SGLT2 inhibition in hyperglycemic and normoglycemic models of the cardiorenal syndrome

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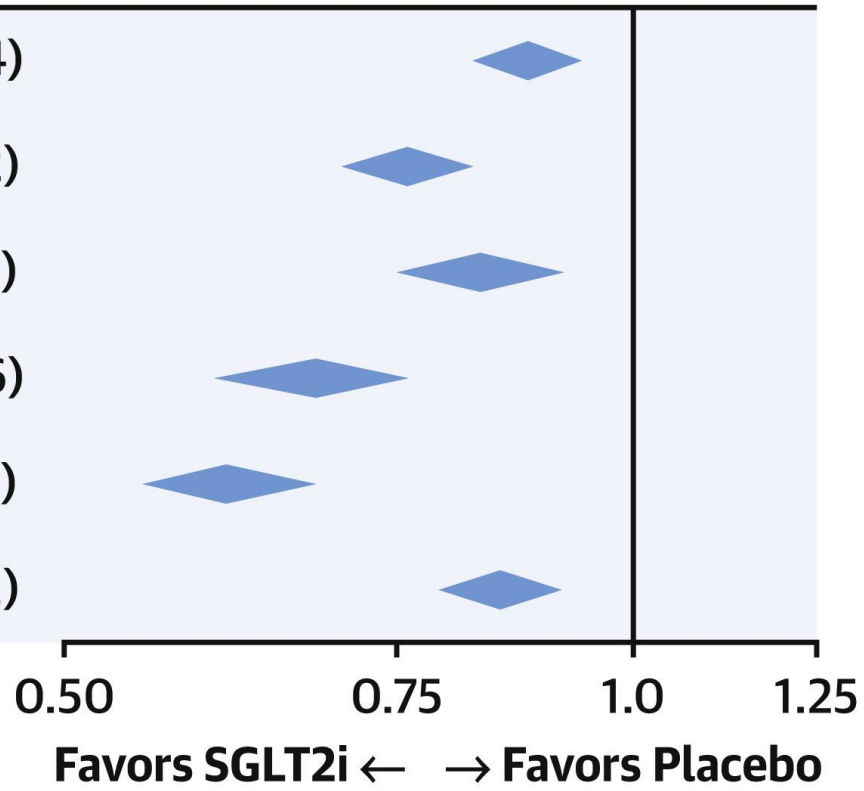
Disclosure belangen spreker: Jaap Joles, DVM, PhD	
Dutch Diabetes Academy – 1 december 2020	
(potentiële) Belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk:	Nederlandse Hartstichting (NHS): RECONNECT consortium Geen honoraria Geen aandelen Gehuwd met Maya Wuhrmann Geen andere relaties

prevents

Treatment Effect of SGLT2i on Cardiorenal Outcomes

Outcome	# Events	HR (95% CI)
MACE	3,828	0.88 (0.82-0.94)
CV death/HHF	2,460	0.76 (0.70-0.82)
CV death	1,506	0.83 (0.75-0.92)
HHF	1,192	0.68 (0.60-0.76)
Composite Renal Endpoint	1,351	0.61 (0.55-0.68)
All-cause Mortality	2,493	0.85 (0.79-0.92)



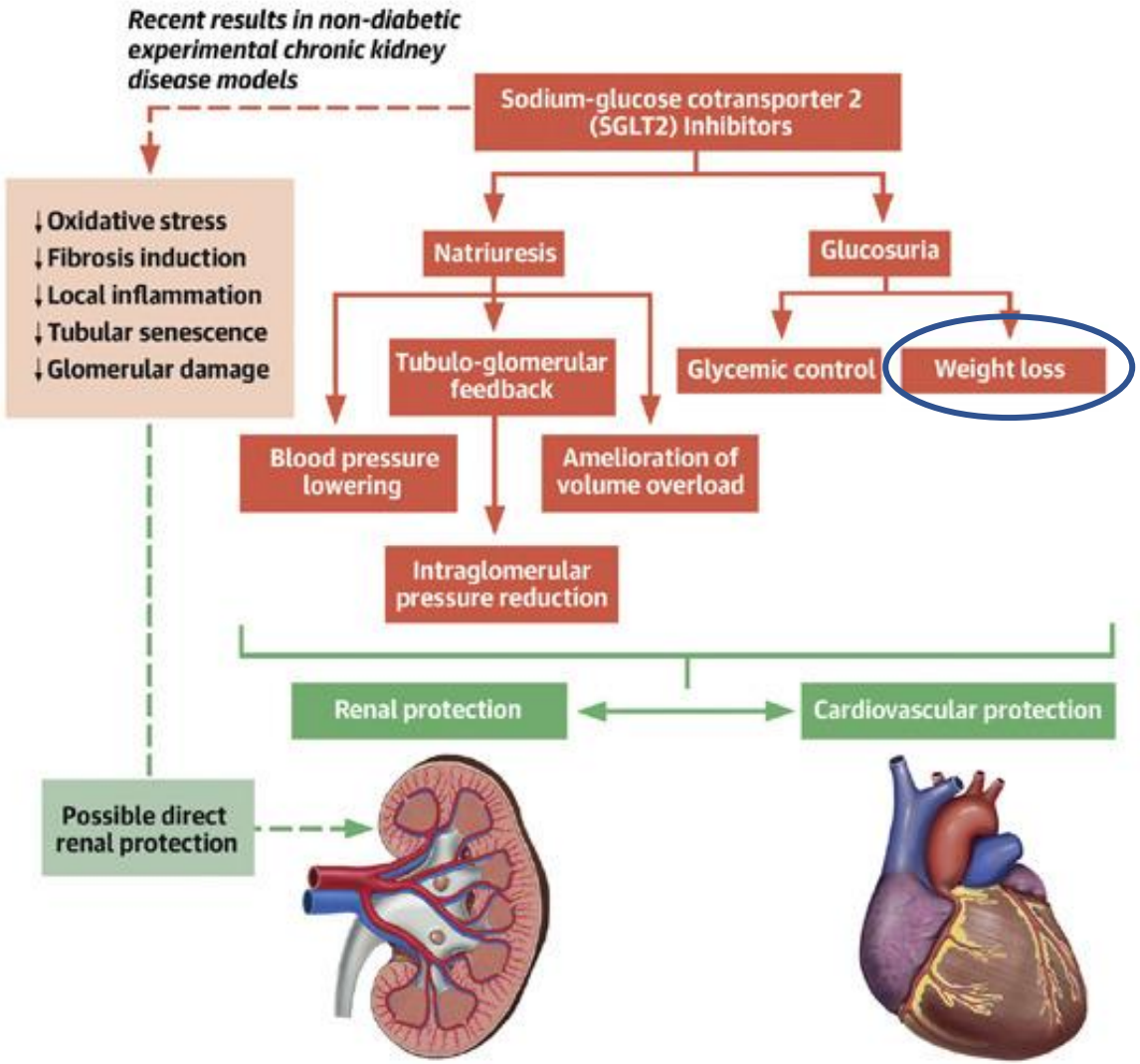
MACE: Major adverse cardiovascular events (i.e., myocardial infarction, stroke, cardiovascular (CV) death)
HHF: hospitalization for heart failure

Zelniker & Braunwald. JACC 2020;75:435-447

Our question today

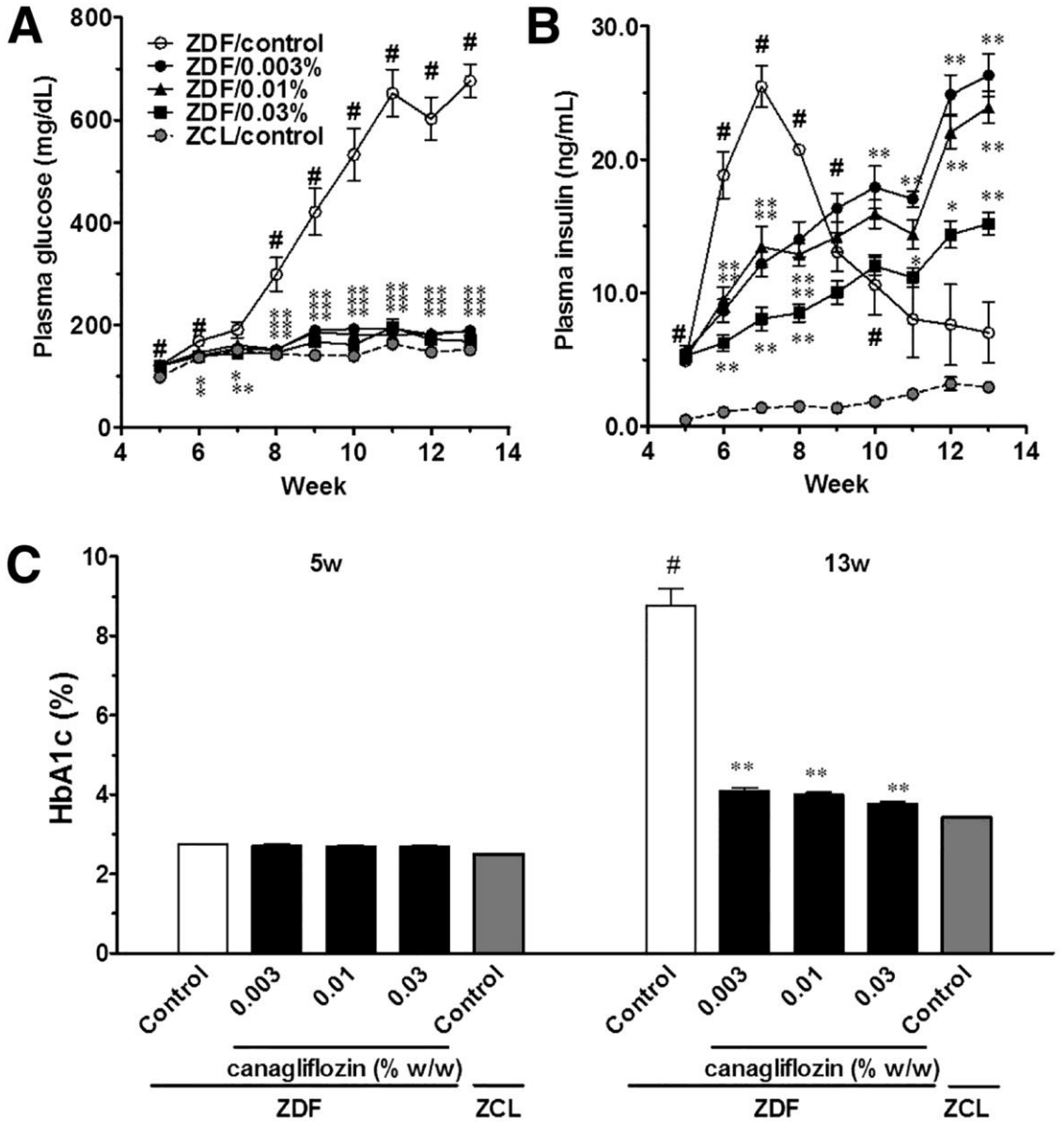
How does SGLT2 inhibition improve cardiovascular outcomes?

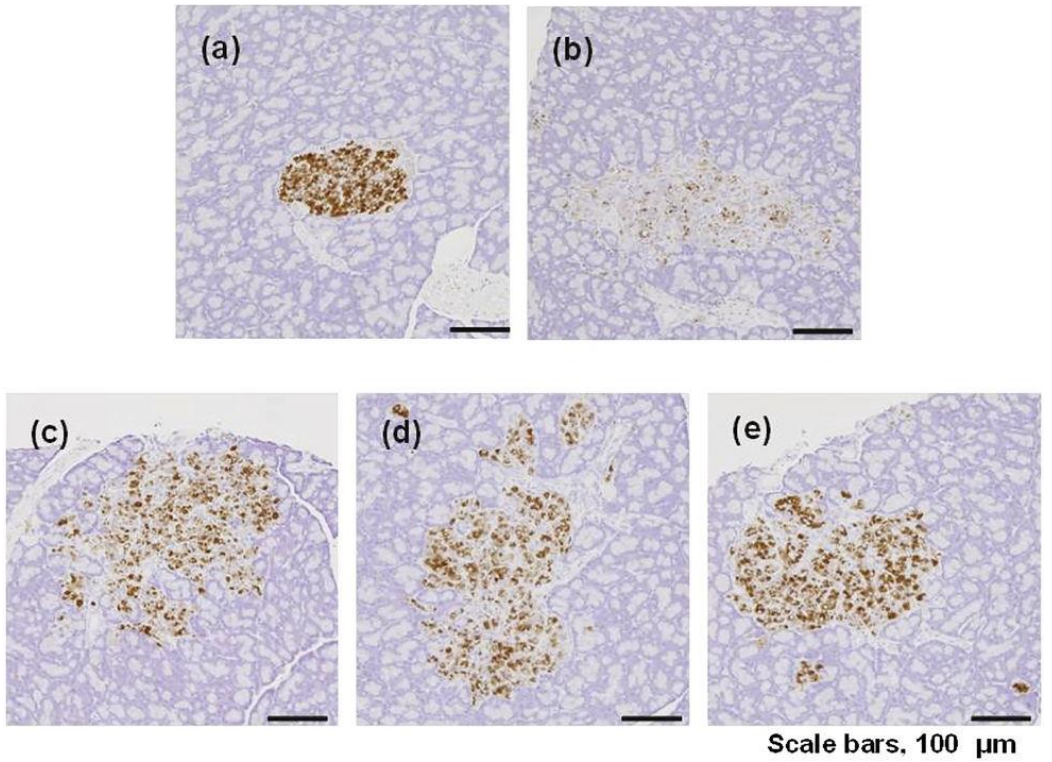
CENTRAL ILLUSTRATION: Sodium-Glucose Cotransporter 2 Inhibitor Cardiorenal Protection Mechanistic Overview



Zelniker, T.A. et al. J Am Coll Cardiol. 2020;75(4):422-34.

