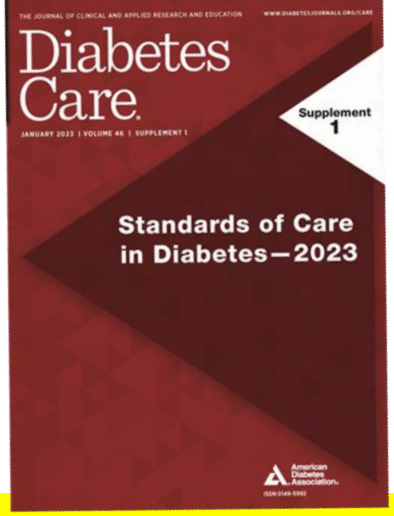
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure



ESC European Society of Cardiology
European Heart Journal (2021) 00, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Vai Trò Nhóm Ức Chế SGLT2 trong các khuyến cáo của các Hiệp Hội Tim Mạch & Đái Tháo Đường

Góc nhìn Chuyên Ngành Nội Tiết Tim Mạch Học

GS.TS.Nguyễn Hải Thuỷ
PCT Hội Nội Tiết ĐTĐ Việt Nam

1. ĐẶT VẤN ĐỀ

An estimated 64.3 million people are living with heart failure worldwide. In developed countries, the prevalence of *known* heart failure is generally estimated at 1% to 2% of the general adult population

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European Journal of Heart Failure (2020) **22**, 1342–1356
doi:10.1002/ejhf.1858

WORLD HEART FEDERATION

1 IN 5

The lifetime risk of developing heart failure

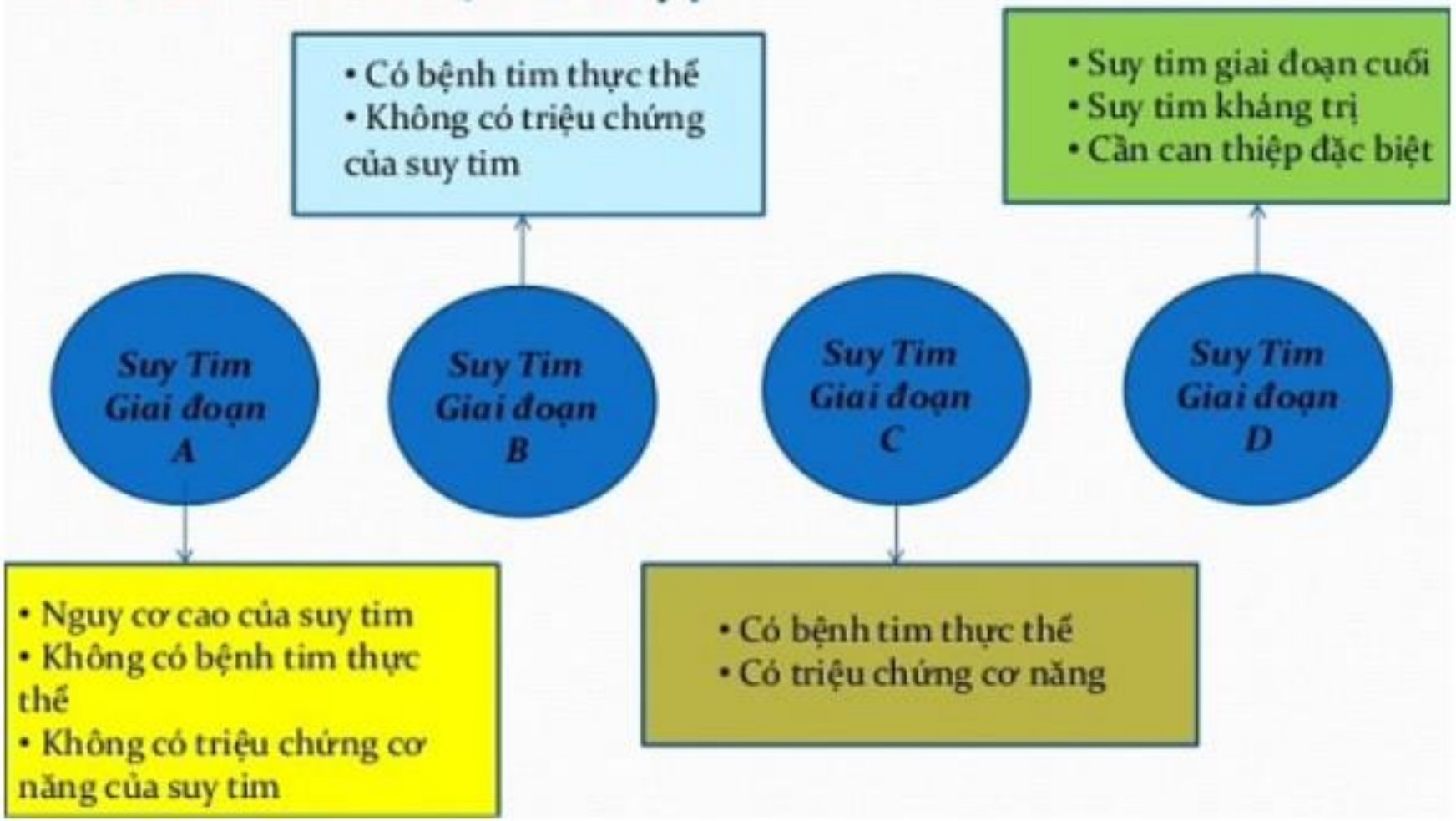
The prognosis for those diagnosed with heart failure is poor:

- 17-45% of patient deaths occur within one year of hospital admission
- 45-60% of deaths occur within five years of admission

Bảng 5. Phân độ suy tim theo chức năng của NYHA

Độ I	Không hạn chế - Vận động thể lực thông thường không gây mệt, khó thở hay hồi hộp.
Độ II	Hạn chế nhẹ vận động thể lực. BN khỏe khi nghỉ ngơi; vận động thể lực thông thường dẫn đến mệt, hồi hộp, khó thở hay đau ngực.
Độ III	Hạn chế nhiều vận động thể lực. Mặc dù BN khỏe khi nghỉ ngơi nhưng chỉ cần vận động nhẹ đã có triệu chứng cơ năng.
Độ IV	Không vận động thể lực nào không gây khó chịu. Triệu chứng cơ năng của suy tim xảy ra ngay khi nghỉ ngơi, chỉ một vận động thể lực nhẹ cũng làm triệu chứng cơ năng gia tăng.

2.3 Phân độ suy tim theo giai đoạn của AHA/ACC (Hội tim mạch Mỹ/ Trường môn Tim mạch Mỹ)



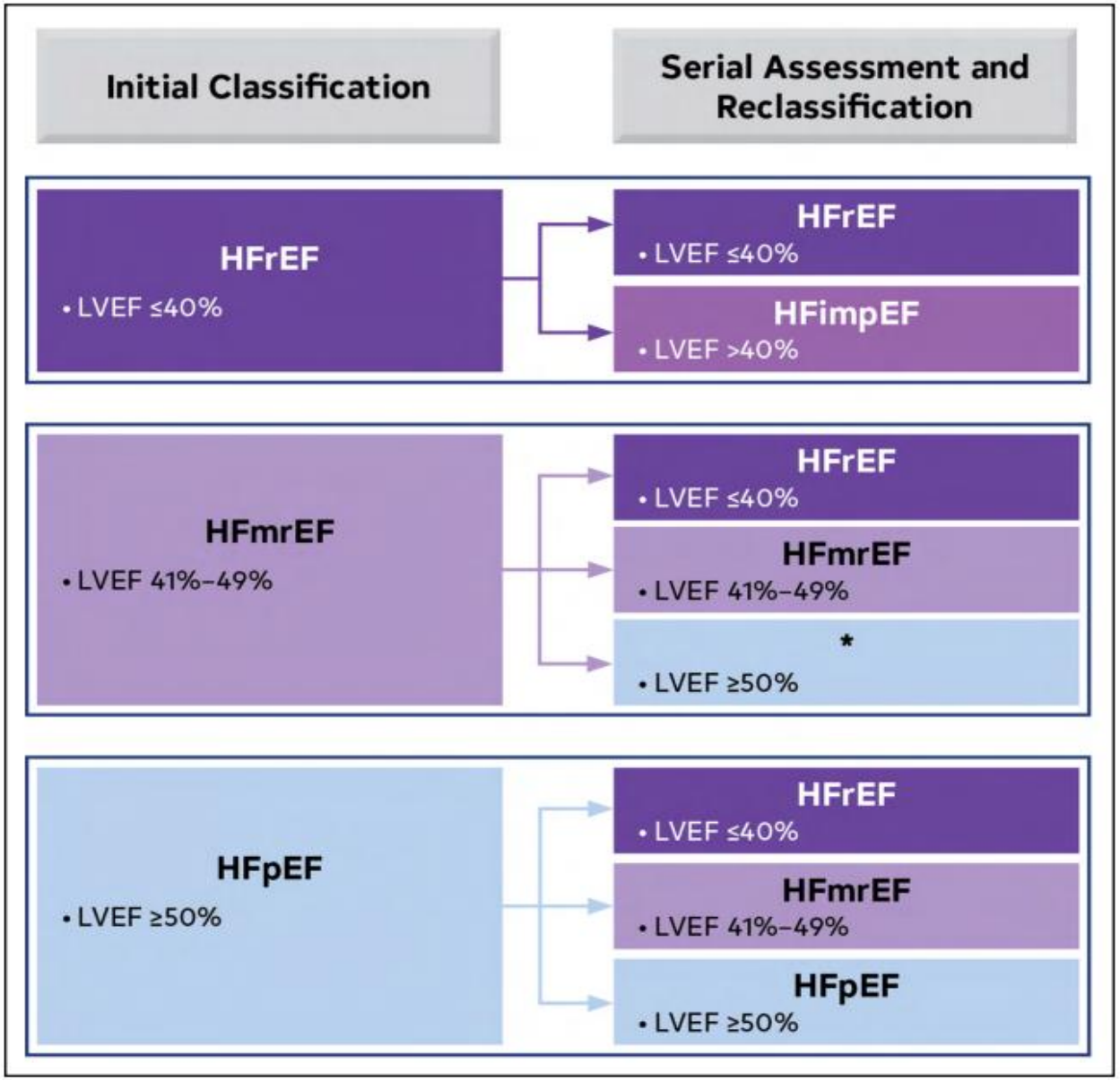
HỘI TIM MẠCH HỌC VIỆT NAM

Bảng 2. Phân loại suy tim

Phân loại	EF	Mô tả
1. Suy tim với EF giảm	≤ 40%	Còn gọi là suy tim tâm thu. Những nghiên cứu lâm sàng ngẫu nhiên chính thu nhận những BN có EF giảm và cho đến nay, các phương pháp điều trị có hiệu quả mới chỉ được chứng minh ở những BN này.
2. Suy tim với EF bảo tồn	≥ 50%	Còn gọi là suy tim tâm trương. Có vài tiêu chuẩn khác nhau được sử dụng để định nghĩa suy tim EF bảo tồn. Chẩn đoán suy tim tâm trương là một thử thách bởi vì phần lớn là chẩn đoán loại trừ những nguyên nhân không do tim khác gây triệu chứng giống suy tim. Đến nay, những phương pháp điều trị hiệu quả chưa được xác nhận.
2a. EF bảo tồn, giới hạn	41%-49%	Những BN này rơi vào giới hạn, hoặc ở nhóm trung gian. Đặc điểm lâm sàng, điều trị và dự hậu tương tự như BN suy tim EF bảo tồn.
2b. EF bảo tồn, cải thiện	> 40%	Người ta nhận thấy có một số ít BN suy tim EF bảo tồn mà trước đó có EF giảm. Những BN này có EF cải thiện hoặc hồi phục có thể có đặc điểm lâm sàng khác biệt với BN suy tim EF bảo tồn hay EF giảm. Cần có thêm nhiều nghiên cứu hơn cho những BN này.

Phân loại & hướng đi của suy tim theo Phân suất tống máu thất trái

Classification and Trajectories of HF Based on LVEF



1.Suy tim phân suất tống máu giảm (HFrEF= Heart failure reduced ejection fraction)

2.Suy tim phân suất tống máu cải thiện (HFimpEF= Heart failure with improved ejection fraction)

3.Suy tim phân suất tống máu giảm nhẹ (HFmrEF = heart failure with mildly reduced ejection fraction)

4. Suy tim phân suất tống máu bảo tồn (HFpEF= Heart failure with preserved ejection fraction)

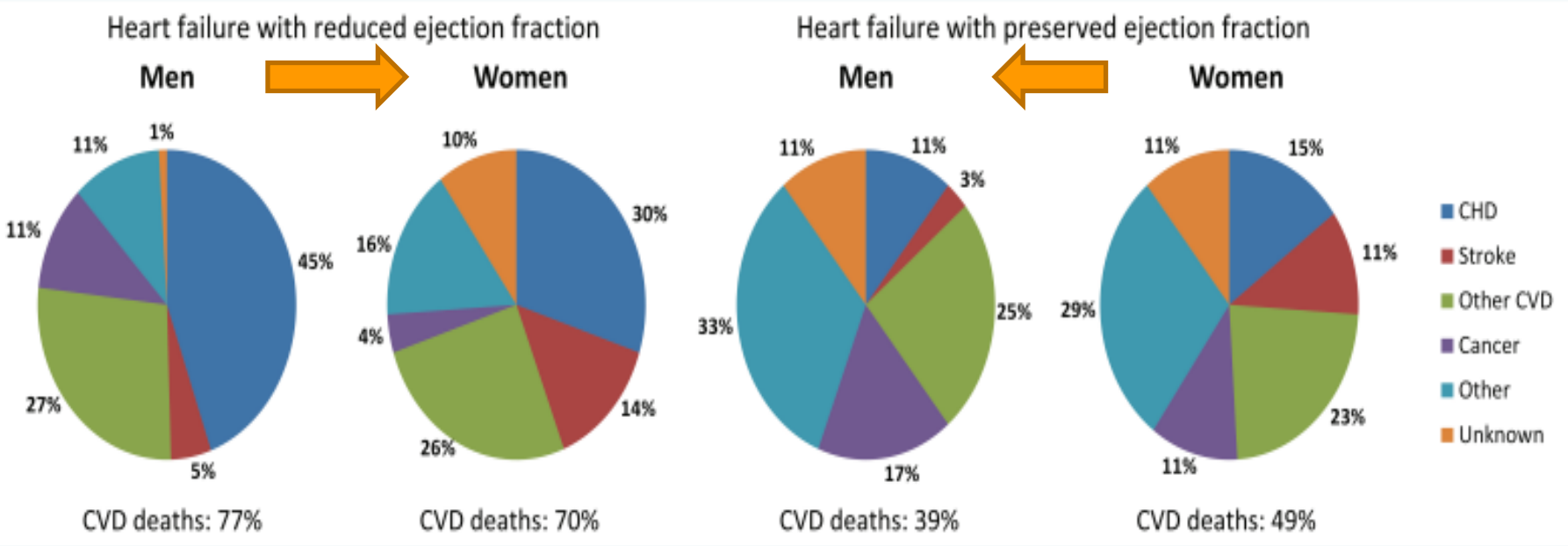


Figure 2 Underlying causes of death by gender and left ventricular ejection fraction in 463 patients in the Framingham Heart Study.[140] CVD, cardiovascular disease; CHD, coronary heart disease. Adapted from Lee *et al.*[140]

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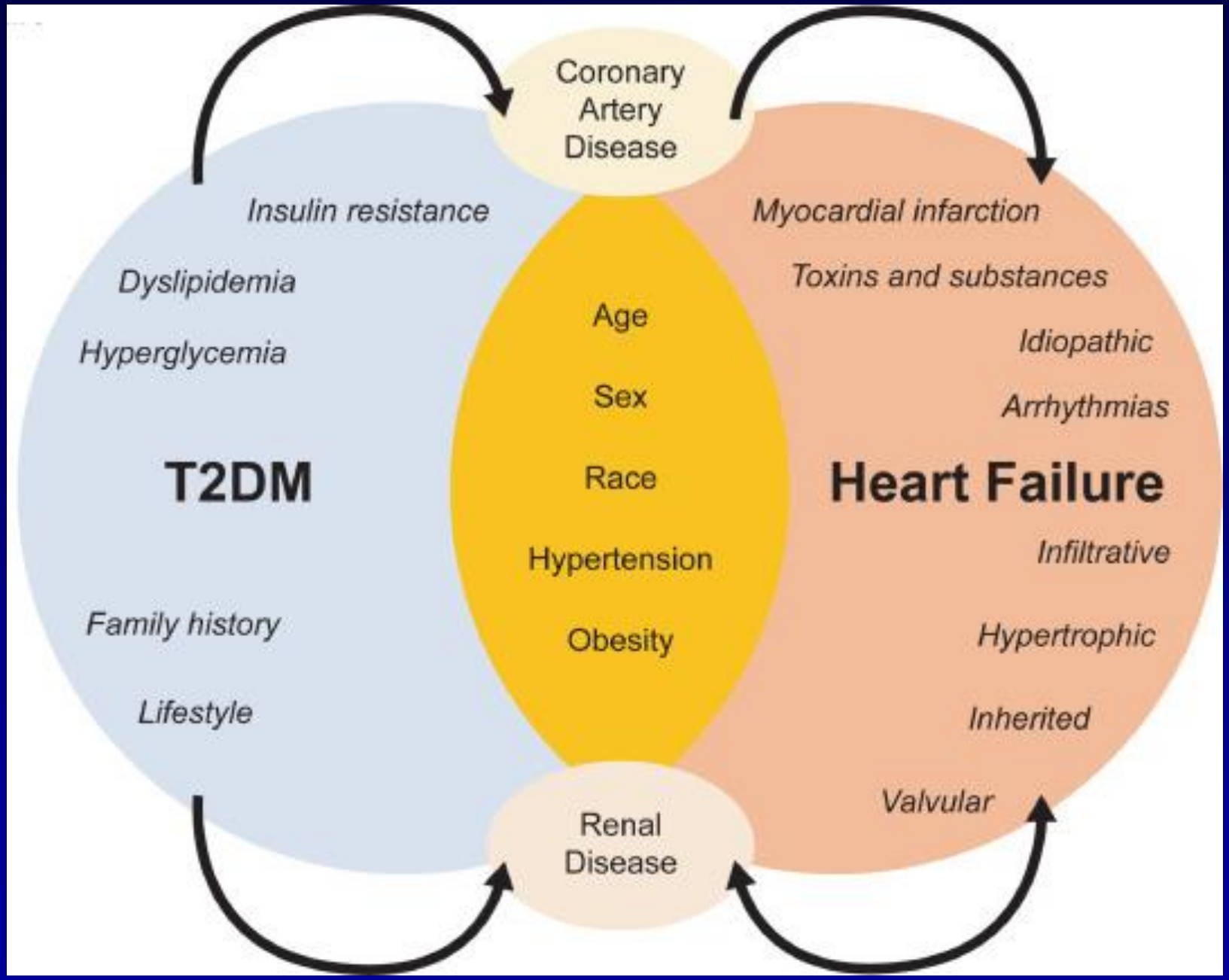
Heart failure in type 2 diabetes: current perspectives on screening, diagnosis and management

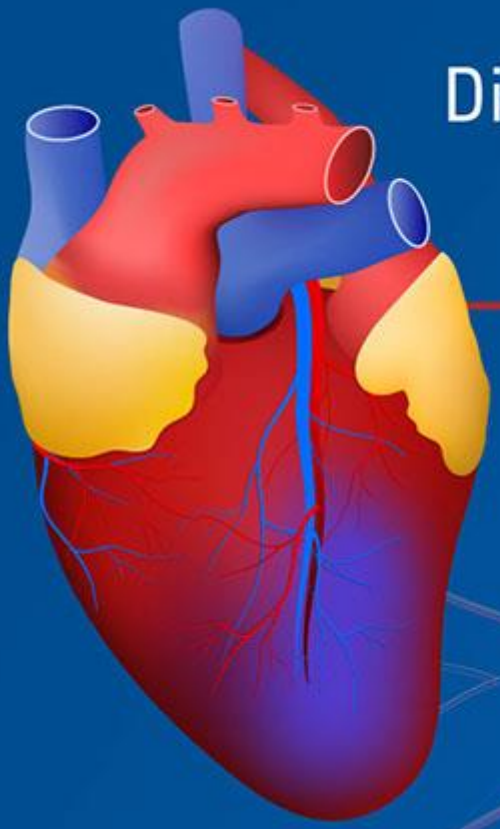
Antonio Ceriello[1*], Doina Catrinoiu[2], Chanchal Chandramouli[3,4], Francesco

Heart failure (HF) has been recognized as a co… …plication of diabetes, with a prevalence of up to 22% in indiv… …diabetes and increasing incidence rates. Data also suggest th… …develop in individuals with diabetes even in the absence of h… …n, coronary heart disease, or valvular heart disease and, as s… …ents a major cardiovascular complication in this vulnerable popula… …HF may also be the first presentation of cardiovascular disease in many individuals with diabetes. Given that during the past decade, the

Tỷ lệ suy tim bệnh nhân ĐTĐ 22%

Ceriello *et al. Cardiovasc Diabetol* (2021) 20:218
https://doi.org/10.1186/s12933-021-01408-1


Coronary Artery Disease
Insulin resistance
Dyslipidemia
Hyperglycemia
T2DM
Family history
Lifestyle
Age
Sex
Race
Hypertension
Obesity
Myocardial infarction
Toxins and substances
Idiopathic
Arrhythmias
Heart Failure
Infiltrative
Hypertrophic
Inherited
Valvular
Renal Disease



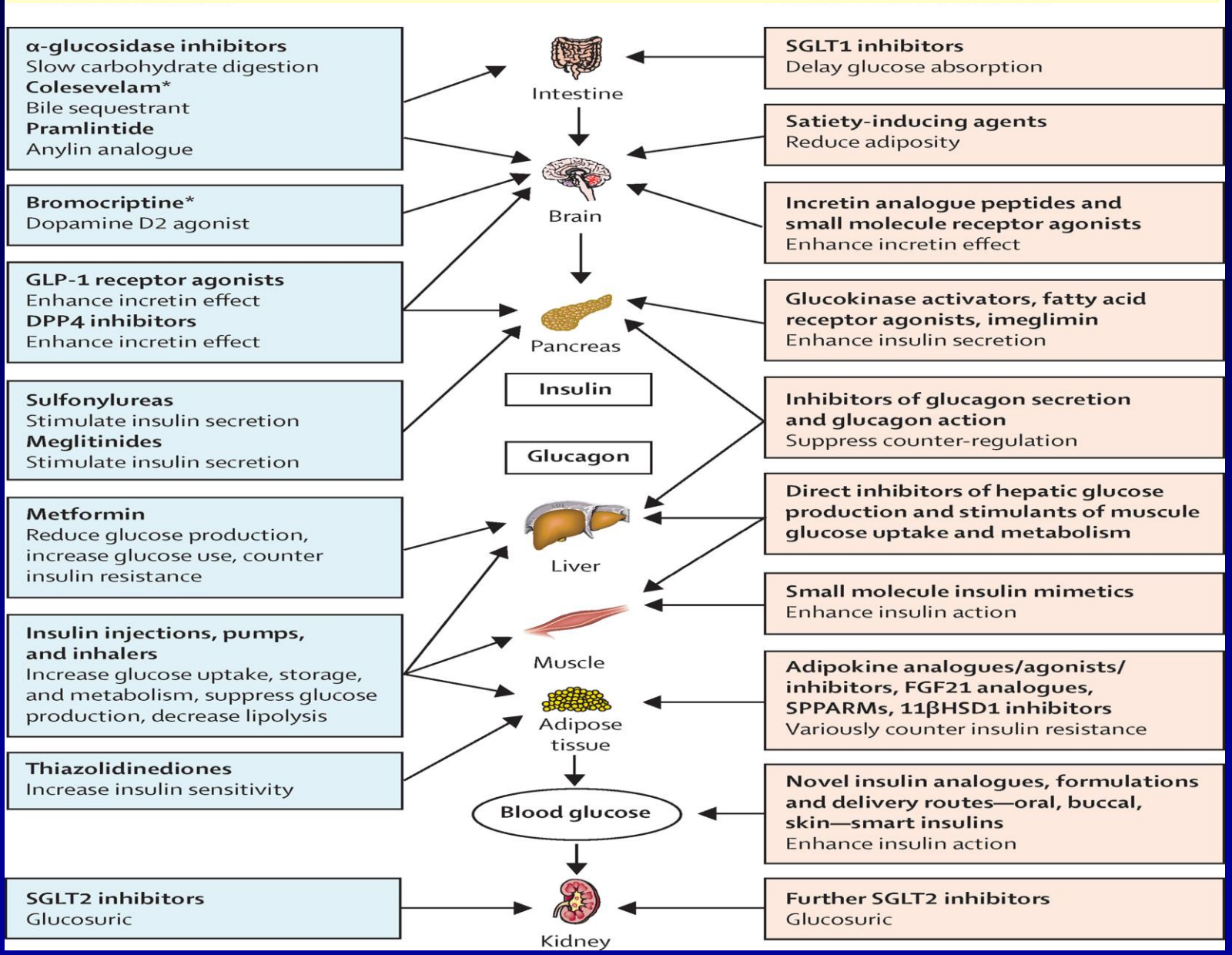
Diabetes and Heart Function:

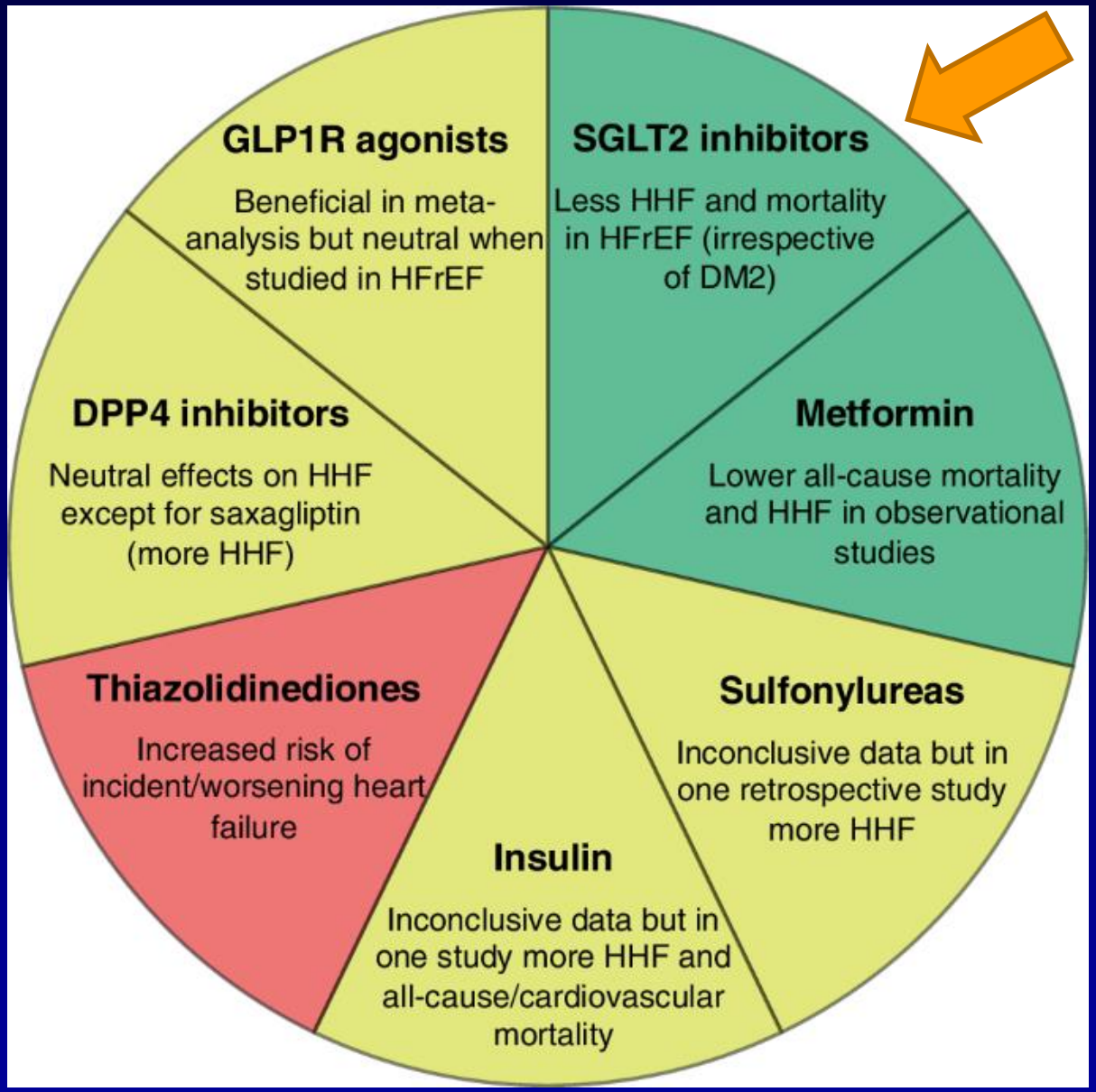
The Staggering Statistics

Nearly 70% of people with type 2 diabetes show signs of heart function loss within 5 years of diagnosis. And up to 50% of people with type 2 diabetes may develop heart failure.

