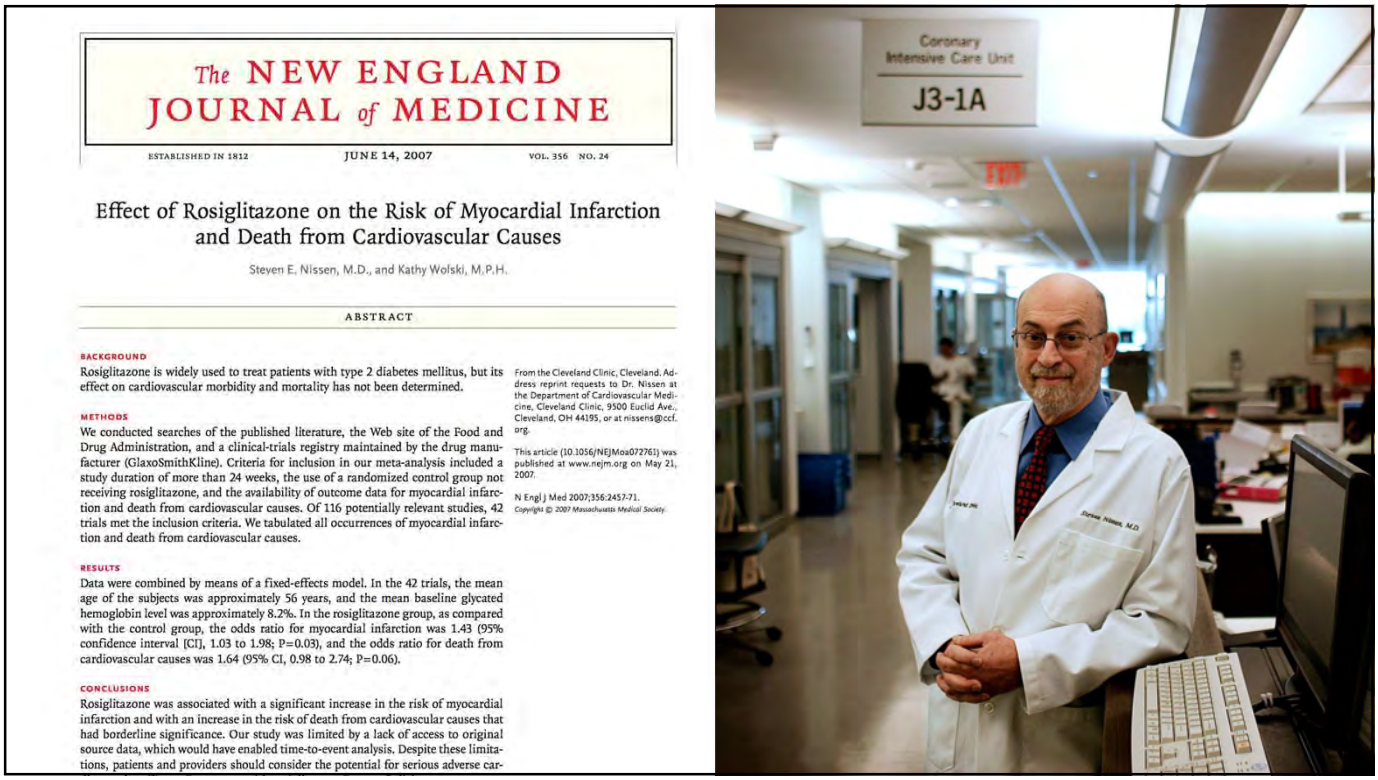

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse car-

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ABSTRACT

BACKGROUND

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

tions, patients and providers should consider the potential for serious adverse car-

June 14, 2007

Acute MI
HR 1.43
(1.03-1.98)

CV Death
HR 1.64
(0.98-2.74)

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BUSINESS DAY

Glaxo Agrees to Pay $3 Billion in Fraud Settlement

By KATIE THOMAS and MICHAEL S. SCHMIDT JULY 2, 2012

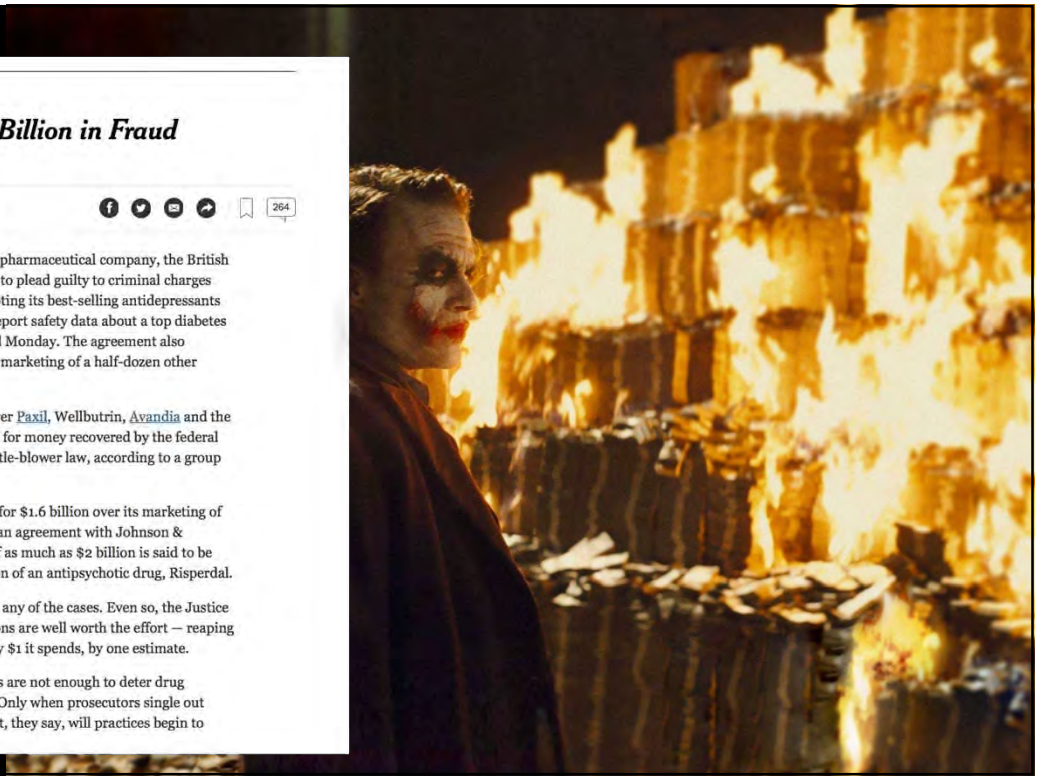
In the largest settlement involving a pharmaceutical company, the British drugmaker GlaxoSmithKline agreed to plead guilty to criminal charges and pay $3 billion in fines for promoting its best-selling antidepressants for unapproved uses and failing to report safety data about a top diabetes drug, federal prosecutors announced Monday. The agreement also includes civil penalties for improper marketing of a half-dozen other drugs.

The fine against GlaxoSmithKline over Paxil, Wellbutrin, Avandia and the other drugs makes this year a record for money recovered by the federal government under its so-called whistle-blower law, according to a group that tracks such numbers.

In May, Abbott Laboratories settled for $1.6 billion over its marketing of the antiseizure drug Depakote. And an agreement with Johnson & Johnson that could result in a fine of as much as $2 billion is said to be imminent over its off-label promotion of an antipsychotic drug, Risperdal.

No individuals have been charged in any of the cases. Even so, the Justice Department contends the prosecutions are well worth the effort — reaping more than $15 in recoveries for every $1 it spends, by one estimate.

But critics argue that even large fines are not enough to deter drug companies from unlawful behavior. Only when prosecutors single out individual executives for punishment, they say, will practices begin to change.



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Before 2009
After 2009
A1c
and
Cardiac
Safety
FDA
U.S. Department of Health and Human Services
FDA Guidance: All new anti-diabetic drugs needed to show no excess cardiovascular risk

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Rosiglitazone
safe
Alogliptin
safe
Saxagliptin
*safe
Exanatide
safe
Degludec
safe
Pioglitazone
safe
*Patients in the saxagliptin group had higher hospitalization for heart failure (3.5% vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; P=0.007)

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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 L3-024, Box 17, Toronto, ONT M5T 3L9, Canada, or at zinman@lunenfeld.ca.

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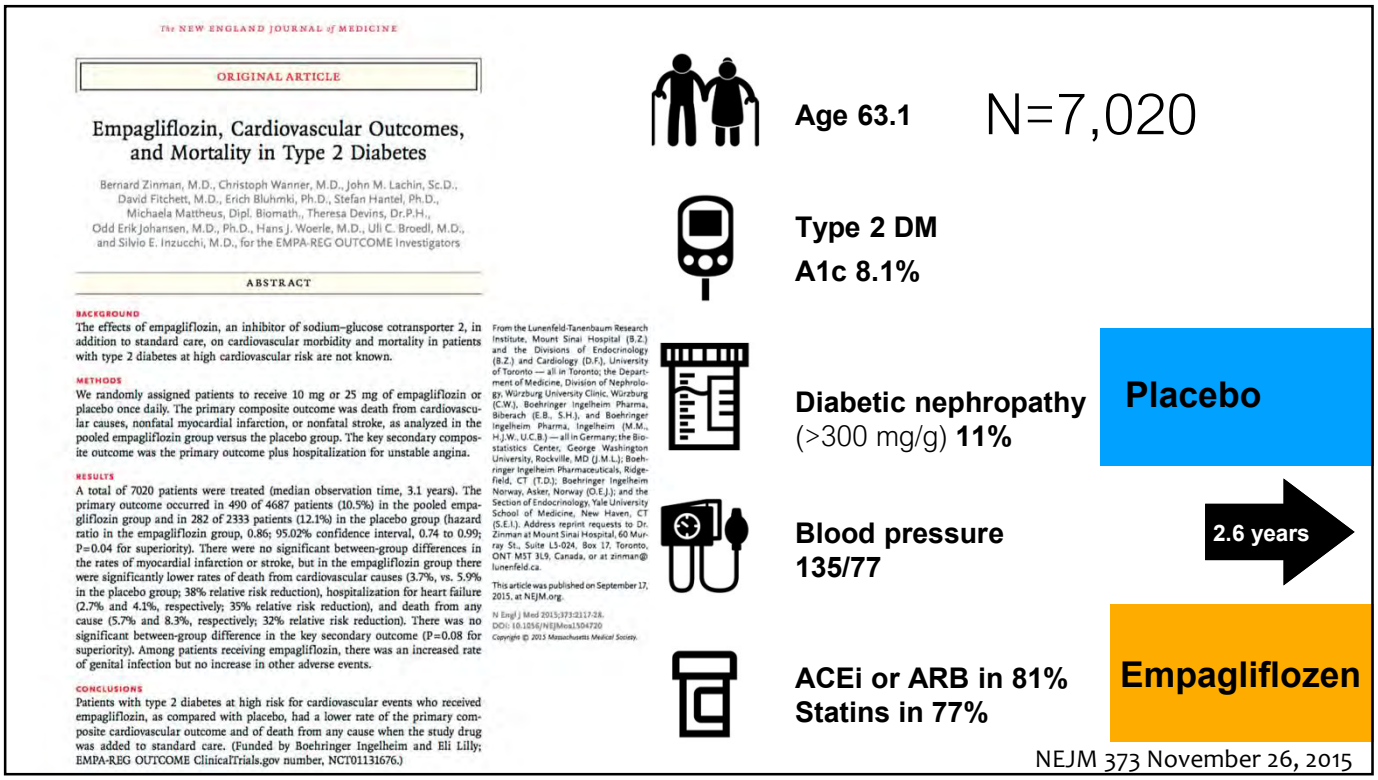

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DOI: 10.1056/NEJMoa1504720
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Age 63.1 N=7,020

Type 2 DM
A1c 8.1%

Diabetic nephropathy (>300 mg/g) **11%**

Blood pressure 135/77

ACEi or ARB in 81%
Statins in 77%

Placebo

2.6 years

Empagliflozen

NEJM 373 November 26, 2015

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EMPA-REG outcomes

Age 63.1

N=7,020

Type 2 DM
A1c 8.1%

Diabetic nephropathy
(>300 mg/g) **11%**

Blood pressure
135/77

ACEi or ARB in 81%
Statins in 77%

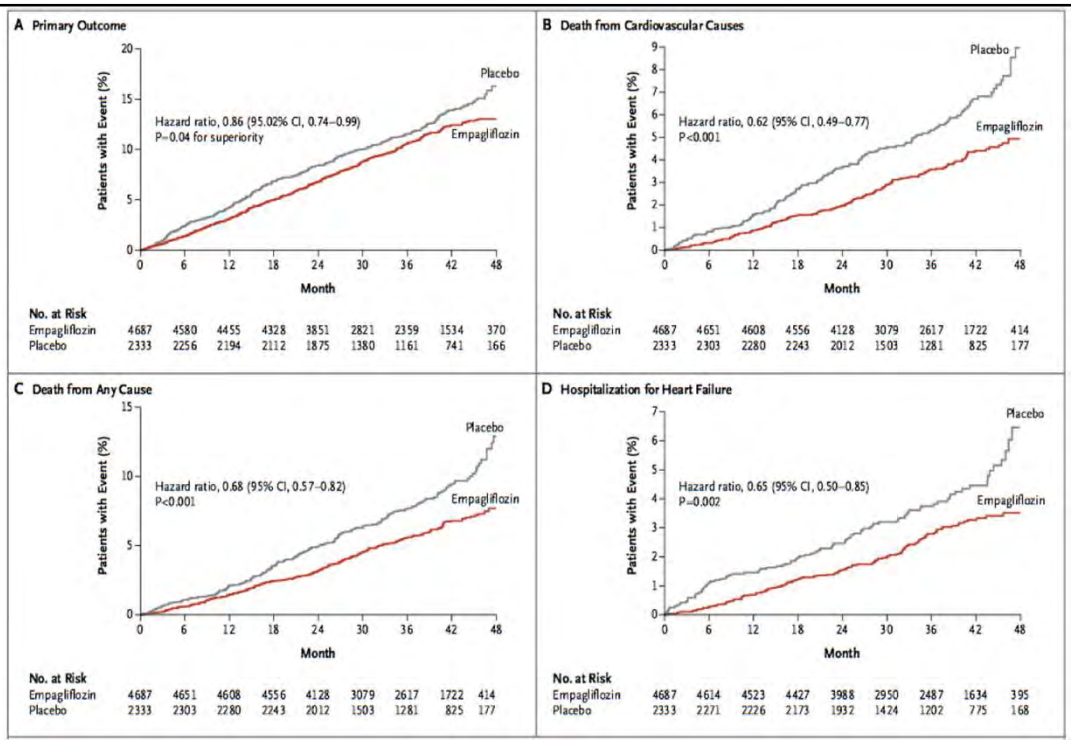
CV Death
Non-fatal MI
Non-fatal stroke

Total mortality

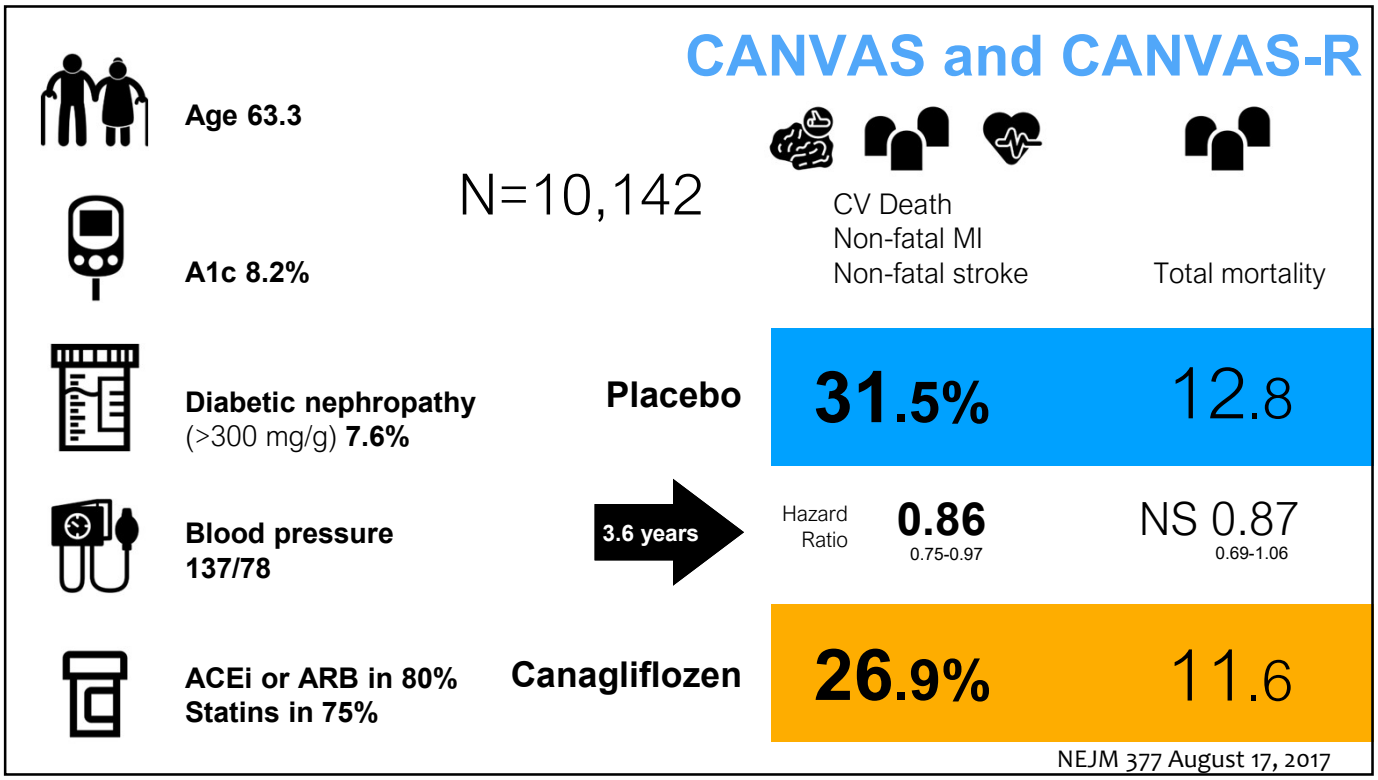
	CV Death, Non-fatal MI, Non-fatal stroke	Total mortality
Placebo	**12.1%**	**8.3%**
2.6 years	Hazard Ratio 0.86 P<0.001	0.68 P<0.001
Empagliflozen	**10.5%**	**5.7%**

NEJM 373 November 26, 2015

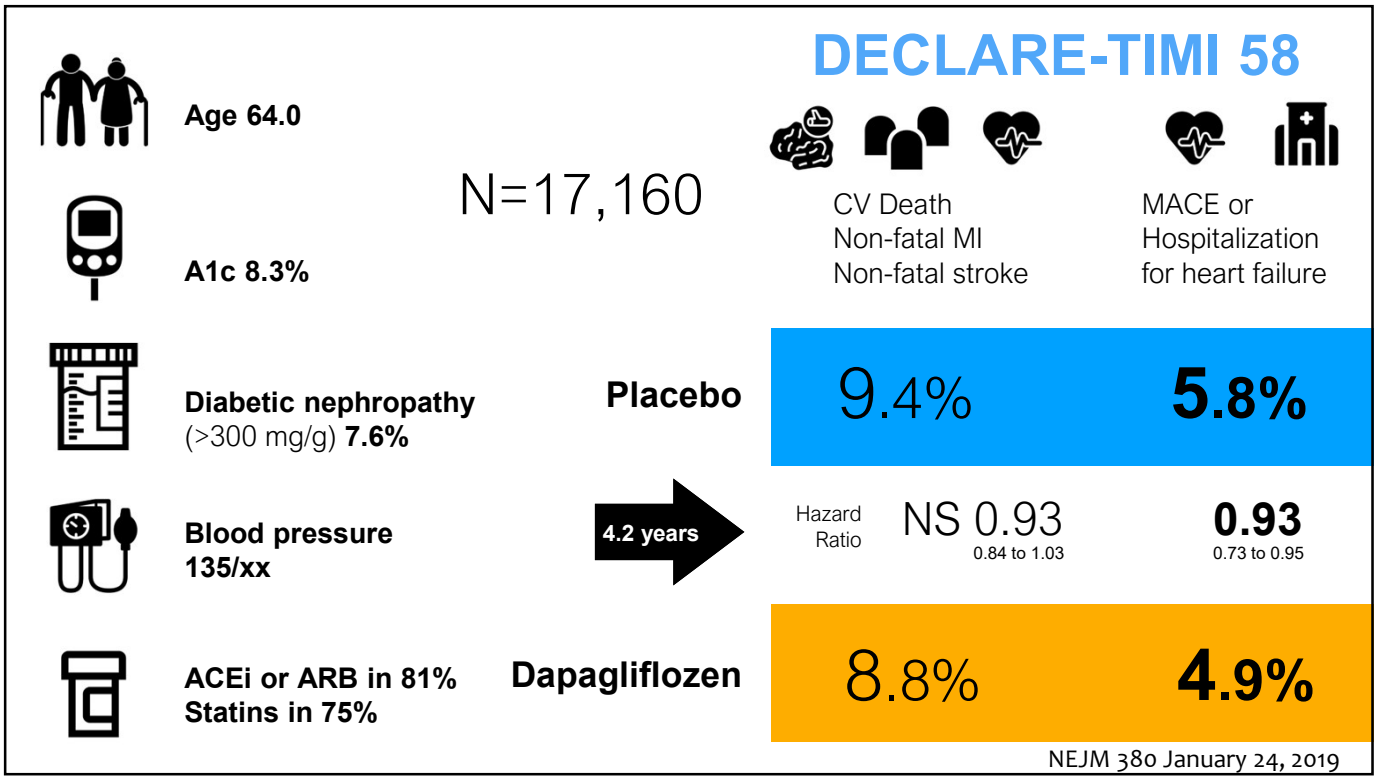
57



58


CANVAS and CANVAS-R
Age 63.3
A1c 8.2%
N=10,142
CV Death
Non-fatal MI
Non-fatal stroke
Total mortality
Diabetic nephropathy
(>300 mg/g) 7.6%
Placebo
31.5%
12.8
Blood pressure
137/78
3.6 years
Hazard Ratio
0.86
0.75-0.97
NS 0.87
0.69-1.06
ACEi or ARB in 80%
Statins in 75%
Canagliflozen
26.9%
11.6
NEJM 377 August 17, 2017

59


DECLARE-TIMI 58
Age 64.0
A1c 8.3%
N=17,160
CV Death
Non-fatal MI
Non-fatal stroke
MACE or
Hospitalization
for heart failure
Diabetic nephropathy
(>300 mg/g) 7.6%
Placebo
9.4%
5.8%
Blood pressure
135/xx
4.2 years
Hazard Ratio
NS 0.93
0.84 to 1.03
0.93
0.73 to 0.95
ACEi or ARB in 81%
Statins in 75%
Dapagliflozen
8.8%
4.9%
NEJM 380 January 24, 2019

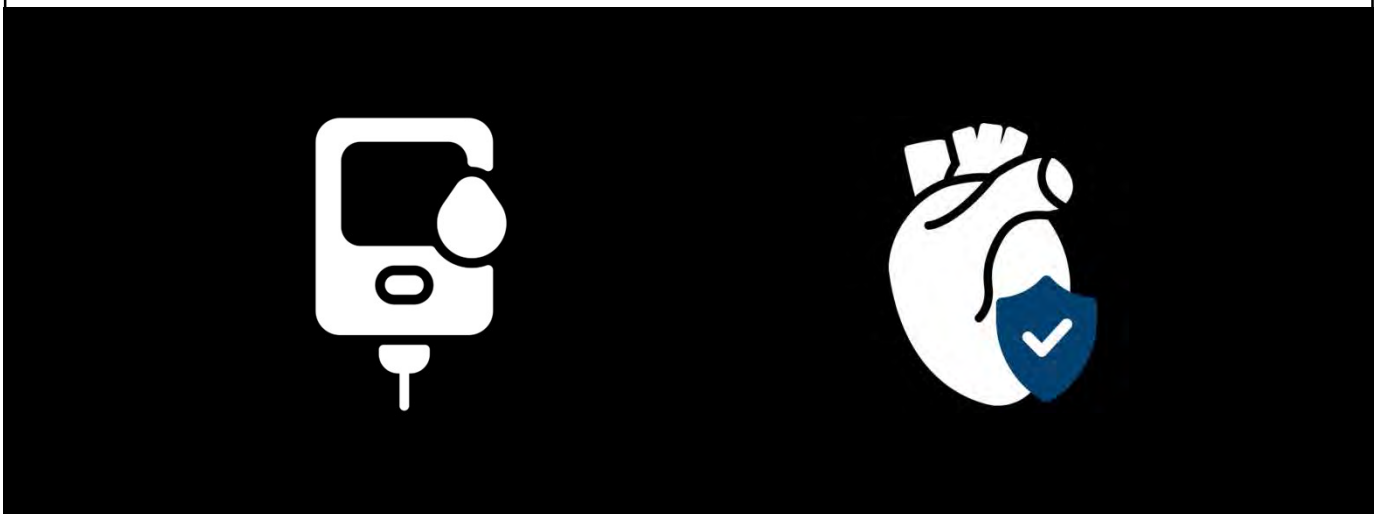
60

All these studies look the same because they are the same. They were all designed in cooperation with the FDA to answer the same question, "If we use these drugs in cardiovascularly fragile patients, is this drug safe?"

They all passed, but the studies demonstrated something more, profound cardioprotection, specifically in heart failure

61

EMPA-REG OUTCOME	November 26, 2015
CANVAS and CANVAS-R	August 17, 2017
DECLARE-TIMI 58	January 24, 2019



62

EMPA-REG OUTCOME	November 26, 2015
CANVAS and CANVAS-R	August 17, 2017
DECLARE-TIMI 58	January 24, 2019

63

EMPA-REG OUTCOME	November 26, 2015
CANVAS and CANVAS-R	August 17, 2017
DECLARE-TIMI 58	January 24, 2019

64

EMPA-REG Kidney

Age 63.1

N=7,020

Type 2 DM
A1c 8.1%

Diabetic nephropathy
(>300 mg/g) **11%**

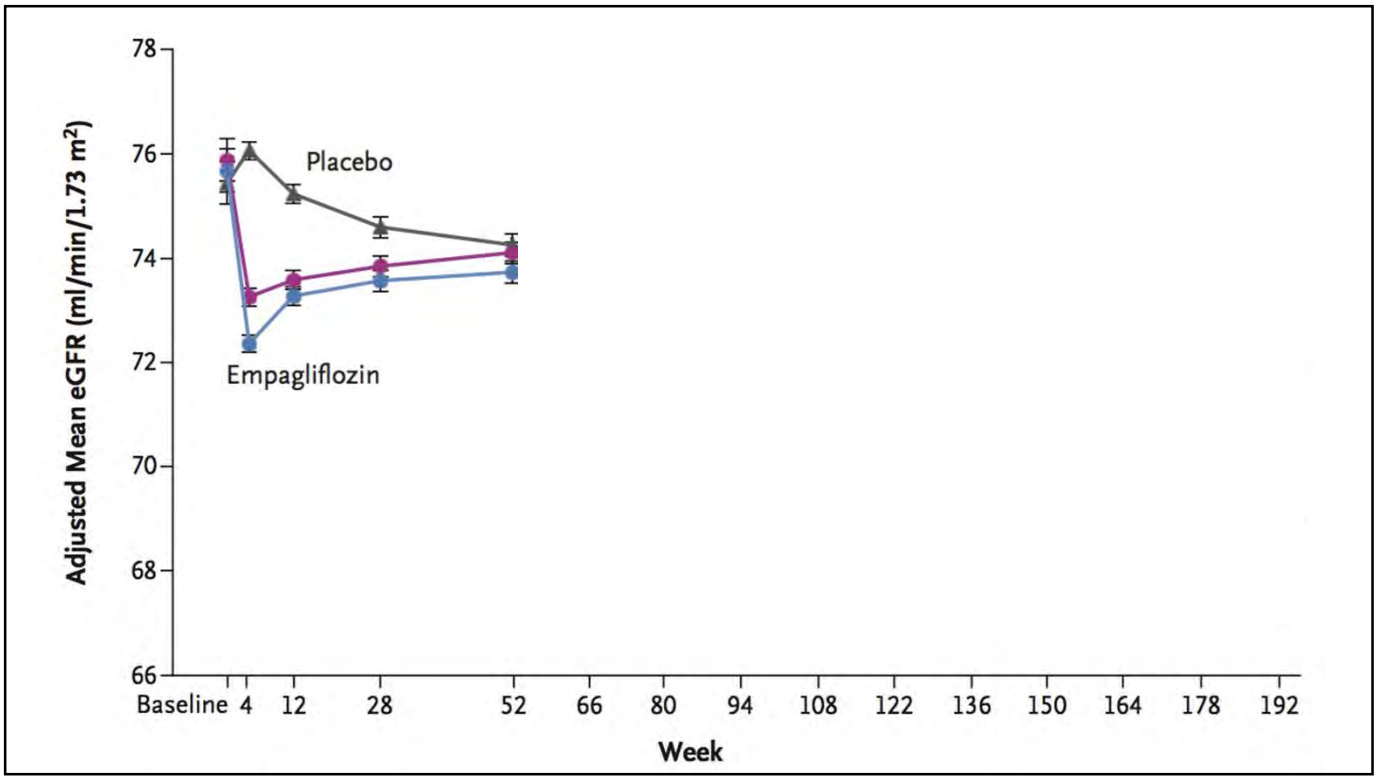
Blood pressure
135/77

Average GFR
74 ml/min

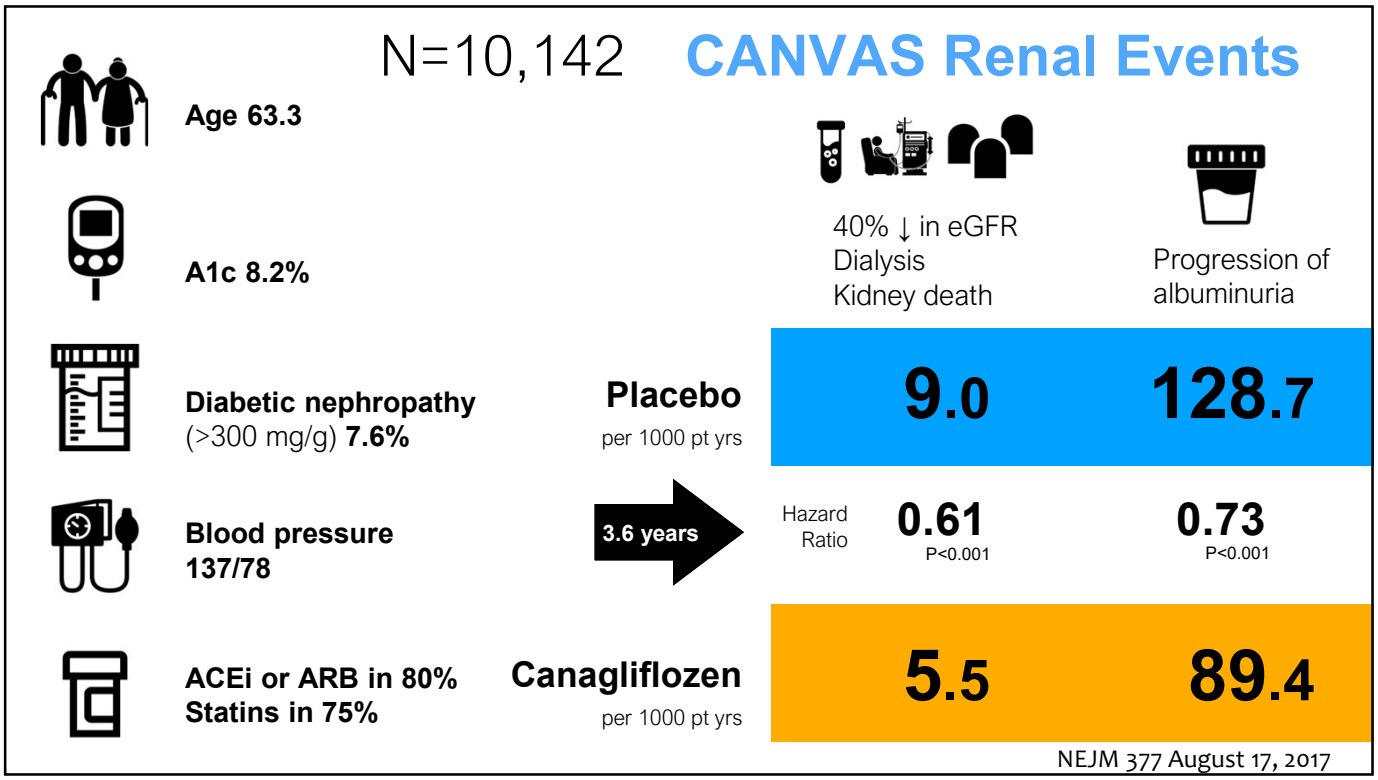
	Macroalbuminuria 2xCr, Dialysis Kidney death	Macroalbuminuria
Placebo	**18.8%**	**16.2%**
Hazard Ratio (2.6 years)	0.61 P<0.001	0.62 P<0.001
Empagliflozen	**12.7%**	**11.2%**