Effects of 8-week treatment with canagliflozin on blood glucose, HbA1c, and plasma insulin levels in male ZDF rats

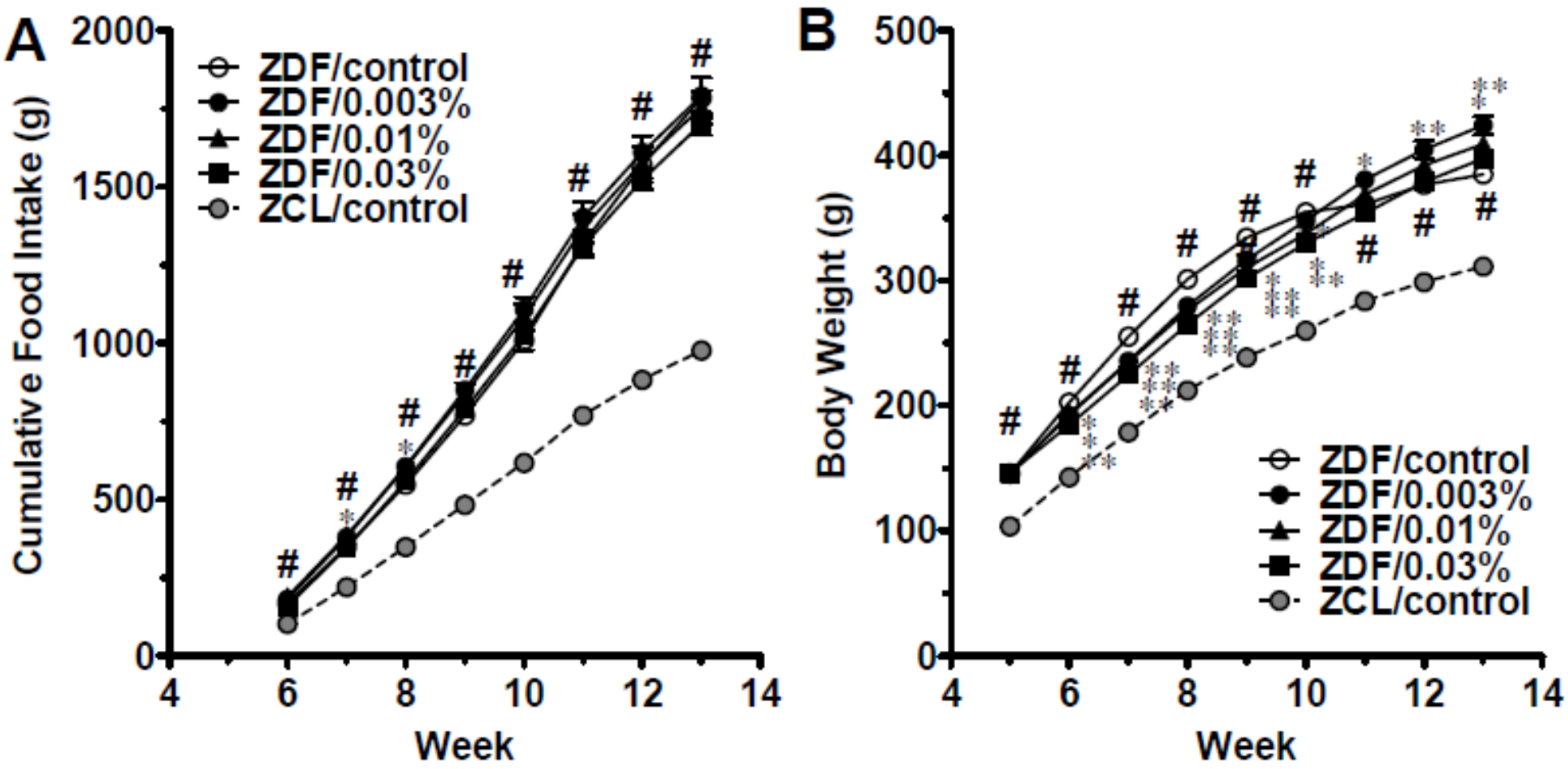




Pancreatic islets immunostained for insulin after 8 weeks
a: ZCL/control rats,
b: ZDF/control rats (b), and
c-e: ZDF/canagliflozin-treated rats
0.003% (c), 0.01% (d), and 0.03% (e)

Kuriyama et al. J Pharmacol Exp Ther 2014;351:423-431

Effect of 8-week treatment with canagliflozin on cumulative food intake and body weight in male ZDF rats



Canagliflozin (0, 0.003, 0.01, and 0.03% w/w in diet) was administered to 5-week-old ZDF rats for 8 weeks.

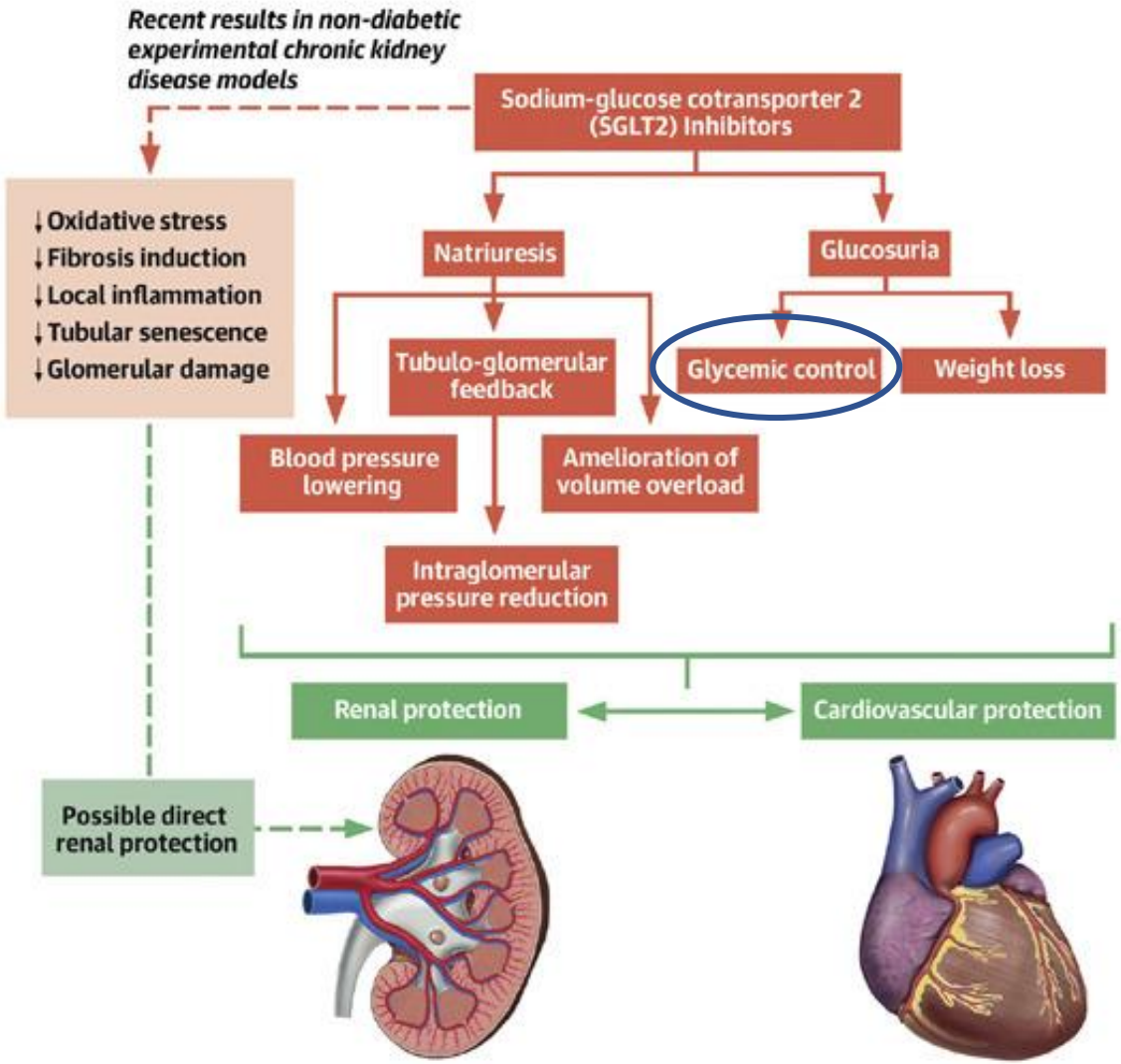
Kuriyama et al. J Pharmacol Exp Ther 2014;351:423-31

Our question today

How does SGLT2 inhibition improve cardiovascular outcomes?

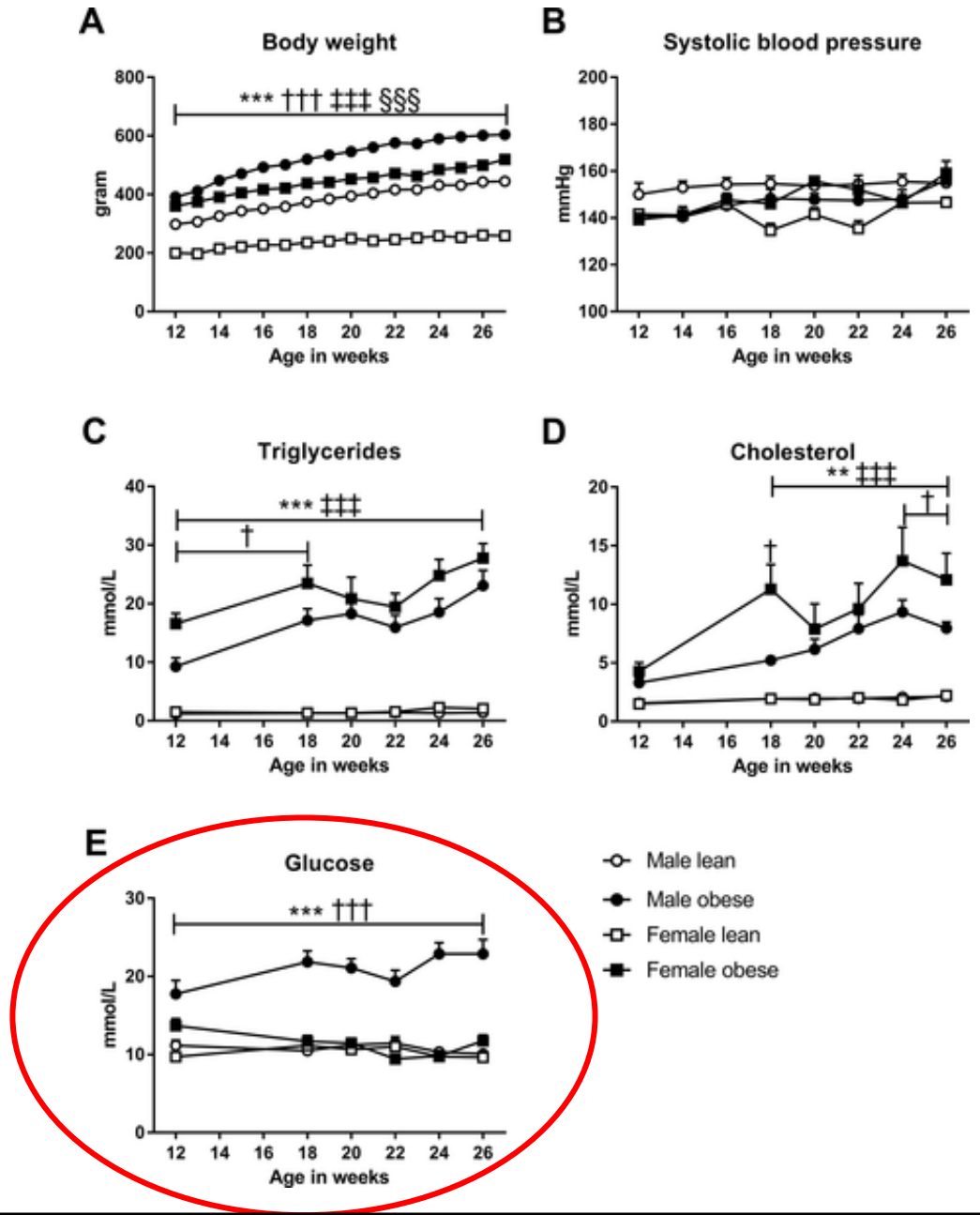
Perhaps not by reducing body weight…

CENTRAL ILLUSTRATION: Sodium-Glucose Cotransporter 2 Inhibitor Cardiorenal Protection Mechanistic Overview



Zelniker, T.A. et al. J Am Coll Cardiol. 2020;75(4):422-34.

