UNIVERSITY ABOUBEKR BELKAID

ACADEMIC HOSPITAL TIDJANI DAMERDJI

SGLT2 inhibitors: more than Glucosuria and Diuresis

AMIWIT 11-LAREDIAB 5

Friday 9and saturday10 December 2022

Dr A.BENSEFIA

INTRODUCTION

- SGLT2 inhibitors are the newest class of oral anti hyperglycemic agents approved for the treatment of T2DM.

- SGLT2 inhibitors have a unique mechanism of action and that lower glucose independent of insulin.

- **Reduced cardiovascular mortality and morbidity** in patients with increased cardiovascular risk.

Physiology of sodium-glucose co-transporters inhibition

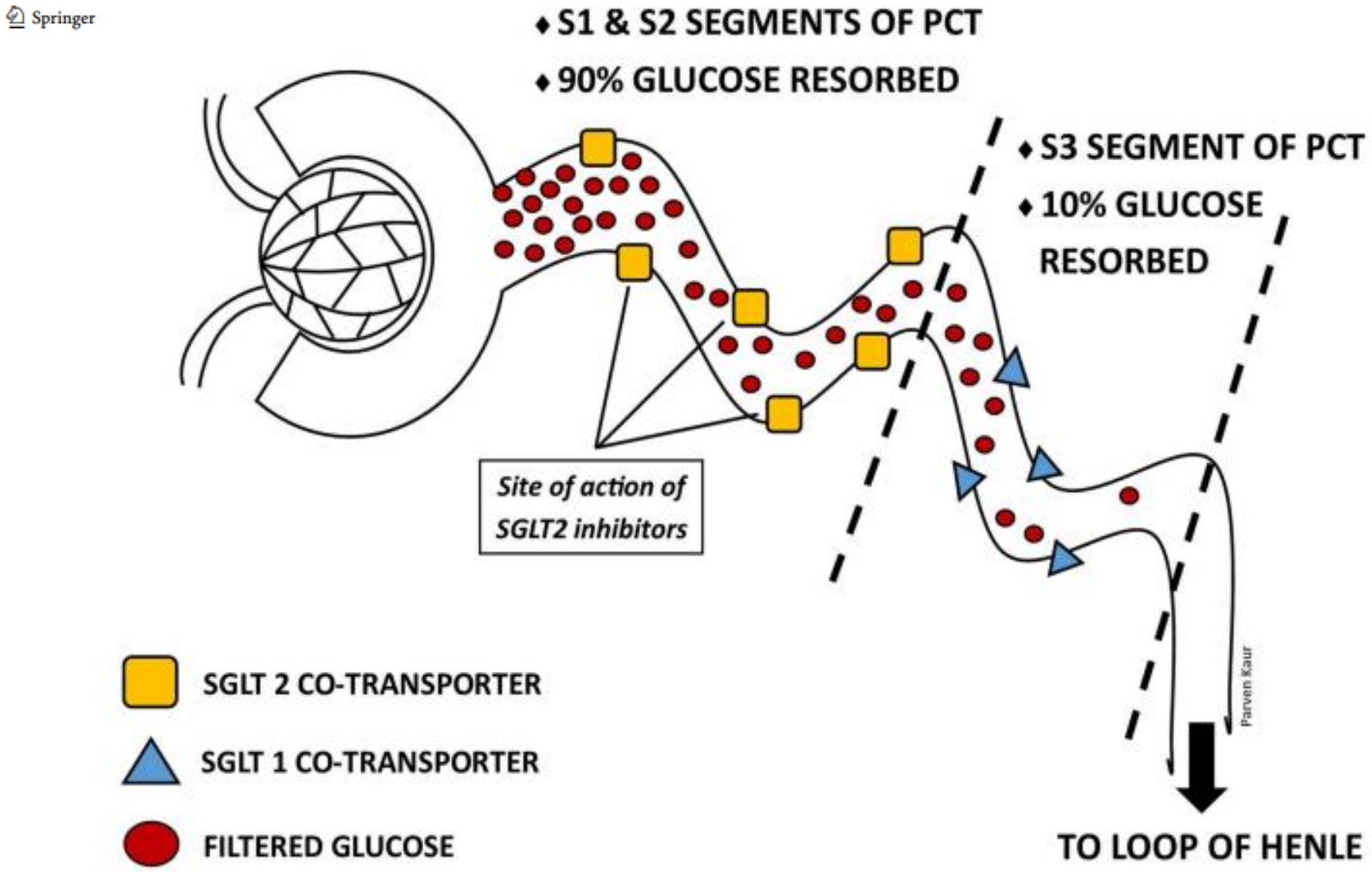


Fig. 1 Normal renal tubular resorption of glucose. The diagram also identifies the site at which SGLT2-inhibitors act [8]. Abbreviations: PCT-proximal convoluted tubules; SGLT-sodium-glucose cotransporter

- Potent SGLT2-inhibition prevents the reabsorption of filtered glucose as well as sodium, resulting in glucosuria and natriuresis.

- Unlike other antidiabetic agents, the glucose lowering effect of SGLT2 inhibitors is independent of pancreatic beta-cell function and insulin sensitivity.

- Other pleotropic benefits of SGLT2-inhibition include:
  -weight loss (1.8 to 2.7 kg),
  -reductions in blood pressure :

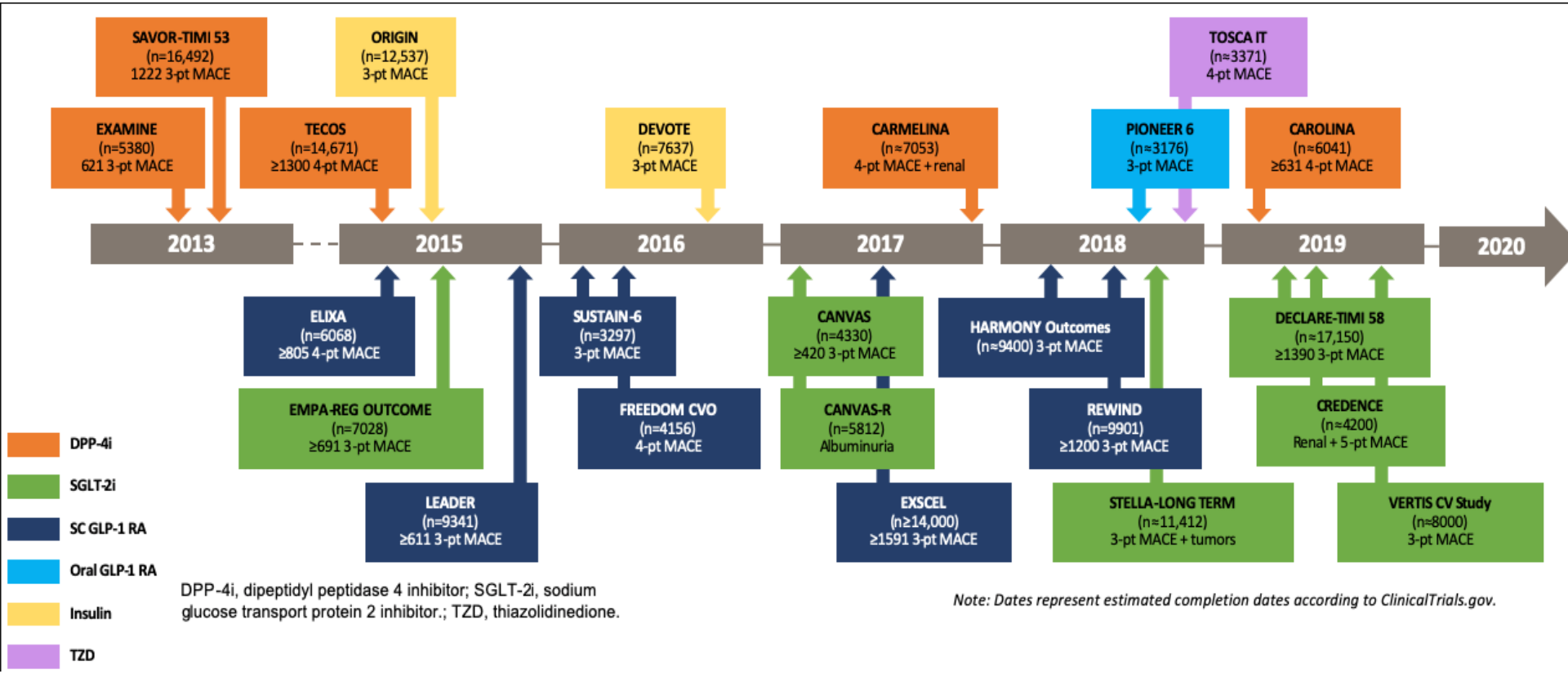
  systolic BP (BP): 1.0–2.6 mmHg; diastolic BP 0.7–2.2 mmHg, *without increases in heart rate.*

  -low potential of inducing hypoglycaemia

List of current Sodium Glucose type2 cotransporter inhibitors

Generic name	Brand name	Available doses (mg)	Administration
Canagliflozin[a]	Invokana	100 and 300	qam before first meal
Dapagliflozin[a]	Farxiga	5 and 10	qam
Empagliflozin[a]	Jardiance	10 and 25	qam
Canagliflozin/metformin[a]	Invokamet	50/500 and 50/1000, 150/500 and 150/1000	BID with meals, max dose 300 mg/2000 mg
Dapagliflozin/metformin[a]	Xigduo XR	5/500 and 5/1000, 10/500 and 10/1000	qam with food, max dose 10 mg/2000 mg
Empagliflozin/metformin[a]	Synjardy	5/500 and 5/1000, 12.5/500 and 12.5/1000	BID with meals, max dose 25 mg/2000 mg
Empagliflozin/linagliptin[a]	Glyxambi	10/5 and 25/5	qam
Ipragliflozin[b]	Suglat	25 and 50	qam, max dose 100 mg
Tofogliflozin[b, c]	Apleway, Deberza	20	qam
Luseogliflozin[c]			
Remogliflozin Etabonate[c]			
Ertugliflozin[c]			
Sotagliflozin[c]			

[a]FDA and EMA approved.
[b]Ministry of Health, Labour and Welfare approved in Japan.
[c]Currently in clinical trials or seeking market approval; qam taken once daily in the morning, BID twice daily.



Timeline for Cardiovascular Outcome Trials Since Publication of the *Guidance for Industry*

SGLT2i: Cardiovascular outcomes trials

Cardiovascular Outcome Trials

EMPA-REG Outcome [18]	Empagliflozin vs. placebo	3.1 years	n = 7020; T2DM with established CVD	3P-MACE (HR 0.86; 95% CI 0.74–0.99)	- 3P-MACE + hospitalisation for UA (HR 0.89; 95% CI 0.78 to 1.01) - CV death (HR 0.62; 95% CI 0.49 to 0.77) - HHF (HR 0.65; 95% CI 0.50 to 0.85) - CV death/HHF (HR 0.66; 95% CI 0.55 to 0.79) - Death from any cause (HR 0.68; 95% CI 0.57 to 0.82)
CANVAS [22]	Canagliflozin vs. placebo	2.4 years	n = 9734; Poorly controlled T2DM plus i) age 30 + and history of symptomatic atherosclerotic CVD or ii) age 50 + and high risk of CVD	3P-MACE (HR 0.86; 95% CI 0.75–0.97)	- CV death (hazard ratio, 0.87; 95% CI 0.72 to 1.06) - Progression of albuminuria (30% increase) (HR 0.73; 95% CI 0.67 to 0.79) - CV death/HHF (HR 0.78; 95% CI 0.67 to 0.91)
DECLARE-TIMI 58 [23]	Dapagliflozin vs. placebo	4.2 years	n = 17,160; age 40 + with T2DM and either history or high risk of atherosclerotic CV events	3P-MACE (HR 0.93; 95% CI 0.84–1.03) CV death/HHF (HR 0.83; 95% CI 0.73–0.95)	- > 40% reduction in eGFR/new ESRD/renal death/CV death (HR 0.76; 95% CI 0.67–0.87) - Death from any cause (HR 0.93; 95% CI 0.82–1.04)
VERTIS CV [28]	Ertugliflozin vs. placebo	6.1 years	n = 8246; T2DM and established ASCVD	3P-MACE (HR 0.97; 95% CI 0.85–1.11)	- CV death/HHF (HR 0.88; 95% CI 0.75–1.03) - HHF (HR 0.70; 95% CI 0.54–0.90) - Progression of renal disease (HR 0.81; 95% CI 0.63–1.04)