NEJM 375 July 28, 2016

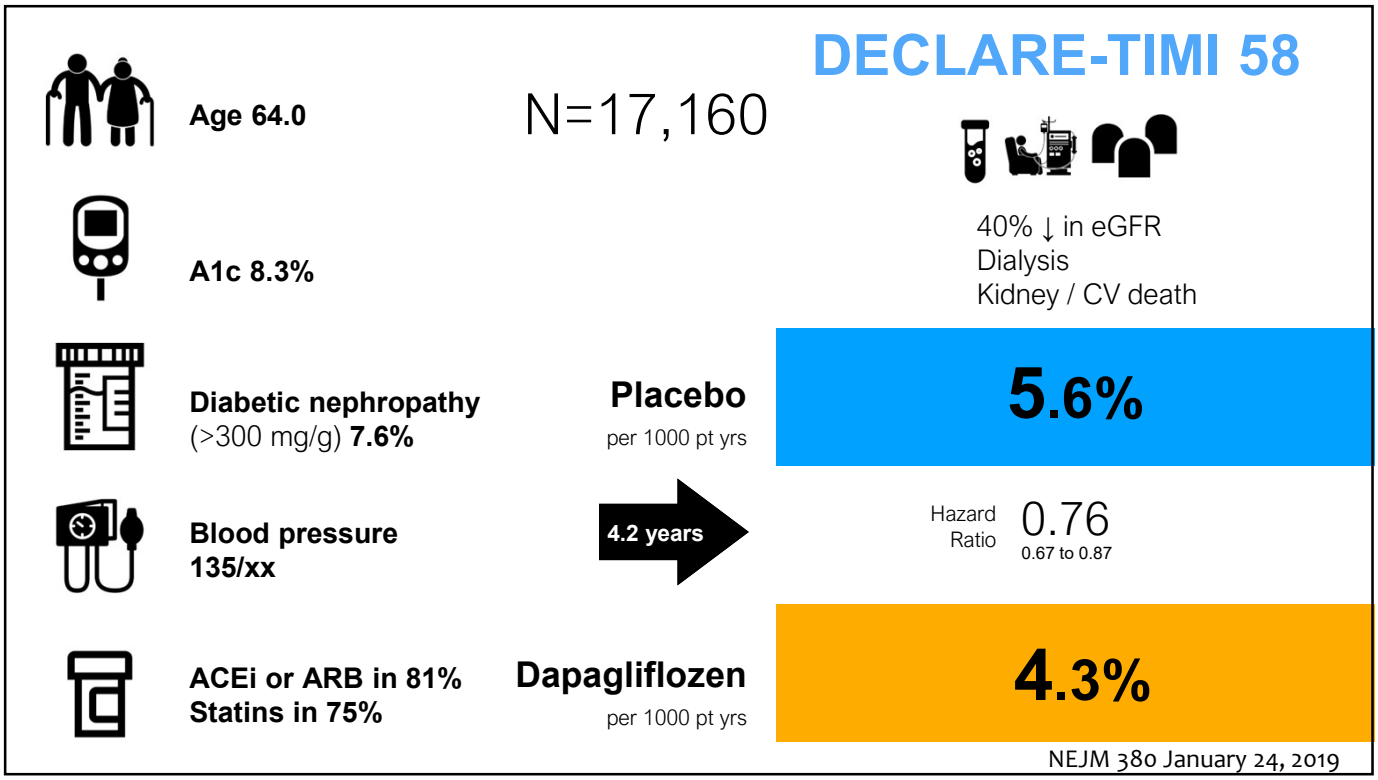
65



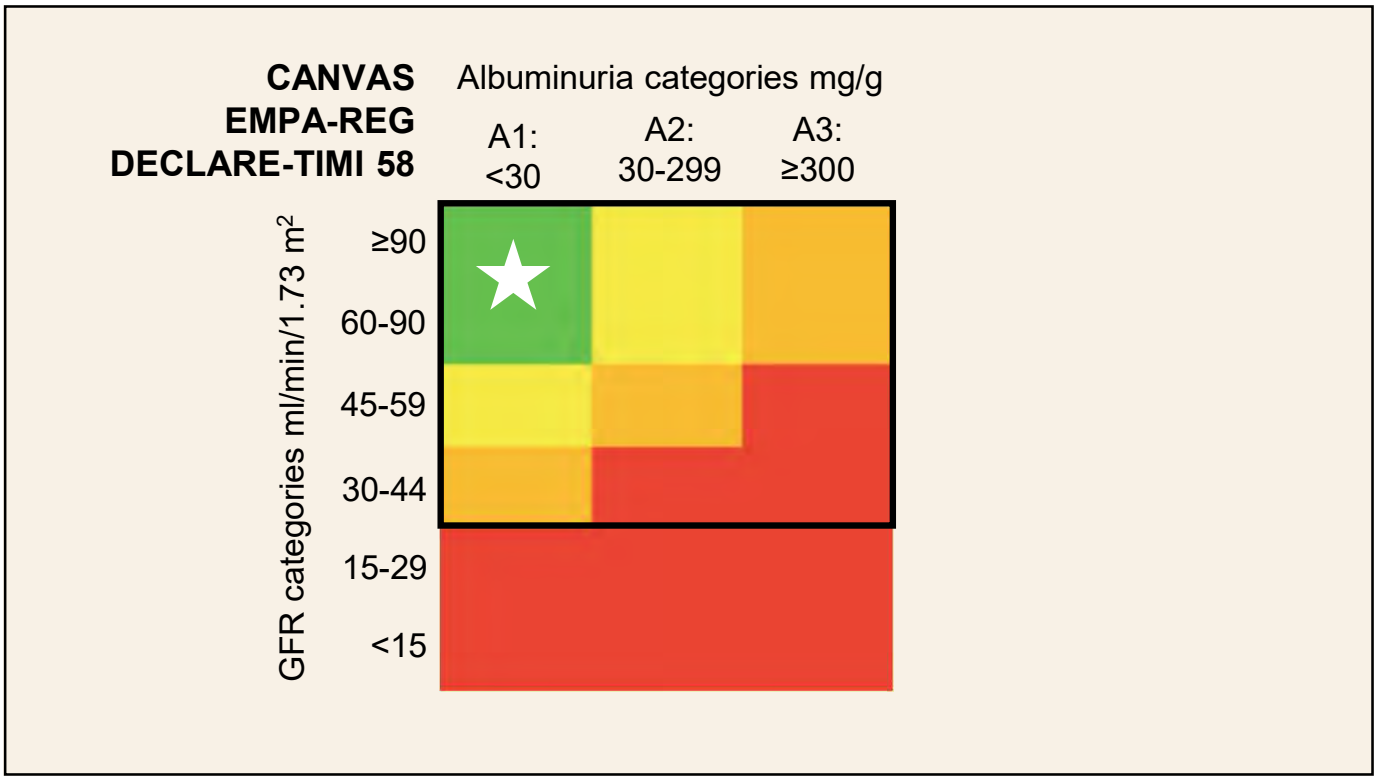
66


N=10,142
CANVAS Renal Events
Age 63.3
A1c 8.2%
Diabetic nephropathy (>300 mg/g) 7.6%
Blood pressure 137/78
ACEi or ARB in 80%
Statins in 75%
40% ↓ in eGFR
Dialysis
Kidney death
Progression of albuminuria
Placebo
per 1000 pt yrs
9.0
128.7
3.6 years
Hazard Ratio
0.61
P<0.001
0.73
P<0.001
Canagliflozen
per 1000 pt yrs
5.5
89.4
NEJM 377 August 17, 2017

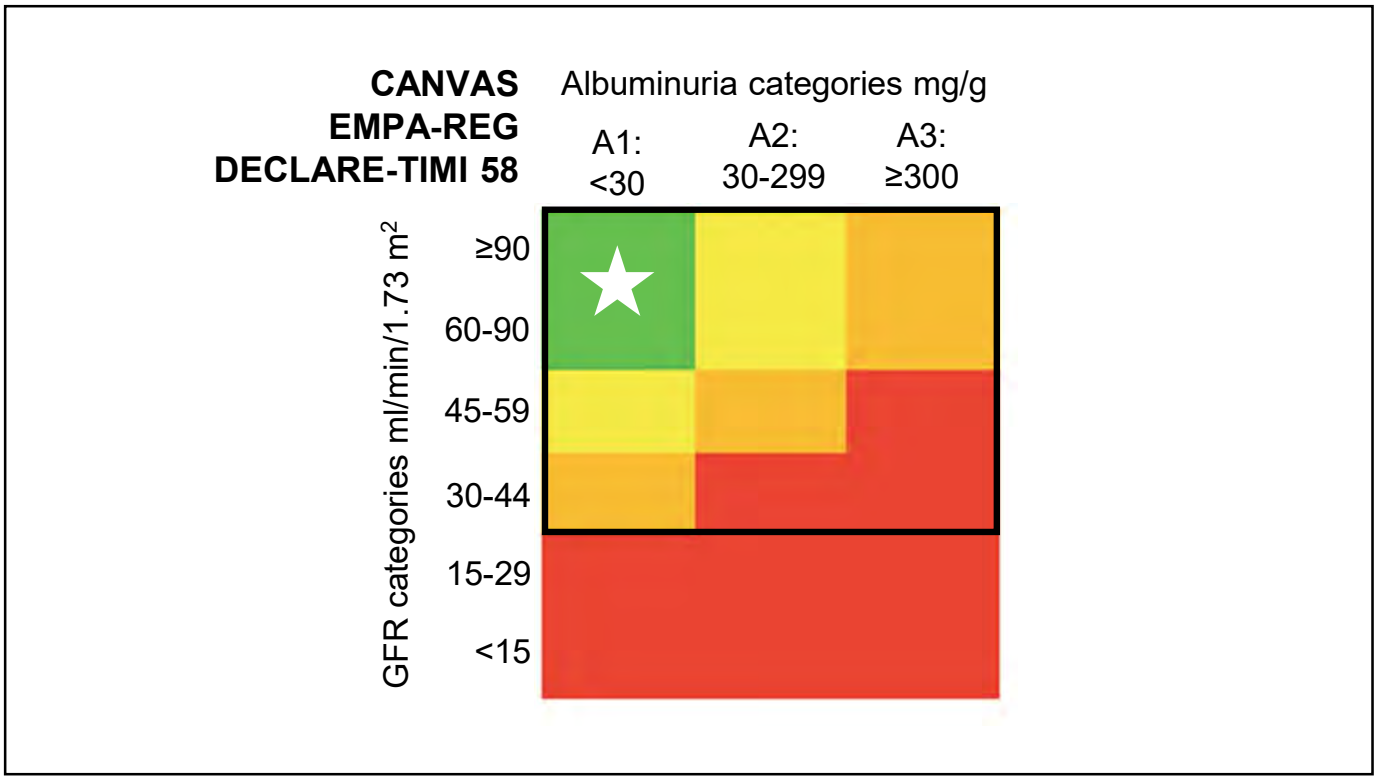
67


DECLARE-TIMI 58
N=17,160
Age 64.0
A1c 8.3%
Diabetic nephropathy (>300 mg/g) 7.6%
Blood pressure 135/xx
ACEi or ARB in 81%
Statins in 75%
40% ↓ in eGFR
Dialysis
Kidney / CV death
Placebo
per 1000 pt yrs
5.6%
4.2 years
Hazard Ratio
0.76
0.67 to 0.87
Dapagliflozen
per 1000 pt yrs
4.3%
NEJM 380 January 24, 2019

68


CANVAS
EMPA-REG
DECLARE-TIMI 58
Albuminuria categories mg/g
A1: <30
A2: 30-299
A3: ≥300
GFR categories ml/min/1.73 m2
≥90
60-90
45-59
30-44
15-29
<15

69


CANVAS
EMPA-REG
DECLARE-TIMI 58
Albuminuria categories mg/g
A1: <30
A2: 30-299
A3: ≥300
GFR categories ml/min/1.73 m2
≥90
60-90
45-59
30-44
15-29
<15

70

EMPA-REG OUTCOME	November 26, 2015
CANVAS and CANVAS-R	August 17, 2017
DECLARE-TIMI 58	January 24, 2019

71

EMPA-REG OUTCOME	November 26, 2015
CANVAS and CANVAS-R	August 17, 2017
DECLARE-TIMI 58	January 24, 2019
CREDENCE	June 13, 2019
DAPA-HF	November 21, 2019
DAPA-CKD	October 8, 2020
EMPEROR-Reduced	October 8, 2020
SOLOist	January 14, 2021
EMPEROR-Preserved	October 14, 2021
EMPULSE	February 28, 2022
DELIVER	August 27, 2022
EMPA-Kidney	November 2022

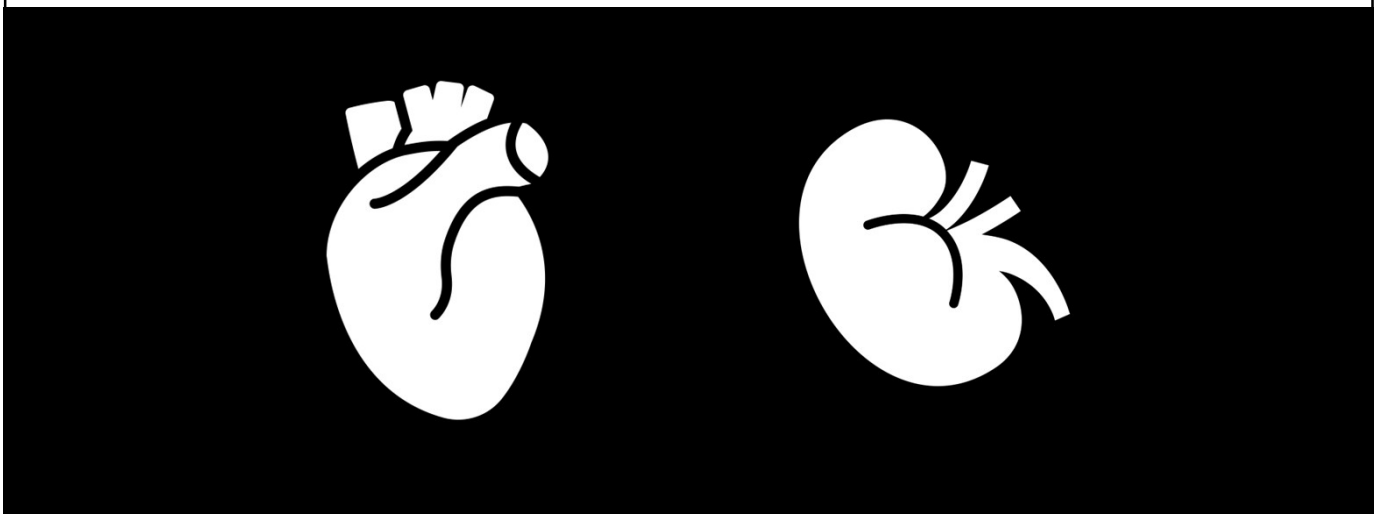
72

The surprise unleashed a torrent of studies to race to fully define the magnitude, scope, and limits of these benefits. To fully understand what these drugs mean for medicine.

So let's start with our basic understanding of the drugs.

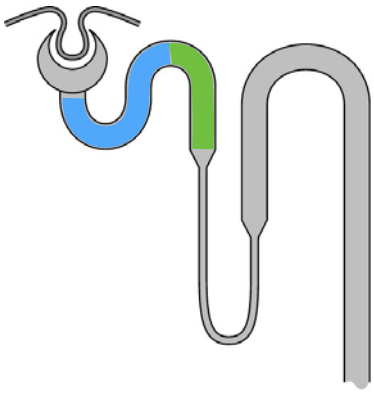
73

EMPA-REG OUTCOME	November 26, 2015
DECLARE-TIMI 58	January 24, 2019
CREDENCE	June 13, 2019



74

The proximal tubule is the sole site for glucose reabsorption. There are two glucose transporters:



SGLT2 found in S1 and S2 of the proximal tubule
- Moderate avidity
- High capacity
- 1 Na^+ reabsorbs 1 glucose
- Reabsorbs 80-90% of filtered glucose

SGLT1 found in S3 of the proximal tubule
- High avidity
- Low capacity
- 2 Na^+ reabsorbs 1 glucose
- Reabsorbs 10-20% of filtered glucose

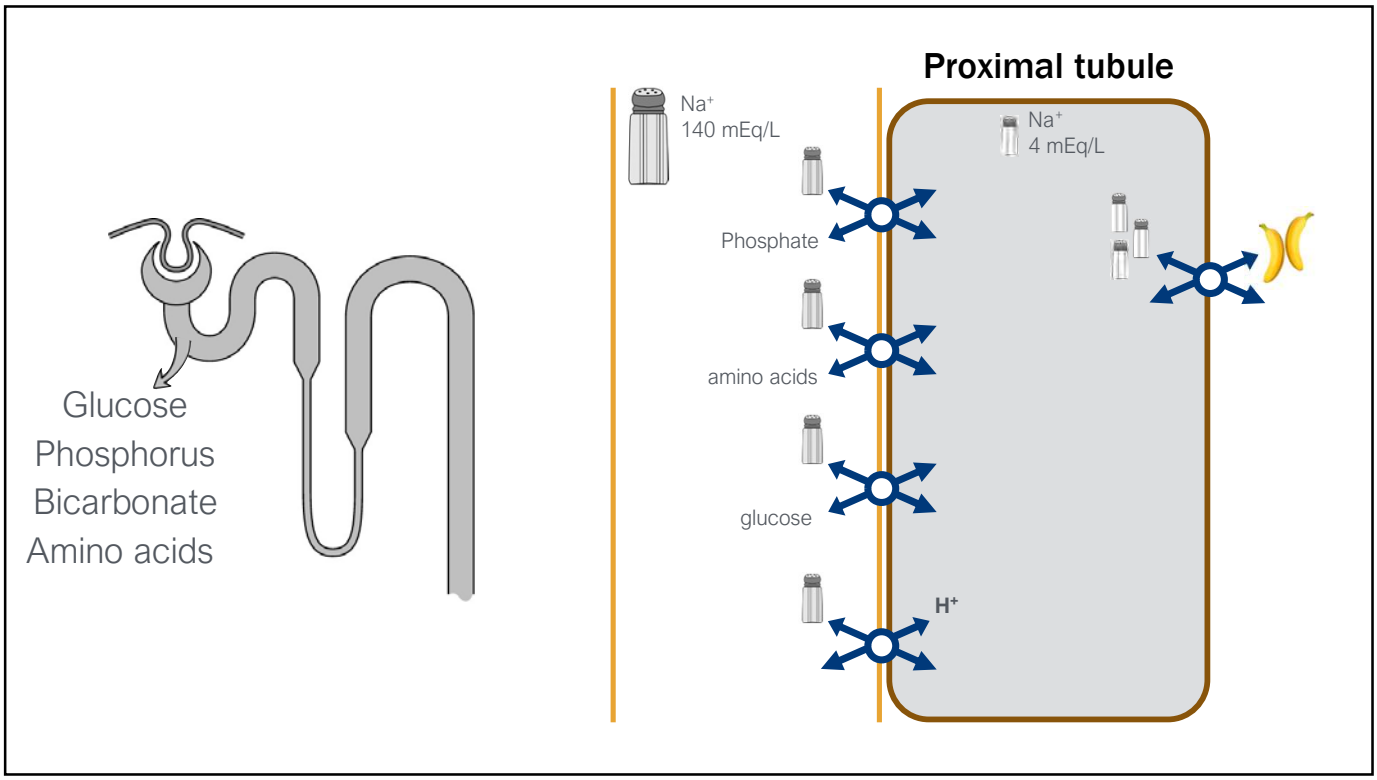
75

Emapgliflozin, dapagliflozin: SGLT2 inhibitor only
Canagliflozin: SGLT2 inhibitor with some SGLT1 inhibitor activity
Sotagliflozin: combined SGLT1 and SGLT2 inhibitor

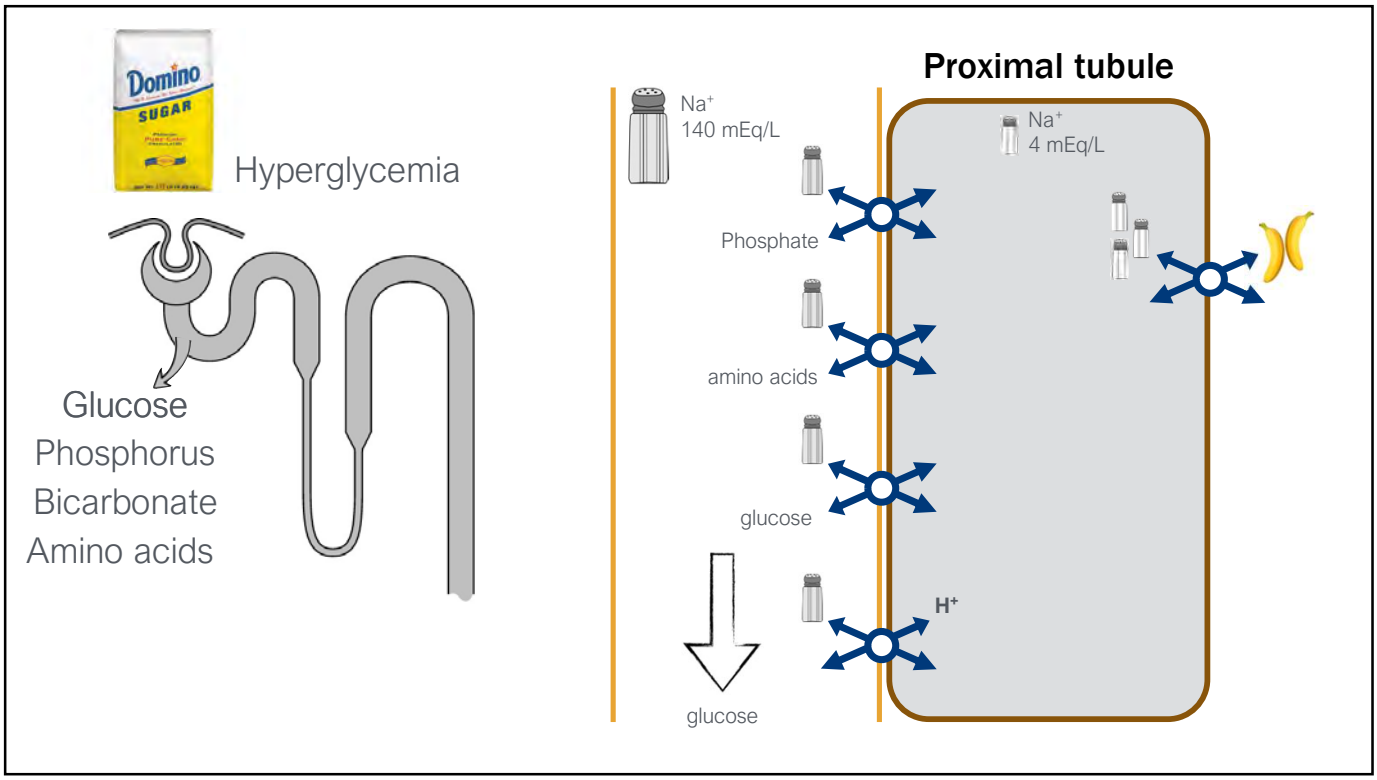
SGLT2 found in S1 and S2 of the proximal tubule
- Moderate avidity
- High capacity
- 1 Na^+ reabsorbs 1 glucose
- Reabsorbs 80-90% of filtered glucose

SGLT1 found in S3 of the proximal tubule
- High avidity
- Low capacity
- 2 Na^+ reabsorbs 1 glucose
- Reabsorbs 10-20% of filtered glucose

76

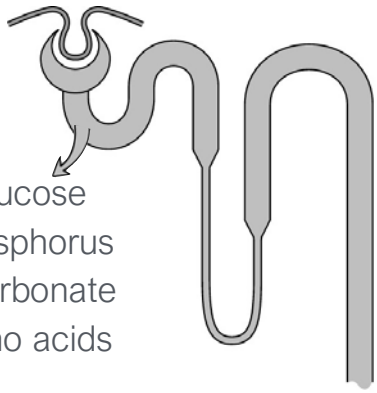

Glucose
Phosphorus
Bicarbonate
Amino acids
Proximal tubule
Na+
140 mEq/L
Na+
4 mEq/L
Phosphate
amino acids
glucose
H+

77

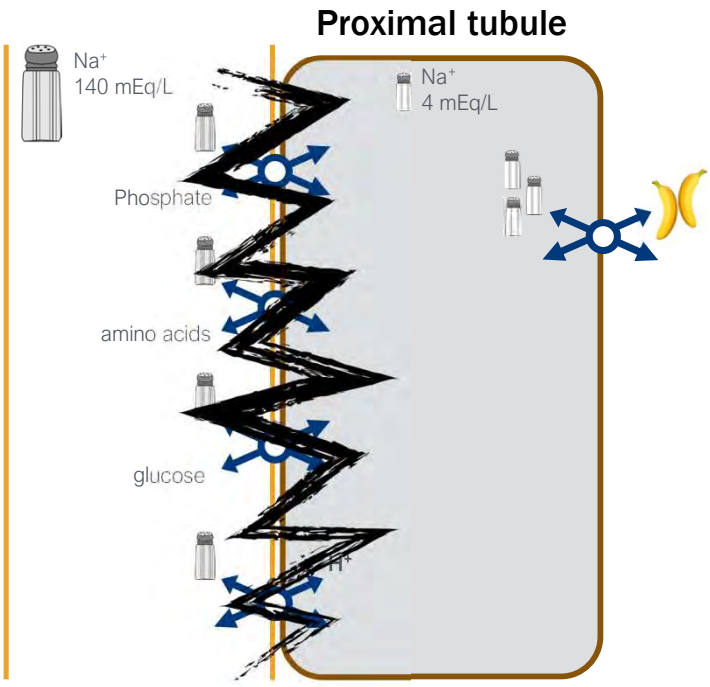

Domino
SUGAR
Hyperglycemia
Glucose
Phosphorus
Bicarbonate
Amino acids
Proximal tubule
Na+
140 mEq/L
Na+
4 mEq/L
Phosphate
amino acids
glucose
H+
glucose

78

Fanconi syndrome

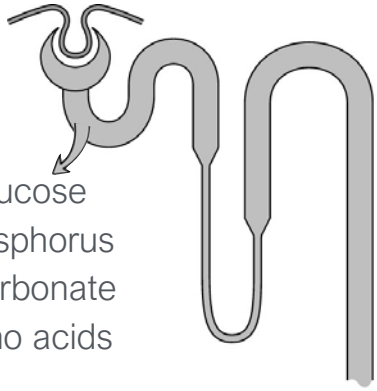


Glucose
Phosphorus
Bicarbonate
Amino acids



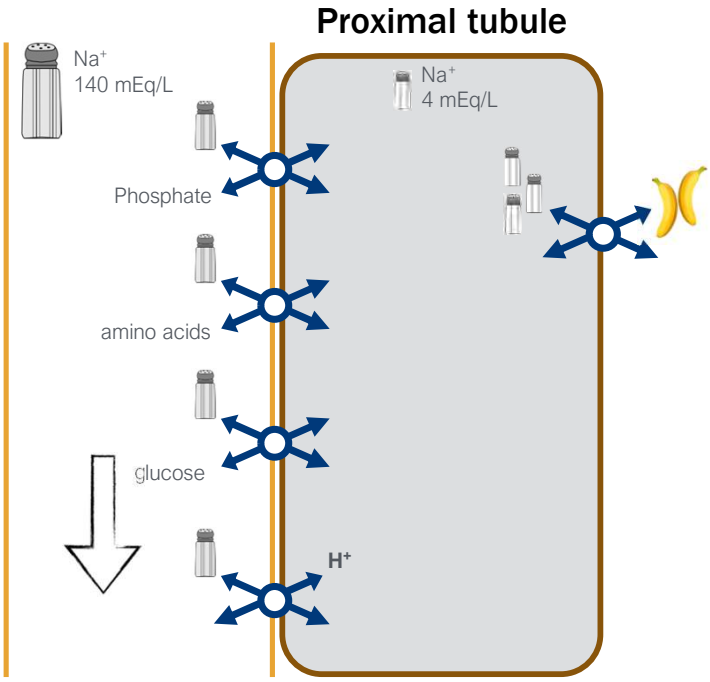
79

SGLT2 inhibitors



Glucose
Phosphorus
Bicarbonate
Amino acids

Sodium

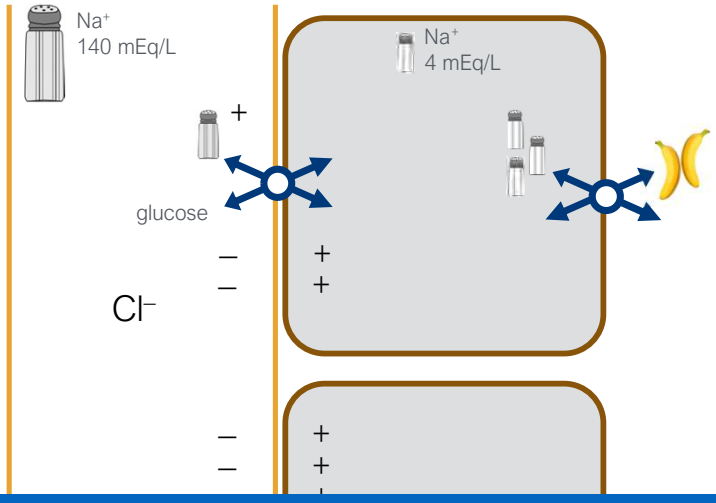


80

Gliflozins, SGLT2 inhibitors, are diuretics

Glucose reabsorption is driven by sodium reabsorption.

Chloride moves passively in response to sodium resorption

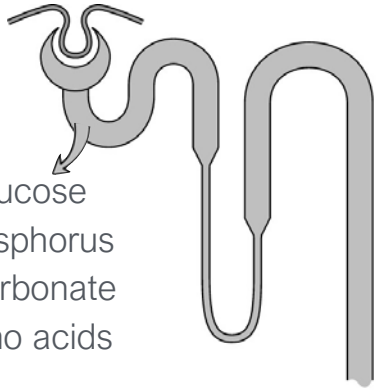


Increased glucose reabsorption increases salt retention

81

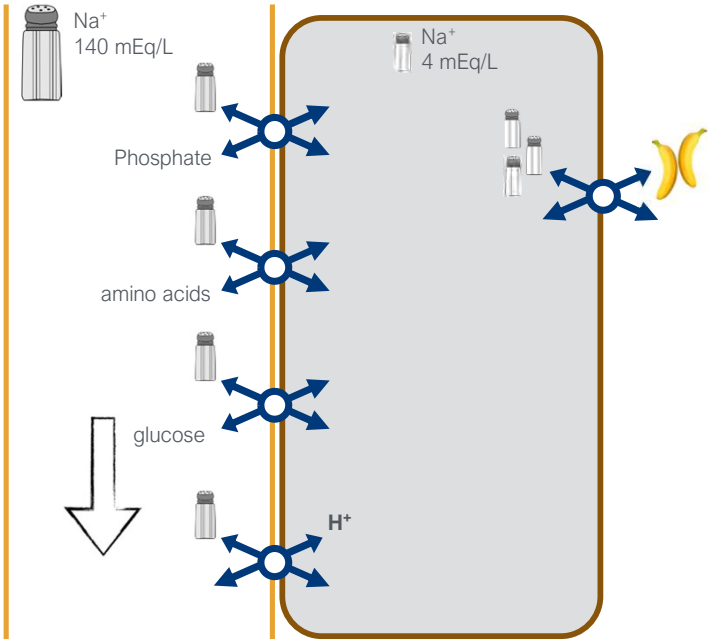
Gliflozins, SGLT2 inhibitors, are diuretics

SGLT2 inhibitors

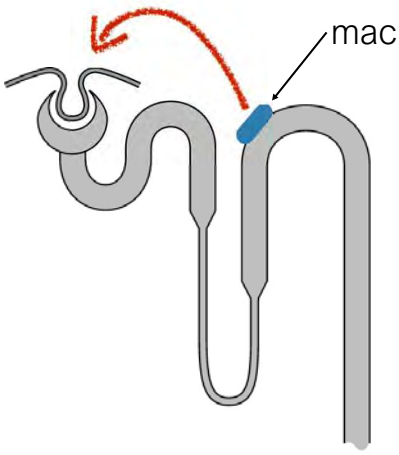


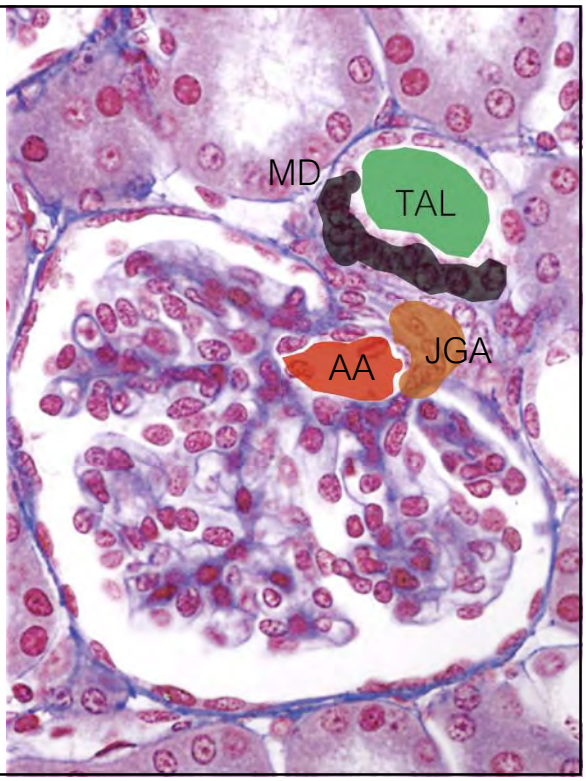
Glucose
Phosphorus
Bicarbonate
Amino acids

Sodium



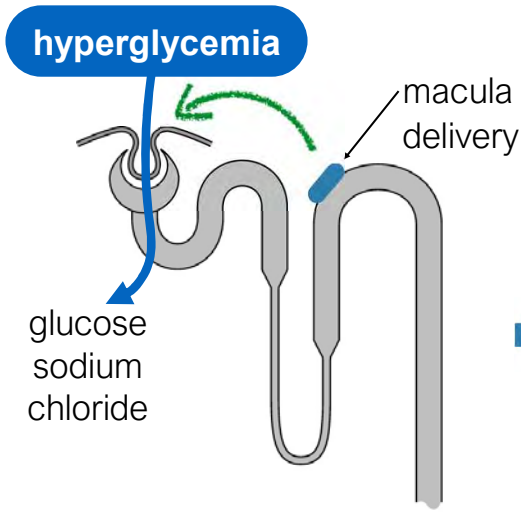
82





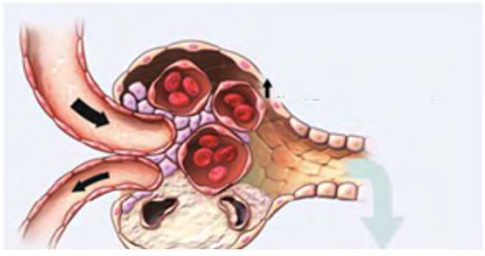
Tubular-Glomerular Feedback

83



Increased glucose, Na, Cl reabsorption at the proximal tubule

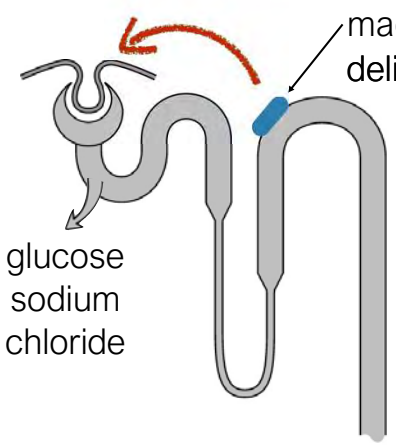
DILATE



Increased GFR
Increased intra-glomerular pressure

hyperfiltration

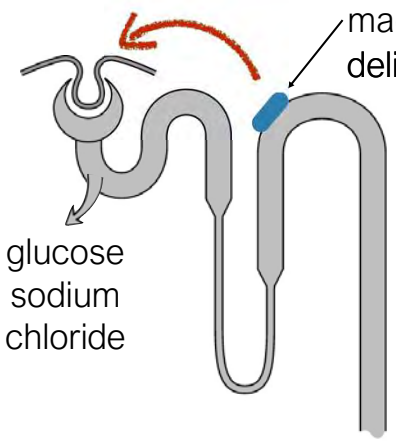
84



Decreased GFR
Decreased intra-glomerular pressure

correction of hyperfiltration

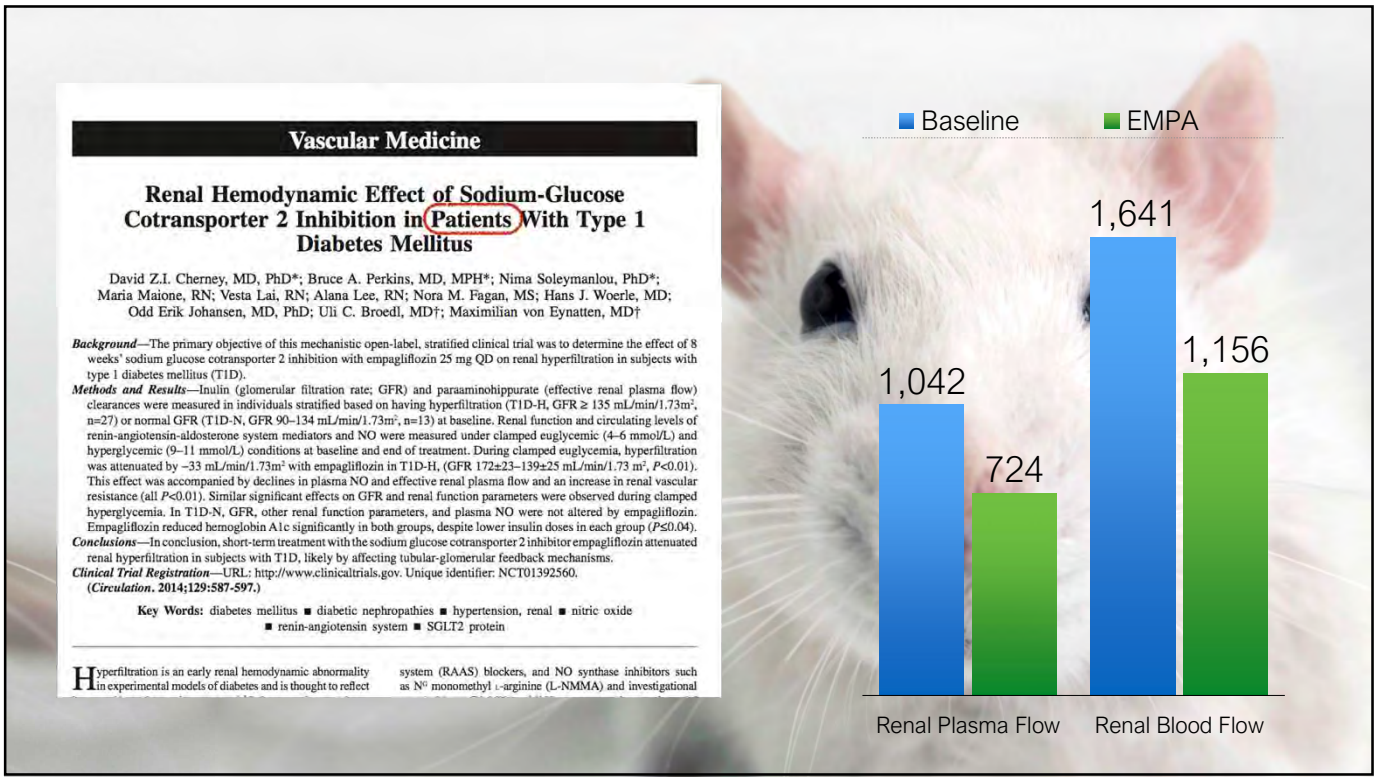
85



Decreased GFR
Decreased intra-glomerular pressure

correction of hyperfiltration

86

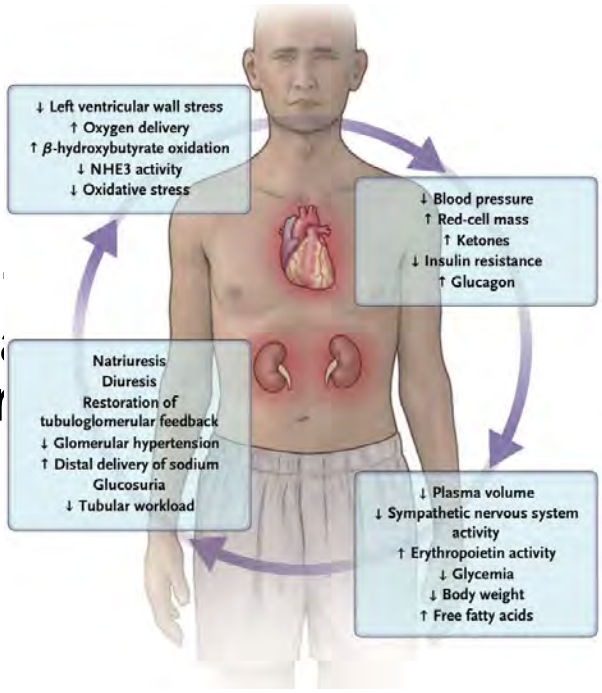


87

While this is the mechanism of action commonly described, it does not explain how people who do not have hyperfiltration, i.e. people without diabetes, get renal benefit. Or how this blocking of TG feedback results in profound heart failure benefits.

