Empagliflozin as One of the Solutions For Diabetes Dilemma?

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Diabetes is a rising global pandemic

IDF Diabetes Atlas

10th edition

2021

atlas@idf.org | www.diabetesatlas.or

PREVALENCE

World wide 2021 ⬆ 46%

2045 ⬆

537---783 millons

Middle east 87%

Diabetes is a growing challenge in Egypt

15.2% of adult population are diabetics

2021

10.9 million

PEOPLE WITH DIABE

2045

20 million

PEOPLE WITH DIABETES

2021

10th

HIGHEST NUMBER OF DIABETICS

2045

9th

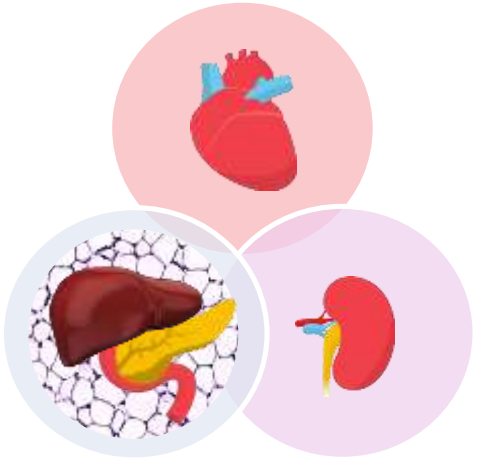
HIGHEST NUMBER OF DIABETICS

Williams, Rhys & Colagiuri, Stephen & Chan, Juliana & Gregg, Edward & Ke, Calvin & Lim, Lee-Ling & Yang, Xilin. (2019). IDF Atlas 9th Edition 2019

What is the CRM system interrelation ??

The cardio-renal-metabolic (CRM) systems are interrelated

The heart is the most "metabolically demanding" organ, susceptible to changes in volume and metabolism[1,2]



Regulation of energy metabolism by liver, pancreas and fat is essential for healthy function of organs, especially the heart and kidneys[1–4]

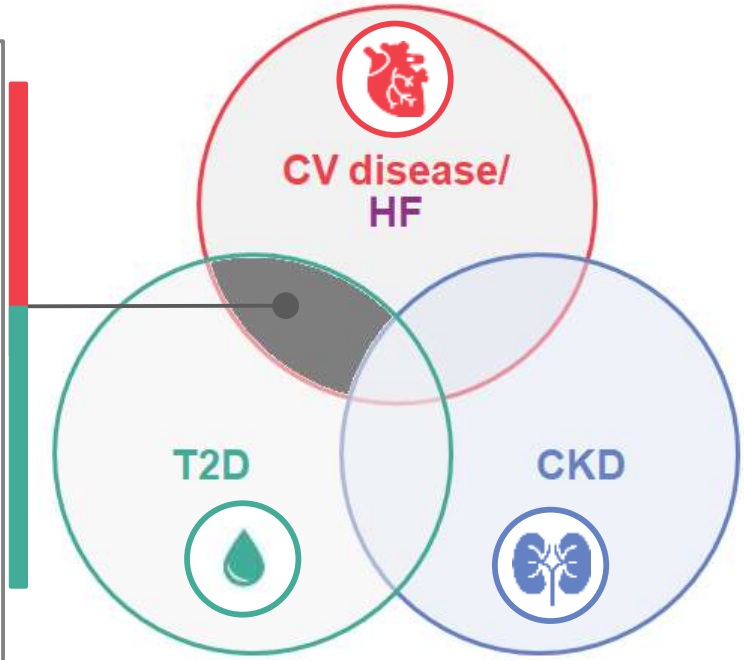
The kidneys play a key role in glucose and volume homeostasis, and blood pressure regulation[5,6]

CRM, cardio-renal-metabolic

1. Lopashuk GD & Ussher JR. *Circ Res* 2016;119:1173; 2. Song MK *et al. J Diabetes Res.*2014;2014:e313718. 3. Connell AW *et al. J Am Soc Hypertens* 2014;8:604; 4. de Boer IH & Utzschneider KM. *Nephrol Dial Transplant* 2017;32:588; 5. García-Donaire JA & Ruilope LM. *Int J Nephrol* 2011;2011:975782; 6. Alsahli M & Gerich JE *Diabetes Res Clin Pract* 2017;133:1

Patients with T2D are at increased risk of complications such as CV disease and HF

- Approximately **one in three** patients with T2D has **CV disease**[1]
- There is a **2- to 5-fold increased risk of HHF*** in patients with T2D†[2]
- **CV** disease is the **leading cause of mortality** in patients with T2D[3,4]

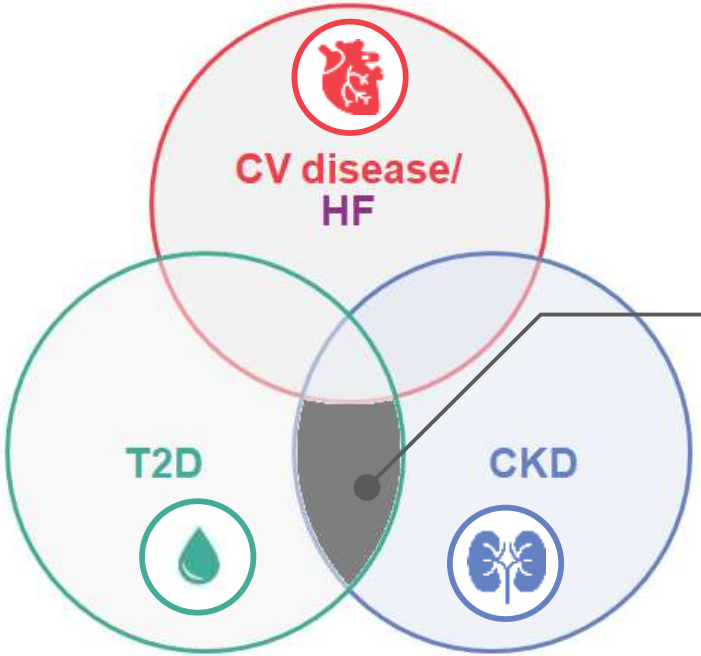


T2D

*Versus those without T2D; †Patients with T2D aged <55 years
HHF, hospitalisation for heart failure

1. International Diabetes Foundation. Diabetes Atlas 9th Edition. http://www.diabetesatlas.org (accessed June 2020); 2. Rosengren A *et al. Diabetologia* 2018;61:2300; 3. Morrish NJ *et al. Diabetologia* 2001;44(Suppl. 2):S14; 4. Davies MJ *et al. Diabetes Care* 2018;41:2669

Patients with T2D are at increased risk of complications such as CKD



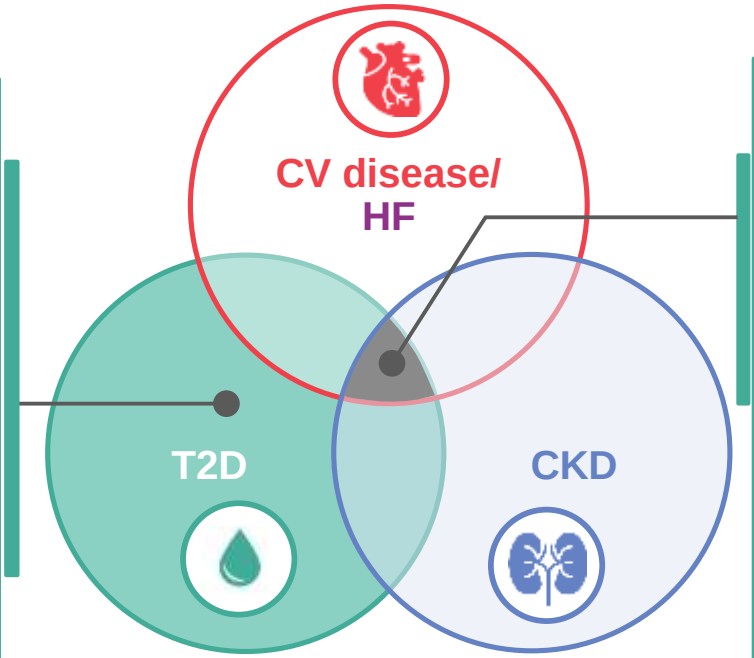
- *CKD affects up to **40%** of patients with T2D[1,2]*
- ***Diabetes and/or hypertension** is the cause of **>80%** of **ESKD** cases worldwide[1]*
- ***Life expectancy** is reduced in patients with T2D and early CKD **by 16 years – 10** more years than CKD alone*[*3]*