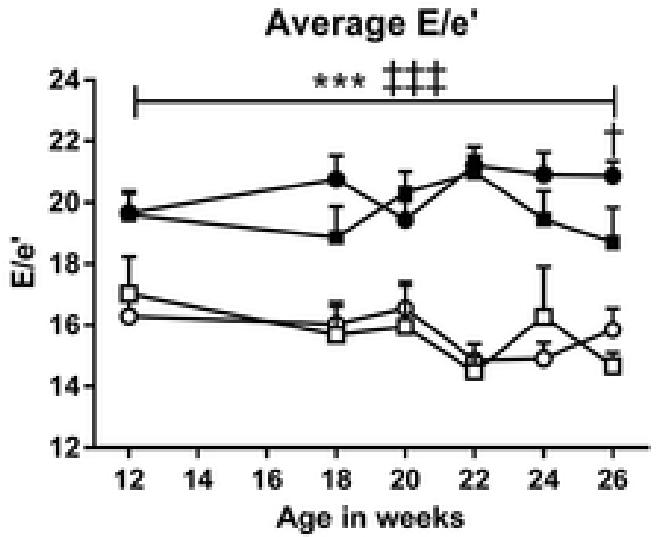
Both male and female obese ZSF1 rats exhibit obesity, dyslipidemia and mild hypertension.

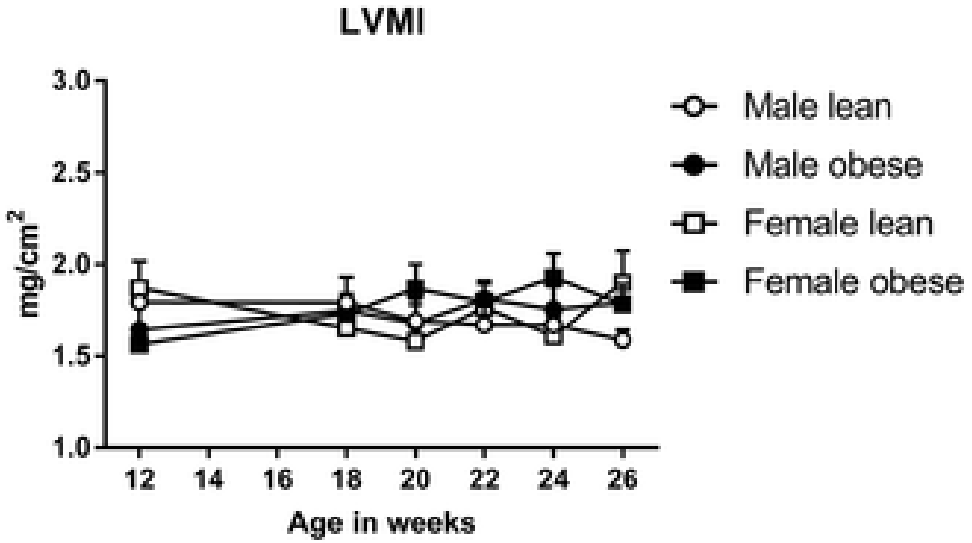


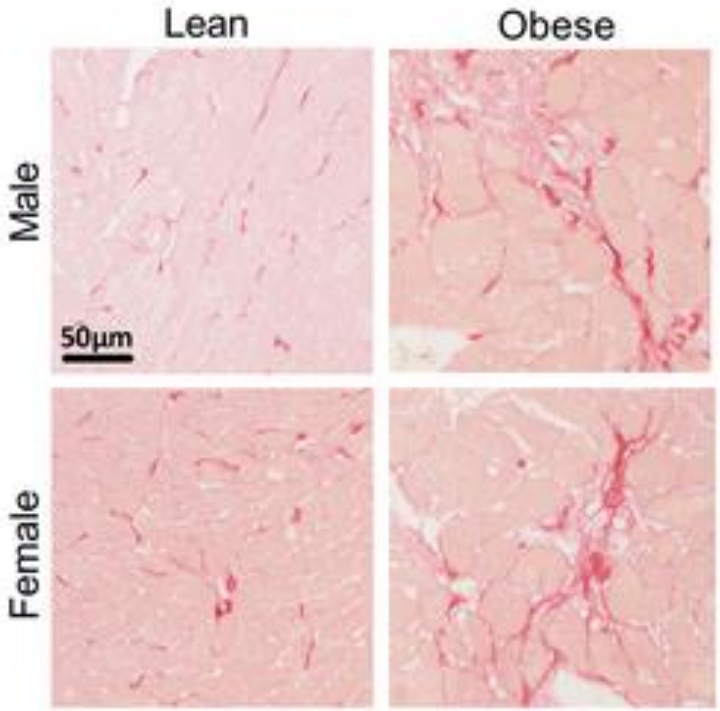
Male obese N = 9
Female obese N = 8
Male lean N = 8
Female lean N = 6
* male obese vs. male lean
† male obese vs. female obese
‡ female obese vs. female lean
§ male lean vs. female lean.
one symbol $P<0.05$
two symbols $P<0.01$
three symbols $P<0.001$

Nguyen et al. (2020). PLOS ONE 15: e0232399.

Obese ZSF1 rats show diastolic dysfunction and cardiac fibrosis

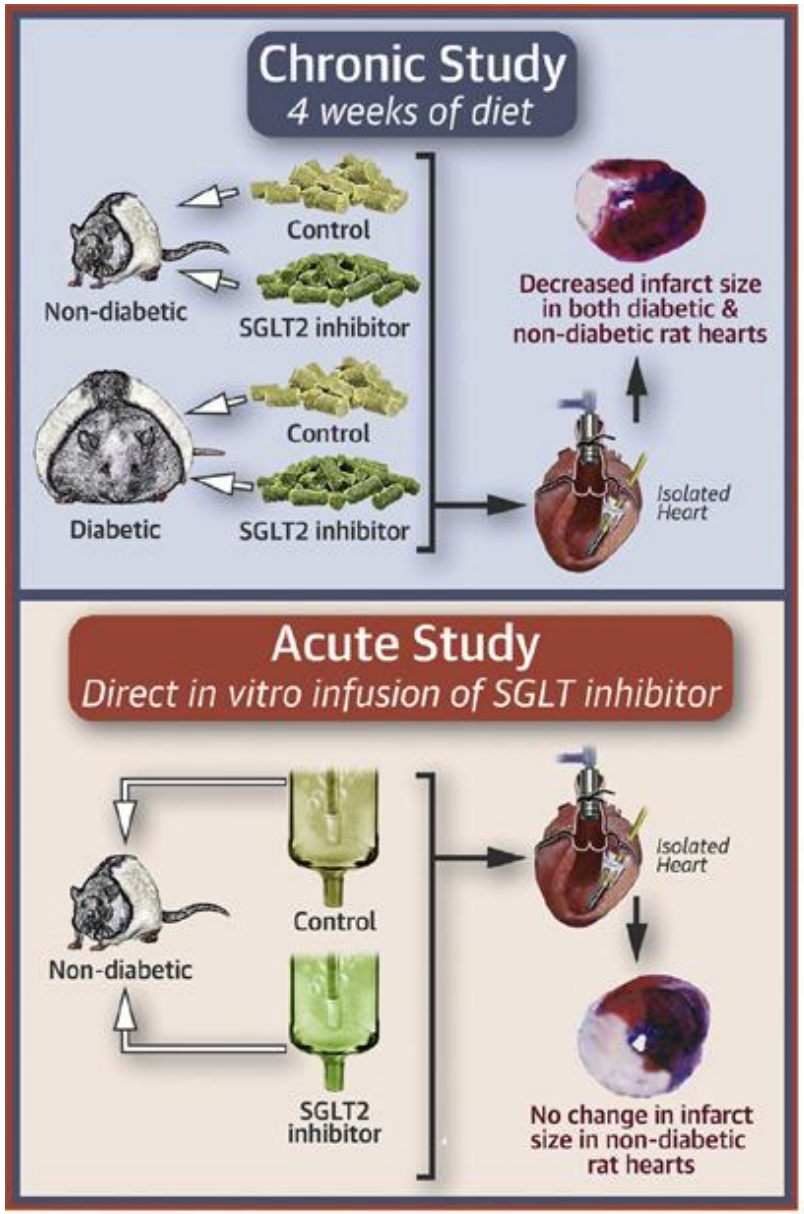


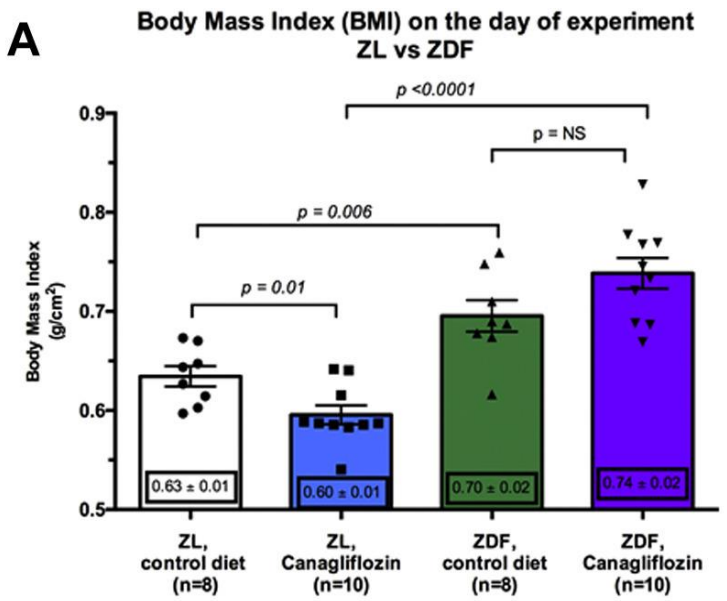


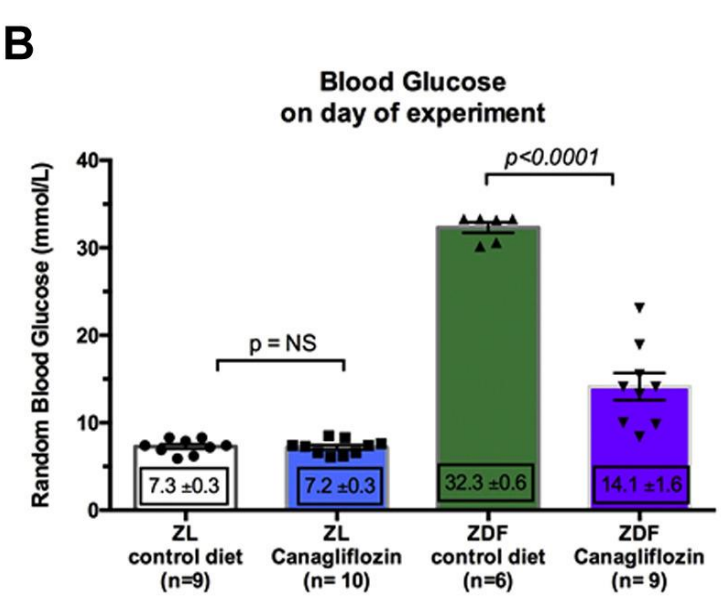


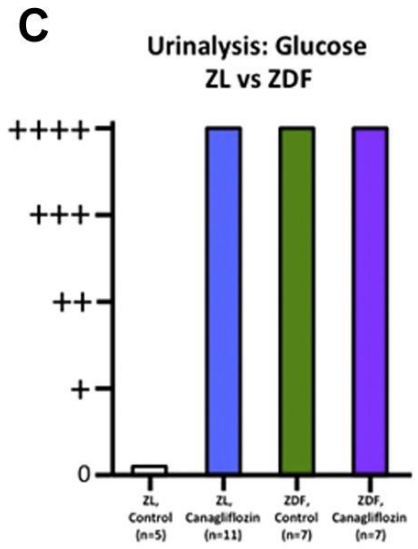
Nguyen et al. (2020). PLOS ONE 15: e0232399.

