Cardiorenal Effects of SGLT2-Inhibitors: A Class Effect?

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Overview

- Overview of cardiovascular and renal effects of diabetes mellitus.
- Physiology of SGLT-1 and SGLT-2.
- Compare available SGLT-2 inhibitors and their differences on receptor affinity.
- Summarize and compare the four SGLT-2 inhibitors clinical trials.
- Explore the potential determinants for their cardiovascular, renal and safety outcomes.
- Class effect?

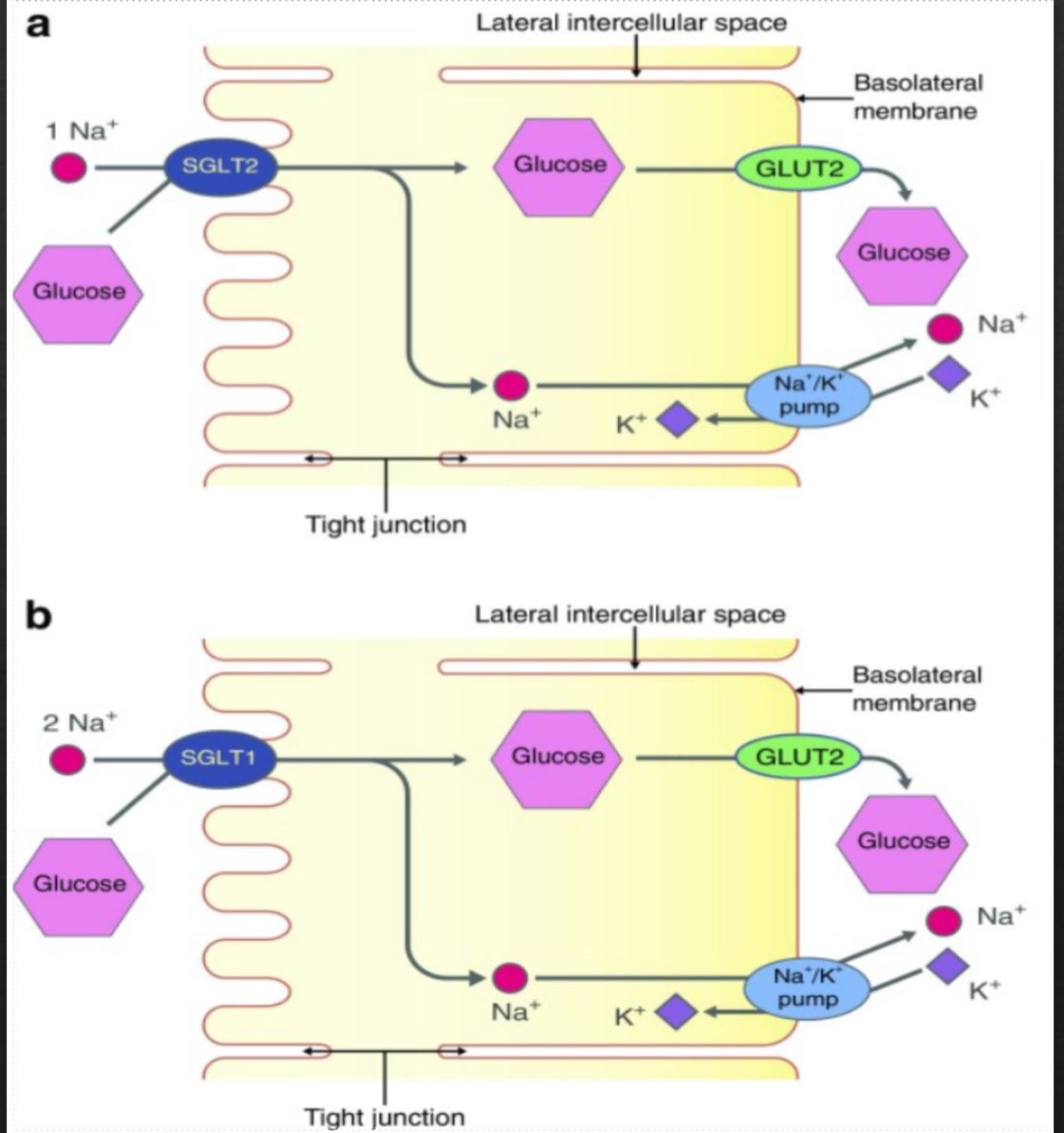
Cardiorenal effects of Diabetes Mellitus

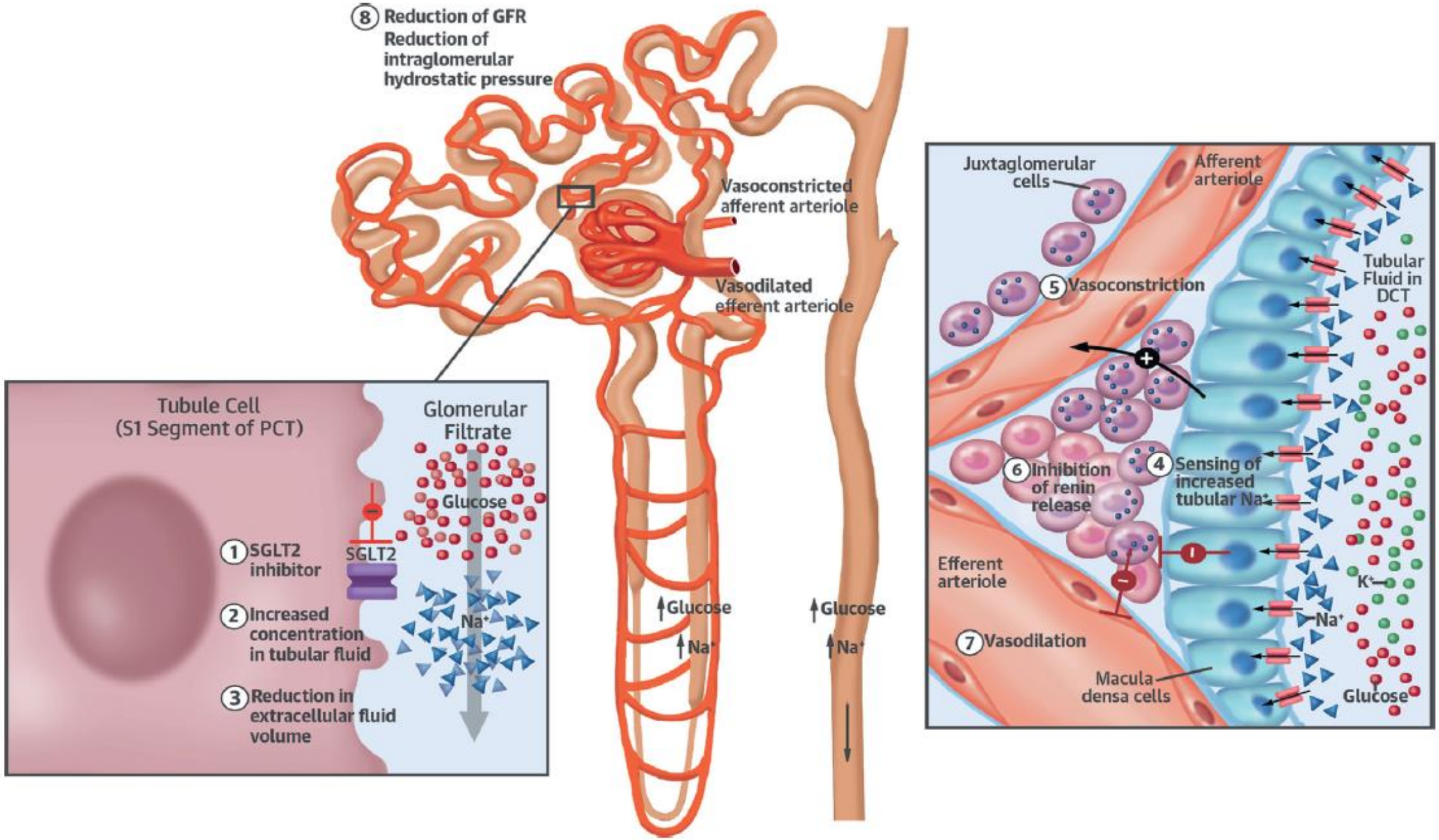
- At least 68 percent of people age 65 or older with diabetes die from some form of heart disease; and 16% die of stroke.
- Adults with diabetes are two to four times more likely to die from heart disease than adults without diabetes.
- The American Heart Association considers diabetes to be one of the seven major controllable risk factors for cardiovascular disease.
- Patients with diabetes mellitus have >2× the risk for developing heart failure. Approximately 44% of hospitalized patients for HF have DM.
- It is also well known that diabetes is linked to kidney failure; about 30% of those with type 1 diabetes and 10% to 40% with type 2 diabetes (T2D) will progress to this stage.

Sodium Glucose Transporters

Characteristic	SGLT1	SGLT2
Location	Small Intestine, Later portion of PTC (segment 3)	Early PTC (segment 1 and 2)
Capacity	Low	High
Affinity	High	Low
Contribution to glucose reabsorption	10%	90%
Disease if mutation occurs	Glucose-Galactose Malabsorption	Familial Renal Glucosuria
Manifestations of disease	Diarrhea at few days of age	None
Course	Fatal if not controlled by low CHO diet	Benign
Inhibitors	Phlorizin	Current Available SGLT2 i

Proximal Convoluted Tubule




8 Reduction of GFR
Reduction of intraglomerular hydrostatic pressure
Vasoconstricted afferent arteriole
Vasodilated efferent arteriole
Tubule Cell (S1 Segment of PCT)
Glomerular Filtrate
Glucose
SGLT2
1 SGLT2 inhibitor
2 Increased concentration in tubular fluid
3 Reduction in extracellular fluid volume
Na+
Glucose
Na+
Glucose
Na+
Juxtaglomerular cells
Afferent arteriole
5 Vasoconstriction
Tubular Fluid in DCT
6 Inhibition of renin release
4 Sensing of increased tubular Na+
Efferent arteriole
7 Vasodilation
Macula densa cells
K+
Na+
Glucose

Four FDA Approved SGLT2 Inhibitors

- **Empagliflozin**
  (EMPA REG Trial)
- **Canagliflozin**
  (CANVAS and CREDENCE)
- **Dapagliflozin**
  (DECLARE-TIMI 58)
- **Ertugliflozin**
  (VERTIS, VERTIS CV)

Selectivity for SGLT2 versus SGLT1

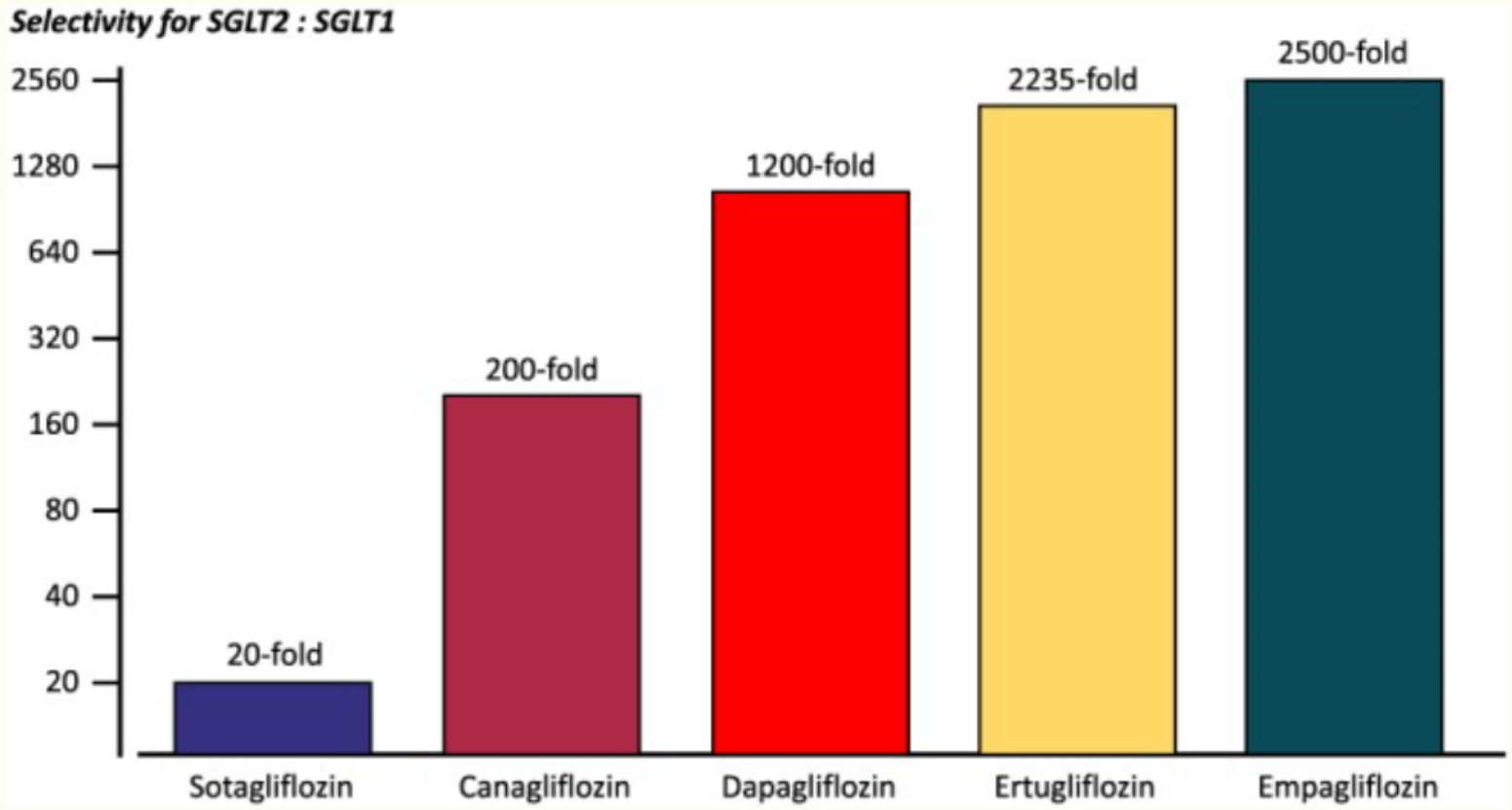


Figure 1

Selectivity of different compounds of the class for the sodium-glucose co-transporter-2 (SGLT2) vs. SGLT1.