88

"Fundamen **onsible for the beneficia** **GLT2 inhibitors ar**



Braunwald, E. (2022). Gliflozins in the Management of Cardiovascular Disease. *The New England Journal of Medicine*, *386*(21), 2024–2034.

89

"Fundamental mechanisms responsible for the beneficial cardiac effects of SGLT2 inhibitors are not clear."

calcium calmodulin-dependent protein kinase II

activity of the sarcolemmal sodium hydrogen exchanger-1

the late inward sodium current

Improved glucose oxidation by cardiac mitochondria

Anti-inflammatory activity

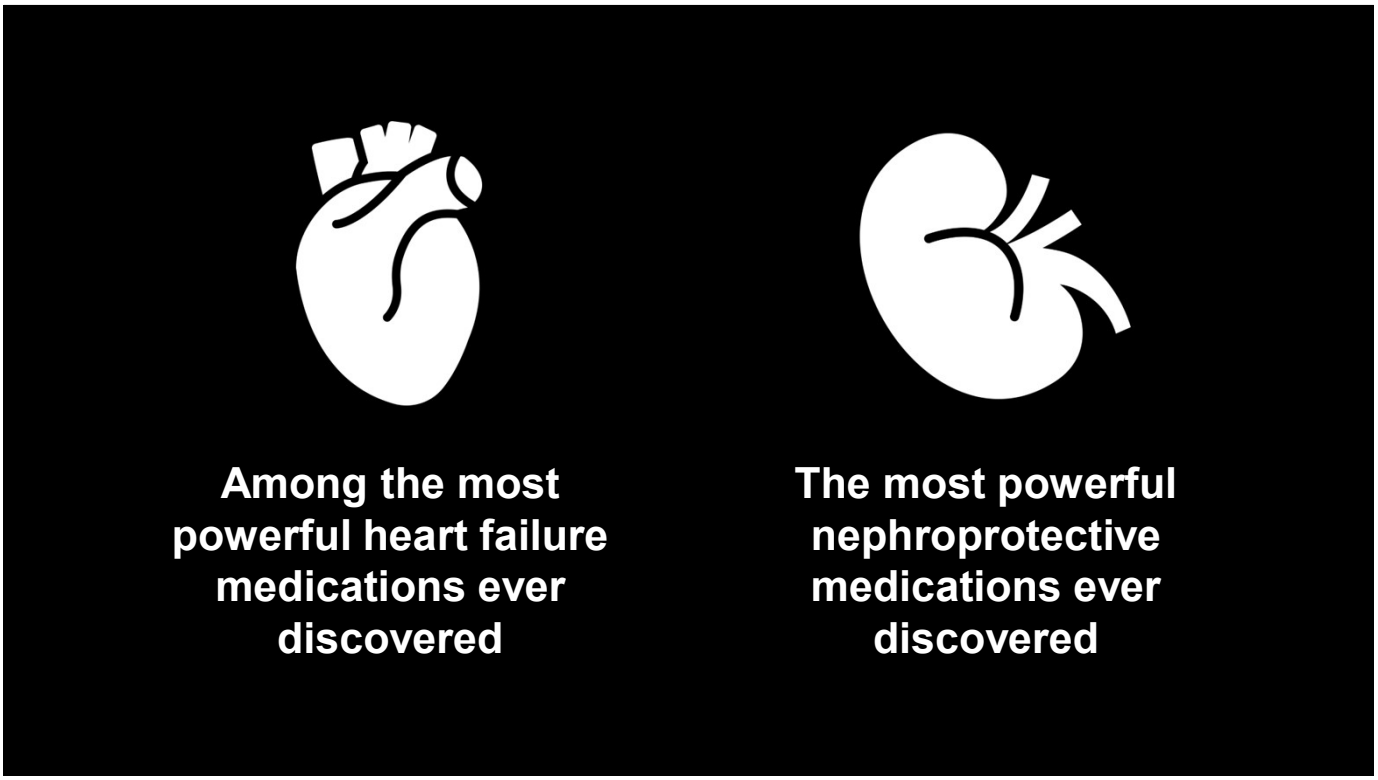
Reduce free radical formation

Improve coronary endothelial function

90


FLOZINATOR
Corina Teodosiu
@CTeodosiu

91


Among the most powerful heart failure medications ever discovered
The most powerful nephroprotective medications ever discovered

92

ACEi and ARB HFrEF

Among the most powerful heart failure medications ever discovered

CONSENSUS NYHA IV	Enalapril	**40% ↓ 6 month total mortality**
SOLVD EF< 35%	Enalapril	**16% ↓ total mortality**
TRACE EF< 35% post-MI	Trandolapril	**22% ↓ total mortality**
CHARM-Alternative EF< 40%	Candesartan vs Placebo	**20% ↓ CV death**
Val-HeFT NYHA 2-4	Valsartan vs Placebo	**13% ↓ MACE**

93

Other agents HFrEF

Among the most powerful heart failure medications ever discovered

MERIT-HF EF< 40%	Metoprolol CR	**34% ↓ CV death**
RALES EF < 35%	Spironolactone	**30% ↓ total mortality**
EPHESUS MI + EF < 40%	Eplerenone	**15% ↓ total mortality**
PARADIGM-HF EF< 40%	Sacubitril/Valsartan	**16% ↓ total mortality**

94

SGLT2i HFrEF

Among the most powerful heart failure medications ever discovered

EMPEROR-Reduced	Empagliflozin	**25% ↓ CV death & hosp HF**
EF< 40%		
DAPA-HF	Dapagliflozin	**18% ↓ CV mortality**
EF < 40%		

95

HFpEF

Among the most powerful heart failure medications ever discovered

PEP-CHF	Perindopril	**Negative trial**
EF < 40%		
CHARM-Preserved	Candesartan	**Negative trial**
EF > 40%		
PARAGON-HF	Sacubitril/Valsartan	**Negative Trial***
EF > 45%		
TOPCAT	Spironolactone	**Negative trial***
EF > 45%		

96

SGLT2i HFpEF

Among the most powerful heart failure medications ever discovered

DELIVER	Dapagliflozin	**18% ↓ CV death & hosp/ED HF**
EF > 40%		
EMPEROR-Preserved	Empagliflozin	**21% ↓ CV death & hosp HF**
EF > 40%		

97

Risk of CV Disease

Among the most powerful heart failure medications ever discovered

CANVAS	Canagliflozin	**13% ↓ CV mortality**
DM2 + CV risk		
EMPA-REG	Empagliflozin	**38% ↓ CV mortality**
DM2 + CVD		
DECLARE-TIMI 58	Dapagliflozin	**17% ↓ CV death & hosp for CHF**
DM2 + CV risk		

98

SOLOIST

1222 patients

Acute decompensated heart failure

Usual care + Placebo
(N=614)

At discharge → **9.2 months** →

Composite of CV death and hospital-ization / ER for heart failure

76%

Usual care + Sotagliflozin
(N=608)

51%

Bhatt, D. L., SOLOIST-WHF Trial Investigators. (2021). Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. NEJM, 384(2), 117–128.

99

EMPULSE

530 patients

Acute decompensated heart failure

Usual care + Placebo
(N=265)

When stable (day 3) → **90 days** →

Usual care + 10 mg Empa
(N=265)

22

Deaths

11

Voors, A. A., Angermann, C. E., Teerlink, J. R., Ponikowski, P. (2022). *Nature Medicine*, *28*(3), 568–574.

100

EMPULSE

530 patients

Acute decompensated heart failure

Usual care + Placebo
(N=265)

When stable (day 3)

90 days

52

Heart failure exacerbation

Usual care + 10 mg Empa
(N=265)

36

Voors, A. A., Angermann, C. E., Teerlink, J. R., Ponikowski, P. (2022). *Nature Medicine*, *28*(3), 568–574.

101

EMPAG-HF

60 patients

Acute decompensated heart failure

Usual care + Placebo

Within 12 hours

5 days

1.0 Kg

Weight loss at 30-days

Usual care + Empa

3.8 Kg

Schulze, P. C., Bogoviku, Busch, M, et al. (2022). Circulation, 146(4), 289–298.

102

EMPAG-HF

60 patients

Acute decompensated heart failure

Usual care + Placebo

8.7 L

Within 12 hours

5 days

Urine output

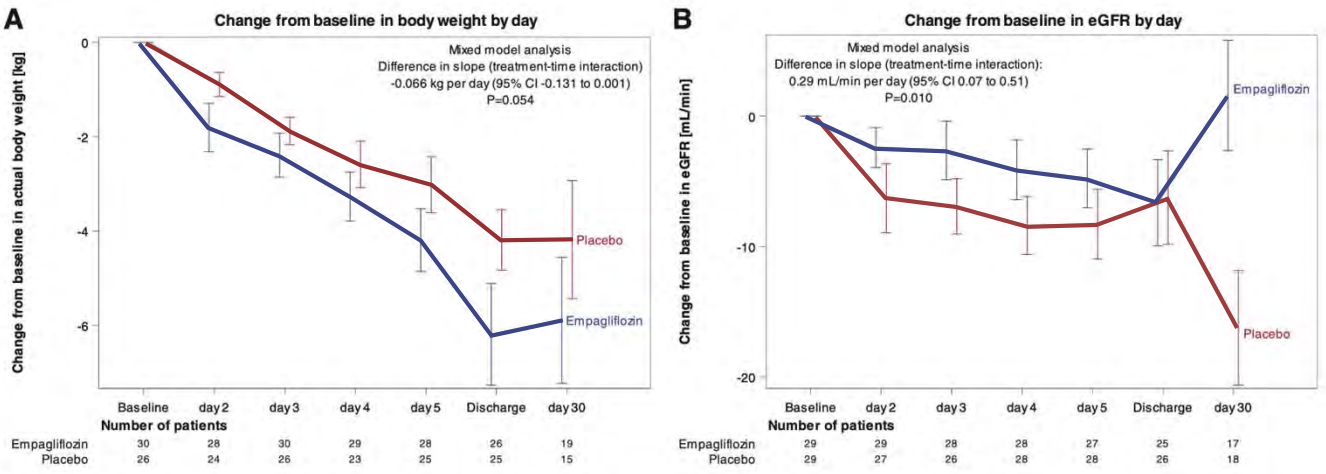
Usual care + Empa

10.8 L

Schulze, P. C., Bogoviku, Busch, M, et al. (2022). Circulation, 146(4), 289–298.

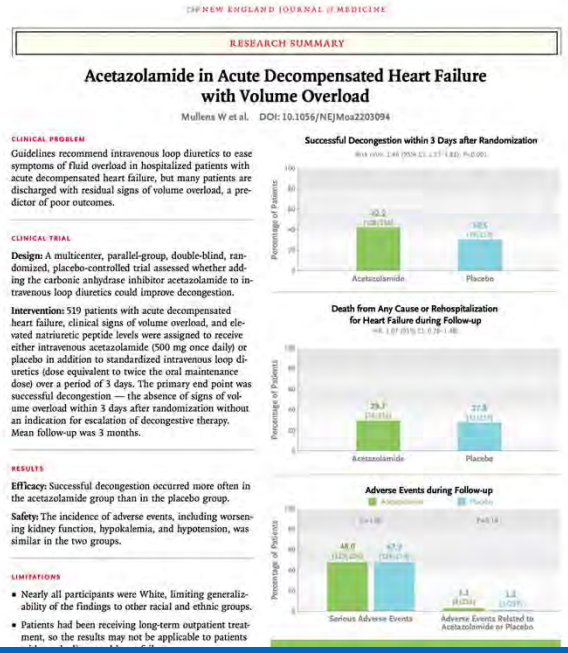
103

EMPAG-HF



Schulze, P. C., Bogoviku, Busch, M, et al. (2022). Circulation, 146(4), 289–298.

104



THE NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

Mullens W et al. DOI: 10.1056/NEJMoa2203094

CLINICAL PROBLEM

Guidelines recommend intravenous loop diuretics to ease symptoms of fluid overload in hospitalized patients with acute decompensated heart failure, but many patients are discharged with residual signs of volume overload, a predictor of poor outcomes.

CLINICAL TRIAL

Design: A multicenter, parallel-group, double-blind, randomized, placebo-controlled trial assessed whether adding the carbonic anhydrase inhibitor acetazolamide to intravenous loop diuretics could improve decongestion.

Intervention: 519 patients with acute decompensated heart failure, clinical signs of volume overload, and elevated natriuretic peptide levels were assigned to receive either intravenous acetazolamide (500 mg once daily) or placebo in addition to standardized intravenous loop diuretics (dose equivalent to twice the oral maintenance dose) over a period of 3 days. The primary end point was successful decongestion — the absence of signs of volume overload within 3 days after randomization without an indication for escalation of decongestive therapy. Mean follow-up was 3 months.

RESULTS

Efficacy: Successful decongestion occurred more often in the acetazolamide group than in the placebo group.

Safety: The incidence of adverse events, including worsening kidney function, hypokalemia, and hypotension, was similar in the two groups.

LIMITATIONS

- Nearly all participants were White, limiting generalizability of the findings to other racial and ethnic groups.
- Patients had been receiving long-term outpatient treatment, so the results may not be applicable to patients

Successful Decongestion within 3 Days after Randomization

Percentage of Patients

Acetazolamide

Placebo

Death from Any Cause or Rehospitalization for Heart Failure during Follow-up

Percentage of Patients

Acetazolamide

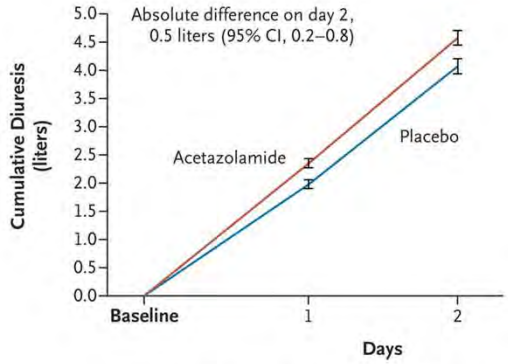
Placebo

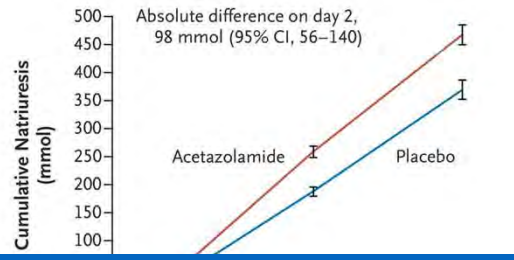
Adverse Events during Follow-up

Percentage of Patients

Serious Adverse Events

Adverse Events Related to Acetazolamide or Placebo





The Proximal Tubule is having its moment

105

Among the most powerful heart failure medications ever discovered

Chronic HFrEF

Chronic HFpEF

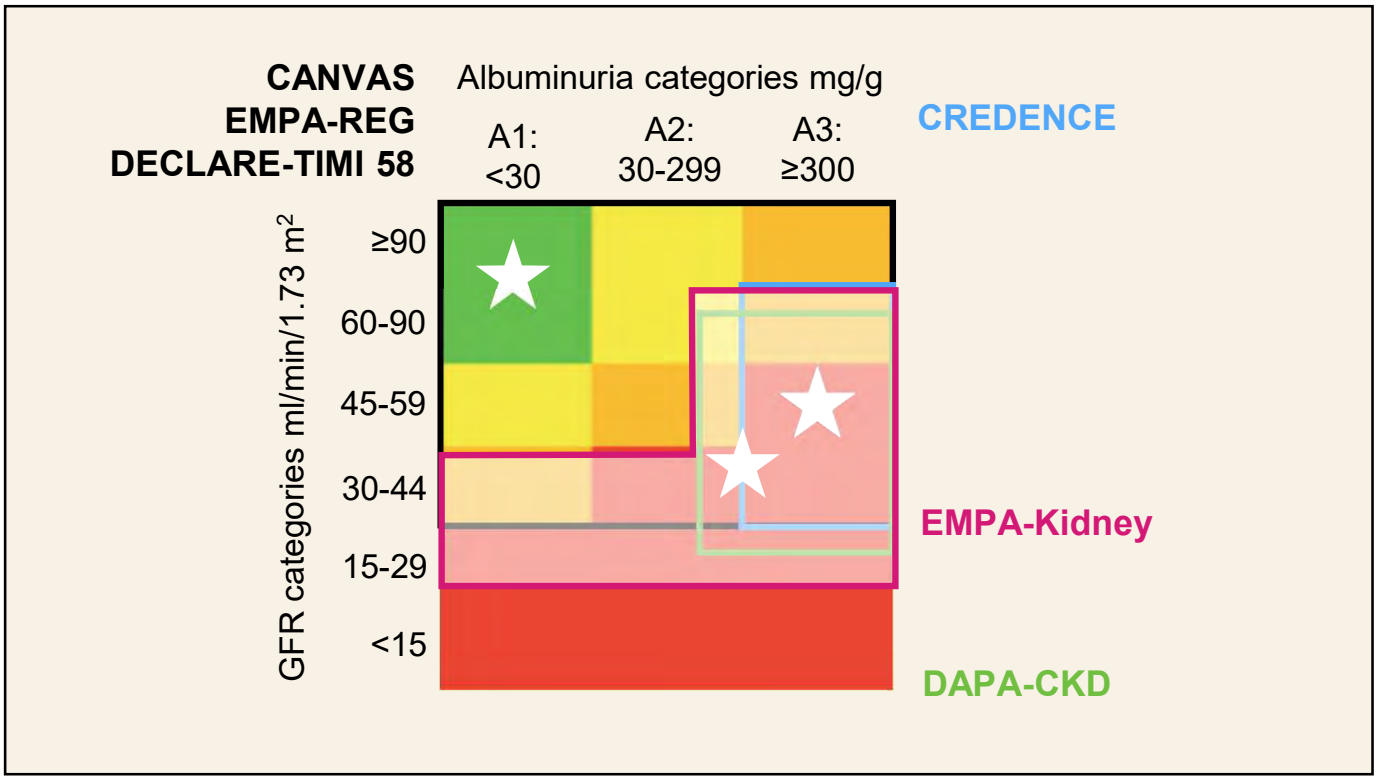
Patients with CV risk factors

Acute decompensated heart failure

106


The most powerful nephroprotective medications ever discovered

107


CANVAS
EMPA-REG
DECLARE-TIMI 58
Albuminuria categories mg/g
A1: <30
A2: 30-299
A3: ≥300
CREDENCE
GFR categories ml/min/1.73 m²
≥90
60-90
45-59
30-44
15-29
<15
EMPA-Kidney
DAPA-CKD

108

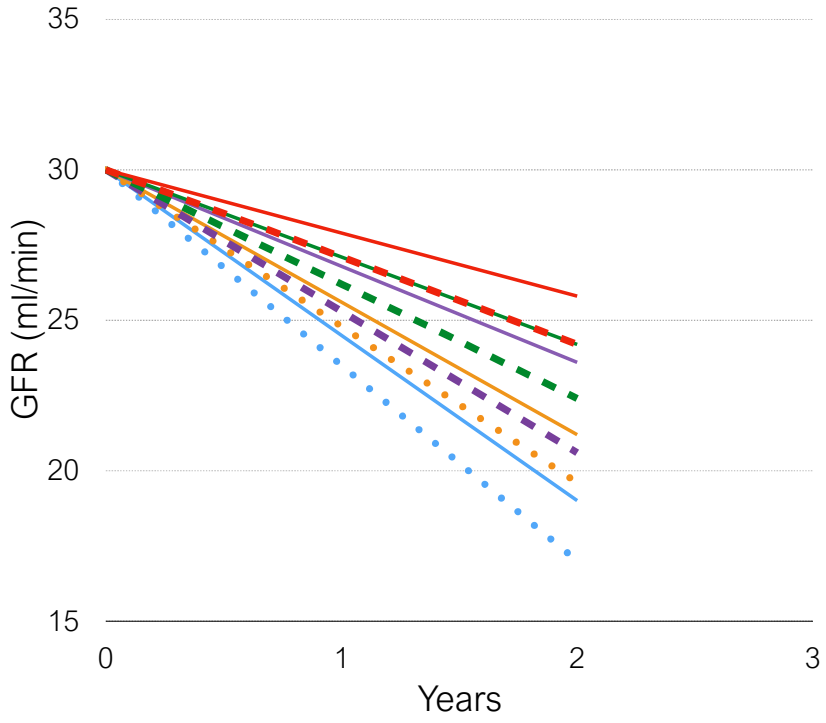
IDNT Placebo 6.5
15.4% Irbesartan 5.5

RENAAL Placebo 5.2
15.4% Losartan 4.4

CREDENCE Placebo 4.7
31.9% Cana 3.2

DAPA-Kidney Placebo 3.8
23.7% Dapa 2.9

EMPA-Kidney Placebo 2.9
27.6% Empa 2.1



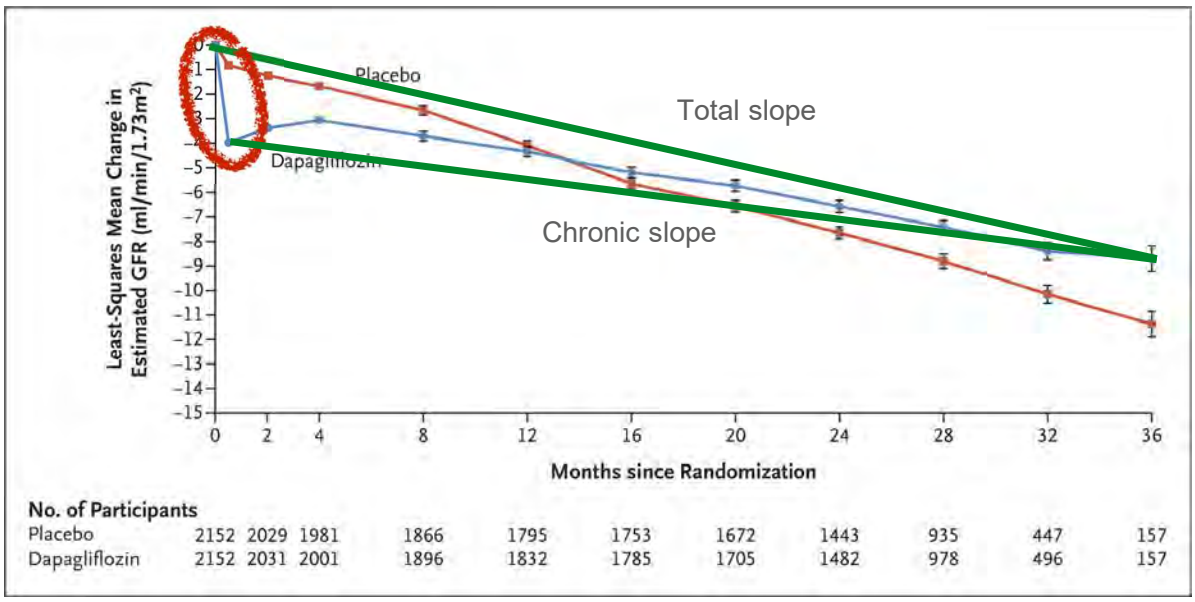
109

Total slope

DAPA-Kidney Placebo 3.8
Dapa 2.9
24%

Chronic slope

DAPA-Kidney Placebo 3.6
Dapa 1.7
52%



110

Total slope

CREDENCE Placebo 4.7

Cana 3.2

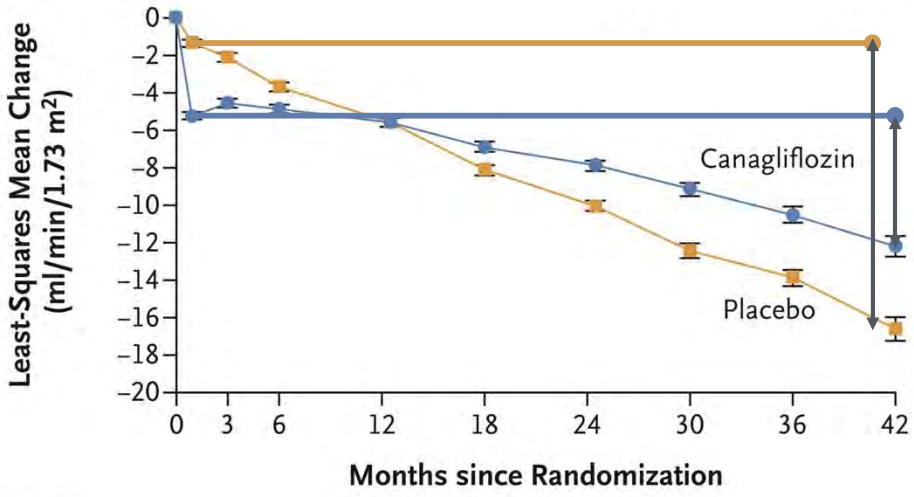
32%

Chronic slope

CREDENCE Placebo 4.2

Cana 2.0

52.4%



7 ml/min / 3.5 years

15 ml/min / 3.5 years

No. of Patients

Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

111

Total slope

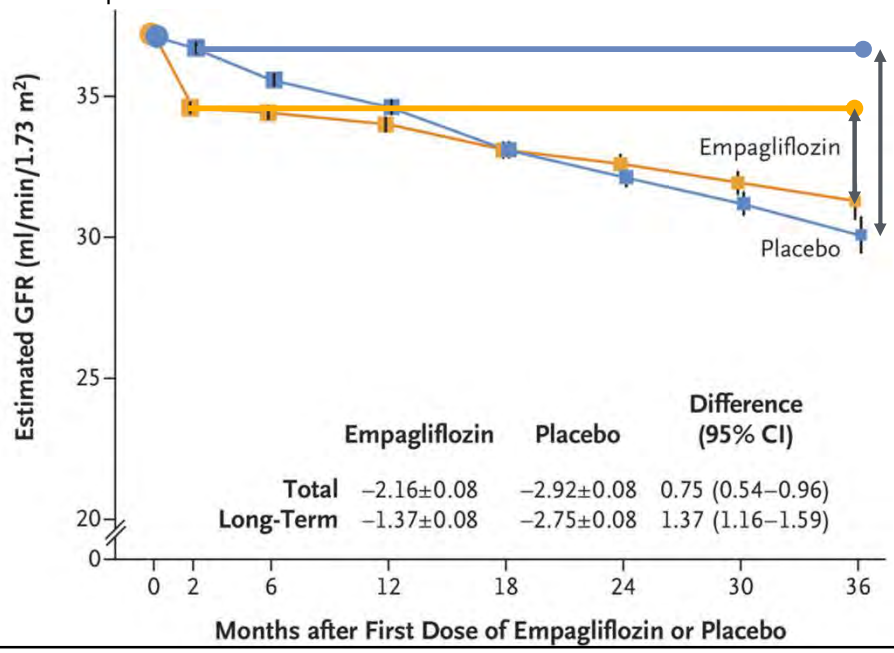
EMPA-Kidney Placebo 2.9

Empa 2.1

Chronic slope

EMPA-Kidney Placebo 2

Empa 1



3 ml/min / 3 years

6 ml/min / 2 years

	Empagliflozin	Placebo	Difference (95% CI)
Total	−2.16±0.08	−2.92±0.08	0.75 (0.54–0.96)
Long-Term	−1.37±0.08	−2.75±0.08	1.37 (1.16–1.59)

112

Chronic loss of GFR in EMPA-Kidney

1.0 ml/min per year

Loss of GFR from having a birthday

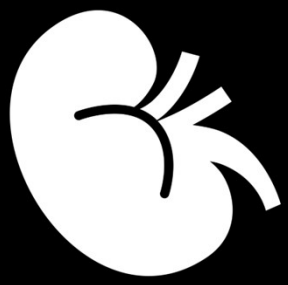
(after age 40)

0.8 ml/min per year

ular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *The Journal of Clinical Investigation*, *29*(5), 496–507.

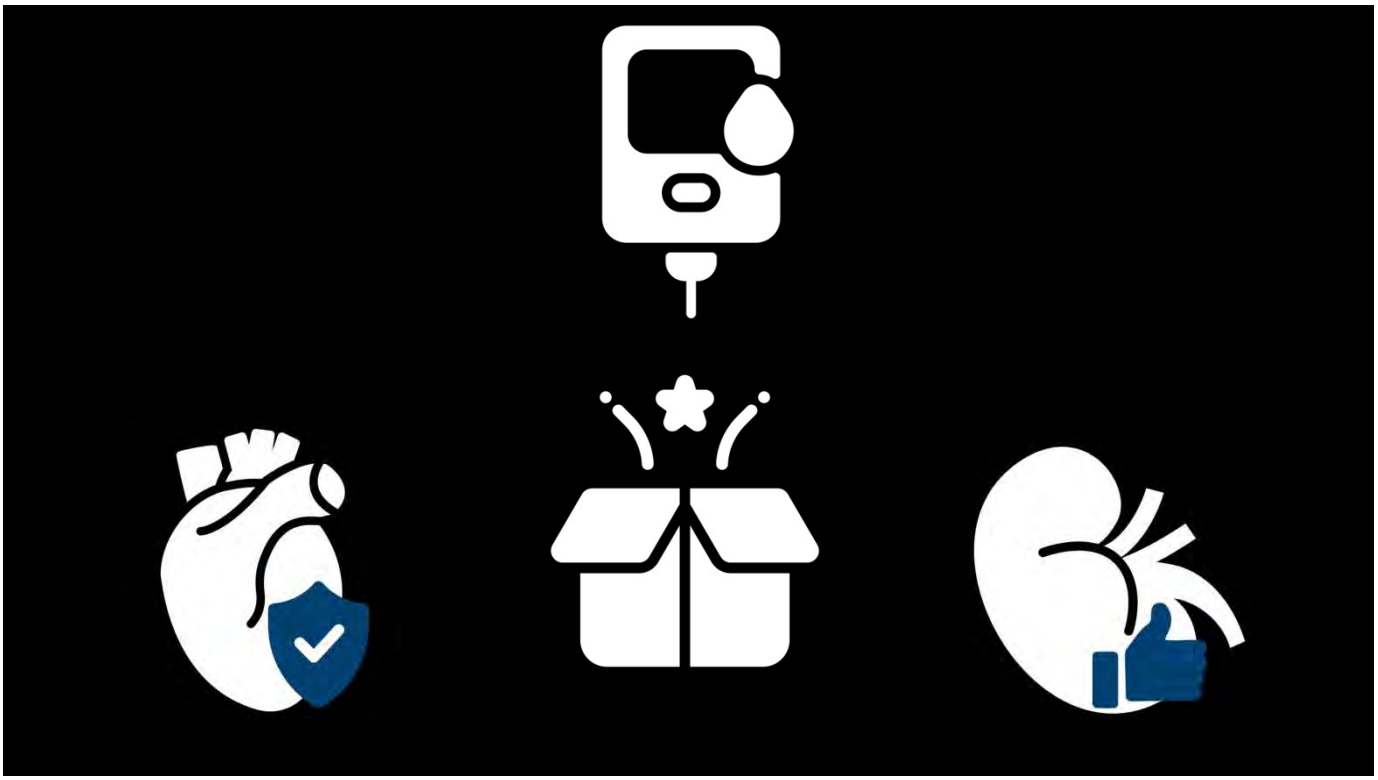
113

Among the most powerful cardioprotective medications ever discovered



The most powerful nephroprotective medications ever discovered

114



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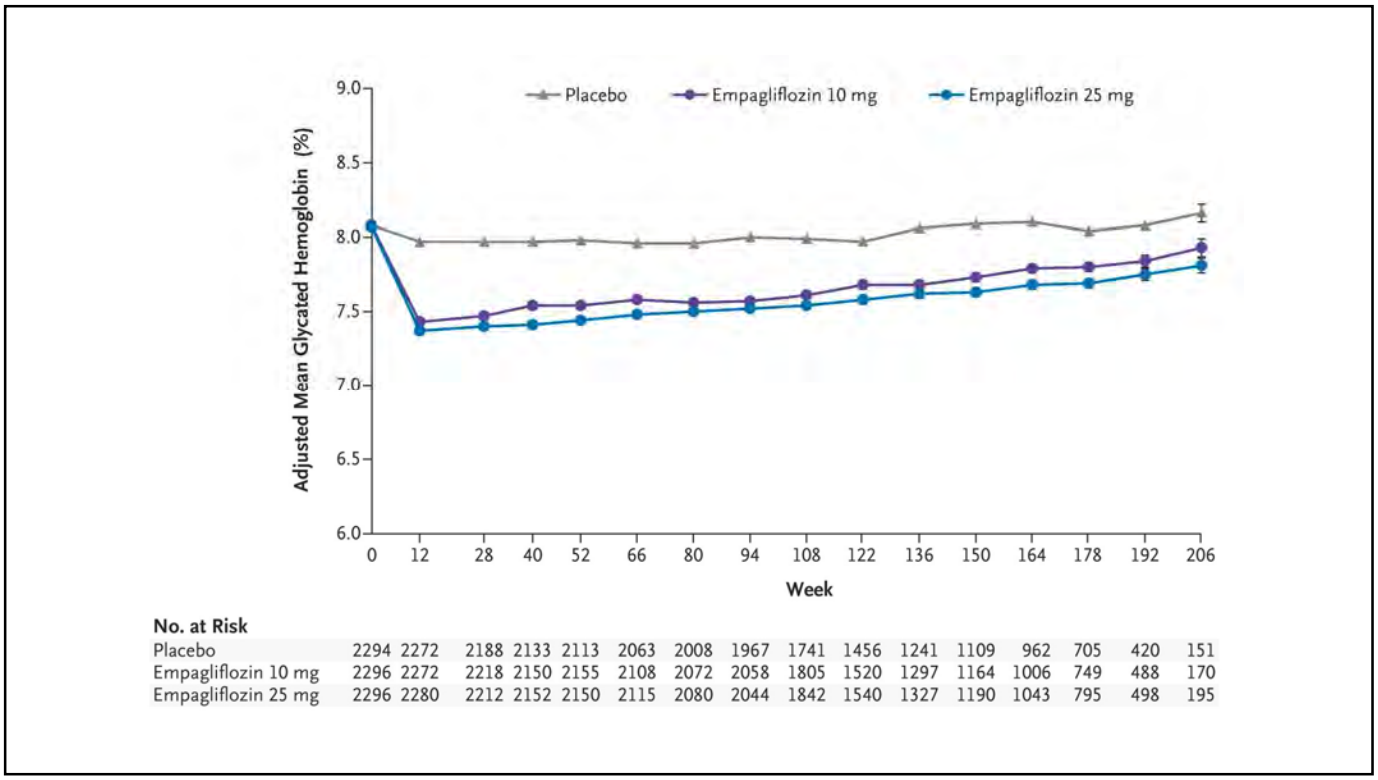


