Exciting Update: The CREDENCE Trial

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Disclosures

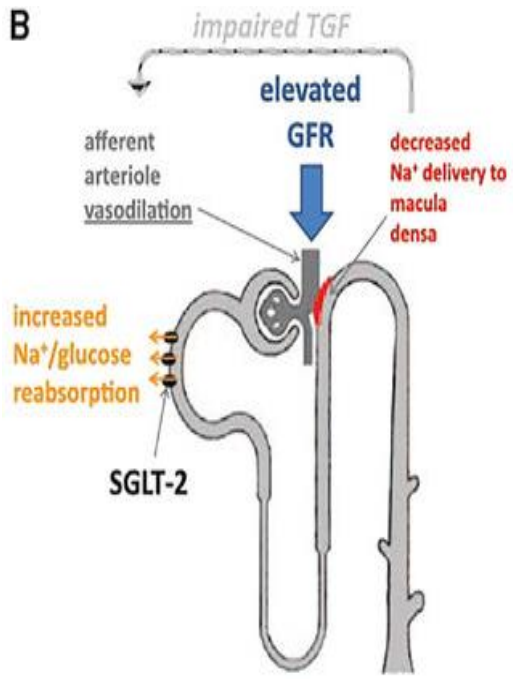
None

Learning Objectives

- Summarize results of the CREDENCE Trial
- Describe the proposed mechanism of the renal protective effect of SGLT-2 Inhibitors
- Understand the impact of renal protective drug therapy and identify the place in therapy of SGLT-2 inhibitors

Diabetic Nephropathy

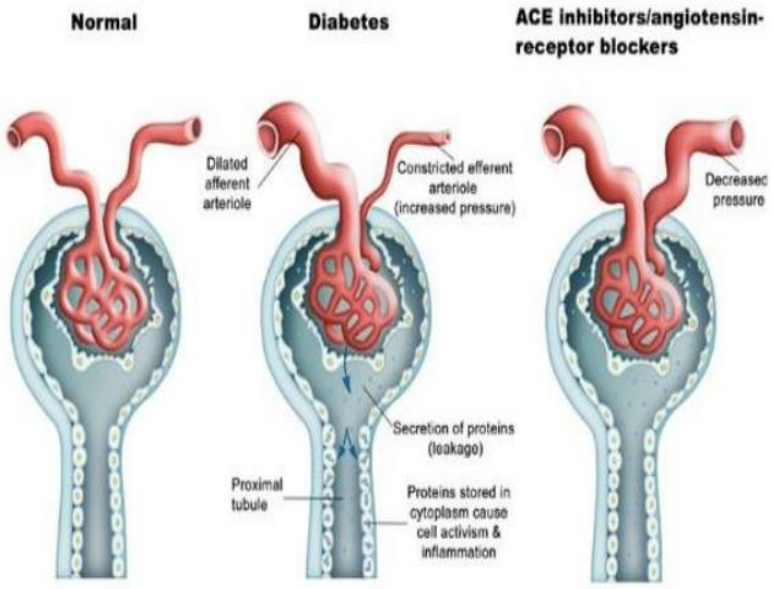
- Glomerular Hyperfiltration
- Albuminuria



Hyperfiltration in early stages of diabetic nephropathy

Diabetic Nephropathy

- Treatment Options
  - Modification of risk factors
  - RAAS inhibition with ACE inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB)



	IDNT (2001)	RENAAL (2001)	ADVANCE (2007)
Drug/Comparator	Irbesartan vs. Placebo Amlodipine vs. Placebo Irbesartan vs. Amlodipine	Losartan vs. Placebo	Perindopril-Indapamide vs. Placebo
n, duration	1,715 for 2.6 years	1,513	11,140 for 4.3 years
Study Design	Prospective, multicenter, Double-blind, RCT	Prospective, multicenter, double-blind, parallel-group, RCT	
Population	Age 30-70 years, T2DM, HTN, proteinuria (≥900 mg/24hr)	Age 31-70 years, T2DM complicated by nephropathy	Mean age 66 years, diabetes 8 years, BMI 28 kg/m^2
Primary Outcome	Doubling of baseline serum creatinine, development of ESRD, or all-cause mortality	Composite of doubling of serum creatinine, ESRD, or all-cause mortality	Composite of major macro and microvascular endpoints, including renal (analyzed jointly and separately)
Result	Irbesartan vs. Placebo 32.6% vs. 39% (RR 0.8,95% CI 0.66-0.97, p = 0.02) Amlodipine vs. Placebo 41.1% vs. 39% (RR 1.04, 95% CI 0.86-1.25, p = 0.69) Irbesartan vs. Amlodipine 32.6% vs. 41.1% (RR 0.77, 95% CI 0.63-0.93, p = 0.006)	43.5% vs. 47.1% (RR 0.84, p = 0.02, NNT 28) Independently, as secondary outcomes, doubling of creatinine and progression to ESRD were reduced significantly, but mortality was not.	15.5% vs. 16.8% (HR 0.91, 95% CI 0.83-1.00, p = 0.04) Significant reduction in BP 5.6 mmHg vs. 2.2 mmHg Reduction in Microalbuminuria 19.6 % vs. 23.6% (HR 0.21, 95% CI 0.14-0.27, p <0.001)
Bottom Line	Irbesartan delays progression of nephropathy due to Type 2 Diabetes. Amlodipine no better than placebo despite similar BP target to Irbesartan group	In patients with diabetic nephropathy, losartan reduced risk of doubling serum creatinine and progression to ESRD but did not have a mortality benefit.	Perindopril/Indapamide reduces incidence of major macro and microvascular endpoints, and the rate of new onset albuminuria