*Average of men/women and compared with those without diabetes or CKD
ESKD, end-stage kidney disease

1. International Diabetes Foundation. Diabetes Atlas 9th Edition. http://www.diabetesatlas.org (accessed June 2020);
2. Umanath K & Lewis JB. *Am J Kidney Dis* 2018;71:884. 3. Wen C *et al. Kidney Int* 2017;92:388

Patients with T2D have multiple risk factors that contribute to CRM diseases

- **~55%** of patients with T2D have **NAFLD**[1]
- **Over half** of patients with T2D are reported to be **obese**[2]



- T2D reduces **life expectancy** by ~6 years*[3]

T2D further reduces life expectancy in patients with cardio–renal comorbidities[3,4]

*Average for men and women aged 60 years
CRM, cardio-renal-metabolic; NAFLD, non-alcoholic fatty liver disease
1. Younossi ZM *et al. J Hepatology* 2019;71:793; 2. Masmiquel L *et al. Cardiovasc Diabetol* 2016;15:29; 3. The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52; 4. Wen C *et al. Kidney Int* 2017;92:388

CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause.(2008 to 2030)

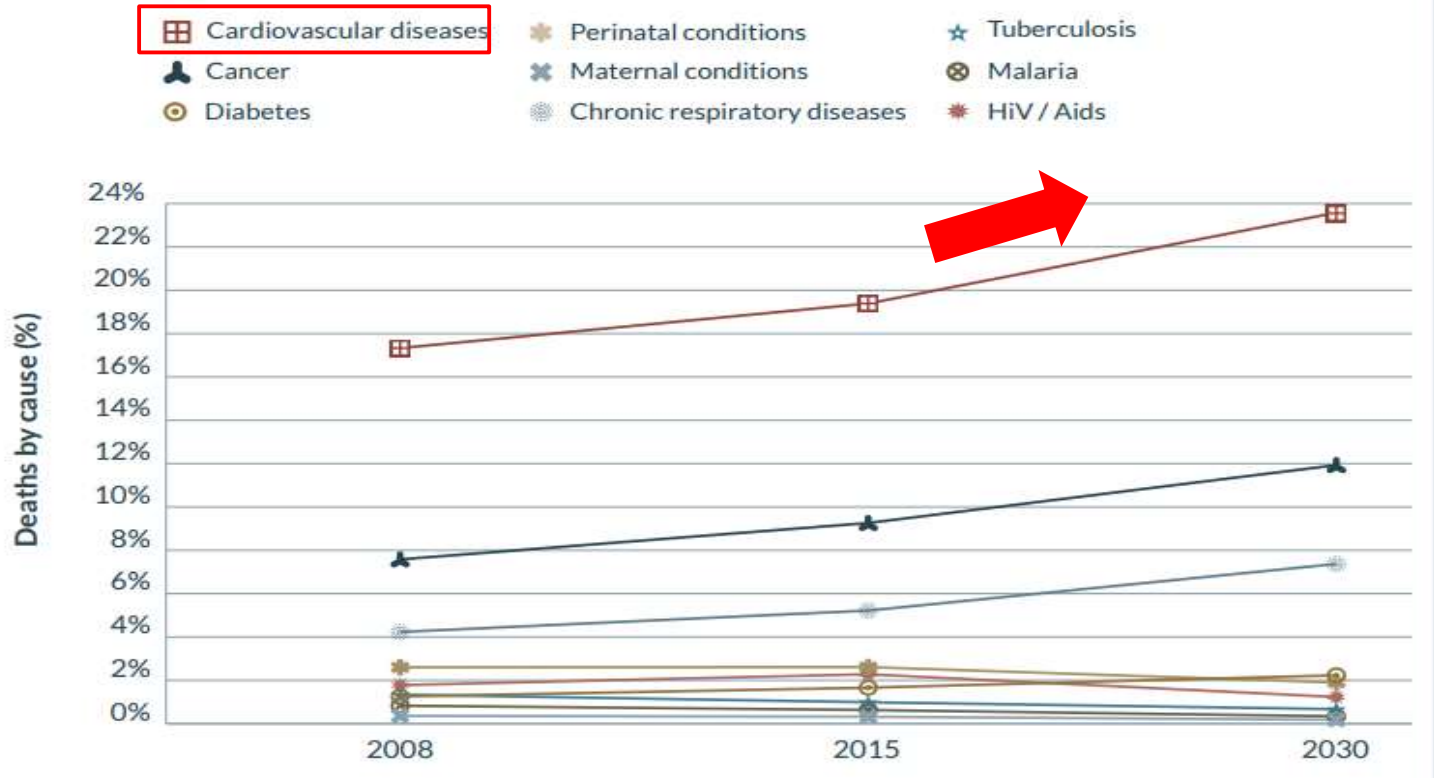


FIGURE 04

THE PROJECTED MORTALITY TREND FROM 2008 TO 2030 FOR MAJOR NONCOMMUNICABLE DISEASES AND COMMUNICABLE DISEASES

Source:

The Global Burden of Disease, 2004 update. Geneva, World Health Organization, 2008.

Is glycemic control alone sufficient to reduce CV risk and renal disease progression?

- ***Yes***
- ***No***
- ***Maybe***

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes

Study[1]	Baseline HbA_{1c} Control vs intensive	Mean duration of diabetes at baseline (years)						
UKPDS	9%→ 7.9% vs 7%	Newly diagnosed	↓		↔		↔	
ACCORD[1–3]	8.3%→ 7.5% vs 6.4%	10.0	↓	↔**	↔	↔	↔	↔
ADVANCE	7.5 %→ 7.3% vs 6.5%	8.0	↓	?	↔	↓	↔	↔
VADT	9.4 %→ 8.4% vs 6.9%	11.5	↓		↔		↔	

Long-term follow-up[1,4,5]

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria[2,3]

**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)[5]

1. Table adapted from Bergenstal et al. Am J Med 2010;123:374.e9–e18. 2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8.

3. Ismail-Beigi et al. Lancet 2010;376:419–30. 4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT). 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

CVD Risk Factors- Modifiable and Non Modifiable risk factors:

AMERICAN COLLEGE of CARDIOLOGY

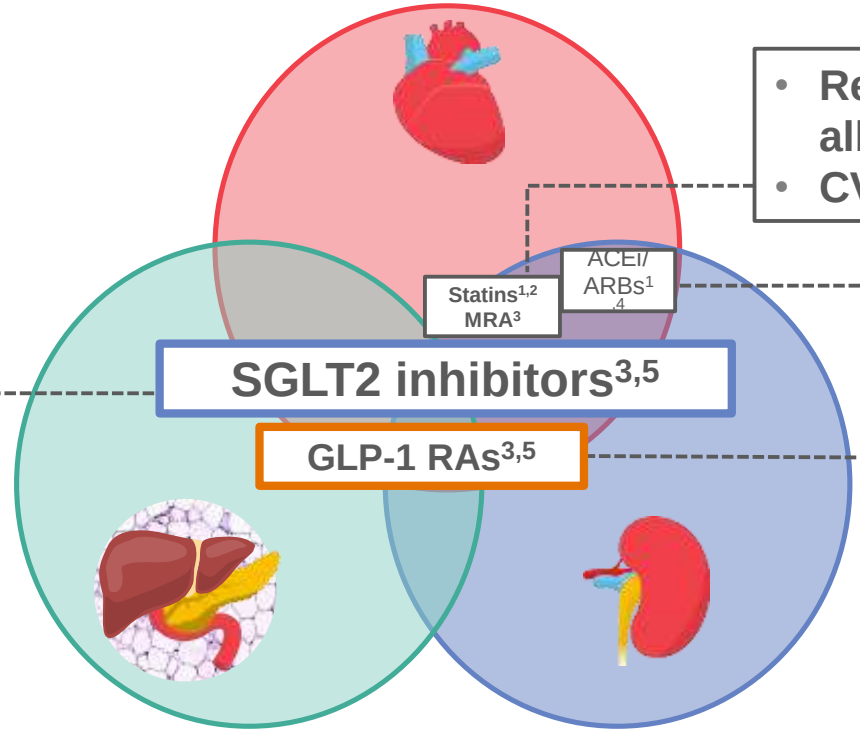
Modifiable Risk Factors*	Relatively Fixed Risk Factors†
• Current cigarette smoking, secondhand smoking. • Diabetes mellitus. • dyslipideamia • HTN • Overweight/obesity. • Physical inactivity/low fitness. • Unhealthy diet.	• CKD. • Family history . • Increased age. • Low socioeconomic/educational status. • Male sex. • Obstructive sleep apnea. • Psychosocial stress.