A1C effect of Available SGLT2 Inhibitors

Drug	Hgb A1C Reduction %
Canagliflozin	-0.73 to -1.08
Dapagliflozin	-0.52 to -0.59
Empagliflozin	-0.62 to -0.66
Ertugliflozin	-0.7 to -1.7

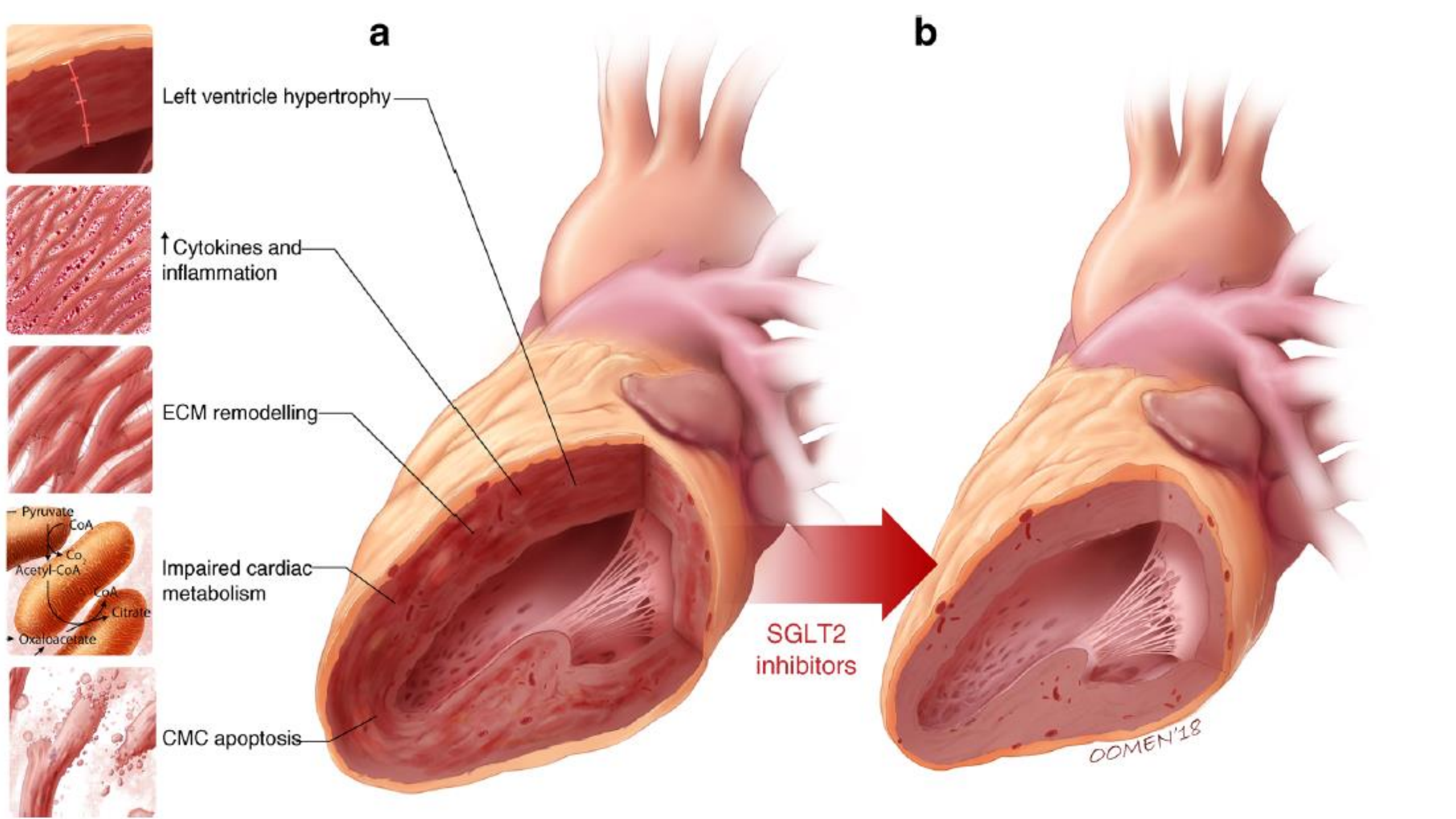
Pleiotropic Effects of SGLT2
Inhibitors: Beyond Glycemic Effect

Body Weight

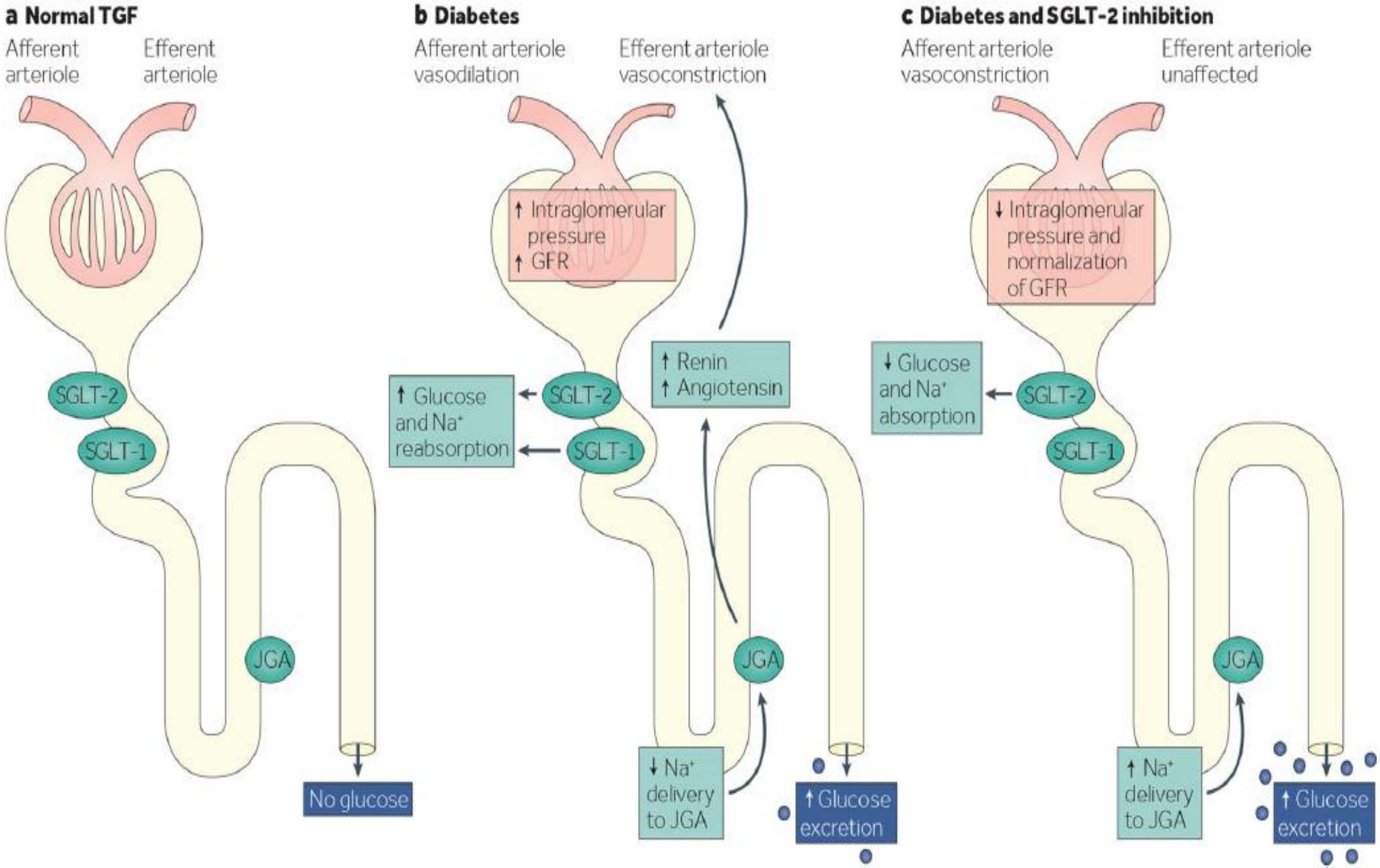
- Believed to result from an increase in urinary glucose excretion.
- Associated with daily glucose losses of 60–80 g or 240–320 calories.
- Body weight reductions observed after 12–24 weeks of therapy are typically in the 2- to 3-kg range.
- Although fluid loss may initially play a role in weight loss, overall reductions in body weight are believed to be mainly the result of fat loss.

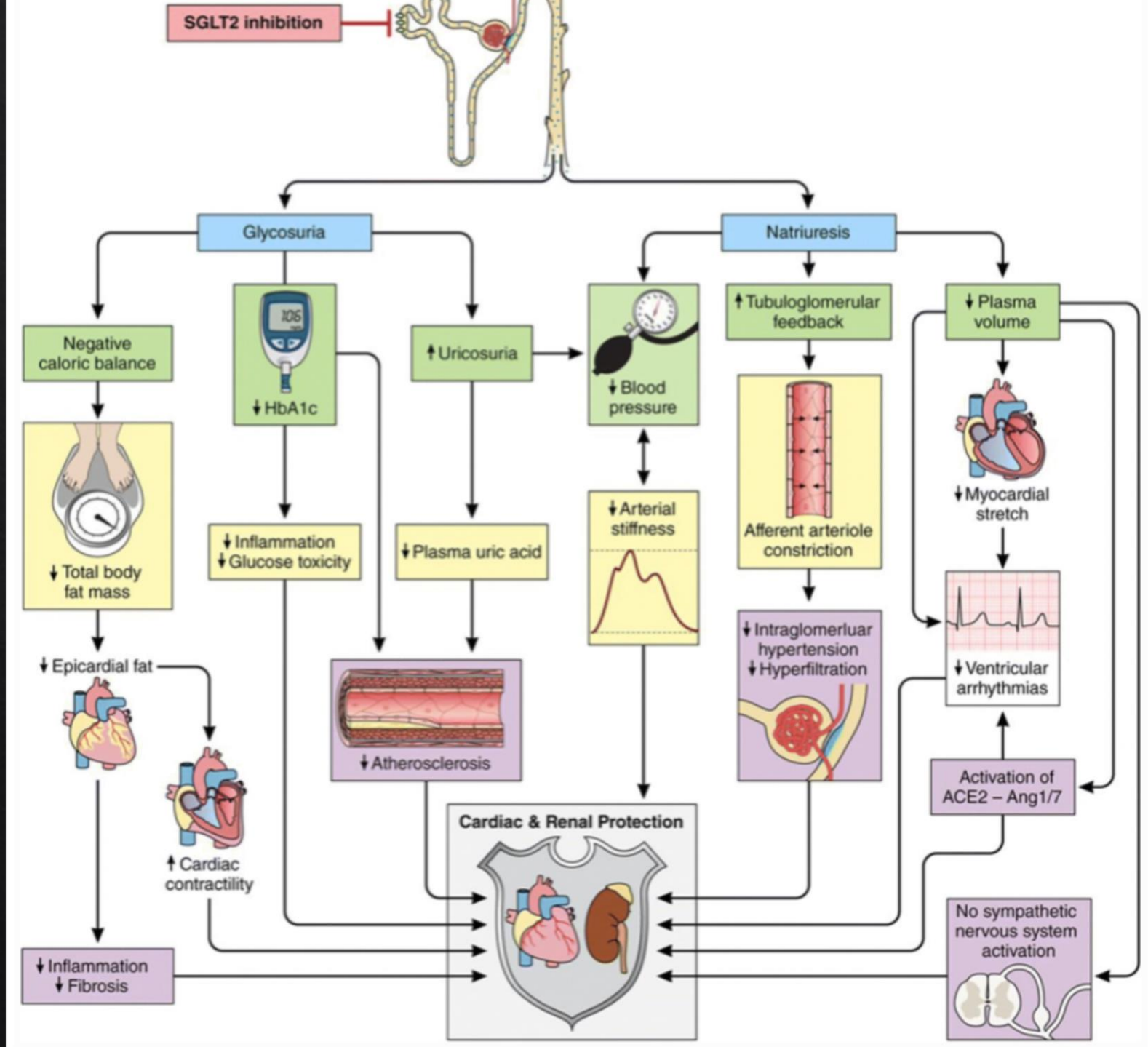
Blood Pressure

- Diuretic effects of SGLT-2is through increased urinary excretion of glucose and sodium.
- This also leads to sustained reductions in intravascular volume, which likely contribute to the antihypertensive effects of SGLT-2i.