1998
UKPDS
Intensive glycemic control reduced micro and macroalbuminuria by 39% and 54%
2001
RENAAL
Losartan reduced risk of doubling of creatinine by 25% and ESRD by 28%. Decreased proteinuria by 35%
2001
IRMA-2
Irbesartan found to be renoprotective independent of BP lowering effect
2001
IDNT
Irbesartan associated with lower risk of creatinine doubling ESRD compared to placebo & amlodipine
2002
MARVAL
Greater decrease of micro-albuminuria with valsartan than amlodipine
2008
ACCORD
Targettng HbA1C <6% resulted in greater mortality compared to 7-7.9%
2012
ALTITUDE
Addition of aliskiren to maximal ARB - Increased risk of Hyperkalemia & hypotension.
2011
BEAM
Bardoxolone resulted in a higher GFR compared with placebo at 52 weeks.
2011
ROADMAP
Olmesartan resulted in a reduction in time to micro-albuminuria onset by 23% but increased CV events
2010
VITAL
Paricalcitol at 2 µg/day reduced albuminuria (20% compared with placebo). However, dose poorly tolerated
2008
AVOID
Aliskiren/losartan combo led to reduction of UACR by 20%
2008
ONTARGET
Combination therapy was associated with increased composite outcome of dialysis, serum creatinine doubling and death
2013
VA-NEPHRON-D
Combination therapy resulted in excessive risk of hyperkalemia & AKI
2013
BEACON
Terminated at 9 mo Bardoxolon led to a sig increase in CV morbidity
2013
CANTATA-SU
Canagliflozin initial decrease in GFR then stabilized glimepiride arm had progressive GFR decline
2015
EMPA-REG
Post hoc analyses - reduction of albuminuria, slowing down of estimated glomerular filtration rate (eGFR) decline, and a 50% reduction in risk of progressing to ESRD
2017
CANVAS
"possible benefits" of canagliflozin treatment for both progression of albuminuria & on composite renal outcome of a sustained 40% reduction in eGFR, need for RRT, or death from renal causes
2019
CREDENCE
Renal failure & CV events- lower in canagliflozin arm than placebo