An action was needed to be taken in our management for better outcome

Here comes the Era of SGLT2i!!

SGLT2 inhibitors- A holistic approach to T2D care addresses the cardio, renal and metabolic aspects of disease

Metabolic effects
Cardio–renal benefits†‡
Reduction of:
- MACE
- CV death
- HHF
- Hard kidney outcomes
- Albuminuria
- eGFR worsening



- Reduce albuminuria*
- CV benefits

Cardio–renal benefits

Metabolic effects
Cardio–renal benefits†‡§
Reduction of:
- MACE
- CV death
- Albuminuria

Expected Clinical Effects of SGLT2 Inhibition

Increased glucose excretion

- **Reduced glycemia** → **HbA1c Reduction 0.6 - 1%**
- **Loss of calories** → **Weight loss 2 – 3 kg**
- **BP reduction 3 – 5 mmHg**

Abdul-Ghani MA, et al. *Endocri Rev.* 2011; 32:S15-S31.

Glycosuria Lowers HbA_{1c} & Reduces Glucose Toxicity

↓ glucose

↓ glucose toxicity and insulin resistance[1]

↓ tissue inflammation and oxidative stress

Potentially improving:[1-5]

- Endothelial function
- Arterial wall structure
- Cardiac function

1. Nolan CJ, *et al. Diabetes* 2015;64:673; 2. Inzucchi SE, *et al. Diabetes Vasc Dis Res* 2015;12:90; 3. Cahill PA, Redmond EM. *Atherosclerosis* 2016;248:97; 4. Cameron JD, *et al. Vasc Health Risk Manag* 2013;9:255; 5. Chilton R, *et al. Diabetes Obes Metab* 2015;17:1180.

Many Mechanisms Have Been Suggested As Contributing To The CV and Kidney Effects of SGLT2 Inhibitors

Glucose[1–5]

↑ Glucosuria	↓ Glucose toxicity ↓ Inflammation ↓ Oxidative stress ↓ Atherosclerosis
↓ Calories	↓ Epicardial fat ↓ Body fat ↓ Inflammation ↓ Fibrosis ↑ Cardiac contractility
↓ Insulin: glucagon ratio	↑ Ketone metabolism ↑ Mitochondrial ATP ↑ Myocardial energy
↑ Uricosuria	↓ Plasma uric acid ↓ Oxidative stress ↓ Atherosclerosis

Sodium[1–5]

↑ TGF	↑ Afferent arteriole constriction ↓ Glomerular hypertension ↓ Albuminuria ↓ Hyperfiltration
↓ Intracellular Na^+ in cardiomyocytes	↓ Cardiac Na^+/H^+ exchange ↓ Oxidative stress
↓ Ventricular arrhythmia	
↓ Blood pressure	↓ Arterial stiffness

Volume[1-4,6]

↑ Haemodynamic changes	↓ Plasma volume ↓ LV wall stress ↓ Arterial wall structure/function
↓ Cardiac preload	↓ Atrial pressure ↓ Myocardial stretch ↓ Risk of arrhythmia
↓ Cardiac afterload	↓ Myocardial O_2 demand
↑ Haematocrit	↑ Myocardial and renal O_2 supply

ATP, adenosine triphosphate; CV, cardiovascular; LV, left ventricular; SGLT2, sodium-glucose co-transporter-2; TGF, tubuloglomerular feedback

1. Verma S *et al. JAMA Cardiol* 2017;2:939; 2. Rajasekeran H *et al. Kidney Int* 2016;89:524; 3. Verma S & McMurray J. *Diabetologia* 2018;61:2108; 4. Pham SV & Chilton RJ. *Am J Cardiol* 2017;120:S53; 5. Abdelgadir E *et al. J Clin Med Res* 2018;10:615; 6. Heerspink HJ *et al. Kidney Int* 2018;94:26

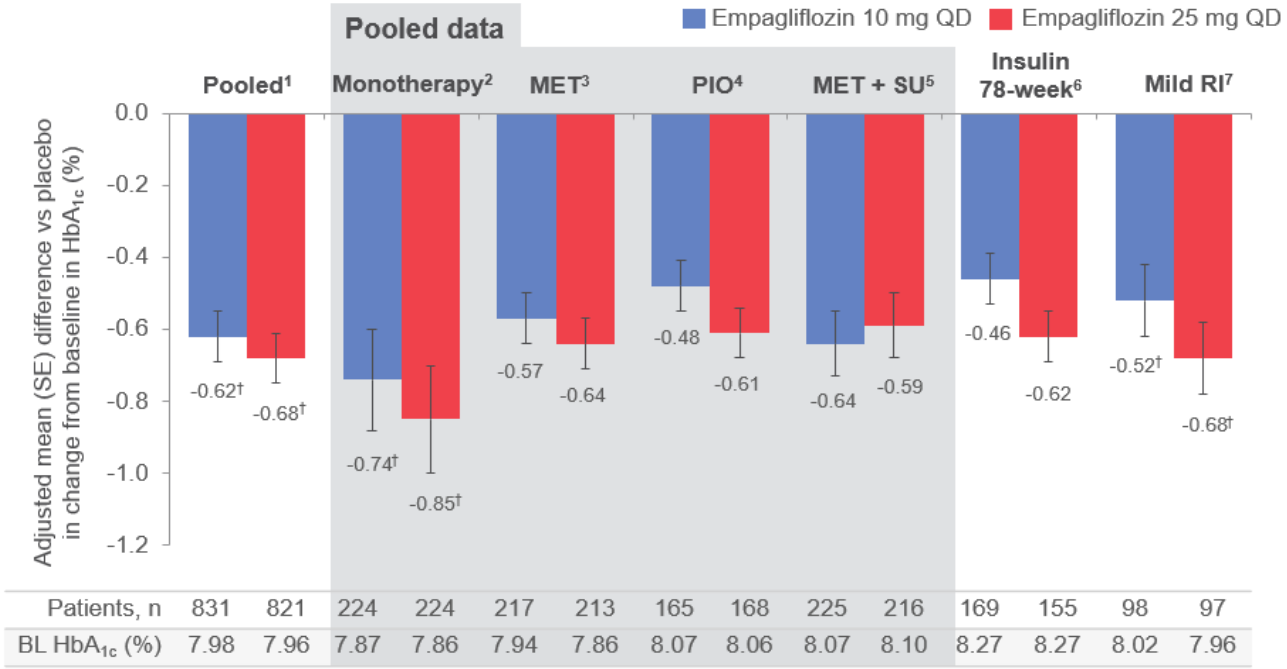
Empagliflozin

Efficacy

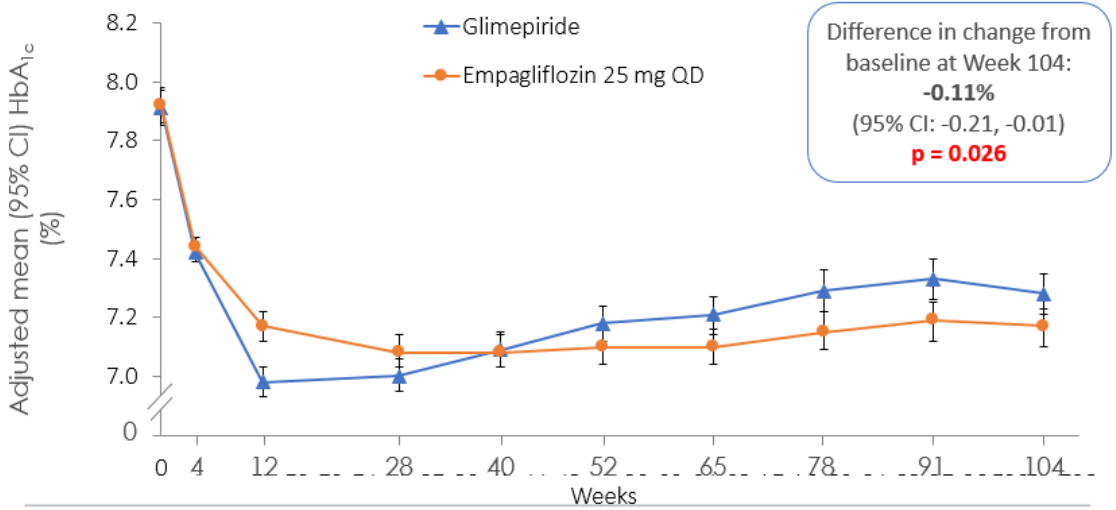
Tolerability

Safety

Empagliflozin pooled Phase III placebo-corrected change from baseline in HbA_{1c}*