No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

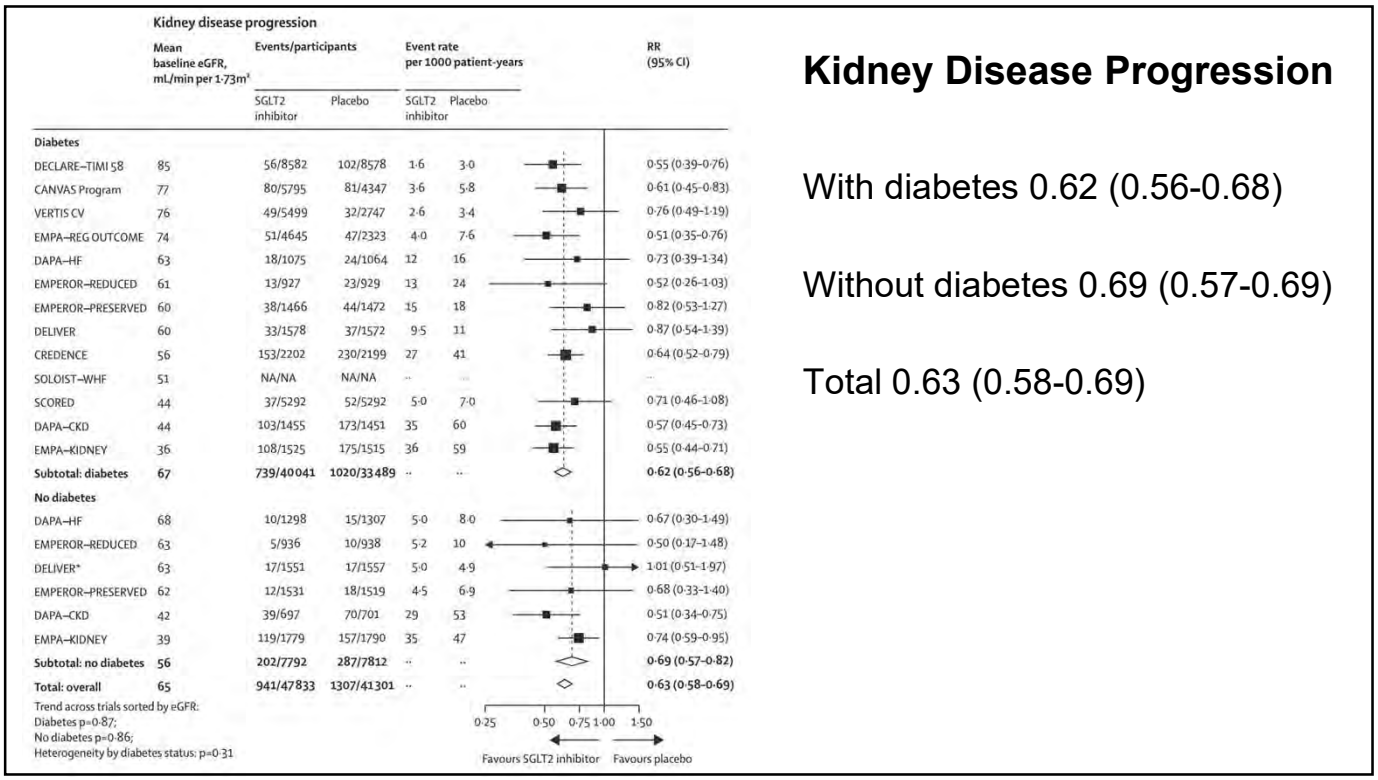
116

	Diabetes (N)	No Diabetes (N)
DAPA-HF	1983	2761
DELIVER	2806	3457
DAPA-CKD	2906	1398
EMPEROR Preserved	2938	3050
EMPEROR Reduced	1856	1874
EMPA Kidney	3040	3569

117

	Diabetes (N)	No Diabetes (N)
DAPA-HF	**0.75** (0.63-0.90)	**0.73** (0.60-0.88)
DELIVER	**0.83** (0.70-0.97)	**0.81** (0.68-0.96)
DAPA-CKD	**0.64** (0.52-0.79)	**0.50** (0.35-0.72)
EMPEROR Preserved	**0.79** (0.67-0.94)	**0.78** (0.64-0.95)
EMPEROR Reduced	**0.72** (0.60-0.87)	**0.78** (0.64-0.97)
EMPA Kidney	**0.64** (0.54-0.77)	**0.82** (0.68-0.99)

118



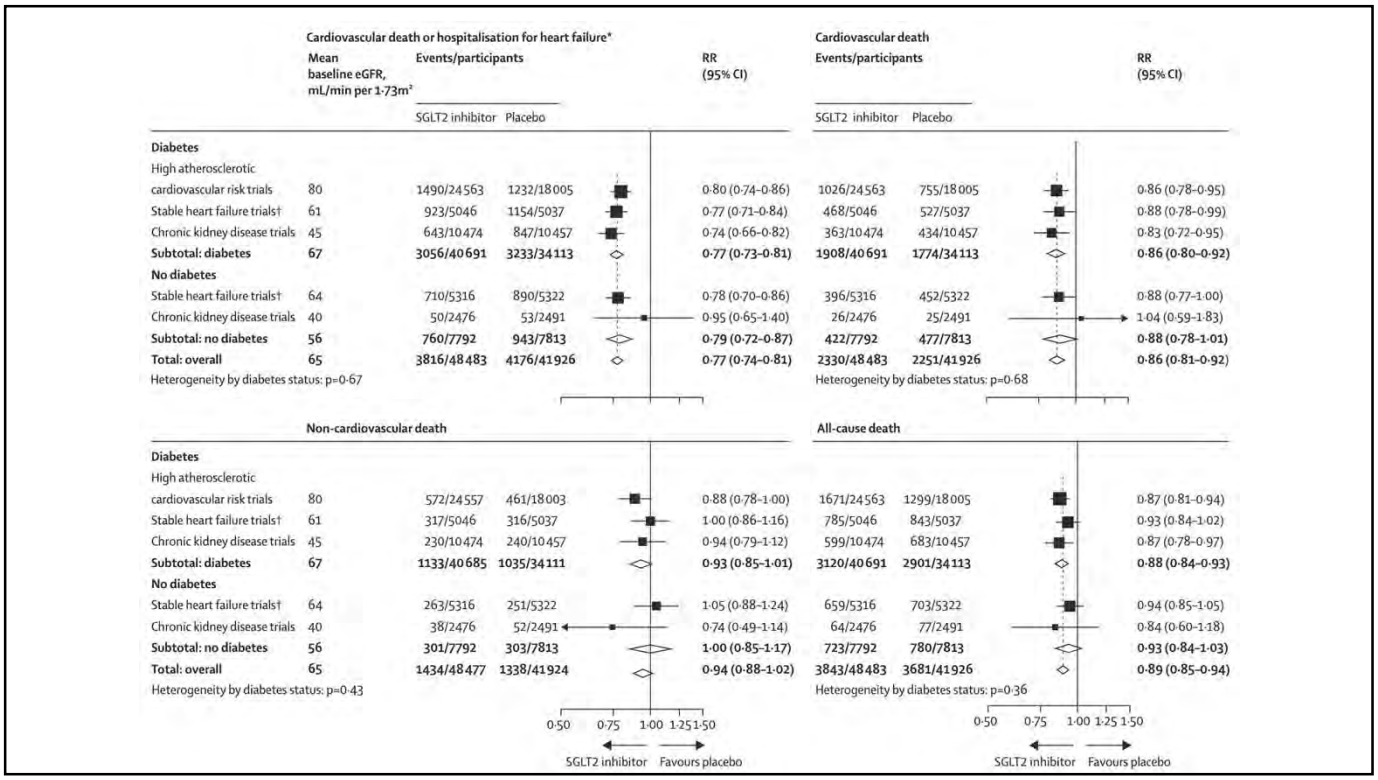
Kidney Disease Progression

With diabetes 0.62 (0.56-0.68)

Without diabetes 0.69 (0.57-0.69)

Total 0.63 (0.58-0.69)

119



120

The Flozins are not diabetes medications
They are breakthrough cardiorenal medicines that just happen to lower the blood sugar…a bit.

121

Unexpected benefits

ble in DAPA-CKD had proteinuria withou

270 of them had IgA Nephropathy

effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney International*, *100*(1), 215–224.

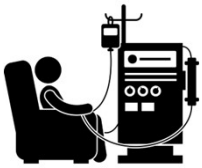
122

# of DAPA-CKD had no proteinuria but nc

270 of them had IgA Nephropathy

HR 0.29

50% decline in eGFR



ESKD

Death from renal disease

effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney International*, *100*(1), 215–224.

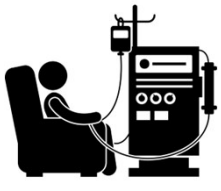
123

If you add in EMPA-Kidney…

1087 of them had IgA Nephropathy

HR 0.49

50% decline in eGFR



ESKD

Death from renal disease

hibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *The Lancet*, *400*(10365), 1788–1801.

124

At what GFR can you start them?
At what GFR should you stop them?

125

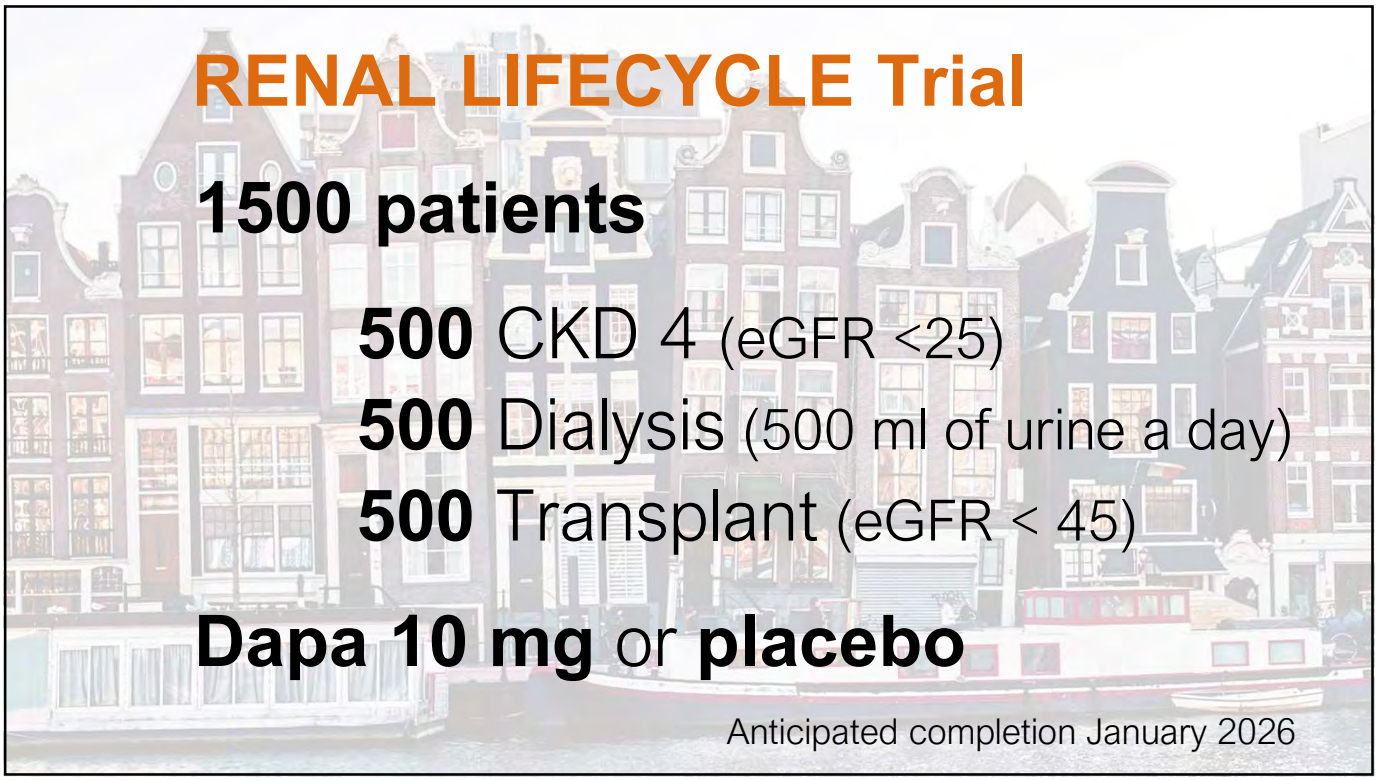
126


How deep can you go?
Limit for hypo-glycemic effect
45 ml/min per 1.73 m2
EMPA Jardiance
CANVAS Invokana
CREDENCE Invokana
30 ml/min per 1.73 m2
DAPA-CKD Farxiga
25 ml/min per 1.73 m2
EMPA-Kidney Jardiance
EMPEROR-Reduced Jardiance
20 ml/min per 1.73 m2

127


DAPA-CKD
25 ml/min per 1.73 m2
EMPA-Kidney
EMPEROR-Reduced
20 ml/min per 1.73 m2
DAPA-CKD
CREDENCE
EMPA-Kidney
0 ml/min per 1.73 m2

128



129

I initiate Flozins down to an eGFR 20 ml/min and I never stop them

130

ACEi/ARB provide remarkable nephroprotection if patients are proteinuric.

No Proteinuria…No Protection

RESEARCH

OPEN ACCESS

Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials

Sripal Bangalore,[1] Robert Fakheri,[1] Bora Toklu,[2] Franz H Messerli[1]

ABSTRACT

OBJECTIVE
To evaluate the outcomes with use of renin angiotensin system (RAS) blockers compared with other antihypertensive agents in people with diabetes.

DESIGN
Meta-analysis.

DATA SOURCES AND STUDY SELECTION
PubMed, Embase, and the Cochrane central register of controlled trials databases for randomized trials of RAS blockers versus other antihypertensive agents in people with diabetes mellitus. Outcomes were death, cardiovascular death, myocardial infarction, angina, stroke, heart failure, revascularization, and end stage renal disease.

RESULTS
The search yielded 19 randomized controlled trials that enrolled 25 414 participants with diabetes for a total of 95 910 patient years of follow-up. When compared with other antihypertensive agents, RAS blockers were associated with a similar risk of death (relative risk 0.99, 95% confidence interval 0.93 to 1.05), cardiovascular death (1.02, 0.83 to 1.24), myocardial infarction (0.87, 0.64 to 1.18), angina pectoris (0.80, 0.58 to 1.11), stroke (1.04, 0.92 to 1.17), heart failure (0.90, 0.76 to 1.07), and revascularization (0.97, 0.77 to 1.22). There was also no difference in the hard renal outcome of end stage renal disease (0.99, 0.78 to 1.28) (power of 94% to show a 23% reduction in end stage renal disease).

CONCLUSIONS
In people with diabetes, RAS blockers are not superior

endpoints. These findings support the recommendations of the guidelines of the European Society of Cardiology/European Society of Hypertension and eighth joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to also use other antihypertensive agents in people with diabetes but without kidney disease.

Introduction
People with diabetes are at increased risk of cardiovascular and renal events.[1] Early placebo controlled trials (such as the Heart Outcomes Prevention Evaluation and European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease) have shown significant benefits from use of renin angiotensin system (RAS) blockers on cardiovascular and renal events in people with diabetes, benefits touted to be independent of the drugs blood pressure lowering efficacy. As such, the 2015 American Diabetes Association guidelines recommend RAS blockers (angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)) as first line treatment for people with diabetes and hypertension.[2] Similarly, the 2013 American Society of Hypertension/International Society of Hypertension guidelines favor RAS blockers as a first line treatment in people with diabetes.[3] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative clinical practice guidelines state in its executive summary that "Hypertensive people with diabetes and chronic kidney disease stages 1-4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic."[4] In contrast, the 2013 European

BMJ: first published as 10.1136/bmj.i438 on 11 February 2016. Downloaded from http://www.bmj.com/ on 6 Octob

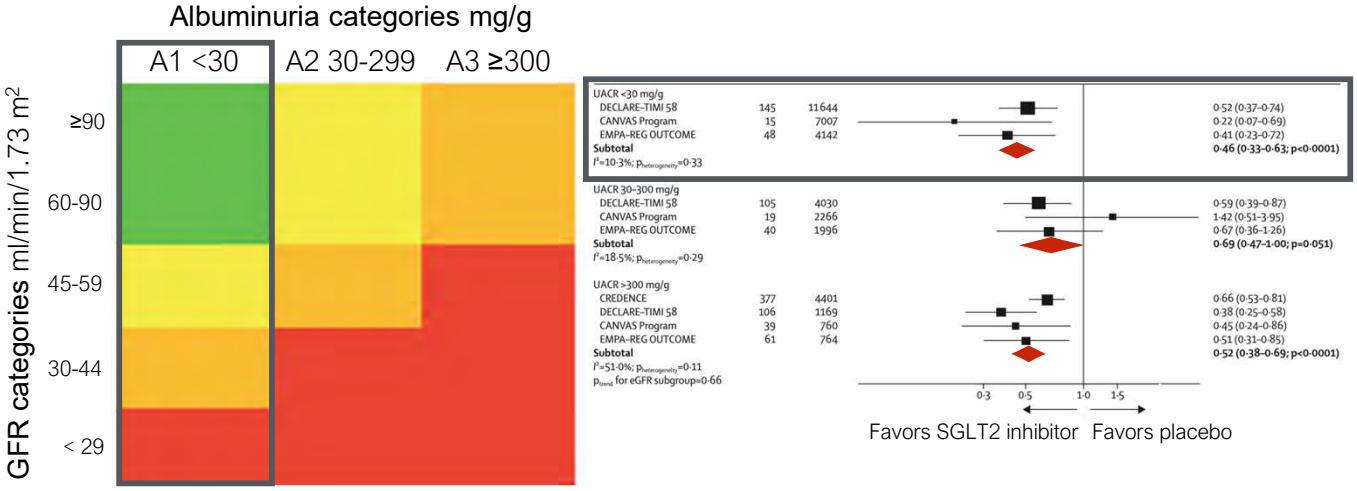
Conclusions

This analysis of head to head comparison trials of RAS blockers versus other antihypertensive agents in people with diabetes (and largely without microalbuminuria or proteinuria) failed to show a superiority of RAS blockers compared with other antihypertensive agents for the prevention of hard outcomes. The results support the recommendation of both the 2013 European Society of Cardiology/European Society of Hypertension guidelines[5] and the 2014 eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[6] that any class of antihypertensive agents can be used in people with diabetes especially in those without renal impairment.

Bangalore, S., Fakheri, R., Toklu, B., & Messerli, F. H. (2016). Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ*, *352*, i438.

131

Proteinuria is not important with #Flozins



n of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *The Lancet. Diabetes & Endocrinology*, *7*(11), 845–854

132

Easy drug
No monitoring
Start it and forget it

133

No monitoring
Start it and forget it

First follow up visit in EMPA-Kidney was 8 weeks

134

Cholesterol

Target LDL, Apo B, Non-HDL

Adjust between normal and high potency statins depending on patient risk factors, CAC, and LDL. Screen for and adjust for myalgia.

Diabetes

Monitor A1c Point of care glucose

Juggle multiple medications, often a mix of oral and injection formulations, to avoid side effects and patient discomfort.

Blood Pressure

Home BP monitoring Sitting and standing BP

Monitor electrolytes and kidney function

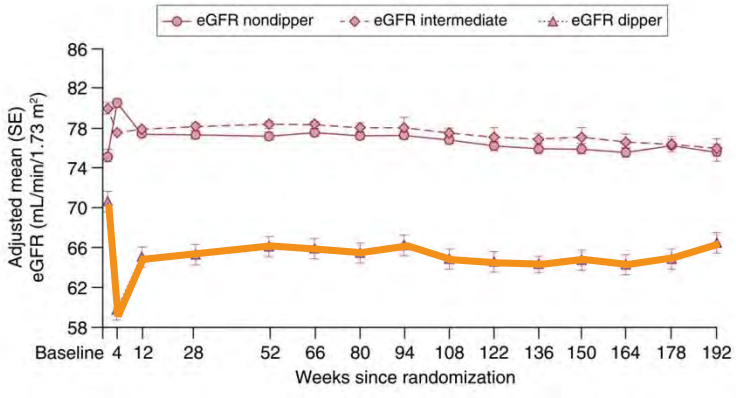
SGLT2i

Prescribe the medication.

135

What about the acute drops in GFR after starting SGLT2i?

EMPA-Reg 28% had >10% drop in GFR
Risk factors: lower GFR, more proteinuria, diuretic use



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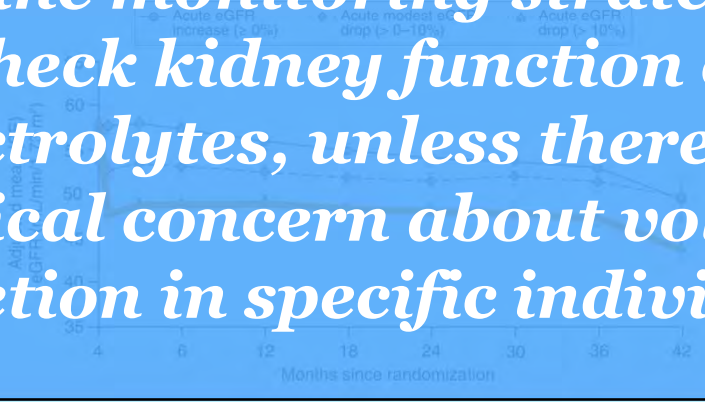
What about the acute drops in GFR after starting SGLT2i?

CREDENCE 4% had >10% drop in GFR
30% drop in GFR in 1 in 200 people



it seems reasonable to conclude that in the majority of patients, there is no need to have a routine monitoring strategy to check kidney function or electrolytes, unless there is a clinical concern about volume depletion in specific individuals

137

What about acute kidney injury?

AKI with DAPA

63 2.9%

AKI with Placebo

91 4.2%

Serious AKI with EMPA

107 1.67
Events per 100 pt yrs

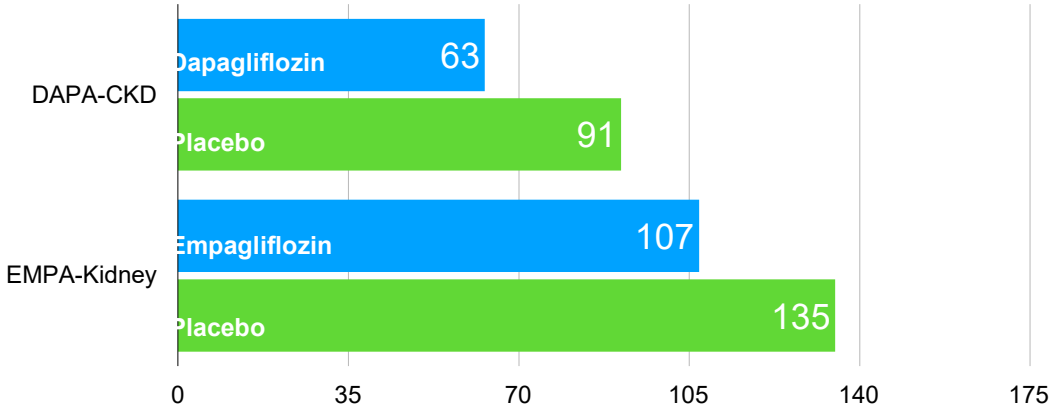
Serious AKI with Placebo

135 2.11
Events per 100 pt yrs

ndomized controlled trial on the incidence of abrupt declines in kidney function. In *Kidney International*. https://doi.org/10.1016/j.kint.2021.09.005

138

What about acute kidney injury?



s in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function. *Kidney International*.
EMPA-KIDNEY Collaborative Group, Et. al. (2022). Empagliflozin in Patients with Chronic Kidney Disease. NEJM.

139

What about amputations?

News & Perspective

EMA: Amputation Warning With SGLT2 Inhibitors Must Be on Label

Miriam E Tucker
February 10, 2017

Add to Email Alerts

A European Medicines Agency (EMA) panel has determined that a warning stating that the sodium glucose cotransporter 2 (SGLT2) inhibitors for type 2 diabetes may increase the risk for lower-limb amputation should be included in the prescribing information for all drugs in this class.

The warning from EMA's Pharmacovigilance Risk Assessment Committee (PRAC) issued today cites data from two ongoing clinical trials with canagliflozin (*Invokana, Vokanamet*, Janssen) in patients at high risk for cardiovascular events, Canagliflozin Cardiovascular Assessment Study (CANVAS) and a related study of renal end points, CANVAS-R.

The EMA had announced its investigation into the possible lower-limb amputation risk with canagliflozin in April 2016 and expanded its investigation to include all SGLT2 inhibitors—that is, dapagliflozin (*Farxiga, Xigduo XR, Ebymect, Edistride, Qtern*, AstraZeneca) and empagliflozin (*Jardiance, Glyxambi, Synjardy*, Boehringer Ingelheim) as well—in July 2016.

"The mechanism by which canagliflozin may increase the risk of amputation is still unclear," according to the latest PRAC statement. "An increased risk has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin. However, data available to date are limited and the risk may also apply to these other medicines. Further data are expected from ongoing studies with canagliflozin, dapagliflozin, and empagliflozin."

canagliflozin (Invokana)

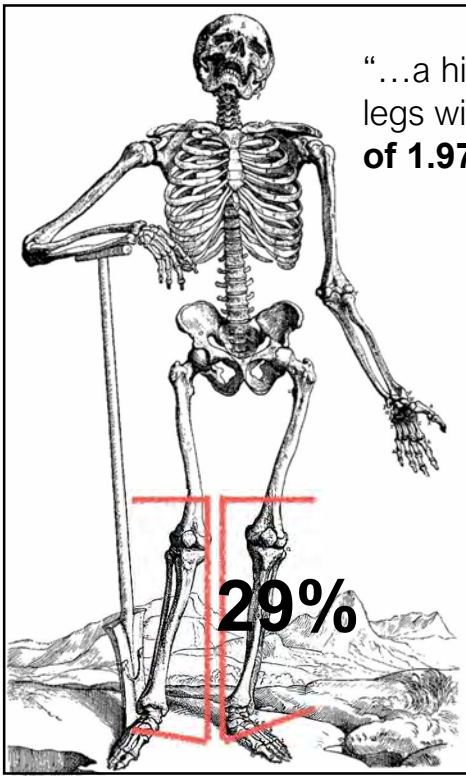
100 mg/d: 7 amputations per 1,000

300 mg/d: 5 amputations per 1,000

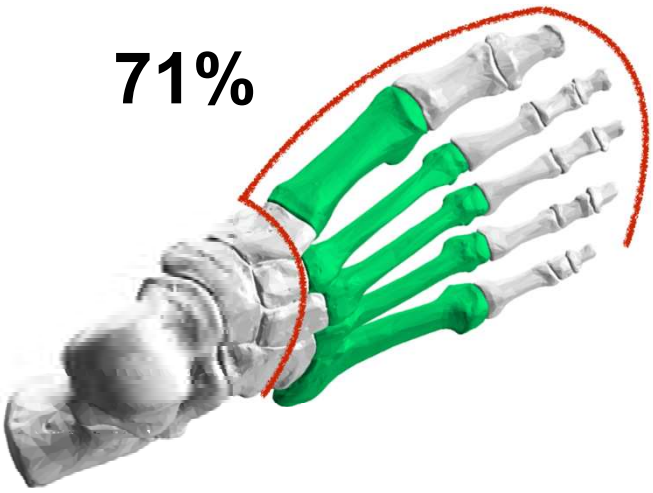
Placebo: 3 amputations per 1,000

"…amputations were most commonly of the toe and middle of the foot…"

140



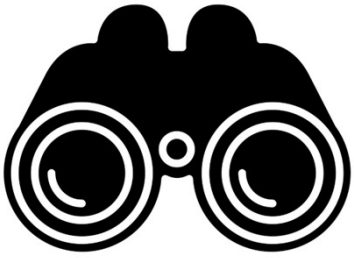
"…a higher risk of amputation of toes, feet, or legs with canagliflozin than with placebo." **HR of 1.97**; 95% CI, 1.41-2.75



141

Empagliflozin did not have an amputation risk

Was this because they weren't looking?



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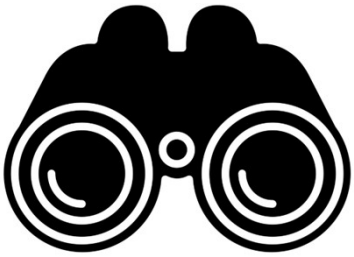
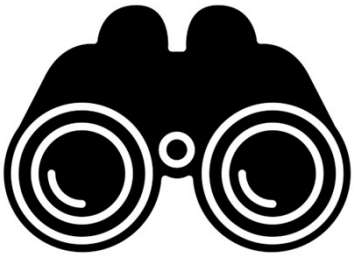
Inzucchi SE, et al. Empagliflozin and Assessment of Lower-Limb Amputations in the EMPA-REG OUTCOME Trial. Diabetes Care. 2017



Any hospital admission during the EMPA-REG OUTCOME trial was to be reported as a serious adverse event. Investigators were asked to provide a detailed narrative with additional medical information for each serious adverse event.

143

Inzucchi SE, et al. Empagliflozin and Assessment of Lower-Limb Amputations in the EMPA-REG OUTCOME Trial. Diabetes Care. 2017



131

Lower Limb Amputations

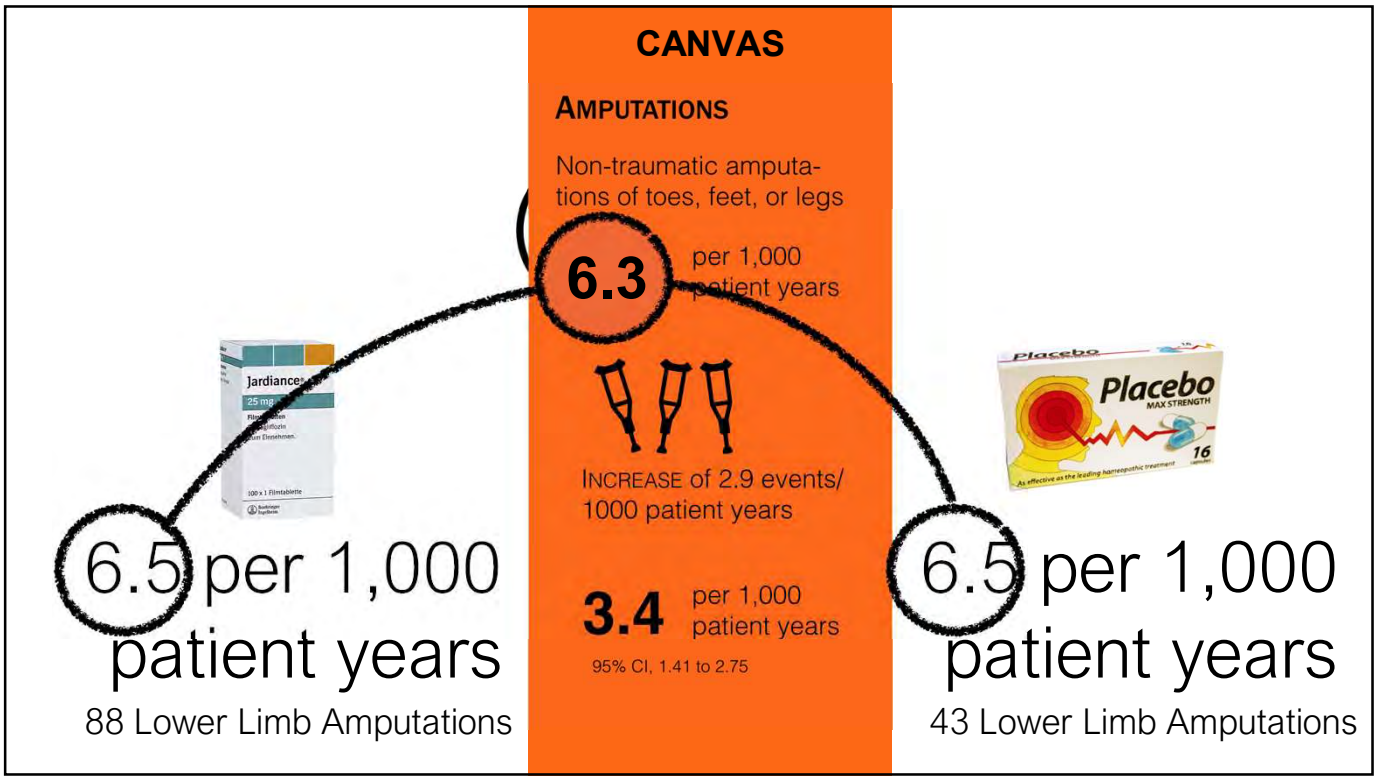
6.5 per 1,000 patient years

88 Lower Limb Amputations

6.5 per 1,000 patient years

43 Lower Limb Amputations

144



145

Amputation risk not seen in CREDENCE

FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)

Based on our review of new clinical trial data

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This information is an update to the FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) issued on May 16, 2017.

Drug Safety Communication (PDF - 58KB)

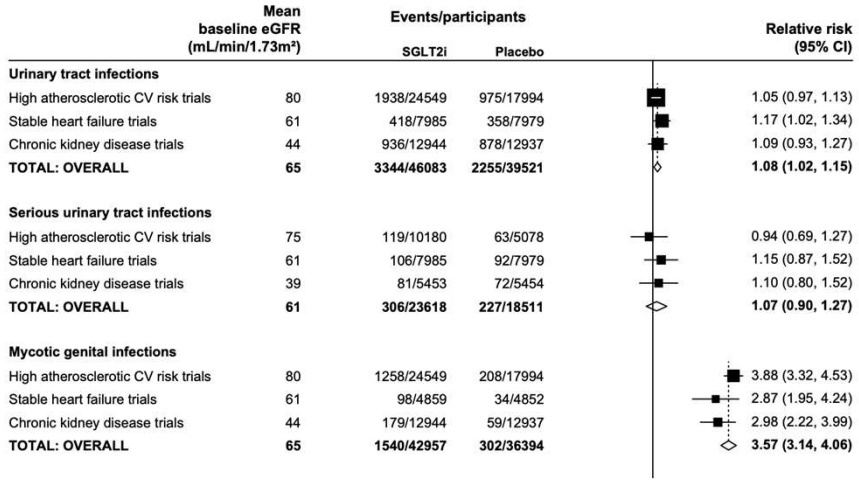
8-26-2020 FDA Drug Safety Communication

Based on a U.S. Food and Drug Administration (FDA) review of new data from three clinical trials, we have removed the *Boxed Warning* about amputation risk from the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) prescribing information.