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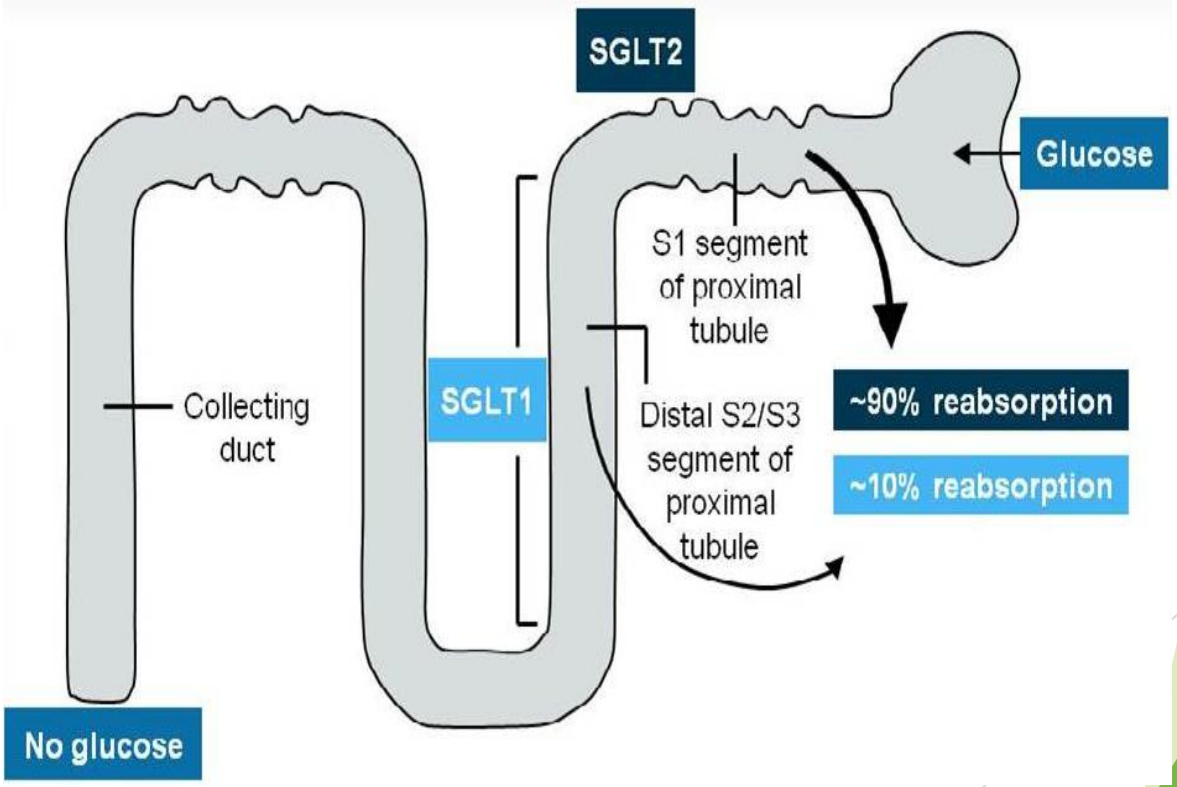
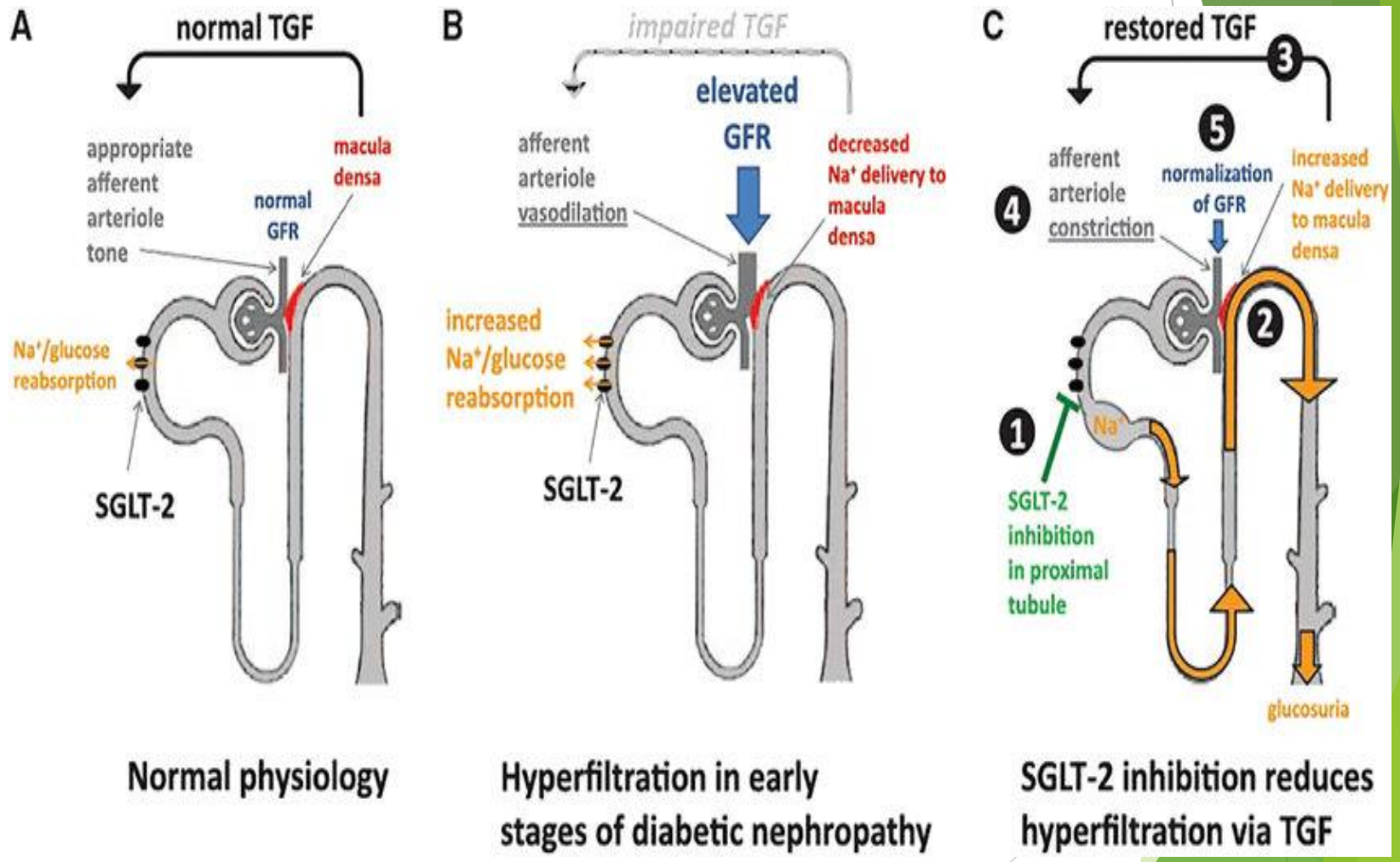
SGLT-2 Inhibitors