104-week study with Empagliflozin H2H versus Glimepiride Change in HbA1c over time



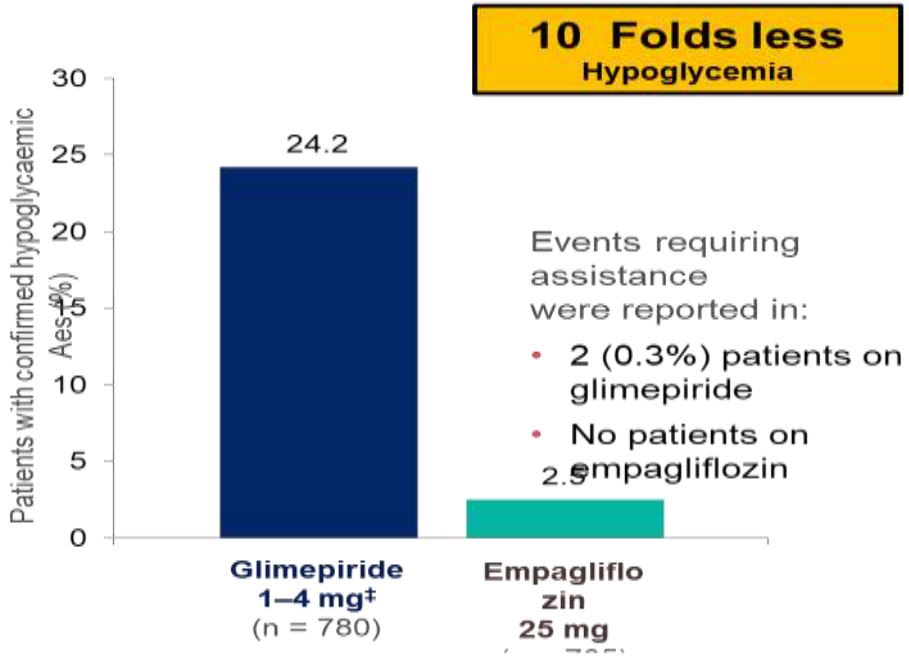
Analysed patients										
Glimepiride	761	758	738	699	660	609	562	524	494	461
Empagliflozin	759	751	734	702	672	646	624	593	568	548

EMPA-REG H2H-SU™: study 1245.28

- CI, confidence interval; H2H, head-to-head; HbA1c, glycosylated haemoglobin; QD, once daily.
- MMRM. FAS (OC).
- Ridderstråle M, et al. *Lancet Diabetes Endocrinol.* 2014;2:691–700.

104-week study with Empagliflozin H2H versus glimepiride

Patients with confirmed hypoglycaemic AEs* over 104 weeks



EMPA-REG H2H-SU™: study 1245.28

Ridderstråle M, et al. *Lancet Diabetes Endocrinol.* 2014;2:691–700..

Adverse reactions: EMPA-REG OUTCOME

Adverse reactions	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Confirmed hypoglycaemic AEs[1]	650 (27.9)	–	656 (28.0)	–	647 (27.6)	–
Urinary tract infection[1]	423 (18.1)	8.21	426 (18.2)	8.02	416 (17.8)	7.75
Complicated urinary tract infection*[1,2]	41 (1.8)	0.71	34 (1.4)	0.57	48 (2.0)	0.80
Genital infection[1]	42 (1.8)	0.73	153 (6.5)	2.66	148 (6.3)	2.55
Volume depletion[1]	115 (4.9)	2.04	115 (4.9)	1.97	124 (5.3)	2.11
Hepatic injury[2]	108 (4.6)	1.91	80 (3.4)	1.35	88 (3.8)	1.48
Diabetic ketoacidosis[1]	1 (<0.1)	0.02	3 (0.1)	0.05	1 (<0.1)	0.02
Venous thrombotic events[1]	20 (0.9)	0.35	9 (0.4)	0.15	21 (0.9)	0.35

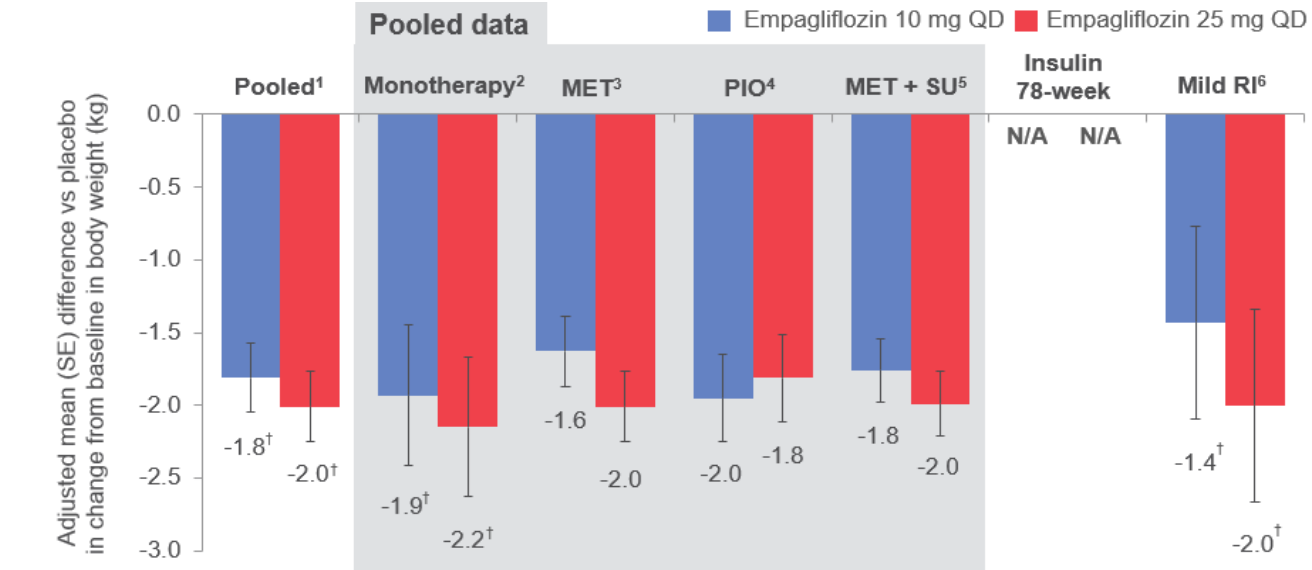
Data from patients treated with ≥1 dose of study drug
*Pyelonephritis, urosepsis or serious AEs consistent with urinary tract infections
PY, patient-years
1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Zinman B. *EASD* 2015; oral presentation

Secondary beneficial effects

Weight reduction

Blood pressure reduction

Empagliflozin pooled Phase III placebo-corrected change from baseline in body weight*

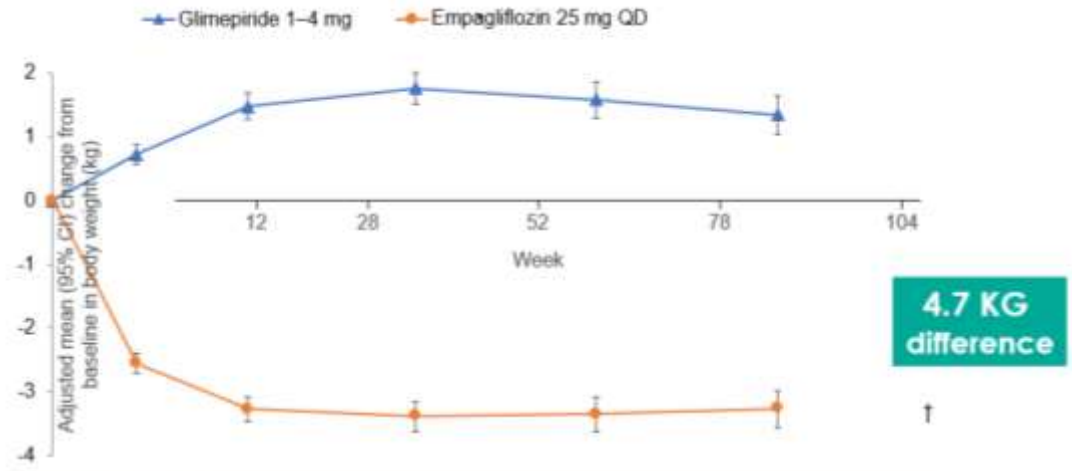


*All statistically significant. †Error bar represents 95% CI. N/A, published data not available.