a
b
Left ventricle hypertrophy
↑Cytokines and inflammation
ECM remodelling
Impaired cardiac metabolism
CMC apoptosis
Pyruvate
CoA
Co2
Acetyl-CoA
CoA
Citrate
Oxaloacetate
SGLT2 inhibitors
OOMEN'18

Renal Effect


a Normal TGF
Afferent arteriole
Efferent arteriole
SGLT-2
SGLT-1
JGA
No glucose
b Diabetes
Afferent arteriole vasodilation
Efferent arteriole vasoconstriction
↑ Intraglomerular pressure
↑ GFR
↑ Glucose and Na+ reabsorption
SGLT-2
SGLT-1
↑ Renin
↑ Angiotensin
JGA
↓ Na+ delivery to JGA
↑ Glucose excretion
c Diabetes and SGLT-2 inhibition
Afferent arteriole vasoconstriction
Efferent arteriole unaffected
↓ Intraglomerular pressure and normalization of GFR
↓ Glucose and Na+ absorption
SGLT-2
SGLT-1
JGA
↑ Na+ delivery to JGA
↑ Glucose excretion

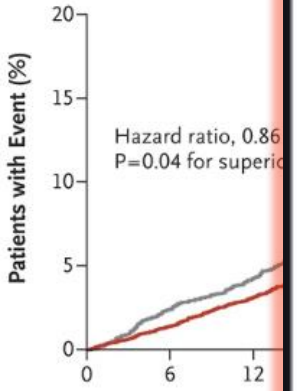

SGLT2 inhibition
Glycosuria
Natriuresis
Negative caloric balance
↓HbA1c
↑Uricosuria
↓Blood pressure
↑Tubuloglomerular feedback
↓Plasma volume
↓Total body fat mass
↓Inflammation
↓Glucose toxicity
↓Plasma uric acid
↓Arterial stiffness
Afferent arteriole constriction
↓Myocardial stretch
↓Epicardial fat
↓Atherosclerosis
↓Intraglomerluar hypertension
↓Hyperfiltration
↓Ventricular arrhythmias
↑Cardiac contractility
Cardiac & Renal Protection
Activation of ACE2 – Ang1/7
↓Inflammation
↓Fibrosis
No sympathetic nervous system activation

SGLT2 Inhibitors Clinical Trials

EMPA REG Trial	CANVAS
• First CVOTs, with 7020 patients with T2DM **and** established CVD. 10 or 25 mg Empagliflozin or placebo. Mean age: 63.1, female: 28%	• Second CVOTs with 10,142 patients with T2DM daily Cana 100 mg with optional increase to300 mg or placebo. Mean age: 63 years, 36% female.
• 3.1 years follow up period. History of myocardial infarction: 47%, multivessel disease: 47%, coronary artery bypass grafting: 25%	• 2.4 years period. Patients must be > 30 years with established CVD or > 50 years with at least 2 risk factors. (65.6% had CVD).
• eGFR > 30 ml/min (MDRD), mean eGFR was 74 +- 21: **(74% pts had eGFR > 60 ml/min).**	• eGFR> 30 ml/min (MDRD). • Mean eGFR: 76.5 +- 20. • 20% had eGFR < 60, 79.9% had eFGR > 60 ml/min
• 4171 patient had microalbuminuria, 769 had macroalbuminuria.	• 69.8% had microalbuminuria • 22.6% had UACR 30-300 and 7.6% had macroalbuminuria
• 5666 patients used ACEi/ARBs (80%)	• 8116 patients used ACEi/ARBs

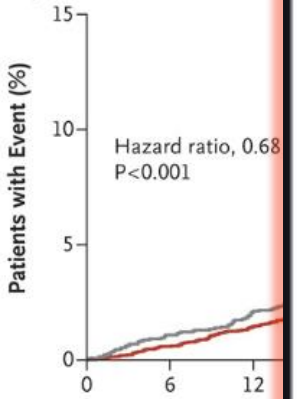
DECLARE-TIMI 58	CREDENCE
• Third CVOTs, with 17,160 patients with T2DM at 10 mg Dapagliflozin or placebo. • Established CVD or > 1 risk factors including men ≥55 years or women ≥60 years.	• 4401 patients with T2DM and CKD. • 100 Canagliflozin or placebo • 50.4% had established CVD, but it was not required for inclusion criteria. • 16% had baseline hx of HF • Required to have albuminuria
• Duration follow up: 4.2 years. • Female 37% • 40% had established CVD	• Duration of follow-up: 2.62 years • Mean patient age: 63.0 years • Percentage female: 33.9%
• Mean eGFR: 85.2 ml/min (CKD-EPI) • 92% of patients had eGFR > 60 ml/min	• Mean eGFR: 56.2 +-18 (CKD-EPI) • 59% eGFR <60 ml/min • Mean UACR: 927 mg/g (only 31 patients had UACR <30)
• 67.9% had UACR < 30mg/g • 23 % had UACR 30-300 mg/g • 6.8% had UACR >300 mg/g	• 11.3% had UACR > 30-300 mg/g • 76.6% had UCAR 300-3000 mg/g • 11.4% had UCAR> 3000 mg/g
• 81.3% used ACEi/ARBs	• 99.9% used ACEi/ARBs (it was required)

A Primary Outcome



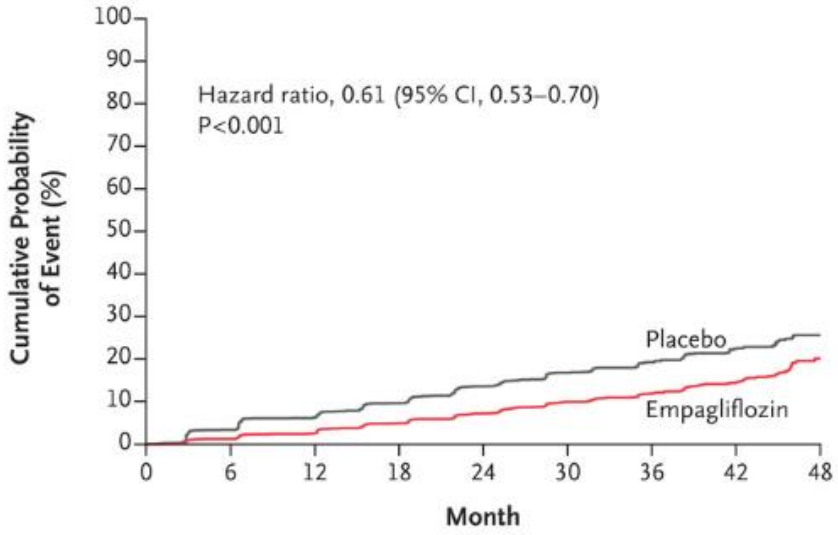
No. at Risk			
Empagliflozin	4687	4580	4455
Placebo	2333	2256	2194

C Death from Any Cause



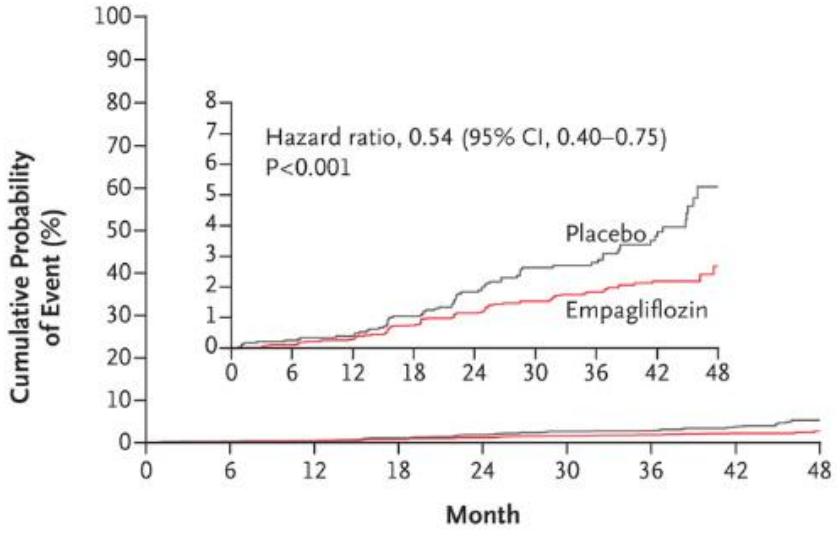
No. at Risk			
Empagliflozin	4687	4651	4608
Placebo	2333	2303	2280

A Incident or Worsening Nephropathy

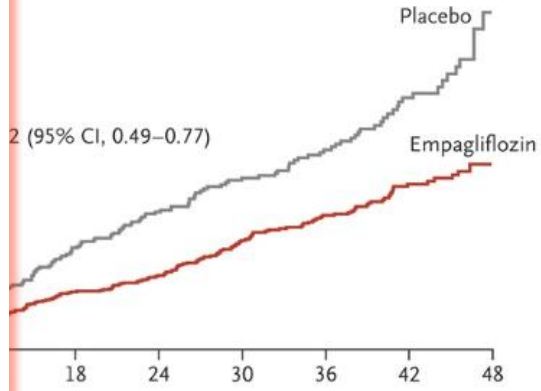


No. at Risk									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

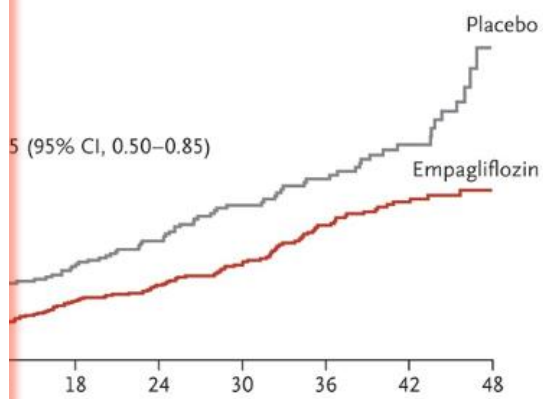
B Post Hoc Renal Composite Outcome



No. at Risk									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144



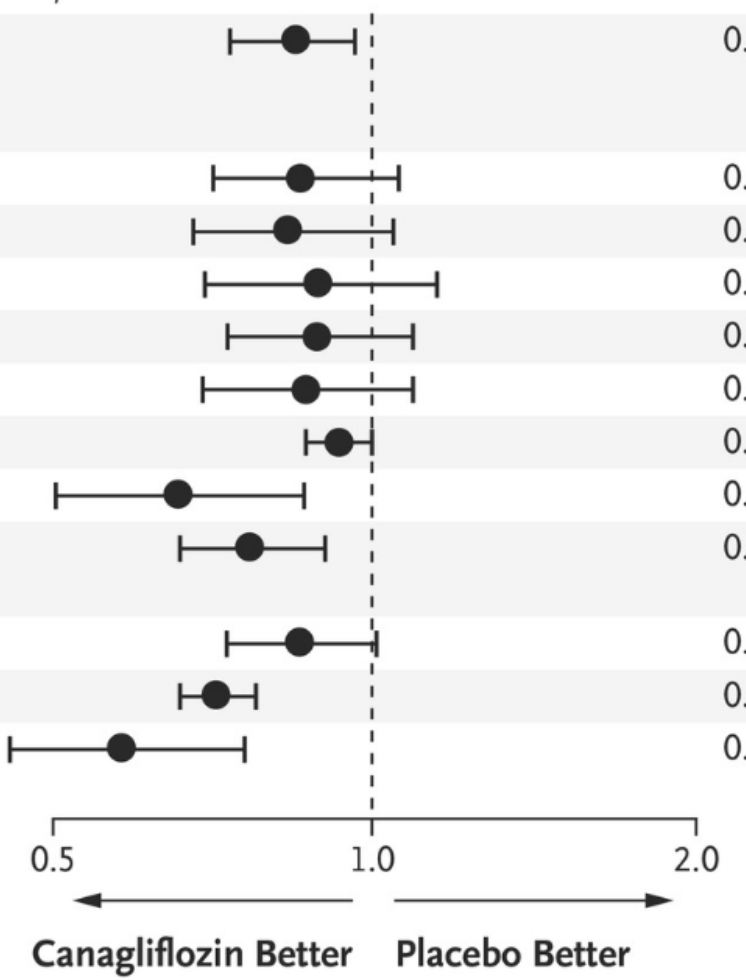
4556	4128	3079	2617	1722	414
2243	2012	1503	1281	825	177