We required the *Boxed Warning* in 2017 based on our assessment that the risk of amputations was very serious in relation to the potential benefit of canagliflozin, which was initially approved to be used with diet and exercise to lower blood sugar in adults with type 2 diabetes. Subsequent FDA reviews of new clinical trial data demonstrated additional heart- and kidney-related benefits, which led to additional approved uses. Specifically, in 2018, canagliflozin was approved to reduce the risk of major heart-related events such as heart attack, stroke, or death in patients with type 2 diabetes who have known heart disease; and, in 2019, it was approved to reduce the risk of end-stage kidney

146

ose to mycotic genital infections. The UT



RR 1.08
(1.02-1.15)

RR 1.07
(0.90-1.27)

RR 3.57
(3.14-4.06)

on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *The Lancet*, *400*(10365), 1788–1801

147

e to mycotic genital infections. The UTI s

	Placebo	Empagliflozen
UTI	18.1%	18.0%
Males	9.4%	10.5%
Females	40.6%	36.4%
Genital infection	1.8%	6.4%
Males	1.5%	5.0%
Females	2.6%	10.0%

EMPA-Reg

148

ctions are associated with urogenital infe

	Placebo per 1000 patient years	Empagliflozen per 1000 patient years	P
UTI	37	40	0.38
Mycotic infection in women	17.5	68.8	<0.001

CANVAS

149

ctions are associated with urogenital infe

	Placebo	Canagliflozen	CI
UTI	10.1%	11.1%	1.08 (0.90-1.29)
Genital infection			
Males	0.2%	1.9%	9.3 (2.83-30.6)
Females	1.4%	2.9%	2.1 (1.00-4.45)

CREDENCE

150

ctions are associated with urogenital infe

	Placebo	Dapagliflozen	P
UTI	17 (0.7%)	13 (0.5%)	0.38

DAPA-HF

151

ctions are associated with urogenital infe

	Placebo	Empagliflozen	P
UTI	1.6%	1.5%	0.54
Mycotic infection in women	0.1%	0.9%	<0.001

DECLARE

152

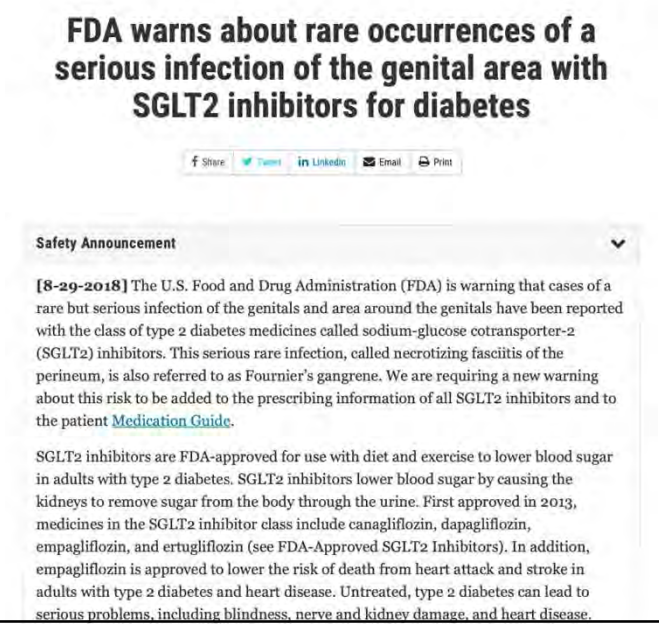
Fournier's gangrene

12 cases

7 men

5 women

1 death



FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes

Share Tweet LinkedIn Email Print

Safety Announcement

[8-29-2018] The U.S. Food and Drug Administration (FDA) is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.

SGLT2 inhibitors are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. First approved in 2013, medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (see FDA-Approved SGLT2 Inhibitors). In addition, empagliflozin is approved to lower the risk of death from heart attack and stroke in adults with type 2 diabetes and heart disease. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

153

Fournier's gangrene

Very rare. Of the 90,000 patients evaluated in the large RCTs,
25 cases were documented.
14 with placebo and
11 with SGLT2i

s on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *The Lancet*, *400*(10365), 1788–1801

154

Fournier's gangrene

In nested case control of 216 cases
5.2 cases per 100,000 patient years

♂ 9.2
♀ 0.8

4.2% were on Flozens

Odds Ratio **0.55** (0.25-1.18)

Flozens appear protective

angrene: A nested case-control study. *Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders*, *11*(3), 711–723.

155

Euglycemic DKA Slides?

Erythrocytosis

https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.26933?campaign=wolearlyview

156

Hints from a flozinator

Every morning, when I look in the mirror, I ask myself, "Are you a Flozinator?"

–Matt Sparks

157

Hints from a flozinator

Patients get more diuresis with higher degrees of glycemia. None of the large RCTs enrolled patients with A1c over 12.

This is a drug that saves hearts and kidneys; your goal is to make it as tolerable as possible. Save it until there is reasonable glycemic control.

158

Hints from a flozinator

Don't introduce it as a new medication.

It is a medication that has been around for a decade (2013), that we are now recognizing as the most powerful kidney protective medication ever discovered; and is also among the most powerful cardioprotective medications.

159

Hints from a flozinator

It is based on a molecule initially isolated from apple bark. I don't know why but that really resonates with some people.

160

161

Ozempic for Weight Loss Is Disrupting Companies' Business Models

- Firms under pressure to decide what action to take, if any
- One CEO says he's already seeing 'kind of nutty thinking'

Ozempic *Photographer: Florian Gaertner/Photothek/Getty Images*

By Leslie Patton
October 7, 2023 at 9:00 AM EDT

Bloomberg

162

Short Fast Food Credit Because of Ozempic, Barclays Says

- Demand for snacks, cigarettes may be hit as drugs proliferate
- Stocks seem to have been hit harder by fear than credits

Novo CEO on Ozempic, Wegovy Demand, Acquisition Strategy

By Michael Tobin
October 3, 2023 at 12:57 PM EDT

Bloomberg

163

Ozempic Is Making People Buy Less Food, Walmart Says

- Retailer is analyzing shopping behavior of people on drug
- Prescriptions for GLP-1s, like Ozempic, are boosting sales

Ozempic Weighs on Walmart Sales *Source: Bloomberg*

By Brendan Case and Shelly Banjo
October 4, 2023 at 3:35 PM EDT
Updated on October 5, 2023 at 3:25 PM EDT

Bloomberg

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BUSINESS

America's Food Giants Confront the Ozempic Era

Nearly 7% of the population is projected to be on weight-loss drugs in 2035

By *Jesse Newman* Follow

Updated Oct. 5, 2023 12:04 am ET

WSJ

Morgan Stanley has projected that 24 million people, or nearly

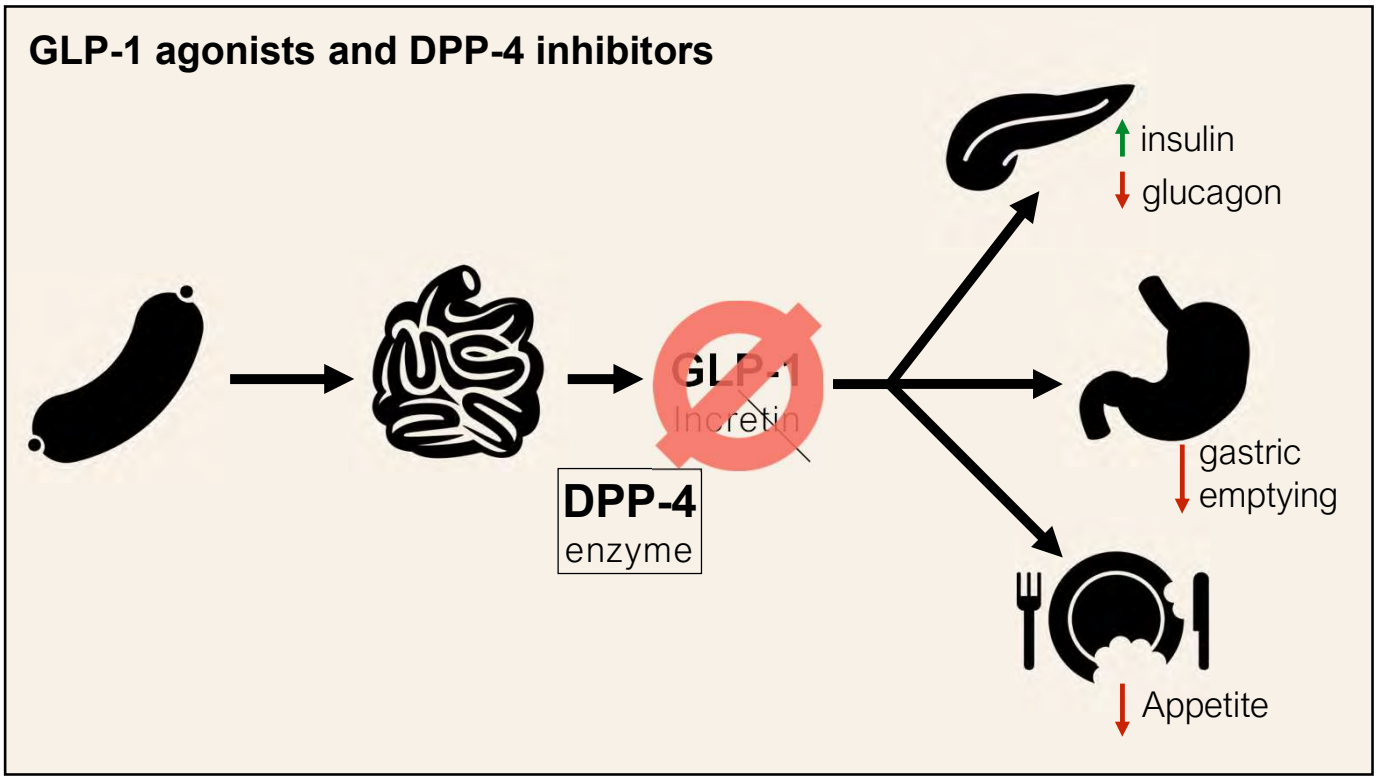
7% of the U.S. population

will be taking such medications by 2035

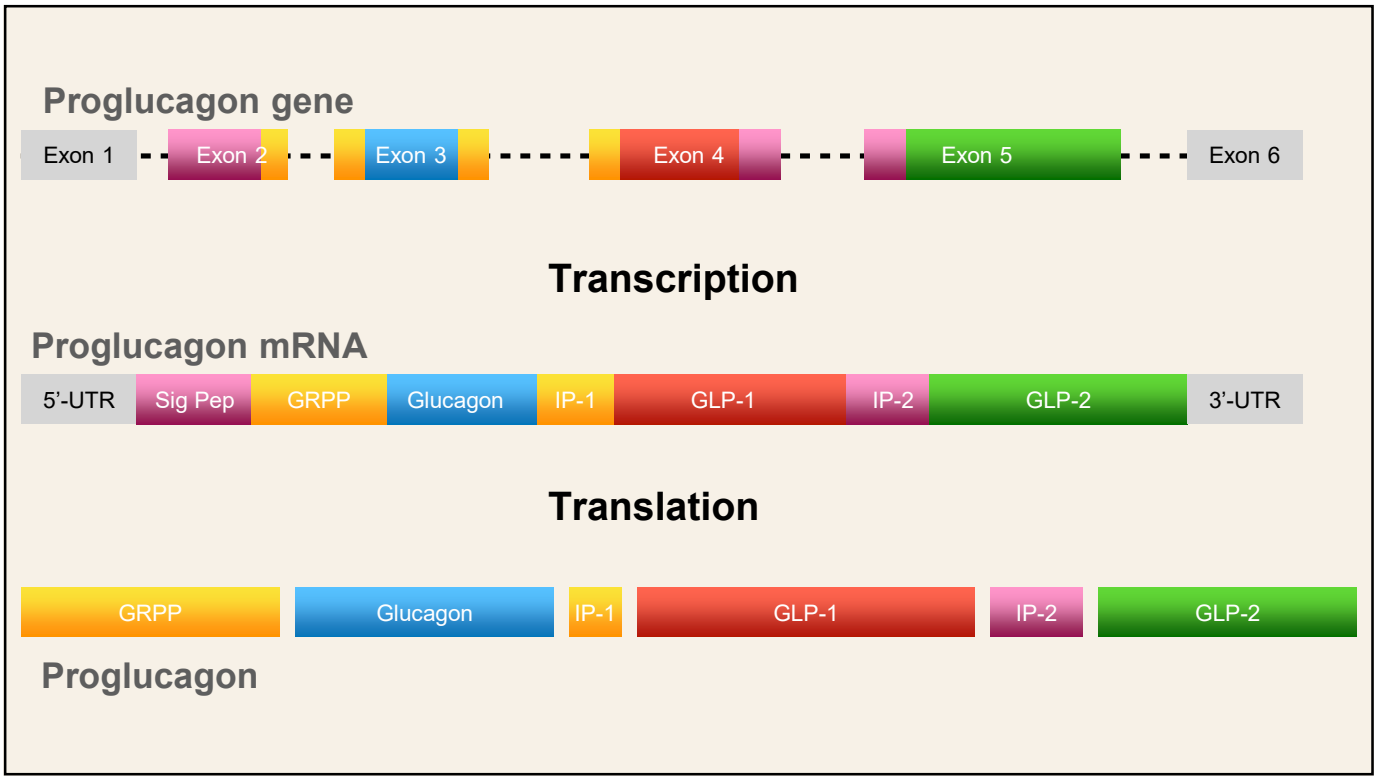
165

Humility

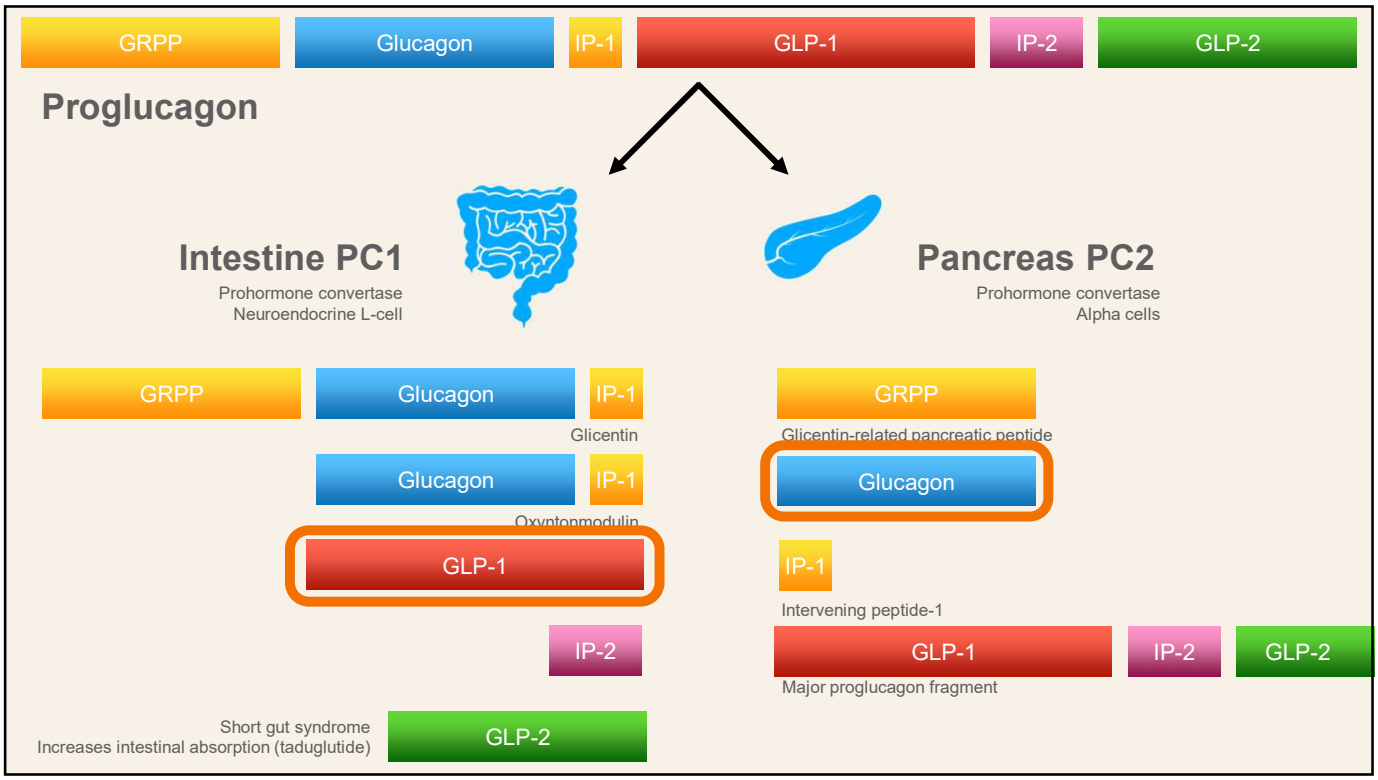
166


GLP-1 agonists and DPP-4 inhibitors
insulin
glucagon
GLP-1
Incretin
DPP-4
enzyme
gastric
emptying
Appetite

167


Proglucagon gene
Exon 1
Exon 2
Exon 3
Exon 4
Exon 5
Exon 6
Transcription
Proglucagon mRNA
5'-UTR
Sig Pep
GRPP
Glucagon
IP-1
GLP-1
IP-2
GLP-2
3'-UTR
Translation
GRPP
Glucagon
IP-1
GLP-1
IP-2
GLP-2
Proglucagon

168



169

GLP-1

Insulin Secretion

Insulin production

170

Islet function

GLP-1 mimetics

Restore normal morphology

171

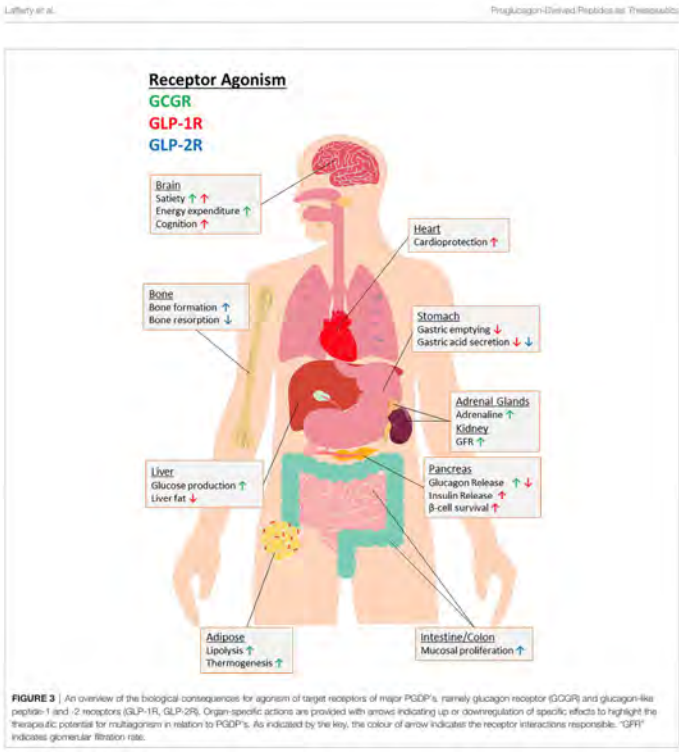


FIGURE 3 | An overview of the biological consequences for agonism of target receptors of major PGDP's, namely glucagon receptor (GCGR) and glucagon-like peptide-1 and -2 receptors (GLP-1R, GLP-2R). Organ-specific actions are provided with arrows indicating up or downregulation of specific effects to highlight the therapeutic potential for multiagonism in relation to PGDP's. As indicated by the key, the colour of arrow indicates the receptor interactions responsible. "GFR" indicates glomerular filtration rate.

172

GLP-1 is rapidly broken down by DPP-4 requiring continuous infusion for biological activity

173

Exendin-4 Substitution of Ala^2 with Gly^2 made it resistant to DPP

Further engineering made it resistant neprolysn and allowed for twice daily dosing

174

Exendin-4 was brought to market a

DPP-4 inhibitors came to market in 2007

175

Lets start with semaglutide

176

Cardiovascular outcome trial (CVOT)

Semaaglutide **SUSTAIN-6**

Marso, S. P., Bain, S. C., Consoli, A., & SUSTAIN-6 Investigators. (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England Journal of Medicine*, *375*(19), 1834–1844.

177

Cardiovascular outcome trial (CVOT)

Semaaglutide **SUSTAIN-6**

3297 patients

64.6±7.4 yrs

20 Countries

92.1±20.6 kg

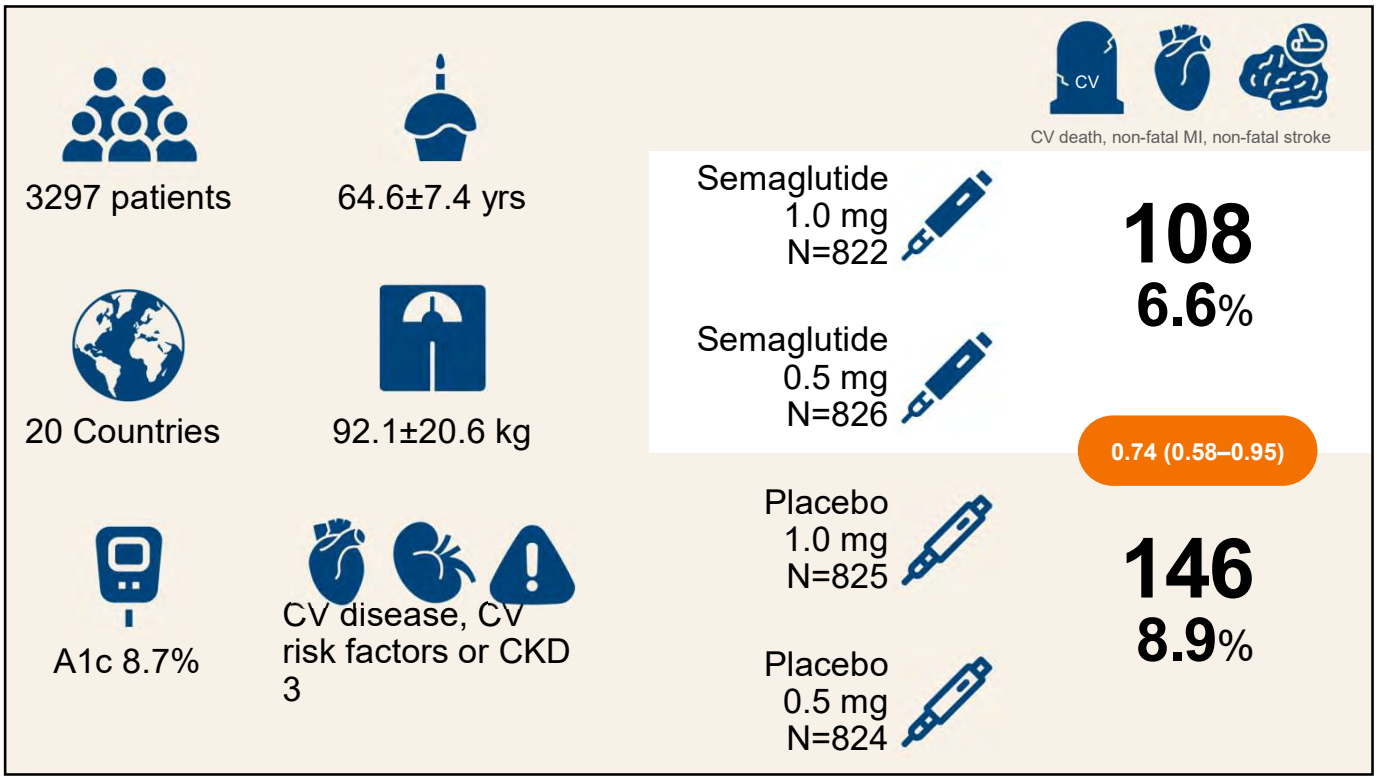
2.1 years follow-up

A1c 8.7%

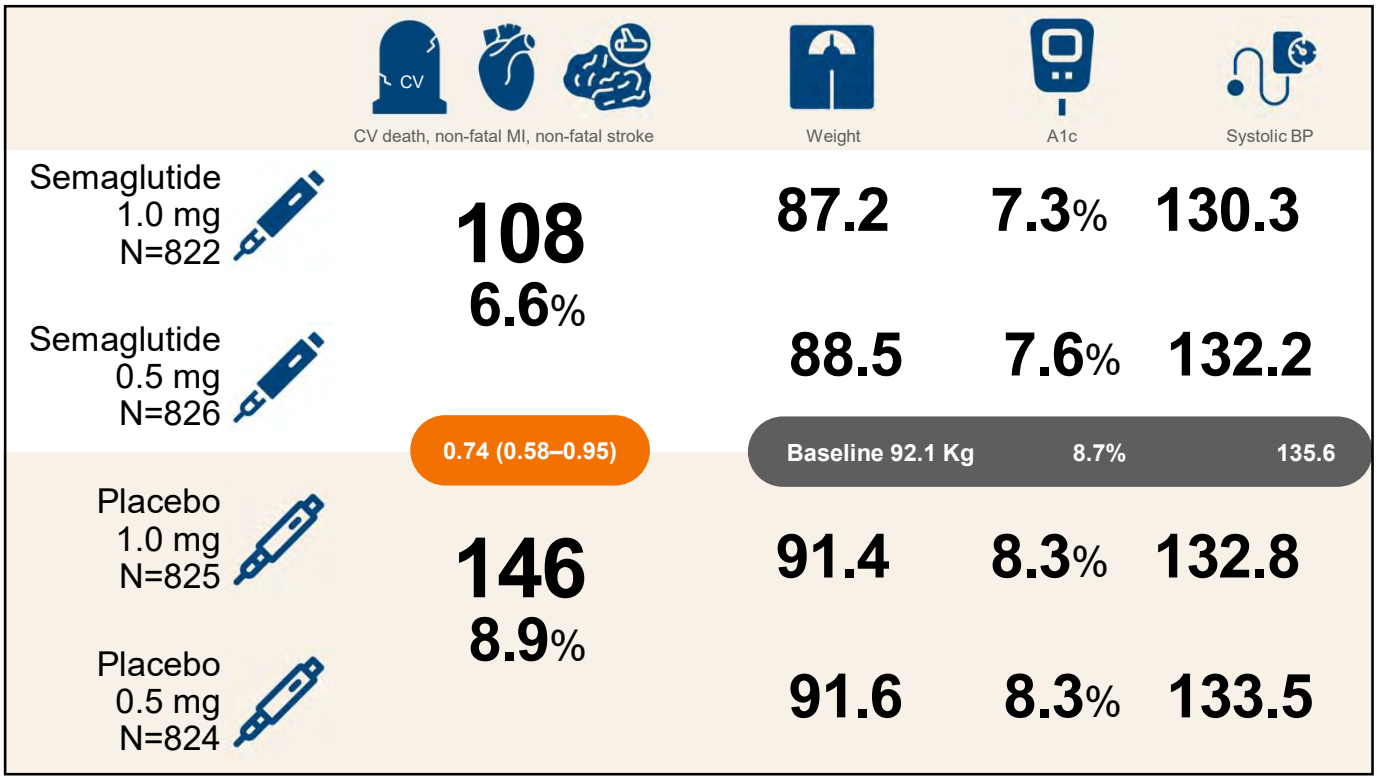
CV disease, CV risk factors or CKD 3

Marso, S. P., Bain, S. C., Consoli, A., & SUSTAIN-6 Investigators. (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England Journal of Medicine*, *375*(19), 1834–1844.

178


3297 patients
64.6±7.4 yrs
20 Countries
92.1±20.6 kg
A1c 8.7%
CV disease, CV risk factors or CKD 3
CV
CV death, non-fatal MI, non-fatal stroke
Semaglutide 1.0 mg N=822
108
6.6%
Semaglutide 0.5 mg N=826
0.74 (0.58–0.95)
Placebo 1.0 mg N=825
146
8.9%
Placebo 0.5 mg N=824

179


CV
CV death, non-fatal MI, non-fatal stroke
Weight
A1c
Systolic BP
Semaglutide 1.0 mg N=822
108
6.6%
87.2
7.3%
130.3
Semaglutide 0.5 mg N=826
88.5
7.6%
132.2
0.74 (0.58–0.95)
Baseline 92.1 Kg
8.7%
135.6
Placebo 1.0 mg N=825
146
8.9%
91.4
8.3%
132.8
Placebo 0.5 mg N=824
91.6
8.3%
133.5

180

	Serious Adverse Event	GI Disorders	Acute pancreatitis	Gall bladder disorders
Semaglutide 1.0 mg N=822	25.2%	52.3%	3	3.2%
Semaglutide 0.5 mg N=826	24.2%	50.7%	6	3.9%
Placebo 1.0 mg N=825	23.5%	35.2%	9	2.8%
Placebo 0.5 mg N=824	26.2%	35.7%	3	4.6%

181

	Cancer	Pancreatic cancer	Thyroid cancer
Semaglutide 1.0 mg N=822	4.9%	1	0
Semaglutide 0.5 mg N=826	3.1%	0	0
Placebo 1.0 mg N=825	4.2%	2	0
Placebo 0.5 mg N=824	4.2%	2	0

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Home / News / Health News / Study Confirms Risk of Gastro..

Study Confirms Risk of Gastro Issues for People Taking Wegovy, Ozempic

By HealthDay Oct. 5, 2023

Save Comment

By Steven Reinberg HealthDay Reporter

THURSDAY, Oct. 5, 2023 (HealthDay News) – While many have raved about the powers of popular weight-loss drugs like Wegovy and Ozempic, new research confirms the medications can trigger some nasty gastrointestinal side effects.

(HEALTHDAY)

FORBES > INNOVATION

BREAKING

Ozempic, Wegovy And Similar Drugs Boost Rare —But Serious—Stomach Issues, Study Shows

Arianna Johnson Forbes Staff

I cover the latest trends in science, tech and healthcare.

Follow

October 5, 2023

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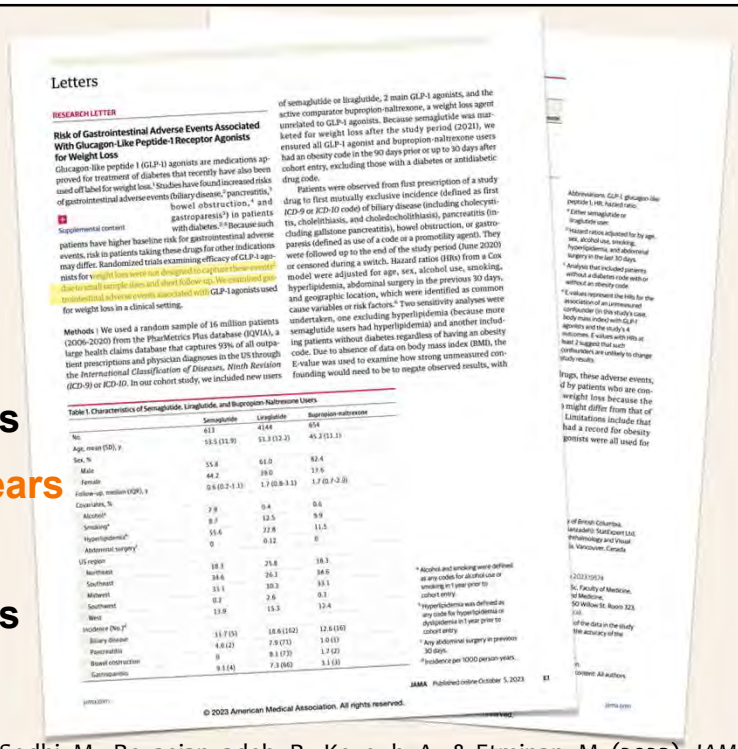
"Randomized trials examining efficacy of GLP-1 agonists for weight loss were not designed to capture these events due to small sample sizes and short follow-up."

Semaglutide N=613
Duration of follow-up, 0.6 years

SUSTAIN-6 had 1648 for 2.1 years

Liraglutide N=4144
Duration of follow-up, 1.7 years

Leader had 4668 for 3.8 years



Letters

RESEARCH LETTER

Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss

Glucagon-like peptide 1 (GLP-1) agonists are medications approved for treatment of diabetes that recently have also been used off label for weight loss.[1] Studies have found increased risks of gastrointestinal adverse events (biliary disease,[2] pancreatitis,[3] bowel obstruction,[4] and gastroparesis[5]) in patients with diabetes.[2,3] Because such patients have higher baseline risk for gastrointestinal adverse events, risk in patients taking these drugs for other indications may differ. Randomized trials examining efficacy of GLP-1 agonists for weight loss were not designed to capture these events due to short small sample sizes and short follow-up. We examined gastrointestinal adverse events associated with GLP-1 agonists used for weight loss in a clinical setting.

Table 1. Characteristics of Semaglutide, Liraglutide, and Bupropion-Naltrexone Users

	Semaglutide	Liraglutide	Bupropion-naltrexone
No.	613	4144	654
Age, mean (SD), y	53.5 (11.9)	51.3 (12.2)	45.2 (11.1)
Sex, %			
Male	55.8	61.0	82.4
Female	44.2	39.0	17.6
Follow-up, median (IQR), y	0.6 (0.2-1.1)	1.7 (0.8-3.1)	1.7 (0.7-2.3)
Covariates, %			
Alcohol[a]	7.9	9.4	8.6
Smoking[a]	8.7	12.5	9.9
Hyperlipidemia[a]	55.6	72.8	11.5
Abdominal surgery[a]	0	0.12	0
US region			
Northeast	18.1	25.8	18.3
Southeast	34.6	26.1	34.6
Midwest	33.1	10.3	33.1
Southwest	0.2	2.6	0.2
West	13.9	15.3	12.4
Incidence (No.)[b]			
Biliary disease	11.7 (5)	10.6 (152)	12.6 (16)
Pancreatitis	4.8 (2)	7.9 (71)	1.0 (1)
Bowel obstruction	0	8.1 (73)	1.7 (2)
Gastroparesis	9.1 (4)	7.3 (66)	3.1 (3)

[a] Alcohol and smoking were defined as any codes for alcohol use or smoking in 1 year prior to cohort entry.
[b] Hyperlipidemia was defined as any code for hyperlipidemia or dyslipidemia in 1 year prior to cohort entry.
[c] Any abdominal surgery in previous 30 days.
[d] Incidence per 1000 person-years.

JAMA Published online October 5, 2023

Sodhi, M., Rezaeianzadeh, R., Kezouh, A., & Etminan, M. (2023). *JAMA*

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Cardiovascular outcome trial (CVOT)

Liraglutide

LEADER

9340 patients

64.3±7.2 yrs

32 Countries

91.7±21.0 kg

3.8 years follow-up

A1c 8.7%

CV disease, CV risk factors or CKD 3

Marso, S. P., LEADER Steering Committee, & LEADER Trial Investigators. (2016). Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine, 375(4), 311–322.

185

9340 patients

64.3±7.2 yrs

32 Countries

91.7±21.0 kg

A1c 8.7%

CV disease, CV risk factors or CKD 3

CV death, non-fatal MI, non-fatal stroke

Liraglutide 0.6-1.8 mg N=4668

608

13.0%

0.87 (0.78–0.97)

Placebo N=4672

694

14.9%

Marso, S. P., LEADER Steering Committee, & LEADER Trial Investigators. (2016). Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine, 375(4), 311–322.