SGLT2i: Cardiovascular outcomes trials

Heart Failure Outcome Trials

al Name	Drug	Duration (median)	Cohort	Primary outcome	Key secondary outcomes
APA-HF [31]	Dapagliflozin vs. placebo	1.5 years	n = 4744; HFrEF (LVEF < 40%); NTproBNP > 400–600 (depending on criteria); with or without T2DM	Time to first occurrence of CV death/ HHF/ urgent HF visit (HR 0.74; 95% CI 0.65–0.85)	- CV Death/HHF (HR 0.75; 95% 0.65–0.85) - ≥ 50% sustained reduction in eG reaching ESRD/renal death (HR 0.71; 95% CI 0.44–1.16) - KCCQ (HR 1.18; 95% CI 1.11–1.26) - Death from any cause (HR 0.83 95% CI 0.71–0.97)
MPEROR-Reduced [32]	Empagliflozin vs. placebo	16 months	n = 3730; HFrEF (LVEF ≤ 40%; NYHA II-IV); NTproBNP > 600–5000 (specific criteria based on diagnosis of AF and EF); with or without diabetes	Time to first occurrence of CV death/ HHF (HR 0.75; 95% CI 0.65–0.86)	- CV death (HR 0.92; 95% CI 0.75–1.12) - First HHF (HR 0.69; 95% CI 0.59–0.81) - HHF (HR 0.70; 95% CI 0.58–0 - Decline in eGFR (1.73 ml/ min/1.73m^2/year slower declin treatment arm; 95% CI 1.10–2 - Death from any cause (HR 0.9 95% CI 0.77 to 1.10)
ELIVER [65] urrently recruiting – est comple-on June 2021)	Dapagliflozin vs. placebo	2.75 years	n = 6100; HFpEF (LVEF > 40%); Elevated NT-proBNP; Ambulatory and hospitalised patients	Time to first occurrence of CV death/ HHF/ urgent HF visit	- KCCQ - Worsening NYHA class - Total number of CV death or H - Time to death from any cause
MPEROR-Preserved [66] t completion Nov 2020)	Empagliflozin vs. placebo	3.2 years	n≈5988; HFpEF (LVEF > 40%) + structural heart disease; NTproBNP > 300; with or without diabetes	Time to first occurrence of CV death/ HHF	- CV death - HHF - All-cause hospitalisation - Change in KCCQ - RRT or sustained reduction of ≥ 40% eGFR - All-cause mortality - Onset of DM

SGLT2i: Cardiovascular outcomes trials

Renal Outcome Trials

Trial Name	Drug	Duration (median)	Cohort	Primary outcome	Key secondary outcomes
CREDENCE [52]	Canagliflozin vs. placebo	2.6 years	n = 4401; T2DM; CKD (eGFR 30 to < 90 ml/ minute/1.73 m^2); albuminuria (UACR > 300 to 5000); on ACEi/ARB therapy	ESRD/ serum creatinine × 2 baseline (30 + days)/ renal or CV death (HR 0.70; 95% CI 0.59 to 0.82)	- CV death/HHF (HR 0.69; 95% CI 0.57 to 0.83) - CV death/ MI/ stroke (HR 0.80; 95% CI 0.67 to 0.95) - HHF (HR 0.61; 95% CI 0.47 to 0.80) - CV death (HR 0.78; 95% CI 0.61 to 1.00) - Death from any cause (HR 0.83; 95% CI 0.68 to 1.02) - CV death/ MI/ stroke/ hospitalization for HF or UA (HR 0.74; 95% CI 0.63 to 0.86)
DAPA-CKD [69]	Dapagliflozin vs. placebo	2.4 years	n = 4304; with or without diabetes; eGFR ≥ 25 and ≤ 75 ml/min/1.73m^2; UACR ≥ 200 or ≤ 5000 mg/g; maximum tolerated daily dose of ACEi or ARB	≥ 50% decline in eGFR/reaching ESRD/CV death/renal death (HR 0.61; 95% CI 0.51–0.72)	- HHF/ CV death (HR 0.71; 95% CI 0.55–0.92) - Death from any cause (HR 0.69; 95% CI 0.53–0.88) - ≥ 50% decline in eGFR/reaching ESRD/renal death (HR 0.56; 95% CI 0.45–0.68)
EMPA-Kidney [70] (est completion June 2022)	Empagliflozin vs. placebo	3.1 years	n≈6000; CKD + risk of kidney disease progression (depending on criteria); g on ACEi or ARB therapy	Time to first occurrence of: (i) Kidney disease progression (ESRD, sustained decline in eGFR to < 10 mL/min/1.73m^2, renal death, decline of ≥ 40% in eGFR) or (ii) Cardiovascular death	Time to: - HHF or CV death - All-cause hospitalisations - Death from any cause - First occurrence of kidney disease progression - CV death - CV death or ESRD

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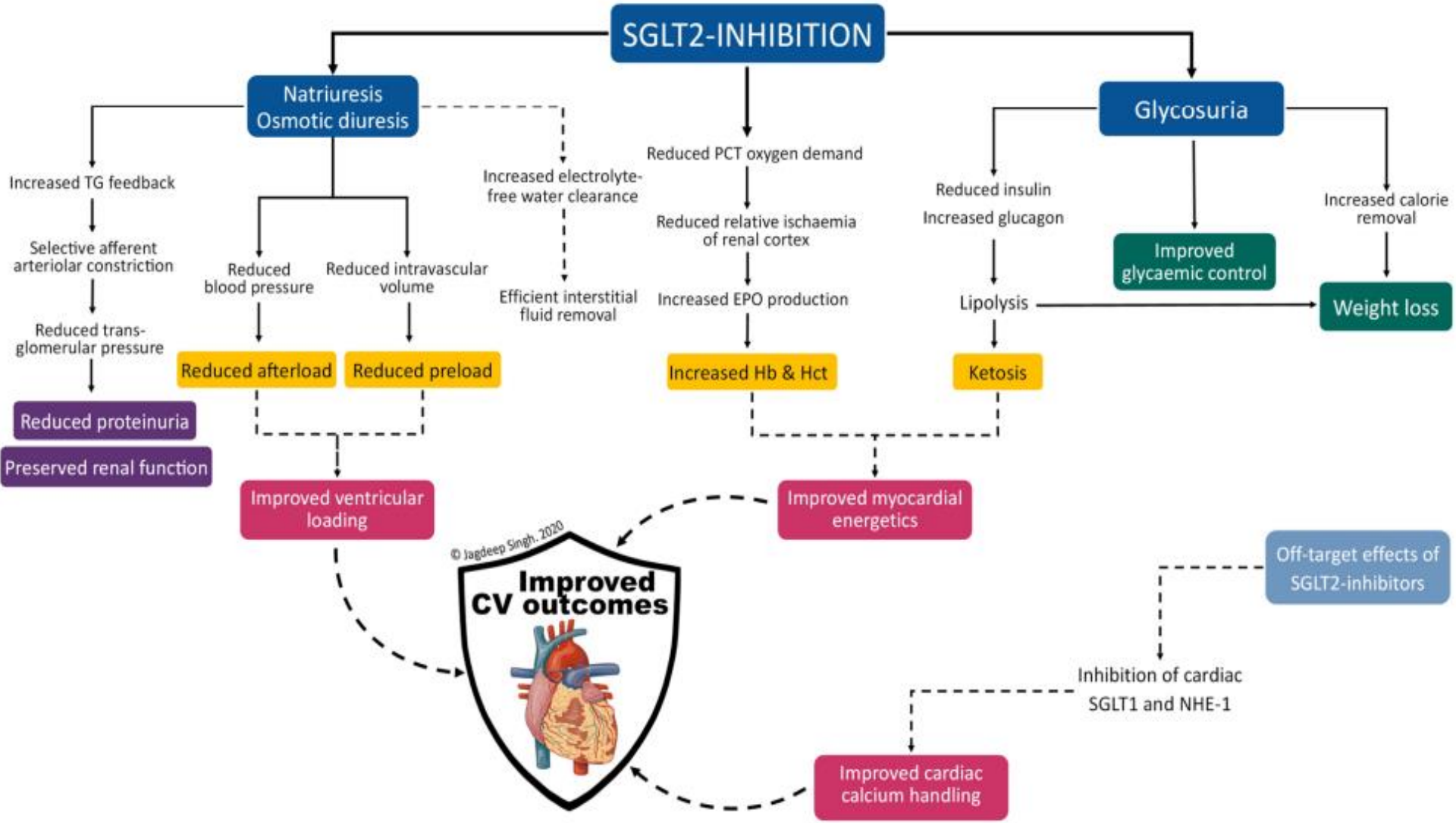
THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

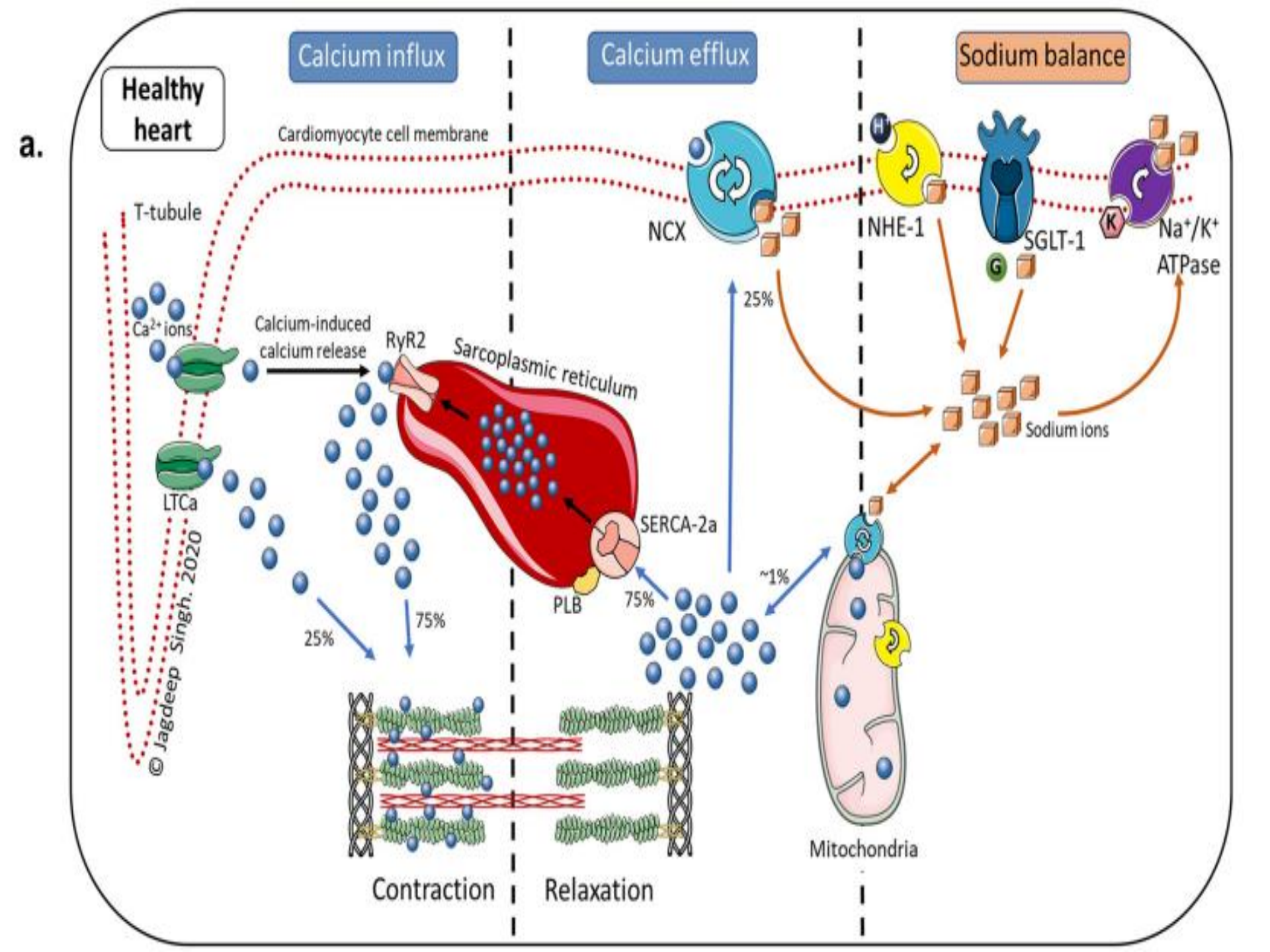
Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors

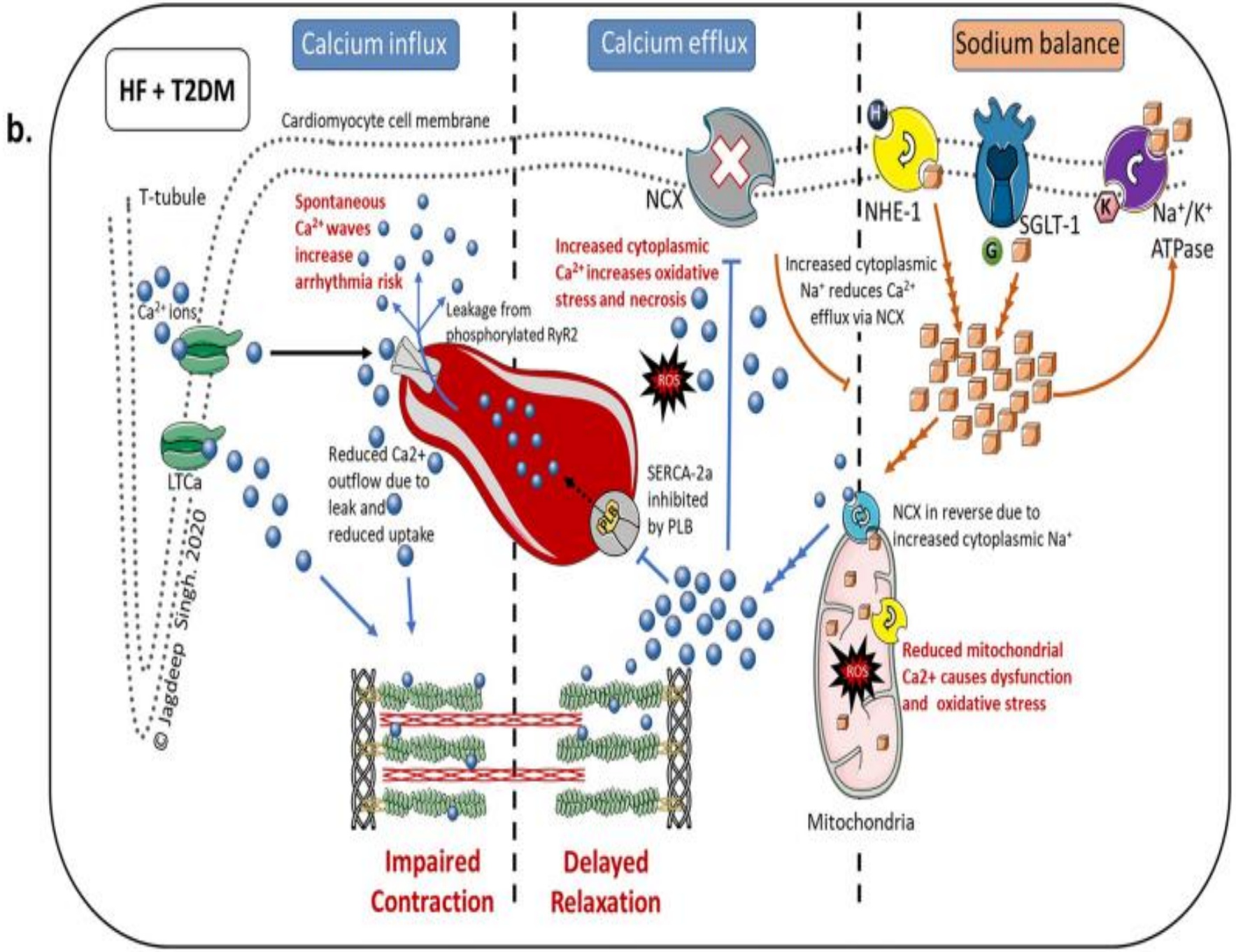
JACC State-of-the-Art Review

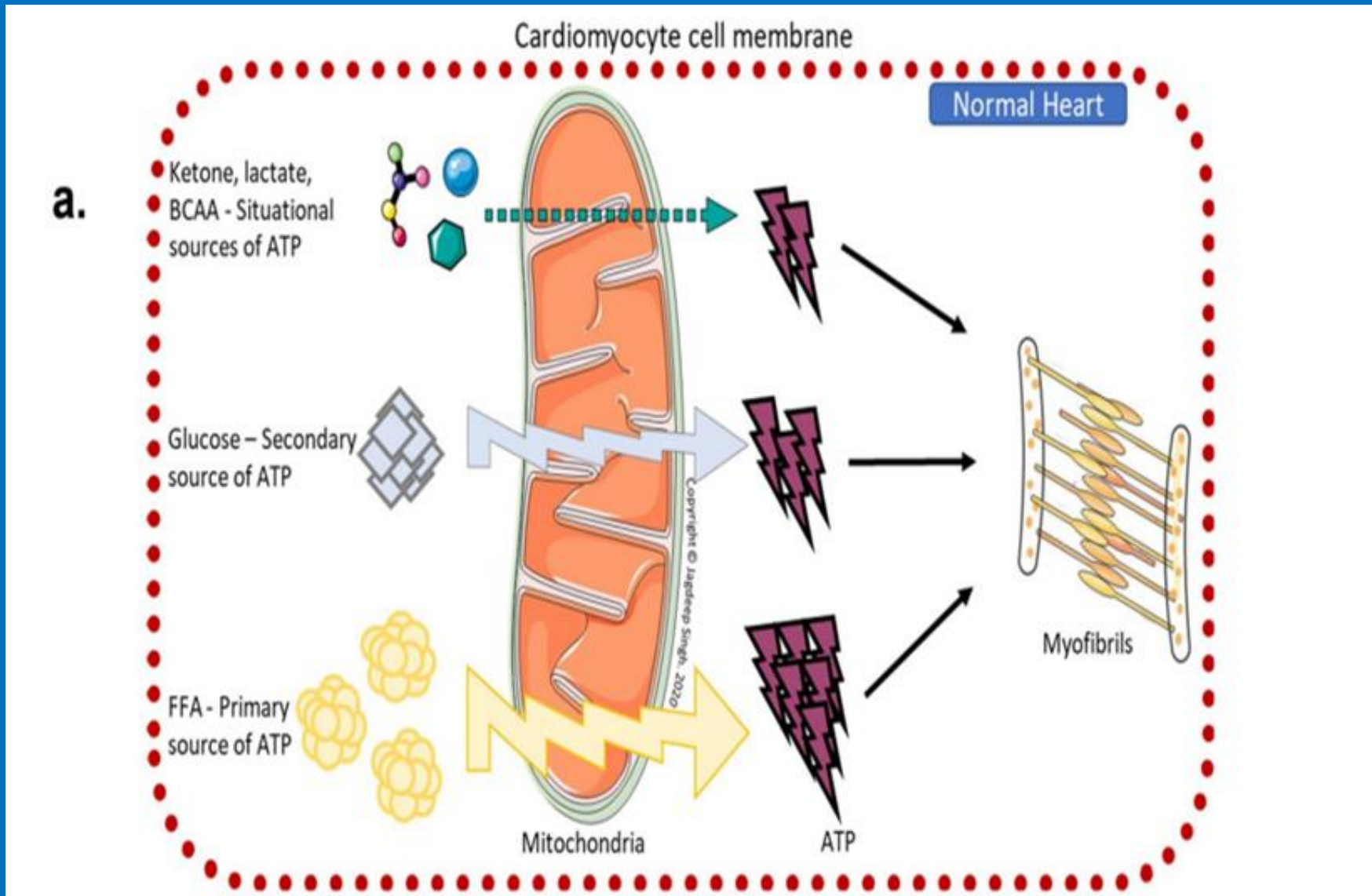
Thomas A. Zelniker, MD, MSc, Eugene Braunwald, MD



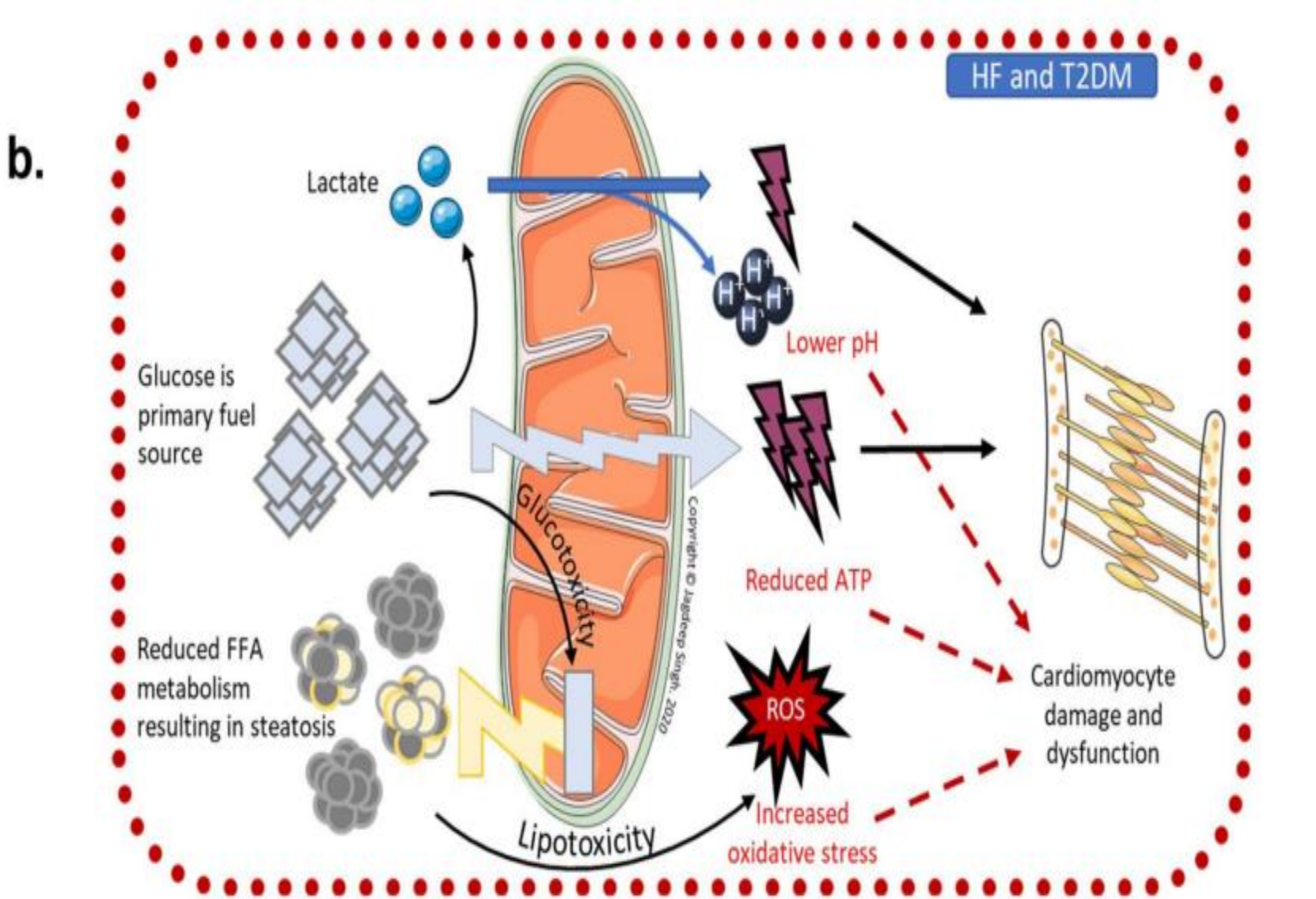
Heart Failure Reviews (2021) 26:623–642


a.
Healthy heart
Calcium influx
Calcium efflux
Sodium balance
Cardiomyocyte cell membrane
T-tubule
NCX
NHE-1
SGLT-1
Na+/K+ ATPase
Ca2+ ions
Calcium-induced calcium release
RyR2
Sarcoplasmic reticulum
LTCa
SERCA-2a
PLB
25%
75%
25%
75%
~1%
Sodium ions
Mitochondria
Contraction
Relaxation
© Jagdeep Singh. 2020

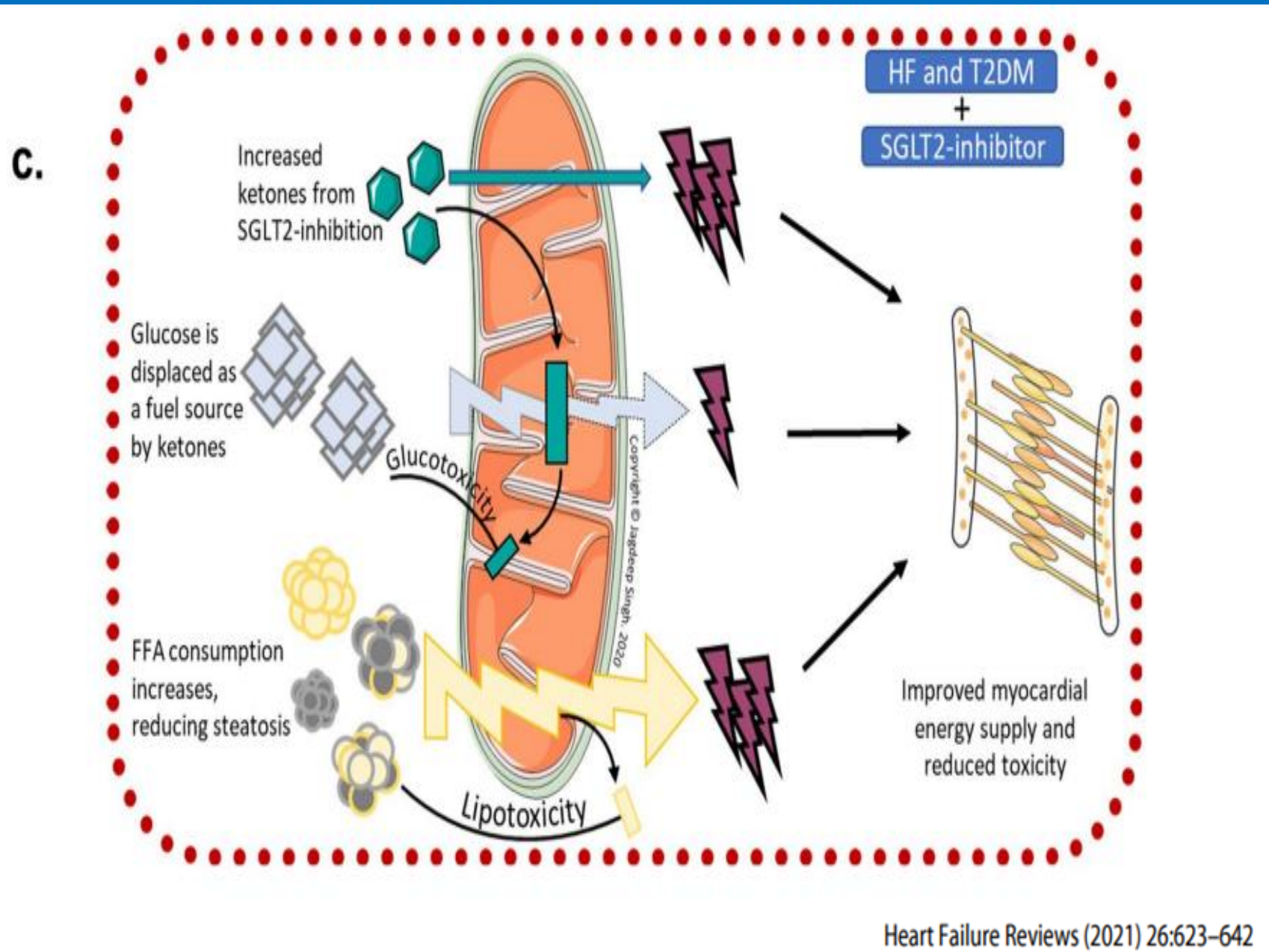

b.
HF + T2DM
Calcium influx
Calcium efflux
Sodium balance
Cardiomyocyte cell membrane
T-tubule
Ca2+ ions
LTCa
Spontaneous Ca2+ waves increase arrhythmia risk
Leakage from phosphorylated RyR2
Reduced Ca2+ outflow due to leak and reduced uptake
Increased cytoplasmic Ca2+ increases oxidative stress and necrosis
ROS
SERCA-2a inhibited by PLB
PLB
NCX
NHE-1
SGLT-1
Na+/K+ ATPase
Increased cytoplasmic Na+ reduces Ca2+ efflux via NCX
NCX in reverse due to increased cytoplasmic Na+
Reduced mitochondrial Ca2+ causes dysfunction and oxidative stress
Mitochondria
Impaired Contraction
Delayed Relaxation
© Jagdeep Singh, 2020