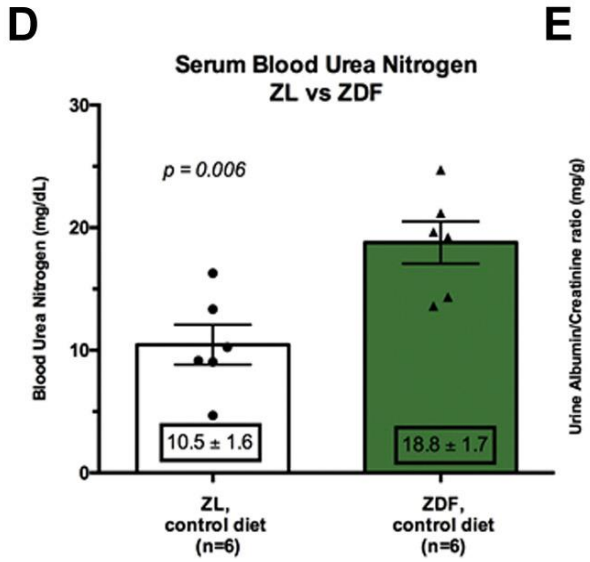
SGLT2 Inhibitor, Canagliflozin, Attenuates Myocardial Infarction in Diabetic and Nondiabetic Rats

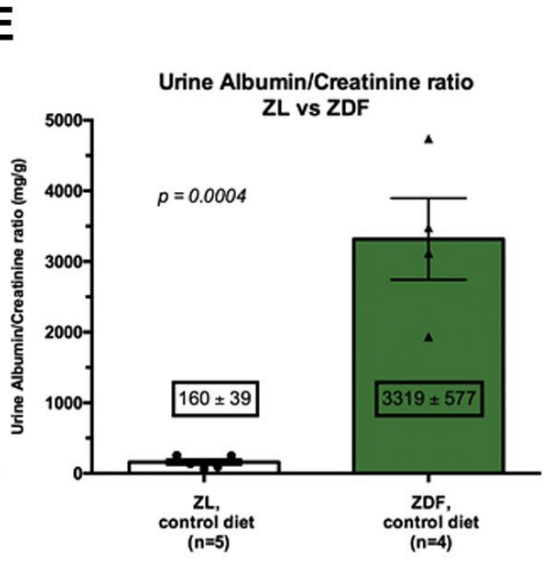






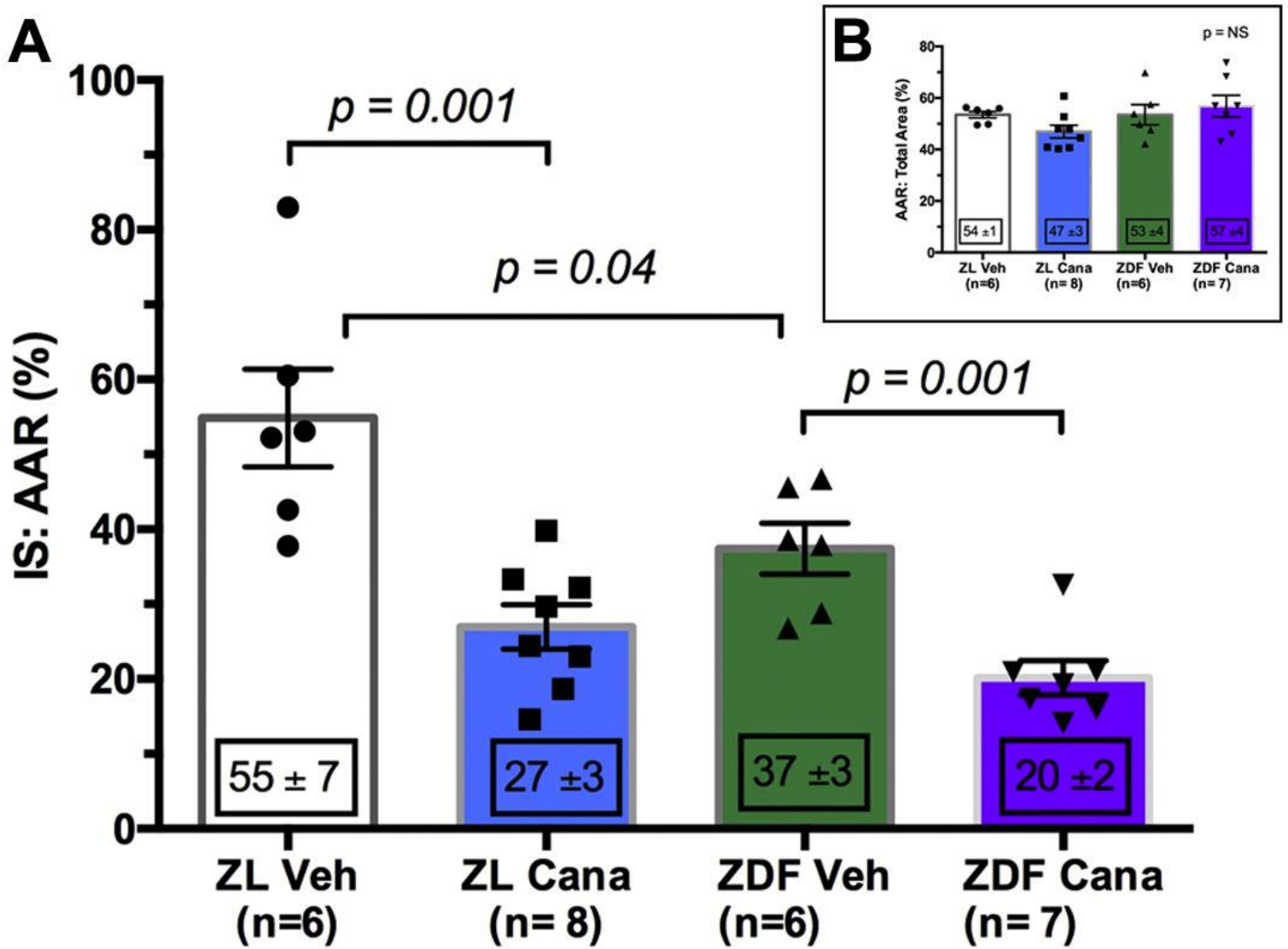






Lim, V.G. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(1):15-26.

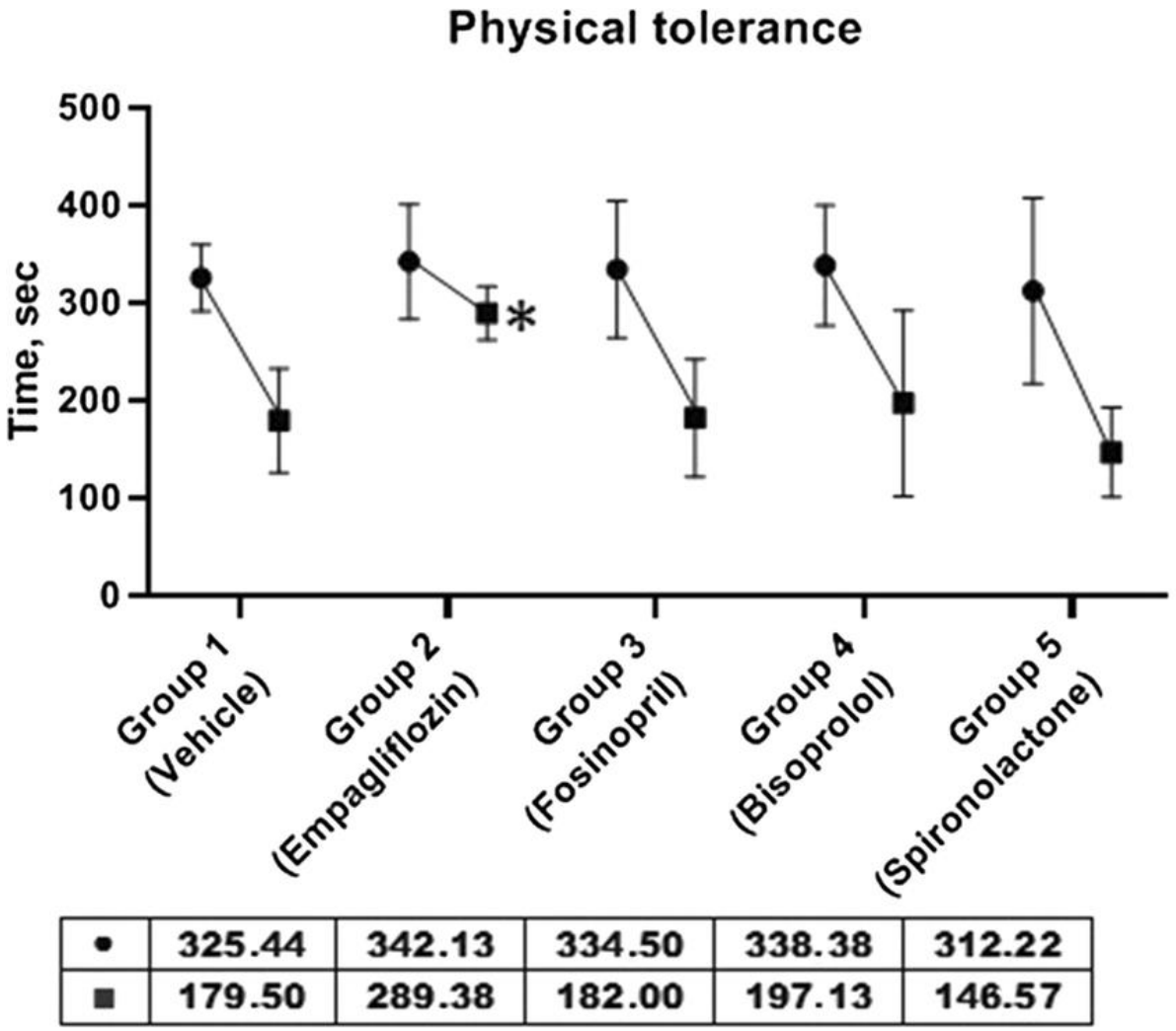
Infarct Size Reduction Following 4-Week Oral Administration of Canagliflozin



(A) In both diabetic ZDF and nondiabetic ZL rats, SGLT2i(Cana) significantly reduced of infarct size compared with control (Veh).
(B) Area at risk in all groups was equivalent
IS:AAR = infarct size/area at risk ratio;

Lim et al. JACC Basic Transl Sci. 2019 30;4:15-26.

Comparative efficacy of empagliflozin and drugs of baseline therapy in post-infarct heart failure in normoglycemic rats



●	325.44	342.13	334.50	338.38	312.22
■	179.50	289.38	182.00	197.13	146.57

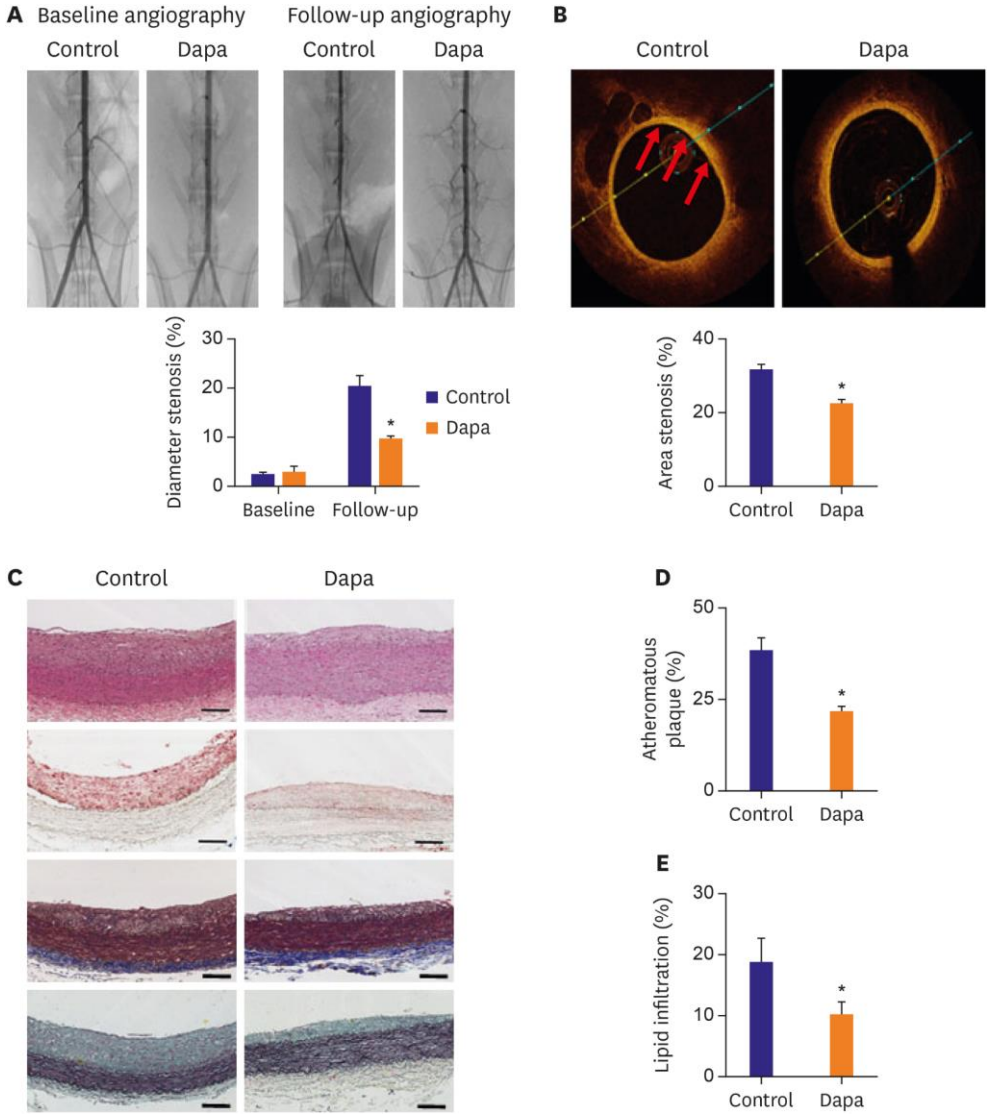
- ● 1 months after MI before starting the drug
- ■ 3 months of treatment = after 2 months of drug

Maximum activity time (MAT) on treadmill

MAT decreased in all groups after 3 months, but in rats treated with empagliflozin,
MAT was higher than in the vehicle, fosinopril, bisoprolol & spironolactone groups (p = 0,0036 by Kruskal-Wallis)

Krasnova et al. Naunyn-Schmiedeberg's Arch Pharmacol 2020:393;1649–58

Progression of atherosclerosis in normoglycemic rabbits



(A) Angiography: diameter stenosis at baseline and follow up.
(B) OCT images: area stenosis. Red arrows point to lipid.
(C) Tissues stained with H&E, ORO, trichrome and pentachrome.
(D) Atheromatous plaque.
(E) Lipid accumulation of plaques (ORO staining).