Penn Medicine
Chester County Hospital

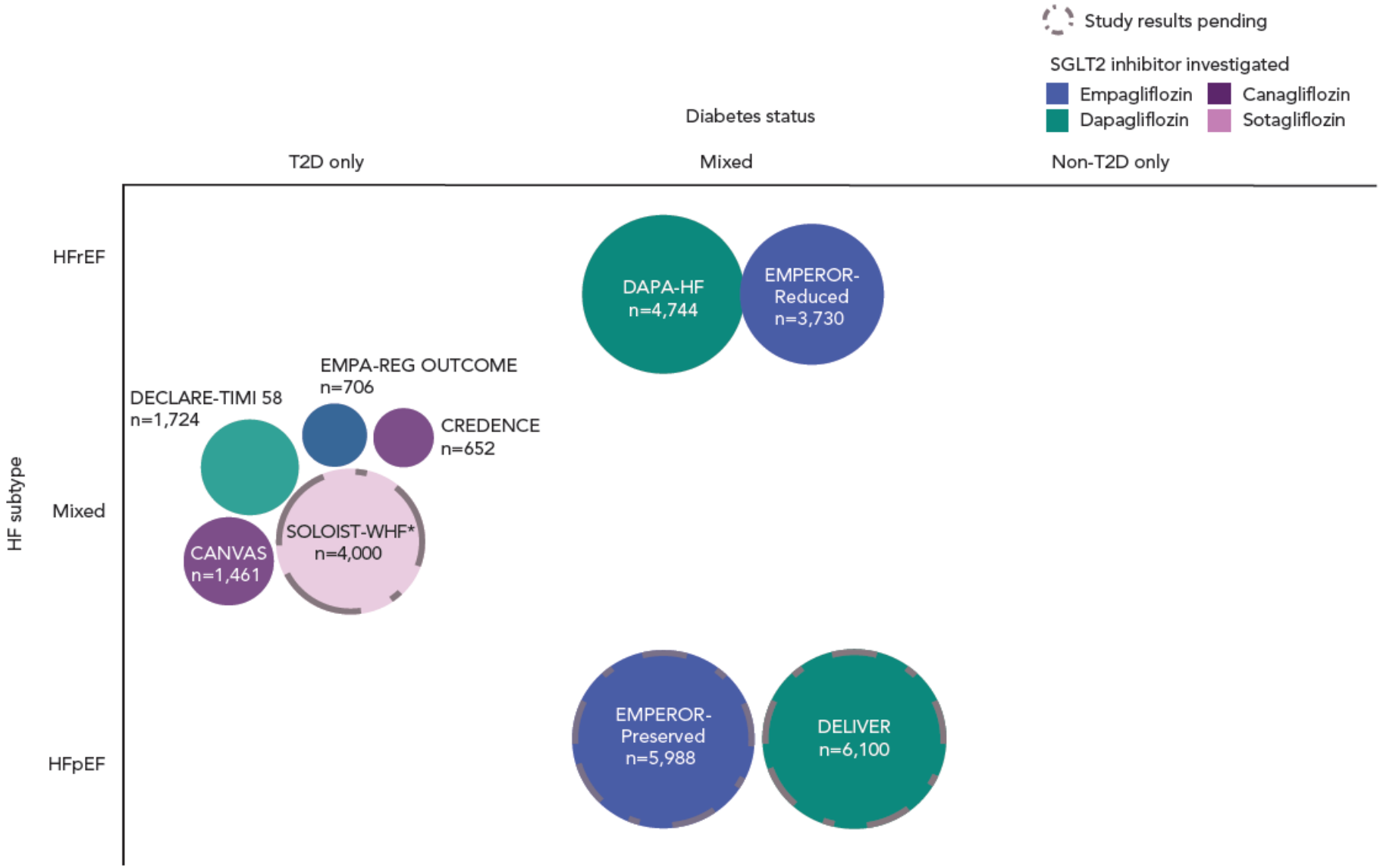
Các nhóm thuốc điều trị ĐTĐ





Các thuộc hạ đường huyết có ảnh hưởng lện suy tim

Figure 2: Number and Clinical Categorisation of Patients With Prior HF in Large-scale Randomised Controlled Trials of SGLT2 Inhibitors



*Each n is the number of patients with reported prior diagnosis of HF within each trial. *SOLOIST-WHF trial was terminated early due to financial concerns; data from the final analysis is pending. HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes. Source: Zinman et al. 2015,[13] Neal et al. 2017,[14] Wiviott et al. 2019,[15] Perkovic et al. 2019,[16] McMurray et al. 2019,[8] NCT03057977, NCT03521934, NCT03057951 and NCT03619213.*

	EMPA-REG OUTCOME (2015)[10]	CANVAS (2017) [7]	DECLARE-TIMI 58 (2019) [19]	VERTIS CV (2020) [11]
Treatment	Empagliflozin Placebo	Canagliflozin Placebo	Dapagliflozin Placebo	Ertugliflozin Placebo
Patient population	Patients (N=7020); T2D and established CVD	Patients (N=10142); T2D and established CVD or ≥2 CVD risk factors	Patients (N=17160); T2D and established CVD or ≥1 CVD risk factors	Patients (N=8246); T2D and established CVD
Established CVD (%)	>99%	65.6%	41%	100%
T2D (%)	100%	100%	100%	100%
Primary outcome	MACE	MACE	MACE CVD death or HHF	MACE
Risk of MACE HR (95% CI); *P* value	0.86 (0.74–0.99); *P* = 0.04	0.86 (0.75–0.97); *P* = 0.02	0.93 (0.84–1.03); *P* = 0.17	0.97 (0.85–1.11); *P* < 0.001 for noninferiority
HHF HR (95% CI); *P* value	–35% 0.65 (0.50–0.85); *P* = 0.002	–33% 0.67 (0.52–0.87); NR	–27% 0.73 (0.61–0.88); NR	–30% 0.70 (0.54–0.90); NR
HHF or CV death HR (95% CI); *P* value	–34% 0.66 (0.55–0.79); *P* < 0.001	–22% 0.78 (0.67–0.91); NR	–17% 0.83 (0.73–0.95); *P* = 0.005	–12% 0.88 (0.75–1.03); *P* = 0.11

	DAPA-HF (2019) [12]	EMPEROR-Reduced (2020) [13]	SOLOIST-WHF (2021) [22]	EMPEROR-Preserved (2021) [30]
Treatment	Dapagliflozin Placebo	Empagliflozin Placebo	Sotagliflozin Placebo	Empagliflozin Placebo
Patient population	Patients (N=4744) with NYHA class II-IV HFrEF	Patients (N=3730) with NYHA class II-IV HFrEF	Patients (N=1222) with HFrEF or HFpEF	Patients (N=5988) with NYHA class II-IV HFpEF
Duration of followup	18.2 months	16 months	9.2 months SOTA; 8.9 months PBO	26.2 months
Ischemic HF (%)	56%	52%	NR	35.4
T2D (%)	42%	50%	100%	49.1
Primary outcome	Worsening HF† or CV death	HHF or CV death	CV death, HHF, and urgent visits for HF	HHF or CV death
Results	**Risk reduction**	**Risk reduction**	**Risk reduction**	**Risk reduction**
Worsening HF‡ or CV death HR (95% CI; *P* value)	↓26%* 0.74 (0.65–0.85); *P* < 0.001; NNT = 21	NR	NR	NR
HHF§ HR (95% CI); *P* value	↓30%† 0.70 (0.59–0.83) NR	↓31%† 0.69 (0.59–0.81); NR	↓36%† 0.64 (0.49–0.83); *P* < 0.001	↓29%† 0.71 (0.60–0.83); NR
HHF or CV death HR (95% CI); *P* value	↓25%† 0.75 (0.65–0.85); *P* < 0.001)	↓25%* 0.75 (0.65–0.86); *P* < 0.001); NNT = 19	NR	↓21%* 0.79 (0.69–0.90); *P* < 0.001
CV death HR (95% CI); *P* value	↓18%† 0.82 (0.69– 0.98); NR	↓8%† 0.92 (0.75–1.12); NR	↓16%† 0.84 (0.58–1.22); NR	↓9%† 0.91 (0.76–1.09) NR
Worsening HF‡ HR (95% CI); *P* value	↓30%† 0.70 (0.59–0.83); NR	NR	NR	NR
CV death, HHF, and urgent visits for HF HR (95% CI); *P* value	NR	NR	↓33%† 0.67 (0.52–0.85; *P* < 0.001	NR

Table 3. SGLT2i trials in renal disease.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
CREDENCE [21] (canagliflozin 100 mg)	↓ ESRD, doubling of sCr, renal death, or CV death 0.70 (0.59–0.82) ($p = 0.00001$)	CREDENCE was the first trial in more than two decades in improving kidney endpoints.
DAPA-CKD [22] (dapagliflozin 10 mg)	↓ Decline in eGFR, new ESRD, renal death, or CV death 0.61 (0.51–0.72) ($p < 0.001$)	Dapagliflozin reduced the risk of eGFR decline, ESRD, and renal or CV death in CKD patients, regardless of diabetic status.
EMPA-KIDNEY [24] (empagliflozin 10 mg)	↓ ESRD, decrease in eGFR, renal death or CV death 0.72 (0.64–0.82) ($p < 0.001$) ↓ Hospitalization 0.86 (0.78–0.95) ($p = 0.003$)	Empagliflozin reduced ESRD, eGFR decline, and renal or CV death in CKD patients, regardless of diabetic status.

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLD, glucose lowering drugs; sCr, serum creatinine.

Chan, J.C.H.; Chan, M.C.Y. SGLT2 Inhibitors: The Next Blockbuster Multifaceted Drug? Medicina 2023, 59, 388. https:// doi.org/10.3390/medicina59020388

Liên quan ức chế SGT2 và Nguy cơ Nhập viện Suy Tim

Table 2. Clinical Trials and effects of the SGLT2i: summary of the clinical trials of SGLT2i, most significant adverse effects, % reduction of hospitalization and primary outcome (* HFrEF: Heart Failure reduced Ejection Fraction).

SGLT2i	Trial	Patients (Number)	Duration of the Study (in Years)	Diabetes	HFrEF *	% Reduction of Primary Outcome	Adverse Effects	% Reduction in Hospitalization
Empagliflozin	EMPEROR-reduced	3730	1.4	With/without	Yes	21%	Uncompleted genital tract infection in patients treated with empagliflozin was reported more frequently compared to the placebo group. However, hypoglycemia, lower limb amputation, and bone fracture were not observed to be significantly different between the two groups.	15.4%
	EMPA-REG	7020	3.1	Yes	N/A	14%		35%
	Emperor-presrved	5988	2.4	With/without	No (LVEF >40%)	N/A		N/A
Dapagliflozin	Declare-TIMI	17,160	4.2	Yes	N/A	N/A	volume depletion, renal dysfunction, and hypoglycemia, were not reported significantly different from the placebo group	17%
	DAPA-HF	4744	1.7	With/without	Yes	21.1%		30%
Canagliflozin	CANVAS	10,142	3.6	Yes	N/A	N/A	with a higher risk of amputation primarily at the level of toe or metatarsal	14.4%
	CREDENCE	4401	2.6	Yes	N/A	N/A		37.5%
Ertugliflozin	VERTIS CV	8246	3.5	Yes	N/A	N/A	urinary infections, observed with ertugliflozin were similar to the known risks of the medicines in the SGLT2 inhibitor class.	N/A
Sotagliflozin	SOLOIST-WHF	1222	0.9	Yes	Yes	33%	Diarrhea (SGLT1 inhibition), diabetic ketoacidosis, genital mycotic infections, and volume depletion, severe hypoglycemia.	30%
	SCORED	10,584	1.3	Yes	N/A	N/A		33%

Saverio Muscoli et als. The New Role of SGLT2 Inhibitors in the Management of Heart Failure: Current Evidence and Future Perspective Pharmaceutics 2022, 14, 1730. https://doi.org/10.3390/pharmaceutics14081730

HEART FAILURE - MEDICATION

NEURO

Ivabradine
- Slows impulses from the sinus node in the right atrium slowing the heart rate
- Recommended for people with systolic HF and sinus rhythm ≥75 bpm, either in combination with standard therapy or if a beta-blocker is not tolerated

Beta-blockers
- Blocks the effects of adrenaline on the beta-receptor in the heart
- Slows the heart rate to reduce arrhythmia and lowers BP

Ace Inhibitors
- Inhibit the conversion of angiotensin I to angiotensin II
- Reduce vasoconstriction and production and retention of aldosterone, reducing BP and therefore the demands on the heart

Sacubitril/valsartan
- Sacubitril inhibits action of the enzyme neprilysin to enhance the beneficial effects of ANP and BNP
- Valsartan, an ARB, blocks angiostein II receptor sites to limit activation of the RAAS and prevent vasoconstriction and sodium and fluid retention by the kidneys

HORMONAL

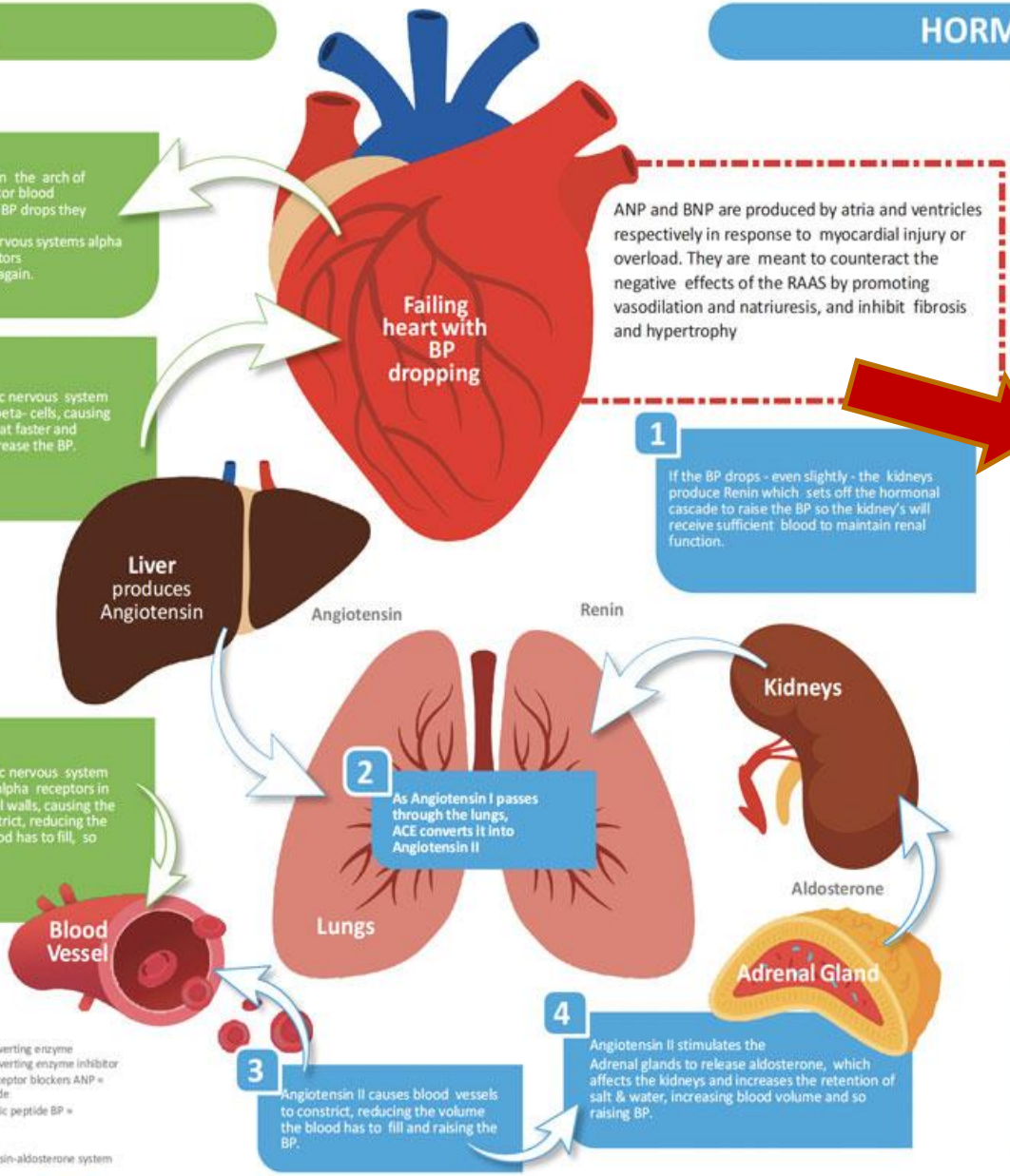
Diuretics
- Reduce sodium reabsorption by the kidneys to increase volume of urine excreted
- Lower workload on the heart and reduce oedema to ease breathing
- Titrate according to need following initiation of other HF therapies

SGLT2 inhibitors (Gliflozins)
- Inhibit glucose reabsorption in the kidney via the sodium glucose transport protein 2
- Diuresis results in glucose excretion
- Evidence of reduced morbidity and mortality in Heart Failure in Diabetic AND non-Diabetic patients

Spironolactone
- Is an aldosterone antagonist
- Prevents fluid retention caused by aldosterone
- Monitor potassium carefully

Eplerenone
- Selective aldosterone antagonist that is more specific than spironolactone with fewer side effects such as gynaecomastia
- Prevents fluid retention caused by aldosterone
- Monitor potassium carefully

ARBs
- Block the angiotensin II receptor sites in the adrenal glands and the blood vessels
- Limit activation of the RAAS to prevent vasoconstriction and sodium and fluid retention by the kidneys



KEY
ACE = angiotensin-converting enzyme
ACEI - angiotensin-converting enzyme inhibitor
ARBs = angiotensin receptor blockers ANP = atrial natriuretic peptide
BNP = B-type natriuretic peptide BP = blood pressure
HF = heart failure
RAAS = renin-angiotensin-aldosterone system

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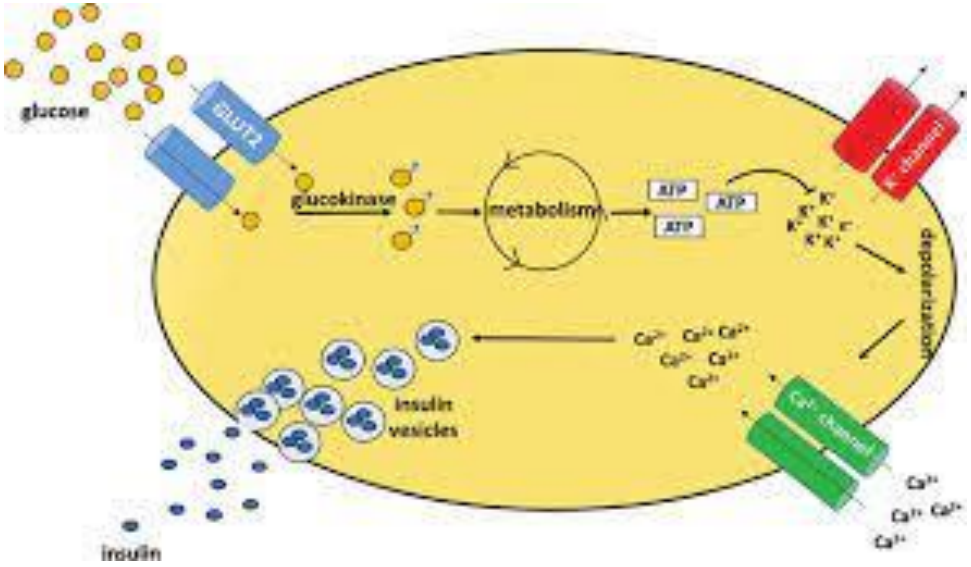
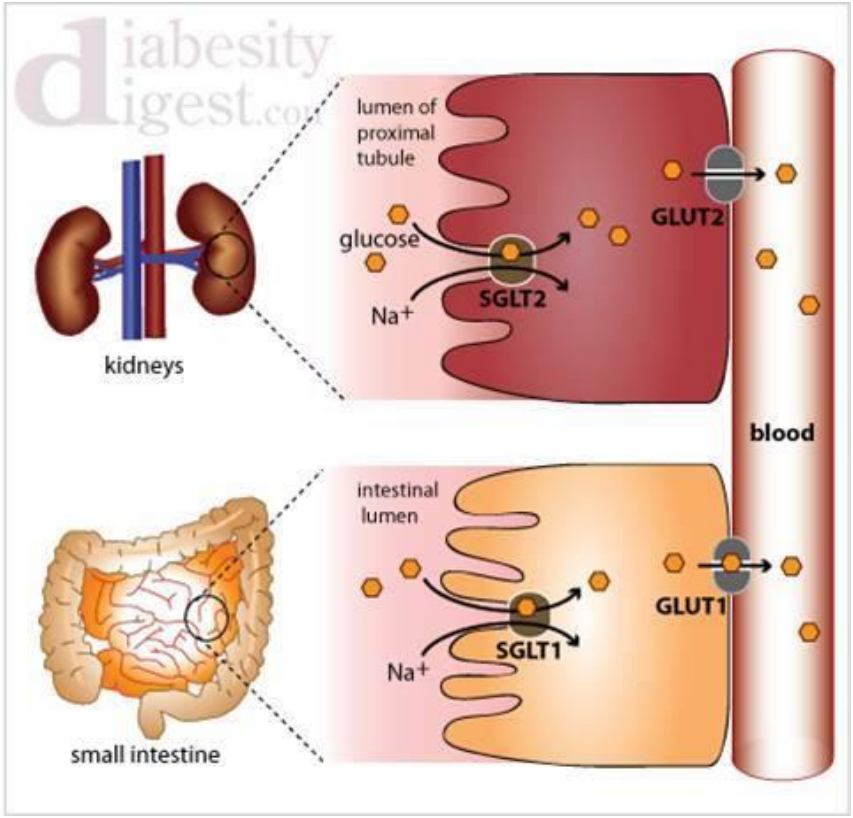
2. NHÓM ỨC CHẾ ĐỒNG VẬN CHUYỂN GLUCOSE –NATRI 2 ?

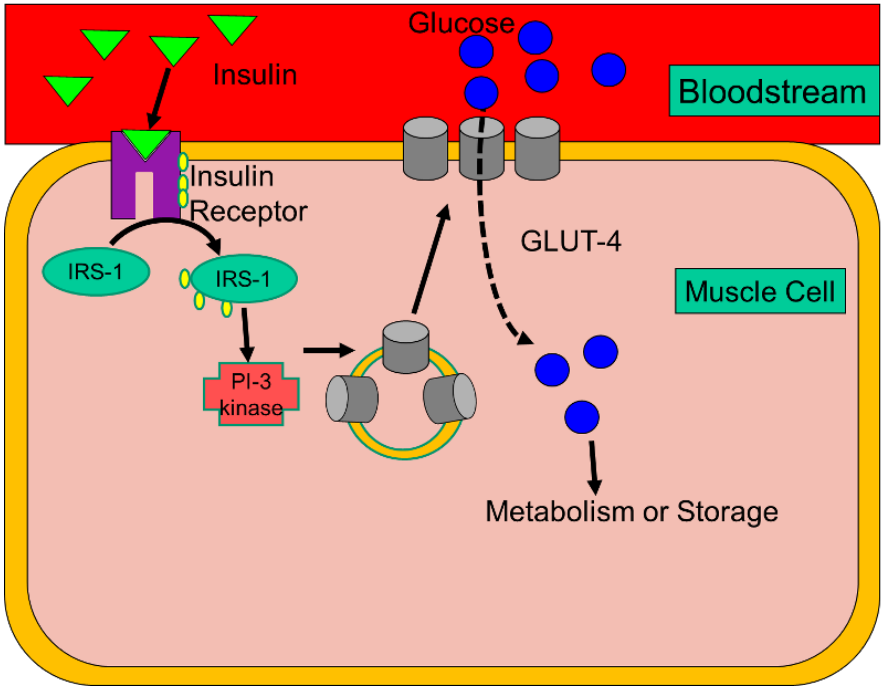
(SGLT2I = Sodium-glucose Cotransporter-2 Inhibitors)

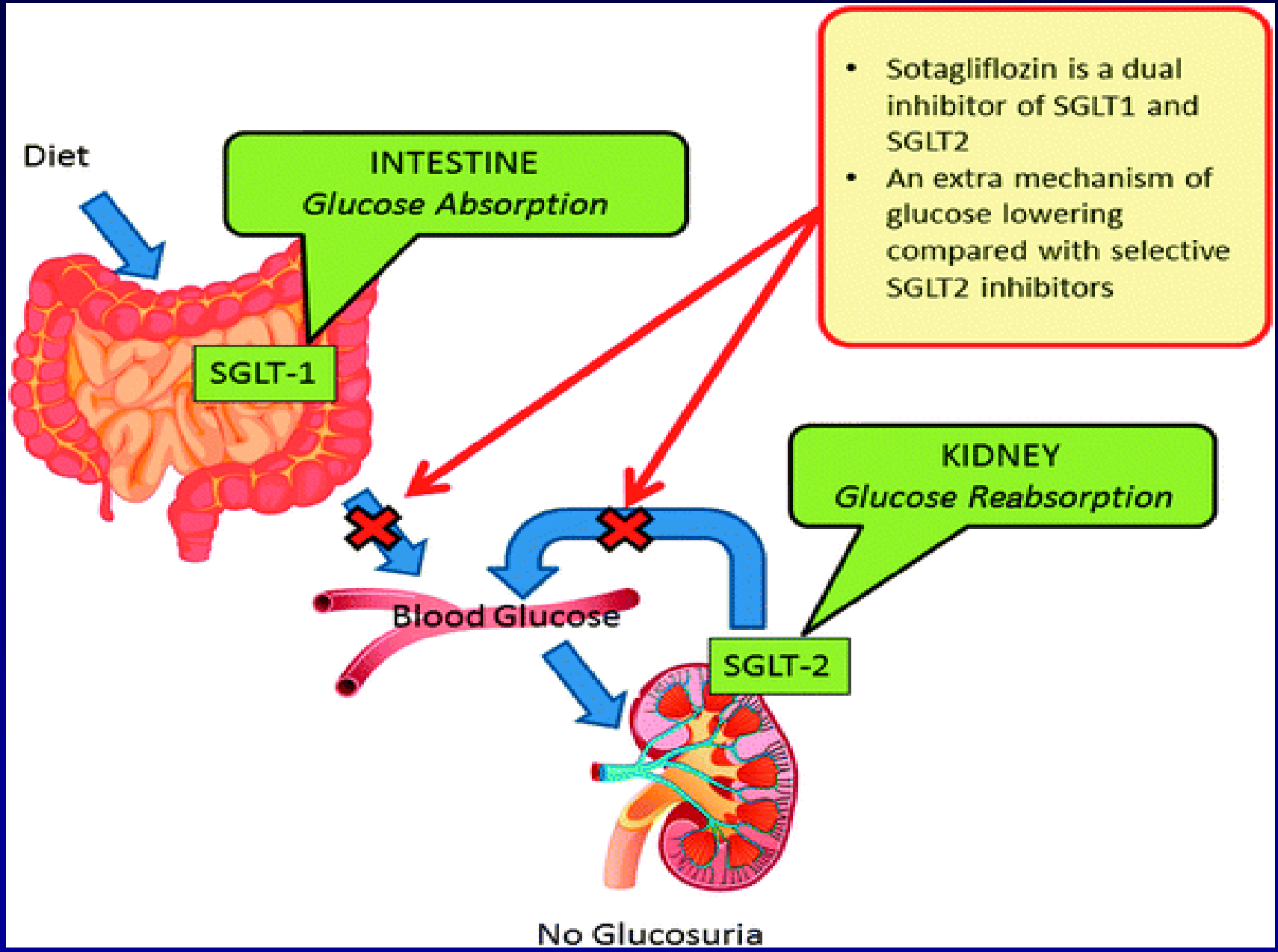
Các nhà hóa học người Pháp (1835) lần đầu tiên phân lập được Phlorizin từ vỏ cây táo, Joseph von Mering (1886) BS người Đức đã tiên phong trong giai đoạn đầu của bệnh ĐTĐ đã chứng minh uống liều cao phlorizin làm tăng thải glucose qua nước tiểu…

Có 3 HỆ THỐNG VẬN CHUYỂN GLUCOSE VÀO NỘI BÀO

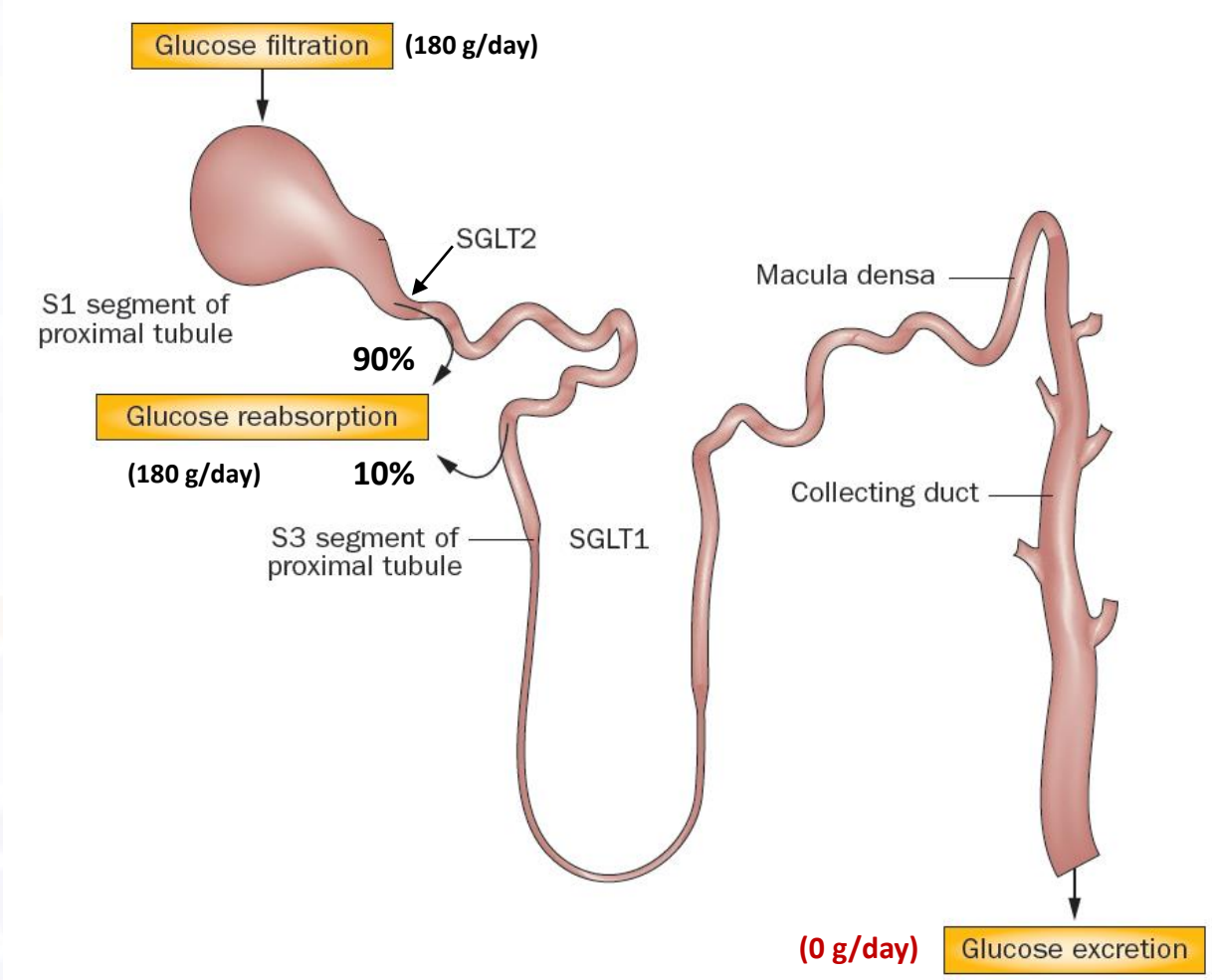






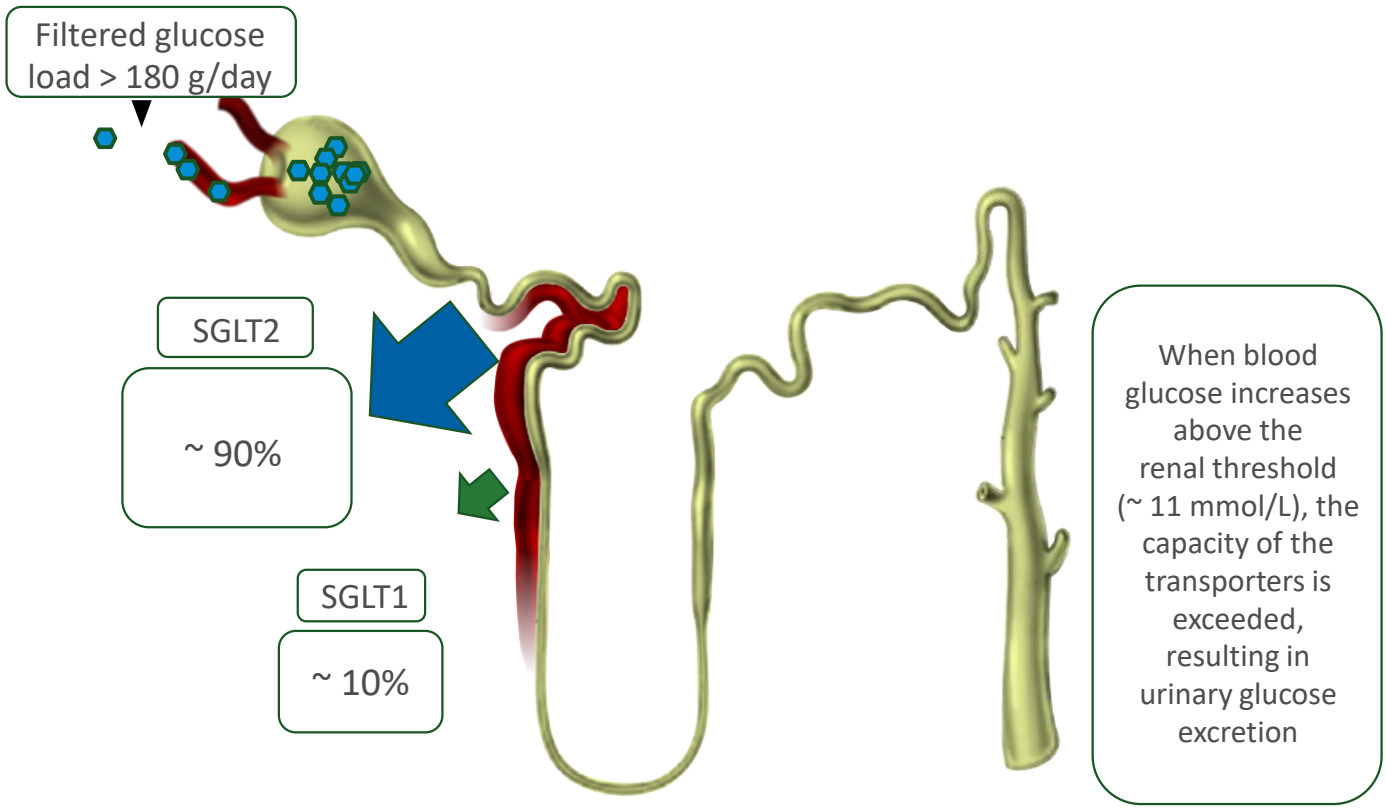

Diet
INTESTINE
Glucose Absorption
SGLT-1
Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2
An extra mechanism of glucose lowering compared with selective SGLT2 inhibitors
KIDNEY
Glucose Reabsorption
Blood Glucose
SGLT-2
No Glucosuria

SGLT2 inhibitors, also called **Gliflozins**



Adapted from Ferrannini E, Solini A. *Nat Rev Endocrinol*. 2012;8:495-502.