- Inhibitors of the sodium-glucose co-transporter 2



	EMPA-REG (2015)	CANVAS (2017)	DECLARE-TIMI (2019)
Drug	Empagliflozin (10 mg and 25 mg)	Canagliflozin (100 mg and 300 mg)	Dapagliflozin (10 mg)
n	7, 020	10, 142	17, 160
GFR at enrolment	≥ 30 mL/min/1.73m^2 Mean GFR ~74 mL/min	≥ 30 mL/min/1.73m^2 Mean GFR ~76.5 mL/min	CrCl ≥ 60 mL/min Mean GFR ~85 mL/min
UACR	No criteria ACR <30 mg/g in ~60% 30-300 mg/g in ~30% >300 mg/g in ~10%	No criteria Median ACR 12.3 mg/g	Not reported/No criteria
Primary Endpoint	MACE	MACE	MACE
Renal Outcome Prespecified?	Prespecified secondary outcome* (Incident or worsening nephropathy defined as progression to microalbuminuria ACR >300 mg/g, doubling of serum creatinine (SCr) + eGFR ≤45 mL/min, initiation of RRT, or death from renal causes)	Yes Progression of albuminuria (secondary) 40% reduction in eGFR, RRT, or renal death (exploratory)	Yes Composite of > 40% decline in GFR to <60 mL/min, ESRD, renal or CV death
Renal Outcome	12.7% vs. 18.8% (HR 0.61, CI 0.53-0.70, p < 0.01) Doubling SCr RRR 44% vs. placebo Initiation of RRT 55% vs. placebo	Albuminuria – HR 0.73; 95% CI, 0.67 to 0.79 Exploratory Outcomes - HR 0.60; 95% CI, 0.47 to 0.77)	4.3% dapagliflozin vs. 5.6% placebo (HR 0.76, 95% CI, 0.67 to 0.87) – *hypothesis generating only as did not meet significance for MACE*

SGLT2 Inhibitors



In patients with diabetes and established, albuminuric chronic kidney disease, can SGLT-2 Inhibitors improve renal outcomes?

CREDENCE

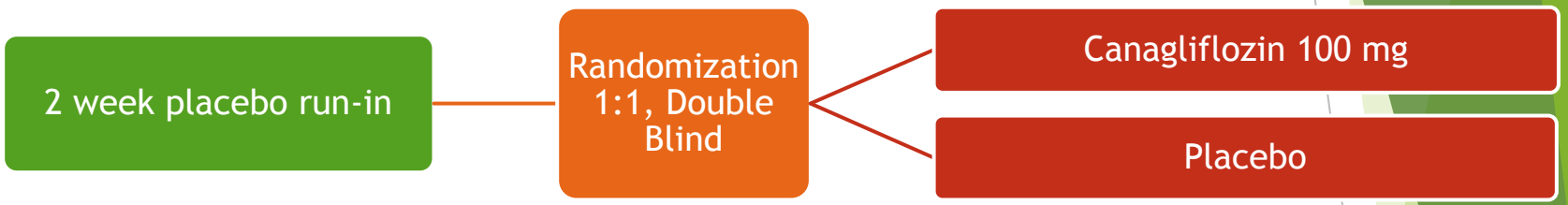
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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

Study Design



- Planned subgroup analyses stratified based on eGFR (30 to < 45 mL, 45 to <60 mL, and 60 to <90 mL/min/1.73m^2)
- Clinic follow up at weeks 3, 13, and 26, then every 13 weeks (alternating between clinic/telephone)
- Continued treatment until observance of primary outcome, completion of trial, occurrence of DKA, or receipt of a disallowed therapy
- Foot care at each clinic follow up added after results of CANVAS in 2016