1. Hach et al. Diabetes 2013;62(suppl 1A):A21(P69-LB). 2. Roden et al. Lancet Diabetes Endocrinol 2013;1:208–19.
3. Häring et al. Diabetes Care 2014;37:1650–9. 4. Kovacs et al. Diabetes Obes Met 2014;16:147–58.
5. Häring et al. Diabetes Care 2013;36:3396–3404. 6. Barnett et al. Lancet Diabetes Endocrinol 2014;2:369–84.

Back

104-week study with Empagliflozin H2H versus Glimepiride Change in body weight over time



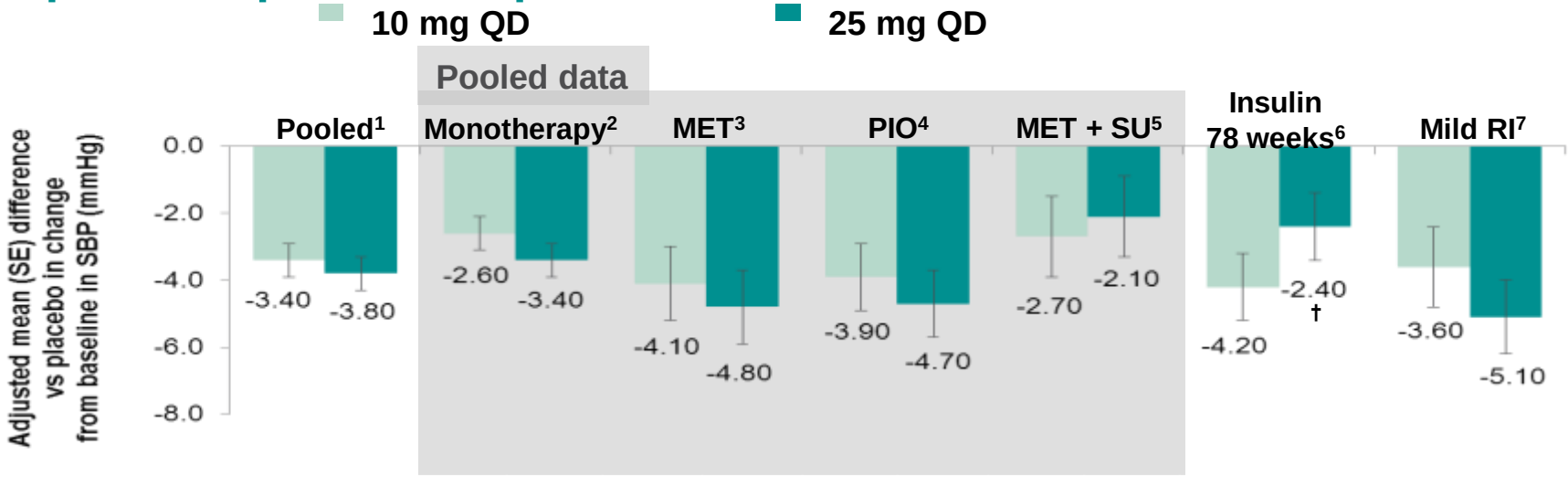
Analysed patients, n						
Glimepiride	745	743	703	610	526	462
Empagliflozin	739	737	706	643	595	555

- CI, confidence interval; H2H, head-to-head; QD, once daily; SD, standard deviation.
- *The mean (SD) highest dose of glimepiride over 104 weeks was 2.71 (1.24) mg; 40.1% of patients received the 4 mg dose. †p < 0.0001 vs glimepiride, MMRM, FAS (OC).

Riddleriddle M, et al. *Lancer Diabetes Endocrinol.* 2014;2:691–700.

EMPA-REG H2H-SU™: study 1245.28

Empagliflozin *reduced SBP** across different background therapies compared with placebo†

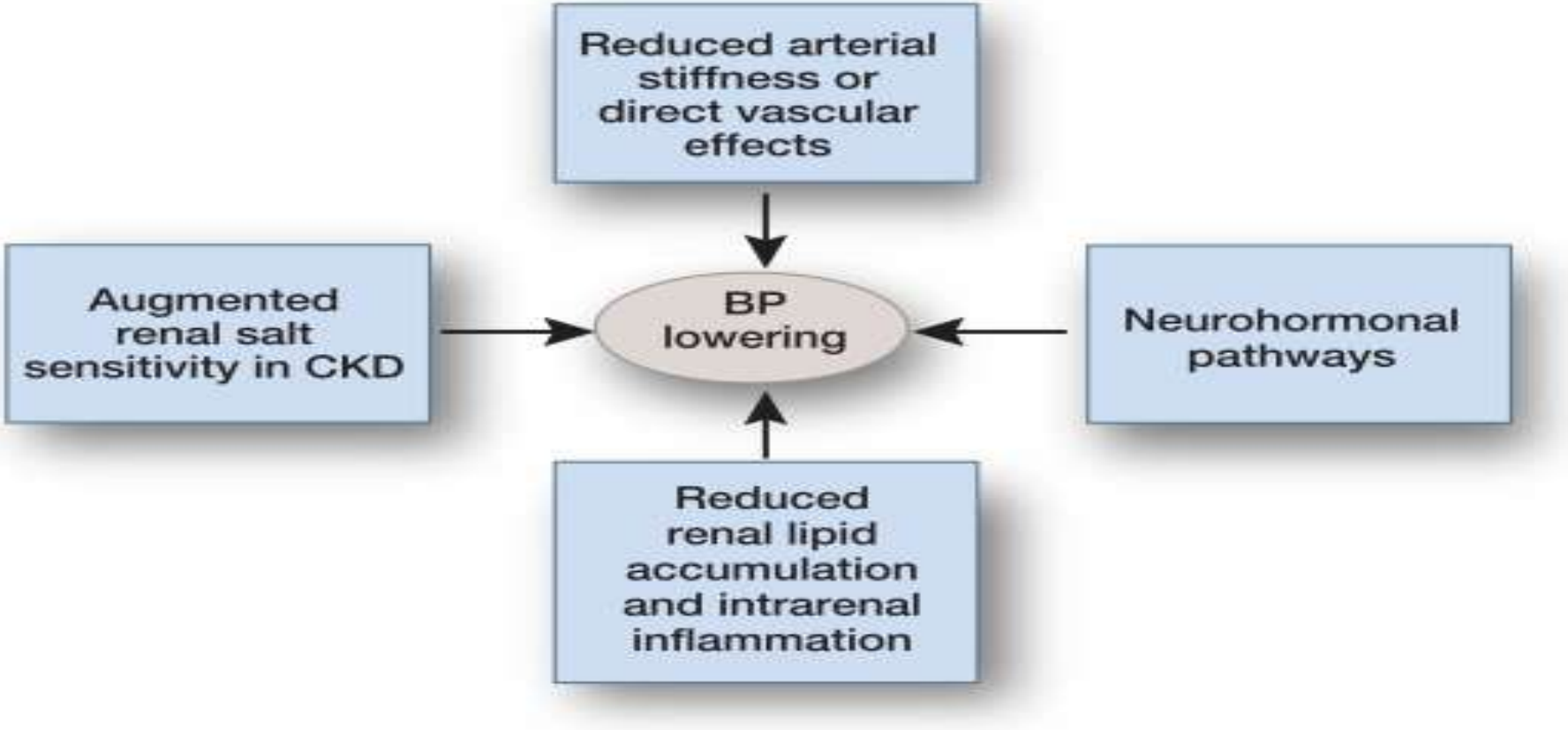


Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL SBP (mmHg)	129.6	129	133	129.9	129.6	130	126.5	125.9	128.7	129.3	132.4	132.8	137.4	133.7