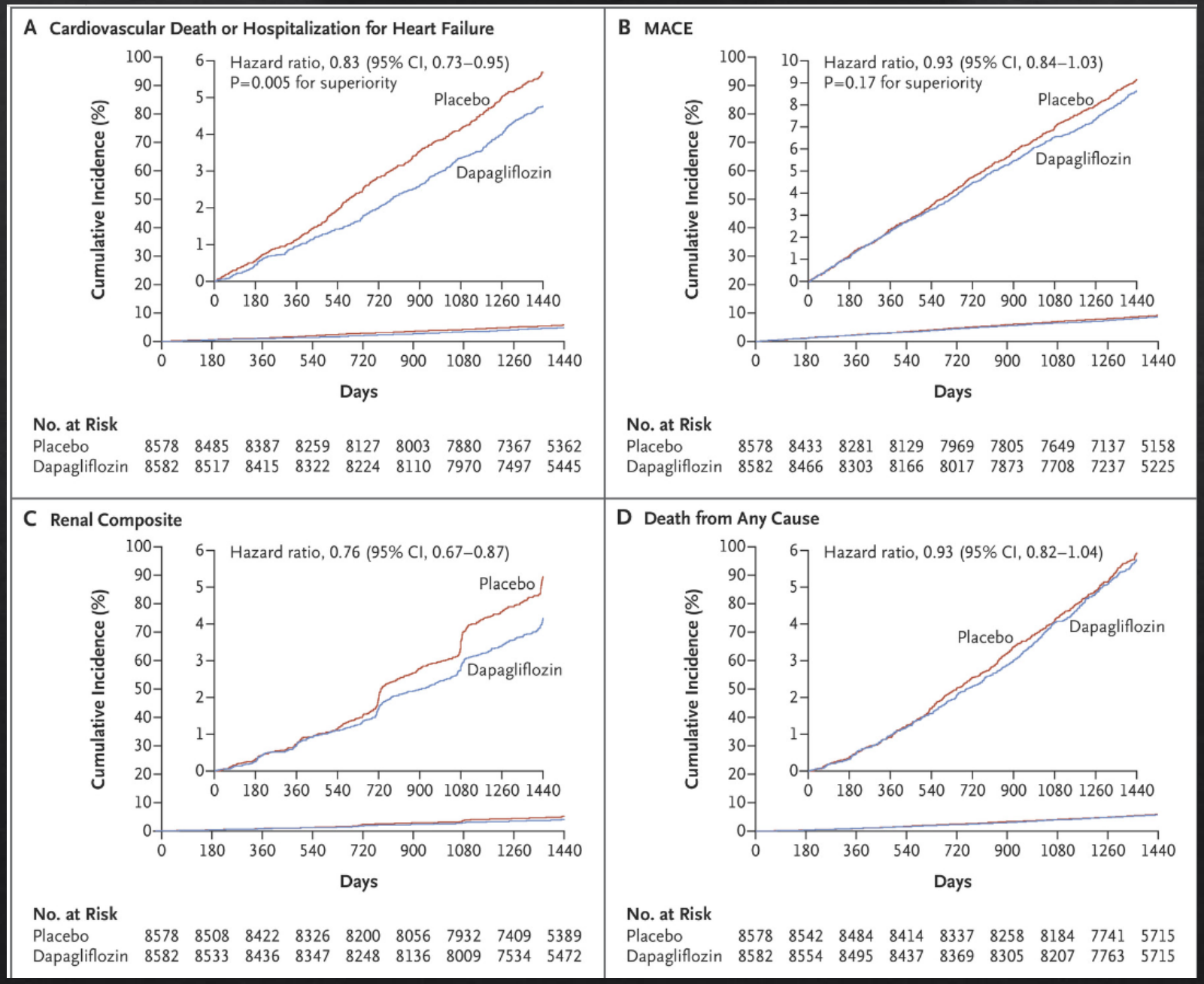
4427	3988	2950	2487	1634	3
2173	1932	1424	1202	775	1

CANVAS Trial

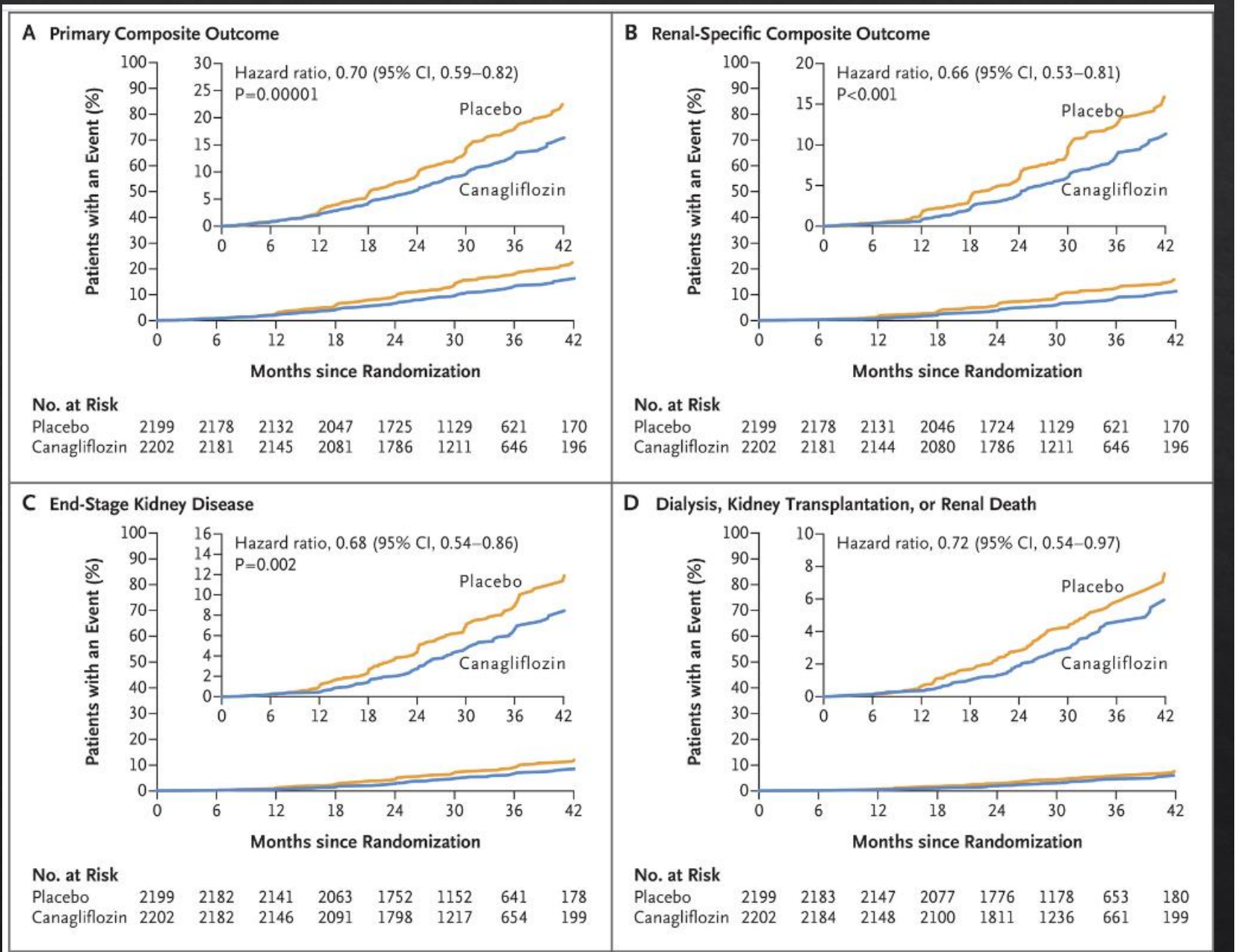
Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