Body weight and plasma concentrations (Mean±SEM)		
Variables	Follow-up	
	Control (n=13)	Dapagliflozin (n=13)
Body weight (kg)	3.63±0.07	3.53±0.06
Blood glucose (mg/dL)	**129±4**	**132±4**
TC (mg/dL)	464±117	381±107
TG (mg/dL)	24±7	22±9
LDL-C (mg/dL)	417±111	337±103
HDL-C (mg/dL)	42±6	40±4

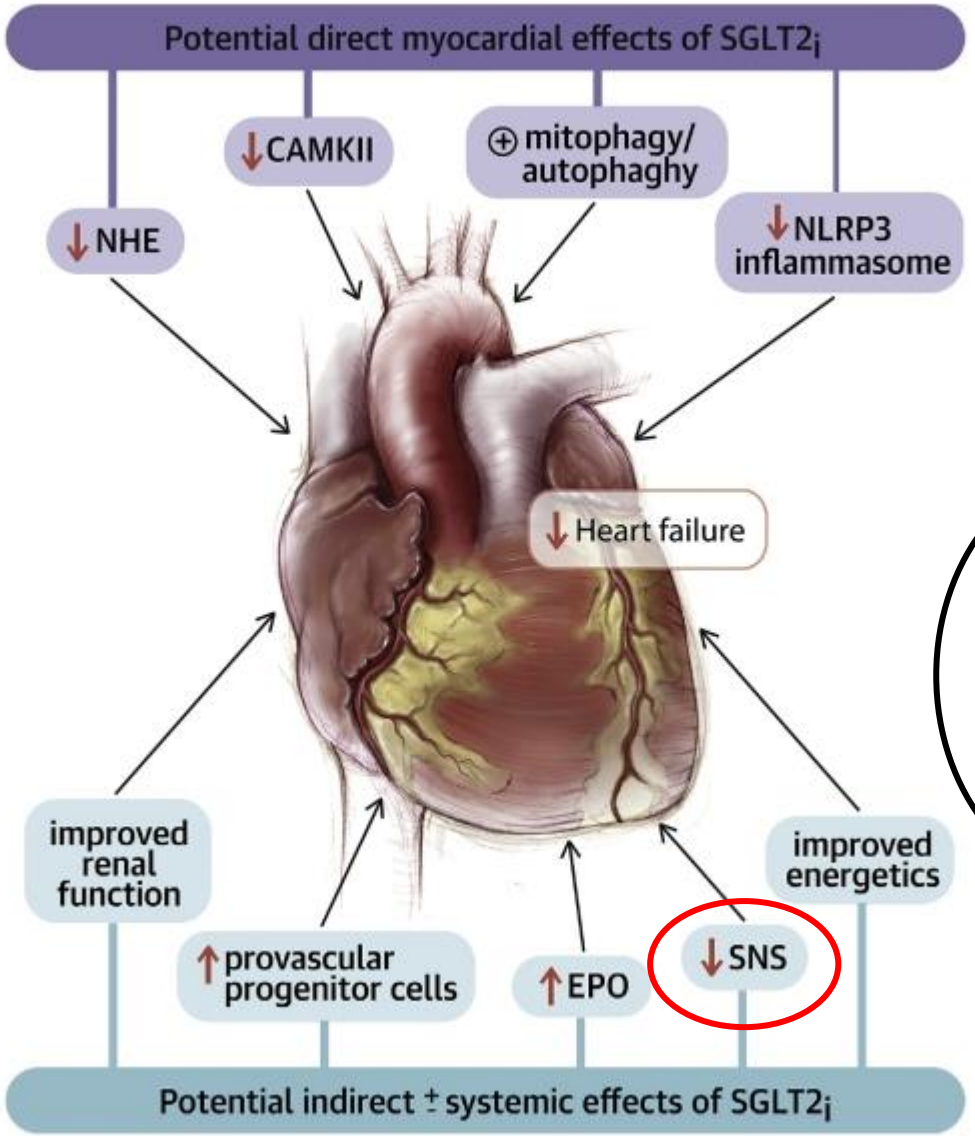
Lee et al. Korean Circ J. 2020;50:443-57

Our question today

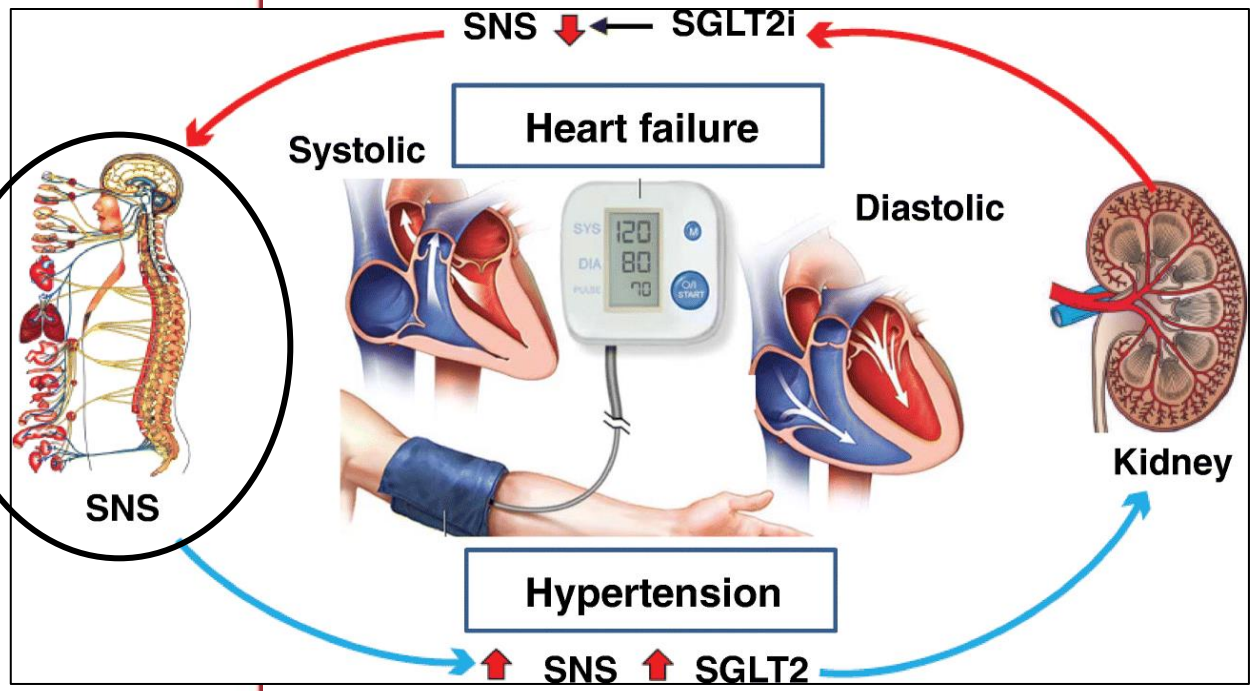
How does SGLT2 inhibition improve cardiovascular outcomes?

Perhaps not by reducing glycemia…

CENTRAL ILLUSTRATION: Potential Direct Myocardial and Indirect ± Systemic Effects of SGLT2i

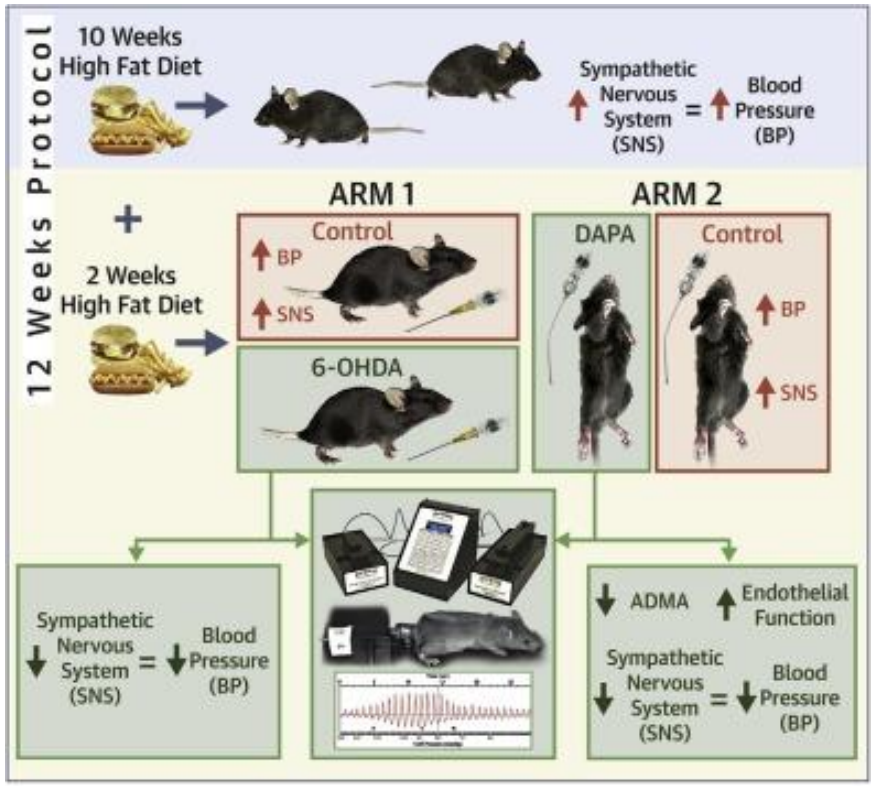


Lopaschuk, G.D. et al. J Am Coll Cardiol Basic Trans Science. 2020;5(6):632-44.



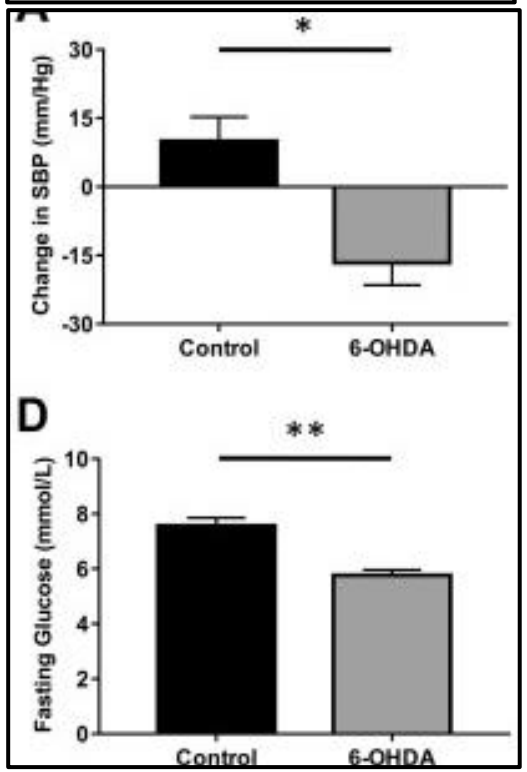
Zelniker & Braunwald. JACC 2020;75:422-34

SGLT2 Inhibitor–Induced Sympathoinhibition

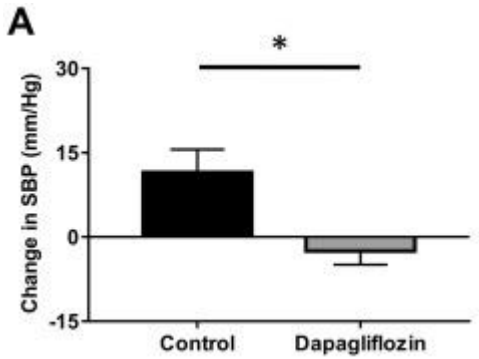


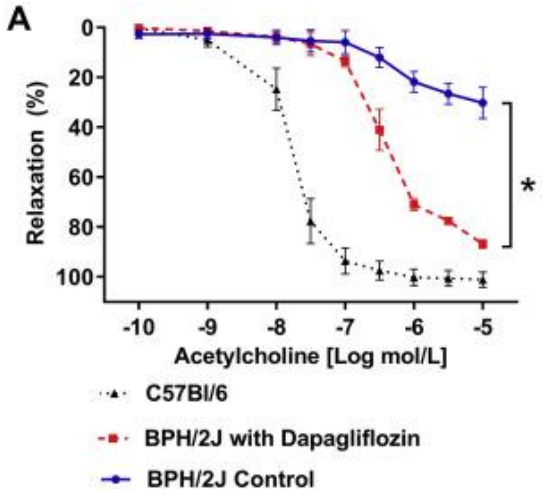
Herat, L.Y. et al. J Am Coll Cardiol Basic Trans Science. 2020;5(2):169-79.