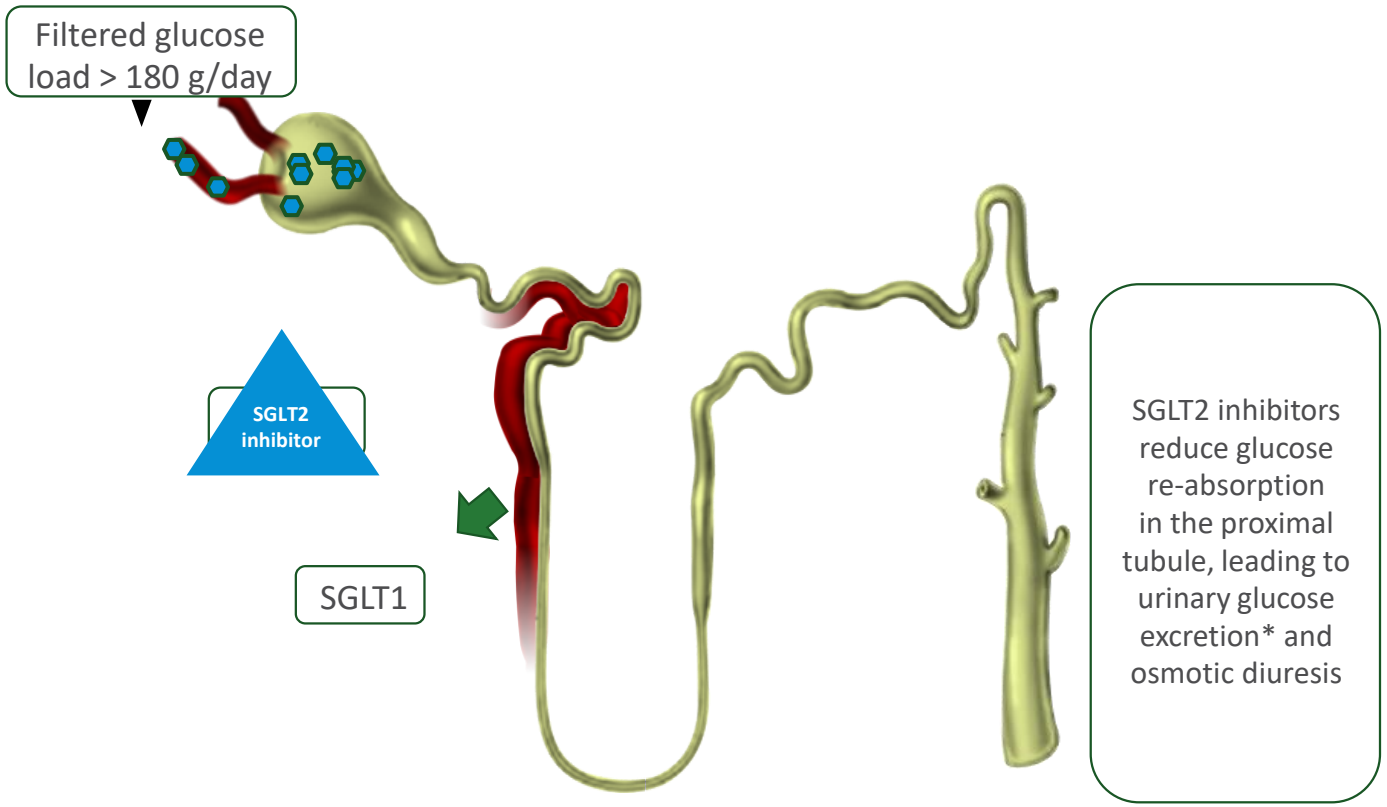
Renal glucose re-absorption in patients with diabetes[1,2]



SGLT, sodium glucose cotransporter.

1. Adapted from: Gerich JE. *Diabet Med*. 2010;27:136–142; 2. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Urinary glucose excretion via SGLT2 inhibition[1]



SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.
1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

11 thuốc nhóm ức chế SGLT2 (2012-2023)

1.Bexagliflozin was approved in the United States under the brand name Brenzavvy in January 2023.[26]

2.Canagliflozin was the first SGLT2 inhibitor to be approved for use in the United States. It was approved in March 2013, under the brand name Invokana and it was also marketed throughout the EU under the same name.[27][28]

3.Dapagliflozin is the first SGLT2 inhibitor approved anywhere in the world by the EU in 2012.[29] It was approved for use in the United States under the brand name Farxiga by the Food and Drug Administration in January 2014.[30] the first oral treatment in combination with insulin to treat type 1 DM in UK and EU.

4.Empagliflozin, approved in the United States in August 2014, under the brand name Jardiance by Boehringer Ingelheim.[31] Of the gliflozins, empagliflozin and tofogliflozin have the highest specificity for SGLT2 inhibition.[1] This oral medicine for type 2 diabetes has been shown to reduce the risk of CVD death.[32]

5.Ertugliflozin was approved in the United States under the brand name Steglatro in December 2017.[33]

6.Ipragliflozin, produced by the Japanese company Astellas Pharma Inc. under the brand name Suglat, approved in Japan January 2014.[34][35]
7.Luseogliflozin was approved in Japan March 2014 under the brand name Lusefi and was developed by Taisho Pharmaceutical.[36]
8.Remogliflozin etabonate was commercially launched first in India by Glenmark in May 2019.
9.Sergliflozin etabonate discontinued after Phase II trials.[37]
10. Sotagliflozin is a dual SGLT1/SGLT2 inhibitor in phase III trials under the brand name Zynquista. Developed by Lexicon pharmaceuticals. It was planned to be the first oral treatment in combination with insulin to treat type 1 diabetes mellitus.[38] The Food and Drug Administration refused its approval for use in combination with insulin for the treatment of type 1 diabetes.[39][40]
11.Tofogliflozin was approved in Japan in March 2014, under the brand names Apleway and Deberza developed by Sanofi and Kowa Pharmaceutical.[41]

PHARMACOKINETIC PARAMETERS OF VARIOUS SGLT-2 INHIBITORS

Name of drug	Bioavailability	Protein binding	tmax (hours)	**t1/2 (hours)**	Cmax	**SGLT2 selectivity over SGLT1**
Canagliflozin	65% (300 mg dose)	99%	1–2	**10.6 (100 mg dose); 13.1 (300 mg dose)**	1096 ng/mL (100 mg dose); 3480 ng/mL (300 mg dose)	**250 fold**
Dapagliflozin	78%	91%	1–1.5	**12.9**	79.6 ng/mL (5 mg dose); 165.0 ng/mL (10 mg dose)	**1200 fold**
Empagliflozin	90–97% (mice); 89% (dogs); 31% (rats)	86.20%	1.5	**13.2 (10 mg dose); 13.3h (25 mg dose)**	259nmol/L (10 mg dose); 687nmol/L (25 mg dose)	**2500 fold**
Ertugliflozin	70-90%	95%	0.5-1.5	**11-17**	268 ng/mL (15 mg dose)	**2000 fold**
Ipragliflozin (50 mg)	90%	96.30%	1	**15–16 (50 mg dose)**	975 ng/mL	**360 fold**
Luseogliflozin	35.3% (male rats); 58.2% (female rats); 92.7% (male dogs)	96.0–96.3%	0.625±0.354	**9.24±0.928**	119±27.0 ng/mL	**1650 fold**
Tofogliflozin (10 mg)	97.50%	83%	0.75	6.8	489 ng/mL	**2900 fold**

Madaan, Tushar; Akhtar, Mohd.; Najmi, Abul Kalam (2016). "Sodium glucose Co Transporter 2 (SGLT2) inhibitors : Current status and future perspective". European Jour*nal of Pharmaceutical Sciences.* ***93****: 244-252–* . doi:10.1016/j.ejps.2016.08.025. PMID 27531551.

3. Cơ chế bảo vệ Tim Mạch của nhóm ức chế SGLT2 ?

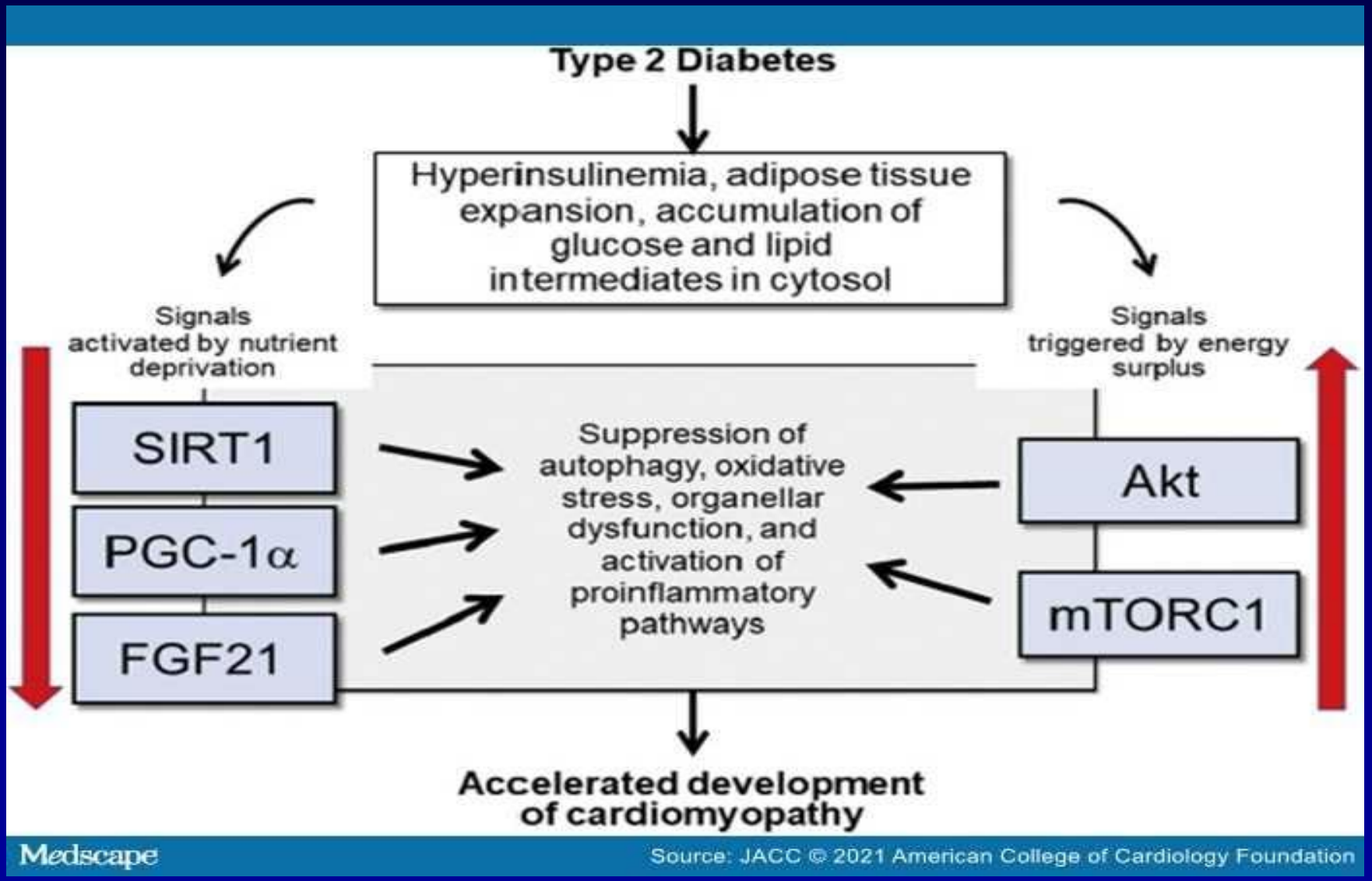
Hệ thống SGLT

Sodium-**Gl**ucose Co**t**ransporter

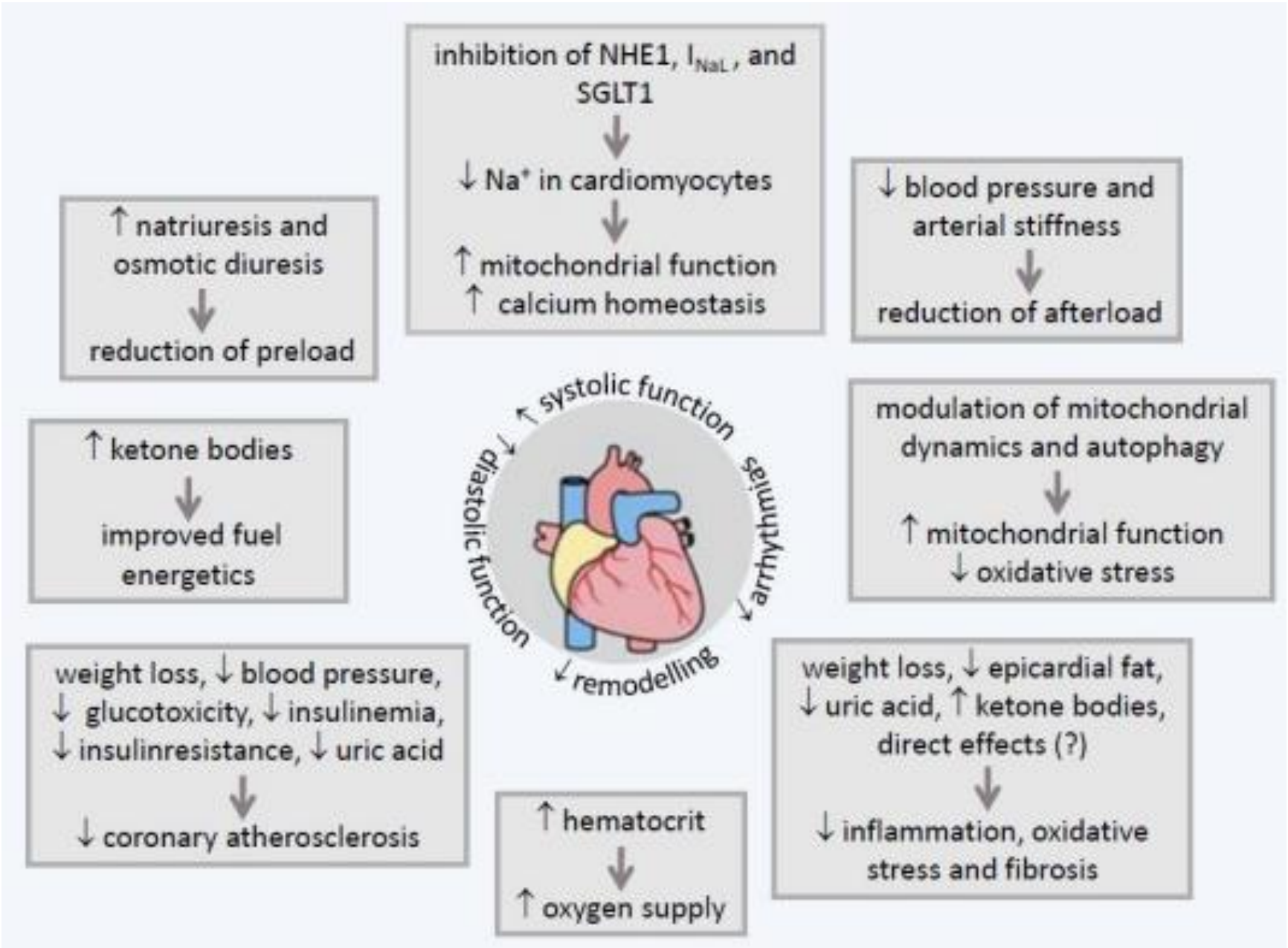
SGLT	Expressed in human tissues
SGLT1	Intestine, trachea, kidney, heart, brain, testis, prostate
SGLT2	**Kidney**, brain, liver, thyroid, muscle, **Heart**

Ratios of activity between SGLT1 and SGLT2 may be helpful in defining expression.

Tiến triển tổn thương Cơ Tim trong ĐTĐ Típ 2

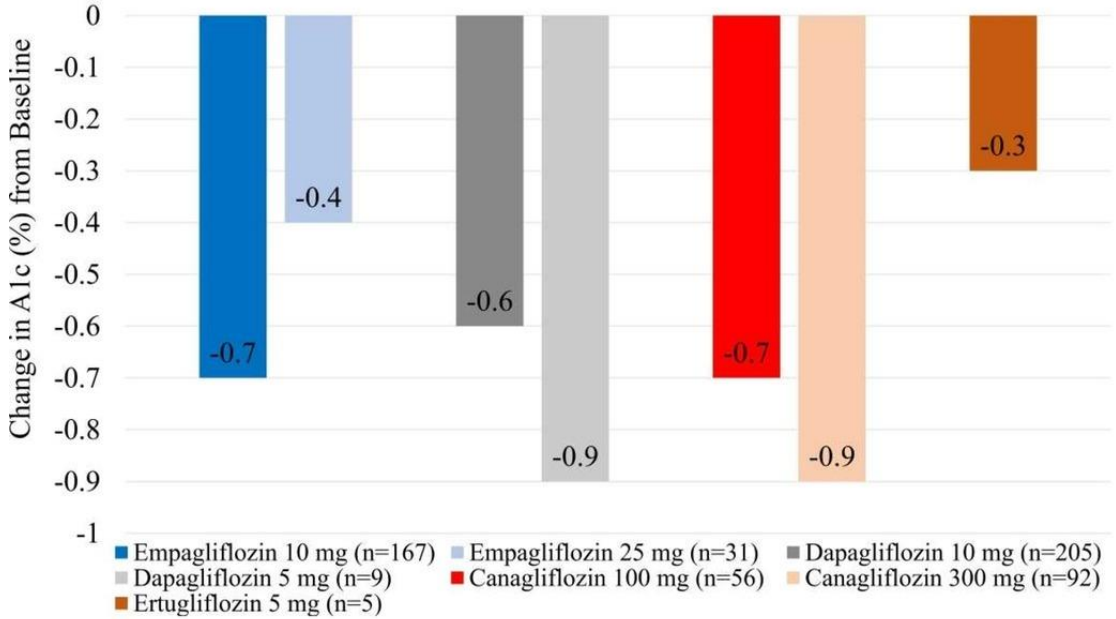


Tác dụng chính bảo vệ Tim của ức chế SGLT2



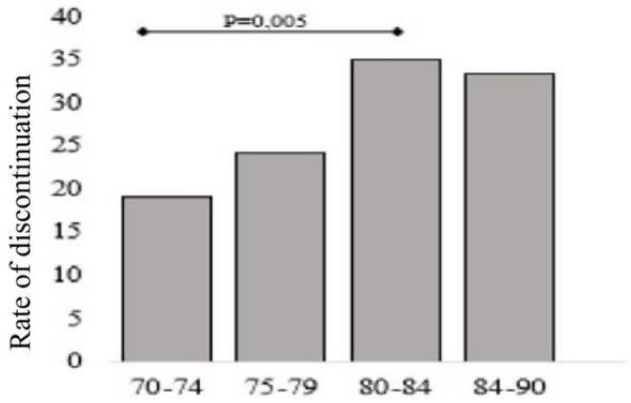
Ức chế SGLT2 giảm HbA1c

Outcomes of the SOLD study



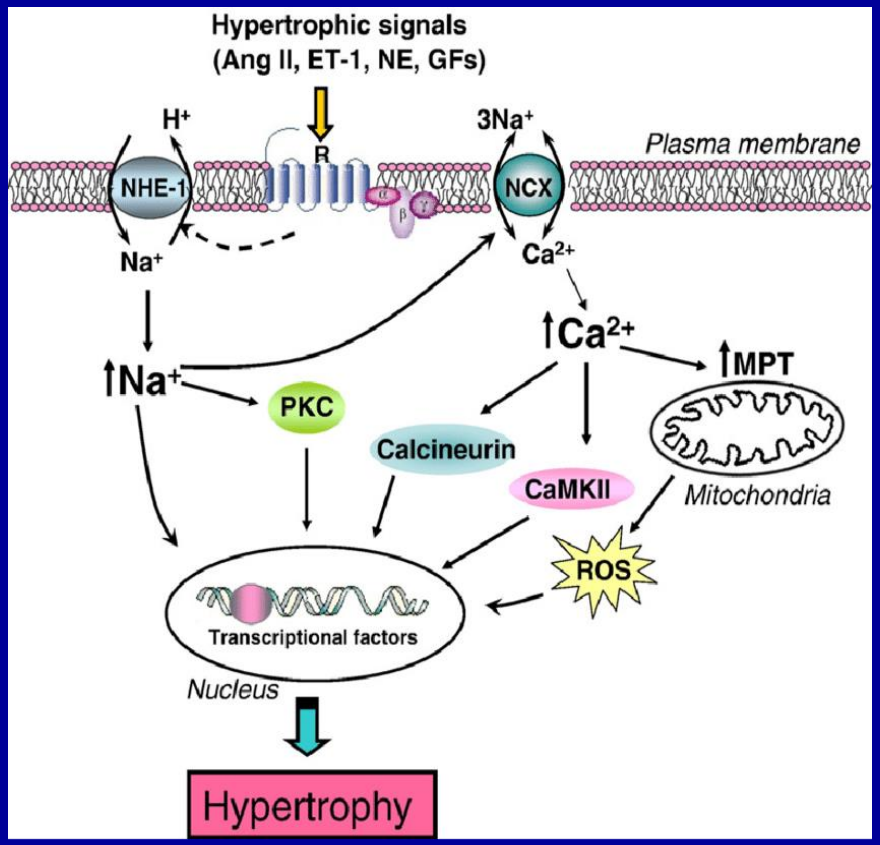
Factors related to a higher probability of SGLT2-i suspension

	OR	P value
Sex	0,804	0,302
Years of disease	0,977	0,084
Age	1,046	0,068
BMI (Kg/m²)	0,920	0,001
FPG (mg/dL)	0,990	0,000
HbA1c (%)	1,927	0,000
S-Creatinine (mg/dl)	2,270	0,207
eGFR (ml/min/1,73 m²)	0,969	0,000
CVD	1,297	0,202

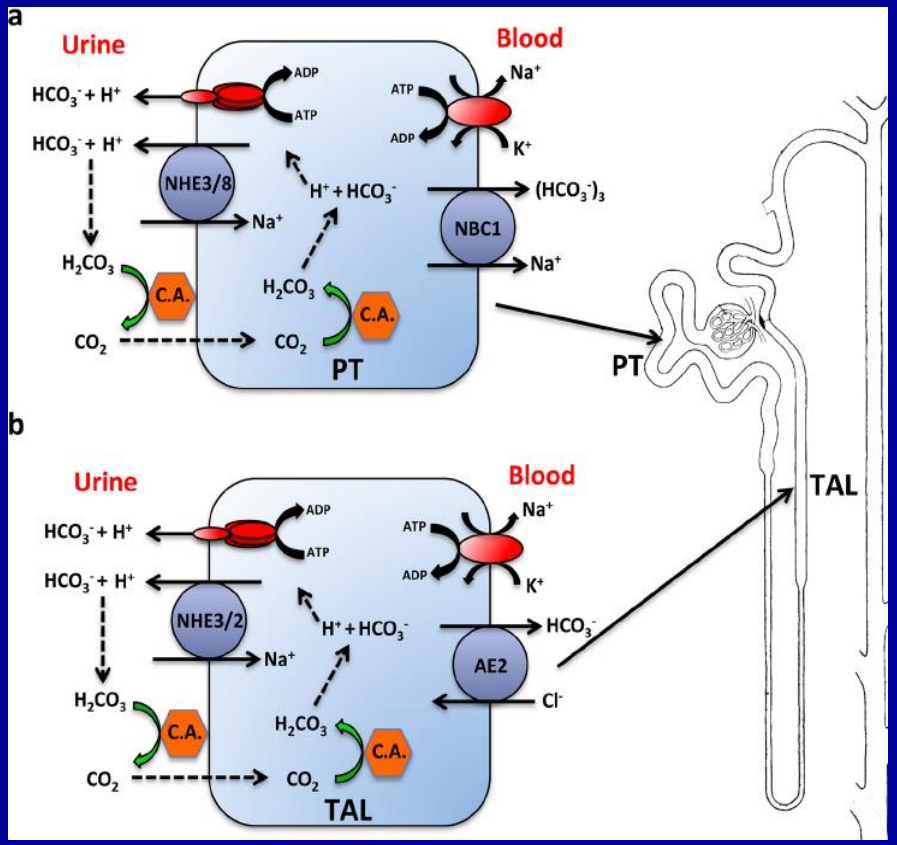


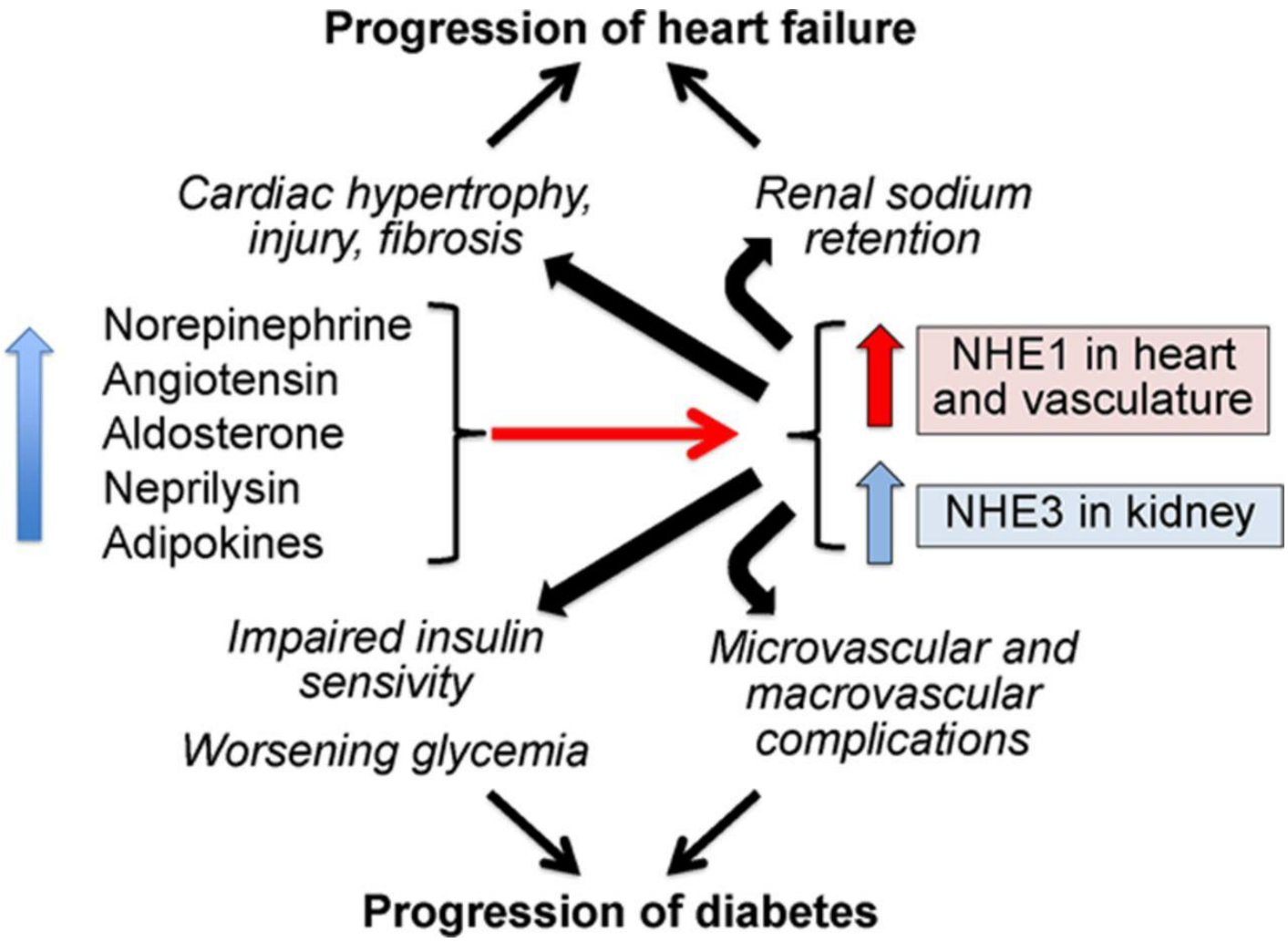
Ức chế SGLT2 & Hệ thống trao đổi Natri–Hydro (Sodium-Hydrogen Exchanger-NHE)

NHE1 (tim)



NHE3 (thận)



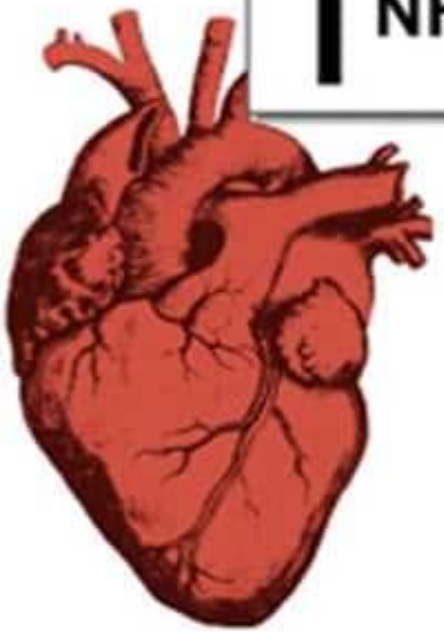


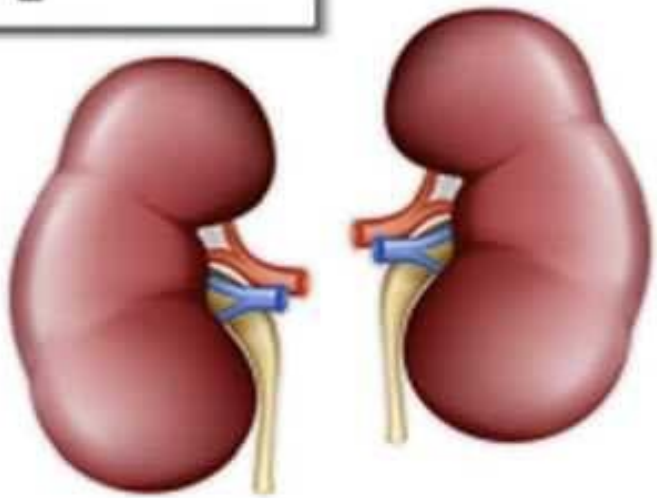
Packer M. (2017) Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With That of Heart Failure. Circulation. 2017 Oct 17;136(16):1548-1559.