Heart Failure Reviews (2021) 26:623–642

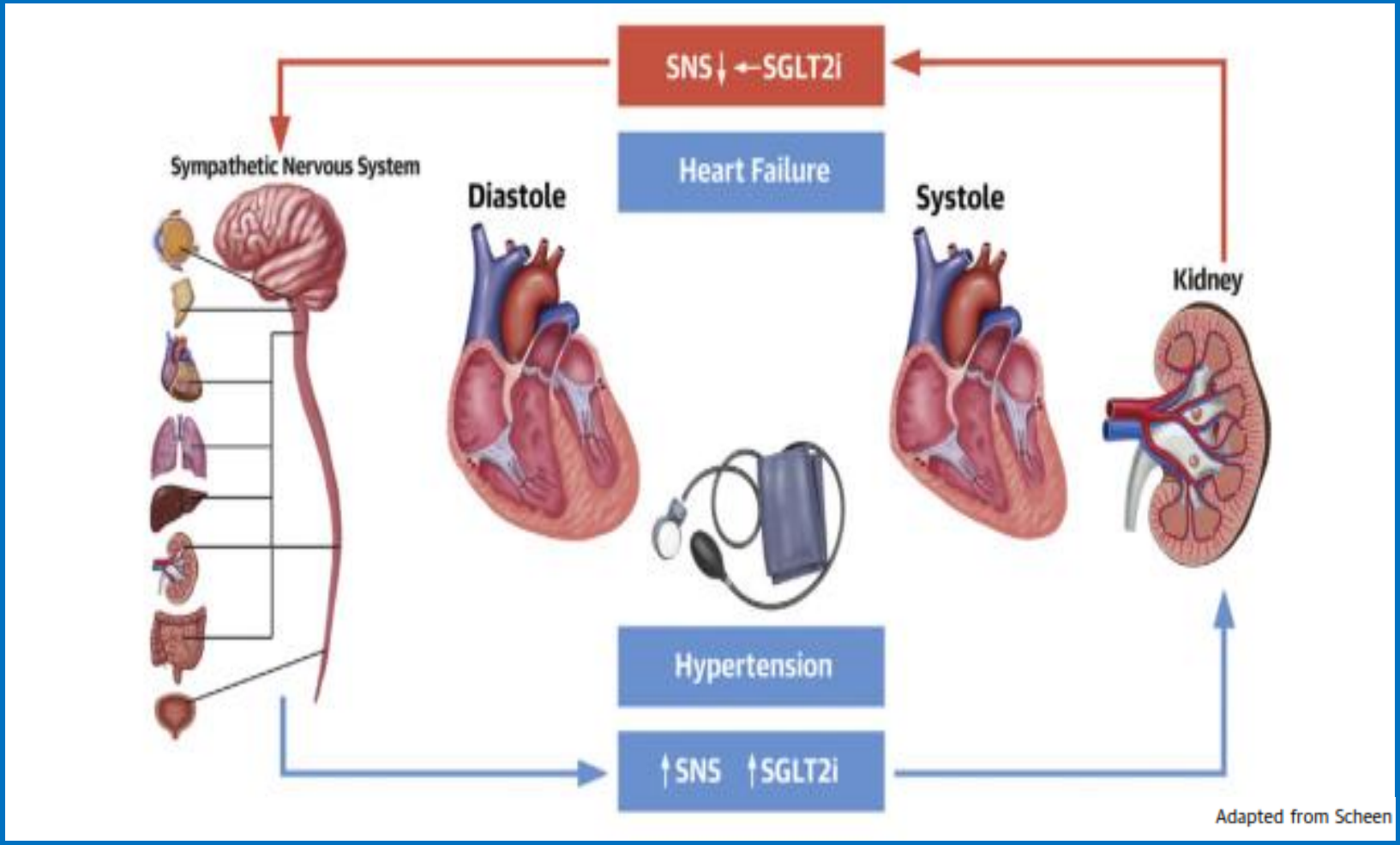


Heart Failure Reviews (2021) 26:623–642

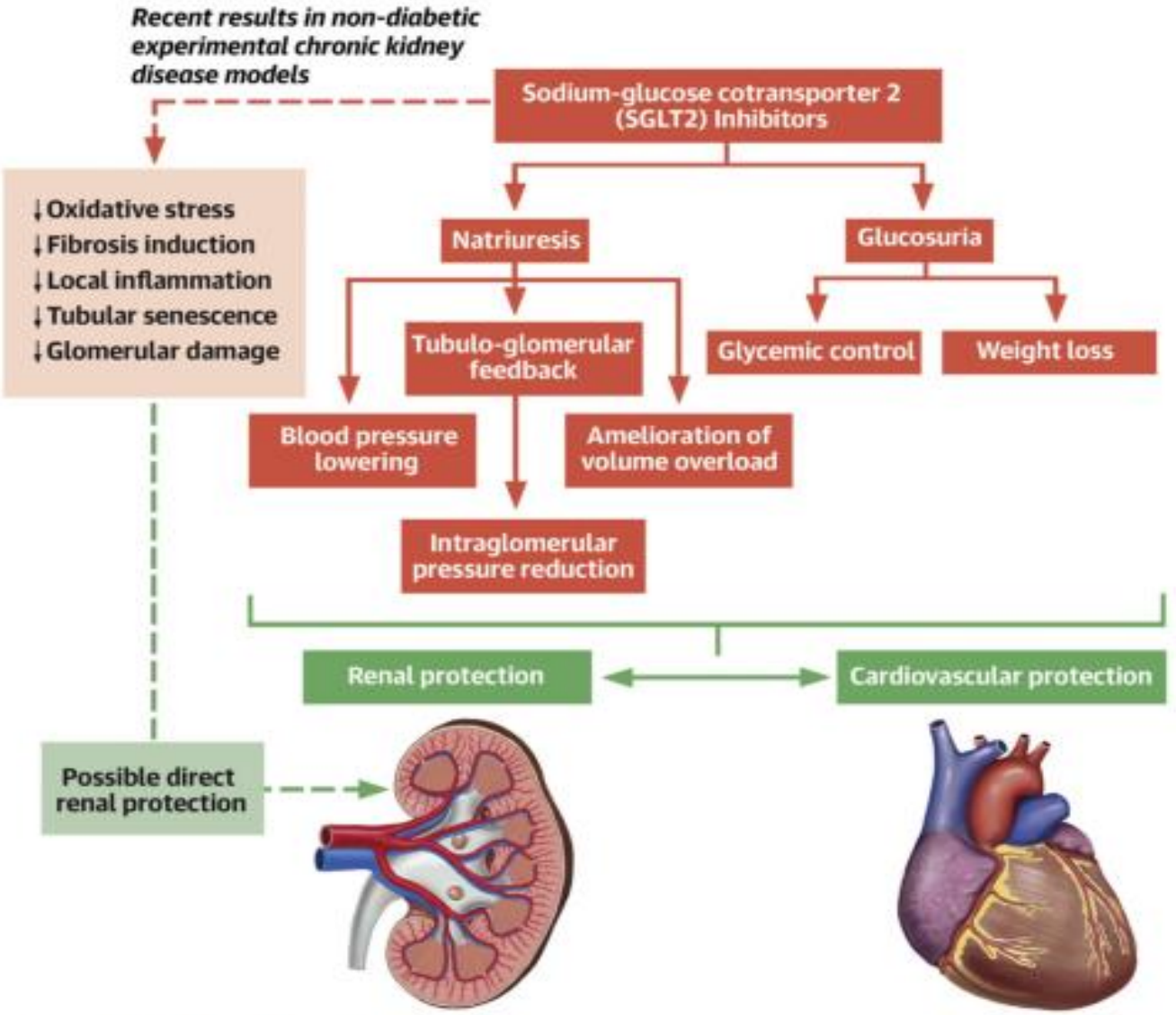


Heart Failure Reviews (2021) 26:623–642

Relationships between SGLT2i and the Sympathetic Nervous System



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



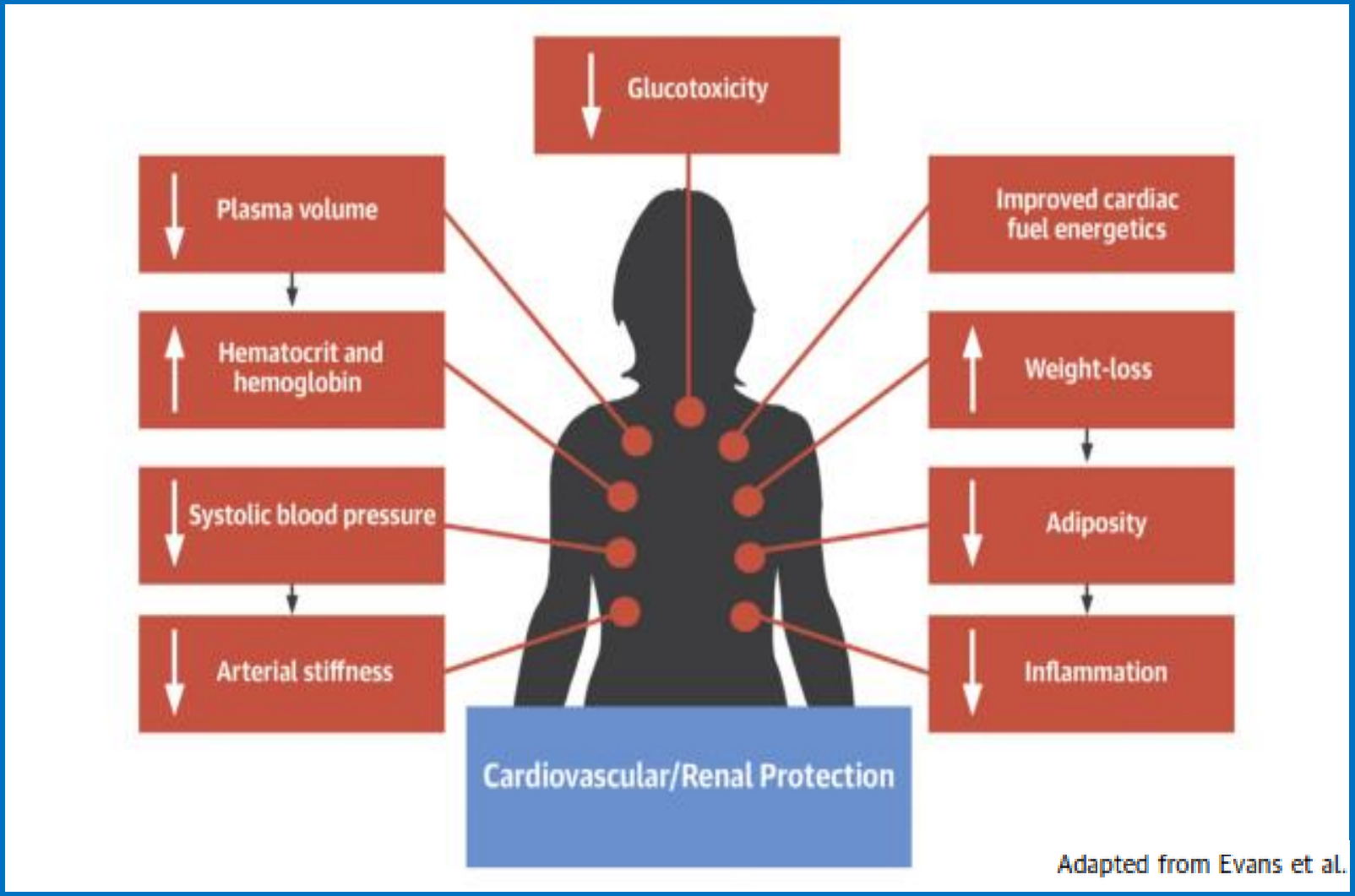
Zelniker, T.A. et al. J Am Coll Cardiol. 2020;75(4):422-34.

Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors

TABLE 3 Overview of Mechanisms of Favorable Cardio-Metabolic-Renal Effects

	Heart Failure	Atherosclerotic Effect	Diabetic Kidney Disease
Glucose lowering			✓
Reduction in body weight	✓	✓	✓
Lowering of blood pressure	✓	✓	✓
Natriuresis	✓		✓
Anti-inflammation	✓	✓	✓
Antifibrotic	✓		✓
Reduction in extracellular matrix turnover	✓		✓
Amelioration of intrarenal hypoxia			✓
Restoration of the tubuloglomerular feedback			✓
Reduction in natriuretic peptides	✓		✓
Reduction in energy demand	✓		✓
Reduction in liver fat		✓	

Suggested Mechanisms for Cardiorenal Protection with SGLT2i



Adapted from Evans et al.

SGLT2i:Mechanistics trials

EASD 2022 STOCKHOLM
58th ANNUAL MEETING
European Association for the Study of Diabetes
19 - 23 September 2022 Stockholm, Sweden
#EASD2022
www.easd.org

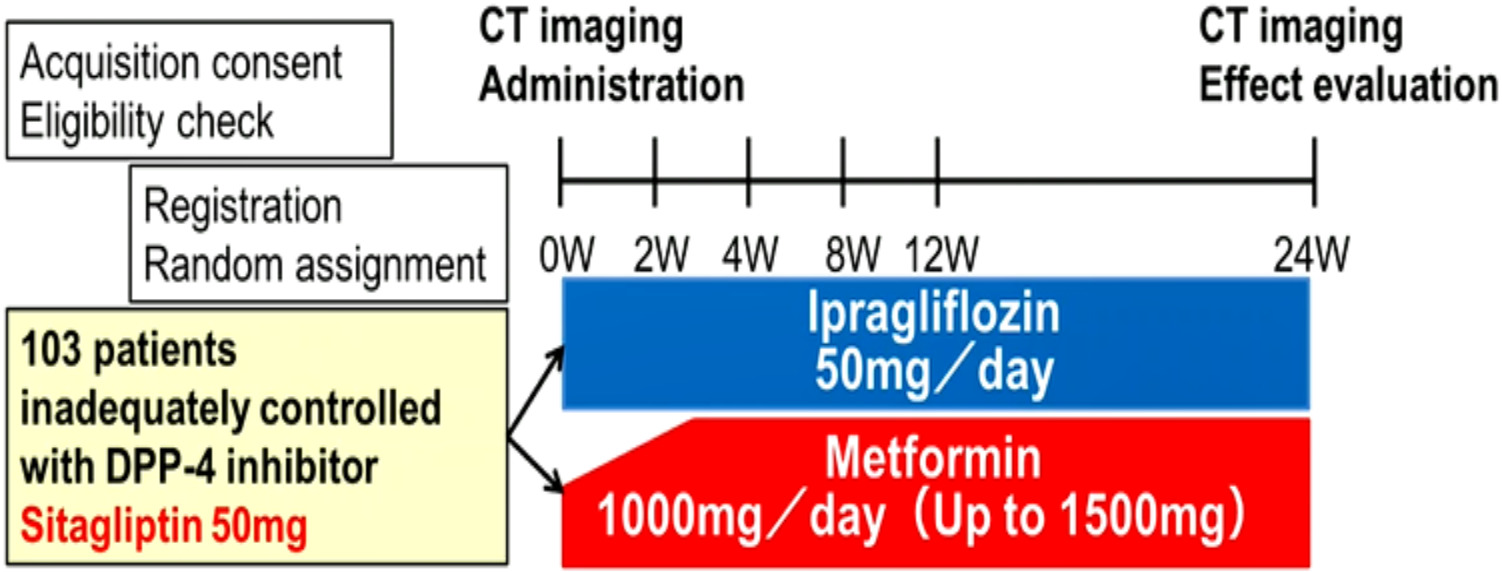
Tuesday Sep 20, 2022 10:00 AM - 11:30AM
Session: OP 02
SGLT2 inhibitors: promiscuous pleiotropy
Presentation number: 9

Metabolome analysis of the effects by SGLT2 inhibitor ipragliflozin and metformin on human metabolites, and relationship with clinical data in a randomized controlled study

Masaya Koshizaka, Ayano Tsukagoshi, Ryoichi Ishibashi, Yoshiro Maezawa, Koutaro Yokote

Department of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, Chiba, Japan

Materials and methods



Study design: a prospective, multicenter, blinded-endpoint, randomized controlled study
Participants: patients with T2DM treated with sitagliptin 50mg daily, HbA1c 7-10% and BMI ≧22 kg/m^2.
Intervention: randomly assigned to ipragliflozin 50mg or metformin 1000-1500mg daily
Primary endpoint: the change of visceral fat area by CT at 24 weeks. Two radiologists, blinded to information, evaluated.
Secondary endpoints: HbA1c, fasting blood glucose, blood pressure, lipid, blood cell counts, bone markers, total and subcutaneous fat area, muscle volume, and bone mineral density measured by CT
Metabolome analysis using blood samples before and 24 weeks after administration was performed to identify changed metabolites.
Trial Registration: UMIN 000015170

Koshizaka M, et al. BMJ Open 2017;7:e015766.
Koshizaka M, et al. Diabetes Obes Metab. 2019; 21: 1990-5.

Results ①

(% change from baseline)	Ipragliflozin n = 15	Metformin n = 15	*P* value
Visceral fat area	-19.8 ± 9.8	-2.5 ± 15.9	0.002
Subcutaneous fat area	-12.1 ± 14.5	3.1 ± 18.5	0.019
Body weight	-4.4 ± 2.8	-1.5 ± 3.7	0.020
BMI	-4.4 ± 2.8	-1.5 ± 3.7	0.020
Abdominal muscle area	-4.1 ± 4.8	-0.6 ± 3.1	0.025
4th lumbar bone concentration	4.5 ± 11.2	-1.4 ± 7.2	0.099
Waist circumference	-4.2 ± 4.1	-1.7 ± 3.0	0.066
HbA1c	-12.8 ± 11.8	-10.3 ± 6.0	0.505
Fasting plasma glucose	-20.8 ± 14.8	-12.9 ± 11.3	0.152
Systolic blood pressure	-4.9 ± 12.9	-0.4 ± 7.9	0.262
Diastolic blood pressure	-9.2 ± 21.5	-0.5 ± 14.4	0.206

Welch t-tests for continuous variables

Mean ± SD

Results ②

(% change from baseline)	Ipragliflozin n = 15	Metformin n = 15	*P* value
Total cholesterol	-1.5 ± 8.4	-7.1 ± 11.7	0.214
HDL cholesterol	8.04 ± 10.5	6.57 ± 22.6	0.822
LDL cholesterol	-1.18 ± 14.0	-14.8 ± 23.7	0.070
Triglyceride	-10.0 ± 25.0	0.87 ± 70.5	0.583
GOT	-22.7 ± 30.5	14.1 ± 56.0	0.081
GPT	**-30.4 ± 26.8**	**7.8 ± 44.3**	**0.030**
γ-GT	**-28.9 ± 15.0**	**-9.6 ± 22.9**	**0.012**
Uric acid	**-11.3 ± 11.1**	**3.0 ± 16.8**	**0.012**
RBC	**7.8 ± 7.0**	**-2.3 ± 4.6**	**<0.001**
Hb	**5.8 ± 6.8**	**-4.3 ± 3.9**	**<0.001**
Ht	**9.9 ± 11.9**	**-2.2 ± 4.0**	**0.002**
BAP	-3.2 ± 36.1	-8.7 ± 20.5	0.620
TRACP-5b	1.7 ± 28.5	9.5 ± 83.6	0.740

Welch t-tests for continuous variables

Mean ± SD

Metabolome analysis results

Compound name	Ipragliflozin-0W vs Metformin-0W		Ipragliflozin-24W vs Ipragliflozin-0W		Metformin-24W vs Metformin-0W		Ipragliflozin-24W vs Metformin-24W	
	Ratio	*p*-value	Ratio	*p*-value	Ratio	*p*-value	Ratio	*p*-value
Methionine	1.4	0.288	0.9	0.625	3.4	0.016	0.3	0.027
Hypotaurine	1.2	0.254	0.8	0.136	1.5	0.030	0.6	0.013
Methyl-2-oxovaleric acid	1.0	0.921	0.9	0.492	2.2	0.030	0.4	0.015
Glutamine	0.9	0.480	1.3	0.068	1.2	0.044	1.0	0.689
Hexic acid (caproic acid)	0.9	0.270	1.2	0.048	0.8	0.040	1.3	0.005
Octanoic acid (caprylic acid)	1.2	0.139	1.0	0.759	0.8	0.006	1.5	<0.001
Citrulline	1.1	0.589	1.0	0.948	0.7	0.003	1.5	0.002
Indole-3-acetaldehyde	0.8	0.150	1.1	0.595	0.7	0.014	1.3	0.238
1-Methyl-4-imidazole acetic acid	0.8	0.203	0.8	0.325	0.6	0.038	1.1	0.763
Inosine	0.4	0.104	2.6	0.029	1.0	0.951	1.0	0.971
N^2-Phenylacetylglutamine	0.8	0.236	1.7	0.004	1.2	0.490	1.2	0.345
8-Hydroxy-2'-deoxyguanosine	0.7	0.076	1.3	0.019	1.3	0.395	0.7	0.301

Red shows significantly increased than baseline.
Green shows significantly decreased than baseline.

Blue shows metabolite in metformin increased than those in ipragliflozin.
Yellow shows metabolite in ipragliflozin increased than those in metformin.

Discussion

- Increased **hexanoic acid (caproic acid)** is a **short-chain fatty acid** and is also used as a ketogenic diet. Short-chain fatty acids affect the composition of the intestinal microbiota and **inhibit fat accumulation**[1,2] .

1) Nogal A, et al. Front Microbiol. 2021;12:711359.
2) Kimura I, et al. Nat Commun. 2013;4:1829.

- **N^2-phenylacetylglutamine**, a metabolite of **phenylalanine** that is involved in **visceral fat reduction**[3,4] , was increased.
  The phenylalanine-N^2-phenylacetylglutamine pathway may have been involved in visceral fat reduction.

3) Sasai H, et al. Diabetes Metab Syndr Obes. 2017; 10: 297-309.
4) Ueda K, et al. Diabetes Metab Syndr Obes. 2018; 11: 23-33.

- **Phenylacetylglutamine** and **3-HBA** are also increased in vegetarian and Mediterranean diets[5-7].

5) O'Sullivan A, et al. Am J Clin Nutr 2011, 93, 314-21.
6) Xu J, et al. Anal Bioanal Chem 2010, 396, 1451-63.
7) Vázquez-Fresno R, et al. J Proteome Res. 2015 Jan 2;14:531-40.

Conclusion

After ipragliflozin administration, N^2-phenylacetylglutamine, metabolite of phenylalanine, increased.

Reportedly, phenylalanine reduces visceral fat.

The patients treated with ipragliflozin may reduce visceral fat by the mechanism of phenylalanine-N^2-phenylacetylglutamine pathway.

Different effects of SGLT-2 inhibitors on subcutaneous and epicardial adipose tissue metabolome in severe heart failure subjects

Kasperová B.J.[1], Mráz M.[1], Kuda O.[4], Čajka T.[4], Hlaváček D.[3], Mahrík J.[3], Laňková I.[1], Štemberková Hubáčková S.[2], Pleyerová I.[2], Rosolová K.[1], Svoboda P.[2], Trnovská J.[2], Ivák P.[3], Melenovský V.[3], Netuka I.[3], Haluzík M.[1]

[1]Diabetes Centre; [2]Experimental Medicine Centre and [3]Cardiac Centre; Institute for Clinical and Experimental Medicine, Prague, Czech Republic

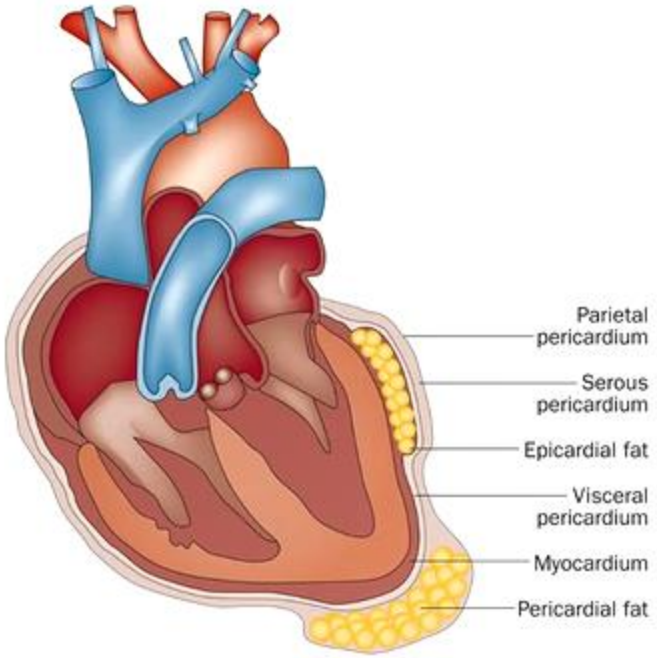
[4]Institute of Physiology; Academy of Sciences of the Czech Republic, Prague, Czech Republic

FYZIOLOGICKÝ ÚSTAV AV ČR

IK+E M

Study aims

To assess the effects of **SGLT2i** on **epicardial adipose tissue** and identify potential **cardioprotective mechanisms** in subjects with **severe heart failure** using **metabolomics** analysis



Methods and baseline characteristics of study subjects

- **Severe heart failure** (NYHA III-IV)
- **Elective cardiac surgery** (mechanical support implantation/heart transplant)
- **Subcutaneous** and **epicardial** adipose tissue + serum/plasma
- **Metabolomic** and **lipidomic** analysis – **HPLC-MS** (high performance liqiud chromatography-mass spectrometry)

2 groups

- **SGLT-2i (dapa-, empagliflozin)**
- **Control** (w/o SGLT2i)

	Control group	SGLT-2i
Number (m/f) (n)	20 (18/2)	21 (19/2)
Age (years)	56.6 ± 1.85	56.86 ±1.90
T2DM (n)	7	15
BMI (kg/m²)	28.01 ± 1.01	28.07 ± 0.93
LV EF (%)	22.75 ± 1.64	20.48 ± 0.54
LVEDd(mm)	68.15 ± 3.27	69.71 ± 2.73
BNP (ng/L)	1496.9 ± 227.3	1206.0 ± 238.6

Data are mean ± SEM.