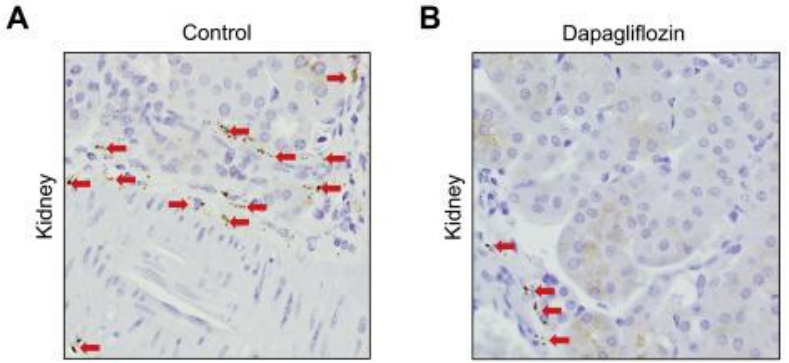
ARM 1

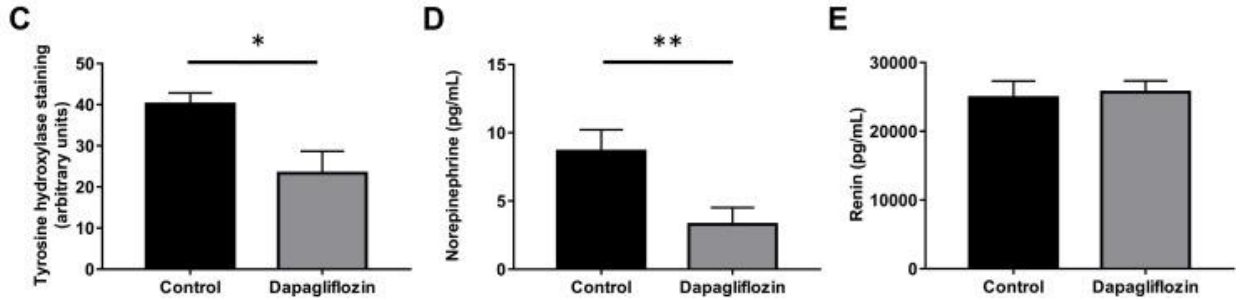


ARM 2



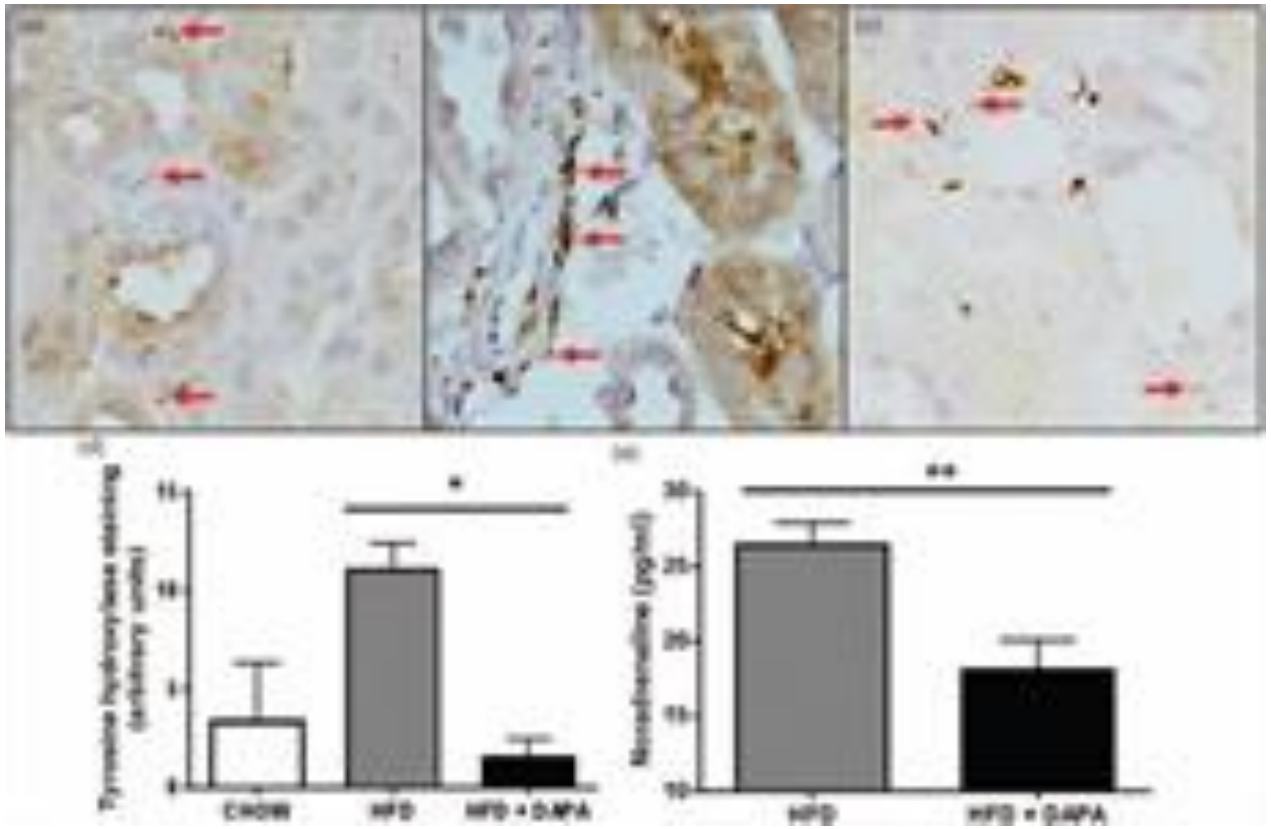




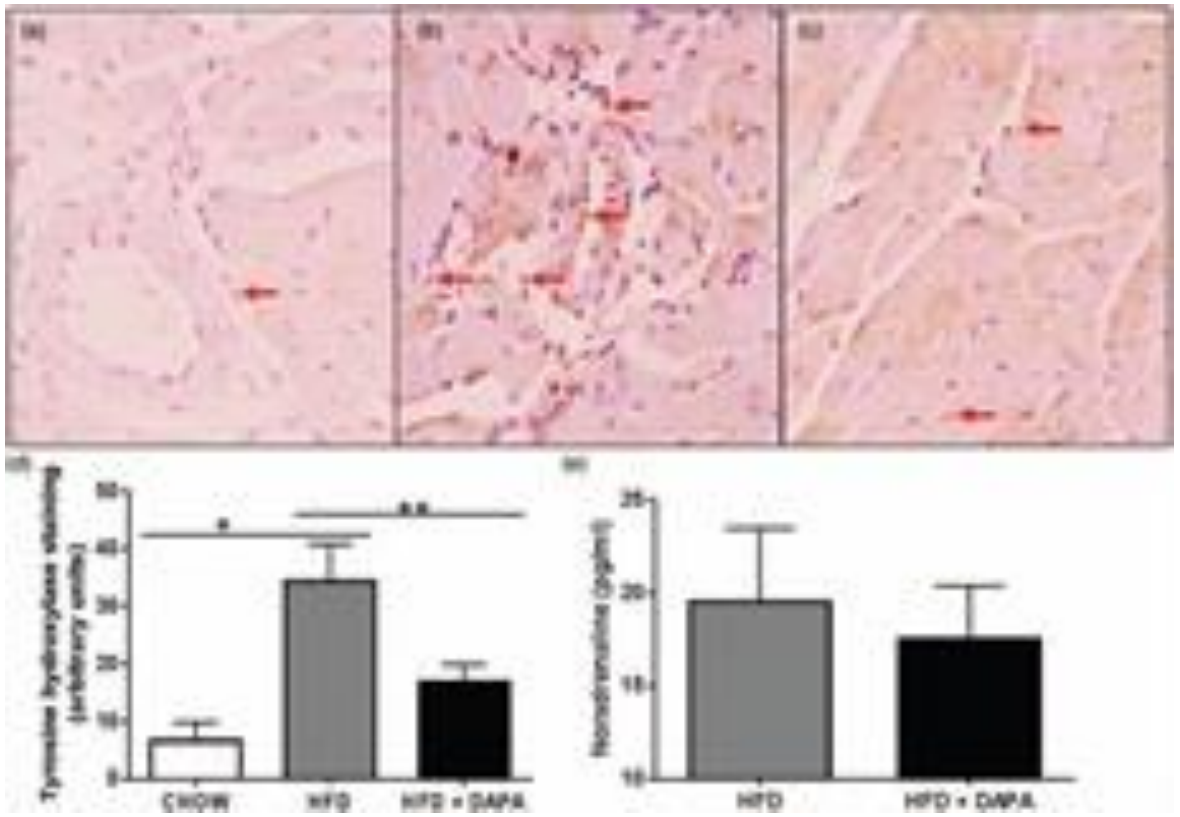


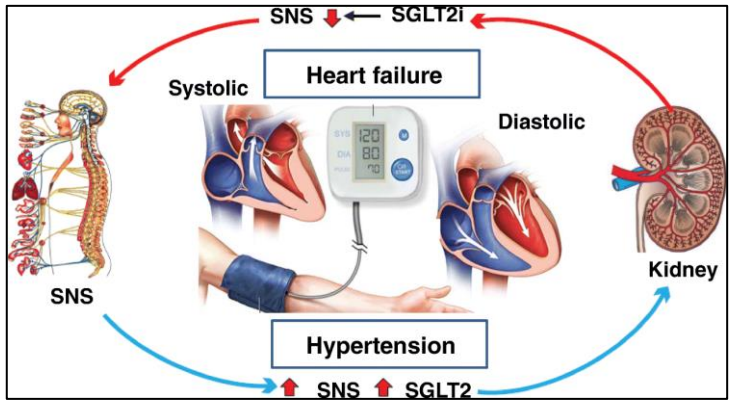
Sympathetic Nervous System in Regulation of Sodium Glucose coTransporter 2

Kidney



Heart





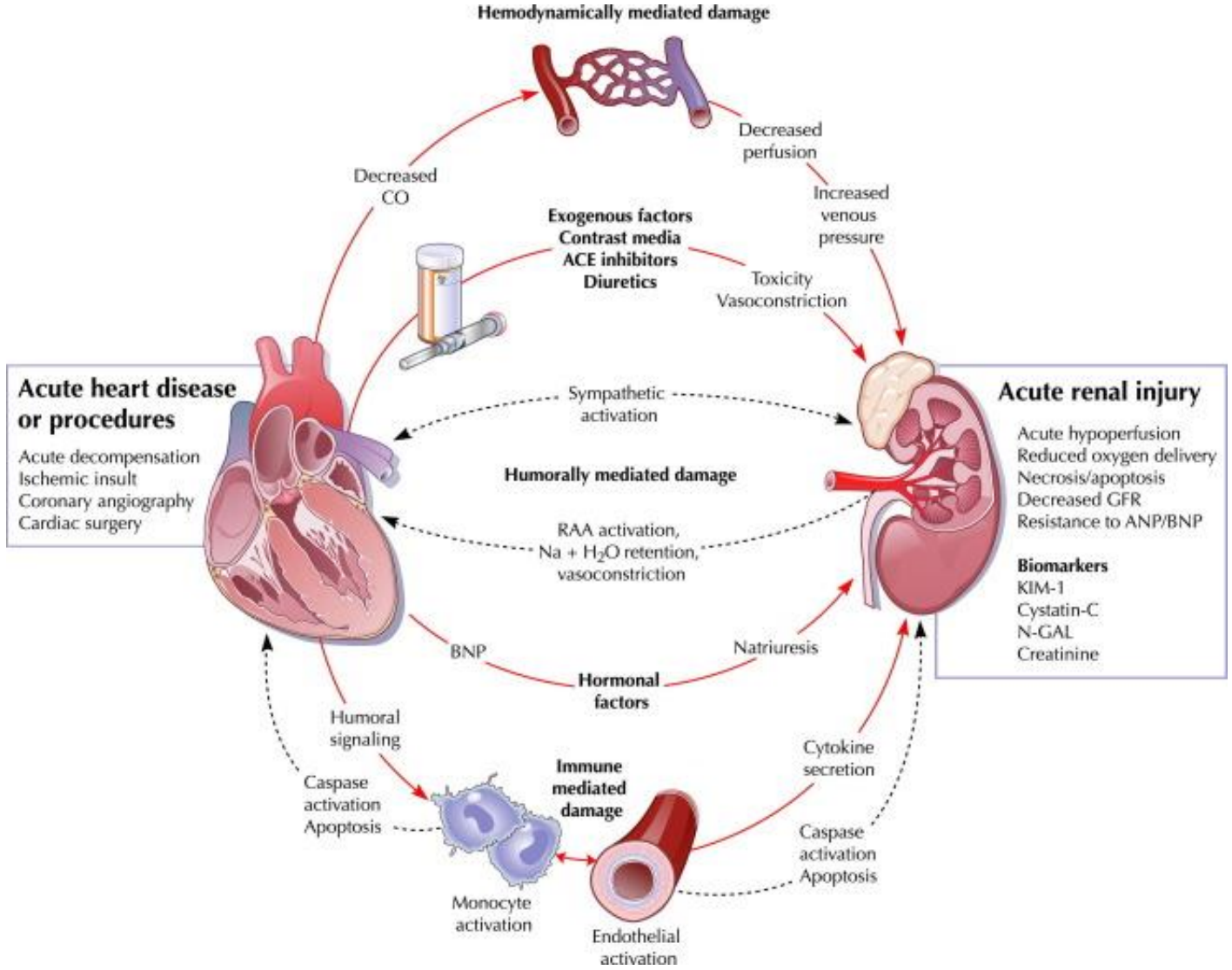
Matthews et al. J Hypertens. 2017;35:2059-68

Our question today

How does SGLT2 inhibition improve cardiovascular outcomes?