Type 2 Diabetes

↑ NHE1

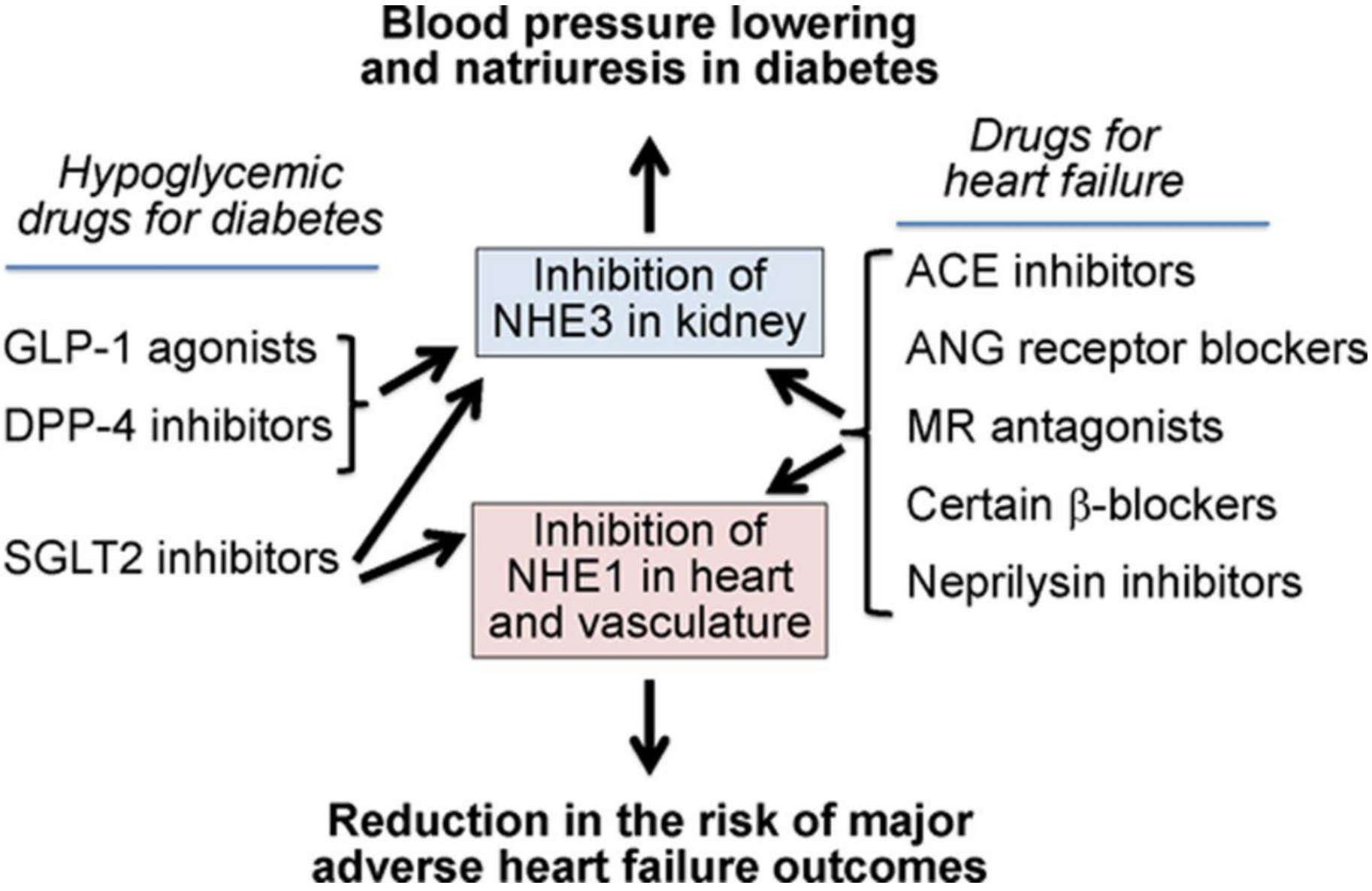
↑ NHE3





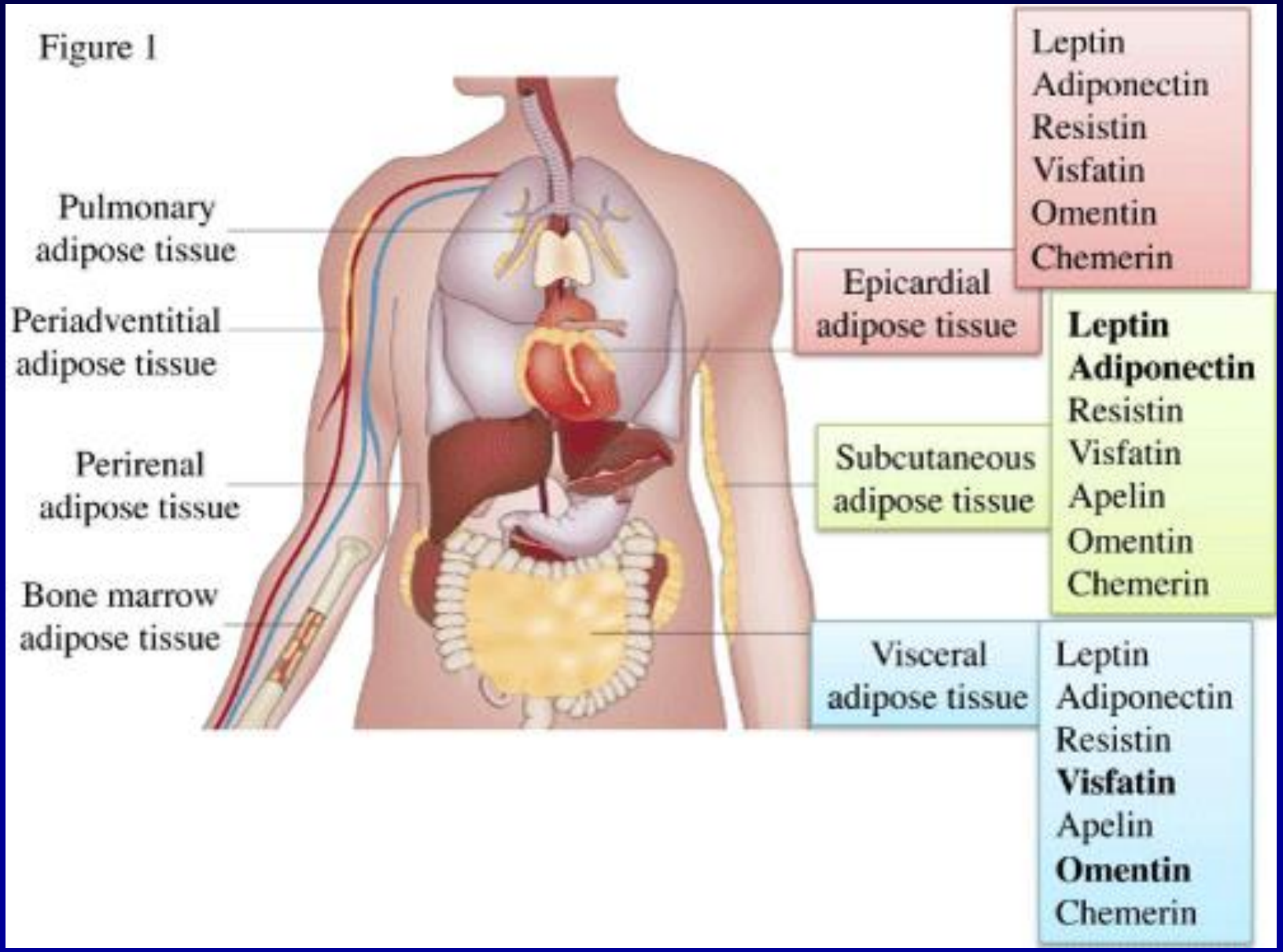
Cardiac injury
Cardiomyopathy

Renal tubular sodium hyperreabsorption



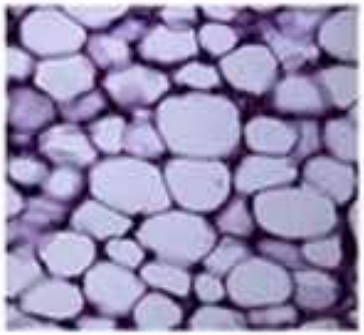
Packer M.(2017) Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With That of Heart Failure. Circulation. 2017 Oct 17;136(16):1548-1559.

Ức chế SGLT2 và Adipocytokine viêm tại các tổ chức mỡ

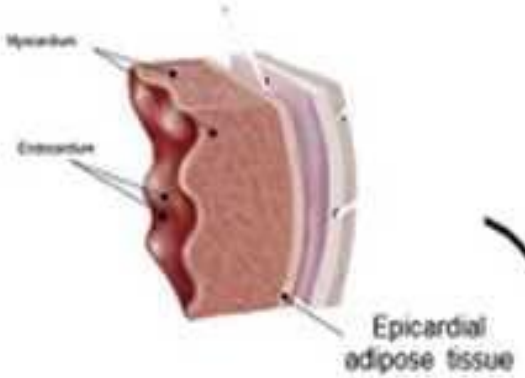


Type 2 Diabetes

Systemic adipose tissue inflammation



Expansion and inflammation of epicardial adipose tissue



Paracrine secretion of proinflammatory adipocytokines

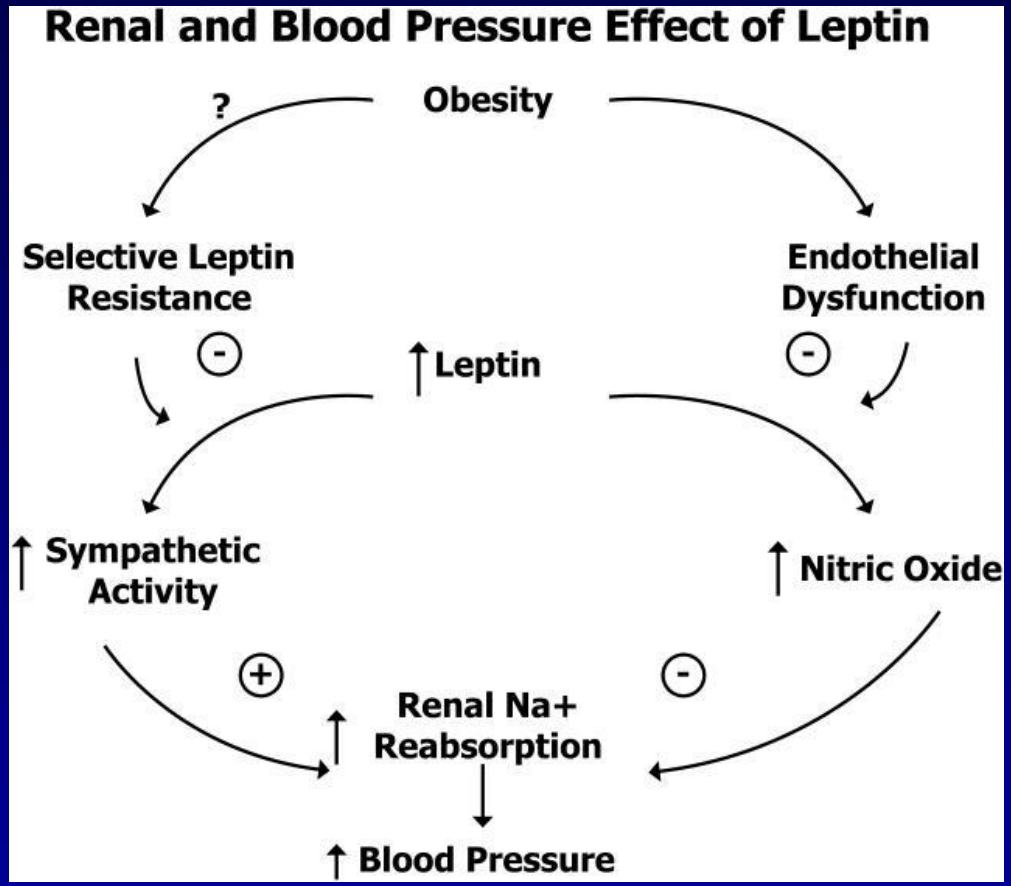
Coronary microcirculatory dysfunction

Microvascular rarefaction, myocardial inflammation and fibrosis

Impaired LV distensibility

Heart failure with preserved ejection fraction

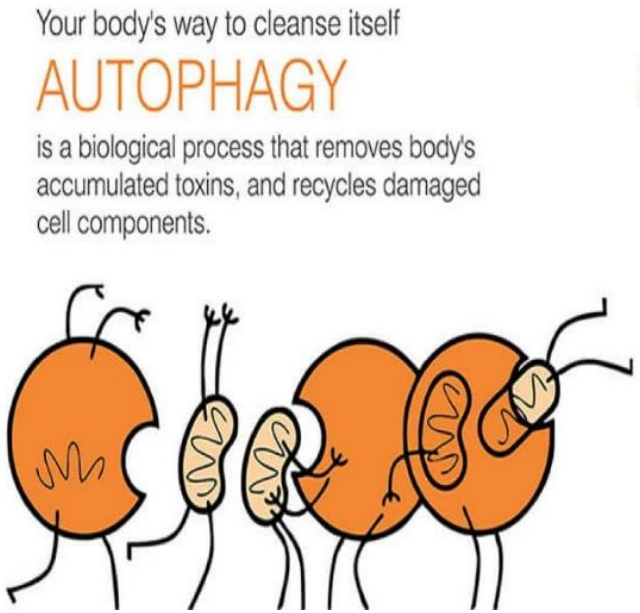
Ức chế SGLT2 giảm Leptin



Ức chế SGLT2 làm giảm sự tích tụ và viêm của quá trình tiết leptin và các hoạt động cận tiết của leptin đối với tim và thận để thúc đẩy quá trình xơ hóa.
Sự xơ hóa góp phần làm suy yếu mô mỡ ở tim, do đó giảm thiểu khả năng căng và chức năng cầu thận đặc trưng cho HFpEF liên quan đến béo phì.

Milton Packer (2018) .Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis .. 23 January 2018

Tự thực tế bào (Autophagy)

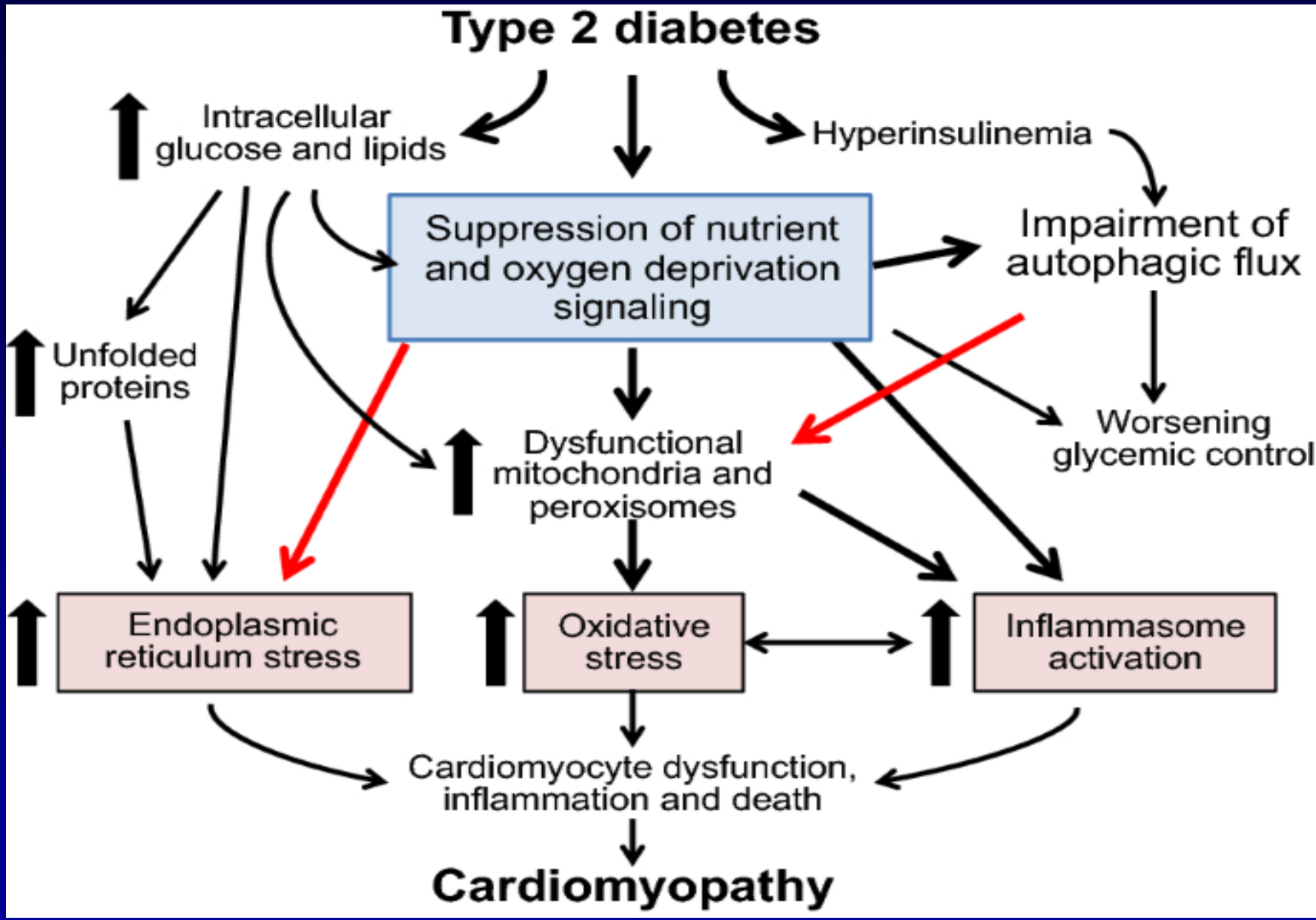


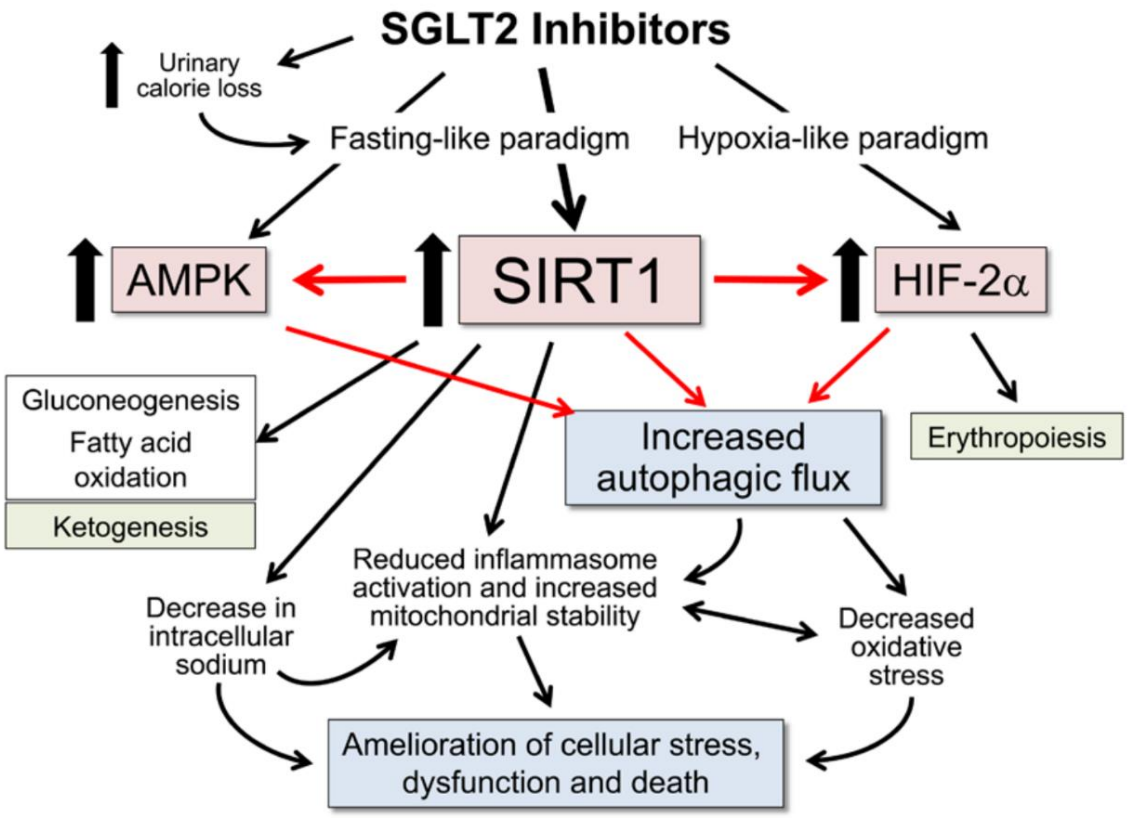
- **Cơ chế "tự thực" để đổi mới**

"Autophagy" là thuật ngữ xuất phát từ tiếng Hy Lạp với thành tố auto (tự) và phagein (ăn, thực).

Cơ chế "tự thực" là một cơ chế cơ bản của việc phân hủy và tái chế các thành phần của tế bào.

Các tế bào "tự ăn" tức làm cho mất đi và "tái chế" tức tạo ra các thành phần của chính mình để đổi mới.


Type 2 diabetes
Intracellular glucose and lipids
Hyperinsulinemia
Suppression of nutrient and oxygen deprivation signaling
Impairment of autophagic flux
Unfolded proteins
Dysfunctional mitochondria and peroxisomes
Worsening glycemic control
Endoplasmic reticulum stress
Oxidative stress
Inflammasome activation
Cardiomyocyte dysfunction, inflammation and death
Cardiomyopathy

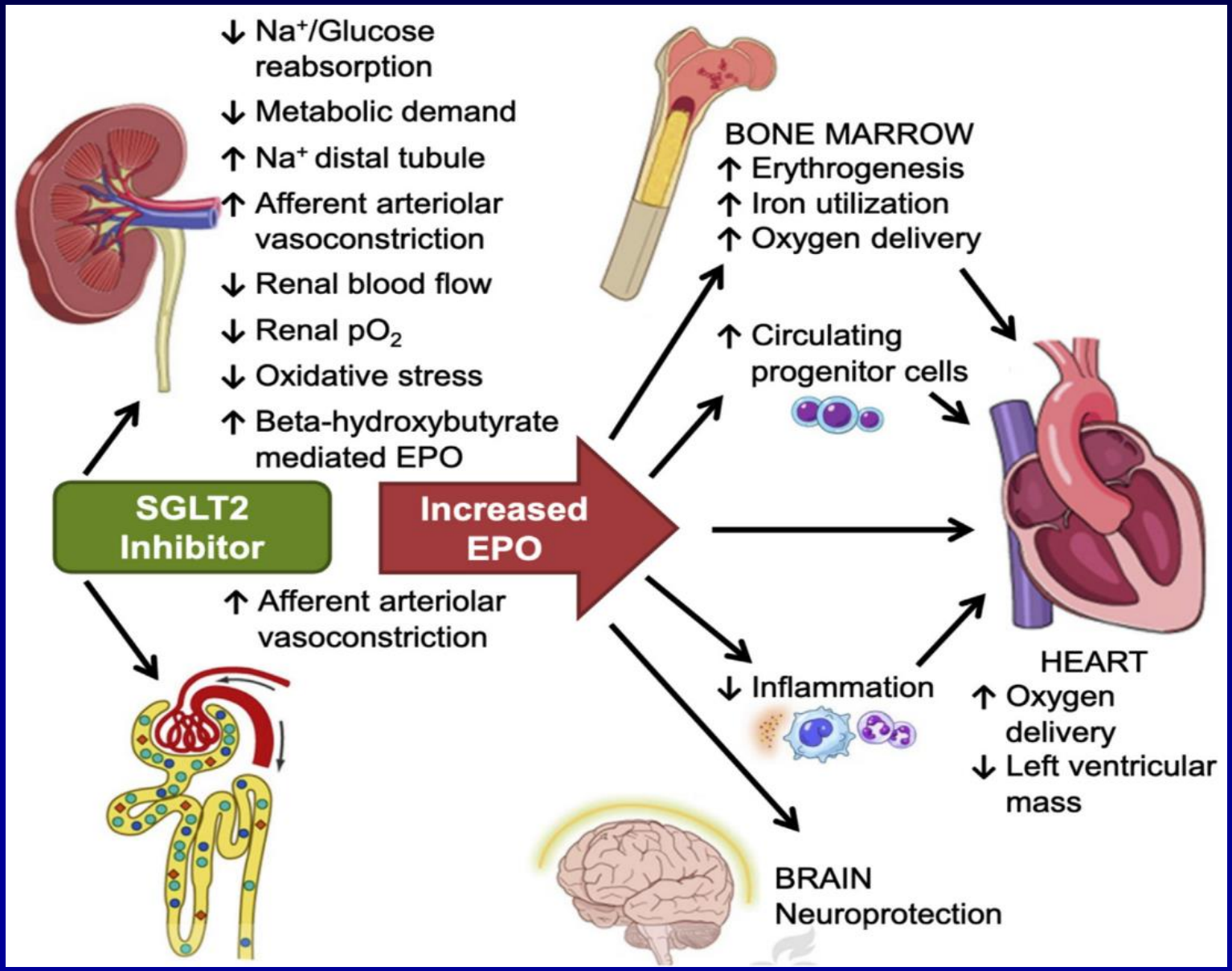


Sơ đồ giải thích các cơ chế phân tử làm cơ sở cho tác dụng ức chế SGLT2 nhằm giảm suy tim nghiêm trọng và các biến cố bất lợi ở thận.

Việc kích hoạt các cảm biến thiếu dinh dưỡng và oxy (màu hồng), trong khi các dấu hiệu sinh học của sự kích hoạt này như keton huyết và tân tạo hồng cầu (xanh lá cây).

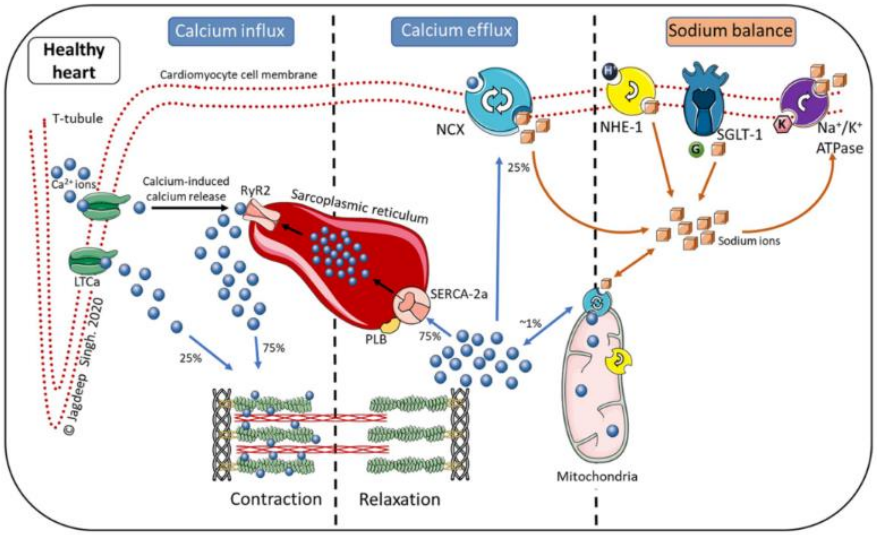
AMPK indicates AMP-activated protein kinase; HIF-2α, hypoxia inducible factor isoform 2α; SIRT1, sirtuin-1

Ức chế SGLT2 và EPO

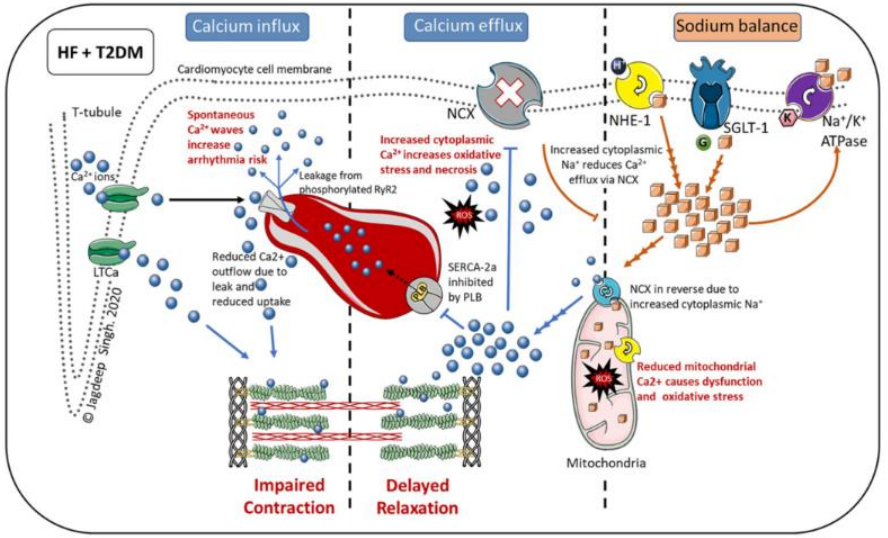


So sánh Cân bằng Natri và Calci trong cơ tim người không ĐTĐ và người ĐTĐ

a.



b.