***Empagliflozin is not indicated for reduction in blood pressure**

Blood pressure change was assessed as a safety or exploratory efficacy endpoint in clinical trials

Empagliflozin Lowers Blood Pressure



CVD &
Renal benefits

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

EMPA-REG OUTCOME®

- Key inclusion criteria
  - T2DM and established CV disease
  - HbA1c 7–10% ; BMI ≤45 kg/m^2; eGFR (MDRD) ≥30 mL/min/1.73m^2
- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- The trial was to continue until ≥691 patients experienced an adjudicated primary outcome event: CV death, non-fatal myocardial infarction, or non-fatal stroke (3-point MACE)

eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

Zinman B et al. N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME®

EMPA-REG OUTCOME®

EMPA-REG OUTCOME®

Empagliflozin in addition to standard of care **reduced CV risk and improved overall survival** in adults with T2D and established CV disease

Relative risk reduction:

3P-MACE	CV death	HHF	Worsening of Nephropathy	All-cause mortality
				
↓14%	↓38%	↓35%	↓39%	↓32%

Reduction in CV outcomes and mortality were **generally consistent across subgroups and analysis populations**

3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HHF, hospitalisation for heart failure; T2D, type 2 diabetes

Zinman B *et al. N Engl J Med* 2015;373:2117; Zinman B. *EASD* 2015; oral presentation

DIACURIMAP
Empagliflozin 10mg, 25mg

EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

Milton Packer MD and Faiez Zannad MD, on behalf of the EMPEROR-Reduced
Executive Committee, Trial Committees, Investigators and Coordinators

Baylor University Medical Center, Dallas TX, Imperial College, London UK
Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France

EMPEROR
HEART FAILURE STUDIES

	**Primary Endpoint** **Composite of cardiovascular death or heart failure hospitalization**	**Achieved** **P < 0.001**	**25%** **RRR**
	**First Secondary Endpoint** **Total (first and recurrent heart failure hospitalizations)**	**Achieved** **P < 0.001**	**30%** **RRR**
	**Second Secondary Endpoint** **Slope of decline in glomerular filtration rate over time**	**Achieved** **P < 0.001**	**50%** **RRR**

EMPEROR-Preserved Trial

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction

Stefan D. Anker, MD PhD & Javed Butler, MD on behalf of the EMPEROR-Preserved Executive Committee, Trial Committees, Investigators & Coordinators

Dept. of Cardiology & BCRT (CVK), Charité Berlin, Germany
University of Mississippi Medical Center, Jackson, Mississippi, USA

ESC CONGRESS 2021
THE DIGITAL EXPERIENCE

Success on all 3 prespecified hierarchical endpoints

	**Primary Endpoint** **Composite of cardiovascular death or heart failure hospitalization**	**21%** in risk **P = 0.0003**
	**First Secondary Endpoint Total (first and recurrent) heart failure hospitalizations**	**27%** in risk **P = 0.0009**
	**Second Secondary Endpoint** **Slope of decline in glomerular filtration rate over time**	**P < 0.0001** Difference: 1.36 mL/min/1.73 m^2 per year

Guidelines and recommendations

ADA guidelines have evolved to recommend SGLT2 inhibitors and GLP-1 RAs with proven CV and kidney benefits in patients with T2D and cardio–renal comorbidities

2016

Glucose lowering[1]

2018

Incorporate an agent proven to reduce CV events and mortality (A)*[2]

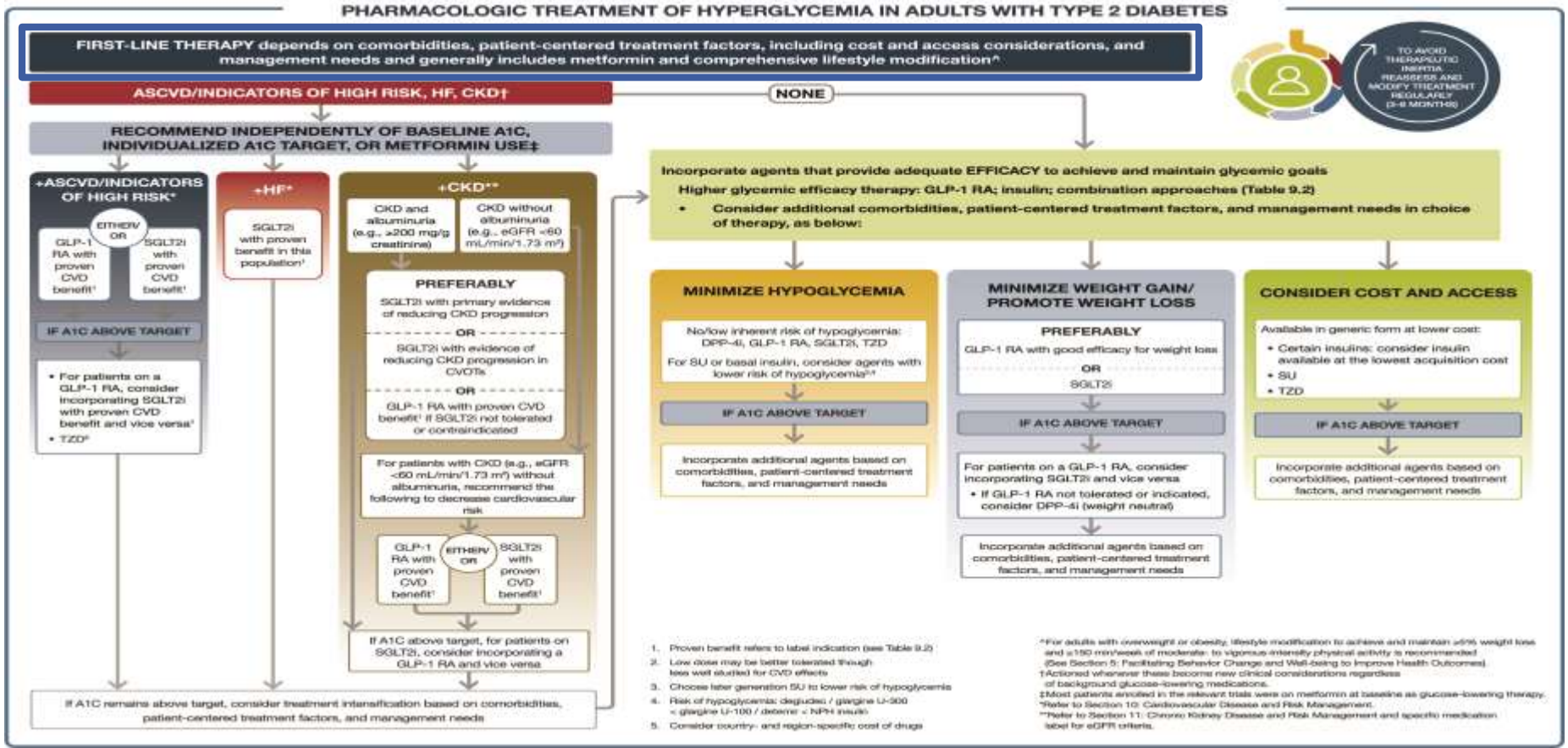
2020

Agents with demonstrated CVD benefit are recommended independent of HbA1c (A)*[3]

2021

Agents with demonstrated CVD benefit are recommended independent of HbA1c and in consideration of specific-risk factors (A)*[4]