T2DM – *type 2 diabetes mellitus*
BMI – *body mass index*
LV EF – *left ventricular ejection fraction*
LVEDd - *Left Ventricular End-Diastolic diameter*
BNP –*B natriuretic peptide*

Baseline biochemical parameters

	Control group (n=20)	SGLT-2i (n=21)
hsCRP (mg/L)	7.4 ± 2.9	4.5 ± 1.1
AST (µkat/L)	0.7 ± 0.1	0.7 ± 0.1
ALT (µkat/L)	0.8 ± 0.1	1.4 ± 0.6
Total cholesterol (mmol/L)	3.3 ± 0.3	3.4 ± 0.3
HDL (mmol/L)	0.8 ± 0.1	0.8 ± 0.1
LDL (mmol/L)	2.0 ± 0.2	1.8 ± 0.2
Triglycerides (mmol/L)	1.1 ± 0.08	1.7 ± 0.2
Fasting blood glucose (mmol/L)	6.4 ± 0.6	7.6 ± 0.6
HbA_{1c} (mmol/mol)	**43.5 ± 1.4**	**53.9 ± 3.3***
Non-esterified fatty acids (mmol/L)	**0.8 ± 0.1**	**1.3 ± 0.1***

Data are mean ± SEM. $p<0.05$: *vs. Control group.

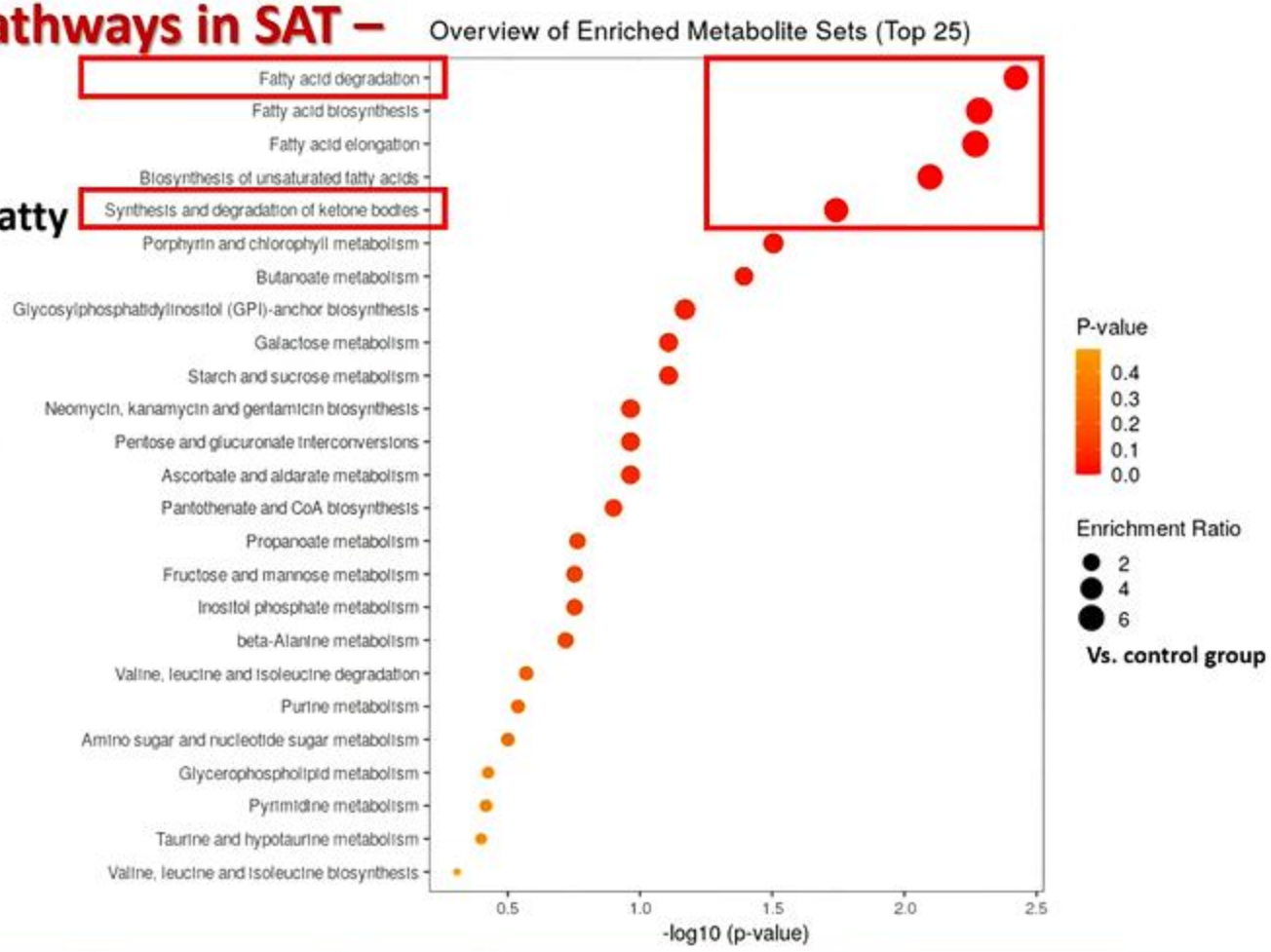
Serum adipokines and inflammatory factors

	Control group (n=20)	SGLT-2i (n=21)
Leptin (mg/L)	15.1 ± 5.1	15.7 ±4.3
FABP3 (ng/mL)	6.4 ± 1.8	5.6 ± 0.7
TNFα (pg/mL)	10.4 ± 1.5	8.3 ± 1.6
INFγ (pg/mL)	26.0 ± 5.0	20.4 ± 2.5
IL6 (pg/mL)	4.4 ± 2.5	2.3 ± 0.6
IL8 (pg/mL)	7.9 ± 2.2	5.7 ± 1.8
IL10 (pg/mL)	16.3 ± 2.1	14.7 ± 1.7
Fractalkine (pg/mL)	252.8 ± 32.0	245.6 ± 27.0

Data are mean ± SEM.
FABP – *fatty acid-binding protein*

Lipid metabolic pathways in SAT – effect of SGLT2i

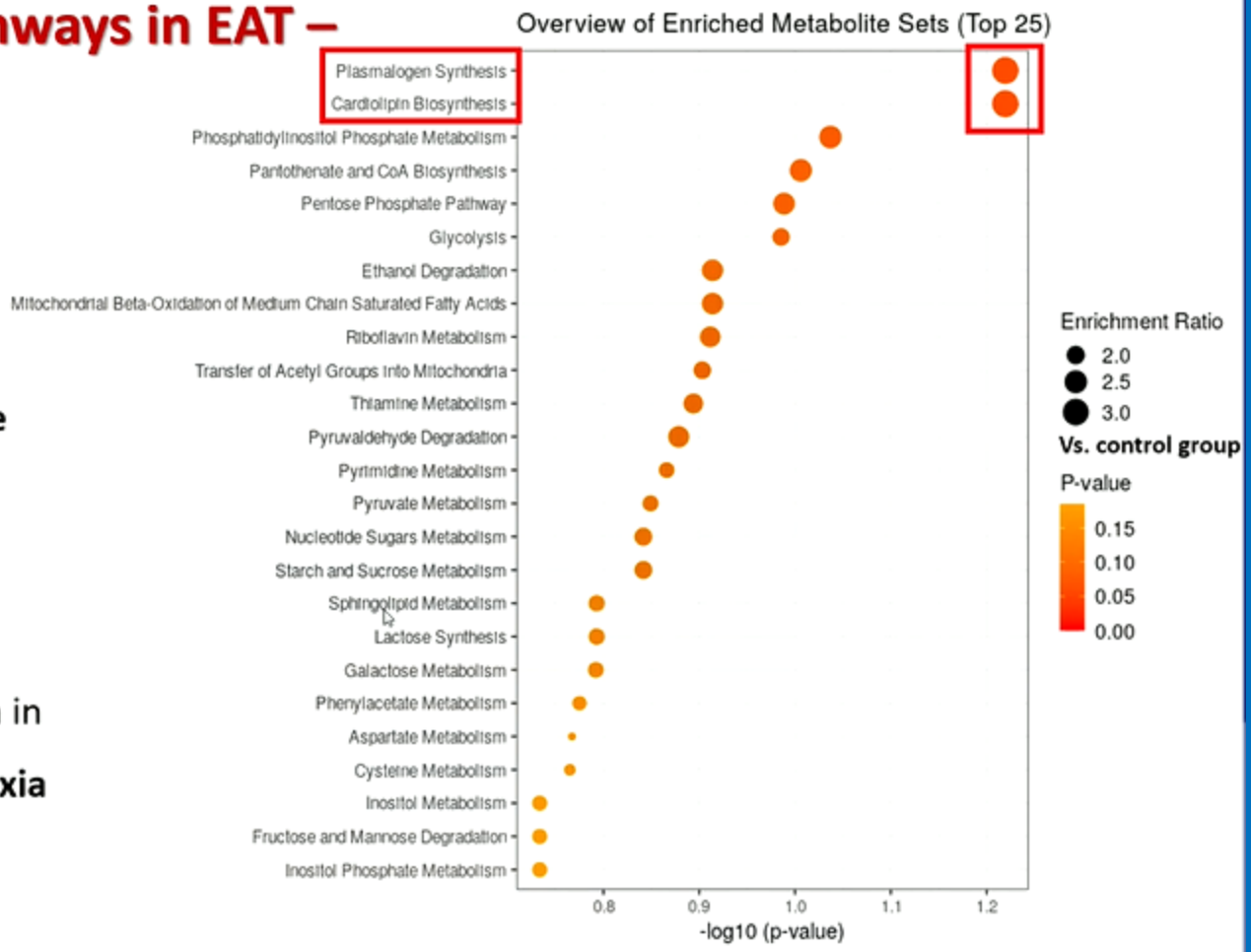
- Active degradation of **fatty acids** (FA)
- Increased **ketogenesis**



Lipid metabolic pathways in EAT – effect of SGLT2i

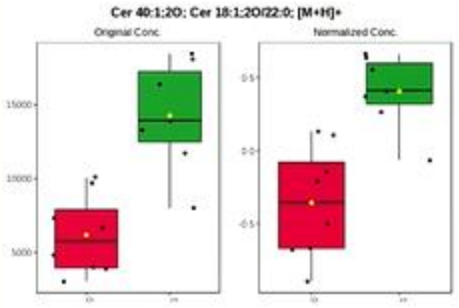
- **Synthesis** of **plasmalogens**
- subgroup of ether **glycerolphospholipids**
- protection against **oxidative stress**

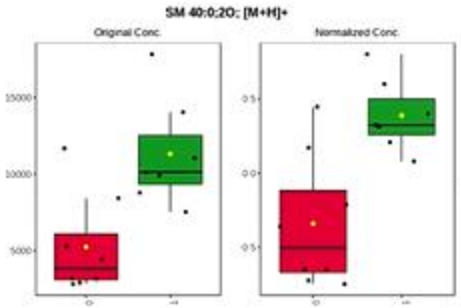
- **Cardiolipin biosynthesis**
- ↑ mitochondrial cardiolipin in subjects with **cardial cachexia**
- triggers **apoptosis**



Comparison of metabolites in EAT – effect of SGLT2i

- Increased amount of **ceramides** and **sphingomyelins** in EAT of SGLT-2i group





p<0.05 vs. Control group

Change in metabolites in EAT of SGLT-2i subjects (relative to control group)

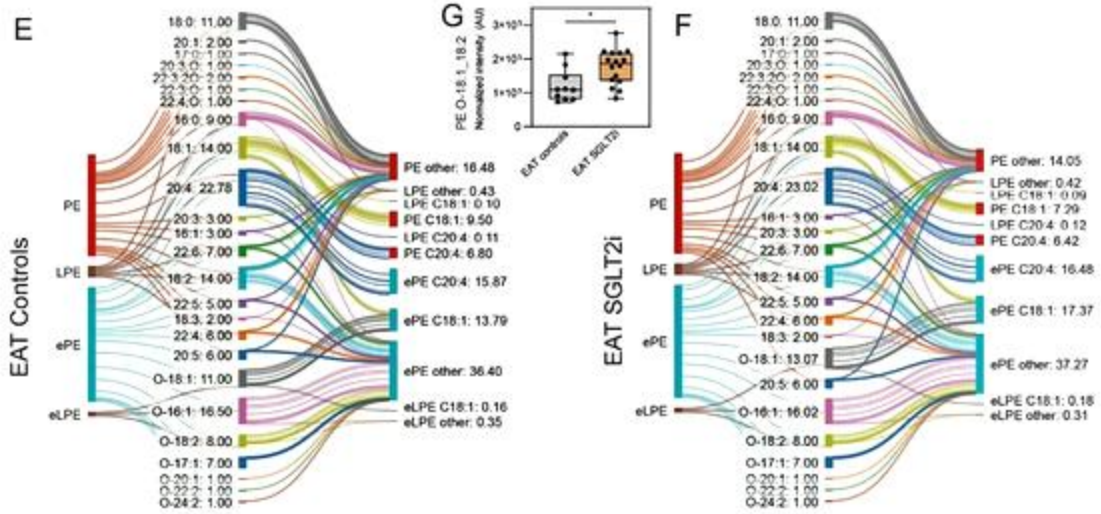
Ceramides

Sphingomyelins

SGLT2i promote lipid remodeling in EAT

- Changes in **ether lipid** species
- Changes in **carbon chains** with **18 carbon atoms**
- **Phosphatidylethanolamines** (PEs)