Study Design

- Primary Outcome
  - Composite of ESRD, doubling of serum creatinine level from baseline, or death from renal or cardiovascular cause
- Secondary Outcomes
  - Composite of CV death or hospitalization for heart failure
  - Composite of cardiovascular death, MI, or stroke
  - Hospitalization for heart failure
  - Composite of ESRD, doubling of serum creatinine, or renal death
  - Cardiovascular death
  - Death from any cause
  - Composite of cardiovascular death, MI, stroke, or hospitalization for heart failure or for unstable angina

Study Design

Inclusion Criteria	Exclusion Criteria
≥ 30 years of age	History of dialysis or kidney transplantation
T2DM, HbA1c 6.5-12%	Dual ACEI/ARB therapy, direct renin inhibitor, or mineralocorticoid receptor antagonist
eGFR 30-90 mL/min/1.73m^2	Serum K^+ ≥ 5.5 mmol/L at screening
uACR 300 to 5000 mg/g	CV event within 12 weeks of screening
ACE inhibitor/ARB therapy at a stable max tolerated dose for ≥ 4 weeks	NYHA Class IV heart failure
	Diabetic Ketoacidosis or T1DM

Study Design

- Event-driven duration, Intention to Treat
  - Pre-determined enrolment of at least 4200 patients for 90% power to detect difference of 20% in primary outcome
- Interim Analysis
  - Pre-specified to be conducted by independent data monitoring committee after 405 occurrences of the primary outcome
  - May recommend to stop trial if clear evidence of benefit seen for primary outcome ($p < 0.01$) or the composite of end-stage kidney disease or death from renal or cardiovascular causes (< 0.025)
- Pre-specified hierarchical testing

Results

- 4401 patients enrolled between March 2014 to May 2017
- Requisite number of primary outcome events (405) to trigger the interim analysis reached in July 2018