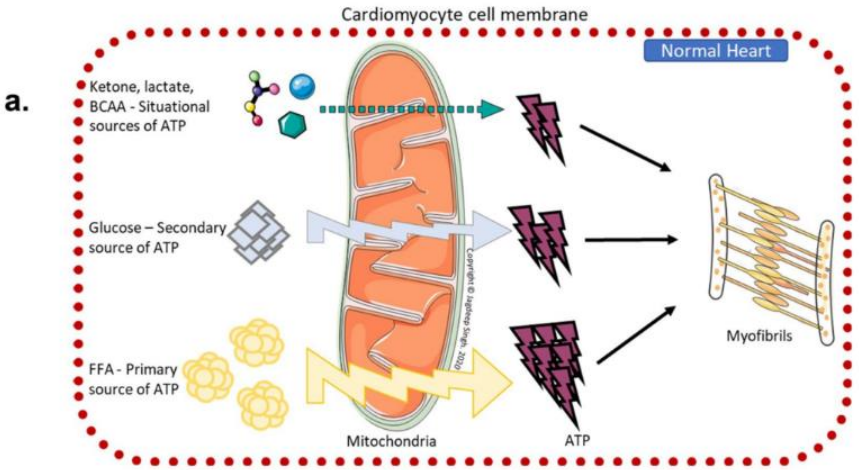


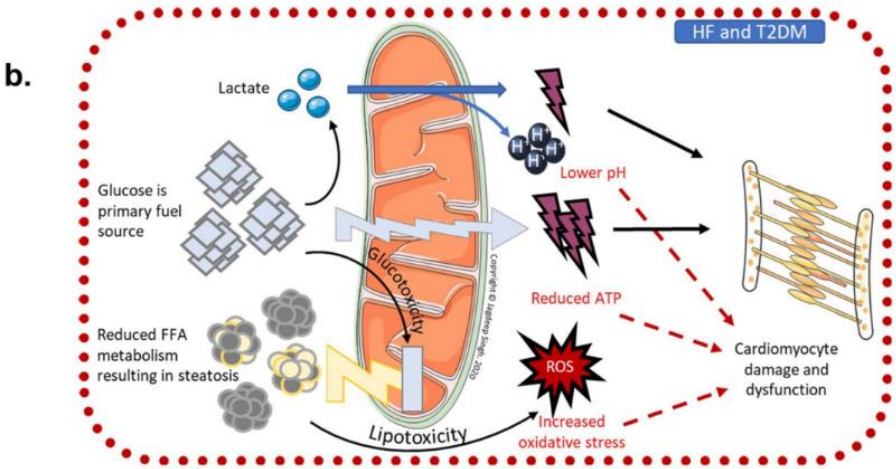
2a: Cân bằng Natri và Calci trong cơ tim trên người bình thường

2b: Mất cân bằng Natri và Calci trong cơ tim trên người suy tim và ĐTĐ típ 2

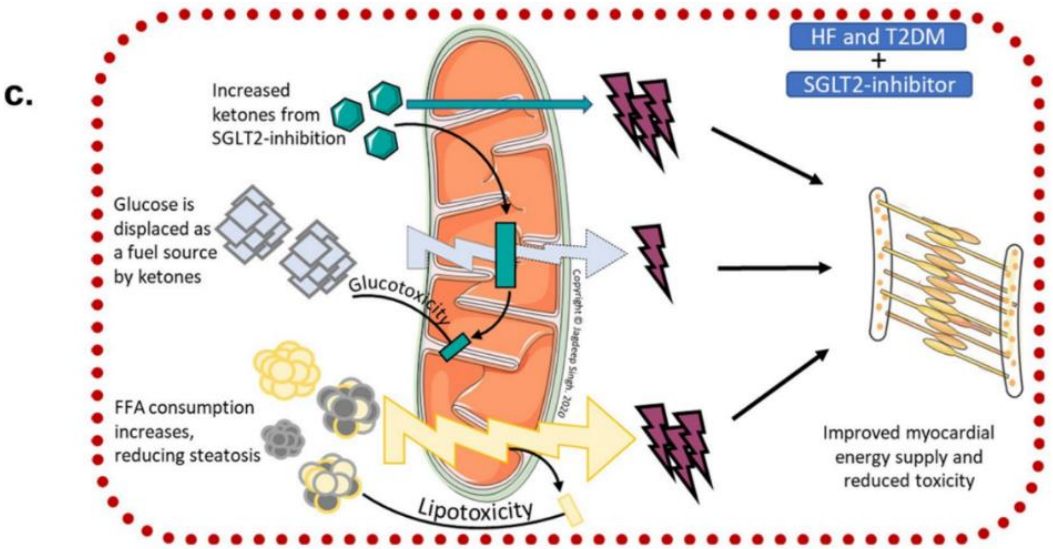
3a: Năng lượng cơ tim ở người khỏe mạnh trong khi nghi ngơi

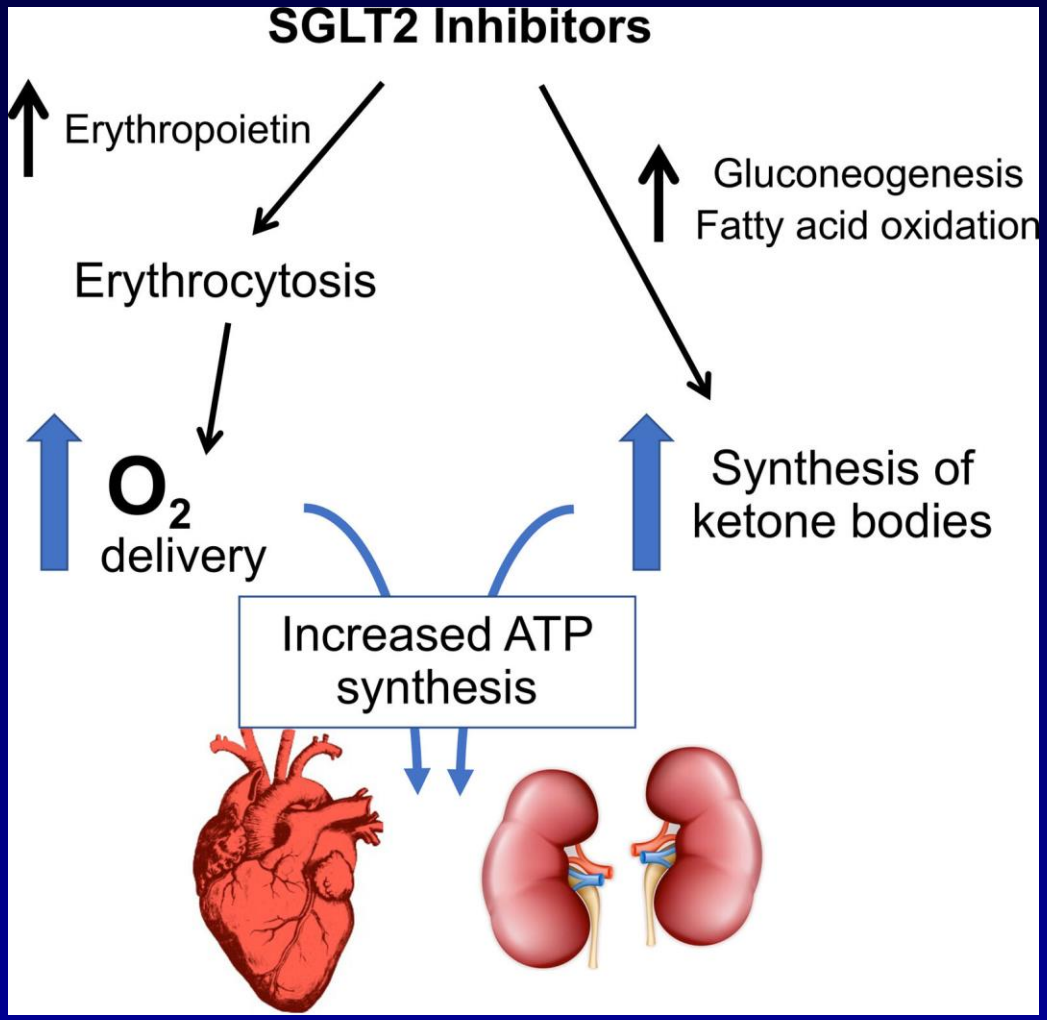
3b: Năng lượng cơ tim của bệnh nhân suy tim và ĐTĐ típ 2.



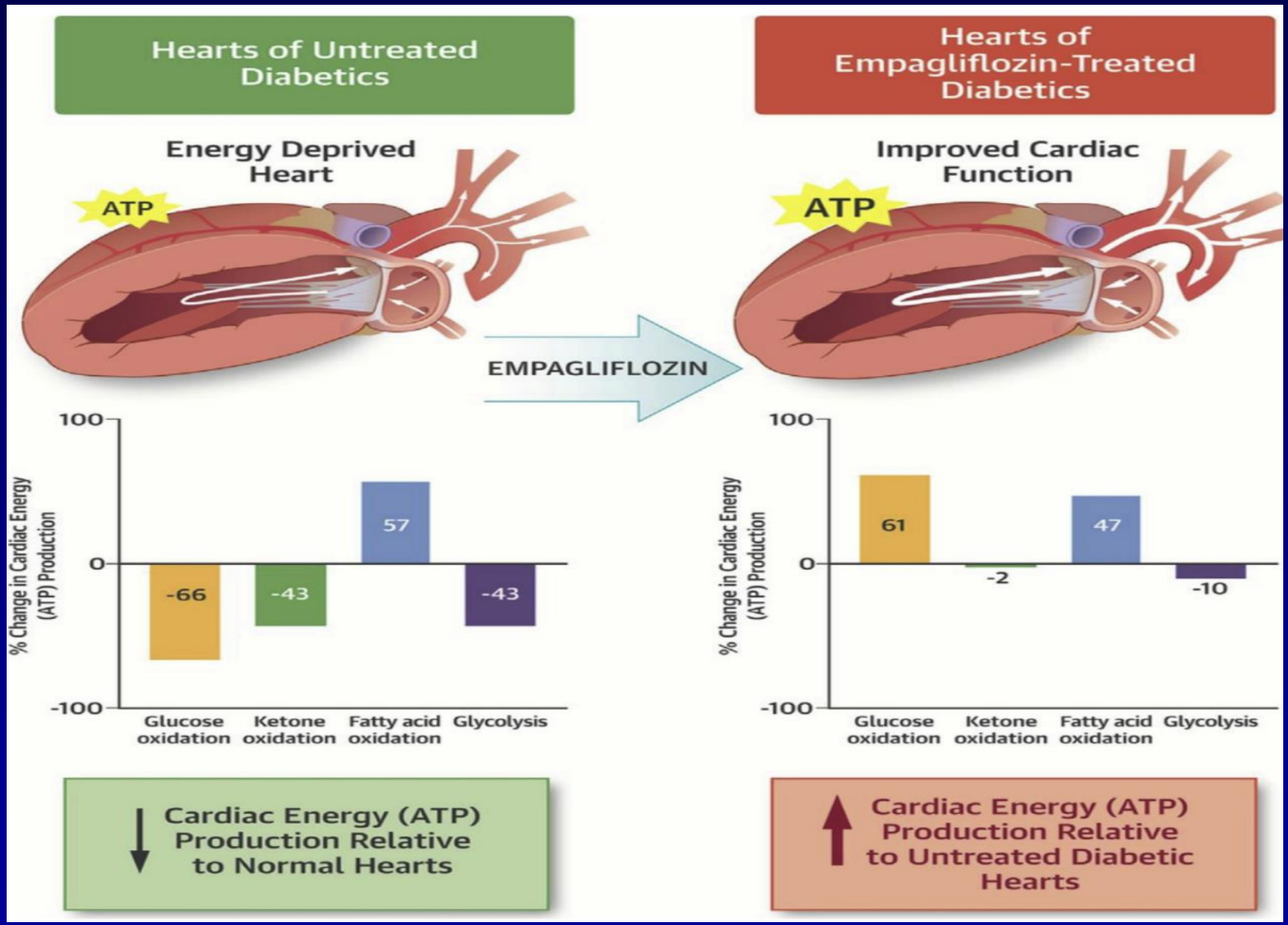


3c. Sự thay đổi về năng lượng cơ tim khi sử dụng ức chế SGLT2 trên bn suy tim và ĐTĐ típ 2

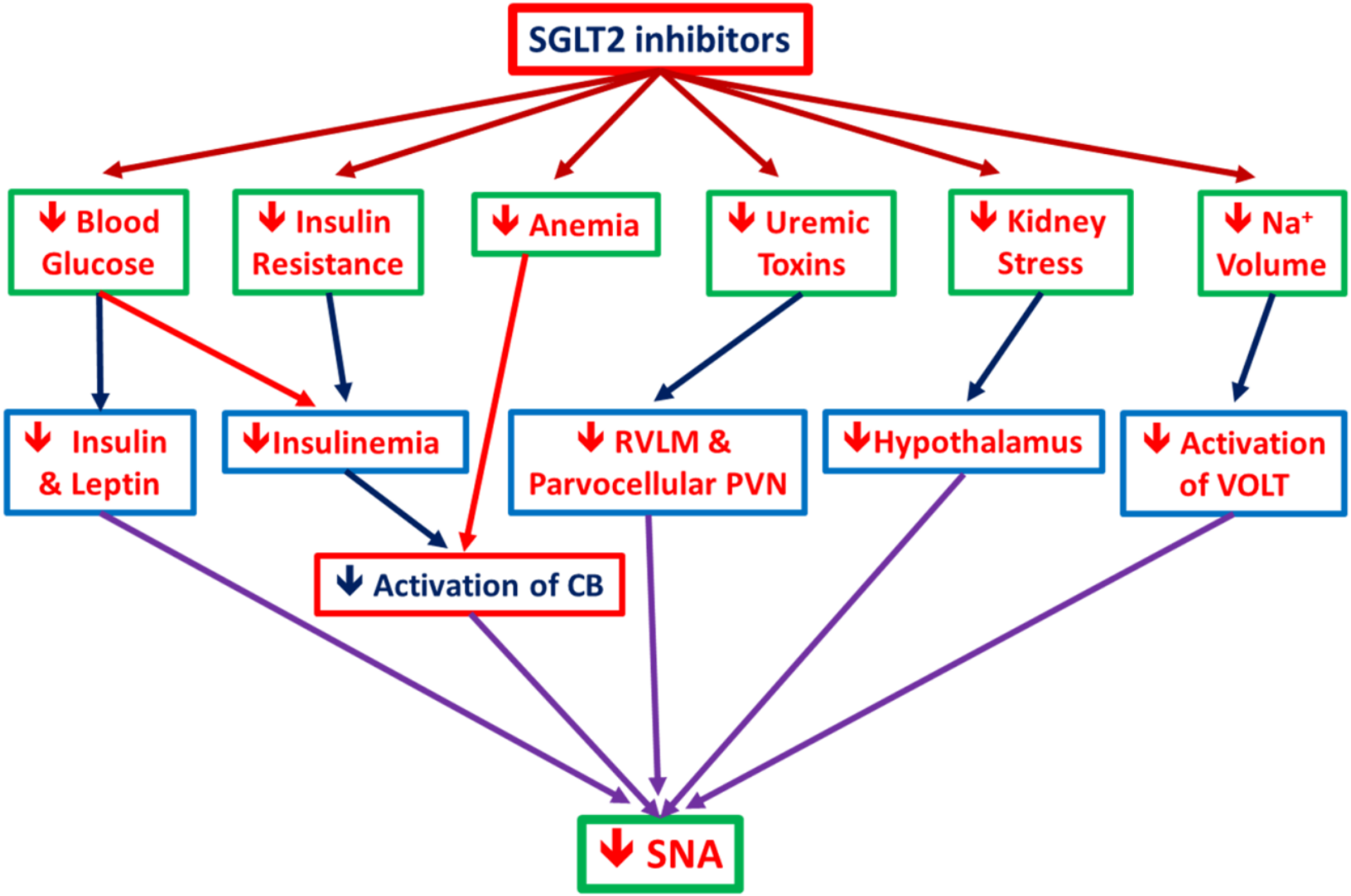




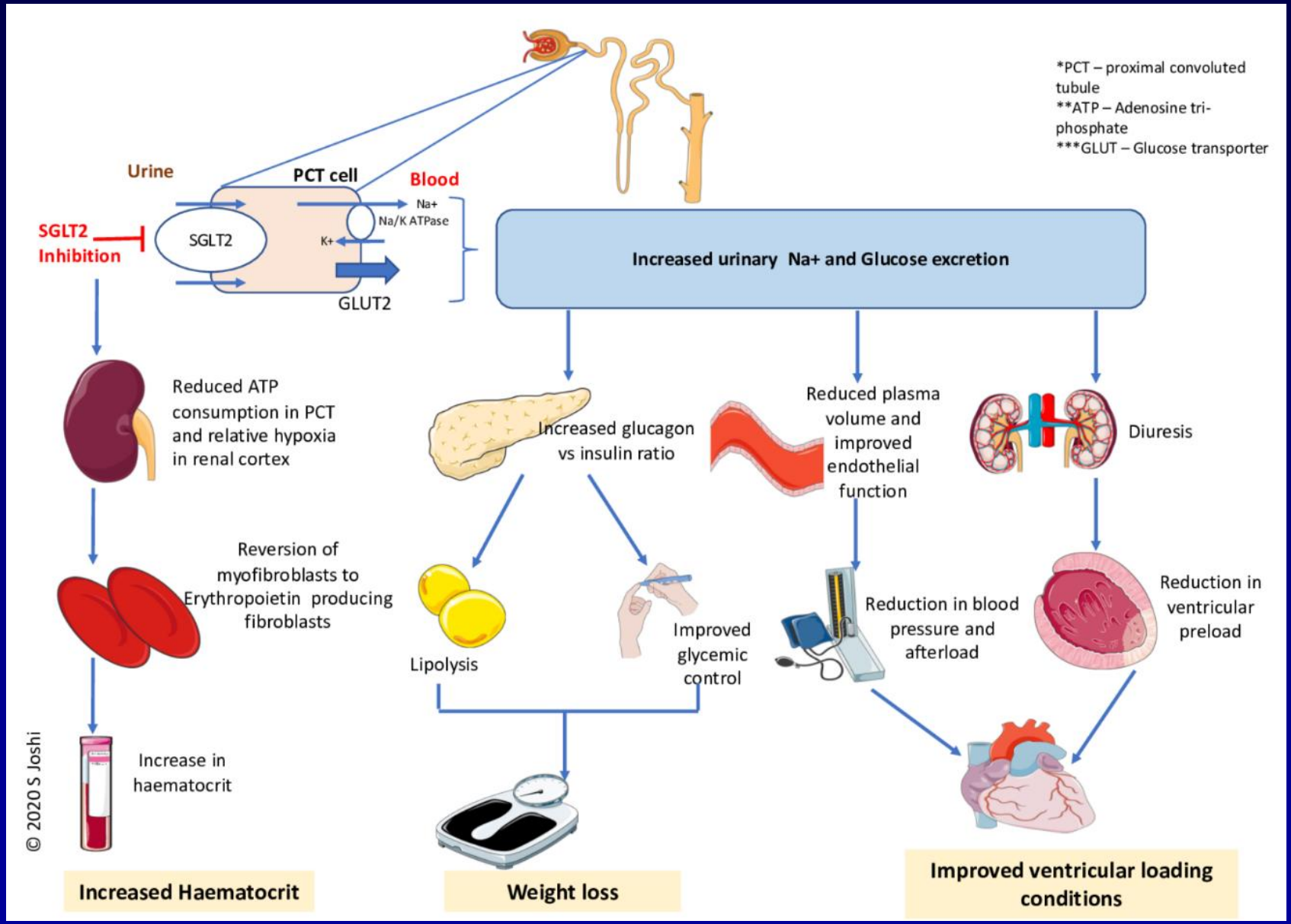
Proposed framework by which SGLT2 inhibitors might act to increase delivery of substrates that could lead to enhanced synthesis of ATP.


Hearts of Untreated Diabetics
Hearts of Empagliflozin-Treated Diabetics
Energy Deprived Heart
Improved Cardiac Function
ATP
ATP
EMPAGLIFLOZIN
% Change in Cardiac Energy (ATP) Production
100
0
-100
-66
-43
57
-43
61
-2
47
-10
Glucose oxidation
Ketone oxidation
Fatty acid oxidation
Glycolysis
Cardiac Energy (ATP) Production Relative to Normal Hearts
Cardiac Energy (ATP) Production Relative to Untreated Diabetic Hearts

Cơ chế của Ức chế SGLT2 về giảm Hoạt Tính Giao Cảm



Ức chế SGLT2 cải thiện yếu tố nguy cơ



JOURNAL ARTICLE

Emerging role for SGLT2 inhibitors in mitigating the risk of hyperkalaemia in heart failure

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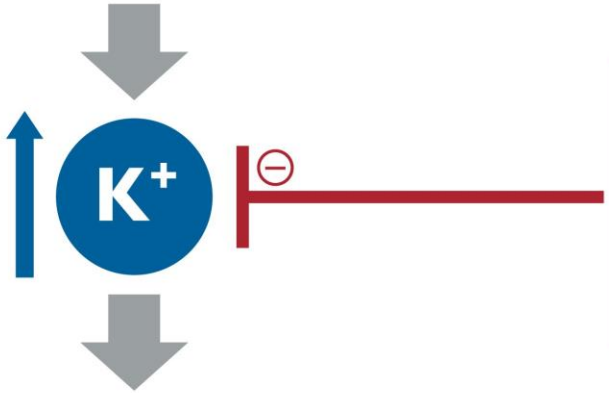
Subodh Verma, Nitish K Dhingra, Arjun K Pandey, Francesco Cosentino ✉

European Heart Journal, Volume 43, Issue 31, 14 August 2022, Pages 2994–2996,
https://doi.org/10.1093/eurheartj/ehac304
Published: 10 June 2022

Risk Factors for Hyperkalaemia in HF

- Medications
  - ACE-i/ARB/ARNI
  - MRAs
- Comorbidities: CKD, DM



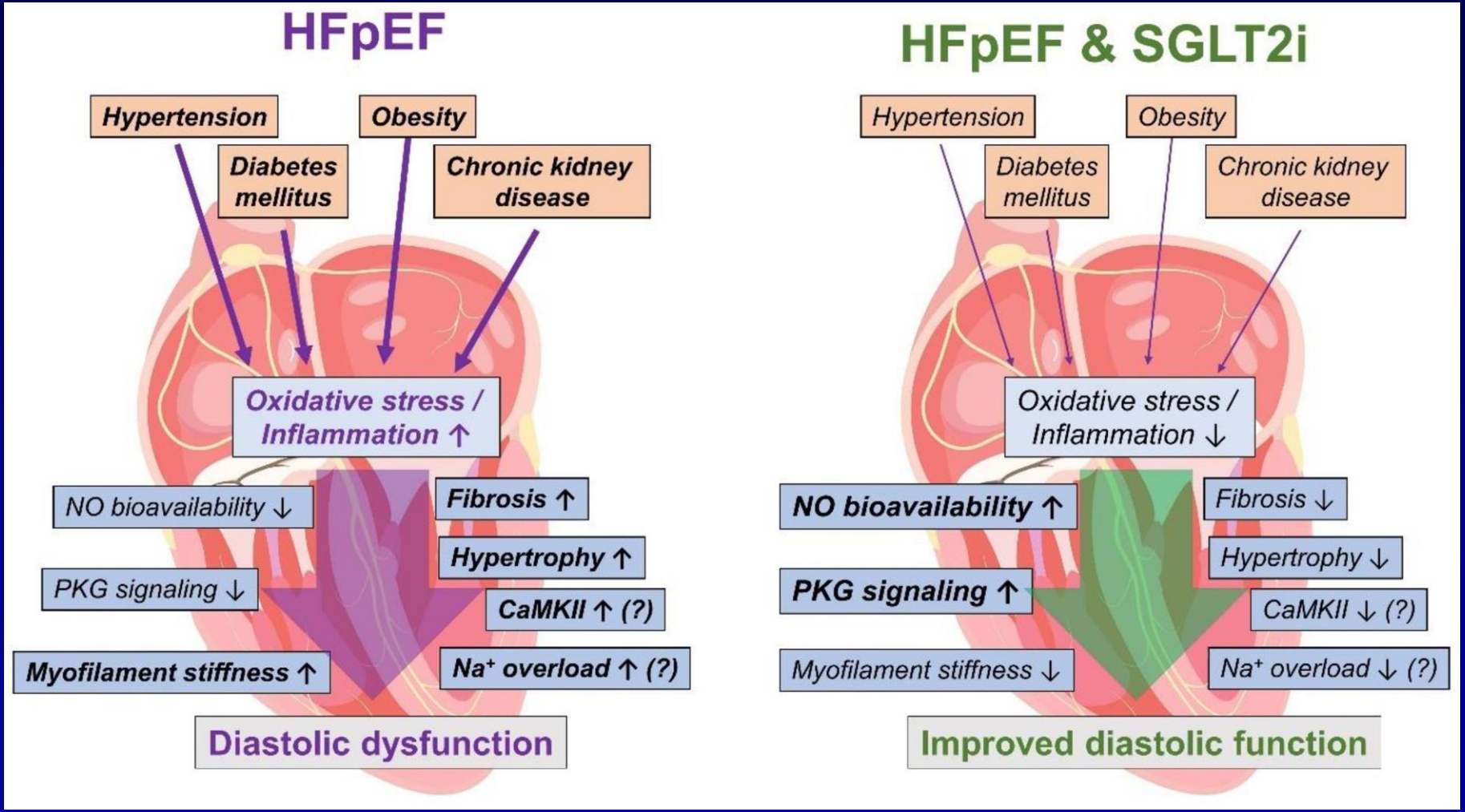
SGLT2 Inhibitors

- EMPEROR trial programme: Empagliflozin associated with ↓ 18% in investigator reported hyperkalaemia or initiation of potassium binders
- Possible mechanisms: ↑Na+ to distal nephron, alterations in RAAS, reduced rate of kidney function decline

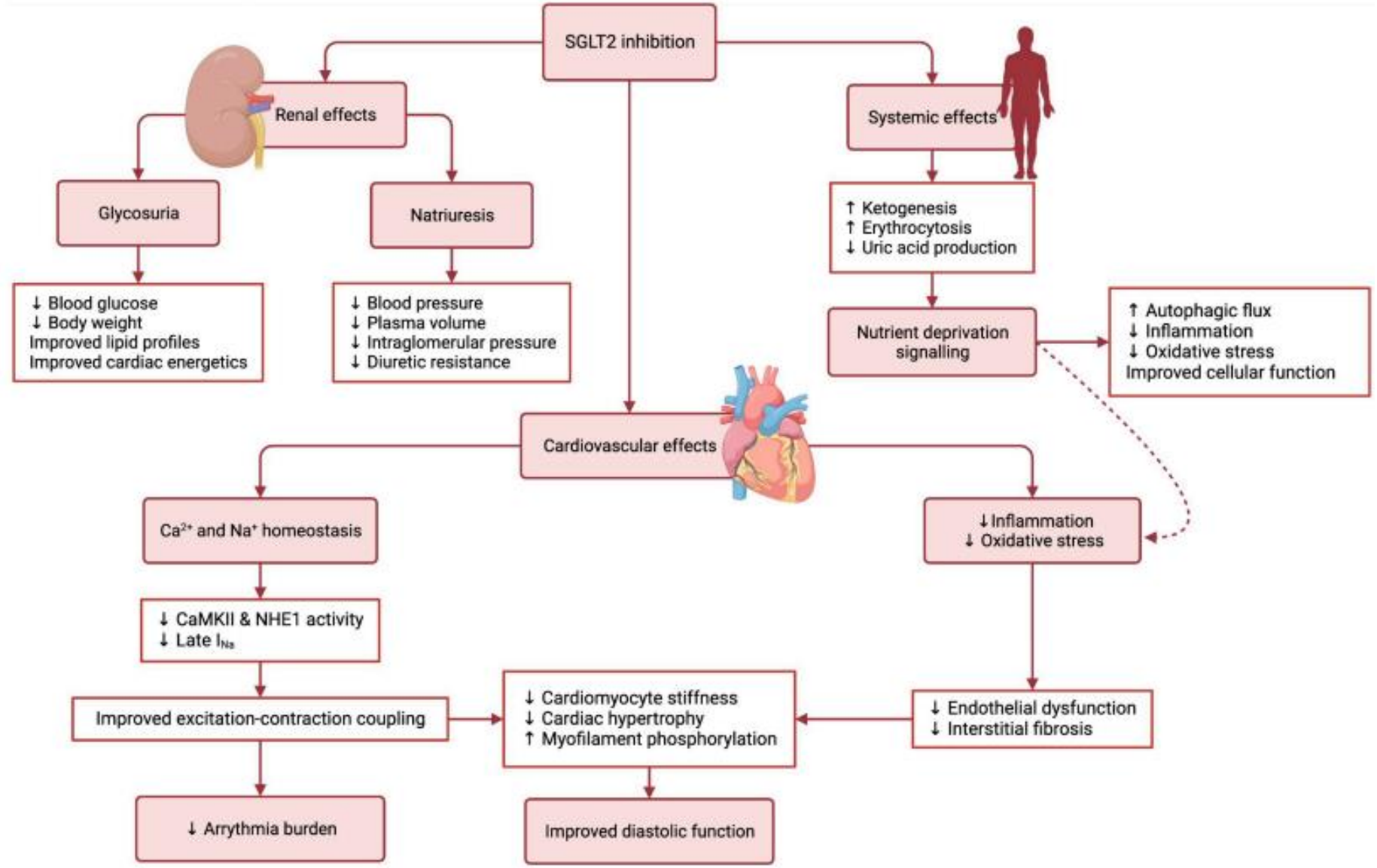
Consequences of Hyperkalaemia in HF

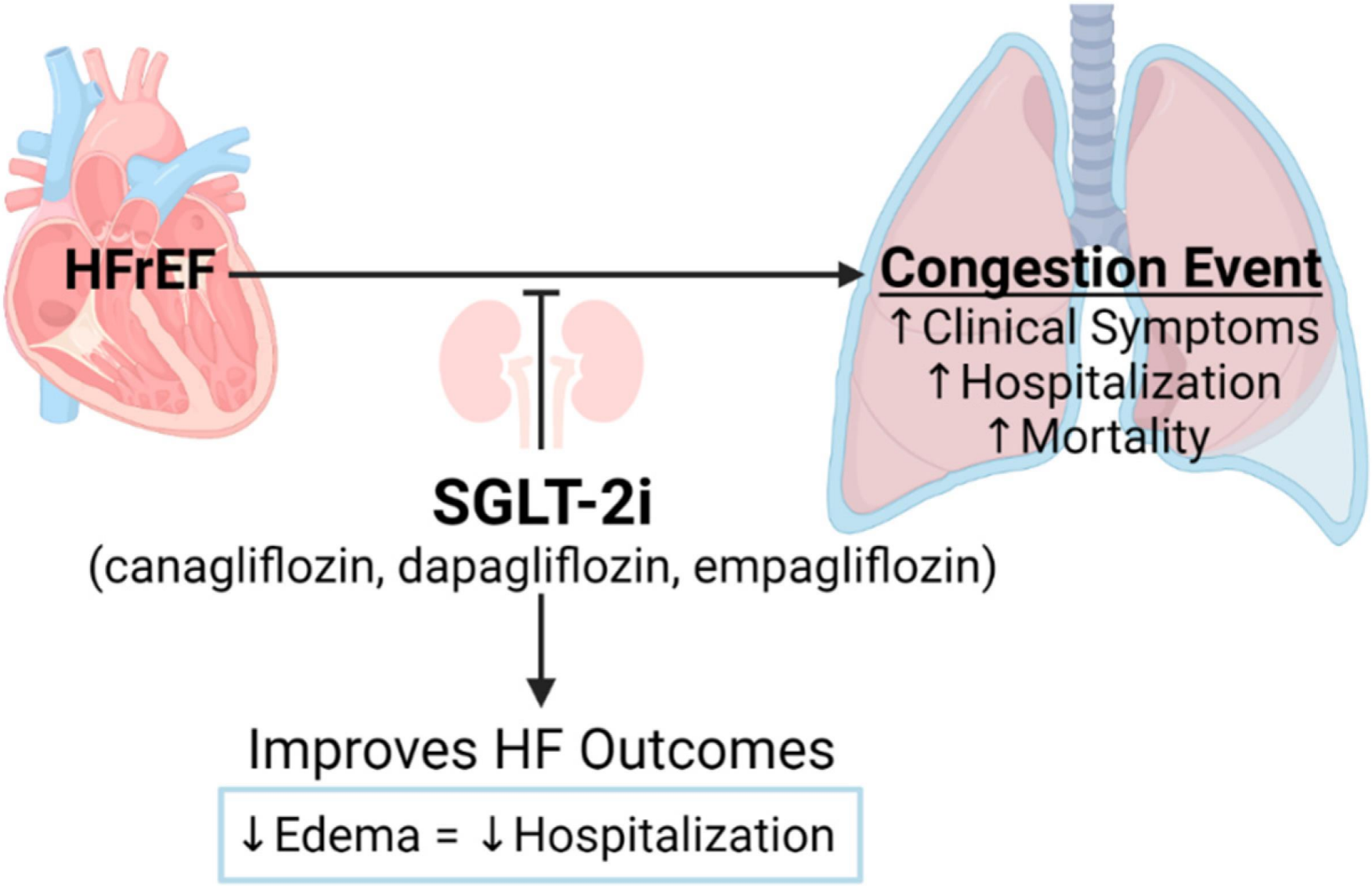
- Arrhythmia
- Poor outcomes (HF Hospitalization, CV Death)
- Reduced initiation/up-titration of HF medications