- increase in **etherPEs** and reduction in **acylPEs** ⇒ **anti-ferroptotic shift**

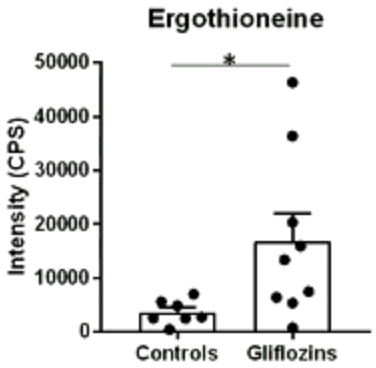


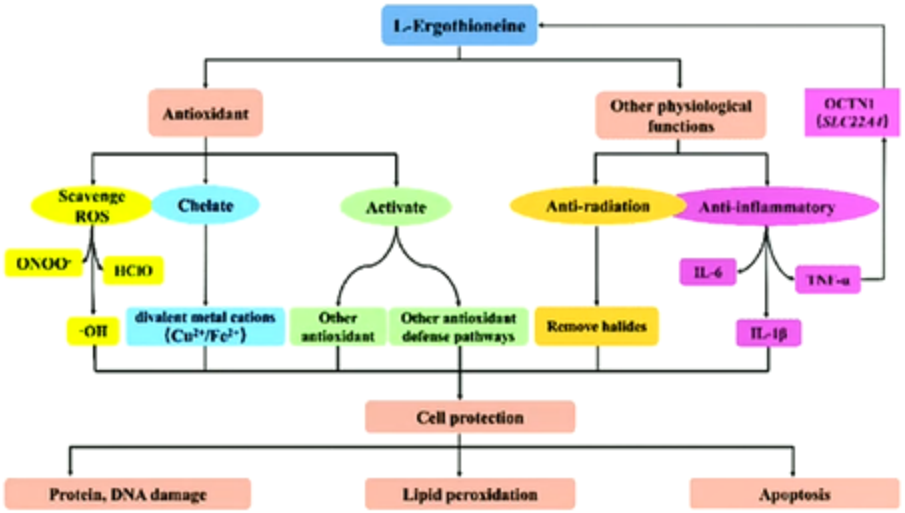
Sankey diagram of PE, lysoPE (LPE), and etherPE (ePE): Left part – species counts, center part – carbon chains (#carbons : #double bonds), right part – lipid sub-classes

Potential cardioprotective factors in SAT

- **Ergothioneine**

- **Antioxidant** with potential therapeutic implications
- Associated with significant reduction of risk of **coronary artery disease**
- Reduces **proinflammatory markers**





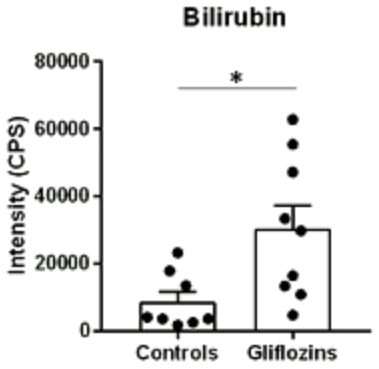
Tong-tong Fu and Liang Shen, *Fronties in Pharmacology, 2022*

Potential cardioprotective factors in SAT

- **Bilirubin**

- Mimics **cytoprotective efects** of hemoxygenase-1 under stress conditions
- High serum bilirubin → increased **antioxidant capacity** a protection against **ROS** (reactive oxygen species)

Serum levels	Control group (n=20)	SGLT-2i (n=21)
Bilirubin (µmol/L)	23.5 ± 3.3	25.4 ±3.8



Conclusion

- **SGLT2i** significantly influence **metabolome** in **subcutaneous** and **epicardial adipose tissue** in subjects with **severe heart failure**
- Effect of SGLT2i on **SAT** and **EAT** largely **differs** – **lipolysis** and **ketogenesis** vs. ↑ **phospho-** and **sphingolipids**
- Role of increased **plasmalogens, sphingolipids** and **lipid remodeling** in EAT unclear – activation of **apoptosis** and **autophagy (⇒ improved senescence)?**

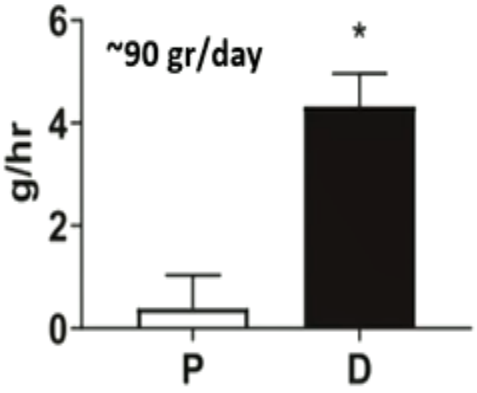
Effect of SGLT2 inhibitor dapagliflozin on skeletal muscle fatty acid metabolism in patients with type 2 diabetes

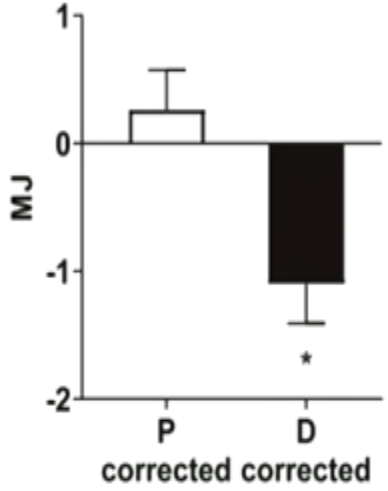
Anne Gemmink

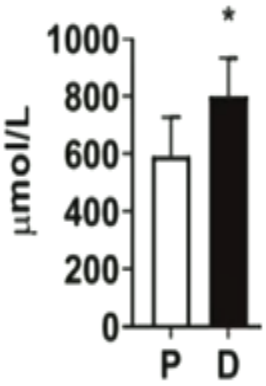
EASD, September 20th 2022

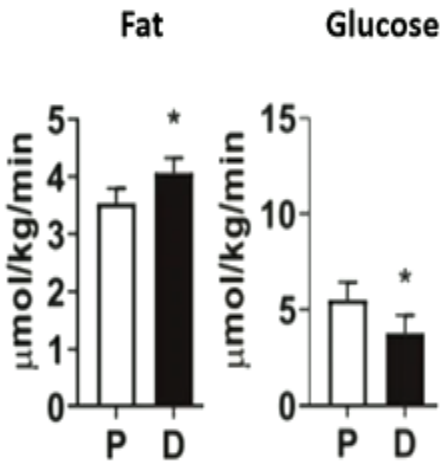
Maastricht University | Maastricht UMC+

Dapagliflozin induces calorie restriction-like effects









op den Kamp et al. 2021 Diabetes Care

Aim

Examine whether SGLT2 inhibition induces calorie restriction-like effects and improves mitochondrial function and fatty acid metabolism in skeletal muscle

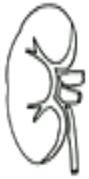
Participants

Type 2 diabetes (m/f)

HbA_{1C} 42-75 mmol/mmol
6-9%

40-70 years

Stable dose of metformin or DPP-4, or be drug naïve

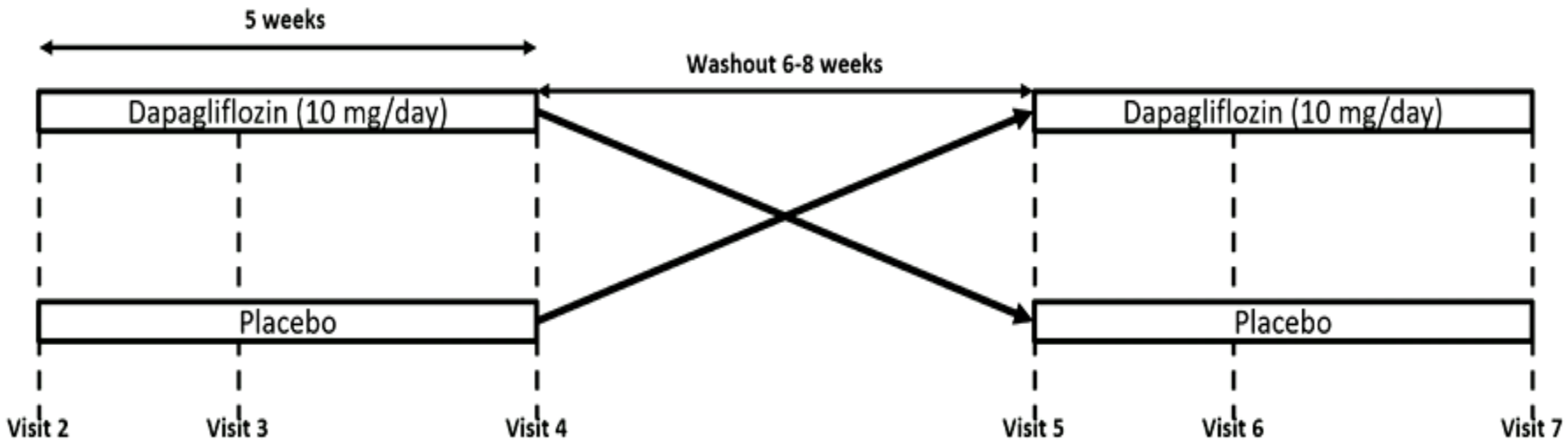


Exclusion
Renal dysfunction

≤38 kg/m^2

Stable weight

Study design



Visit 2 or 5: measurements safety markers

Visit 3 or 6: safety visit

Visit 4 or 7:

- **Muscle biopsy**
- Hyperinsulinemic euglycemic clamp
- **MRS**
- Body composition
- Respiration chamber

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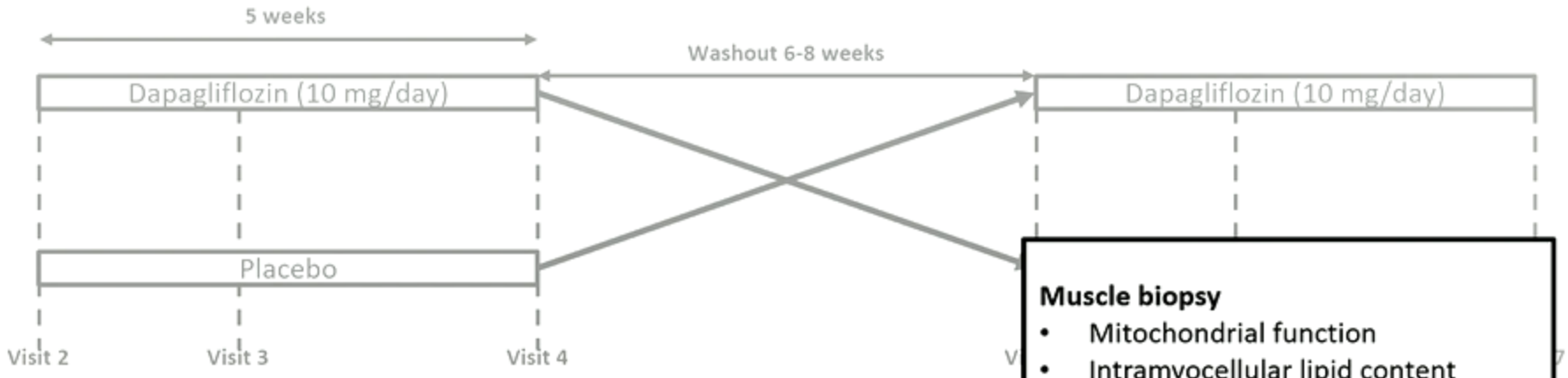
Study design



Visit 2 or 5: measurements safety markers

Visit 3 or 6: safety visit

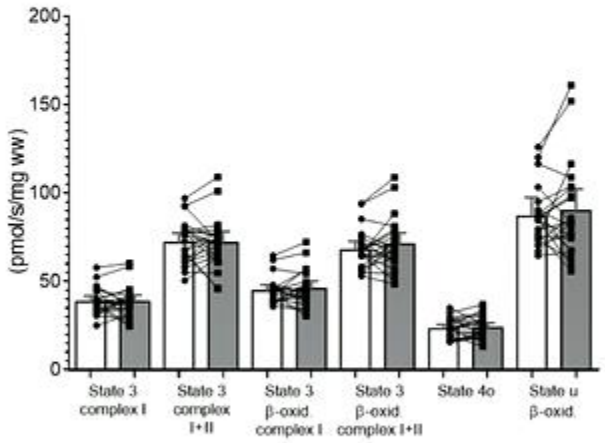
Visit 4 or 7:
- **Muscle biopsy**
- Hyperinsulinemic euglycemic clamp
- **MRS**
- Body composition
- Respiration chamber