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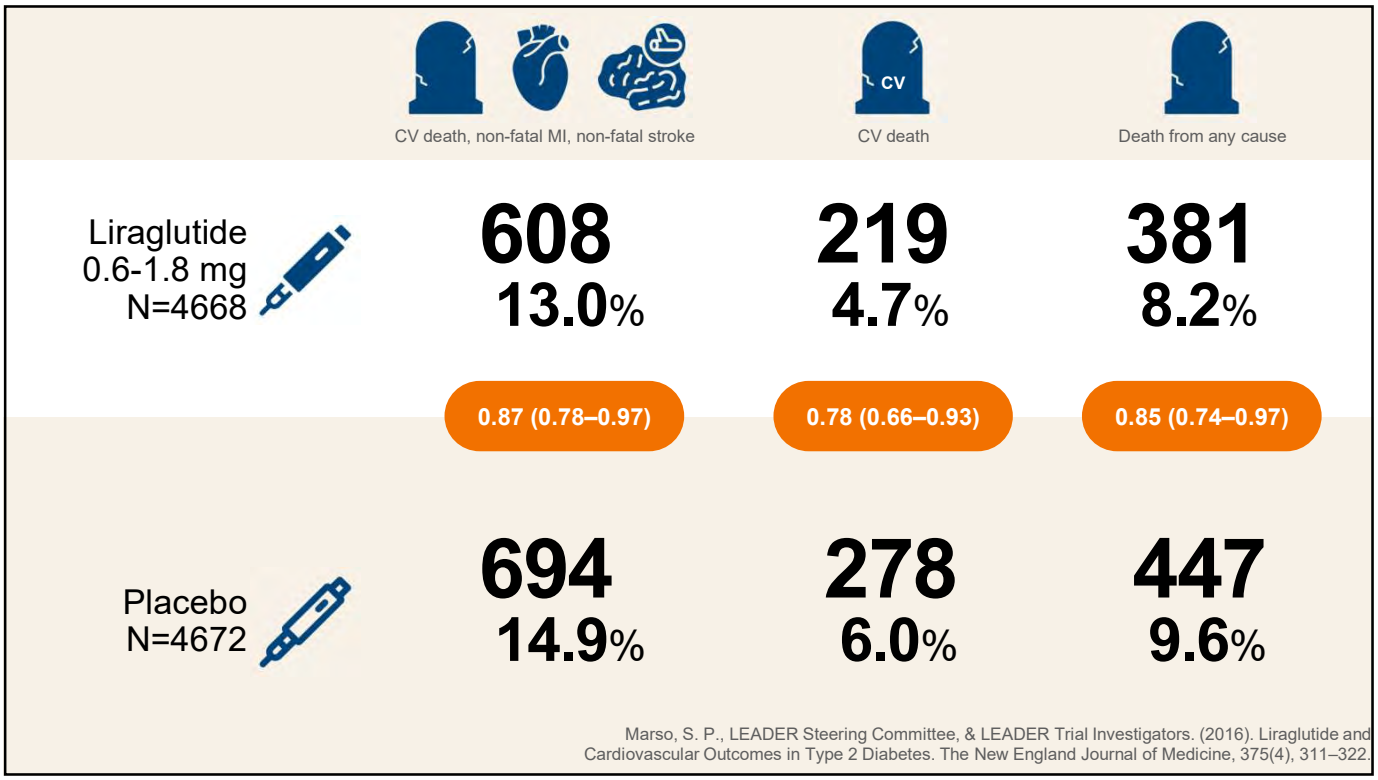

Marso, S. P., LEADER Steering Committee, & LEADER Trial Investigators. (2016). Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine, 375(4), 311–322.

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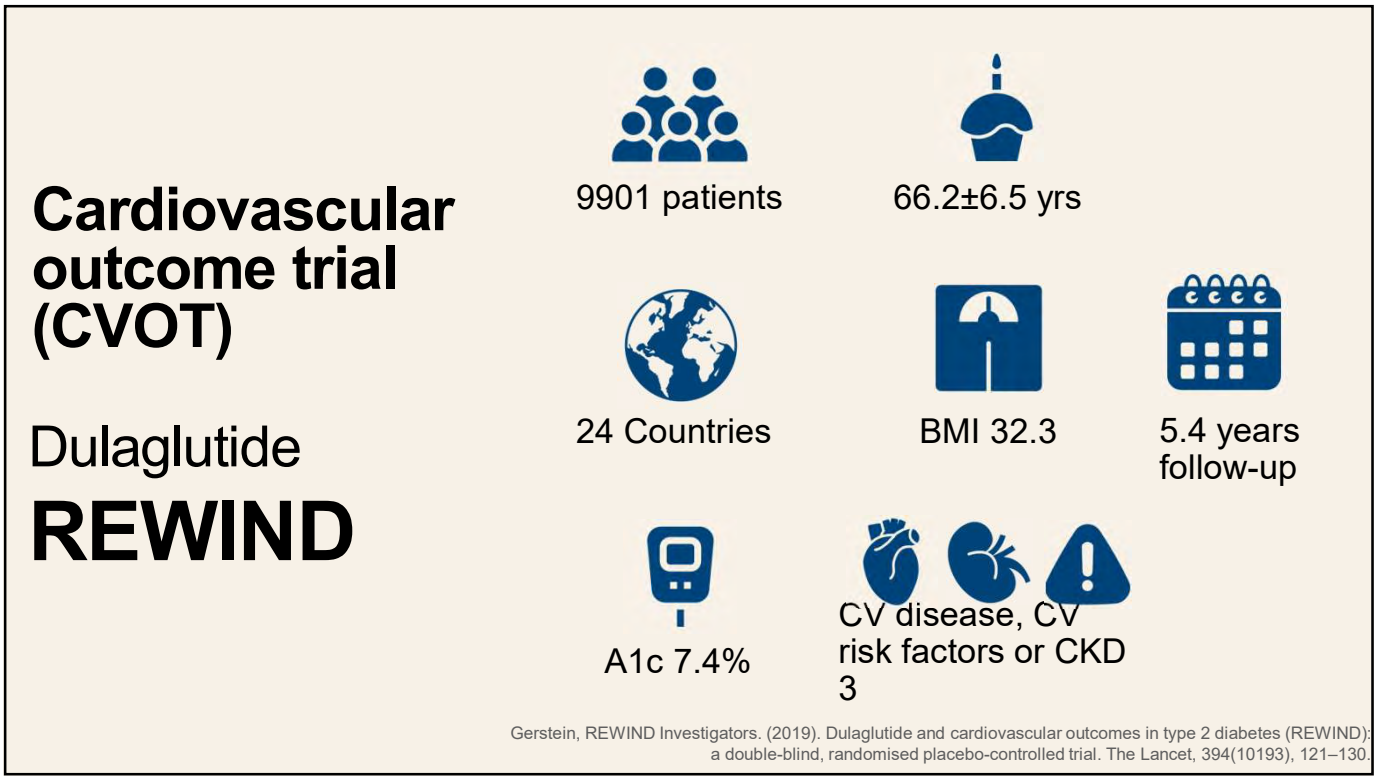

Gerstein, REWIND Investigators. (2019). Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The Lancet, 394(10193), 121–130.

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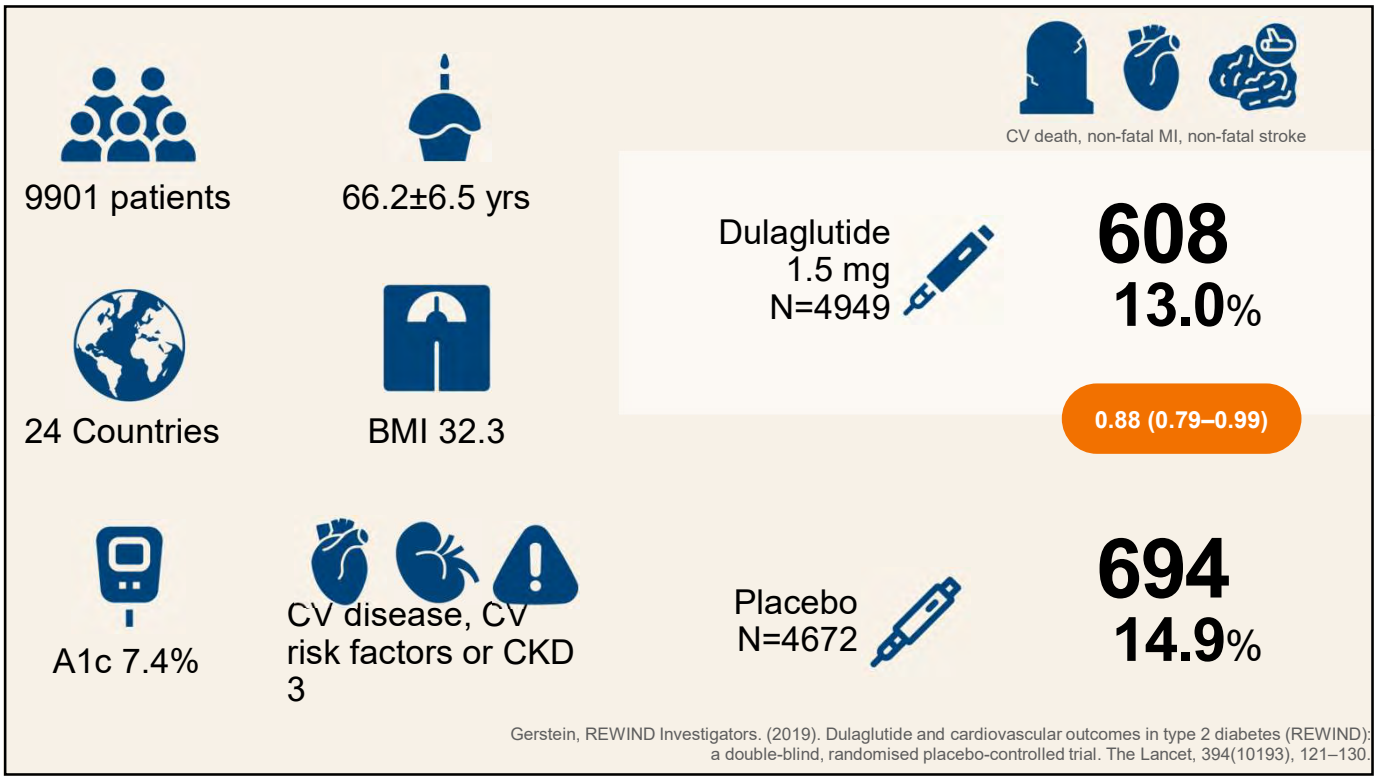
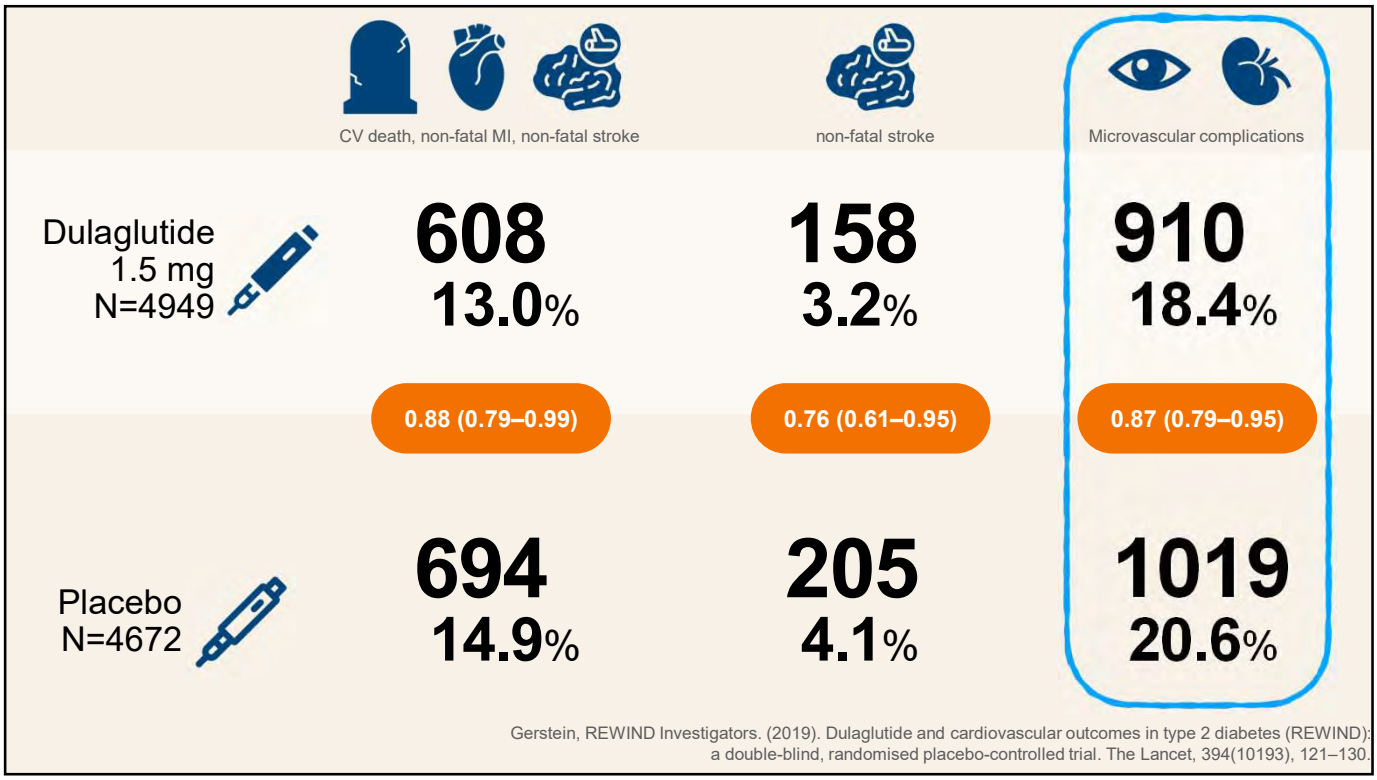
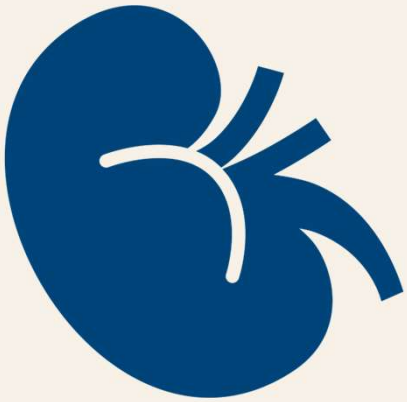

9901 patients
66.2±6.5 yrs
24 Countries
BMI 32.3
A1c 7.4%
CV disease, CV risk factors or CKD 3
CV death, non-fatal MI, non-fatal stroke
Dulaglutide 1.5 mg N=4949
608
13.0%
0.88 (0.79–0.99)
Placebo N=4672
694
14.9%
Gerstein, REWIND Investigators. (2019). Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The Lancet, 394(10193), 121–130.

189


CV death, non-fatal MI, non-fatal stroke
non-fatal stroke
Microvascular complications
Dulaglutide 1.5 mg N=4949
608
13.0%
158
3.2%
910
18.4%
0.88 (0.79–0.99)
0.76 (0.61–0.95)
0.87 (0.79–0.95)
Placebo N=4672
694
14.9%
205
4.1%
1019
20.6%
Gerstein, REWIND Investigators. (2019). Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The Lancet, 394(10193), 121–130.

190



At this time we do not have kidney specific trials, however we do have the CVOT that recorded renal outcomes.

191

REWIND Dulaglutide	New albuminuria (>300 mg/g)	↓eGFR >30%	Initiation of KRT	HR **0.85** 0.77-0.93
EXCEL Exenatide	New albuminuria (>300 mg/g)			HR **0.87** 0.70-1.07
ELIXA Lixisenatide	Albuminuria			uACR **↓31.2%** ↓68.5 to ↓9.8%

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ELIXA
Lixisenatide

Albuminuria

uACR **↓31.2%**
↓68.5 to ↓9.8%

LEADER
Liraglutide

New albuminuria | 2x sCR | Initiation of KRT | Kidney death

HR **0.78**
0.67-0.92

SUSTAIN-6
Semaglutide

New albuminuria | 2x sCR + eGFR < 45 | Initiation of KRT

HR **0.64**
0.46-0.88

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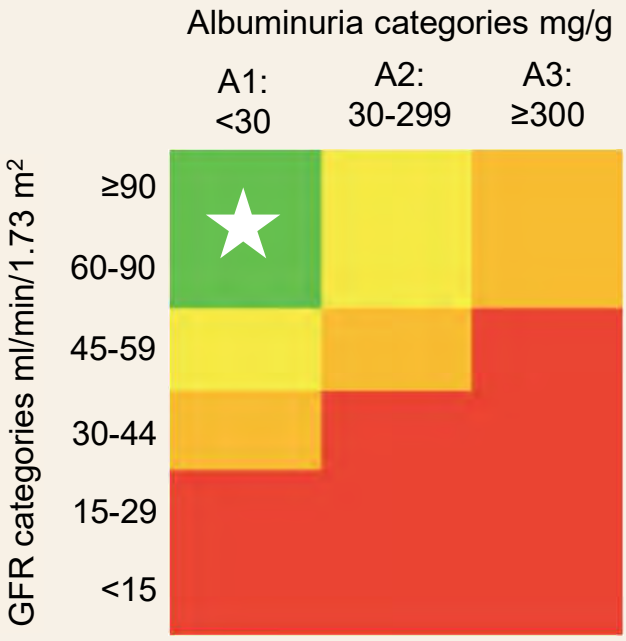
LEADER — **75% eGFR > 60**, **11% with albuminuria**

SUSTAIN-6 — **70% eGFR > 60**, **? with albuminuria**

REWIND — **80% eGFR > 60**, **34% with albuminuria**



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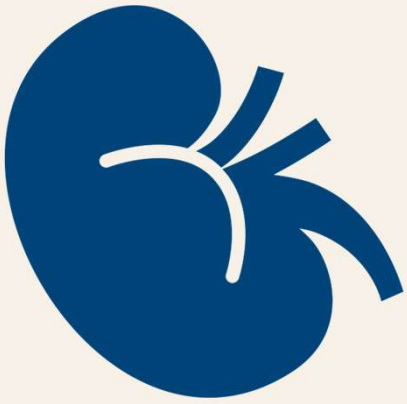

FLOW is an RCT of semaglutide in patients at high risk of kidney outcomes. Expect results in 2024

195

N=3534

47 ml/min

568 mg/g

Semaglutide (1 mg)
vs placebo

5 years

Kidney failure

↓≥50% eGFR

CV or kidney death

Rossing, P. (2023). The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. *Nephrology, Dialysis, Transplantation 38*(9), 2041–2051.

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10/10/23

FLOW is positive

Full results in early 2024

company announcement

Novo Nordisk will stop the once-weekly injectable semaglutide kidney outcomes trial, FLOW, based on interim analysis

Bagsværd, Denmark, 10 October 2023 – Novo Nordisk today announced the decision to stop the kidney outcomes trial FLOW (Effect of semaglutide versus placebo on the progression of renal impairment in people with type 2 diabetes and chronic kidney disease).

The decision to stop the trial is based on a recommendation from the independent Data Monitoring Committee (DMC) concluding that the results from an interim analysis met certain pre-specified criteria for stopping the trial early for efficacy.

Based on the decision to stop the trial at interim, the process of closing the trial will be initiated. To protect the integrity of the trial, Novo Nordisk remains blinded to the results until trial completion. Novo Nordisk expects that FLOW will read out during the first half year of 2024.

About FLOW

FLOW is a randomised, double-blind, parallel-group, placebo-controlled, superiority trial comparing injectable semaglutide 1.0 mg with placebo as an adjunct to standard of care on kidney outcomes for prevention of progression of renal impairment and risk of renal and cardiovascular mortality in people with type 2 diabetes and chronic kidney disease (CKD). 3,534 people are enrolled in the trial which has been conducted in 28 countries at more than 400 investigator sites. The FLOW trial was initiated in 2019.

The key objective of the FLOW trial is to demonstrate delay in progression of CKD and to lower the risk of kidney and cardiovascular mortality through the composite primary endpoint consisting of the following five components: onset of persistent ≥ 50% reduction in eGFR[1] according to the CKD-EPI[2] equation compared with baseline, onset of persistent eGFR[1] (CKD-EPI[2]) < 15 mL/min/1.73 m2, initiation of chronic kidney replacement therapy (dialysis or kidney transplantation), death from kidney disease or death from cardiovascular disease in people with type 2 diabetes and chronic kidney disease. Key secondary endpoints include annual rate of change in eGFR[1] (CKD-EPI[2]), major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) and all-cause death. The trial protocol provides for an interim analysis when a prespecified number of primary endpoint events has occurred.

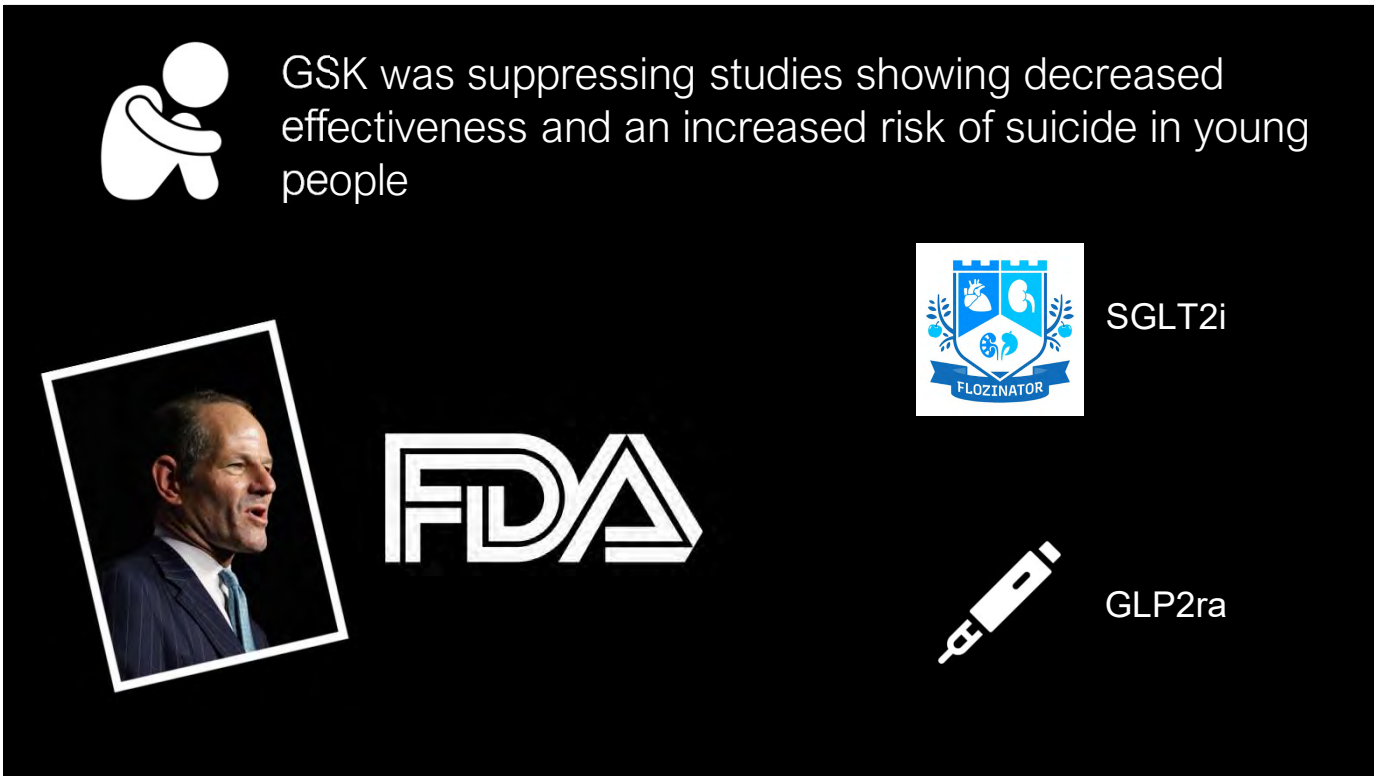
197

GSK was suppressing studies showing decreased effectiveness and an increased risk of suicide in young people

198


GSK was suppressing studies showing decreased effectiveness and an increased risk of suicide in young people
FDA

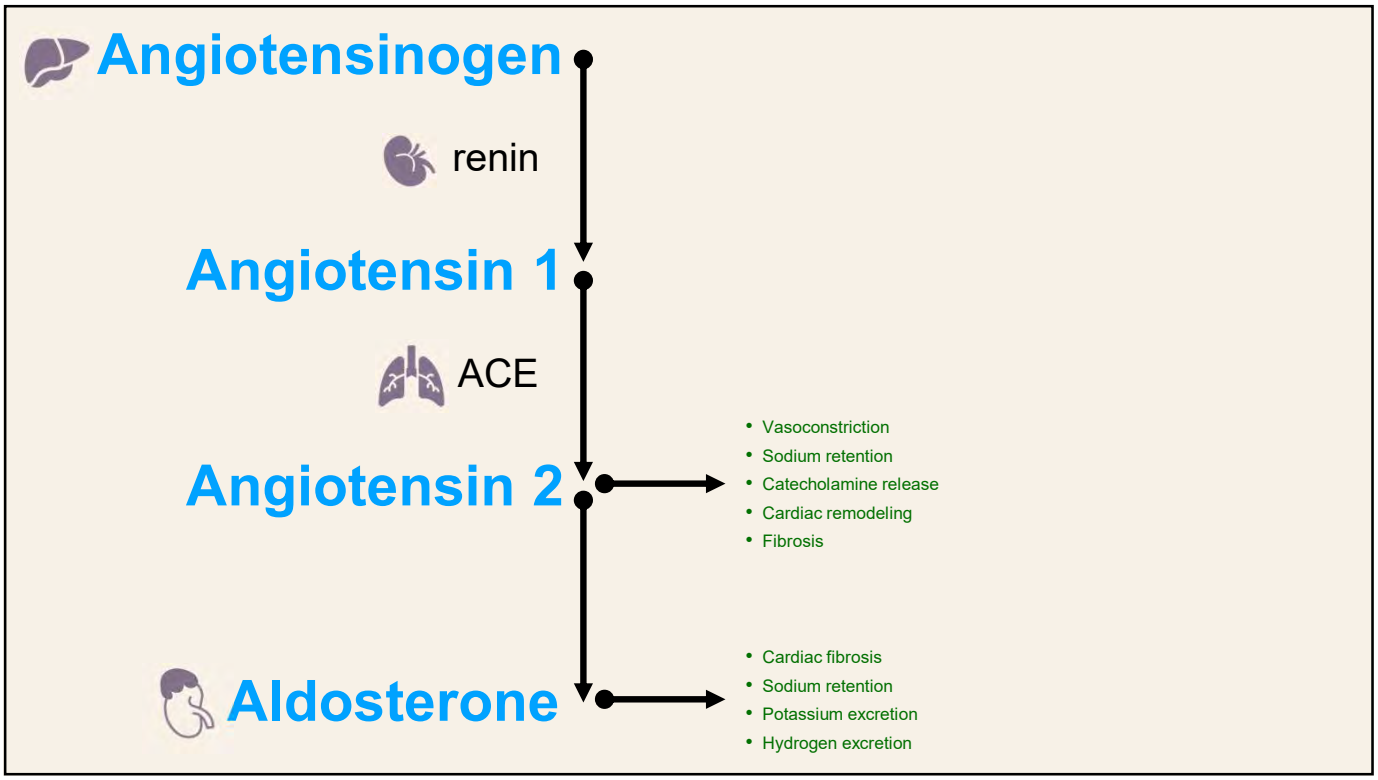
199


GSK was suppressing studies showing decreased effectiveness and an increased risk of suicide in young people
FLOZINATOR
SGLT2i
FDA
GLP2ra

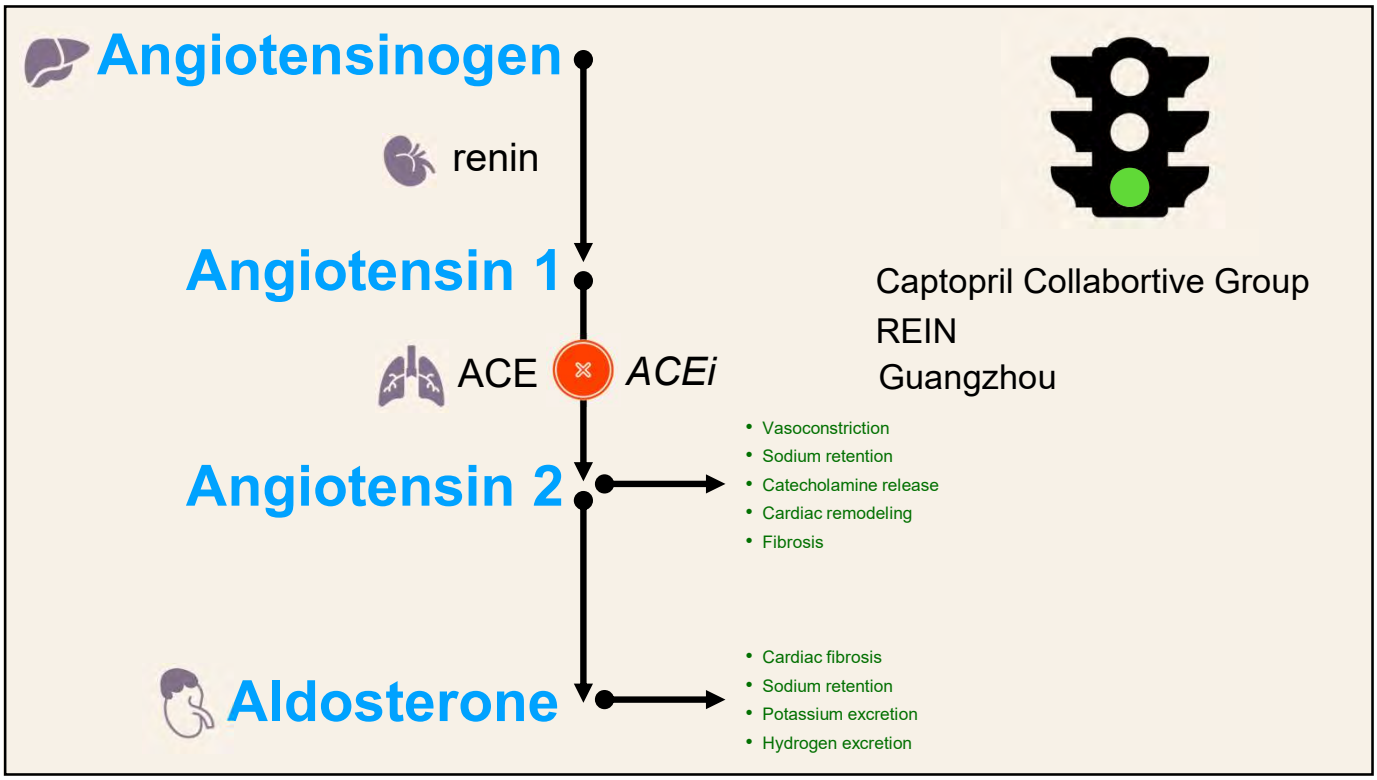
200

Finerenone

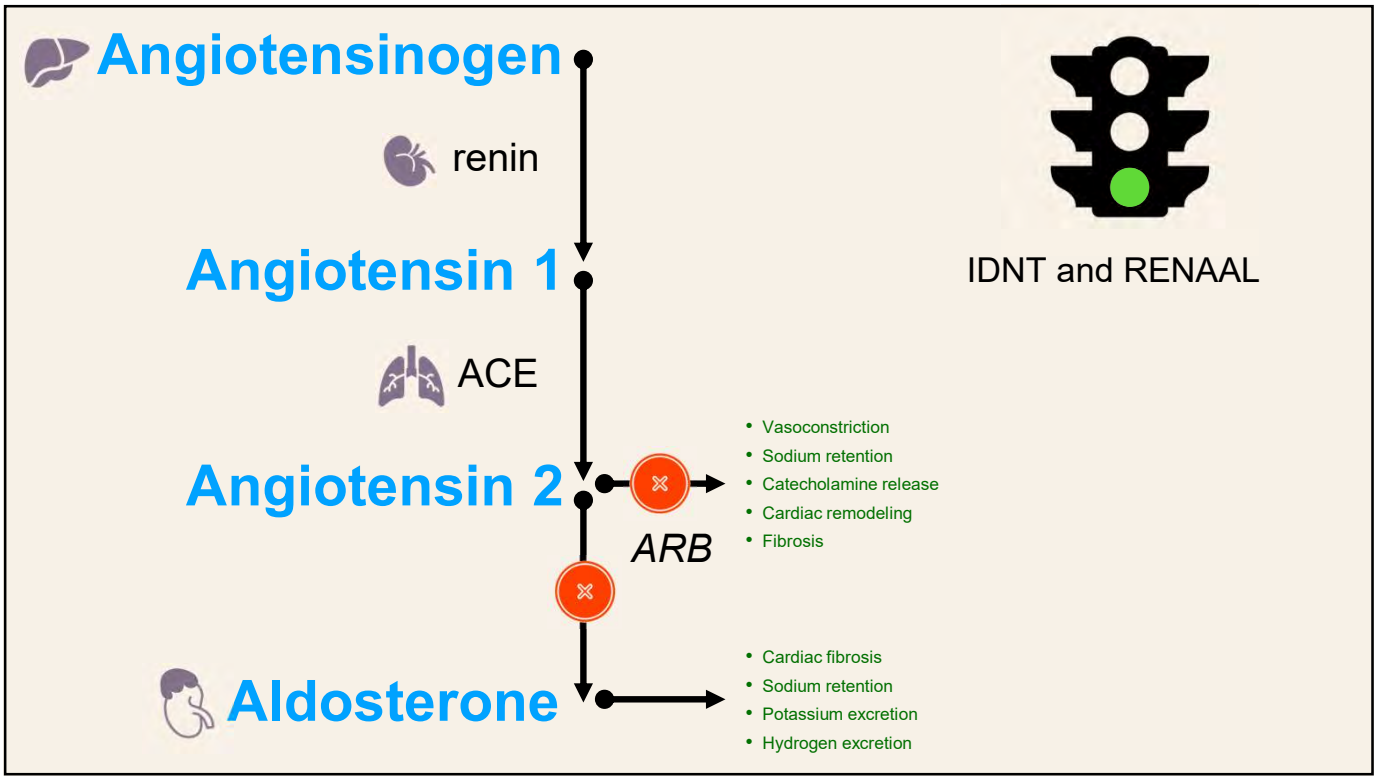
201



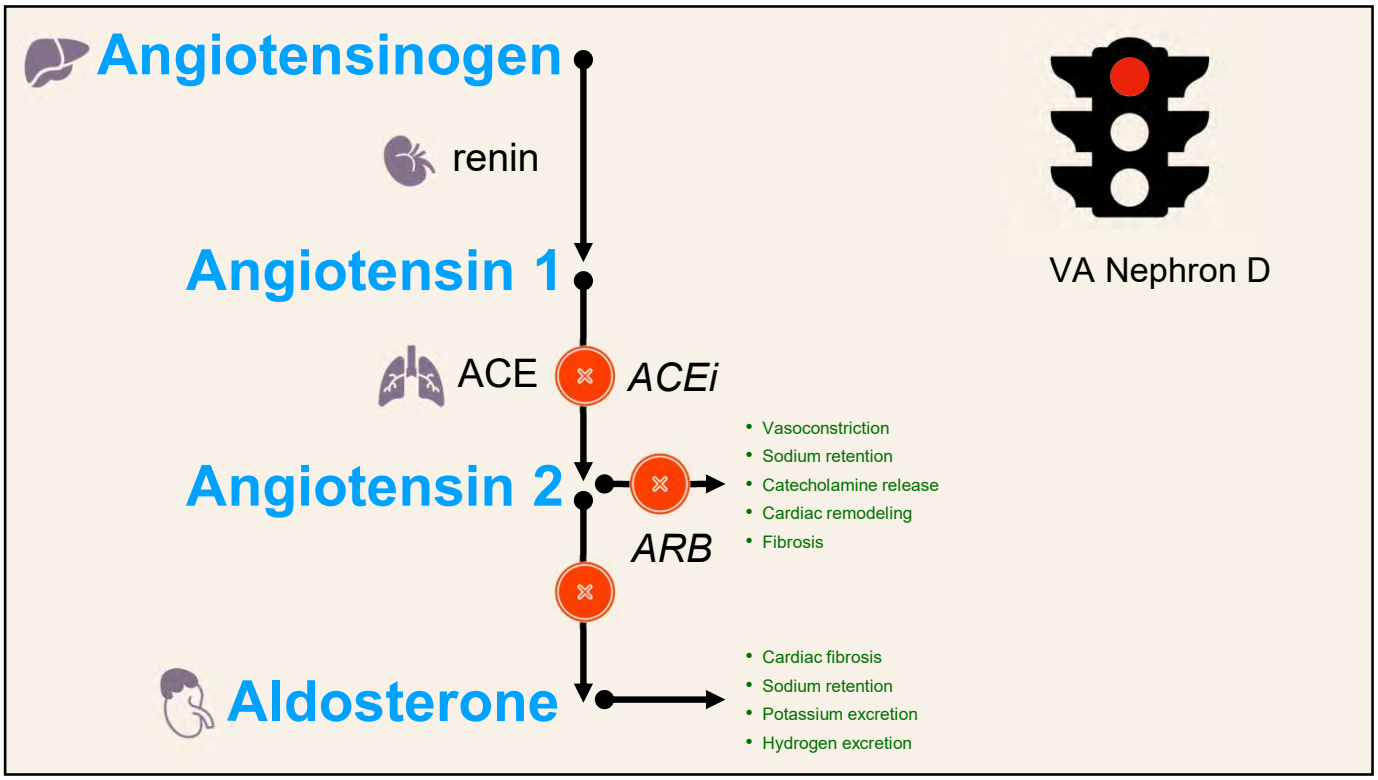
202


Angiotensinogen
renin
Angiotensin 1
ACE
ACEi
Angiotensin 2
Aldosterone
Captopril Collabortive Group
REIN
Guangzhou
• Vasoconstriction
• Sodium retention
• Catecholamine release
• Cardiac remodeling
• Fibrosis
• Cardiac fibrosis
• Sodium retention
• Potassium excretion
• Hydrogen excretion