The 2022 ADA Guidelines



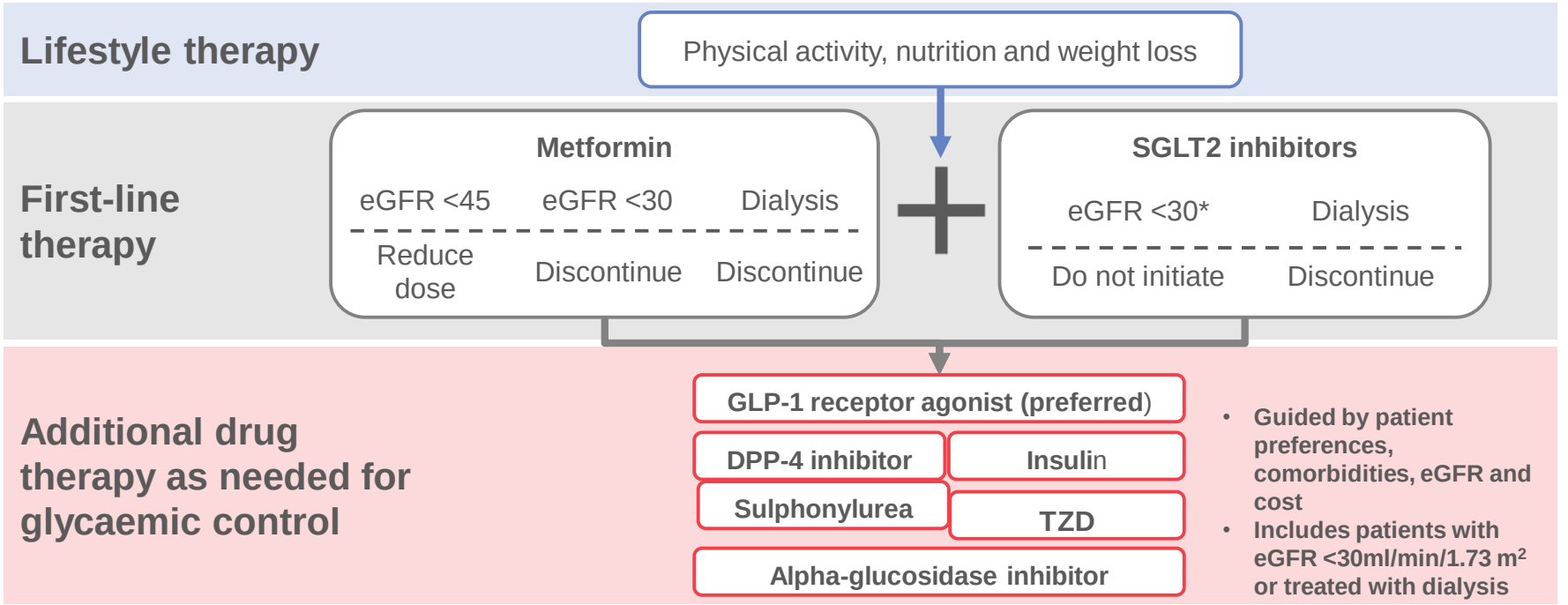
AHA & ESC 2021/2022 Guidelines

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B

KDIGO 2020 *treatment algorithm for selecting antihyperglycaemic drugs for patients with T2D and CKD*

Lifestyle therapy in addition to first-line therapy is the cornerstone of glycaemic management for patients with T2D and CKD

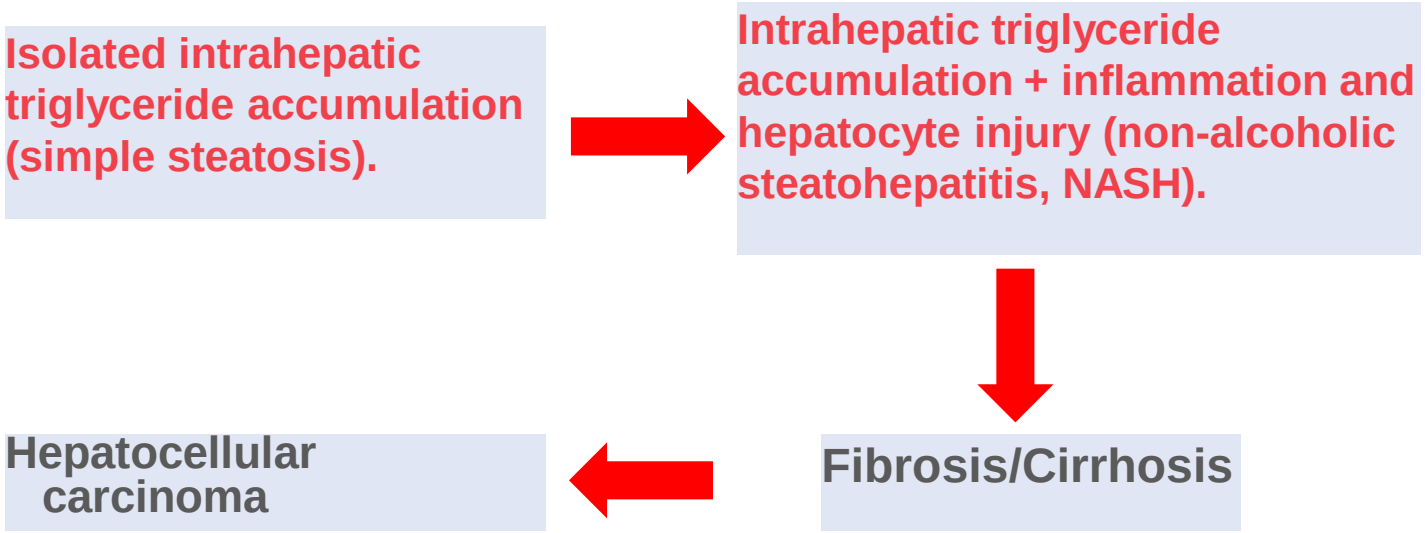


eGFR values are ml/min per 1.73 m². *For agent-specific recommendations, please refer to the manufacturers' prescribing information. KDIGO, Kidney Disease Improving Global Outcomes; TZD, thiazolidinedione. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int* 2020;98:S1

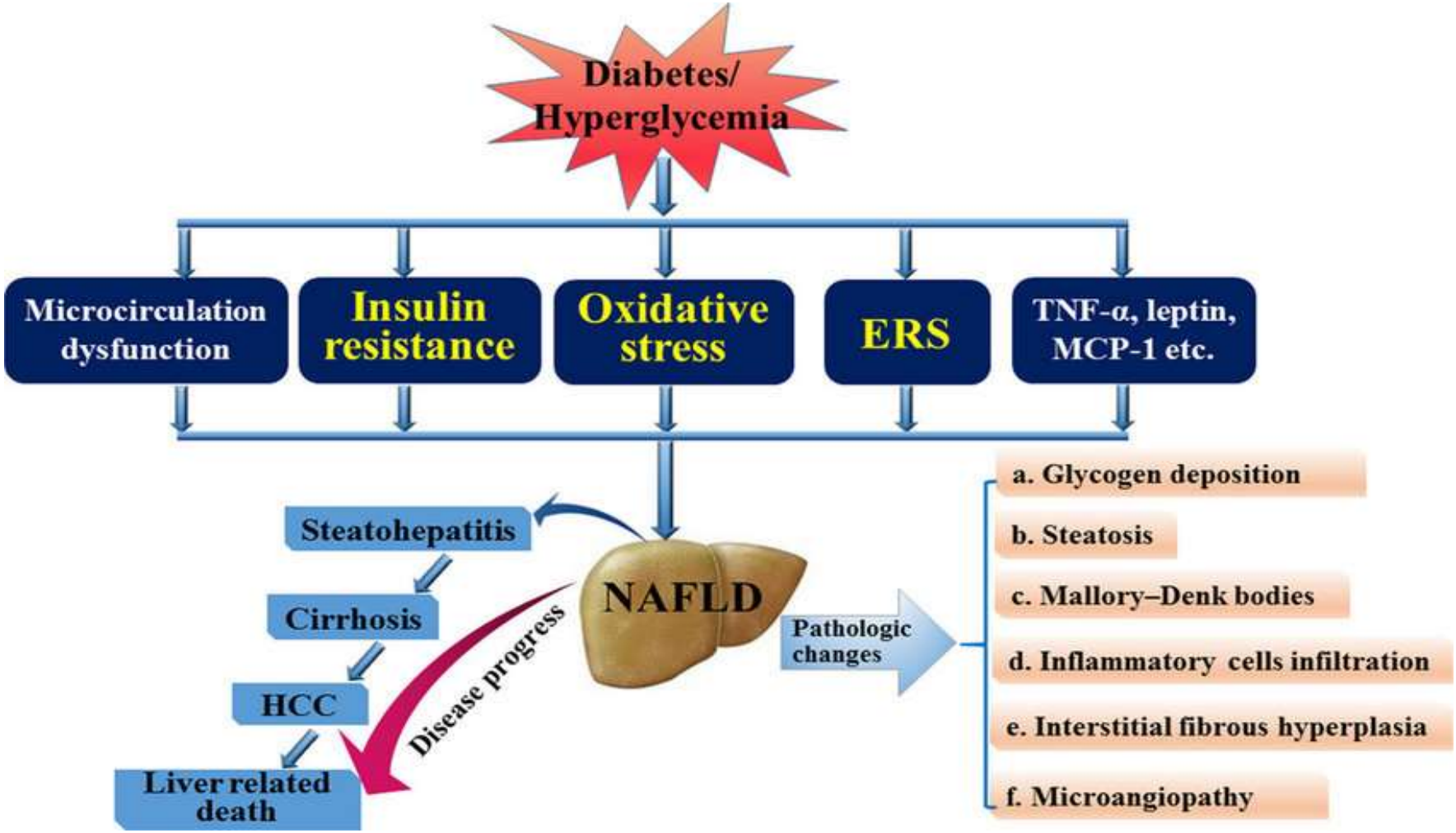
(NAFLD): a multisystem disease. Reported associations between NAFLD and various human diseases.