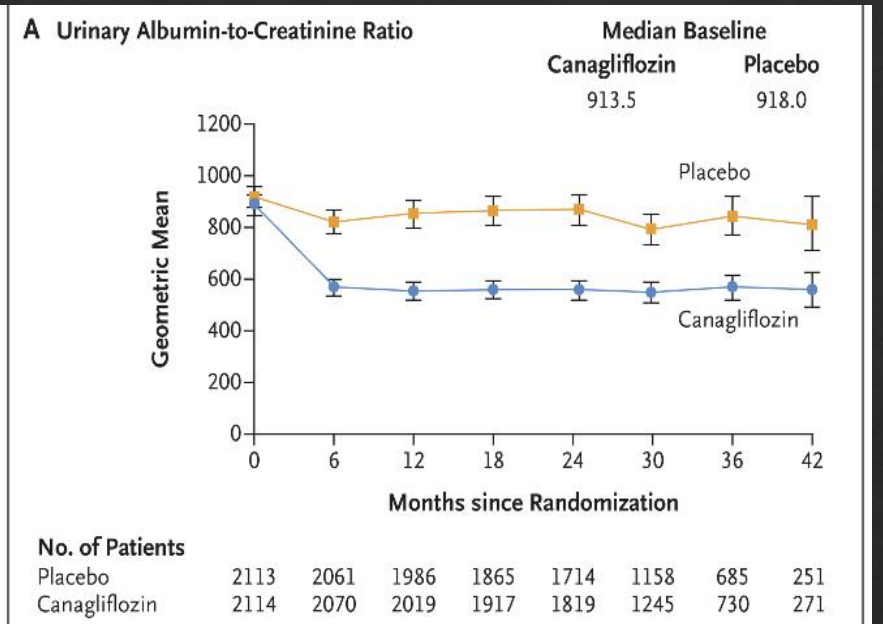


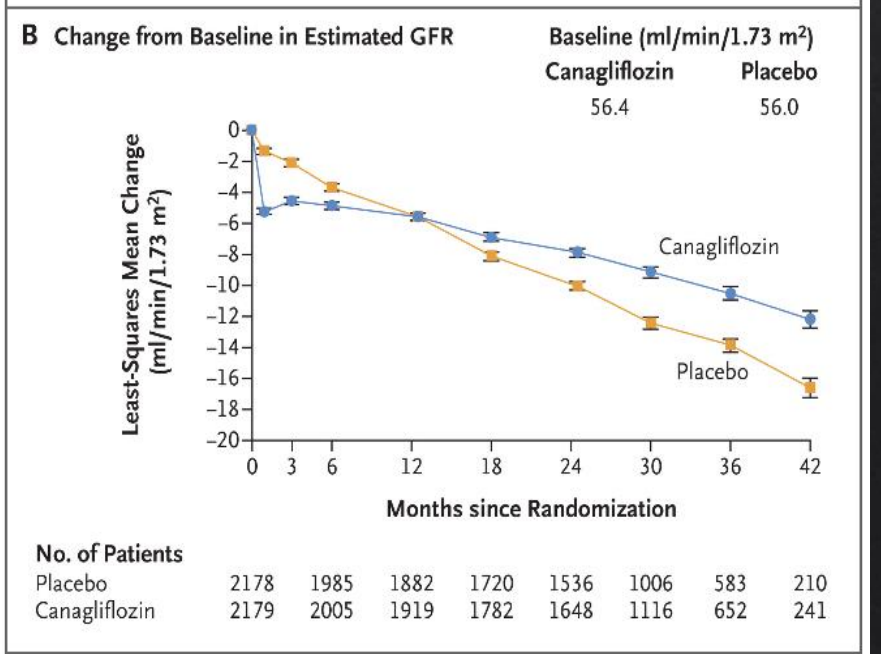
DECLARE-TIMI 58



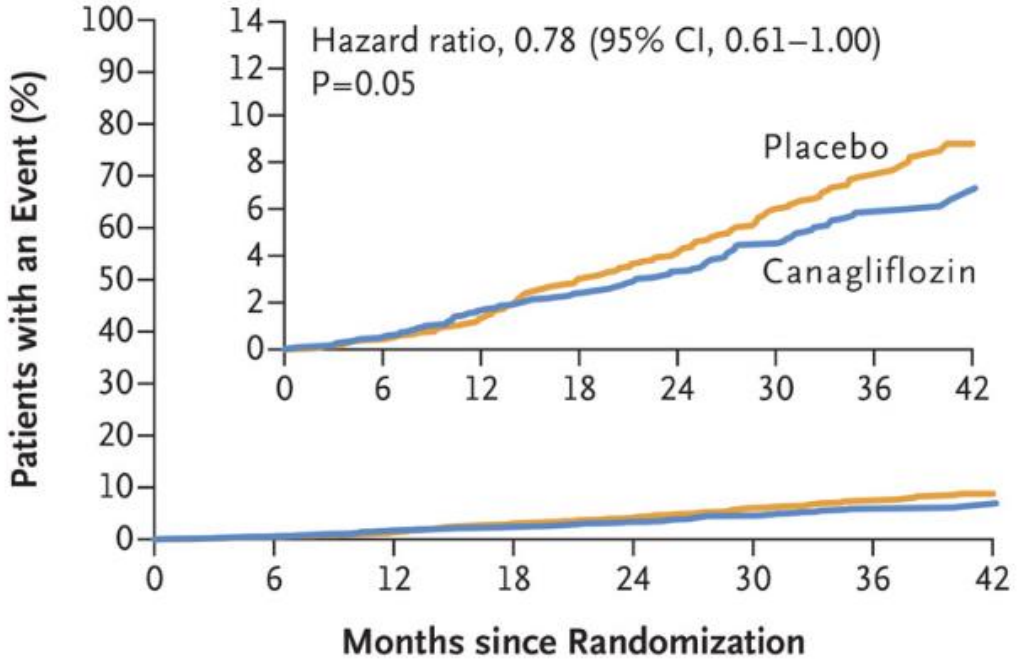
CREDENCE Trial





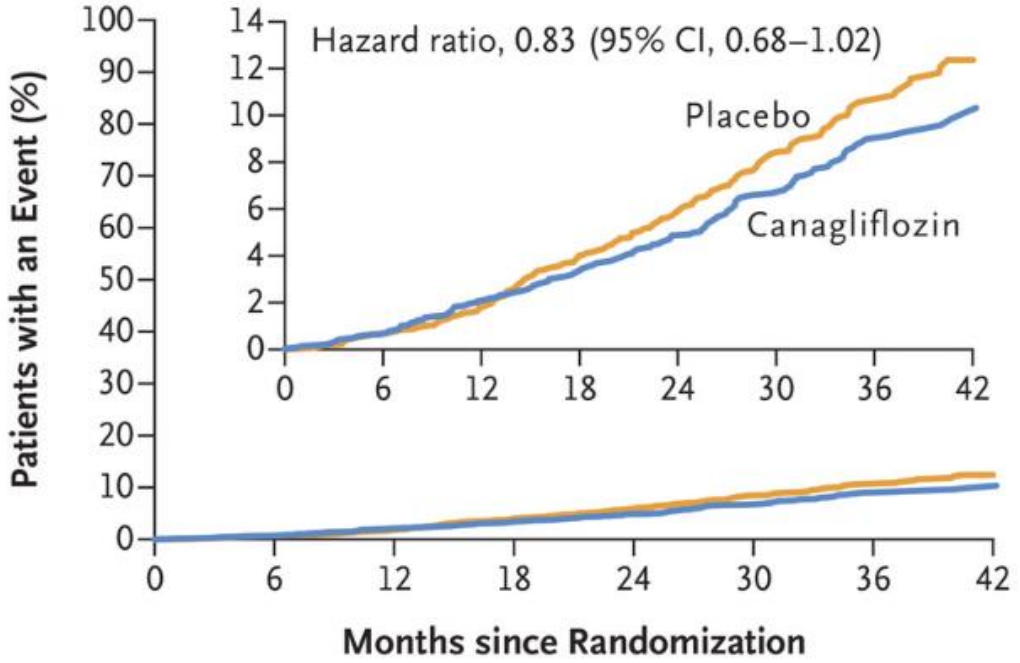


E Death from Cardiovascular Cause



No. at Risk								
Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

F Death from Any Cause



No. at Risk								
Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

Comparing Clinical Trials

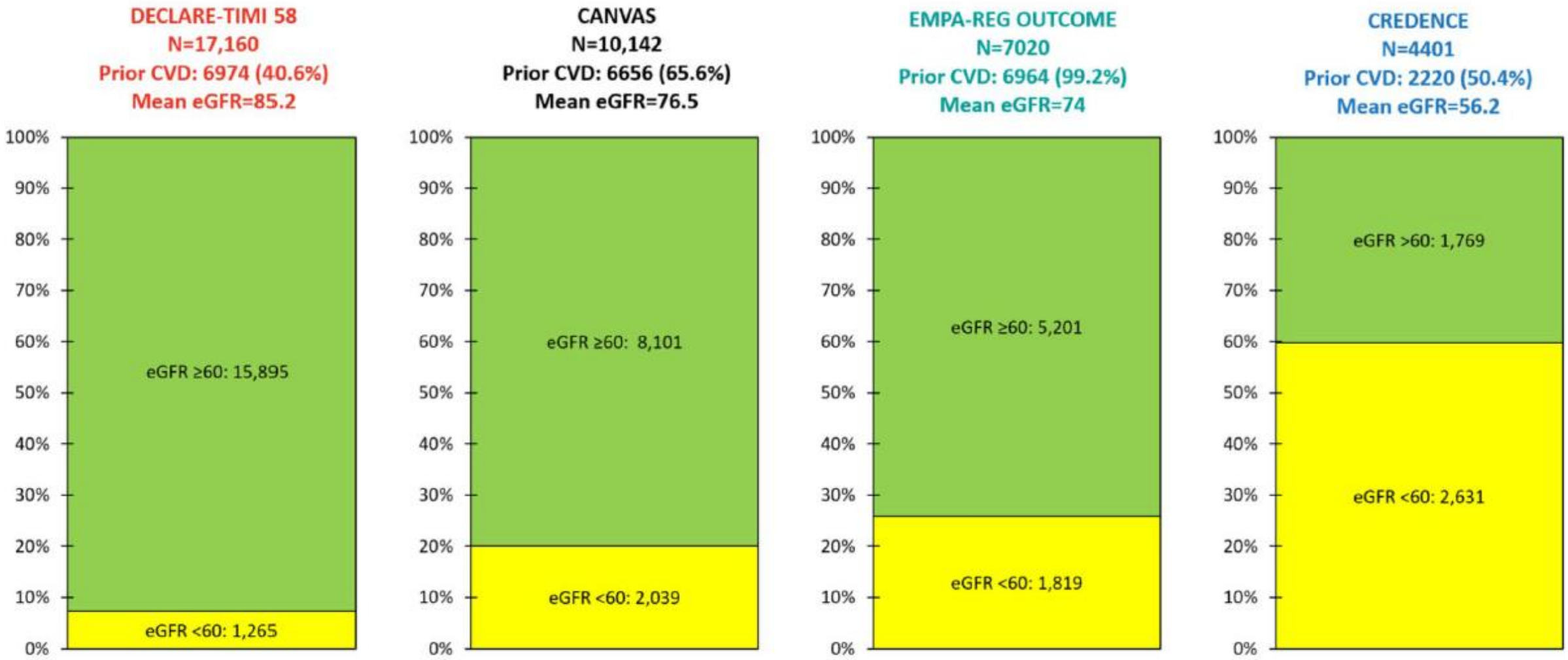
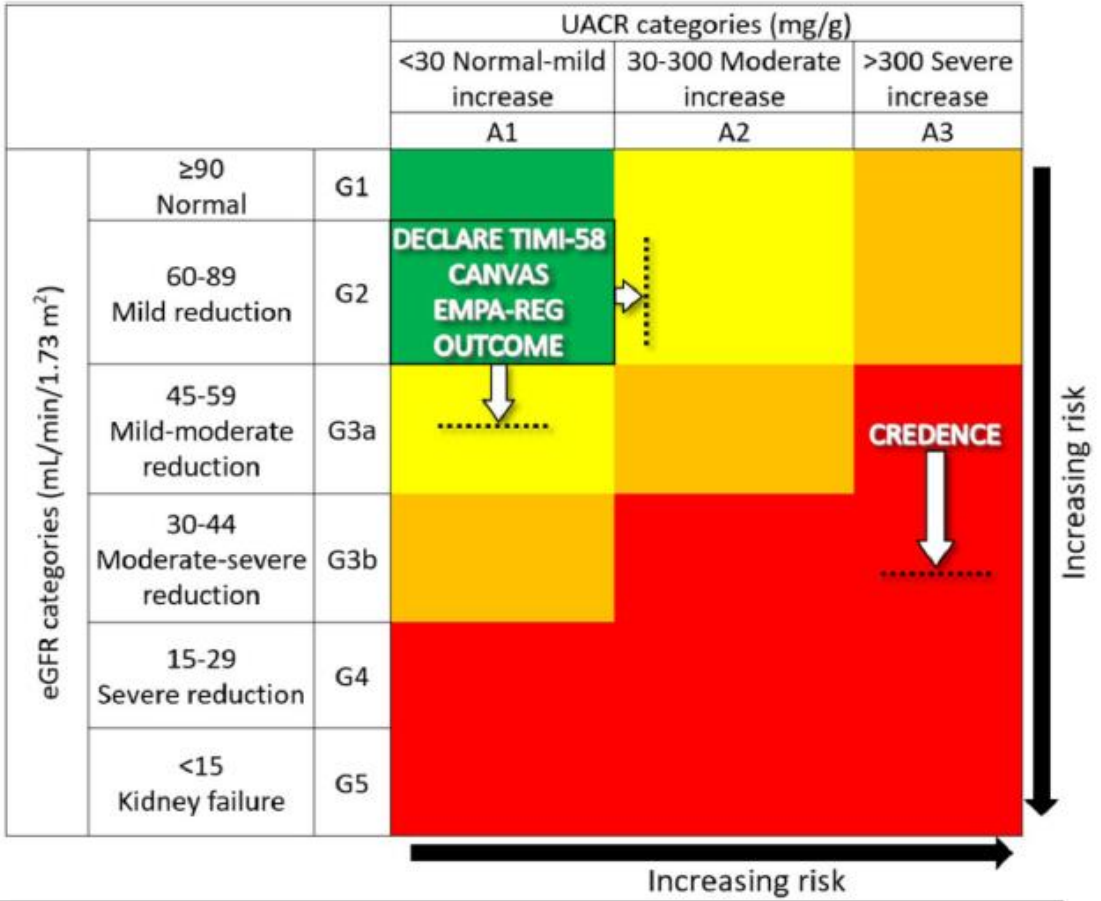


Fig. 1 Baseline estimated glomerular filtration rates (eGFRs) and prior cardiovascular disease (CVD) rates in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Prior CVD displayed as incidence (percentage)



DECLARE-TIMI 58
Baseline renal status: eGFR=85.2; UACR = 13.1 [6.0, 43.6]; n=17,160.
Composite renal outcome: ≥40% reduction in eGFR to <60, ESRD (dialysis ≥90 days, transplant or sustained eGFR<15), or renal/CV death

CANVAS
Baseline renal status: eGFR=76.5±20.5; UACR = 12.3 [6.65, 42.1]; n=10,142.
Composite renal outcome: ≥40% reduction in eGFR, RRT (transplant, chronic dialysis, or sustained eGFR<15), or renal death

EMPA-REG OUTCOME
Baseline renal status: eGFR=74±21; 59.4% UACR<30, 28.6% UACR >30-300, 11.0% UACR >300; n=7020.
Composite renal outcome: Doubling of serum Cr with eGFR ≤45, RRT, or renal death

CREDENCE
Baseline renal status: eGFR=56.2±18.2; UACR = 927 [463, 1833]; n=4401.
Composite renal outcome: Doubling of serum Cr, ESRD (eGFR <15, dialysis, or renal transplant), renal/CV death

Table 1 Renal drug guidelines, entry criteria, mean estimated glomerular filtration rate, and composite outcome definitions in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials

Trial	FDA indicated guidelines	Study renal entry criteria			Results	
	Minimum recommended eGFR	eGFR minimum	eGFR equation	Additional renal criteria	Mean eGFR	Composite renal outcome
DECLARE-TIMI 58	45	N/A	CKD-EPI	CrCl 60 mL/min (Cockroft-Gault equation)	85.2	≥ 40% reduction in eGFR to < 60, ESRD (dialysis ≥ 90 days, transplant or sustained eGFR < 15), or renal/CV death
CANVAS	45	30	MDRD	N/A	76.5	≥ 40% reduction in eGFR, RRT (transplant, chronic dialysis, or sustained eGFR < 15), or renal death
EMPA–REG OUTCOME	45	30	MDRD	N/A	74	Doubling of serum Cr with eGFR ≤ 45, RRT, or renal death
CREDENCE	45	30	CKD-EPI	UACR 300–5000	56.2	Doubling of serum Cr, ESRD (eGFR < 15, dialysis, or renal transplant), renal/CV death

All eGFRs are in mL/min/1.73 m^2

eGFR estimated glomerular filtration rate, *MDRD* modification of diet in renal disease, *CKD-EPI* chronic kidney disease epidemiology collaboration, *RRT* renal-replacement therapy, *ESRD* end-stage renal disease, *CV* cardiovascular, *CrCl* creatinine clearance, *Cr* creatinine, *UACR* urinary albumin-creatinine ratio in mg/g