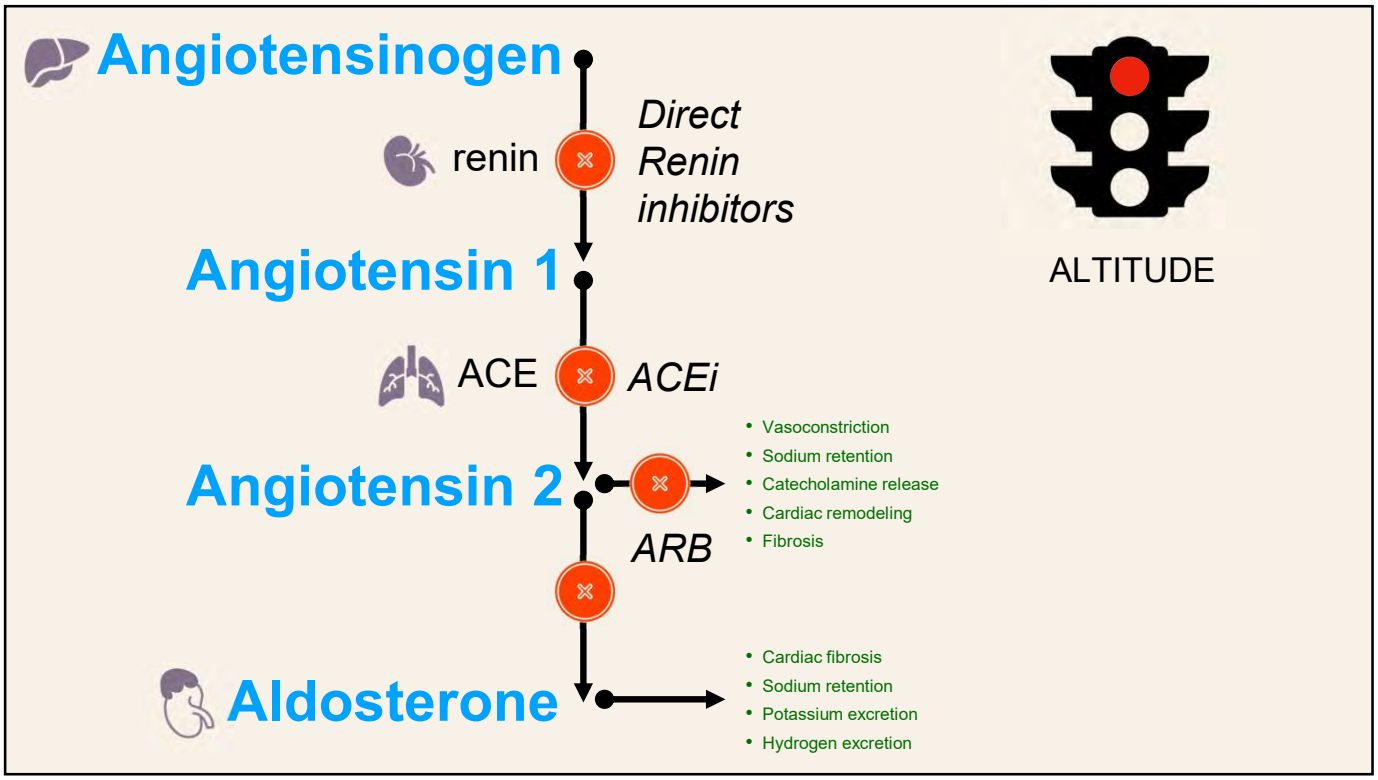
203


Angiotensinogen
renin
Angiotensin 1
ACE
Angiotensin 2
ARB
Aldosterone
IDNT and RENAAL
• Vasoconstriction
• Sodium retention
• Catecholamine release
• Cardiac remodeling
• Fibrosis
• Cardiac fibrosis
• Sodium retention
• Potassium excretion
• Hydrogen excretion

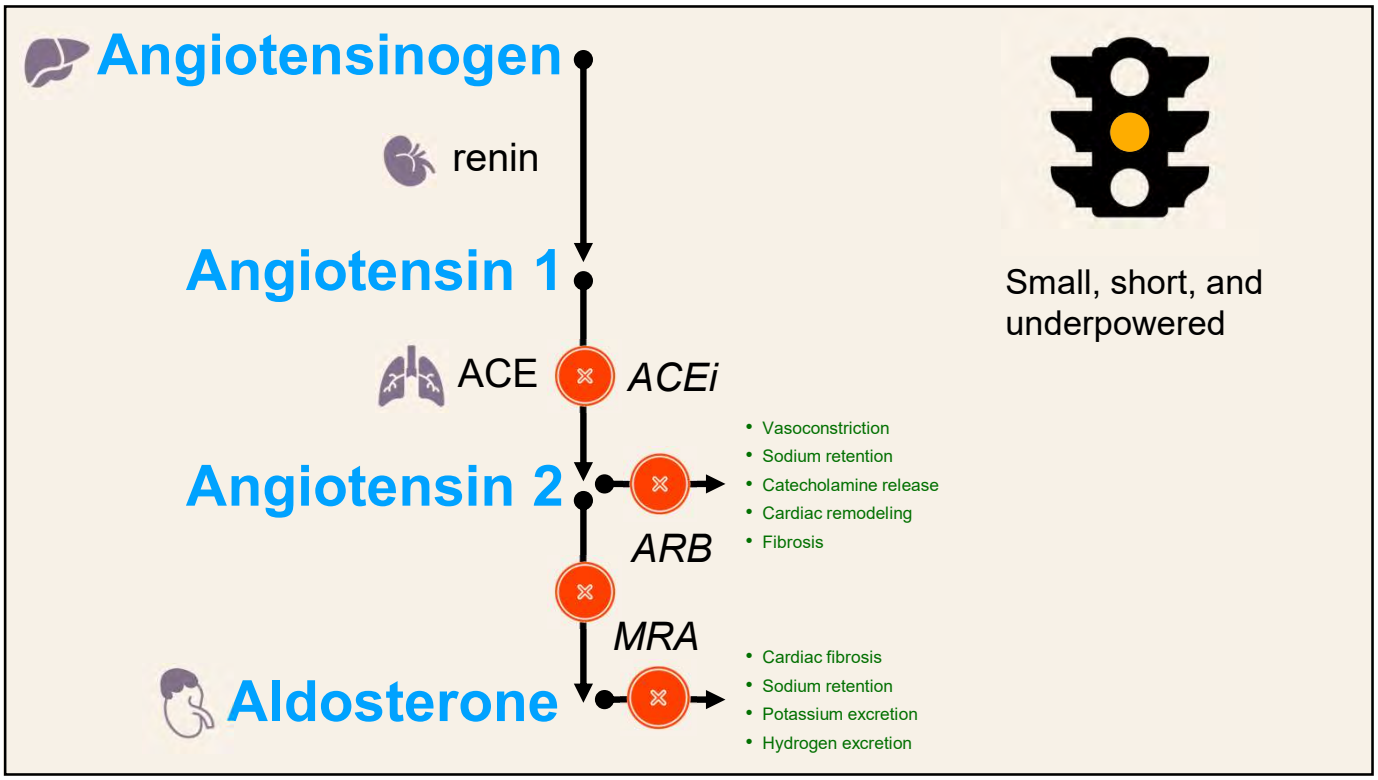
204


Angiotensinogen
renin
Angiotensin 1
ACE
ACEi
Angiotensin 2
ARB
Aldosterone
• Vasoconstriction
• Sodium retention
• Catecholamine release
• Cardiac remodeling
• Fibrosis
• Cardiac fibrosis
• Sodium retention
• Potassium excretion
• Hydrogen excretion
VA Nephron D

205


Angiotensinogen
renin
Direct
Renin
inhibitors
Angiotensin 1
ACE
ACEi
Angiotensin 2
ARB
Aldosterone
• Vasoconstriction
• Sodium retention
• Catecholamine release
• Cardiac remodeling
• Fibrosis
• Cardiac fibrosis
• Sodium retention
• Potassium excretion
• Hydrogen excretion
ALTITUDE

206



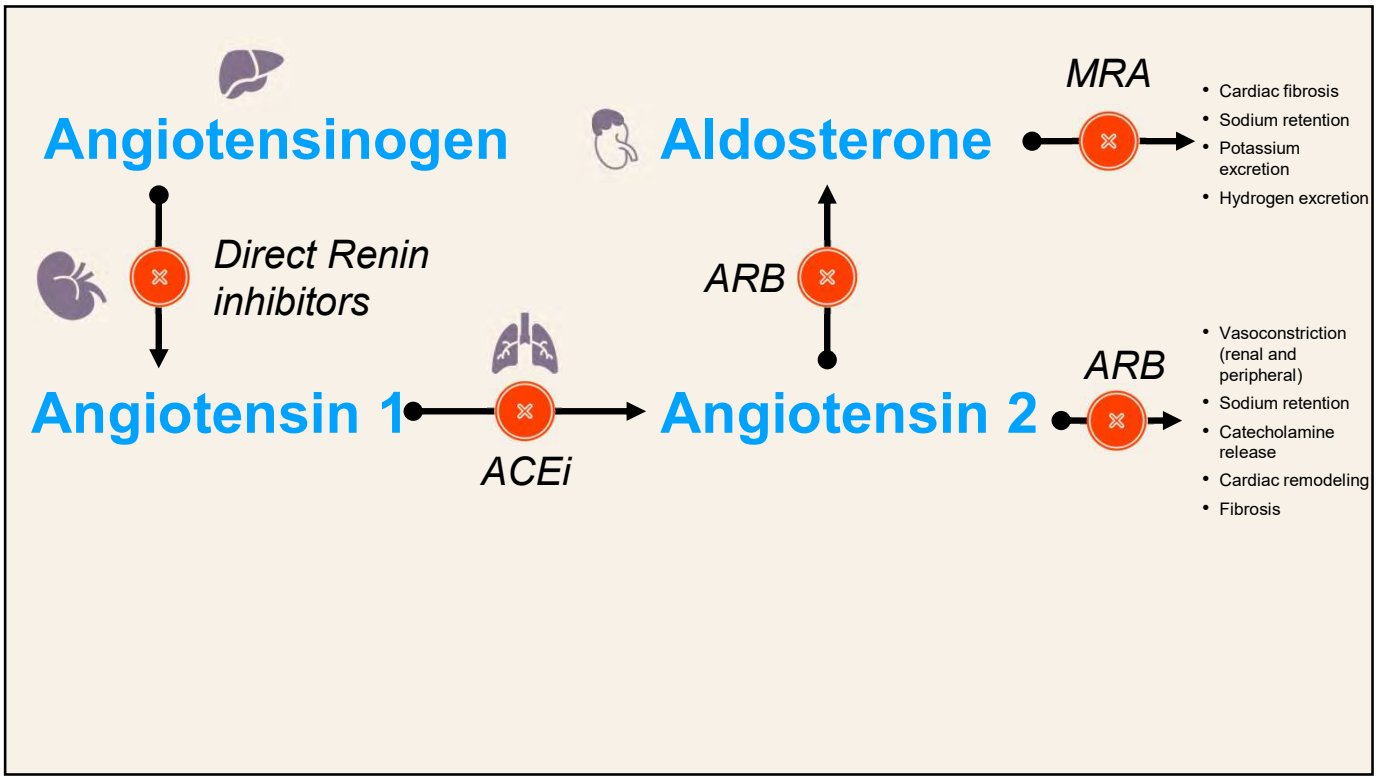
207

ACEi inhibitors are nephroprotective

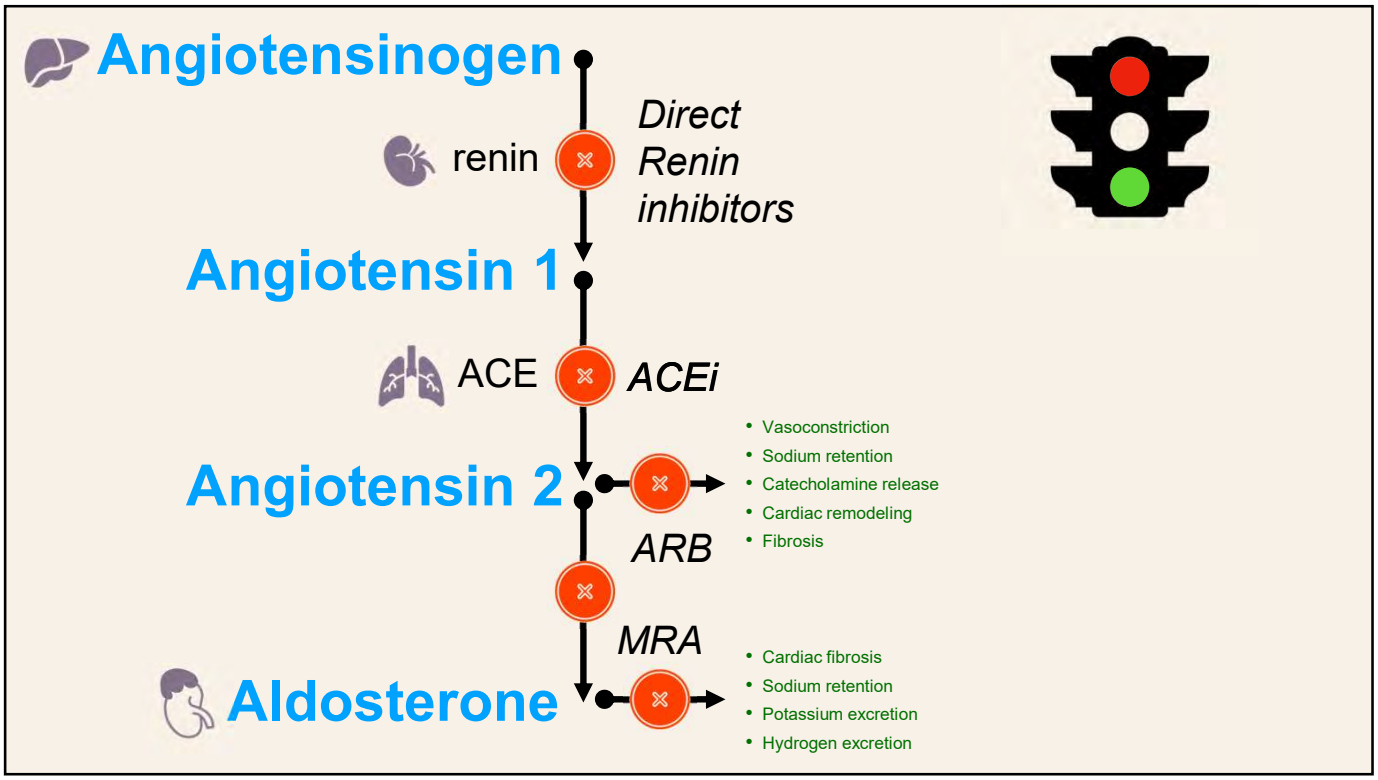
ARB inhibitors are nephroprotective

Duel blockade of the renin angiotensin aldosterone system is problematic

208


Angiotensinogen
Direct Renin inhibitors
Angiotensin 1
ACEi
Angiotensin 2
Aldosterone
MRA
• Cardiac fibrosis
• Sodium retention
• Potassium excretion
• Hydrogen excretion
ARB
ARB
• Vasoconstriction (renal and peripheral)
• Sodium retention
• Catecholamine release
• Cardiac remodeling
• Fibrosis

209


Angiotensinogen
renin
Direct Renin inhibitors
Angiotensin 1
ACE
ACEi
Angiotensin 2
• Vasoconstriction
• Sodium retention
• Catecholamine release
• Cardiac remodeling
• Fibrosis
ARB
MRA
Aldosterone
• Cardiac fibrosis
• Sodium retention
• Potassium excretion
• Hydrogen excretion

210

Spironolactone and ACEi/ARB

	N	Relative Risk	GRADE
Kidney failure	84	**3.0** (0.33-27.65)	**Very low**
Death	421	**0.58** (0.10-3.50)	**Low**
CV events	1067	**0.95** (0.26-3.56)	**Low**
Hyper-kalemia	**3001**	**2.17** (1.47-3.22)	**Moderate**
AKI	**1446**	**2.04** (1.05-3.97)	**Moderate**

Chung, E. Y., Ruospo, M. (2020). *Cochrane Database of Systematic Reviews* , *10*(10), CD007004.

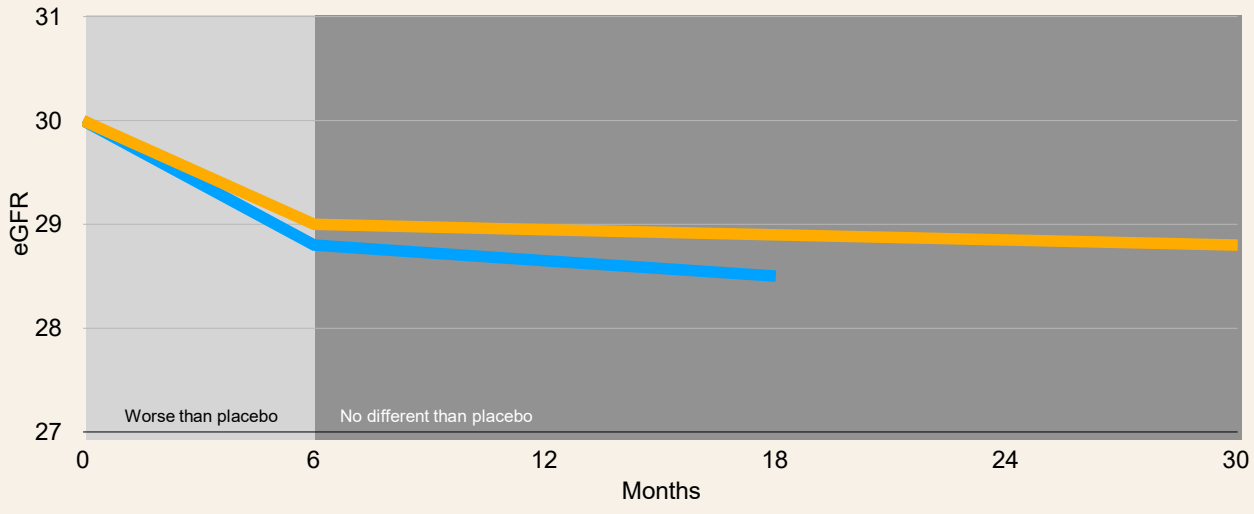
211

EMPHASIS-HF

N=2743, 18 months eplerenone v placebo, HFrEF

TOPCAT

N=3445, 33 months spironolactone v placebo, HFpEF



coid receptor antagonists on acute and chronic estimated glomerular filtration rate slopes in patients with chronic heart failure. European Journal of Heart Failure, 24(9), 1586–1590.

212

Finerenone

Non-steroidal MRA

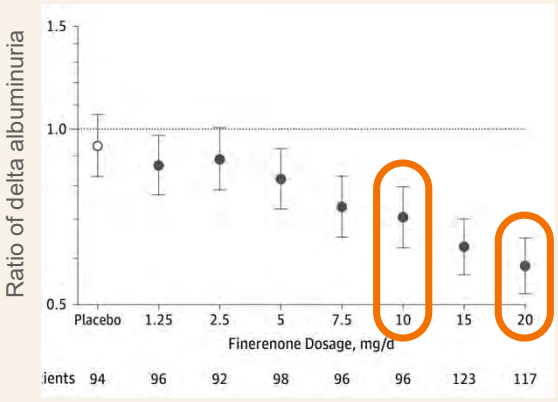
No sexual side effects,
More cardioselective,
No active metabolites, shorter acting

90 days

823 people

Diabetes

200 mg/g



Bakris, G. L., Agarwal, R., Chan, Et al. (2015). Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy: A Randomized Clinical Trial. *JAMA*, *314*(9), 884–894

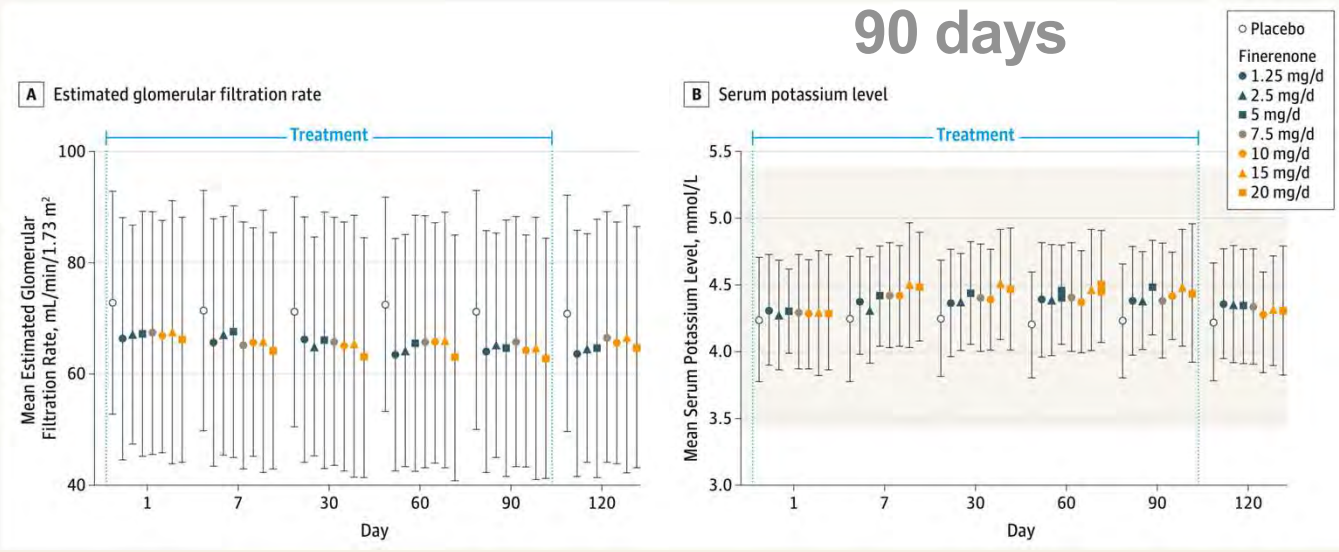
213

Finerenone

Non-steroidal MRA

No sexual side effects,
More cardioselective,
No active metabolites, shorter acting

90 days



Bakris, G. L., Agarwal, R., Chan, Et al. (2015). Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy: A Randomized Clinical Trial. *JAMA*, *314*(9), 884–894

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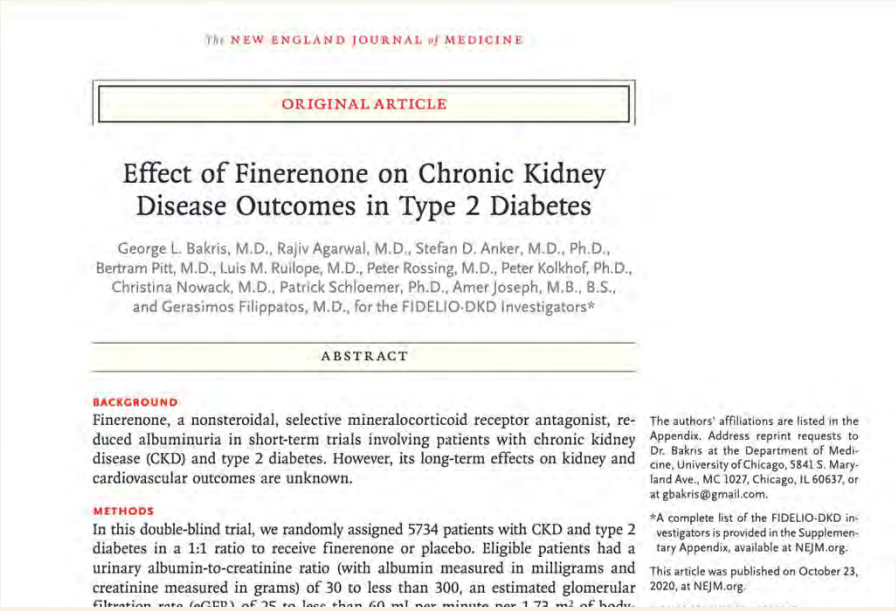
Finerenone Fidelio Phase 3



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

ABSTRACT

BACKGROUND
Finerenone, 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.

METHODS
In 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

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bakris at the Department of Medicine, University of Chicago, 5841 S. Maryland Ave., MC 1027, Chicago, IL 60637, or at gbakris@gmail.com.

*A complete list of the FIDELIO-DKD investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 23, 2020, at NEJM.org.

patos, G. (2020). Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *The New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2025845

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Fidelio Inclusion

- Type 2 Diabet — A1c 7.7%
- 30-300 mg/g, GFR 25-59, retinopathy
- 300-5000 mg/g GFR 25-74 — 87%
- Potassium ≤ 4.8

Results

- 65.5 years
- 70% male
- GFR 44
  52% 25-44
- Diuretics 57%

216

Fidelio

Type 2 Diabetes

30-300 mg/g,
GFR 25-59,
retinopathy

300-5000 mg/g
GFR 25-74

Potassium ≤ 4.8

4-16 week run-in to maximize ACE/ARB

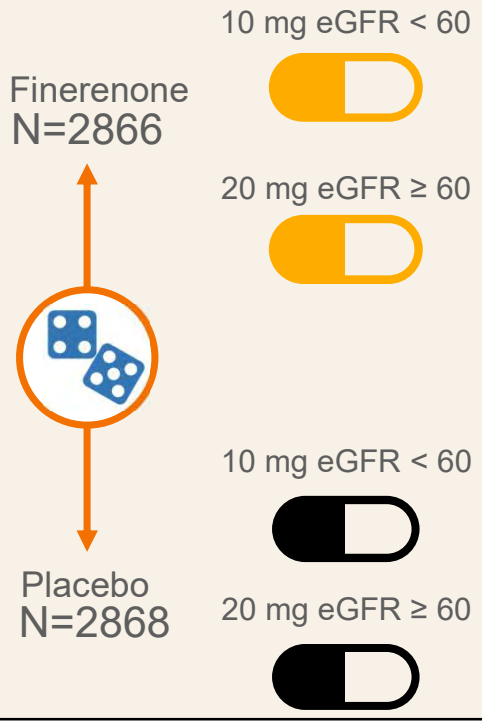
Then re-screened

217

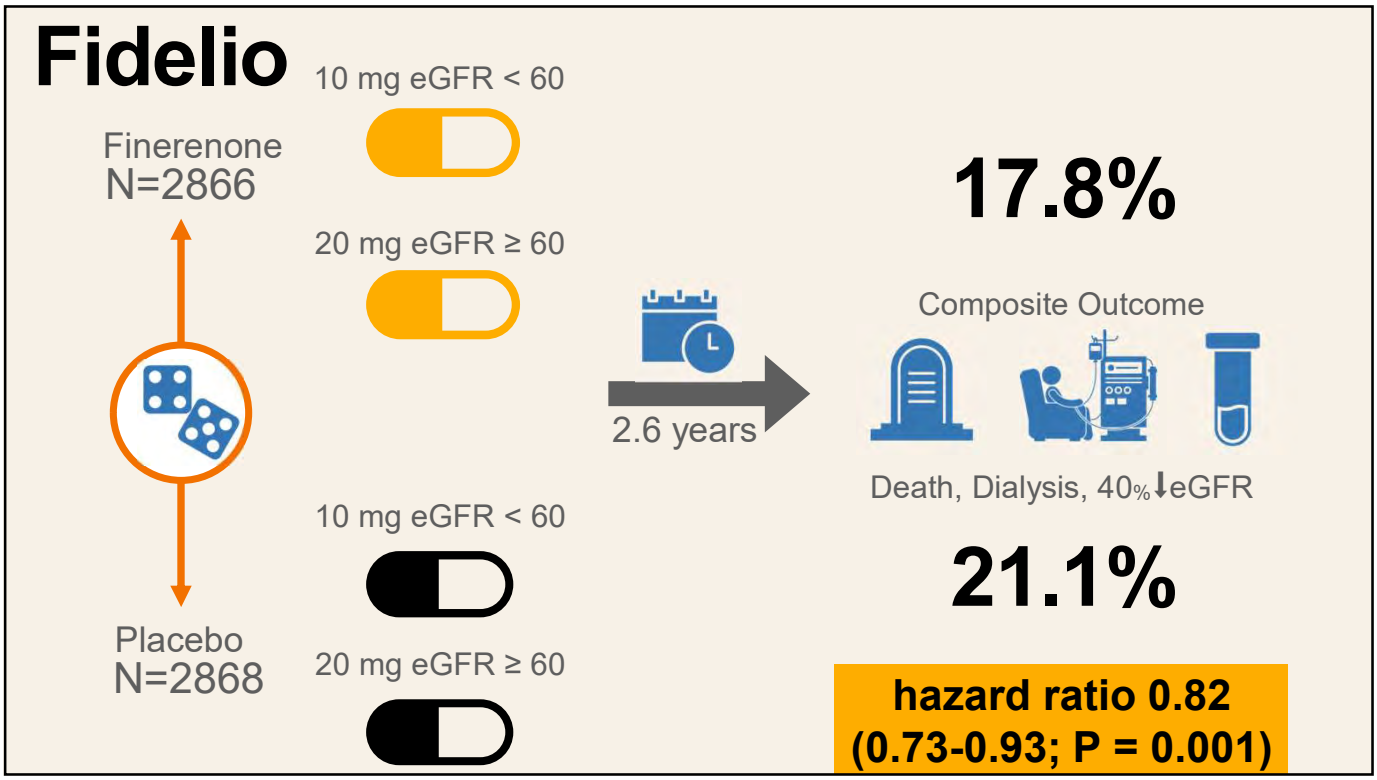
Fidelio

4-16 week run-in to maximize ACE/ARB

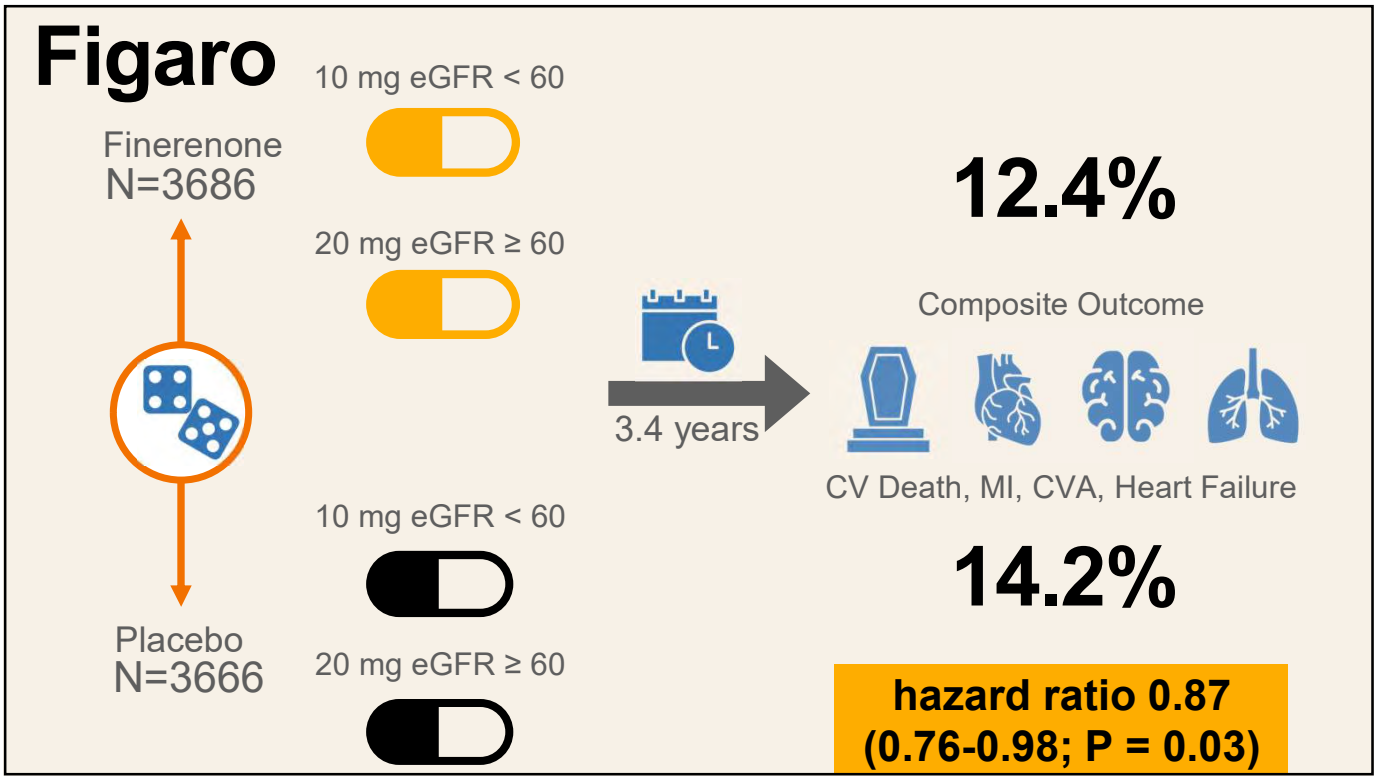
Then re-screened



218


Fidelio
Finerenone
N=2866
10 mg eGFR < 60
20 mg eGFR ≥ 60
Placebo
N=2868
10 mg eGFR < 60
20 mg eGFR ≥ 60
2.6 years
17.8%
Composite Outcome
Death, Dialysis, 40%↓eGFR
21.1%
hazard ratio 0.82
(0.73-0.93; P = 0.001)

219


Figaro
Finerenone
N=3686
10 mg eGFR < 60
20 mg eGFR ≥ 60
Placebo
N=3666
10 mg eGFR < 60
20 mg eGFR ≥ 60
3.4 years
12.4%
Composite Outcome
CV Death, MI, CVA, Heart Failure
14.2%
hazard ratio 0.87
(0.76-0.98; P = 0.03)

220

Fidelio

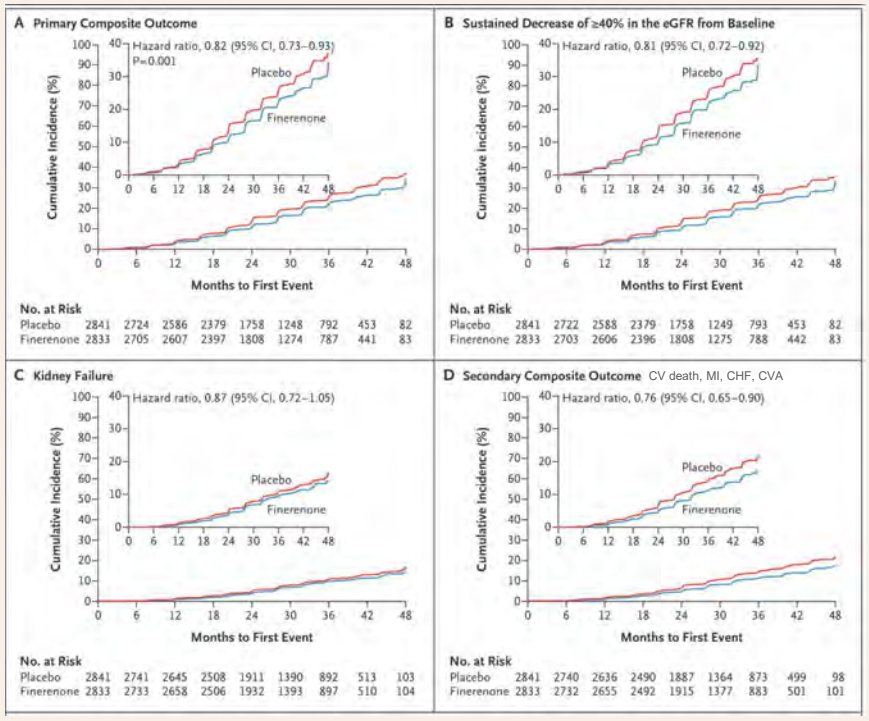
17.8%

Composite Outcome

Death, Dialysis, 40%↓eGFR

21.1%

hazard ratio 0.82 (0.73-0.93; P = 0.001)



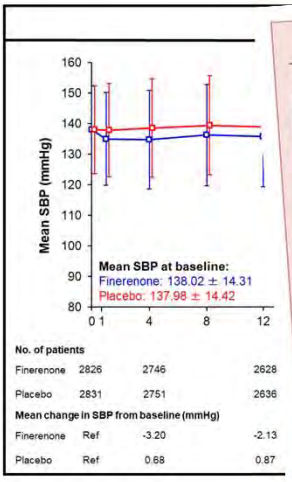
221

Potassium	>5.5	>6.0	K-Binders
Finerenone N=2866	21.7%	4.5%	10.8%
Placebo N=2868	9.8%	1.4%	6.5%

222

Fidelio Blood pressure

Williams, B. (2015). Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *The Lancet*, *386*(10008), 2059–2068



	Blood pressure (mm Hg)	Change from baseline (mm Hg)
Mean		
Spironolactone	134·9 (134·0 to 135·9)	−12·8 (−13·8 to −11·8)
Doxazosin	139·0 (138·0 to 140·0)	−8·7 (−9·7 to −7·7)
Bisoprolol	139·4 (138·4 to 140·4)	−8·3 (−9·3 to −7·3)
Placebo	143·6 (142·6 to 144·6)	−4·1 (−5·1 to −3·1)
Mean differences		
Spironolactone vs placebo	8·70 (−9·72 to −7·69)	p<0·0001
Spironolactone vs mean bisoprolol and doxazosin	−4·26 (−5·13 to −3·38)	p<0·0001
Spironolactone vs doxazosin	−4·03 (−5·04 to −3·02)	p<0·0001
Spironolactone vs bisoprolol	−4·48 (−5·50 to −3·46)	p<0·0001

Data are mean (95% CI). Home systolic blood pressure throughout the treatment cycle for each drug (includes data from mid-cycle at week 6 and the final visit at week 12). Least squares means from mixed effects models adjusted for baseline covariates. Hierarchical primary endpoints each tested only if the preceding tests were significant.