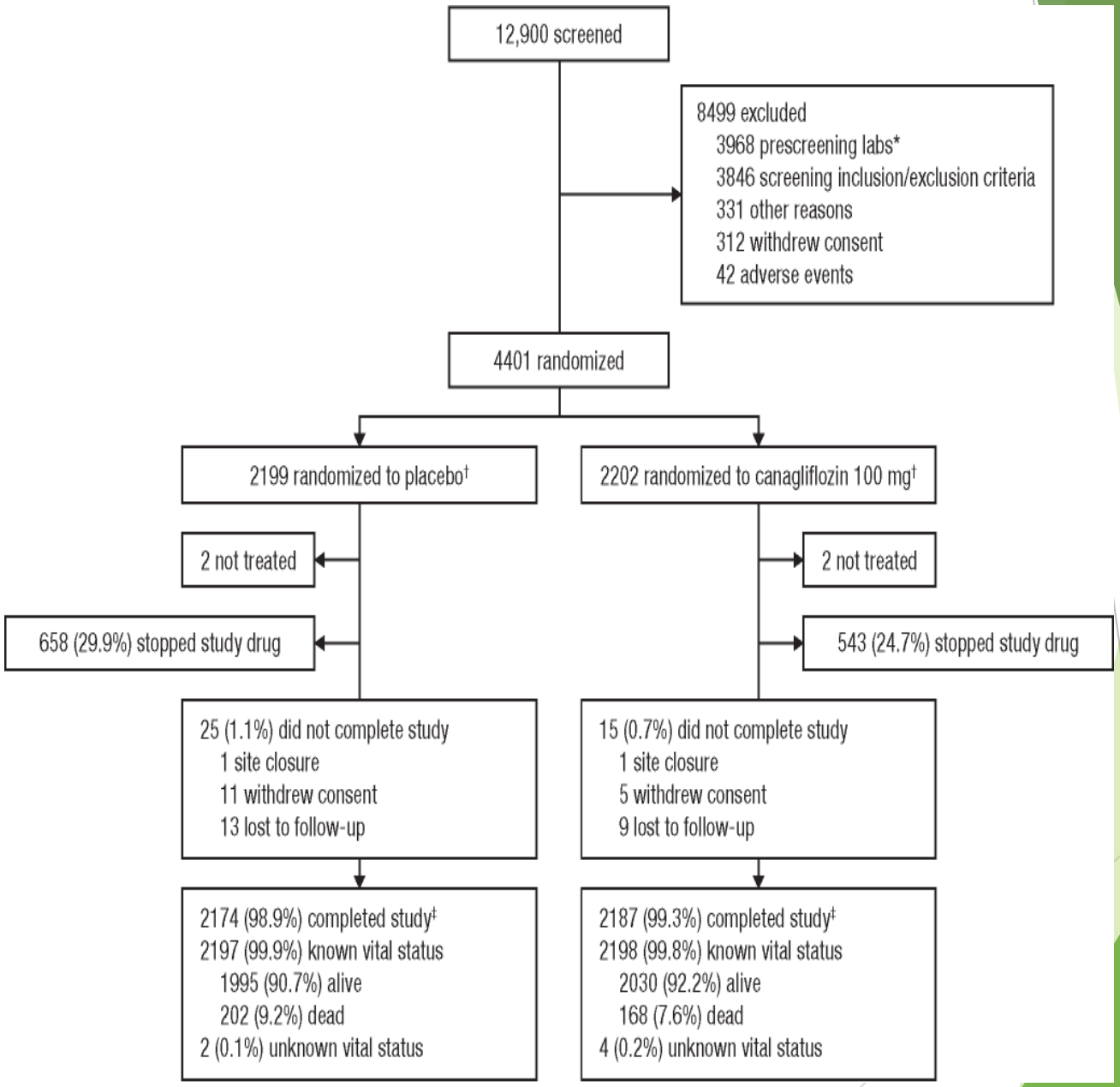

12,900 screened
8499 excluded
3968 prescreening labs*
3846 screening inclusion/exclusion criteria
331 other reasons
312 withdrew consent
42 adverse events
4401 randomized
2199 randomized to placebo†
2202 randomized to canagliflozin 100 mg†
2 not treated
2 not treated
658 (29.9%) stopped study drug
543 (24.7%) stopped study drug
25 (1.1%) did not complete study
1 site closure
11 withdrew consent
13 lost to follow-up
15 (0.7%) did not complete study
1 site closure
5 withdrew consent
9 lost to follow-up
2174 (98.9%) completed study‡
2197 (99.9%) known vital status
1995 (90.7%) alive
202 (9.2%) dead
2 (0.1%) unknown vital status
2187 (99.3%) completed study‡
2198 (99.8%) known vital status
2030 (92.2%) alive
168 (7.6%) dead
4 (0.2%) unknown vital status

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Canagliflozin (N=2202)	Placebo (N=2199)	All Patients (N=4401)
Age — yr	62.9±9.2	63.2±9.2	63.0±9.2
Female sex — no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race or ethnic group — no. (%)†			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black	112 (5.1)	112 (5.1)	224 (5.1)
Asian	425 (19.3)	452 (20.6)	877 (19.9)
Other	178 (8.1)	191 (8.7)	369 (8.4)
Current smoker — no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
Hypertension — no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure — no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes — yr	15.5±8.7	16.0±8.6	15.8±8.6
Cardiovascular disease — no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Amputation — no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body-mass index‡	31.4±6.2	31.3±6.2	31.3±6.2
Blood pressure — mm Hg			
Systolic	139.8±15.6	140.2±15.6	140.0±15.6
Diastolic	78.2±9.4	78.4±9.4	78.3±9.4
Glycated hemoglobin — %	8.3±1.3	8.3±1.3	8.3±1.3
Estimated GFR — ml/min/1.73 m^2§	56.3±18.2	56.0±18.3	56.2±18.2
Median urinary albumin-to-creatinine ratio (IQR)¶	923 (459–1794)	931 (473–1868)	927 (463–1833)

Results

Table 2. Efficacy and Safety.*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR <15 ml/min/1.73 m^2	78/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05