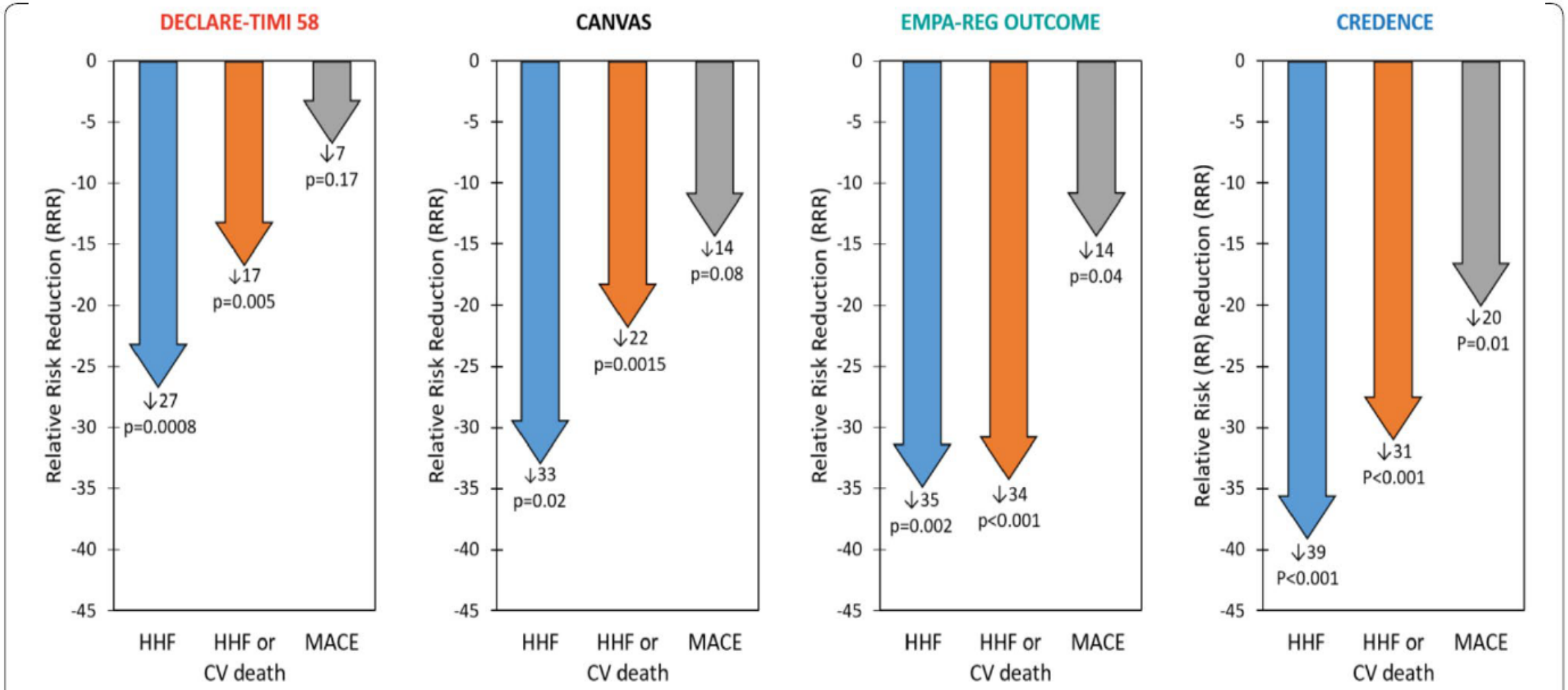
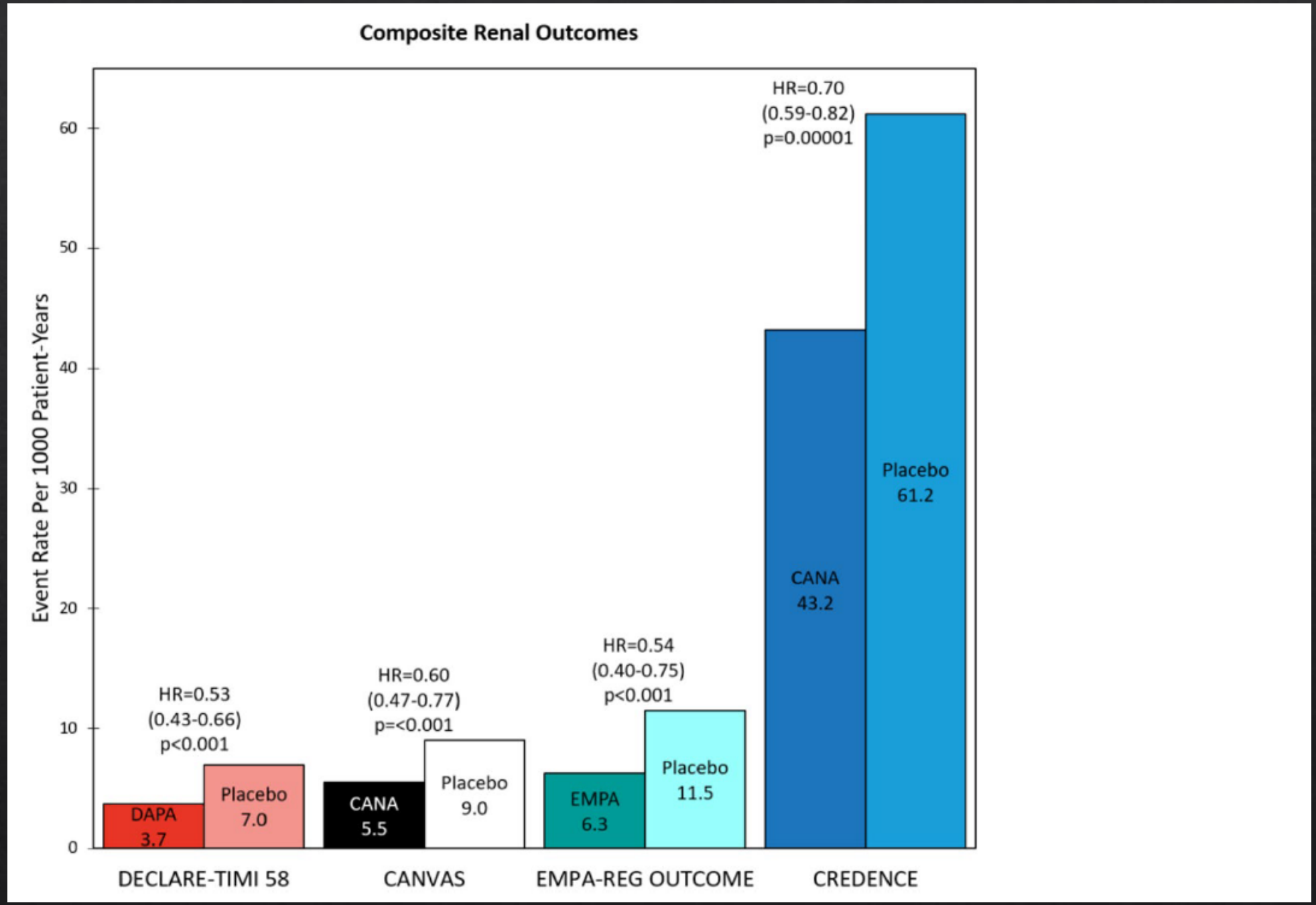


Fig. 4 Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) relative risk reductions (RRRs) in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Statistical outcomes displayed as RRR, p-value. RRRs were calculated from hazard ratios

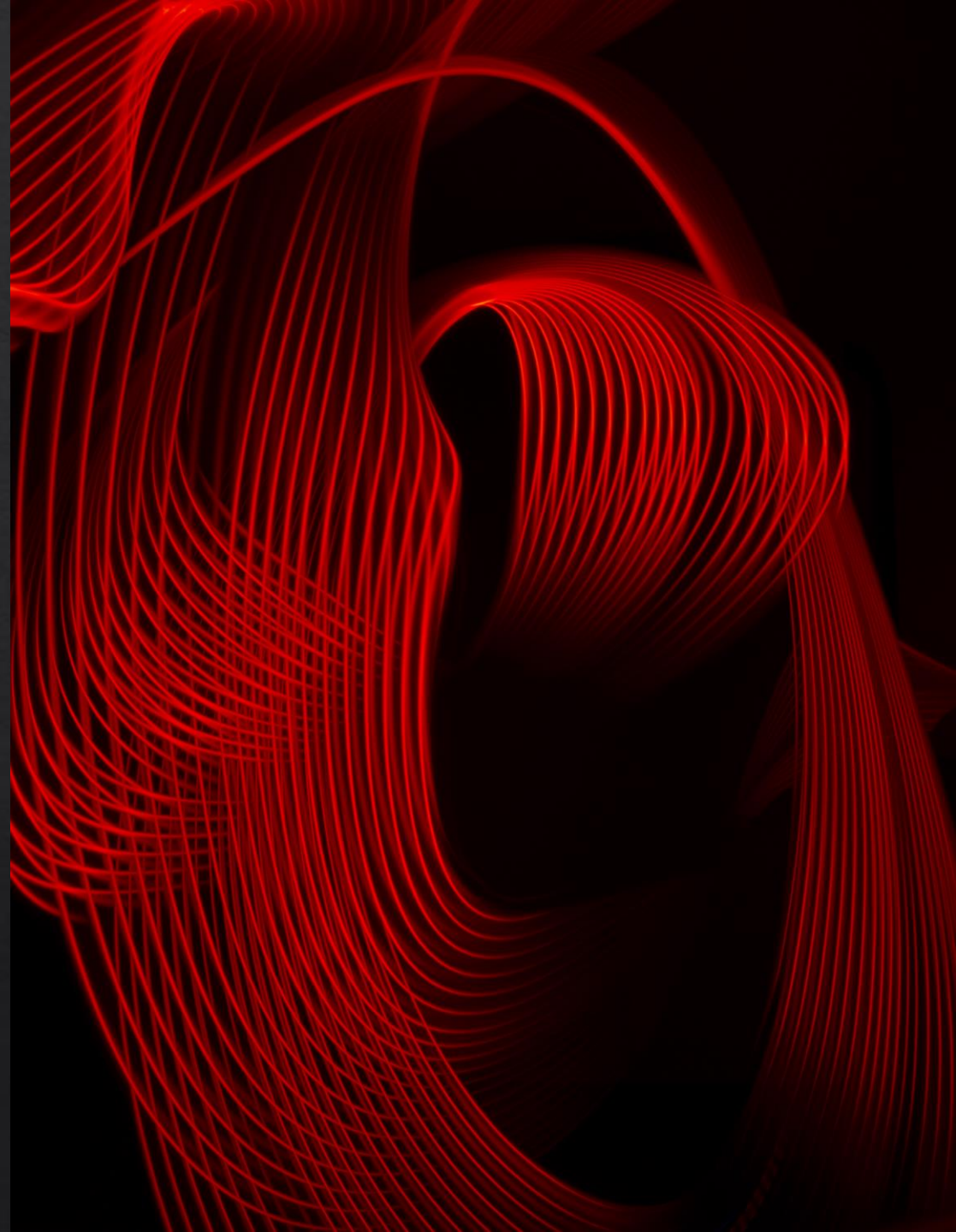

Composite Renal Outcomes
Event Rate Per 1000 Patient-Years
0
10
20
30
40
50
60
HR=0.53
(0.43-0.66)
p<0.001
DAPA
3.7
Placebo
7.0
HR=0.60
(0.47-0.77)
p=<0.001
CANA
5.5
Placebo
9.0
HR=0.54
(0.40-0.75)
p<0.001
EMPA
6.3
Placebo
11.5
HR=0.70
(0.59-0.82)
p=0.00001
CANA
43.2
Placebo
61.2
DECLARE-TIMI 58
CANVAS
EMPA-REG OUTCOME
CREDENCE

- When considering the four SGLT2i trials, overall relative risk reductions for HHF and CV death were externally consistent among them.

- The relative reductions in HHF were considerably greater than those for ischemic events including nonfatal MI and ischemic stroke.

- The absolute risks of CV events appeared to be more related to baseline renal filtration than the baseline CVD rate.

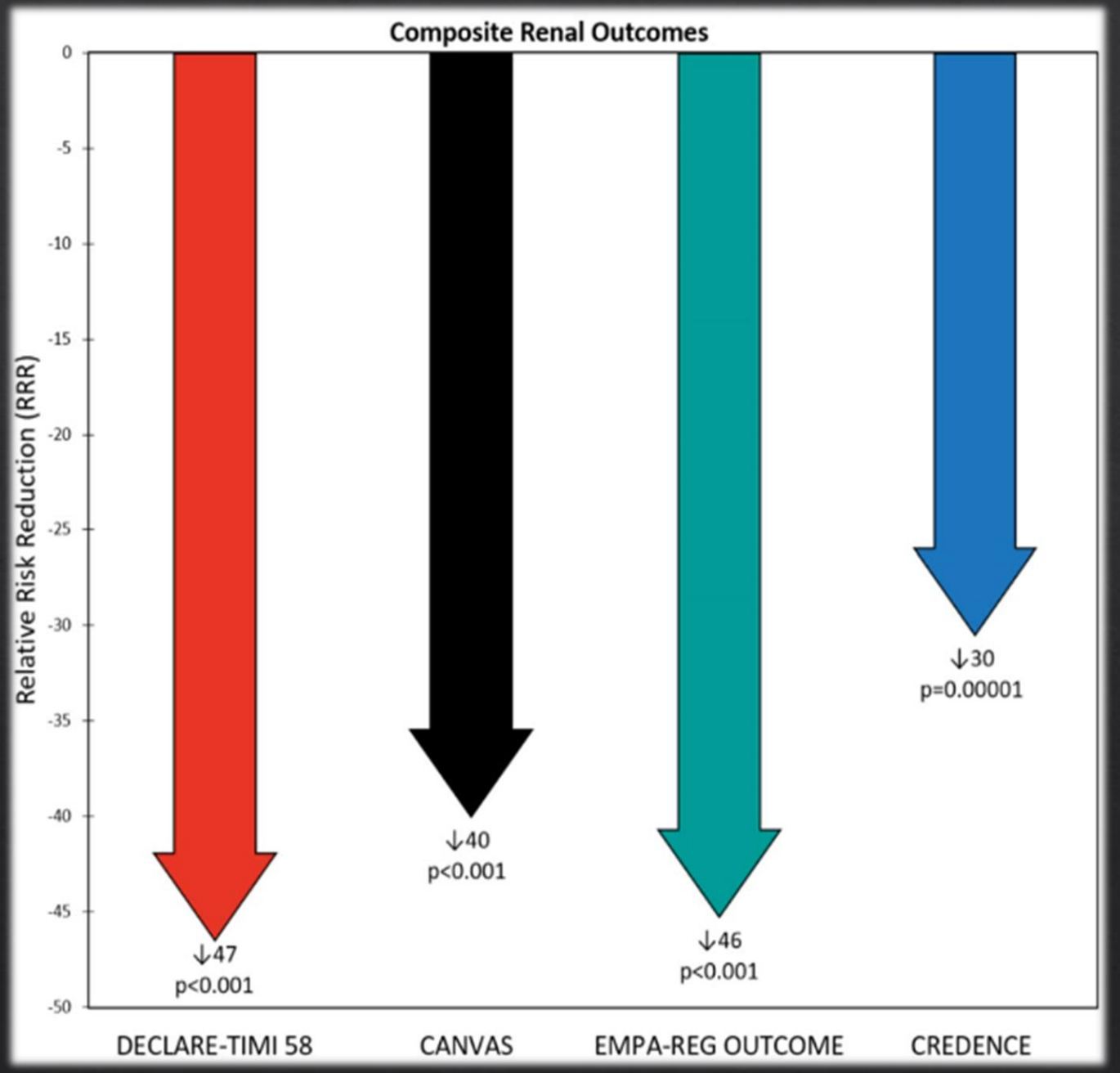
- Together, these trials establish the UACR as a risk predictor not only for renal events but also CV outcomes.



- **The composite renal outcome RRR is another intriguing result when comparing the four trials**.

> In a reversal of the trend seen with the other outcomes, CREDENCE had the smallest RRR and DECLARE-TIMI 58 the largest.