Muscle biopsy
- Mitochondrial function
- Intramyocellular lipid content
- Metabolomics
- Gene expression
- CrAT activity

MRS
- Intramyocellular lipid content

5 weeks of dapagliflozin does not affect mitochondrial function

1. Mitochondrial respiration



5 weeks of dapagliflozin does not affect mitochondrial function

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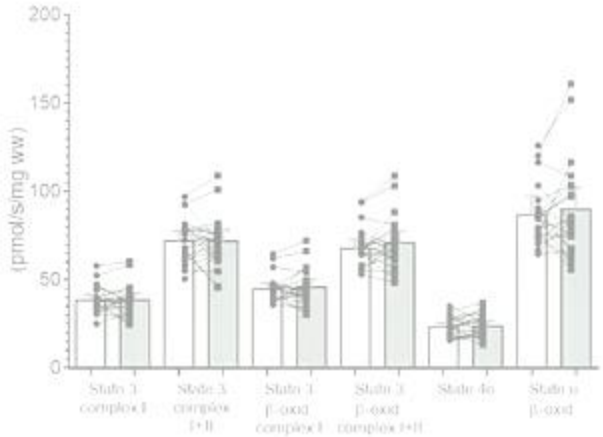
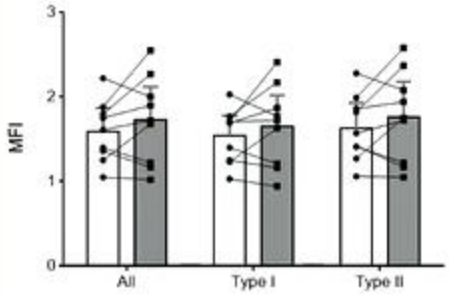
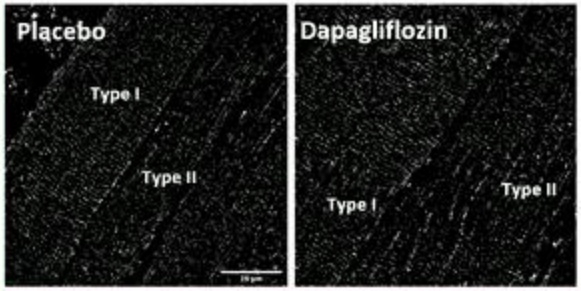


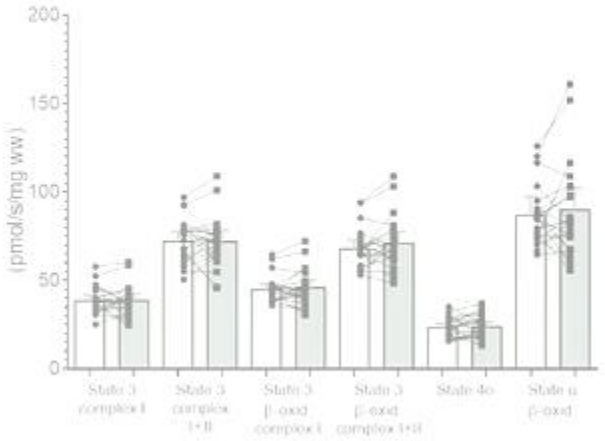
2. Mitochondrial network integrity





5 weeks of dapagliflozin does not affect mitochondrial function

1. Mitochondrial respiration



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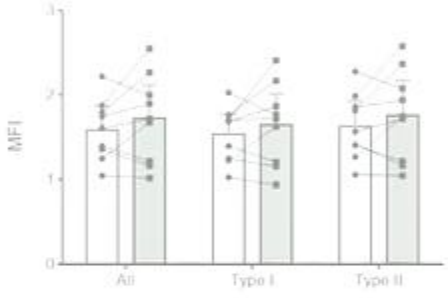
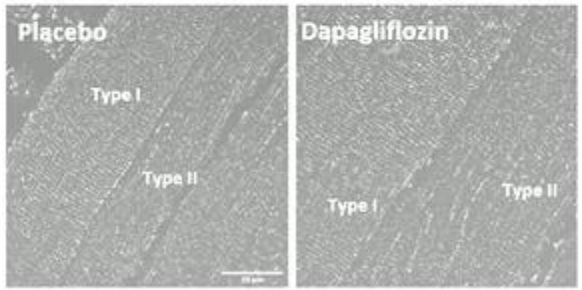
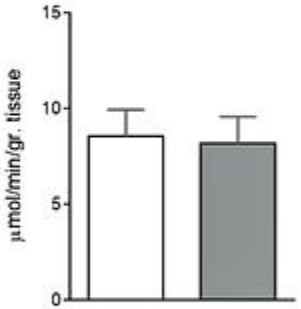




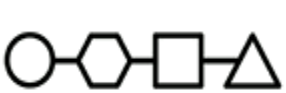
3. Citrate synthase activity



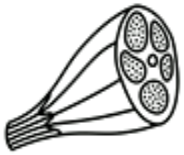
5 weeks of dapagliflozin…

1. Mitochondrial function ↔

3. Long-chain acylcarnitines ↑



5. Amino acids ↓



2. Intramyocellular lipids

4. FA oxidation ↑

6. TCA cycle intermediates ↓

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Conclusion

Dapagliflozin treatment for 5 weeks resulted in changes in skeletal muscle cellular metabolism resembling a state of calorie restriction

Five weeks of dapagliflozin treatment resulted in changes in skeletal muscle favoring the metabolism of fatty acids and moving away from glycolytic flux

Dapagliflozin reduced amino acid levels, which may indicate mobilization of muscle-derived amino acids for hepatic gluconeogenesis

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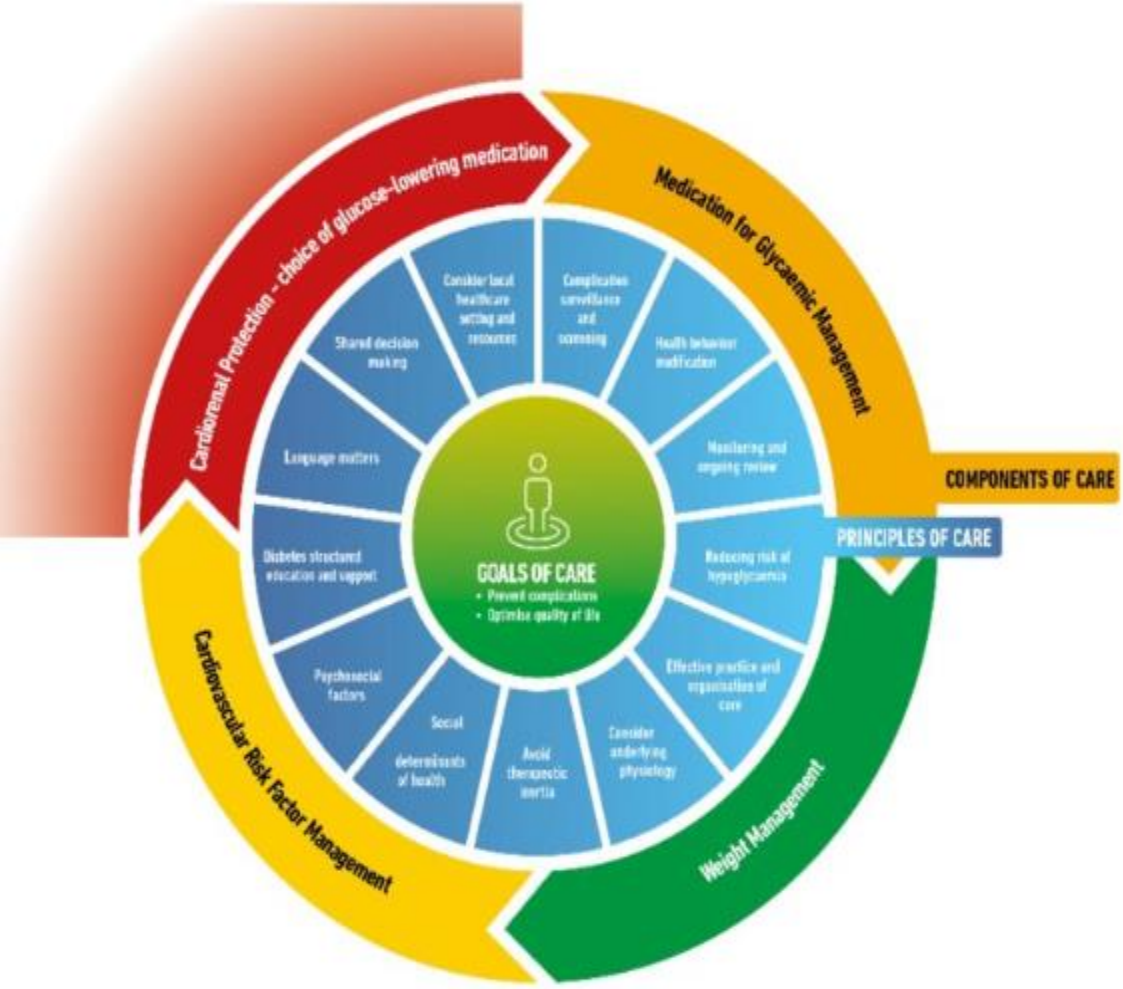
Cardiorenal protection-choice of glucose-lowering medications

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+HF

SGLT2i with proven HF benefit in this population

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144-74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium–Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

American Diabetes Association

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2

EASD European Association

Choosing glucose-lowering medication in people with heart failure

In people with heart failure SGLT2i should be used because they improve heart failure and kidney outcomes.

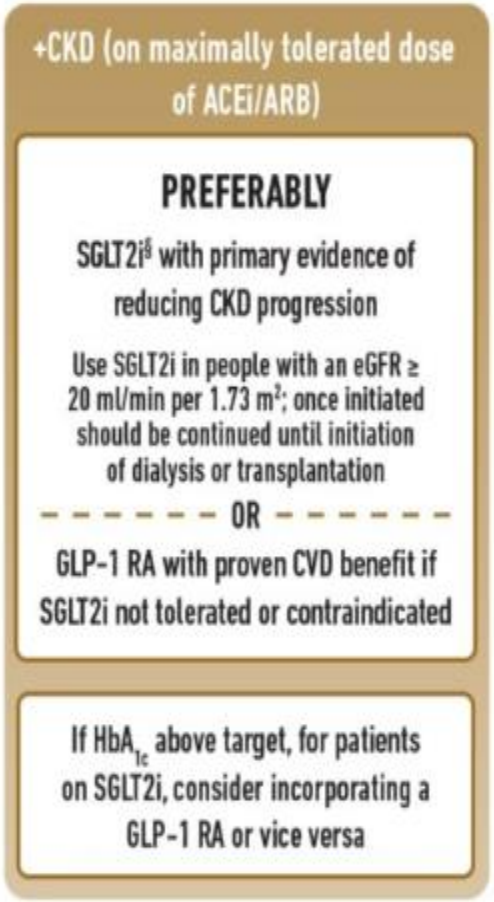
American Diabetes Association.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-[illegible]

EASD European Association for the Study of Diabetes

Choosing glucose-lowering medication in people with chronic kidney disease



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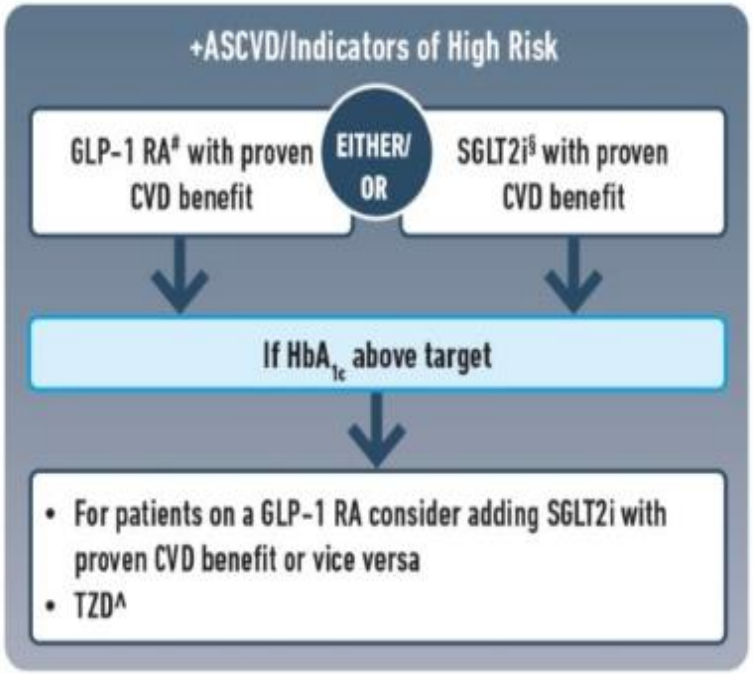
American Diabetes Association.

EASD European Association for the Study of Diabetes

Choosing glucose-lowering medication in people with CVD



ASCVD = atherosclerotic cardiovascular disease

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

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American Diabetes Association.

EASD European Association for the Study of Diabetes

Conclusion

- SGLT2-inhibitors have demonstrated great promise in the prevention and treatment of HF and CKD.
- Beyond its initial intended use as a diabetes drug and with a clearer understanding of these molecular mechanisms, we will be able to fully harness its true potential and perhaps even pave the way for a new era of molecular therapeutic agents in this against HF and CKD.

Merci de votre attention