Results

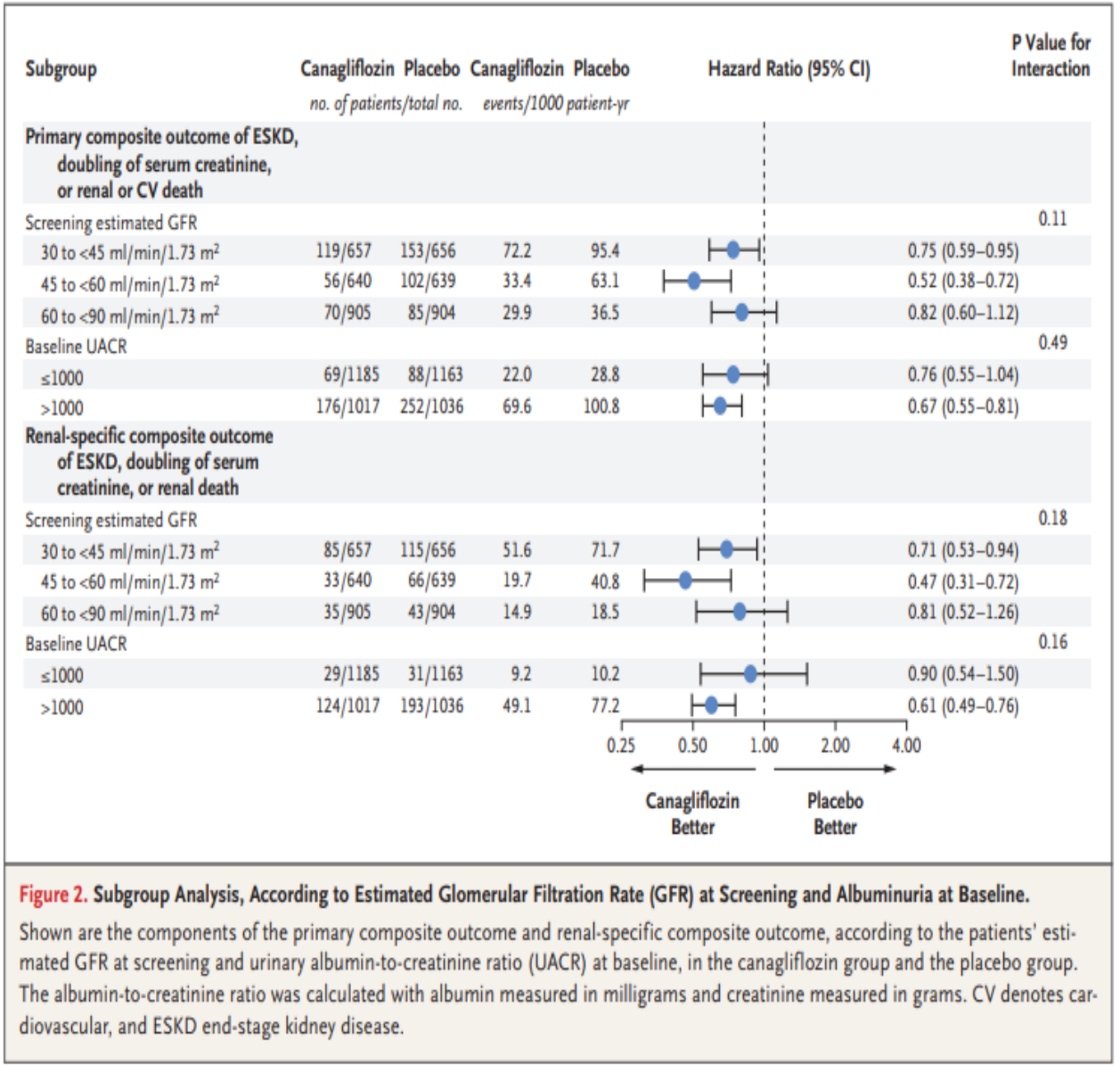


Figure 2. Subgroup Analysis, According to Estimated Glomerular Filtration Rate (GFR) at Screening and Albuminuria at Baseline.

Shown are the components of the primary composite outcome and renal-specific composite outcome, according to the patients' estimated GFR at screening and urinary albumin-to-creatinine ratio (UACR) at baseline, in the canagliflozin group and the placebo group. The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams. CV denotes cardiovascular, and ESKD end-stage kidney disease.

Results

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Secondary outcomes						
1 Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (0.57–0.83)	<0.001
2 Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (0.67–0.95)	0.01
3 Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (0.47–0.80)	<0.001
4 End-stage kidney disease, doubling of serum creatinine level, or renal death	153/2202	224/2199	27.0	40.4	0.66 (0.53–0.81)	<0.001
6 Death from any cause	168/2202	201/2199	29.0	35.0	0.83 (0.68–1.02)	NA
7 Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina	273/2202	361/2199	49.4	66.9	0.74 (0.63–0.86)	NA
End-stage kidney disease, renal death, or cardiovascular death†	214/2202	287/2199	37.6	51.2	0.73 (0.61–0.87)	NA
Dialysis, kidney transplantation, or renal death†	78/2202	105/2199	13.6	18.6	0.72 (0.54–0.97)	NA
5 Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05

Results

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Safety‡						NA
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Fracture	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)	NA
Cancer						
Renal-cell carcinoma	1/2200	5/2197	0.2	0.9	NA	NA
Breast cancer§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)	NA
Bladder cancer	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)	NA
Acute pancreatitis	5/2200	2/2197	1.0	0.4	NA	NA
Hyperkalemia¶	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)	NA
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)	NA
Diabetic ketoacidosis‖	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)	NA