- **Interestingly, the CREDENCE and EMPA–REG OUT-COME had similar MACE incidence rates (48.7 and 43.9/1000 patient-years, respectively), despite different baseline UACR and eGFR.**



Safety

- The four trials demonstrated several general safety trends.
- They were generally associated with increased risk of diabetic ketoacidosis, dehydration, orthostatic hypotension, and amputation and decreased risk of acute kidney injury.
- Increased risk of genital infections; however, this is expected due to the glucosuria.
- Fournier's gangrene.

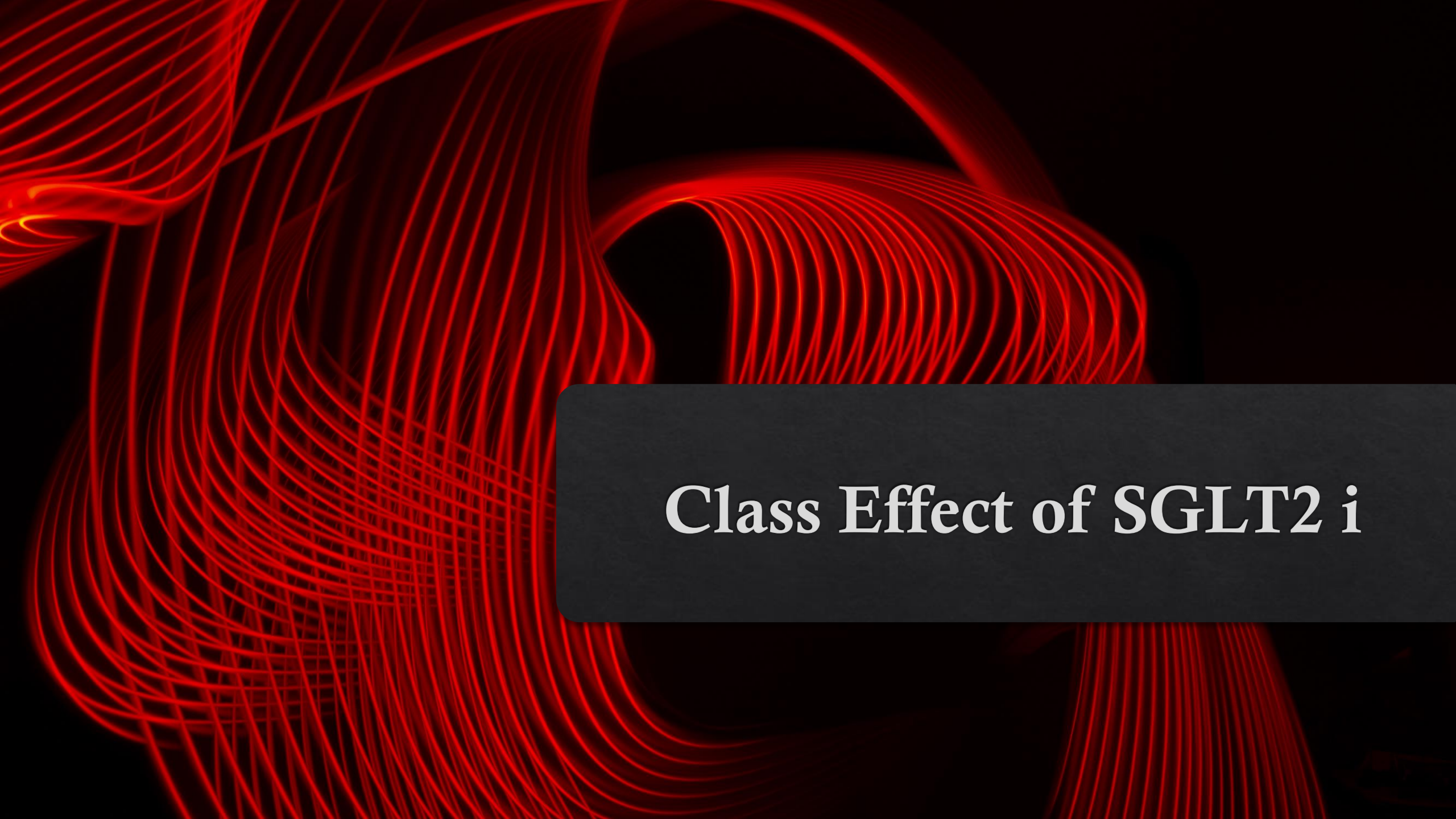
Table 3 Risk associated with study drug compared to placebo for adverse events in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials

	DECLARE-TIMI 58	CANVAS	EMPA–REG OUTCOME	CREDENCE
Male genital infection[a]	+[b]	+[b]	+[b]	+[b]
Female genital infection[a]		+[b]	+[b]	+
Any AE	N/A	N/A	–[b]	–[b]
Serious AE	–[b]	–[b]	–[b]	–[b]
AE causing discontinuation	+[b]	+	–[b]	N/A
Hypoglycemia	–[b]	+	–	–
UTI	–	+	–	+
Fracture	+	+[b]	–	–
Hyperkalemia	N/A	+	N/A	–
Amputation	+	+[b]	N/A	+
AKI	–[b]	–	–[b]	–
Breast cancer	0	+	N/A	+
Bladder cancer	–[b]	–	N/A	+
DKA	+[b]	+	+	+[b]

AE adverse event, *N/A* not available, *UTI* urinary tract infection, *AKI* acute kidney injury, *DKA* diabetic ketoacidosis

[a] DECLARE-TIMI 58 did not differentiate genital infection by sex

[b] indicates statistical significance at the $\alpha = 0.05$ level. "+" = increased risk, "–" = decreased risk, "0" = no difference in risk


Class Effect of SGLT2 i

- What does class effect mean?
- Should be based on three concepts: a similar chemical structure, a similar mechanism of action and similar pharmacological effects, and adverse reactions.
- “class labeling”
- The trials are externally consistent with each other, showing reliable cardiorenal benefit (according to baseline risk) and comparable adverse effects.
- The SGLT2i studied have similar known mechanisms of action resulting in losses of glucose and sodium in the urine and reductions in blood pressure and body weight.

Class Effect of SGLT-2 Inhibitors

Cardiorenal Effects	Hazard Ratios	Class Effect
MACE	↓ ↓ ↔ ↓ (EMP CAN DEC CRE)	NO: 3/4
Heart failure	↓ ↓ ↓ ↓ (EMP CAN DEC CRE)	YES: 4/4
DKD	↓ ↓ ↓ ↓ (EMP CAN DEC CRE)	YES: 4/4

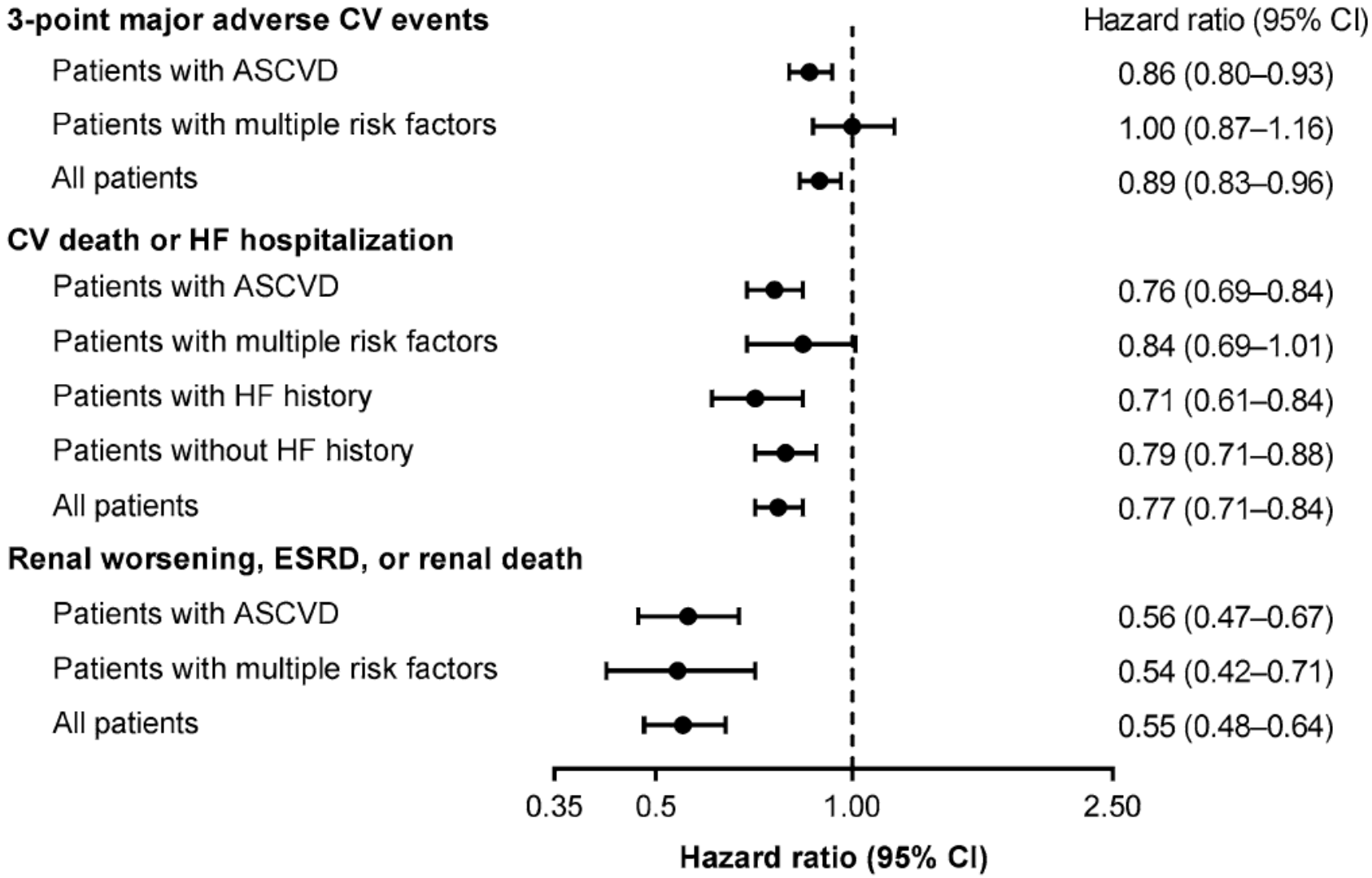
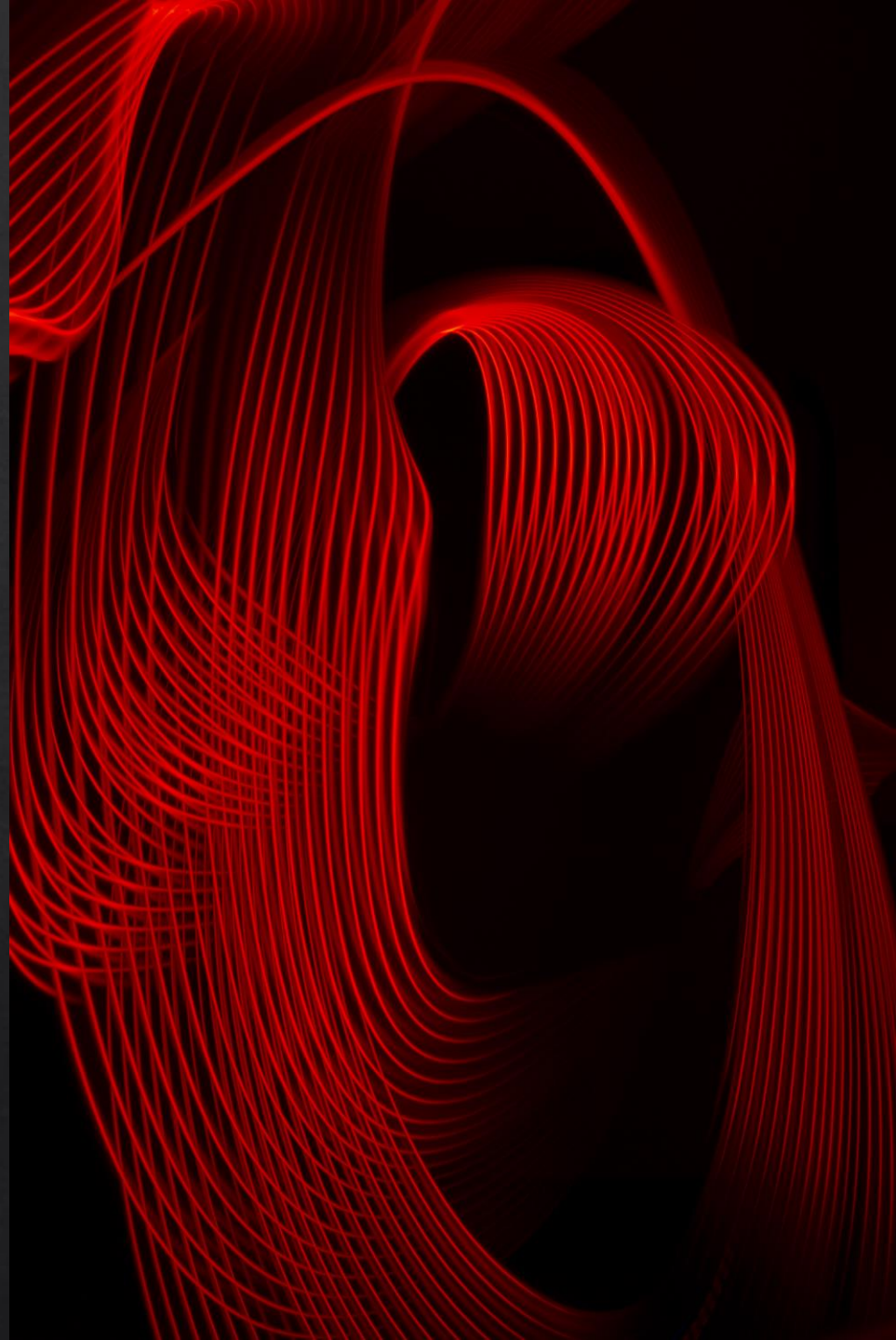