Ức chế SGLT2 và Suy tim EF bảo tồn



Cơ chế bảo vệ tim của ức chế SGLT2 trong suy tim EF bảo tồn




HFrEF
Congestion Event
↑ Clinical Symptoms
↑ Hospitalization
↑ Mortality
SGLT-2i
(canagliflozin, dapagliflozin, empagliflozin)
Improves HF Outcomes
↓ Edema = ↓ Hospitalization

Ức chế SGLT2
Suy tim EF giảm

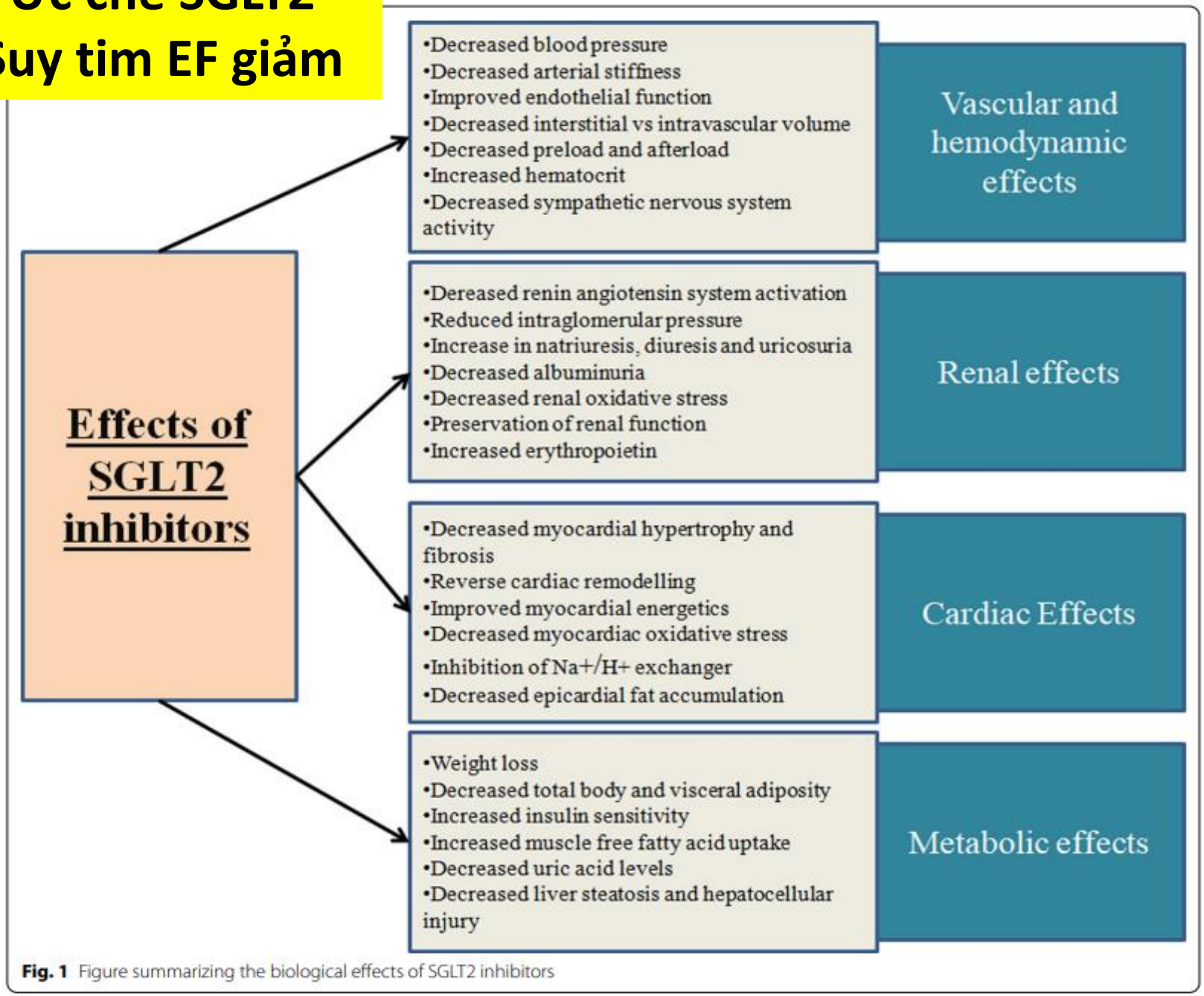
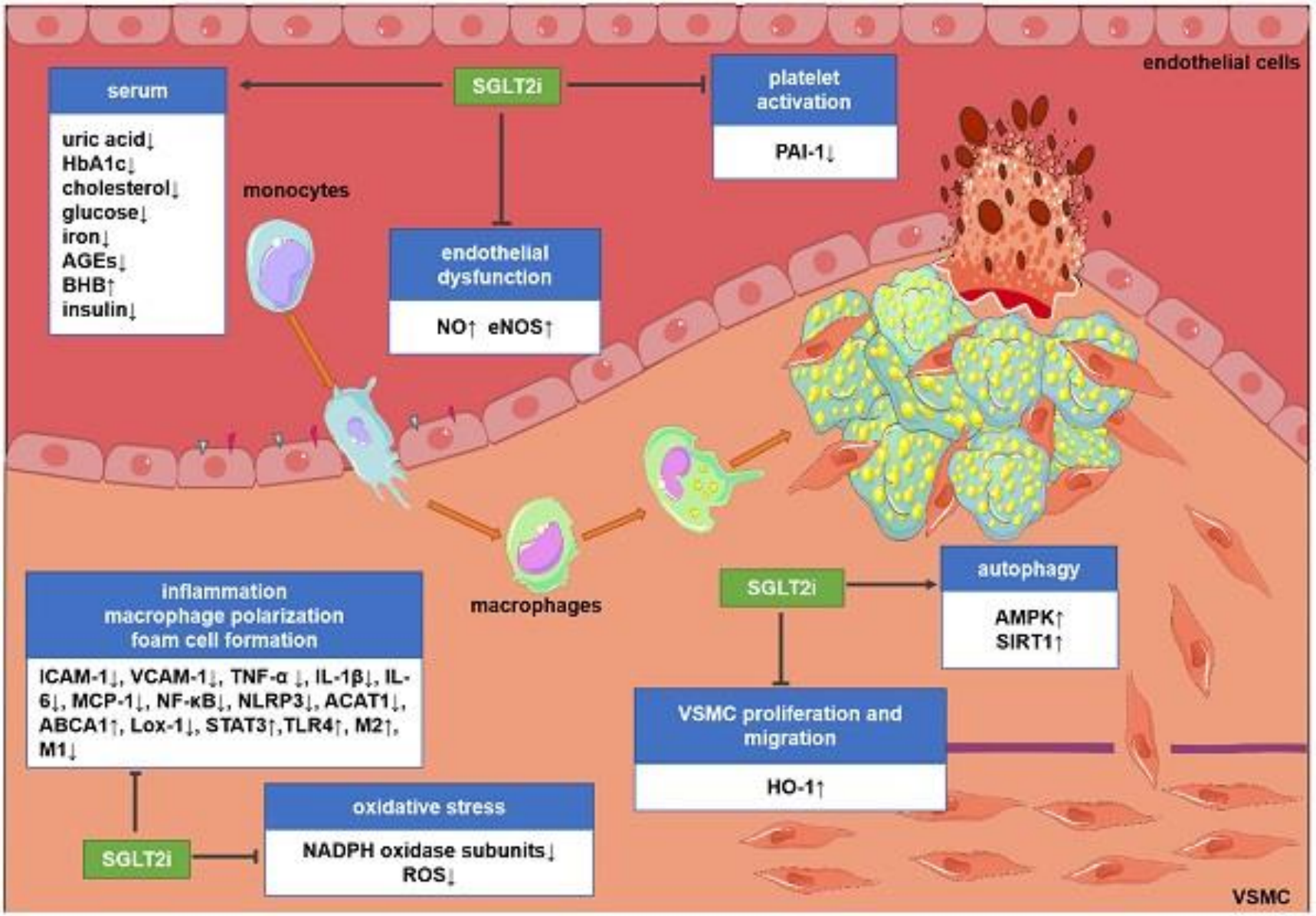
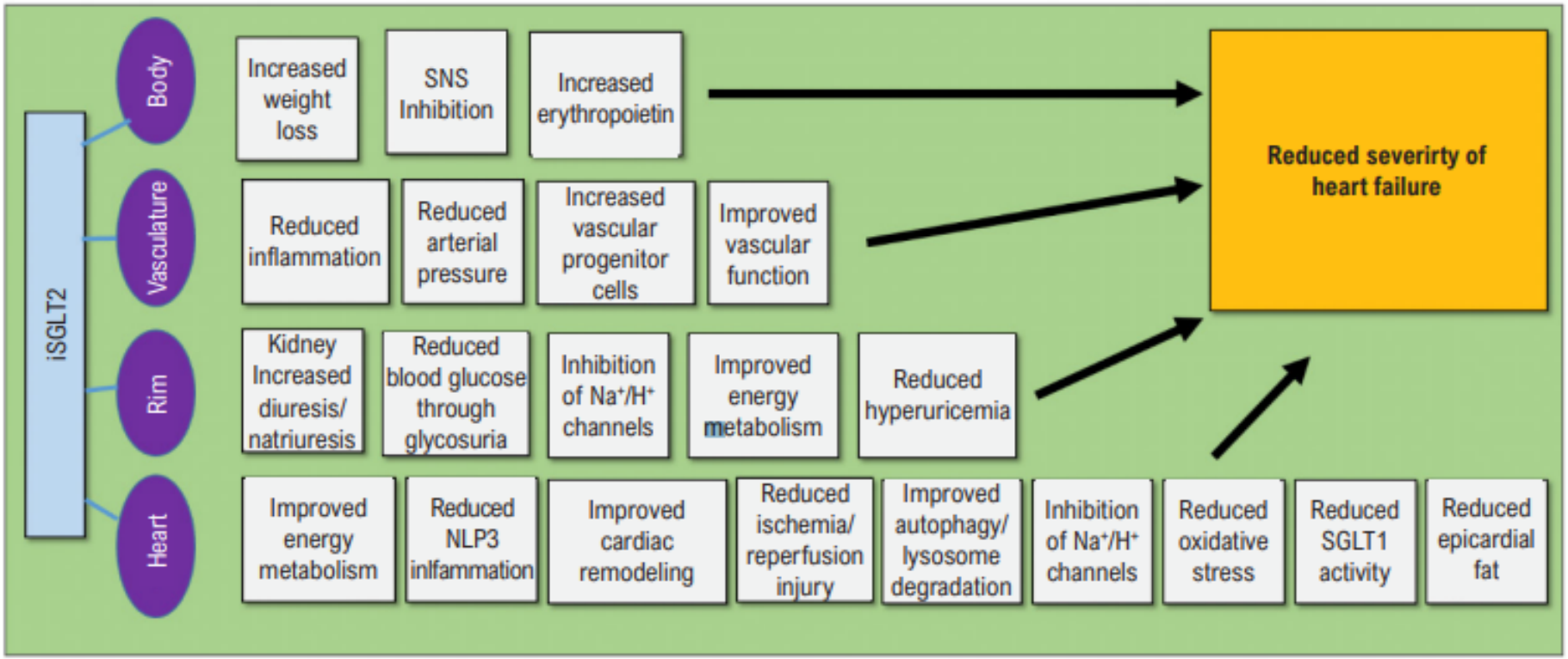


Fig. 1 Figure summarizing the biological effects of SGLT2 inhibitors

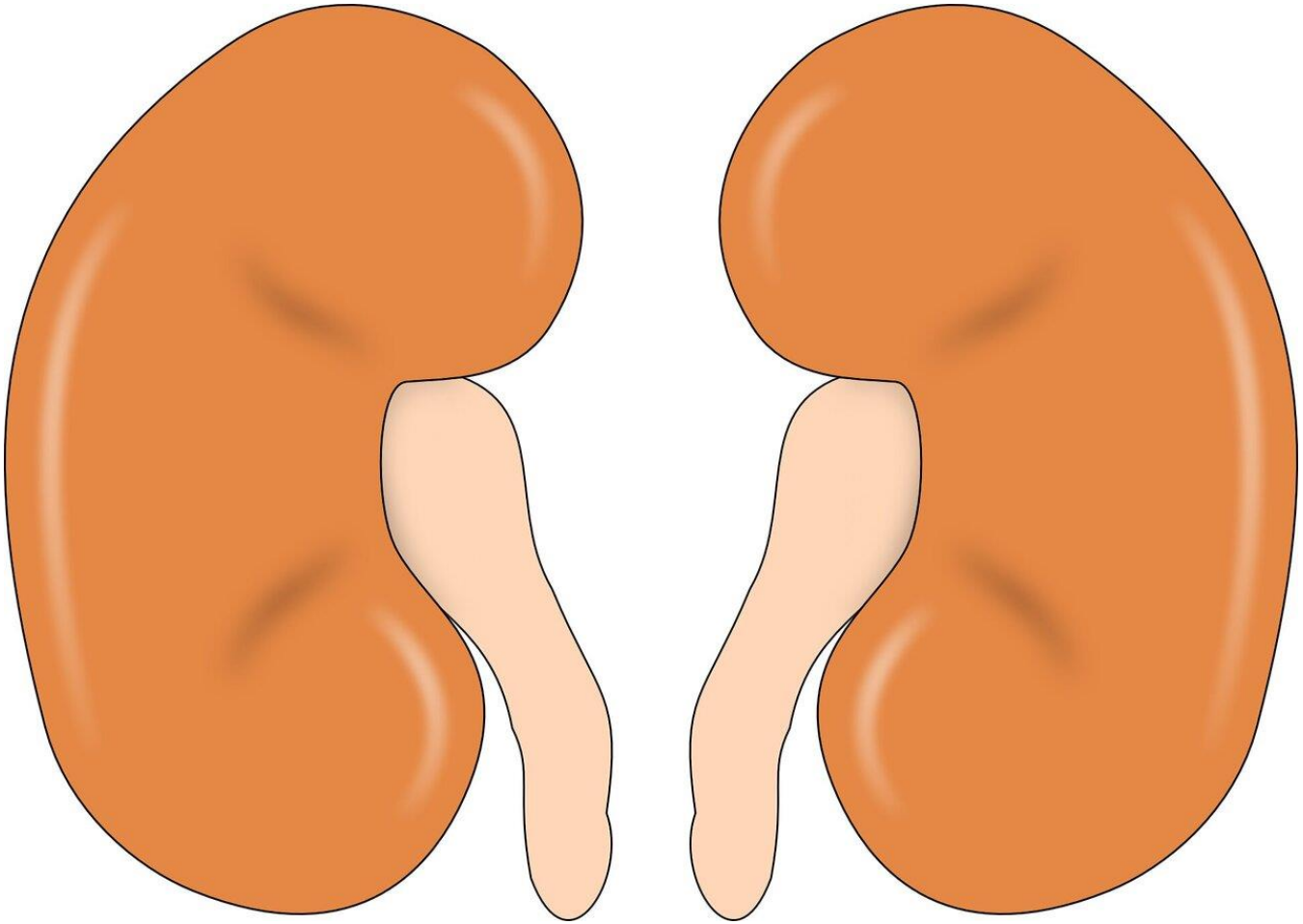
Tác động ức chế SGLT2 trên xơ vữa động mạch

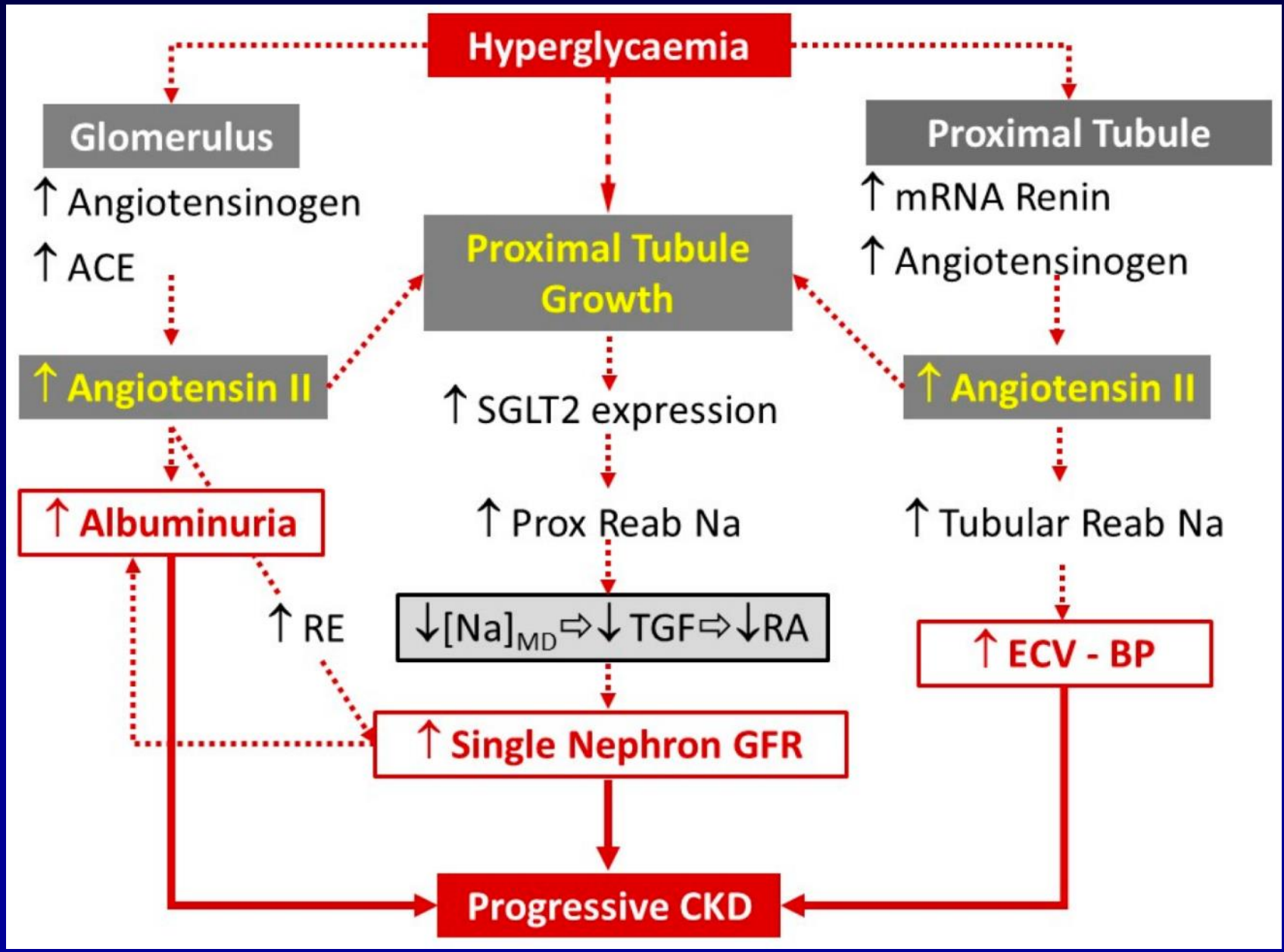


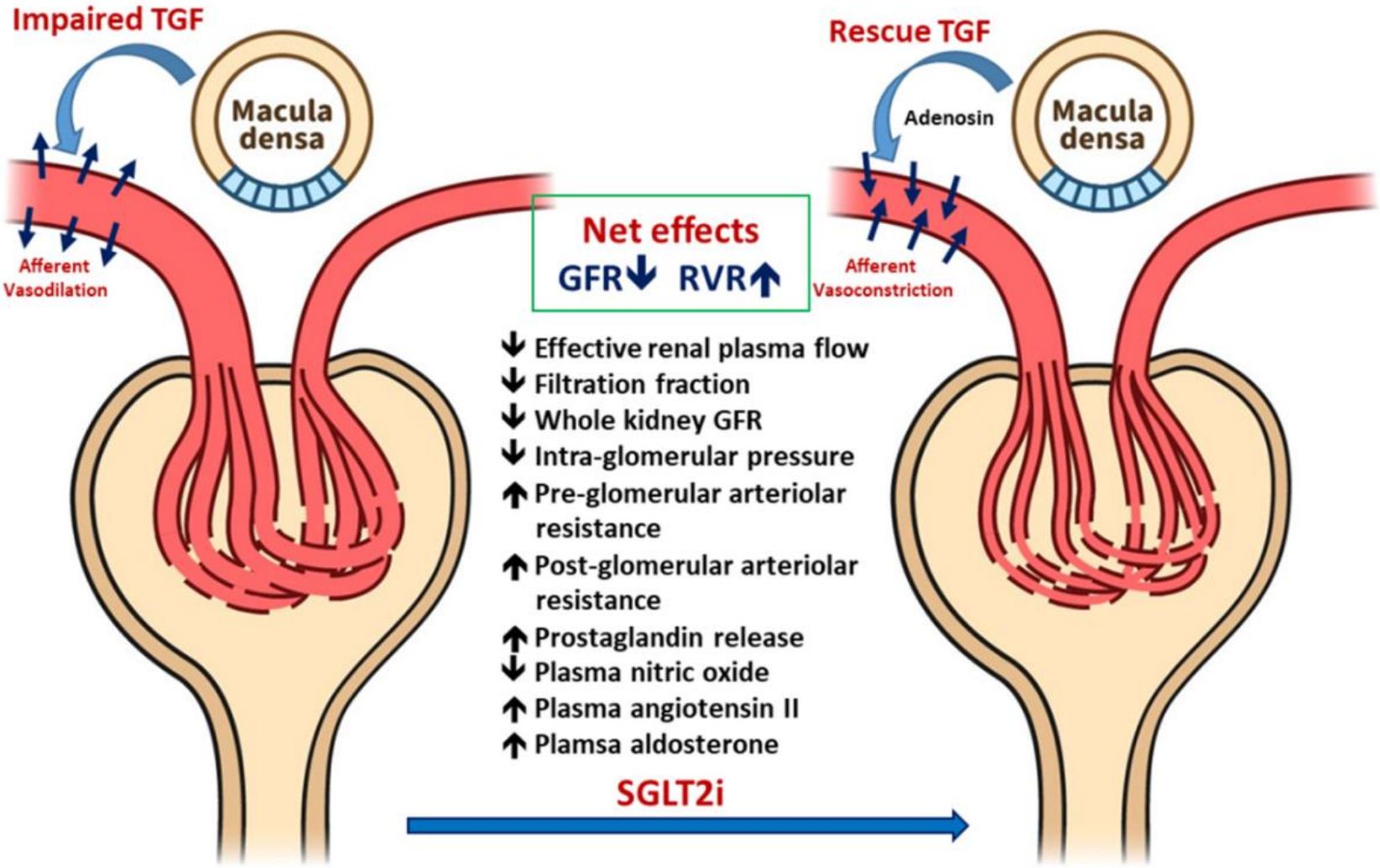


Possible mechanisms through which SGLT2 inhibitors improve heart failure outcomes, NLRP3: nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing;

Ức chế SGLT2 và Bảo vệ Thận

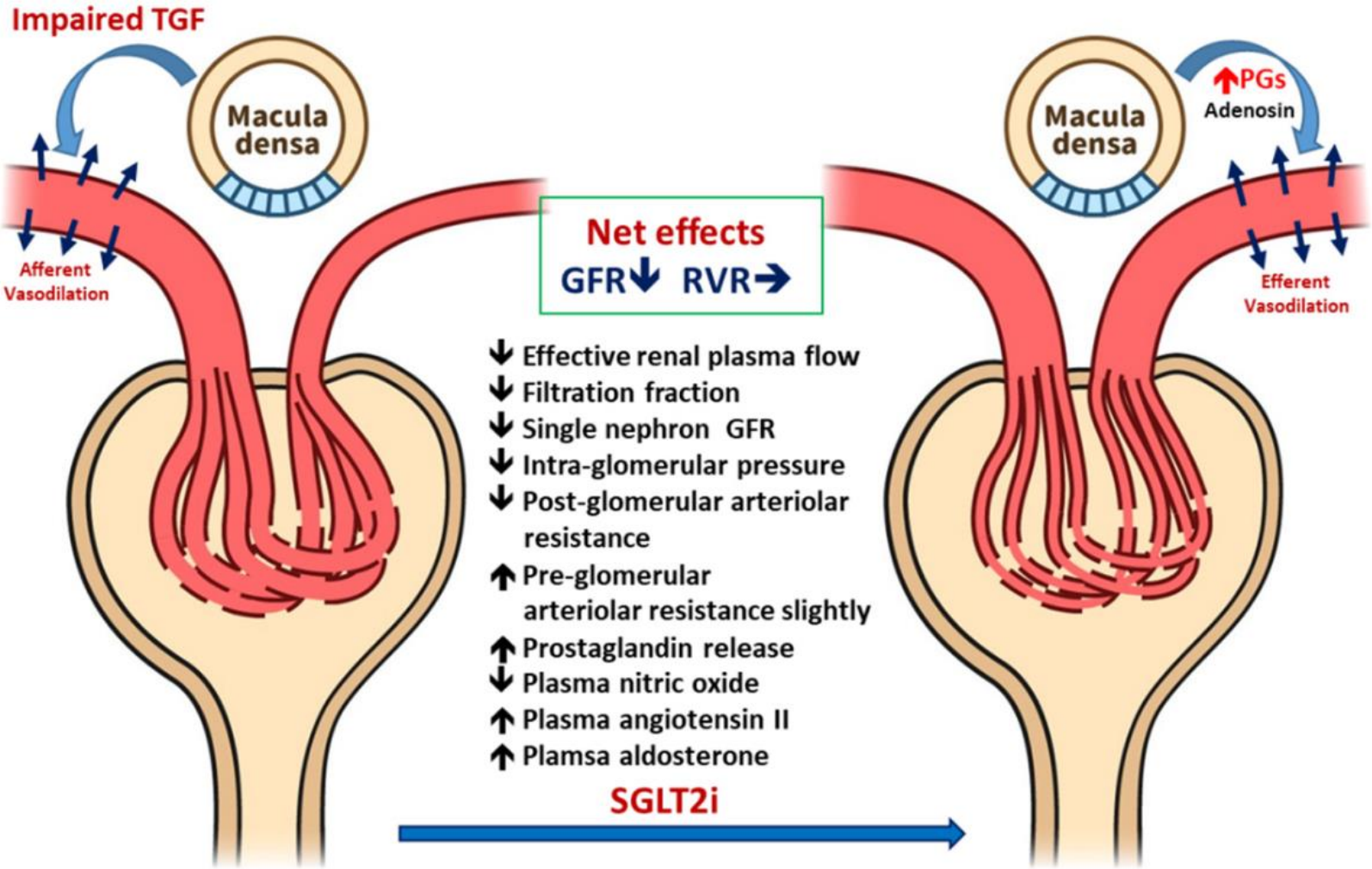



Hyperglycaemia
Glomerulus
↑ Angiotensinogen
↑ ACE
Proximal Tubule
↑ mRNA Renin
↑ Angiotensinogen
Proximal Tubule Growth
↑ Angiotensin II
↑ Angiotensin II
↑ SGLT2 expression
↑ Albuminuria
↑ Prox Reab Na
↑ Tubular Reab Na
↑ RE
↓[Na]MD ⇨ ↓ TGF ⇨ ↓RA
↑ ECV - BP
↑ Single Nephron GFR
Progressive CKD



Đáp ứng huyết động học của ức chế SGLT2 ở giai đoạn sớm bệnh nhân ĐTĐ típ 1

Hemodynamic responses to a SGLT2i in patients with early stage T1DM:



Đáp ứng huyết động học của ức chế SGLT2 ở giai đoạn sớm bệnh nhân ĐTĐ típ 2

Hemodynamic responses to SGLT2i in patients with early stage T2DM:

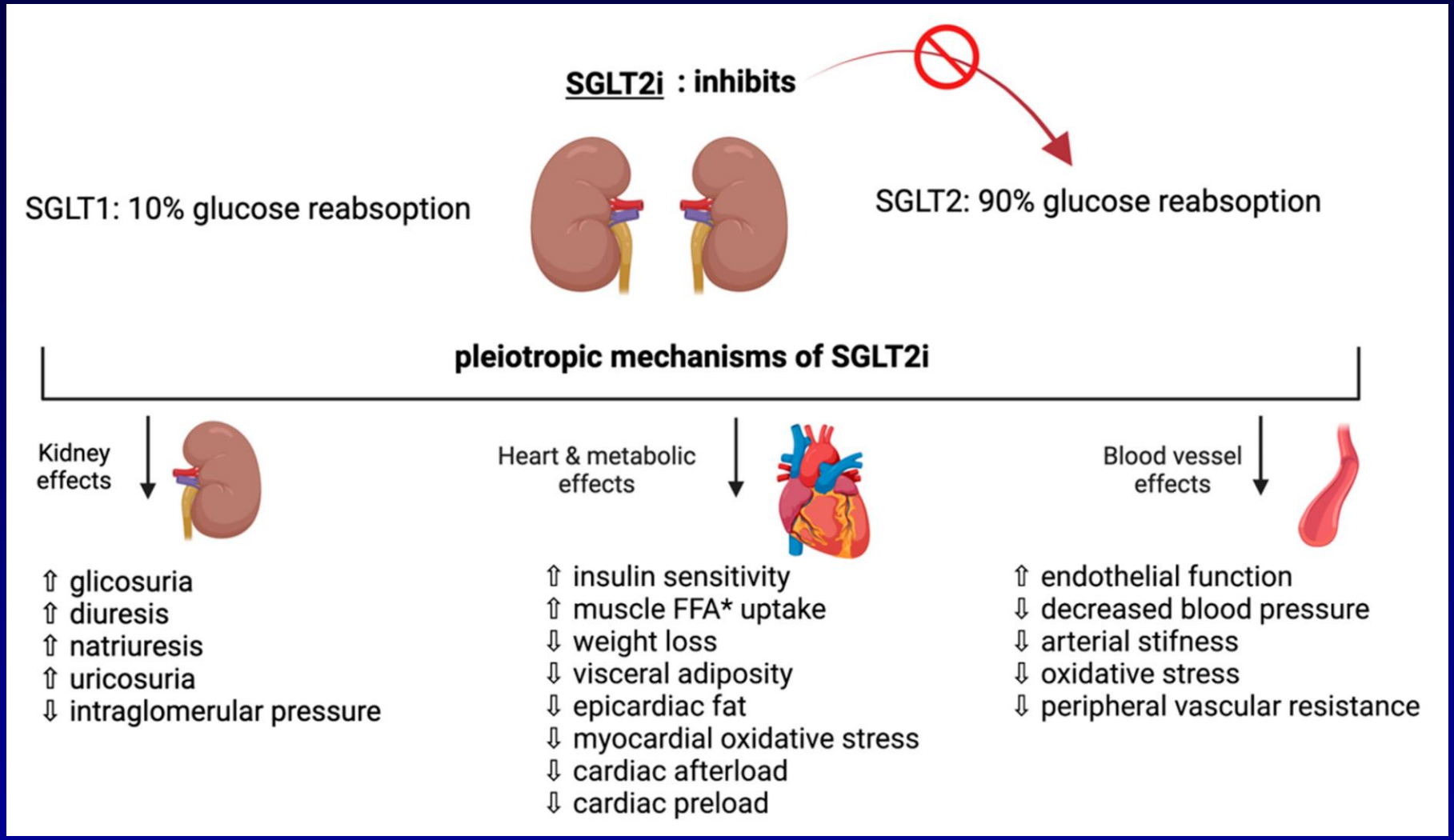
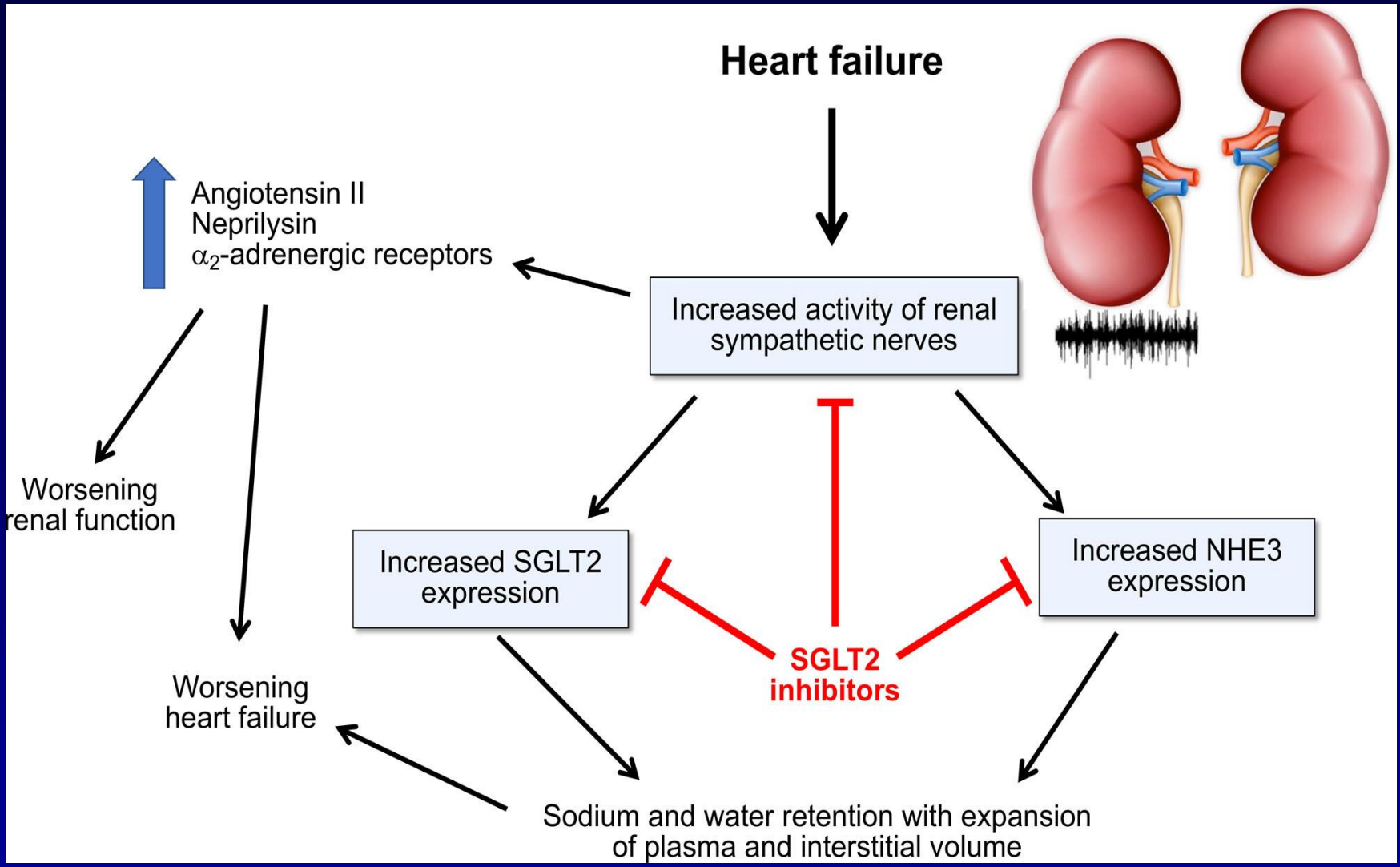


Figure 3. Pleiotropic effects of SGLT2i: recent evidence supports the efficacy of SGLT2i in reducing cardiovascular complication and hospitalizations in patients with and without diabetes by ameliorating renal, cardiometabolic, and vascular effects.



Proposed framework by which SGLT2 inhibitors might exert cardioprotective and nephroprotective effects by acting to mute renal sympathetic nerve activity and promote natriuresis and osmotic diuresis.

Giảm Magnesium máu gây rối loạn chức năng thận

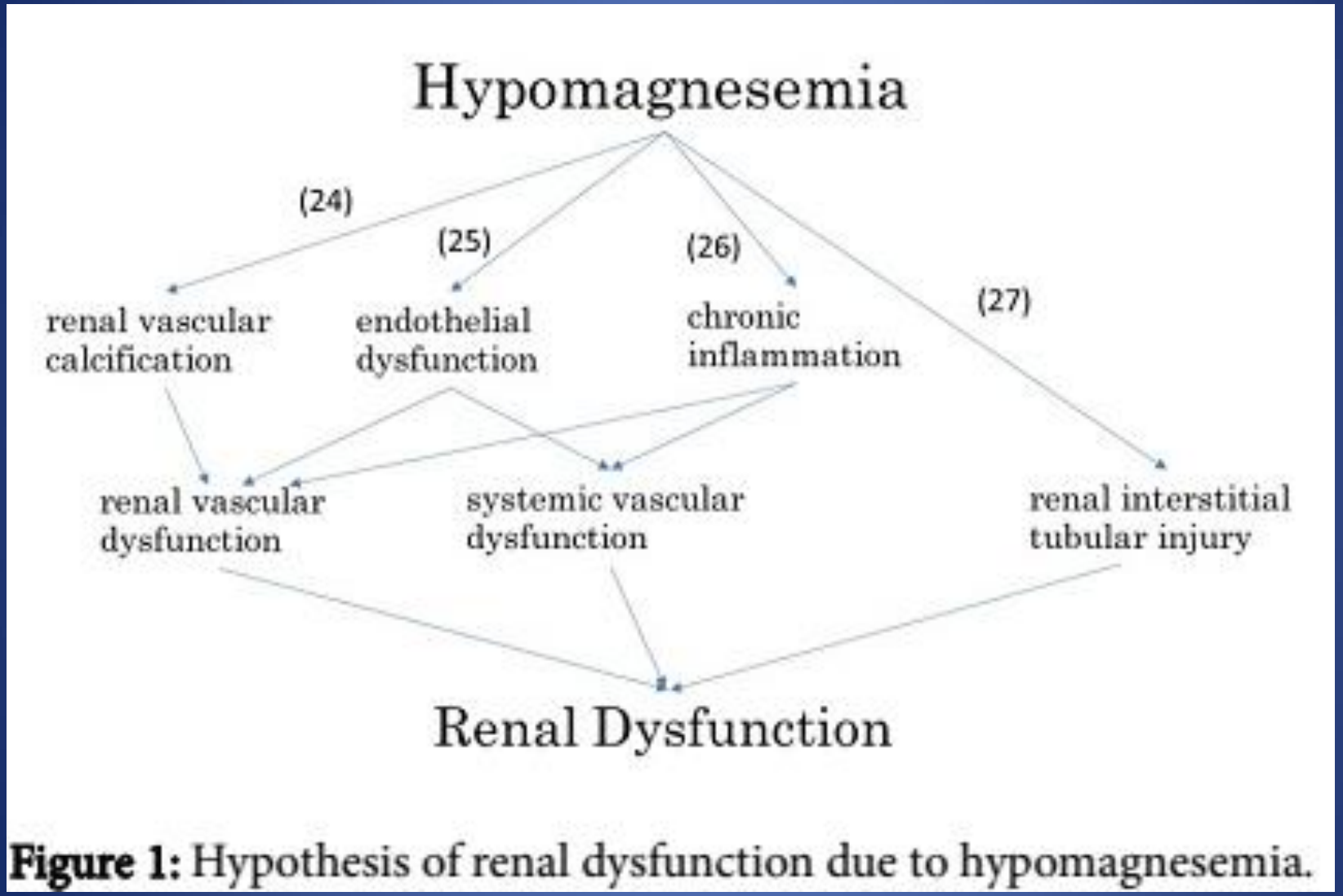


Figure 1: Hypothesis of renal dysfunction due to hypomagnesemia.

Journal of Diabetes and Metabolism
ISSN: 2155-6156
Yanagawa, J Diabetes Metab 2017, 8:11
DOI: 10.4172/2155-6156.1000772
Commentary
Open Access

Is the Renoprotective Effect of SGLT2 Inhibitors due to their Beneficial Effect on Hypomagnesemia?

Tatsuo Yanagawa*

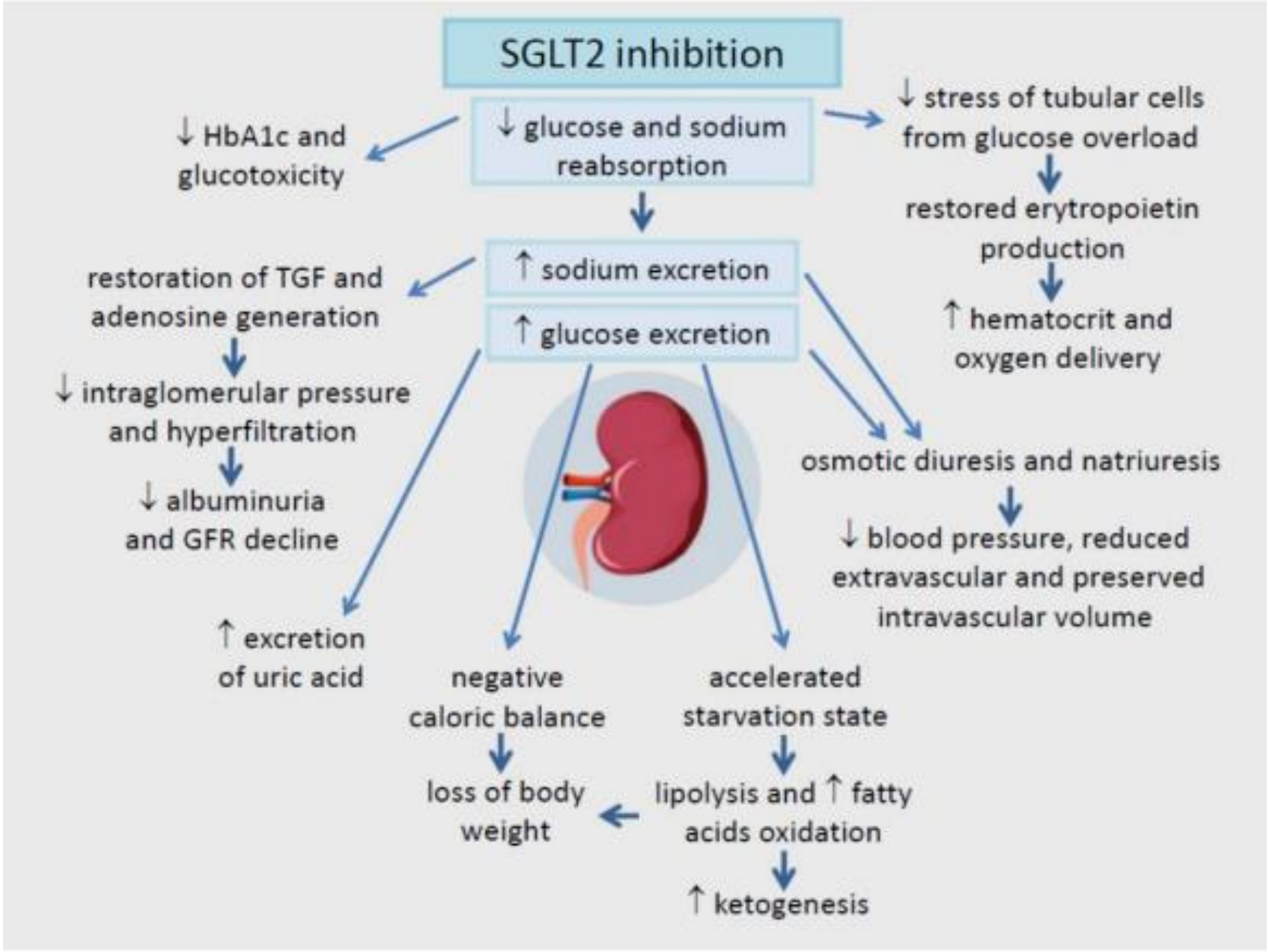
Magnesium Deficiency is linked to Diabetes, Hypertension and Cardiovascular Events

Mg Concentration Increases with SGLT2 Inhibitor Treatment

Is the Renoprotective Effect of SGLT2 Inhibitors also related to Increase of the Serum Mg Concentration?

Conclusion

We would like to put forth the hypothesis that SGLT2 inhibitor therapy suppresses risk of CV events and exerts a renoprotective effect by improving the serum magnesium levels.



Tóm tắt cơ chế bảo vệ TIM THẬN của ức chế SGLT2.

Ức chế SGLT2 và Suy giảm nhận thức

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journal homepage: www.elsevier.com/locate/yphrs

Review

Cognitive impairment and type 2 diabetes mellitus: Focus of SGLT2 inhibitors treatment

Maria Rosaria Rizzo [a,*], Irene Di Meo [a], Rita Polito [a], Maria Chiara Auriemma [a], Antonio Gambardella [b], Gabriella di Mauro [c], Annalisa Capuano [c], Giuseppe Paolisso [a]

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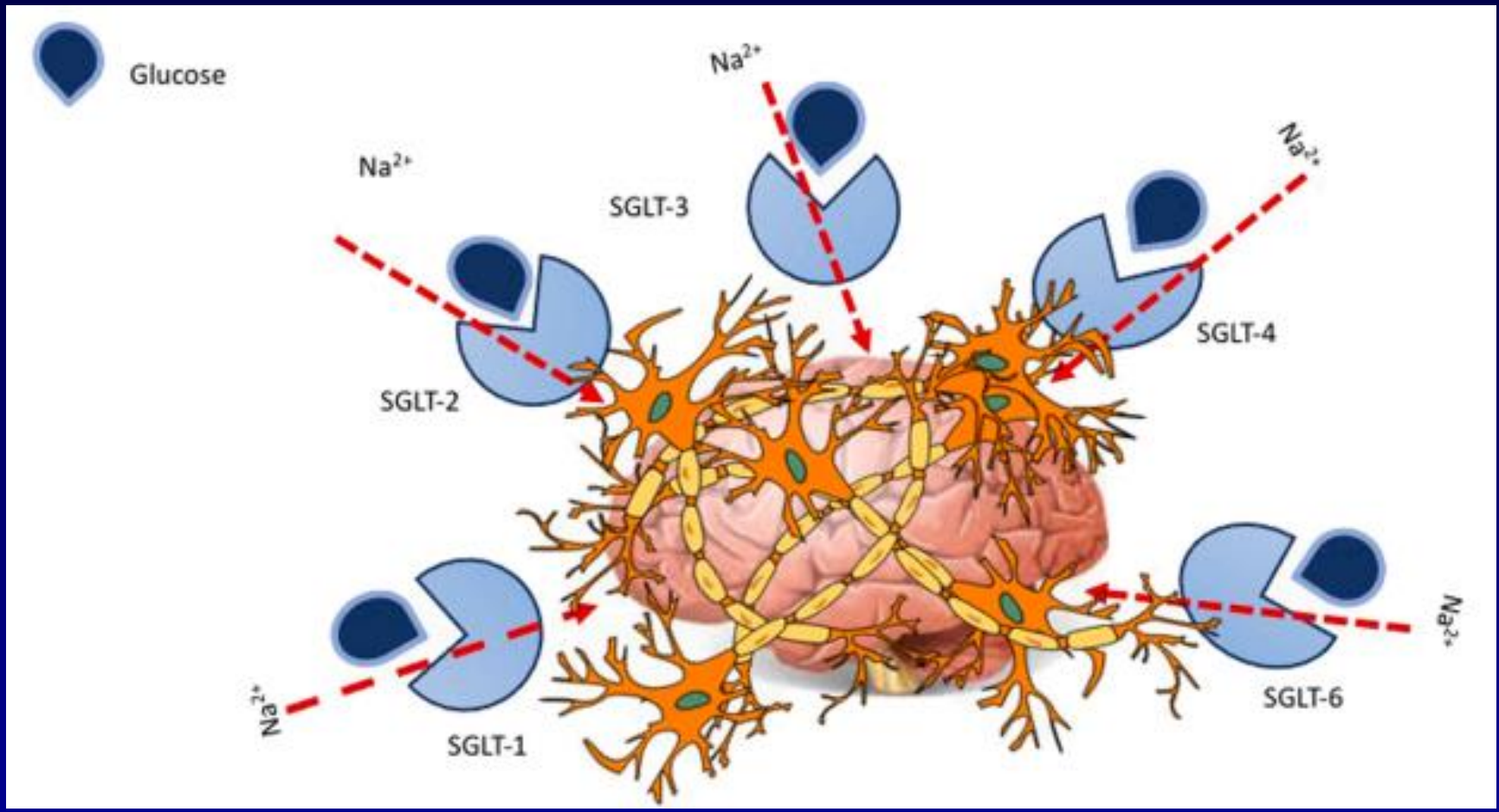
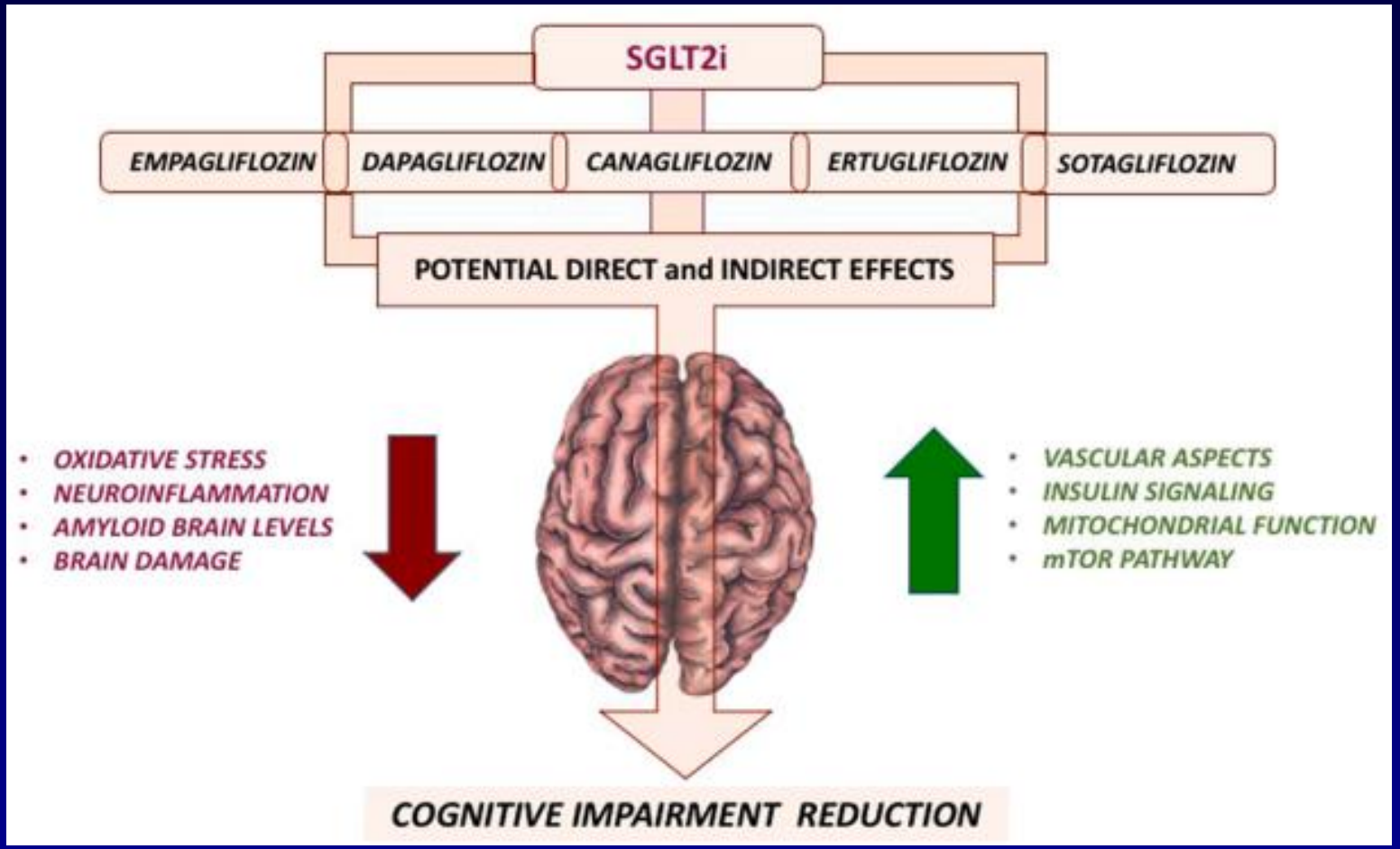
[c] Department of Experimental Medicine - Section of Pharmacology "L. Donatelli", University of Campania "Luigi Vanvitelli", 80138 Naples, Italy

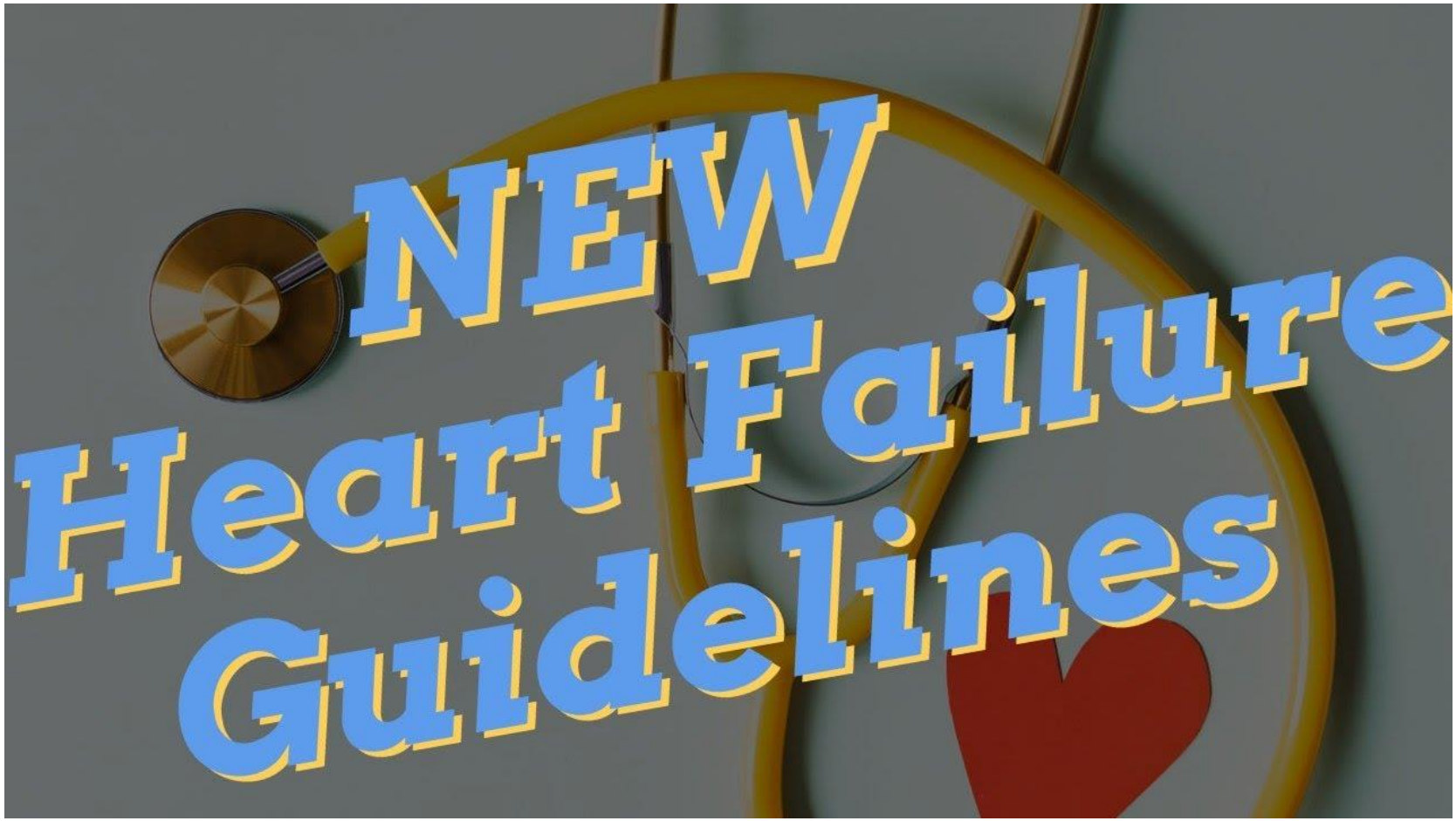


The principal SGLTs expressed in the brain. SGLTs are fundamental in the mechanism of glucose entry into the brain cell. SGLTs transport glucose into the cell along a sodium gradient. SGLT1, SGLT2, SGLT3, SGLT4, SGLT6 have been identified in the brain. The distribution of the brainexpressed SGLTs differs strongly and, unfortunately, not all brain SGLTs have been studied extensively



The potential directs and indirect effects of SGLT2i on cognitive impairment. Empaglifozin, Dapaglifozin, Canaglifozin, Ertugliflozin and Sotagliflozin, the most used SGLT2i in laboratory models and clinical studies, exert an improving effect on cognitive impairment. Reduction of oxidative stress, neuroinflammation, amyloid brain levels and in general brain damage, and positive impact on vascular health, insulin signaling, mitochondrial function and mTOR pathway are considered the possible underlying mechanisms.

4. Khuyến Cáo Suy Tim
ESC 2021, AHA 2022 và ADA 2023
Liên quan ức chế SGLT2



ESC
European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

2.1 What is new

SGLT2.Inhibitors

Khuyến cáo điều trị ở bệnh nhân Suy tim (NYHA II-IV) với EF ≤ 40%

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

Khuyến cáo điều trị suy tim ở bệnh nhân ĐTĐ

Recommendation	Class[a]	Level[b]
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.[293–297]	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.[108,109,136]	I	A

Khuyến cáo dự phòng tiên phát suy tim ở bệnh nhân ĐTĐ có các nguy cơ gây khởi phát

Recommendations for the primary prevention of heart failure in patients with risk factors for its development

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.[293–297]	I	A

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association
Joint Committee on Clinical Practice Guidelines

American Heart Association.
American College of Cardiology
Heart Failure Society of America.