Perhaps by reducing sympathetic tone…

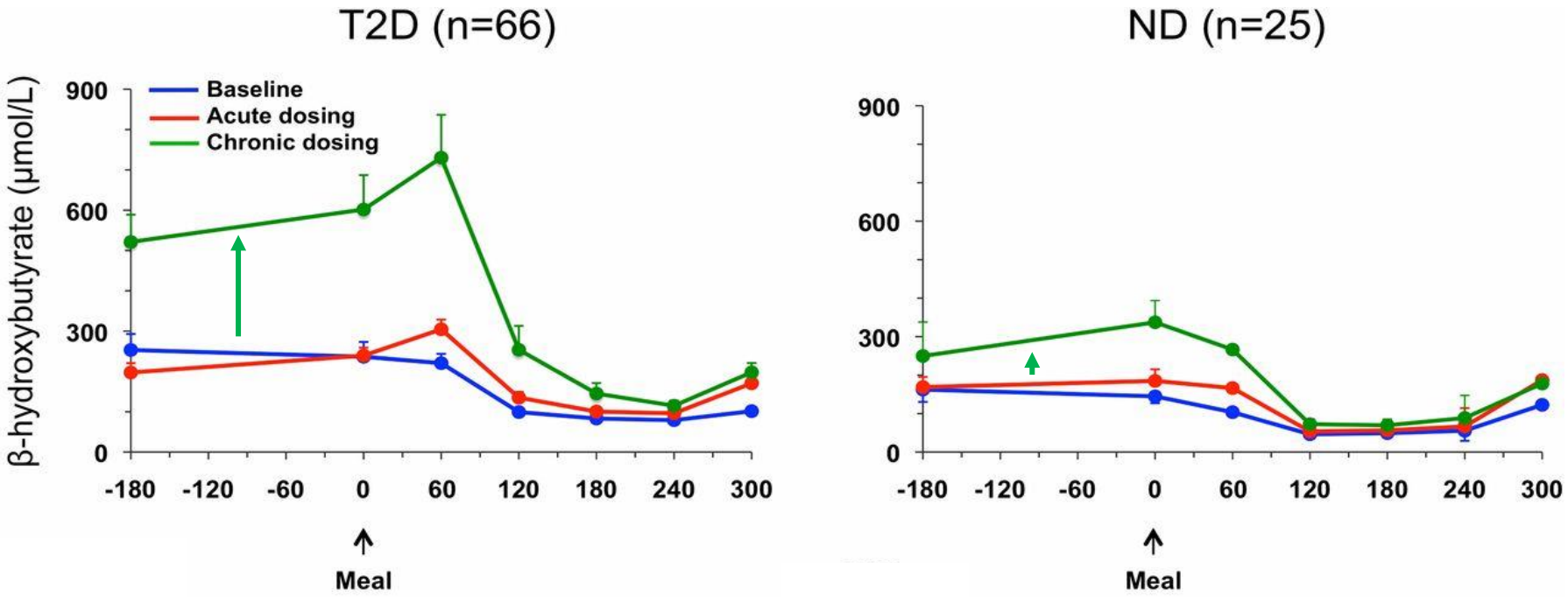
type 1 CardioRenal Syndrome



Pathophysiological interactions between heart and kidney in type 1 cardiorenal syndrome (CRS) or "acute CRS" (abrupt worsening of cardiac function, e.g., acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury.

Ronco et al. J Am Coll Cardiol. 2008;52:1527-39

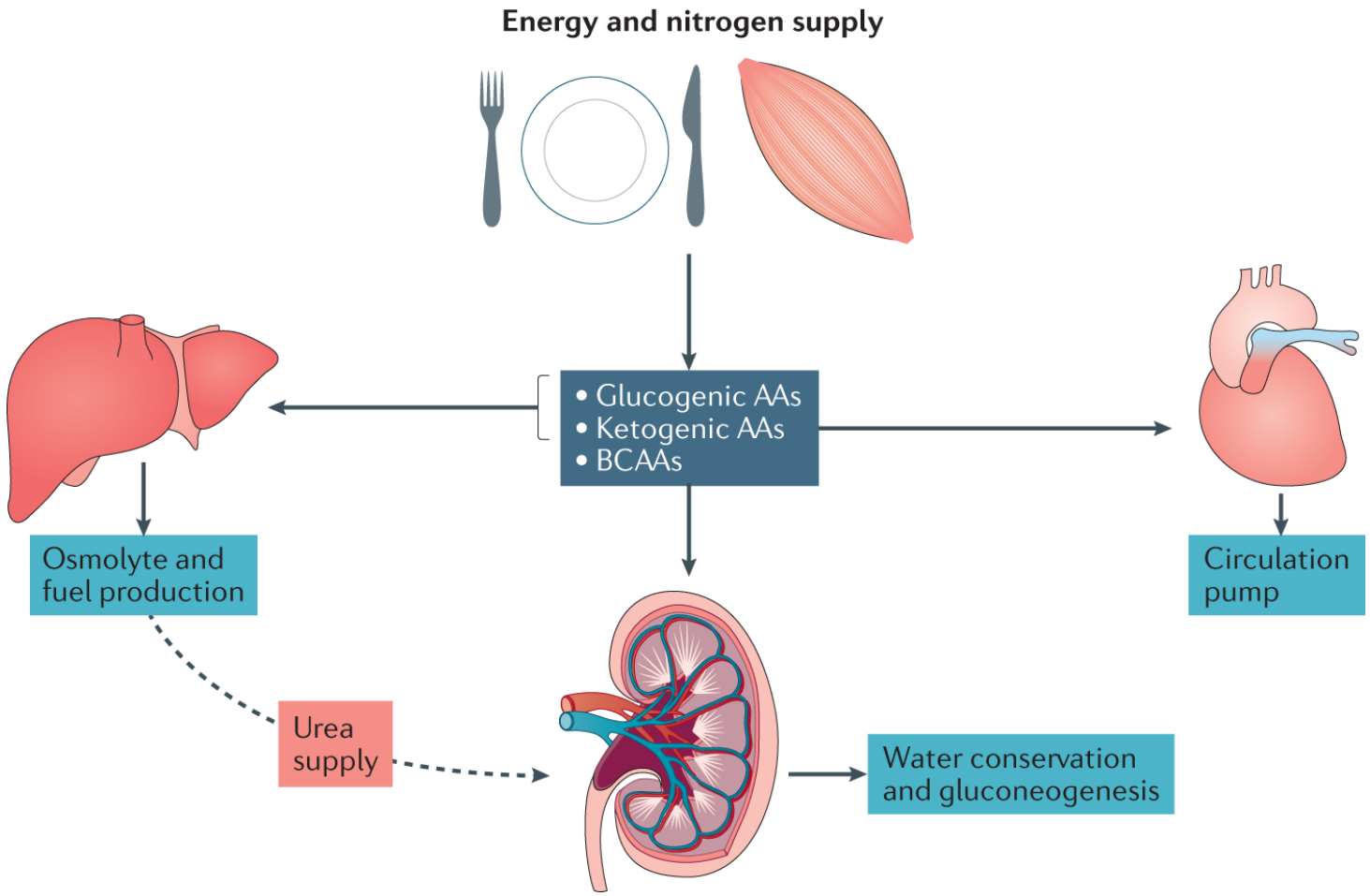
Plasma β-hydroxybutyrate concentrations during 3 h of fasting and 5 h after meal ingestion at baseline and after acute and chronic empagliflozin administration in patients with T2D and subjects without diabetes (ND)



Chronic SGLT2 inhibition increases ketone levels during fasting, especially in T2D

Ferrannini et al. Diabetes 2016;65:1190-5

Hypothesized key organ-specific metabolic changes in SGLT2 inhibition



In response to acute renal fuel and water loss due to glucosuria, organs activate conserved metabolic aestivation to stabilize function.

This metabolic survival pattern includes reprioritization of metabolic processes in the liver, kidney and heart to economize organ workload and compensate for the loss of fuel and water over a prolonged period.

Function of these key organs is supported by skeletal muscle, which serves as fuel and nitrogen reservoir through catabolic processes, providing nutrients necessary for successful adaptation to the renal glucose leak when dietary protein is not available (for example, during sleep).

AAs, amino acids; BCAAs, branched-chain amino acids.

Marton A, Kaneko T, Kovalik JP, Yasui A, Nishiyama A, Kitada K, **Titze J.** Nat Rev Nephrol. 2020. Online ahead of print.

Canagliflozin normalizes renal susceptibility to type 1 cardiorenal syndrome through reduction of renal oxidative stress in diabetic rats

Table 1. Analyses before myocardial infarction

	n	Blood glucose (mg/dL)	β-hydroxy-butyrate (mmol/L)
Protocol 1 (without fasting before surgery)			
OLETF	21	343 ± 28	0.35 ± 0.03
OLETF + canagliflozin	23	184 ± 9§	0.39 ± 0.02
Protocol 2 (fasted before myocardial infarction)			
OLETF	10	164 ± 17	0.54 ± 0.05
OLETF + canagliflozin	9	149 ± 9	0.79 ±0.06‡‡

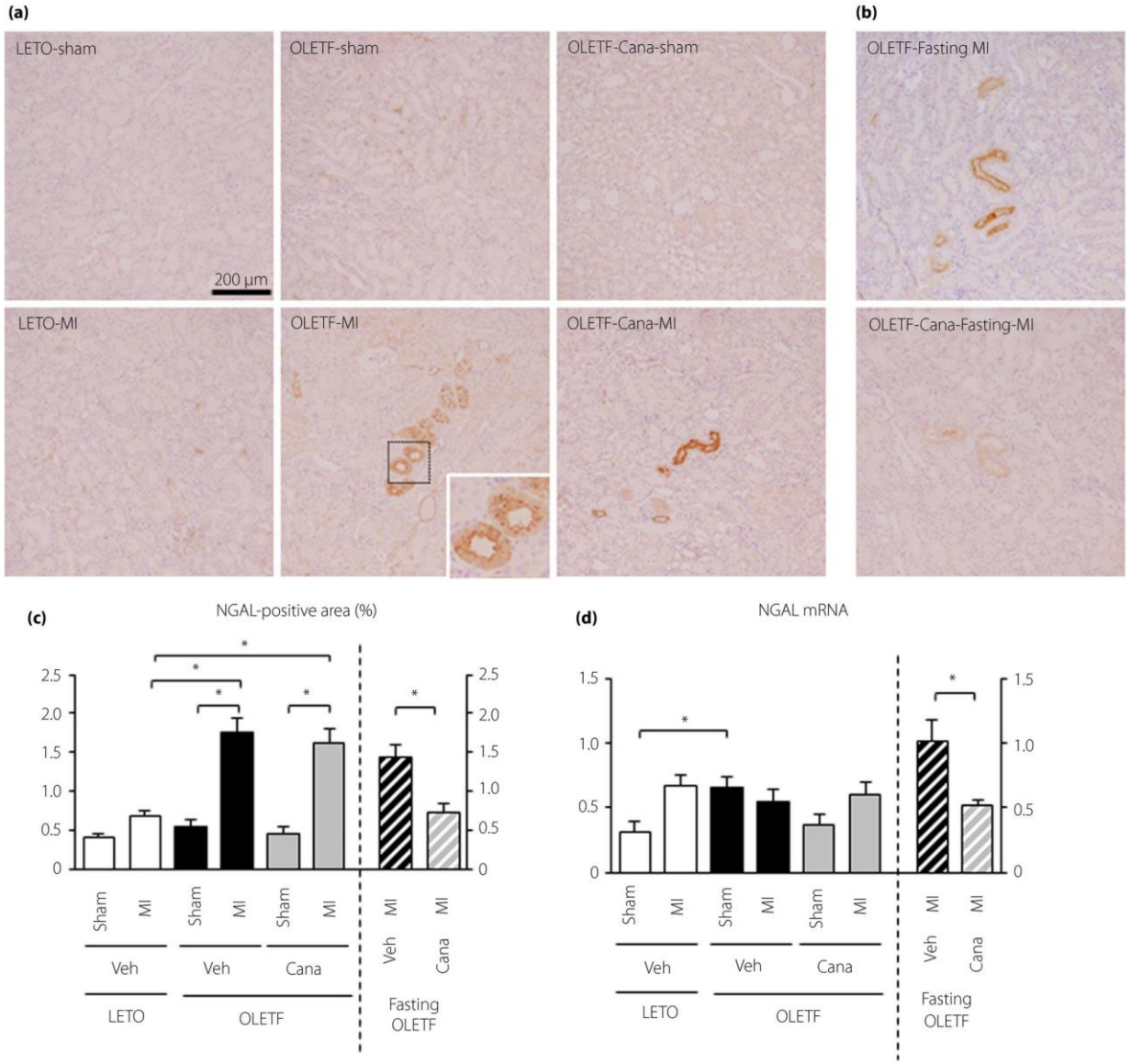
§ $P < 0.05$ versus Otsuka Long-Evans Tokushima Fatty rats (OLETF)-Sham.
¶ $P < 0.05$ versus OLETF-MI.
†† $P < 0.05$ versus corresponding sham-operated rats.
‡‡ $P < 0.05$ versus OLETF with fasting.