Fig. 3 Summary of cardiovascular and renal outcomes with SGLT-2is as determined by a meta-analysis of the EMPA-REG OUTCOME, CANVAS, and DECLARE–TIMI 58 studies [30]. *ASCVD* atherosclerotic cardiovascular disease, *CI* confidence interval, *CV* cardiovascular, *ESRD* end-stage renal disease, *HF* heart failure, *SGLT-2i* sodium–glucose cotransporter-2 inhibitor

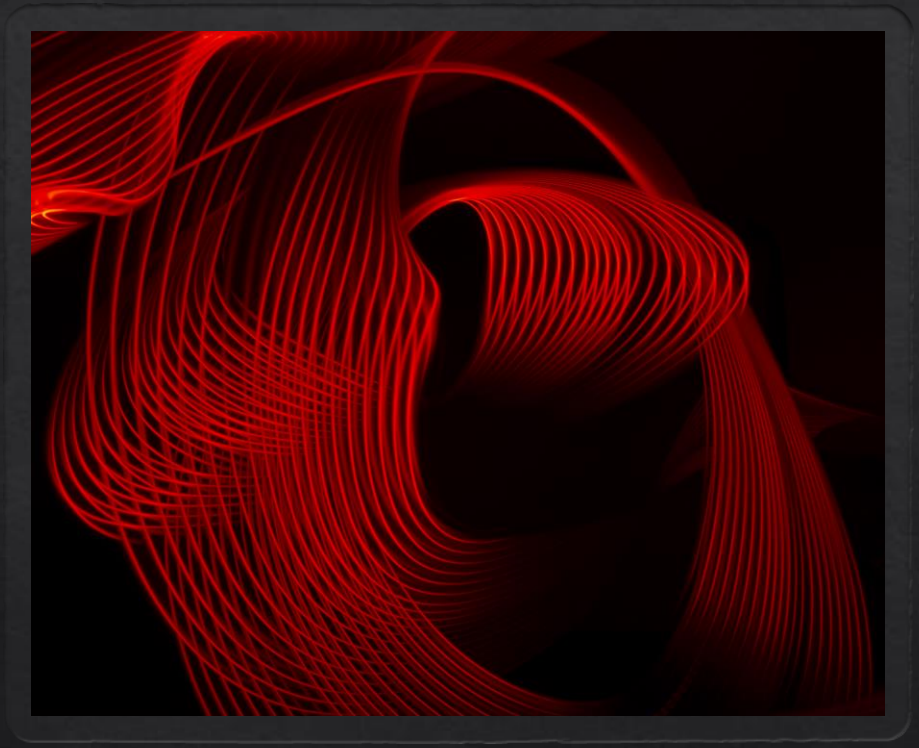
Future Potential Benefits

- SGLT2i have demonstrated a host of positive effects of interest for future research.
- In animal models of T2DM female mice, empagliflozin ameliorated kidney injury by promoting glycosuria, and possibly by reducing systemic and renal artery stiffness.
- Canagliflozin attenuated the progression of atherosclerosis, reducing hyperlipidemia, hyperglycemia, and inflammation by lowering the expression of some inflammatory molecules.

- **Class of medication to treat patients beyond diabetes…**

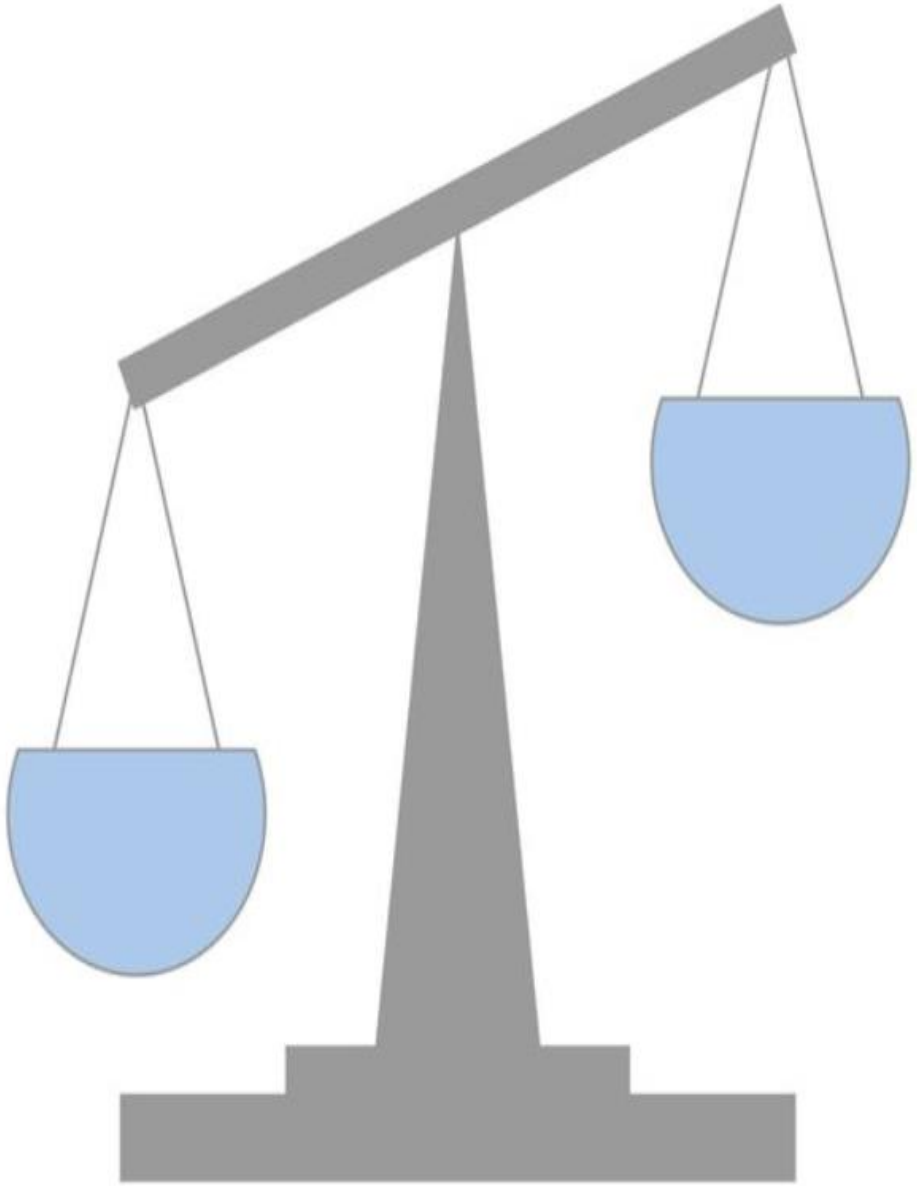


Take Home Message



- Dapagliflozin, empagliflozin, and canagliflozin have internally and externally consistent class effects on cardiorenal outcomes and similar safety profiles.
- Baseline renal filtration function and degree of albuminuria are the most significant indicators of risk for both CV and renal events.
- Thus, these two factors also anticipate the greatest clinical benefit for SGLT2i.

Favorable effects
Reduction of pre-load (diuretic effects)
Reduction of afterload (blood pressure, arterial stiffness)
Improvement of mitochondrial efficiency
Delay of decline in eGFR
Delay of micro- and macroalbuminuria
Weight loss
Reduction in epicardial adipose tissue
Improvement in glycemia
Reduction in uric acid



Unfavorable effects
Amputations (in particular toe, metatarsal)
Volume depletion/Hypotension
Diabetic ketoacidosis
Fractures
Urinary and genital infections

	VERTIS-CV (N = 8,237)	EMPA-REG (N = 7,034)	CANVAS (N = 10,142)	DECLARE (N = 17,160)
	Ertugliflozin	Empagliflozin	Canagliflozin	Dapagliflozin
Age (years)	64.4 ± 8.1	63.1 ± 8.6	63.3 ± 8.3	63.8 ± 6.8
Men, n (%)	5,763 (70.0)	5,026 (72)	6,509 (64.2)	10,738 (62.6)
Race				
White	7,231 (87.8)	5,089 (72)	7,944 (78.3)	79.6%
Black	235 (2.9)	357 (5)	336 (3.3)	3.5%
Asian	497 (6.0)	1,518 (22)	1,284 (12.7)	13.4%
Other	274 (3.3)	70 (1)	578 (5.7)	3.5%
Diabetes duration (years)	12.9 ± 8.3	NA	13.5 ± 7.8	NA
A1C (%)	8.3 ± 0.9[a]	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2
BMI (kg/m^2)	32.0 ± 5.4	30.6 ± 5.3	32.0 ± 5.9	32.1 ± 6.0
eGFR (mL/min/1.73 m^2)	76.0 ± 20.9	74 ± 21	76.5 ± 20.5	86.1 ± 21.8
≥90	2,044 (24.8)	1,534 (22)	2,474 (24.4)	6,855 (39.9)
60 to <90	4,385 (53.2)	3,671 (52)	5,620 (55.5)	8739 (50.9)
30 to <60	1,776 (21.6)	1,796 (26)	2,010 (19.8)	1566 (9.1)[e]
Established CV Disease (%)	99	99	65.6	40.6
Myocardial Infarction	3,940 (47.8)	3,275 (47)		3,580 (20.9)
Coronary Revascularization				
CABG	1,808 (21.9)	1,738 (25)	5721 (56.4)[c]	1,678 (9.8)
PCI	3,402 (41.3)	NA		3,655 (21.3)
Stroke	1,723 (20.9)	1,631 (23)	1,958 (19.3)[d]	1,107 (6.5)[f]
Peripheral arterial disease	1,546 (18.8)	1449 (21)	2,113 (20.8)	1,025 (6.0)
History of Heart Failure	1,777 (21.6)	706 (10.1)[b]	1,461 (14.4)	1,698 (9.9)

Data are n (%) or mean ± SD, unless otherwise shown. NA = data not available. [a]A1C data from screening visit; [b] Percentage based 7,020 patients; [c] Coronary atherosclerotic disease; [d] Cerebrovascular disease; [e] <60 mL/min/1.73m^2; [f] Ischemic stroke.
A1C = glycosylated hemoglobin. BMI = body-mass index. CABG = coronary artery bypass graft. eGFR = estimated glomerular filtration rate by MDRD. PCI = Percutaneous Coronary Intervention.

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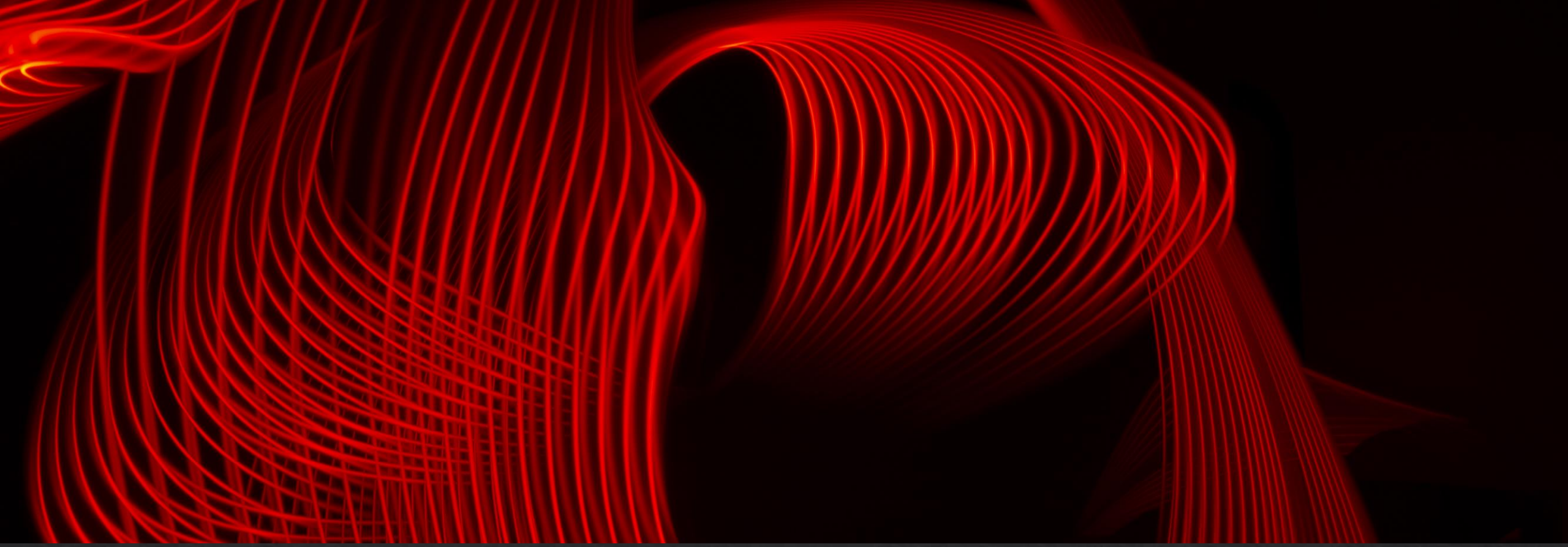

Thank You