Limitations

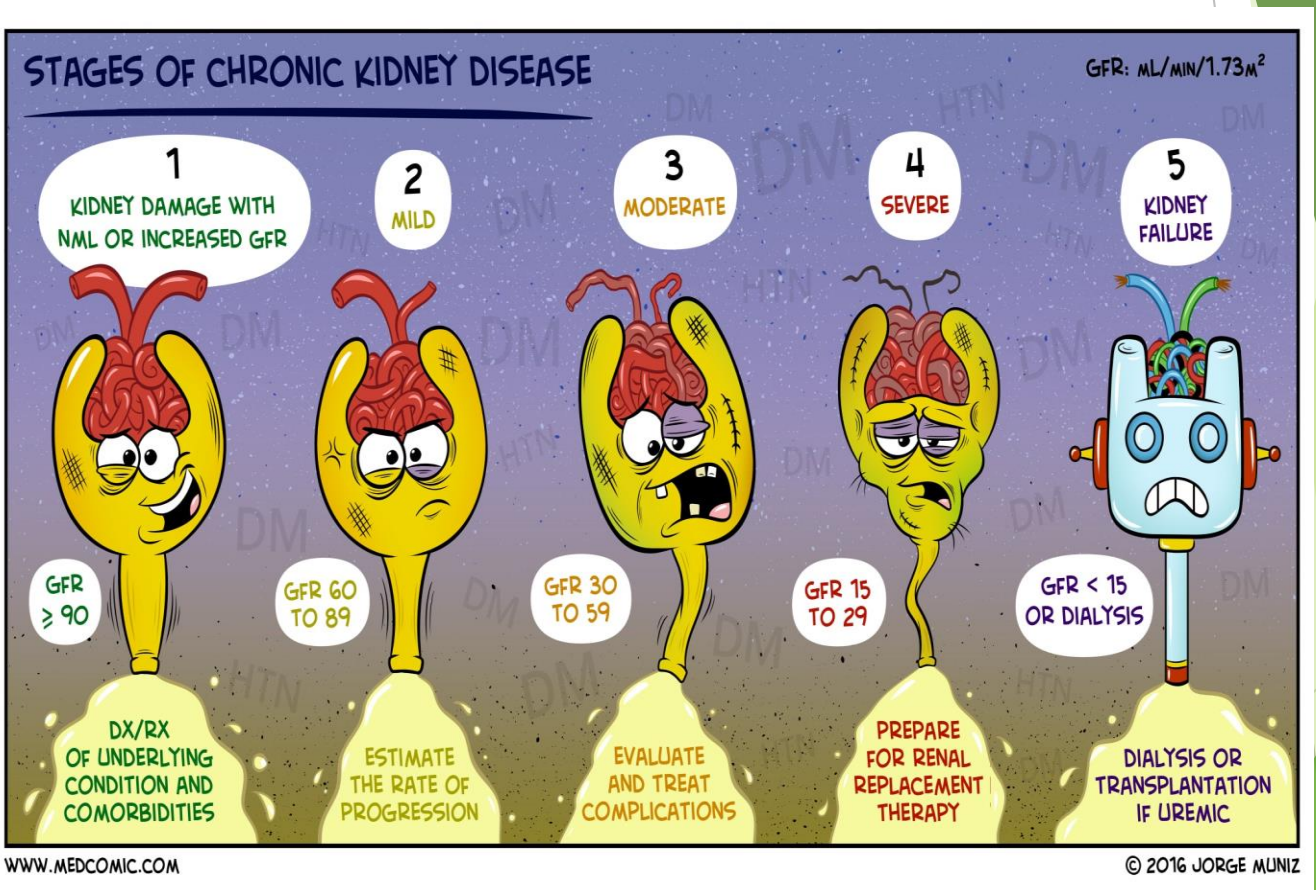
- Stopped early, results based on Interim Analysis
- Short follow up period, median 2.62 years
- Excluded patients with eGFR <30 mL/min
- Limited applicability to patients with non-albuminuric or microalbuminuric kidney disease, transplant patients, or to patients with other causes of kidney disease
- Unknown effect of variations in dose

Conclusions

Author's Conclusion:

"In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years."

Questions?


STAGES OF CHRONIC KIDNEY DISEASE
GFR: ML/MIN/1.73M²
1
KIDNEY DAMAGE WITH NML OR INCREASED GFR
2
MILD
3
MODERATE
4
SEVERE
5
KIDNEY FAILURE
GFR ≥ 90
GFR 60 TO 89
GFR 30 TO 59
GFR 15 TO 29
GFR < 15 OR DIALYSIS
DX/RX OF UNDERLYING CONDITION AND COMORBIDITIES
ESTIMATE THE RATE OF PROGRESSION
EVALUATE AND TREAT COMPLICATIONS
PREPARE FOR RENAL REPLACEMENT THERAPY
DIALYSIS OR TRANSPLANTATION IF UREMIC
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