5.1. Patients at Risk for HF (Stage A: Primary Prevention)

Recommendations for Patients at Risk for HF (Stage A: Primary Prevention)
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic HF.[1–9]
1	A	2. In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT2i should be used to prevent hospitalizations for HF.[10–12]
1	B-NR	3. In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF.[13–21]
2a	B-R	4. For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF.[22,23]
2a	B-NR	5. In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident HF.[24–26]

7.3.4. Sodium-Glucose Cotransporter 2 Inhibitors

Recommendation for SGLT2i
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[1,2]
Value Statement: Intermediate Value (A)		2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.[3,4]

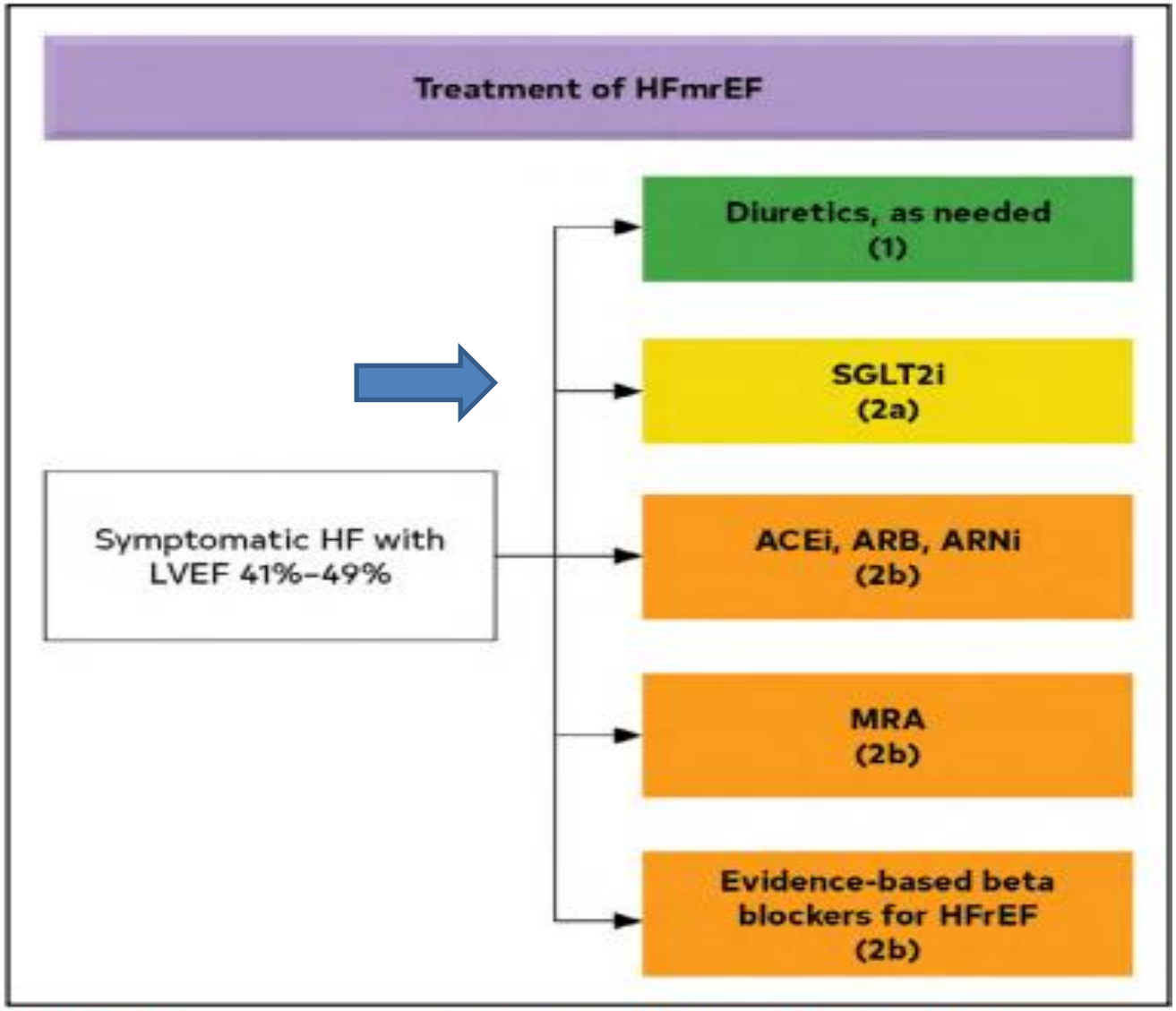


Figure 11. Recommendations for Patients With Mildly Reduced LVEF (41%–49%).

ARNi, angiotensin receptor-neprilysin inhibitor; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter 2 inhibitor

7.6.1. HF With Mildly Reduced Ejection Fraction

Recommendations for HF With Mildly Reduced Ejection Fraction
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
2a	B-R	1. In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[1]
2b	B-NR	2. Among patients with current or previous symptomatic HFmrEF (LVEF, 41%–49%), use of evidence-based beta blockers for HFrEF, ARNi, ACEi, or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum.[2–9]

7.7.1. HF With Preserved Ejection Fraction

Recommendations for HF With Preserved Ejection Fraction* Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.[12,13]

Section 10.

Cardiovascular Disease and Risk Management

American Diabetes Association.
Connected for Life

Cardiovascular Disease and Type 2 Diabetes

As outlined in more detail in Section 9, “Pharmacologic Approaches to Glycemic Treatment,” and Section 10, “Cardiovascular Disease and Risk Management,” the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (70):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C target.

Cardiovascular Disease—Treatment

10.41 Among people with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (Table 10.3B and Table 10.3C) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. A

10.41a In people with type 2 diabetes and established atherosclerotic cardiovascular disease, multiple atherosclerotic cardiovascular disease risk factors, or diabetic kidney disease, a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. A

Cardiovascular Disease—Treatment (continued)

10.41c In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, combined therapy with a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit and a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit may be considered for additive reduction in the risk of adverse cardiovascular and kidney events. A

10.42a In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. A

10.42b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to improve symptoms, physical limitations, and quality of life. A

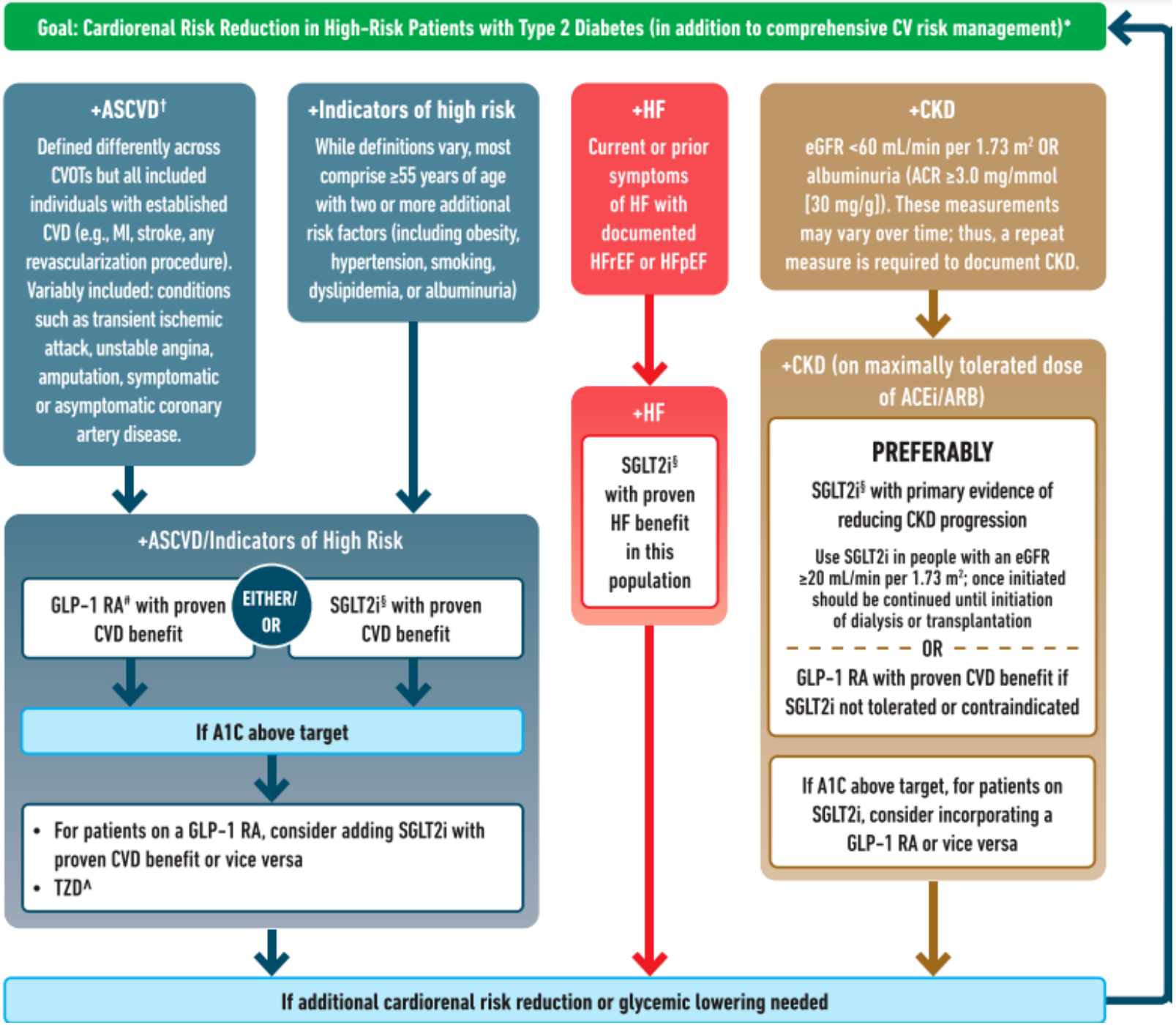
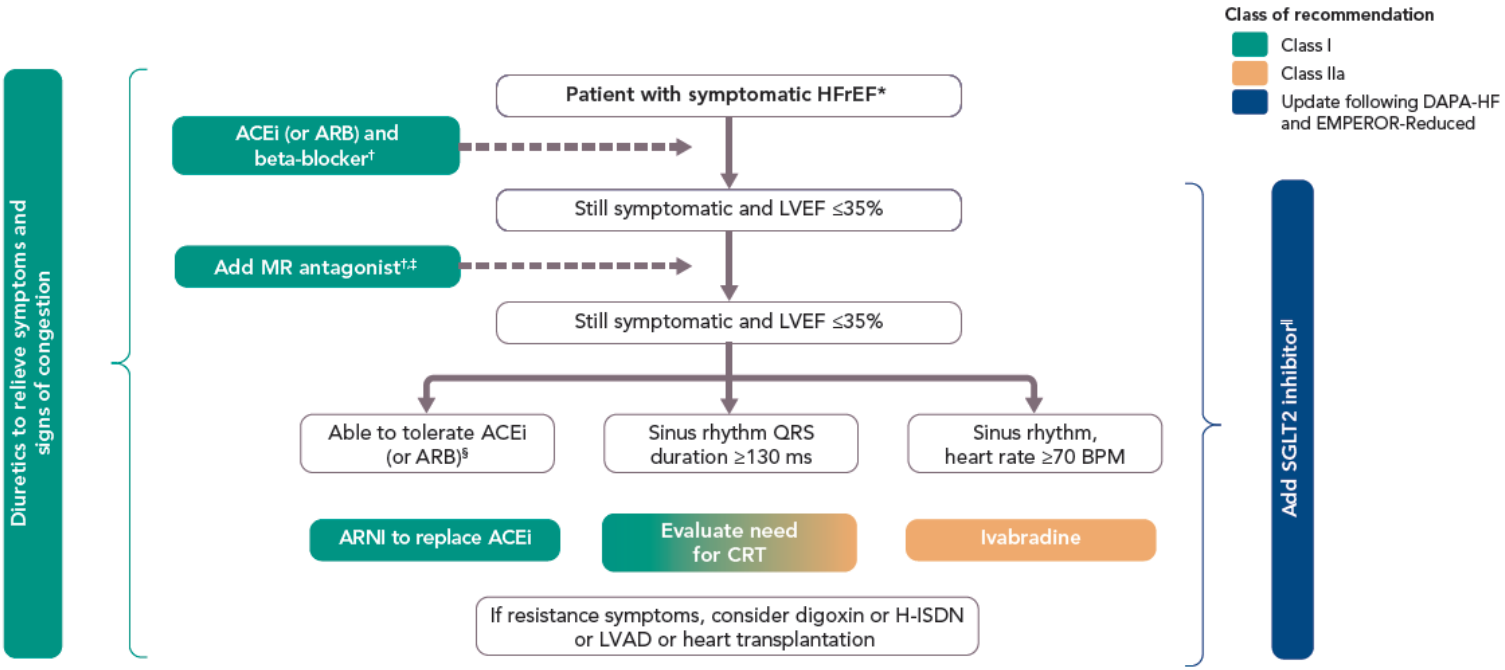

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*
+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.
+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.
+ASCVD/Indicators of High Risk
GLP-1 RA# with proven CVD benefit
EITHER/ OR
SGLT2i§ with proven CVD benefit
If A1C above target
• For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
• TZD^
+HF
SGLT2i§ with proven HF benefit in this population
+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 A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiorenal risk reduction or glycemic lowering needed

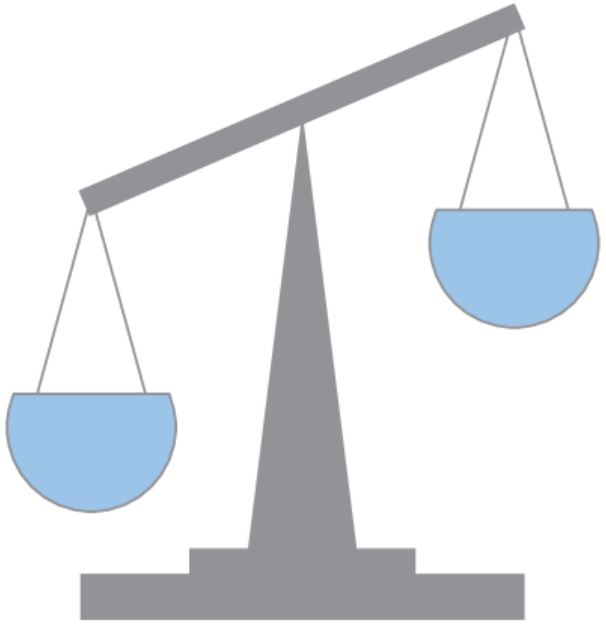
Figure 4: Proposed Modification to the Therapeutic Algorithm for a Patient with Symptomatic Heart Failure with Reduced Ejection Fraction Following Results From DAPA-HF and EMPEROR-Reduced



*Green indicates a class I recommendation; orange indicates a class IIa recommendation; blue indicates the suggested revision to the algorithm based on recent DAPA-HF trial results. *NYHA class II–IV, LVEF <40%; †Up-titrate to maximum tolerated evidence-based dose; ‡With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP >250 pg/ml or NT-proBNP >500 pg/ml in men and 750 pg/ml in women); §With an elevated plasma natriuretic peptide level (BNP ≥150 pg/ml or plasma NT-proBNP ≥600 pg/ml, or if HF hospitalisation within 12 months plasma BNP ≥100 pg/ml or plasma NT-proBNP ≥400 pg/ml); ‖Dapagliflozin is the only SGLT2 inhibitor that has demonstrated significant and clinically meaningful reductions in both the CV deaths and worsening HF components of the primary composite endpoint in patients with HFrEF, both with and without T2D. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronisation therapy; H-ISDN = hydralazine and isosorbide dinitrate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SGLT2 = sodium–glucose co-transporter 2. Source: Ponikowski et al. 2016.[46] Reproduced with permission from Oxford University Press.*

5. Một số khuyến cáo khi sử dụng nhóm Ức chế SGLT2

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

Favorable and unfavorable effects that have been reported for sodium-glucose co-transporter (SGLT2) inhibitors. eGFR = estimated glomerular filtration rate.

28,100 ca có tác dụng không mong muốn.

Hệ thống báo cáo tác dụng phụ do thuốc của FDA (FAERS)

THUỐC	THỜI GIAN	TÁC DỤNG PHỤ	BIẾN CỐ NẶNG	TỬ VONG
Invokana	2013 - 2018	18,131	10,796	255
Farxiga	2014 - 2018	3,923	1,119	62
Jardiance	2014 - 2018	6,046	3,100	116
Steglatro	1/2018 – 9/2018	59	7	0

FAERS : FDA Adverse Events Reporting System

Một số khuyến cáo khi sử thuốc ức chế SGLT2 trên lâm sàng

Tiểu nhiều mất nước hạ HA	Tư vấn cho BN về tác dụng có thể xảy ra • Giáo dục về việc duy trì đủ nước (lưu ý về bất kỳ hạn chế chất lỏng nào cần thiết cho bệnh thận hoặc suy tim) • Đối với BN đang sử dụng thuốc lợi tiểu, hãy xem xét giảm liều lợi tiểu nếu thể tích cân bằng tại thời điểm bắt đầu dùng ức chế SGLT2 bằng cách theo dõi cân nặng tại nhà • Lưu ý mức độ nghiêm trọng của đa niệu thường phụ thuộc vào đường huyết (cải thiện tình trạng tăng đường huyết không kiểm soát được bằng các thuốc khác có thể làm giảm đa niệu) • Đối với BN cao tuổi hoặc những người đang điều trị bằng thuốc hạ HA khác, nên đánh giá HA lại từ 1 đến 2 tuần sau khi dùng ức chế SGLT2

Nhiễm trùng bộ phận sinh dục	Tư vấn cho cả nam và nữ nếu có khả năng bị ảnh hưởng do thuốc • Khuyến khích giữ gìn vệ sinh bộ phận sinh dục • Khuyên BN đi khám nếu có các triệu chứng nhiễm trùng niệu sinh dục • Dùng thuốc chống nấm tại chỗ và tạm thời ngưng SGLT2 nếu có các triệu chứng nhiễm trùng niệu sinh dục • Cân nhắc ngừng điều trị nếu nhiễm nấm Candida dai dẳng hoặc tái phát

Nhiễm trùng đường tiết niệu (UTI)	Khuyên BN đặc biệt là phụ nữ, có nguy cơ tiềm ẩn. Thuốc ức chế SGLT2 có thể không thích hợp ở những BN có tiền sử nhiễm trùng tiểu tái phát • Ngừng sử dụng thuốc ức chế SGLT2 trong trường hợp nhiễm trùng tiểu đáng kể (viêm bể thận, viêm tuyến tiền liệt, nhiễm trùng tiểu, diễn tiến lâm sàng kéo dài) • Cân nhắc ngừng thuốc nếu BN bị nhiễm trùng tiểu tái phát

Nhiễm ceton đẫng đường	Ngừng ức chế SGLT2 trong hai ngày trước và vào ngày phẫu thuật lựa chọn • Khuyên BN ngưng khi nhịn ăn hoặc khi không khỏe • Khuyên BN nên đi khám nếu không khỏe, đặc biệt nếu buồn nôn, nôn hoặc đau bụng, để xem xét đo ceton • Các phòng khám liên quan đến việc chăm sóc những người bệnh ĐTĐ nên được xét nghiệm ceton. Xét nghiệm ceton trong nước tiểu là không đáng tin cậy • Cung cấp cho BN thông tin bằng văn bản về kế hoạch quản lý ngày ốm và thủ tục trước

Hạ đường huyết	• Khi bắt đầu sử dụng ức chế SGLT2 ở Bn đang dùng SU hoặc insulin , cần tư vấn theo dõi đường huyết thường xuyên tại nhà và hướng dẫn Bn về triệu chứng và cách xử trí hạ đường huyết • Nếu Bn dễ bị hạ đường huyết hoặc kiểm soát đường huyết chặt chẽ, cần xem xét giảm liều SU hoặc insulin khi bắt đầu dùng thuốc ức chế SGLT2. Việc ngừng điều trị insulin đồng thời nên tránh vì điều này đã góp phần vào các trường hợp nhiễm toan ceton do ĐTĐ .

Đoạn chi dưới	Liên quan đến nguy cơ đoạn chi dưới chưa rõ • Nên xem xét và chăm sóc bàn chân thường xuyên cho tất cả bệnh nhân sử dụng thuốc • Cân nhắc thuốc ức chế SGLT2 ở những BN có bệnh bàn chân ĐTĐ đặc biệt thể thiếu máu do nguy cơ cao đang tiến triển hoặc giảm tưới máu động mạch ngoại vi

Cân nhắc giữa ngày ốm và giai đoạn chu phẫu với thuốc ức chế SGLT2

Bối cảnh lâm sàng	Cân nhắc ngày ốm và chu phẫu
Các thủ thuật trong ngày, bao gồm nội soi dạ dày	Ngừng thuốc ức chế SGLT2 vào ngày làm thủ thuật
Phẫu thuật và các thủ thuật khác yêu cầu nhập viện hoặc 'chuẩn bị súc ruột'	Ngừng ức chế SGLT2 ít nhất 3 ngày trước khi phẫu thuật (2 ngày trước khi phẫu thuật và ngày phẫu thuật). Mức đường huyết cần được theo dõi và có thể cần tăng các thuốc hạ đường huyết khác.
Giai đoạn chu phẫu thuật	Nếu Bn không khỏe hoặc uống hạn chế kéo dài, thực hiện cả theo dõi đường huyết và ceton máu.
Bệnh cấp tính	Ngừng ức chế SGLT2, đặc biệt nếu giảm ăn uống hoặc nôn. Bn nên theo dõi nồng độ đường huyết và BS nên cân nhắc kiểm tra nồng độ ceton, đặc biệt nếu có buồn nôn, nôn hoặc đau bụng.

KẾT LUẬN

- Qua các nghiên cứu lâm sàng về nhóm ức chế SGLT2 cho thấy lợi ích của thuốc không những có tác dụng hạ đường huyết mà còn có lợi ích trên bệnh lý tim mạch và thận trong đó ba nhóm bệnh nhân hưởng lợi từ thuốc ức chế SGLT2 bao gồm
- 1. Bệnh nhân đái tháo đường típ 2;
- 2. Bệnh nhân suy tim phân suất tống máu bất kỳ;
- 3. Bệnh nhân mắc bệnh thận mãn tính.
- Nhóm ức chế SGLT2 hiện không chỉ đơn thuần là một loại thuốc trị ĐTĐ mà thực sự là một tác nhân bổ sung trong bệnh lý tim mạch và thận.
- Hiện được xếp vào nhóm “Blockbuster drugs” .

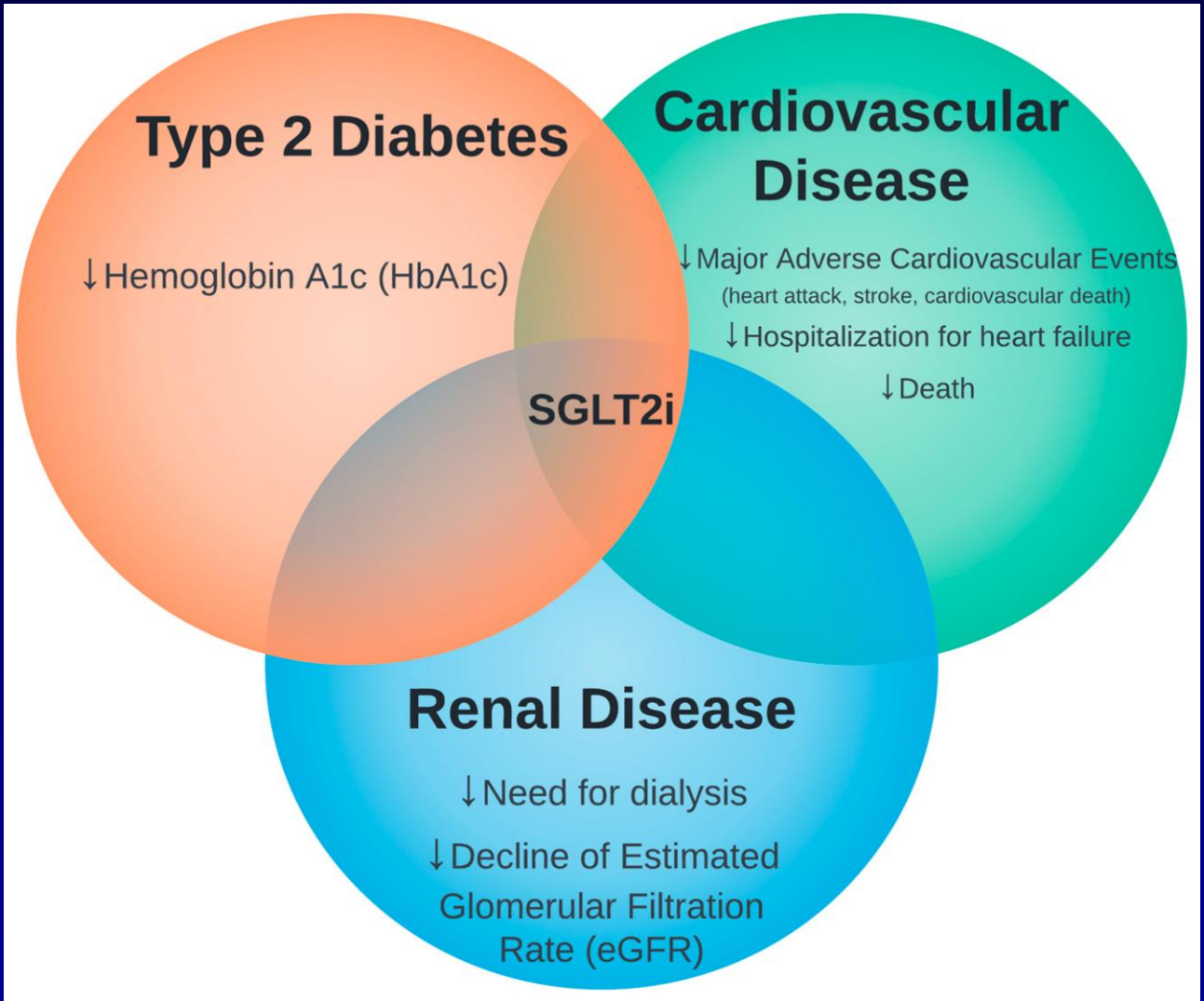


Figure 1. The intersection of sodium glucose cotransporter 2 inhibitors (SGLT2i) therapy in type 2 diabetes, cardiovascular disease, and renal disease.

Practical approach to SGLT2 inhibitors for treatment of cardiovascular disease

Indications

Patients with Type 2 DM[1]

or

Patients with chronic kidney disease (eGFR 25-90, UACR>20 mg/mmol)[2]

or

Patients with chronic HFrEF[3]

Contraindications

- CLI[3]
- eGFR<25[4]
- Allergy or intolerance to SGLT2i[§]

→ Do not initiate SGLT2i

Caution

- Volume depletion[5]
- Active GMI[6]
- Hypotension (Blood pressure<95 mmHg)[*,7]
- Prior CLI
- DKA[5] [specific to DM]
- History of severe hypoglycemia[†] [specific to DM]

→ Delay initiation of SGLT2i until condition resolved/ therapies modified to reduce risk

Outpatient Initiation

Start 10 mg od qam:

- Dapagliflozin[5]
- Empagliflozin[8]

Start 100 mg od qam:

- Canagliflozin[9]

Special Considerations

- Monitor for GMIs, counsel on proper hygiene[6]
- Concomitant dehydrating illness (SADMANS)[‡,10]
- Borderline renal function[§,5,6]
- Volume depletion[‖,5]

Potential drug-drug effects with:

Loop diuretics

- Optional dose reduction[¶] if euvolemic; 30–50% dose reduction if volume depletion occurs[3]

Insulin or SU

- If DM w/A1C<7.5, consider dose reduction (i.e., 10–20% insulin, and/or 50% SU)[11]
- If episodes of hypoglycemia[#], stop SU and dose reduce insulin[11]

Follow-up

Follow up routine as per underlying condition:

- Weight[6]
- Symptoms of hypotension[6]
- Adherence[6]
- Renal function (eGFR)[**,††,6]
- Blood glucose[6] [specific to DM]

Abbreviations:

CLI: critical limb ischemia; **DKA:** diabetic ketoacidosis; **DM:** diabetes mellitus; **eGFR:** estimated glomerular filtration rate; **GMI:** genital mycotic infections; **HFrEF:** heart failure with reduced ejection fraction; **SGLT2i:** SGLT2 inhibitors; **SU:** sulfonylurea; **UACR:** urine albumin to creatinine ratio

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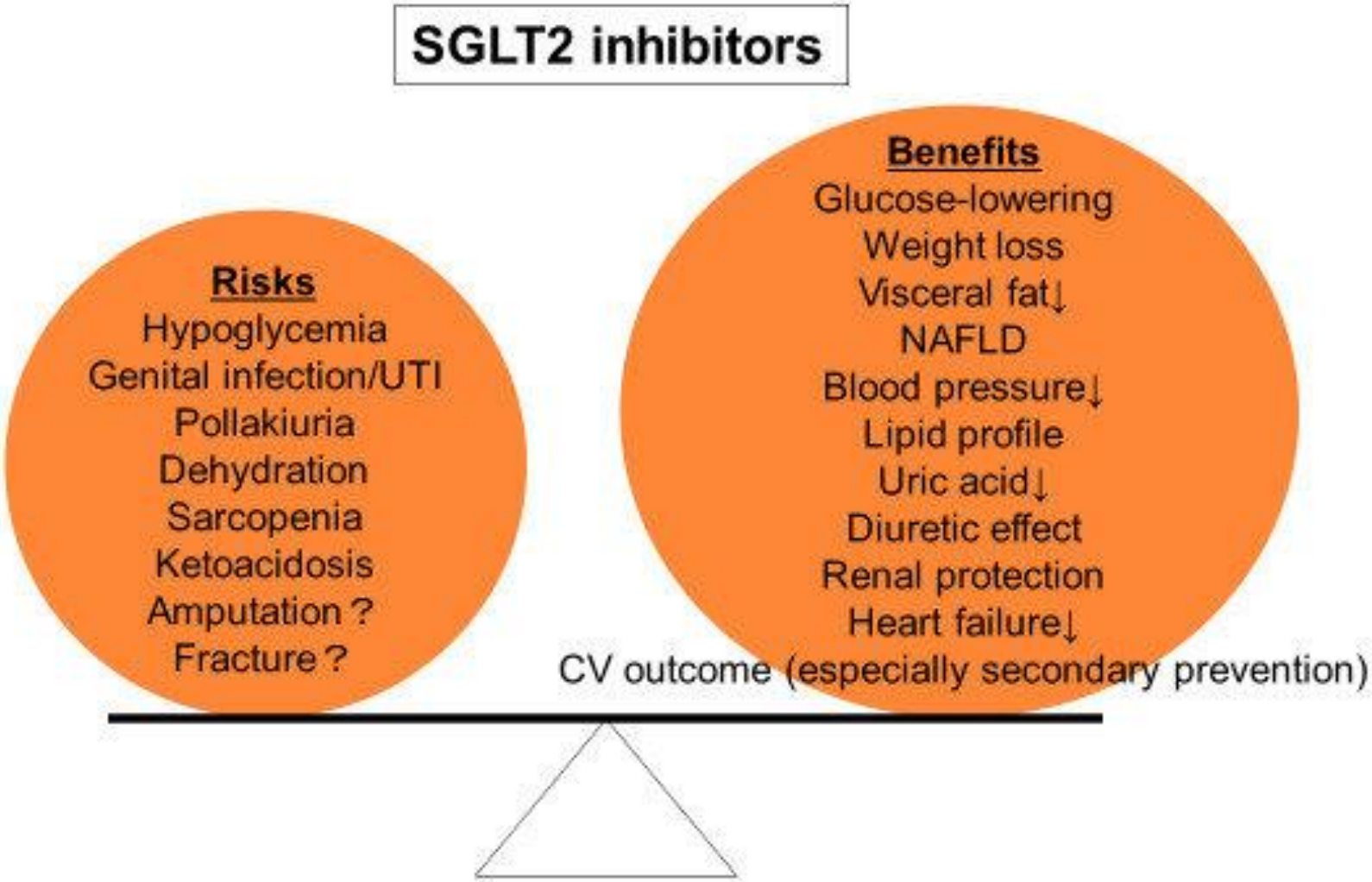
CHFS SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque


SGLT2 inhibitors
Risks
Hypoglycemia
Genital infection/UTI
Pollakiuria
Dehydration
Sarcopenia
Ketoacidosis
Amputation ?
Fracture ?
Benefits
Glucose-lowering
Weight loss
Visceral fat↓
NAFLD
Blood pressure↓
Lipid profile
Uric acid↓
Diuretic effect
Renal protection
Heart failure↓
CV outcome (especially secondary prevention)

Chân thành cám ơn
sự theo dõi của quý đồng nghiệp

Kính mời quý đồng nghiệp tham gia báo cáo và tham dự
1. Hội Nghị Nội Tiết- Đái Tháo Đường Đà Nẵng lần thứ I tại Đà Nẵng ngày **16-17/06/2023**
2. Hội Nghị Nội Tiết – ĐTĐ Miền Trung và Tây Nguyên Mỡ Rộng lần thứ XIV tại Đà Nẵng ngày **9-10/9/2023**

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