Introduction

NAFLD represents a spectrum of progressive liver disease occurring in the absence of excessive alcohol consumption that ranges from:



Anstee QM, et al.,Nat Rev Gastroenterol Hepatol 2013;10:330–44.


Diabetes/
Hyperglycemia
Microcirculation dysfunction
Insulin resistance
Oxidative stress
ERS
TNF-α, leptin, MCP-1 etc.
Steatohepatitis
Cirrhosis
HCC
Liver related death
Disease progress
NAFLD
Pathologic changes
a. Glycogen deposition
b. Steatosis
c. Mallory–Denk bodies
d. Inflammatory cells infiltration
e. Interstitial fibrous hyperplasia
f. Microangiopathy

Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial)

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Diabetes Care 2018;41:1801–1808 | https://doi.org/10.2337/dc18-0165

CONCLUSIONS

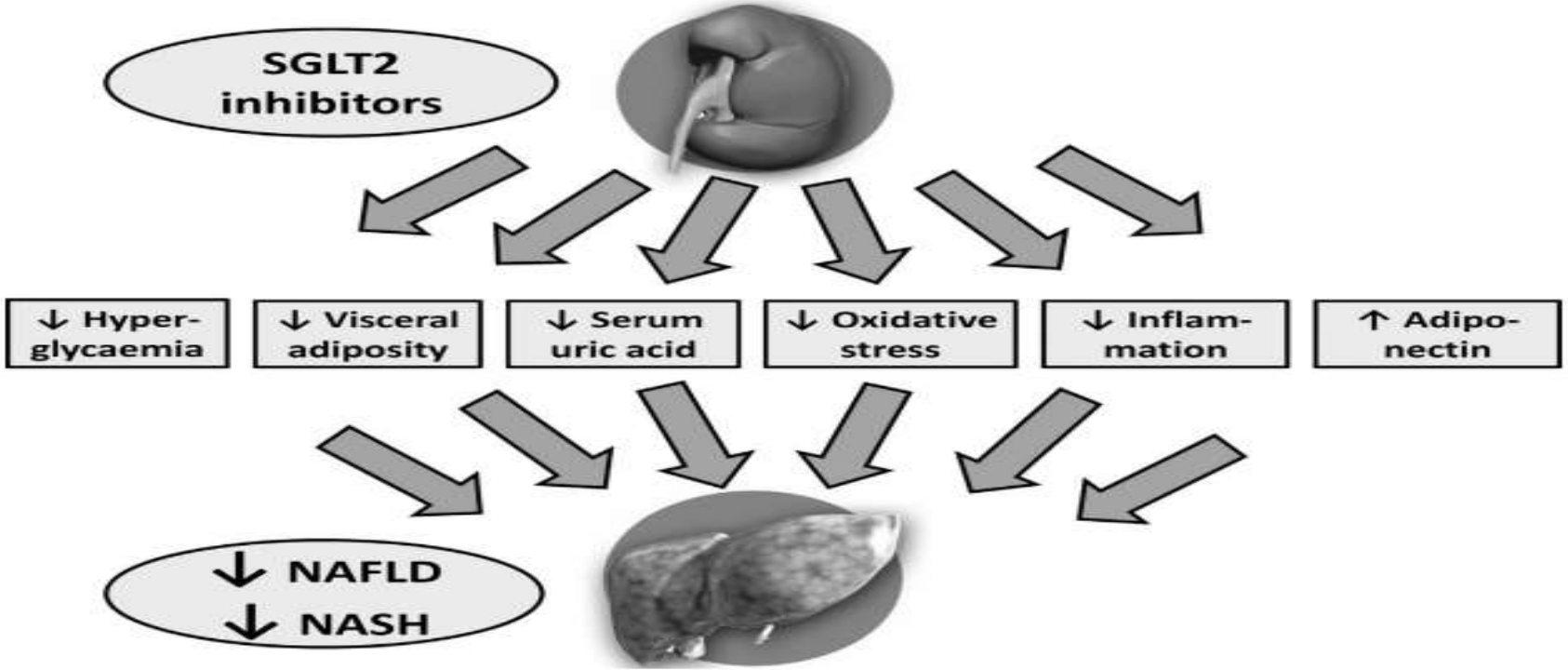
When included in the standard treatment for type 2 diabetes, Empagliflozin :

1. **Reduces liver fat**

2. **Improves ALT levels in patients with type 2 diabetes and NAFLD.**

3. ***SGLT2 Inhibitors Are Capable Of Attenuating The Abnormal Oxidative Response & Inflammatory Responses***

Potential Mechanisms Contributing To Improvement of Fatty Liver with SGLT2 Inhibitor Treatment



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Understanding the interrelated CRM systems: ***summary***

The CRM **systems are interrelated**; dysfunction in one organ or system can induce or contribute to dysfunction in the others[1]

T2D, CV disease, HF and CKD are interrelated and the presence of T2D is associated with cardiac and renal disease progression[2–6]

A **holistic approach to T2D care** is necessary to address the CV, renal and metabolic aspects of disease[7]

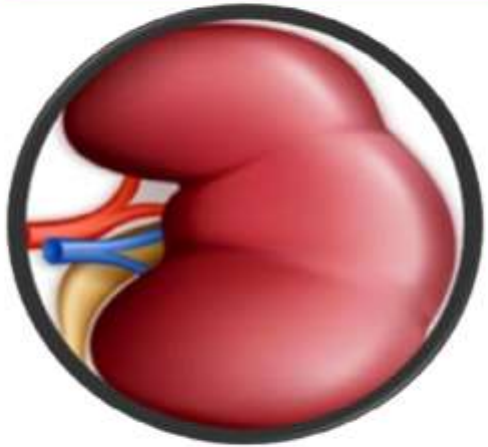
Guidelines and societies recommend the use of agents with CRM benefits, such as SGLT2 inhibitors and GLP-1 receptor agonists for the treatment of patients with T2D[8,9]

CRM, cardio-renal-metabolic
See slide notes for full list of references

- ↑ Energetics (free fatty acids, glucose, ketones)
- ↓ Preload and afterload
- ↑ Ejection fraction
- ↓ Reverse cardiac remodeling

- ↑ Glycosuria
- ↑ Natriuresis and diuresis
- ↑ Uricosuria
- ↓ Glomerular pressure
- ↓ Proteinuria

- ↓ Blood pressure
- ↓ Volume load
- ↑ Hematocrit
- ↑ Elasticity



- ↓ Insulin
- ↑ Glucagon

- ↓ Weight
- ↑ Negative caloric balance
- ↓ Glucotoxicity
- ↓ Insulin resistance

- ↓ HbA1c and glucose
- ↓ Triglycerides
- ↓ Inflammatory markers
- ↑ Ketones
- ↓ Uric acid

THANK YOU