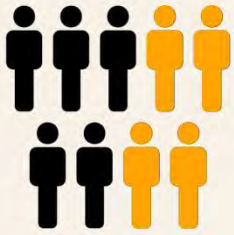
Table 2: **Home systolic blood pressure averaged across both visits for each cycle**

Finerenone **-3.0** (1 month) **-2.1** (6 month)

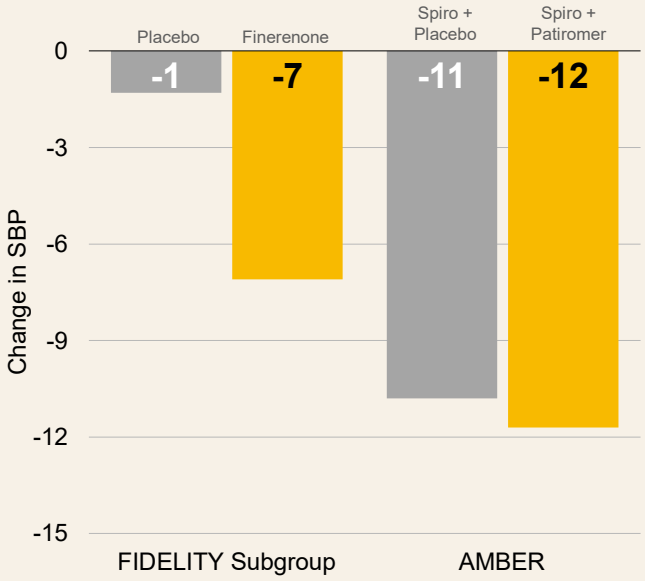
Placebo **-0.1** (1 month) **+0.9** (6 month)

223

Fidelity Blood pressure



Matched to AMBER

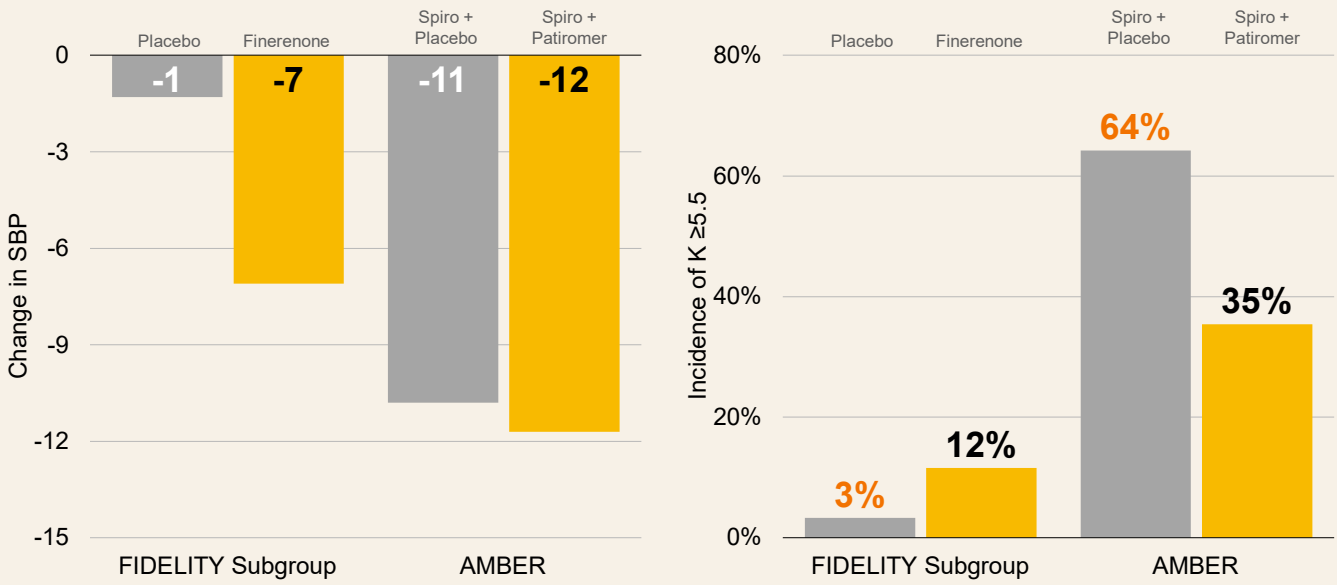


AMBER

Spironolactone + patiromer for **resistant hypertension** with **CKD** (eGFR 25-45) **and potassium 4.3-5.1**

224

Fidelity Blood pressure



225

CV disease/risk? A1c increased? GLP1ra

Initiate RASi
Then add Flozins
Then maximize RASi
Then optimize BP
Then assess, "Residual albuminuria?"
Potassium less than 4.8?
Then finerenone

226

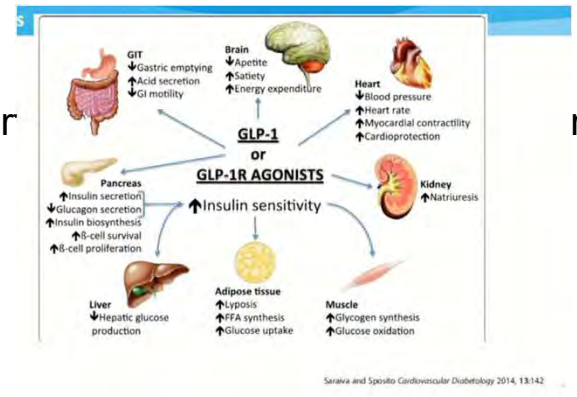
227

Gila monster saliva

It is an incretin

L cwell of the go tract

Receptors located every where hear rt



228

Decreased thirsty plus diuretic eff4ect, bad combination?

GIP another incretin twincretinb single molercukle hits both

Available GLP1s

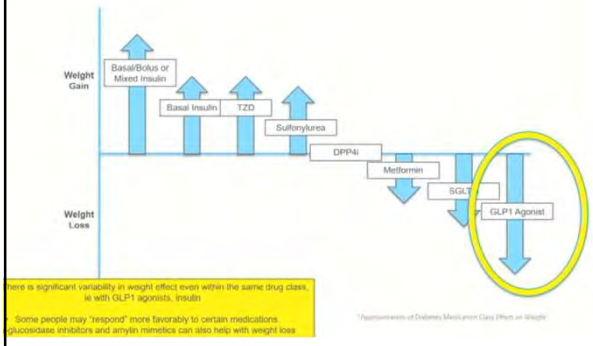
Generic	Brand Name	Year Approved	Dosing	Titration Intervals
Exenatide BID	*Byetta*	2005	5→10mcg twice daily	4 weeks
Liraglutide qD	*Victoza*	2010	0.6→1.2→1.8mg daily	1 week
	Saxenda	2014	**Saxenda* 1.8→2.4→3mg daily	
Exenatide qW	*Bydureon*	2012	2mg weekly	none
Dulaglutide qW	*Trulicity*	2014	0.75→1.5→3→4.5mg weekly	4 weeks
Lixisenatide qD	*Adlyxin*	2017	10→20mcg daily	2 weeks
Semaglutide qW (subq)	*Ozempic*	2017	0.25→0.5→1→2mg weekly	4 weeks
	Wegovy	2021	**Wegovy* 1mg→1.7mg→2.4mg weekly	
Semaglutide qD (oral)	*Rybelsus*	2019	3→7→14mg daily	4 weeks
Tirzepatide qW (w/ GIP)	*Mounjaro*	2022	2.5→5→7.5→10→12.5→15mg weekly	4 weeks

229

5-10% weight loss is good

Minimal hypoglycemia

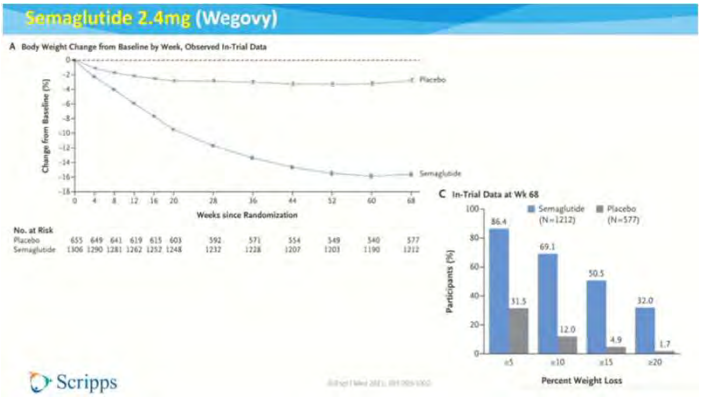
Use in alcoholism?

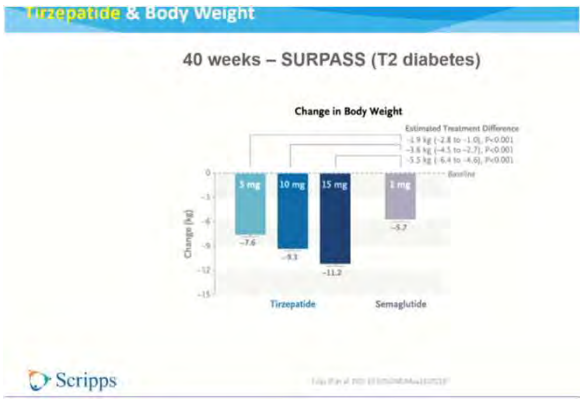


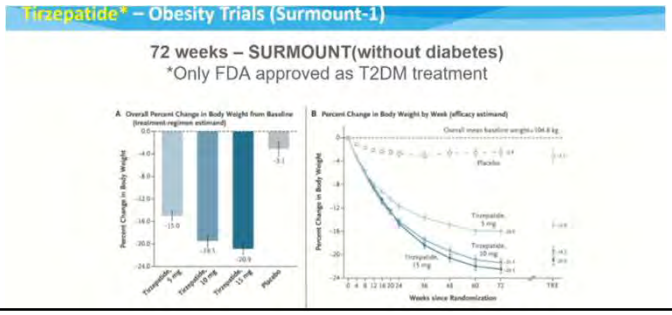
Less weight loos with dm

- **Weight loss !**
- **Glucose lowering (with minimal hypoglycemia)**
  - **Highest potency:**
    - Semaglutide sq
    - Tirzepatide
    - Dulgalutide (high dose)
- **Potential cardiovascular and renal benefits**
- **Other benefits**
  - Dementia
  - NAFLD/NASH
  - Inflammatory states

230



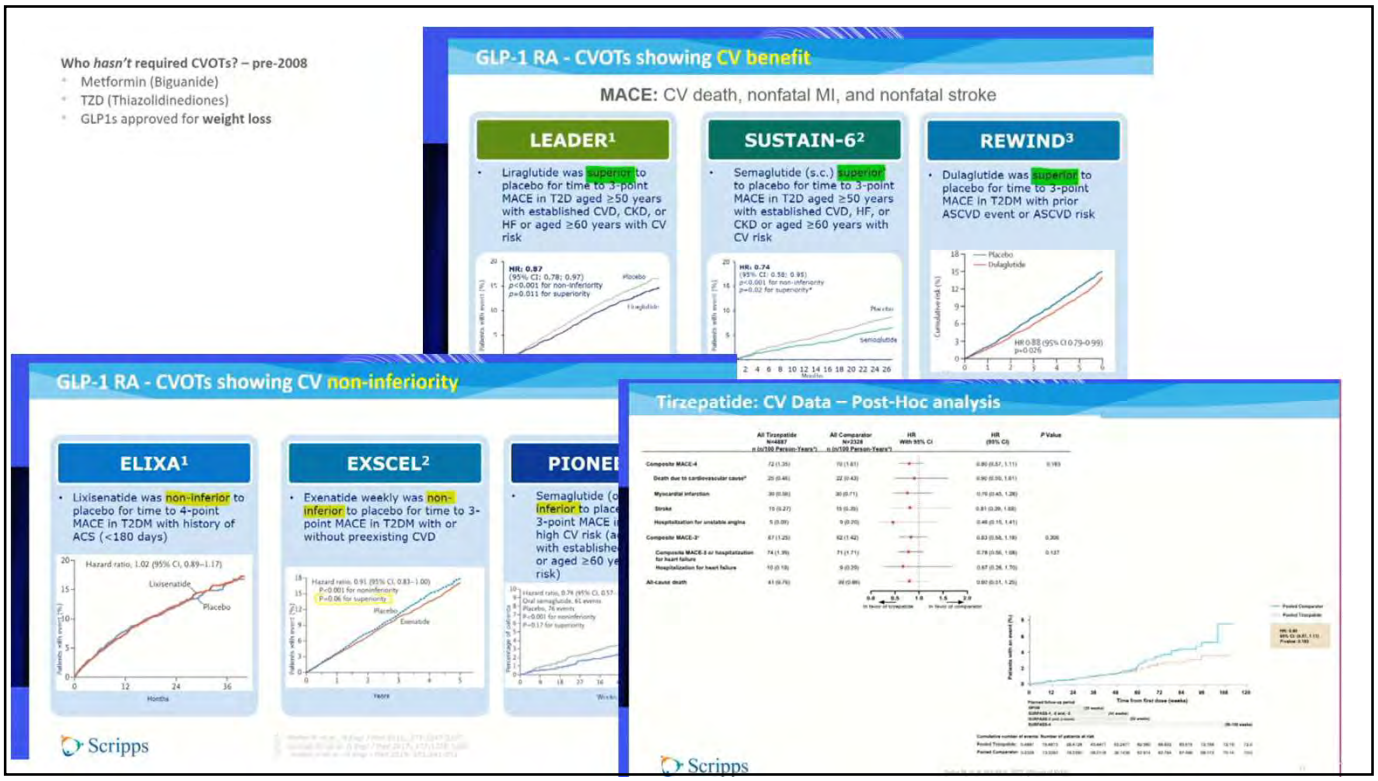




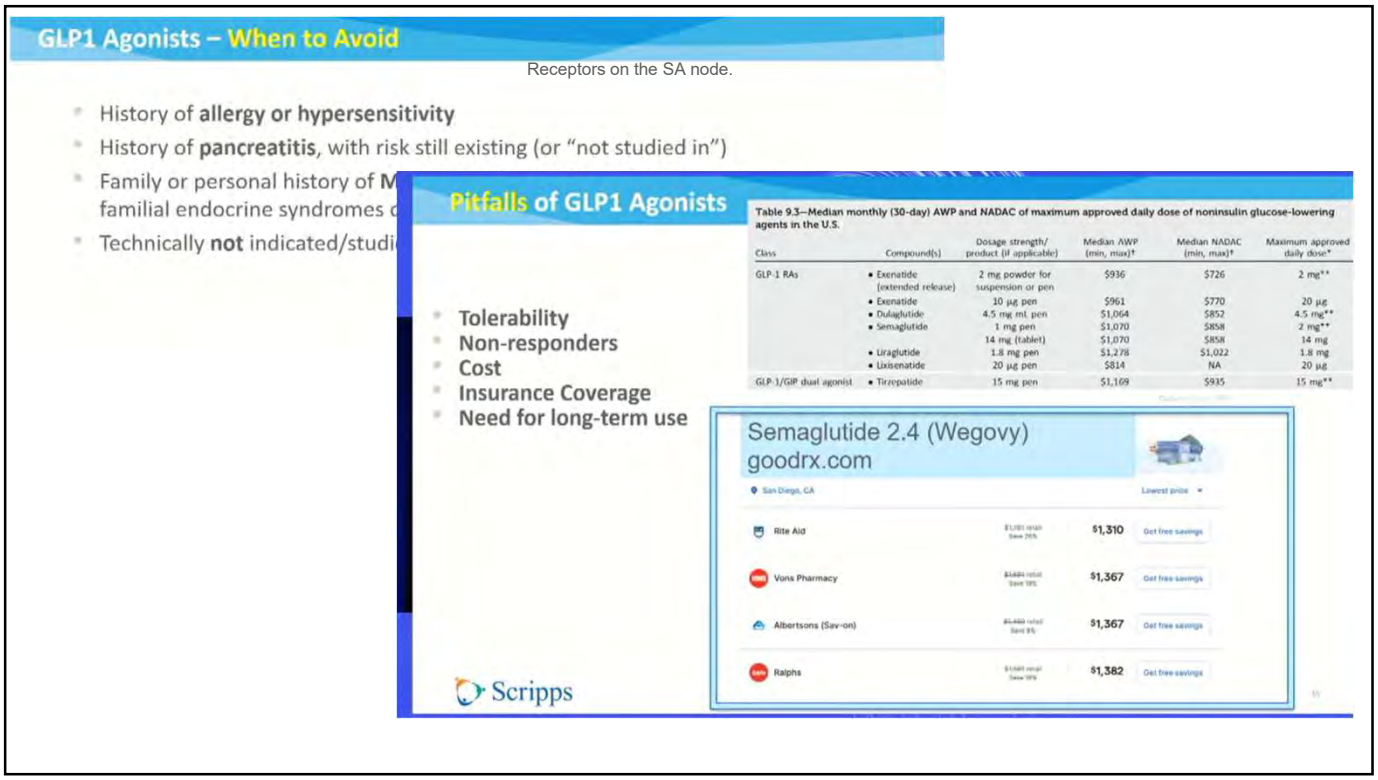
231

https://twitter.com/elonmusk/status/1576198504913199104

232


Who *hasn't* required CVOTs? – pre-2008
Metformin (Biguanide)
TZD (Thiazolidinediones)
GLP1s approved for **weight loss**
GLP-1 RA - CVOTs showing CV benefit
MACE: CV death, nonfatal MI, and nonfatal stroke
LEADER¹
Liraglutide was superior to placebo for time to 3-point MACE in T2D aged ≥50 years with established CVD, CKD, or HF or aged ≥60 years with CV risk
SUSTAIN-6²
Semaglutide (s.c.) superior to placebo for time to 3-point MACE in T2D aged ≥50 years with established CVD, HF, or CKD or aged ≥60 years with CV risk
REWIND³
Dulaglutide was superior to placebo for time to 3-point MACE in T2DM with prior ASCVD event or ASCVD risk
GLP-1 RA - CVOTs showing CV non-inferiority
ELIXA¹
Lixisenatide was non-inferior to placebo for time to 4-point MACE in T2DM with history of ACS (<180 days)
EXSCEL²
Exenatide weekly was non-inferior to placebo for time to 3-point MACE in T2DM with or without preexisting CVD
Tirzepatide: CV Data – Post-Hoc analysis
Scripps

233


GLP1 Agonists – When to Avoid
Receptors on the SA node.
History of **allergy or hypersensitivity**
History of **pancreatitis**, with risk still existing (or "not studied in")
Family or personal history of M
familial endocrine syndromes
Technically **not** indicated/studi
Pitfalls of GLP1 Agonists
Tolerability
Non-responders
Cost
Insurance Coverage
Need for long-term use
Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.
Class
Compound(s)
Dosage strength/ product (if applicable)
Median AWP (min, max)†
Median NADAC (min, max)†
Maximum approved daily dose*
GLP-1 RAs
Exenatide (extended release)
2 mg powder for suspension or pen
$936
$726
2 mg**
Exenatide
10 µg pen
$961
$770
20 µg
Dulaglutide
4.5 mg mL pen
$1,064
$852
4.5 mg**
Semaglutide
1 mg pen
$1,070
$858
2 mg**
14 mg (tablet)
$1,070
$858
14 mg
Liraglutide
1.8 mg pen
$1,278
$1,022
1.8 mg
Lixisenatide
20 µg pen
$814
NA
20 µg
GLP-1/GIP dual agonist
Tirzepatide
15 mg pen
$1,169
$935
15 mg**
Semaglutide 2.4 (Wegovy)
goodrx.com
San Diego, CA
Lowest price
Rite Aid
$1,310
Vons Pharmacy
$1,367
Albertsons (Sav-on)
$1,367
Ralphs
$1,382
Scripps

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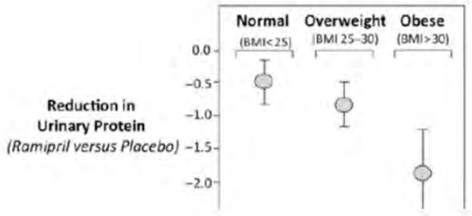
Hemodynamic Changes in Obesity



sity: CKD Risk Factor?

nanente Cohort, linked w/ USRDS

ents, risk of ESRD compared to nl weight

ght: 1.9

.6

6.1

7.1

ac-
tion
s

naci et al JASN
Ramipril Effica

J Am Soc Nephrol. 2013 May;24(6):987-94. doi: 10.1681/ASN.2012050460. Epub 2013 Apr 11.

Central body fat distribution associates with unfavorable renal hemodynamics independent of body mass index

Arjan J Kwakernaak [1], Dorien M Zelle, Stephan J L Bakker, Gerjan Navis

- 315 healthy people (mean BMI 24.9, iothal GFR 109 mL/min)
- Increasing WHR (central adiposity), associa with
  - Lower GFR
  - Lower effective renal plasma flow
  - Higher filtration fraction
  - *even after adjusting for sex, age, MAP, and B

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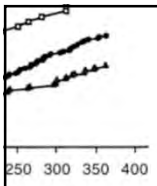

ots for the underweight (□),
(▲). (A) All of the patients

999.

		vitamin deficiency	injury possibly from oxalate nephropathy		
Phentermine (Adipex-P, Lomaira)	Sympathomimetic, anorexic	Hypertension, ischemia, palpitations, dry mouth, constipation	Excreted primarily via the urine	15–29: maximum 15 g/d	<15: avoid use (not been studied)
Phentermine/ Topiramate (Qsymia)	Sympathomimetic, anorexic	Tachycardia, paresthesias, dry mouth, constipation, paresthesias, proximal (type 2) renal tubular acidosis, upper respiratory infections	Excreted primarily via the urine	CrCl<50 ml/min: maximum dose 7.5/46 mg once daily	Dialysis: avoid use (not been studied)
Bupropion-Naltrexon (Contrave)	Inhibits NE/dodopamine	Nausea, constipation,	Excreted primarily via	*Moderate or severe	Not recommended

RCT's: GLP1 Agonists

Liraglutide (Saxenda)

Study	Population	Intervention | Follow-up Time	Weight and Selected Cardiometabolic Outcomes	Kidney Outcomes
Marso et al (SUSTAIN-6)[43] (2016) **Semaglutide**	Multicenter RCT of 3,297 adults w/ T2DM, HbA_{1c} ≥ 7%, CVD or CKD; excluded dialysis patients (eGFR < 60 in 24%, mean age 65 y, weight 92 kg, HbA_{1c} 8.7%)	Arm 1: SC semaglutide 1.0 mg/d; arm 2: placebo; arm 3: SC semaglutide 0.5 mg/d; arm 4: placebo | Duration: median 2.1 y	Overall: Weight loss greater at 2 y for both semaglutide doses vs placebo (arm 1: −4.3 kg, arm 3: −2.9 kg); semaglutide reduced risk for MACE (primary): HR, 0.74 (95% CI, 0.58-0.95) eGFR < 60 subgroup (n = 795): reduced MACE (HR, 0.69; 95% CI, 0.57-0.85)	Semaglutide reduced risk for composite kidney outcome (HR, 0.64; 95% CI, 0.46-0.88), largely driven by persistent macroalbuminuria (HR, 0.54; 95% CI, 0.37-0.77) Other kidney outcomes: Scr doubling or eGFR < 45: HR, 1.28 (95% CI, 0.64-2.58); KFRT: HR, 0.91 (95% CI, 0.40-2.07)
LEADER[42] (2018) **Liraglutide**	Multicenter RCT of 9,340 adults w/ T2DM, HbA_{1c} ≥ 7%, CVD risk factors, CVD, or CKD; excluded dialysis patients (eGFR < 60 in 23%, albuminuria ≥ 30 mg/g in 37%, mean age 64 y, BMI 33 kg/m², HbA_{1c}	Arm 1: SC liraglutide 1.8 mg/d (diabetes dose); arm 2: placebo | Duration: median 3.5 y	Overall: Liraglutide reduced weight at 3 y vs placebo (−2.3 kg); liraglutide reduced MACE (primary; HR, 0.87; 95% CI, 0.78-0.97) eGFR < 60 subgroup (n = 2,158): MACE HR, 0.69 (95% CI, 0.57-0.85) Albuminuria subgroup (n = 3,422): MACE HR, 0.83 (95% CI, 0.71-0.97)	Overall: Liraglutide reduced risk for kidney composite (HR, 0.78; 95% CI, 0.67-0.92), mostly driven by new-onset persistent macroalbuminuria (HR, 0.74; 95% CI, 0.60-0.91) eGFR < 60 subgroup (n = 2,158): kidney

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Test for subgroup differences: Not applicable

Fig. 4 Forest plot comparing proteinuria before surgery versus after surgery

Bilha et al 2018; Obesity Surgery

Baseline characteristics

Characteristics	Hyperfiltration (GFR>125 mL/min)	Normal (GFR 125–90 mL/min)	CKD stage 2 (GFR 89–60 mL/min)
Patient, n	61	127	39
Age, yr	33.1±9.7 *	39.4±10.4	39.1±10
Female	39	77	23
Male	22	50	16
BMI, kg/m²	38.9±8.8	39.8±9.3	40.5±12.2
Waist, cm	116.4±19.5	116.3±19.1	118.2±19.6
GFR, mL/min	146.4±17.1	105.7±9.6 *	76.8±16.7 *

Comparison of postoperative clinical factors 1 year after

Characteristics	H (C
BMI, kg/m²	2(
WL, %	2(
Waist, cm	9(
GFR, mL/min	1:

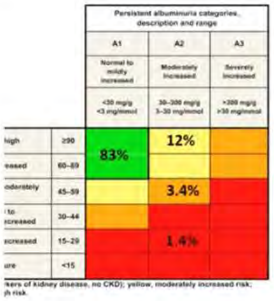
Effect of Bariatric Surgery on CKD Risk JASN 2018

Allon N. Friedman,[1] Abdus S. Wahed,[2] Junyao Wang,[2] Anita P. Courcoulas,[3] Gregory Dakin,[4] Marcelo W. Hinojosa,[5] Paul L. Kimmel,[6] James E. Mitchell,[7] Alfons Pomp,[5] Walter J. Pories,[8] Jonathan Q. Purnell,[9] Carel le Roux,[10] Konstantinos Spaniolas,[11] Kristine J. Steffen,[12] Richard Thirlby,[13] and Bruce Wolfe[14]

- 1807 participants, prospective cohort
  - 71% Roux-en-Y and 24% gastric banding
  - CKD risk categories at baseline

Bariatric Surgery and CKD Risk

83%



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	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
35	153.7	255	55.05	139.1	255	5.4%	-24.70 [-50.14, 0.74]
84	2.12	20	25.54	27.76	20	10.0%	-16.70 [-28.90, -4.50]
6.5	7.17	137	6.1	7.79	233	13.4%	0.40 [-1.16, 1.96]
8	3.5	34	36.35	2.6	34	13.4%	-28.35 [-29.82, -26.88]
9	8.6	136	27	47.2	136	11.7%	-18.00 [-26.06, -9.94]
12	10.3	38	35.3	66.6	38	6.5%	-23.30 [-44.73, -1.87]
5.9	24.88	145	5.7	20.45	191	12.8%	0.20 [-4.78, 5.18]
0.2	1.2	158	21.5	3.2	158	13.5%	-11.30 [-11.83, -10.77]
54	4.75	34	10.84	7.39	34	13.2%	-4.36 [-7.25, -1.35]
		957			1099	100.0%	-12.46 [-20.11, -4.82]

76; Chi² = 779.42, df = 8 (P < 0.00001); I² = 99%
3.20 (P = 0.001)

; Obesity Surgery

GFR Pre vs Post-Surgery

Study or Subgroup	post-surgery Mean	SD	Total	pre-surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.2 GFR<90 group								
Nikhil Mirajkar2016-4	85.4	4.5	25	78	6.9	25	12.0%	7.40 [4.17, 10.63]
Nikhil Mirajkar2016-3	72.5	18.7	4	46.5	9.5	4	2.4%	26.00 [5.45, 46.55]
Nikhil Mirajkar2016-2	56.4	9.7	11	48.4	9.4	11	7.9%	8.00 [0.02, 15.98]
Nikhil Mirajkar2016-1	84.1	13.7	44	76.7	8.1	44	10.7%	7.40 [2.70, 12.10]
Nikhil Mirajkar2016	79.6	19.7	5	75.2	8.8	5	2.7%	4.40 [-14.51, 23.31]
Nehus2017	102	28	48	76	12	59	7.5%	26.00 [17.51, 34.49]
Neff2017	68	7	19	52	2	19	11.9%	16.00 [12.73, 19.27]
Hung2020	82.4	24.7	44	72.6	16.3	76	7.7%	9.80 [1.63, 17.97]
Hou2013 (<60)	66.8	19.3	6	49.5	6.6	6	3.4%	17.30 [0.98, 33.62]
Hou2013	93.3	20.4	39	76.8	16.7	39	7.6%	16.50 [8.23, 24.77]
Holcomb2018	81.6	24.5	62	68.9	15.6	62	8.5%	12.70 [5.47, 19.93]
Garcia2020	90.6	15.3	41	75.8	11.6	41	9.7%	14.80 [8.92, 20.68]
Abouchacra2013	103.6	19	41	80.99	18	41	7.9%	22.61 [14.60, 30.62]
Subtotal (95% CI)			389			432	100.0%	13.81 [10.31, 17.32]

Heterogeneity: Tau² = 24.00; Chi² = 40.14, df = 12 (P < 0.0001); I² = 70%
Test for overall effect: Z = 7.72 (P < 0.00001)

Huang et al 2021; Obesity Surgery

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JAMA Surgery | Original Investigation

Effect of Gastric Bypass vs Best Medical Treatment on Early-Stage Chronic Kidney Disease in Patients With Type 2 Diabetes and Obesity

A Randomized Clinical Trial Cohen et al August 2020

- 100 patients with T2DM, BMI 30-

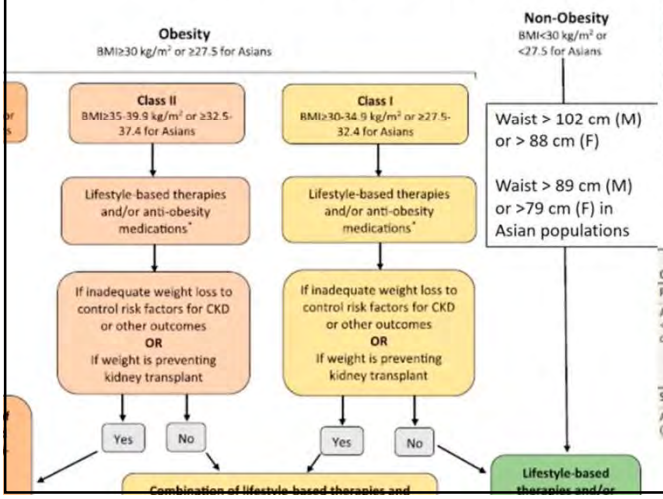
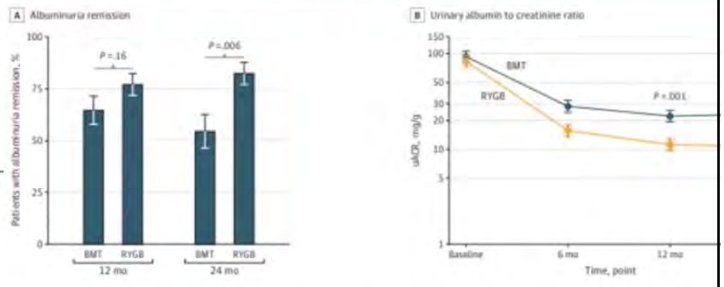


Figure 2. Albuminuria Remission Rates at 12 and 24 Months of Follow-up and Longitudinal Biochemical Measures of Urinary Albumin-Creatinine Ratio (uACR) and Metabolic Control



Outcome	Best medical treatment (n = 49)	RYGB (n = 51)	Difference (95% CI)
Primary outcome			
Albumin to creatinine ratio <30 mg/g of creatinine (remission)			
iTT analysis, %	54.6 (38.8 to 70.3)	82.3 (72.1 to 92.6)	27.8 (8.7 to 46.8)
Complete case analysis, No. (%)[b]	24 (56)	36 (84)	27.9 (9.4 to 46.4)
Secondary outcomes			
Albuminuria, geometric mean (95% CI), mg/g of creatinine	23.6 (17.9 to 31.2)	10.7 (8.1 to 14.1)	0.45 (0.30 to 0.67)[c]

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