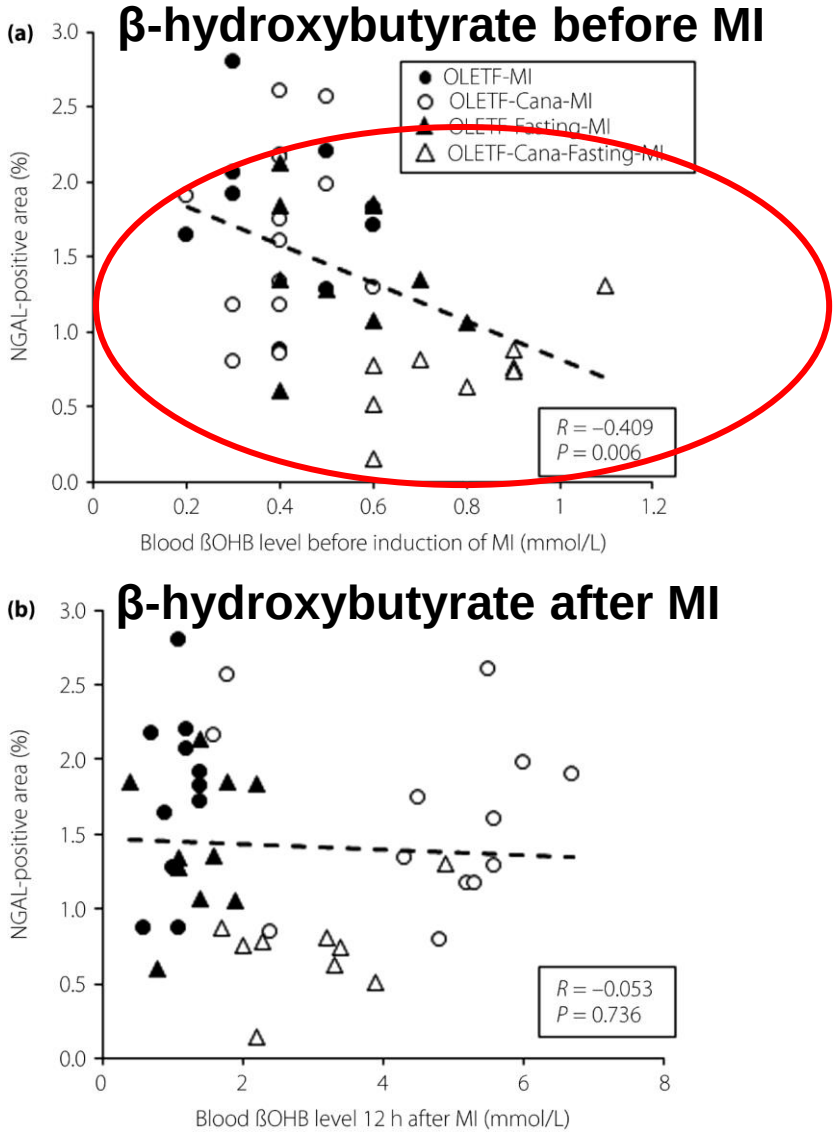
Table 2. Analyses 12 h after surgery

	n	Blood glucose (mg/dL)	β-hydroxy-butyrate (mmol/L)	Mortality
Protocol 1 (without fasting before surgery)				
OLETF				
Sham	10	196 ± 26	0.31 ± 0.04	0/10
MI	11	249 ± 23	1.09 ± 0.08	5/16
OLETF + canagliflozin				
Sham	10	130 ± 9§	0.70 ± 0.05	0/10
MI	13	176 ± 15¶	4.56 ± 0.45¶††	6/19
Protocol 2 (fasted before myocardial infarction)				
OLETF				
MI	10	166 ± 15	1.37 ± 0.17	5/15
OLETF + canagliflozin				
MI	9	123 ± 7‡‡	2.99 ± 0.34‡‡	5/14

Kimura et al. Journal of Diabetes Investigation 2019;10: 933-46

Canagliflozin normalizes renal susceptibility to type 1 cardiorenal syndrome through reduction of renal oxidative stress in diabetic rats





Kimura et al. Journal of Diabetes Investigation 2019;10: 933-46

Our question today

How does SGLT2 inhibition improve cardiovascular outcomes?

Perhaps by increasing ketones during fasting…

Our question today

How does SGLT2 inhibition improve cardiovascular outcomes?

Actually we don't know…

Limited synergy of obesity and hypertension in onset and progression of heart failure with preserved ejection fraction

Pathway analysis and mitochondrial gene expression in the left ventricle

(A) Three most affected pathways

Ingenuity Analysis;

orange = activation, blue = repression

grey = no direction available.

(B-D) RNAseq

Differentially expressed genes for each individual rat, relative to average in lean group.

(B) Fatty acid oxidation

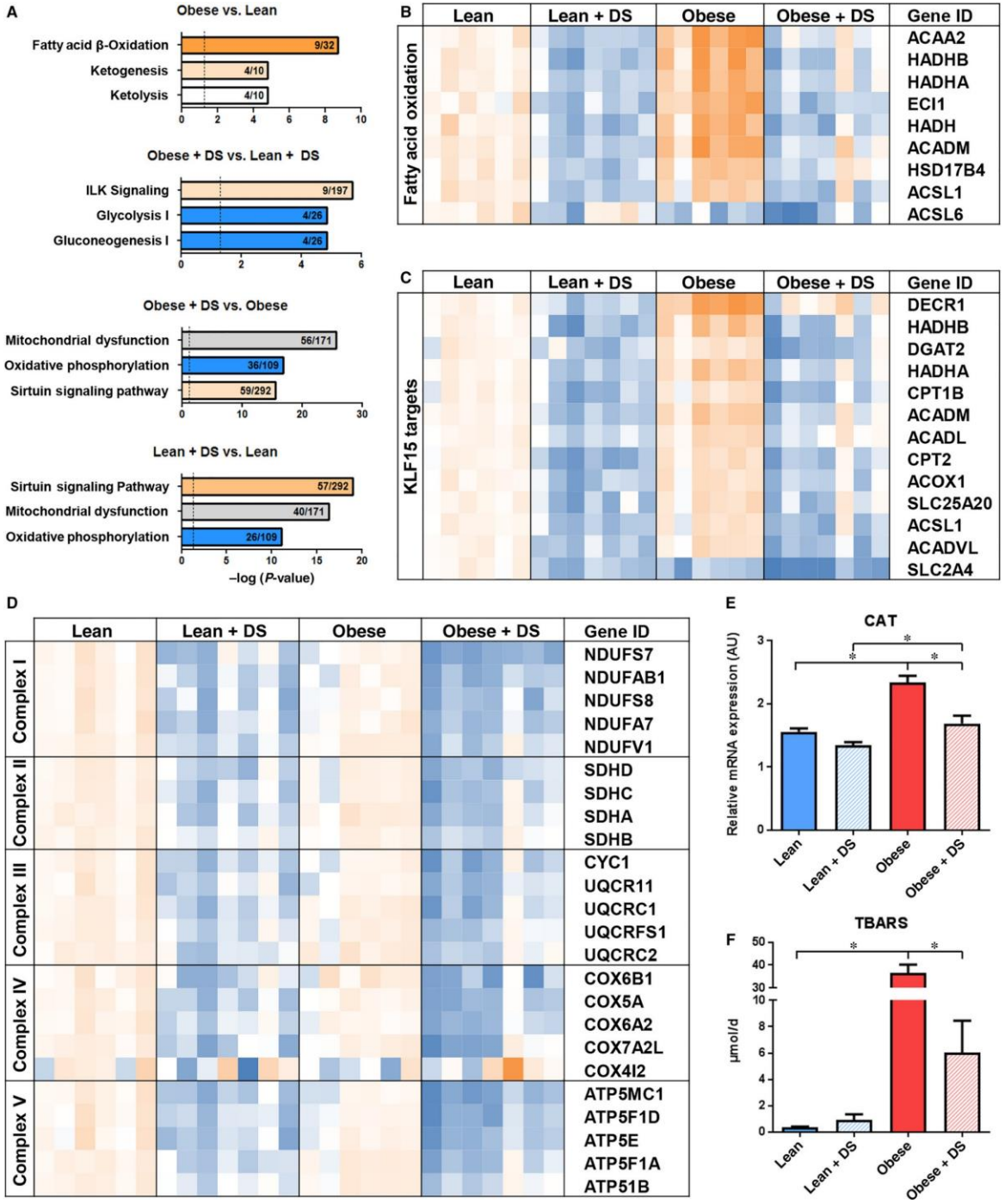
(C) KLF15-induced transcription (induces mitochondrial fatty acid substrate use)

(D) Oxidative phosphorylation (mitochondrial)

(E-F) Oxidative stress markers

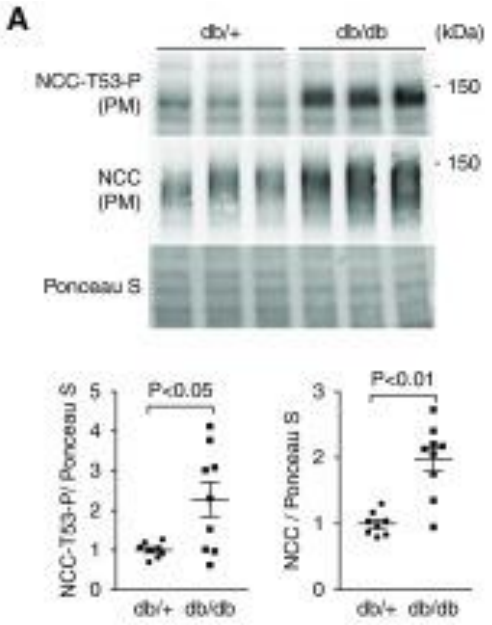
(E) catalase (CAT, qPCR in left ventricle)

(F) Urinary TBARS excretion

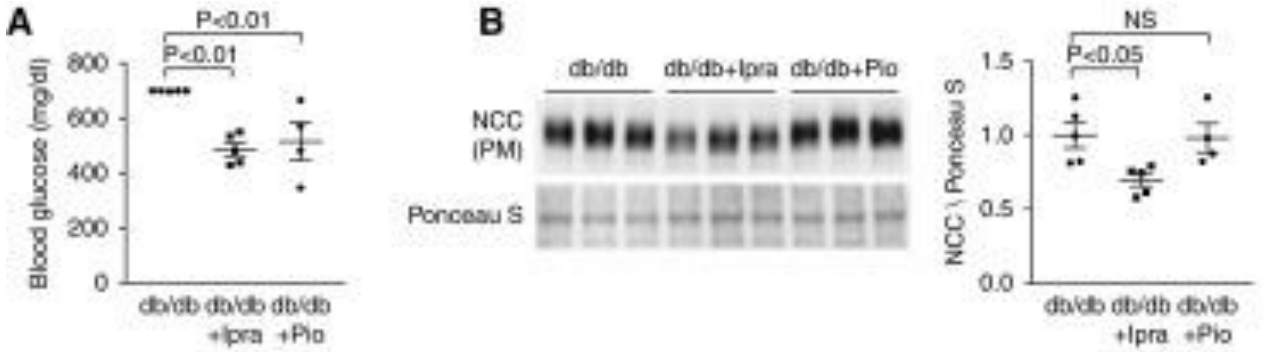


Brandt, Nguyen et al.
Journal of Cellular and Molecular Medicine 2019; 23:6666-78

Inhibition of SGLT2 Attenuates Dysregulation of NaCl Cotransporter in Obese Diabetic Mice



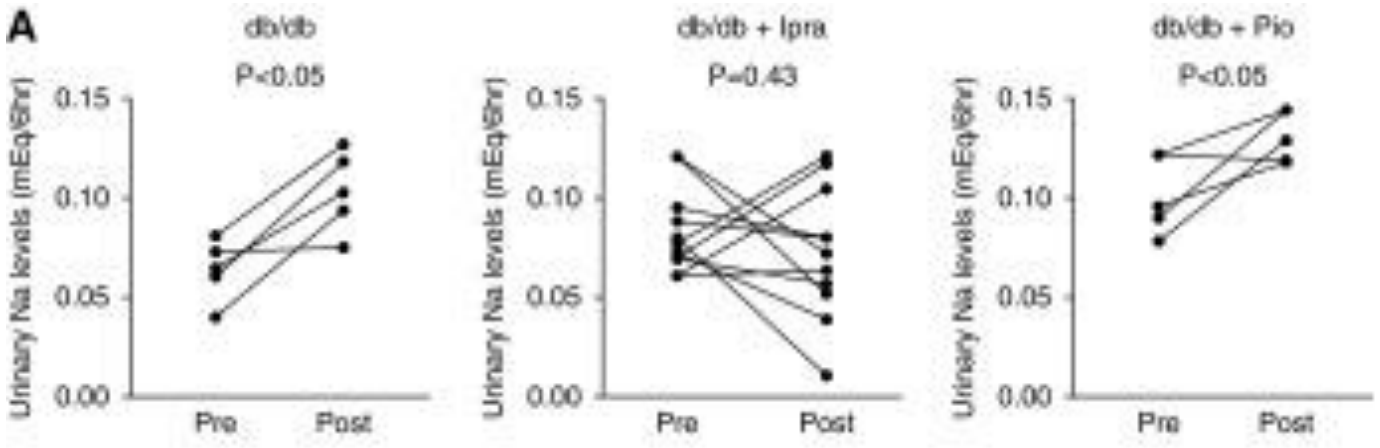
Expression of NCC in the plasma membrane–enriched fraction (PM) in the kidneys of db/+ and db/db mice in biologic replicates.



Ipragliflozin, but not pioglitazone, reduces NaCl cotransporter (NCC) levels *in vivo* in db/db mice.

(A) Blood glucose levels in the indicated groups. In db/db, blood glucose levels >700 mg/dl were regarded as 700 mg/dl. Both ipragliflozin, SGLT2 inhibitor, and pioglitazone, PPARγ agonist, effectively reduce blood glucose levels in db/db mice.

(B) Effects of ipragliflozin and of pioglitazone on NCC levels in plasma membrane–enriched fraction of kidneys.



NaCl cotransporter (NCC) activity is increased in db/db mice and is attenuated by ipragliflozin.

(A) Indicated groups received hydrochlorothiazide (an NCC inhibitor; 25 mg/kg body wt), and the urinary Na^+ excretion was compared before and after hydrochlorothiazide injection.