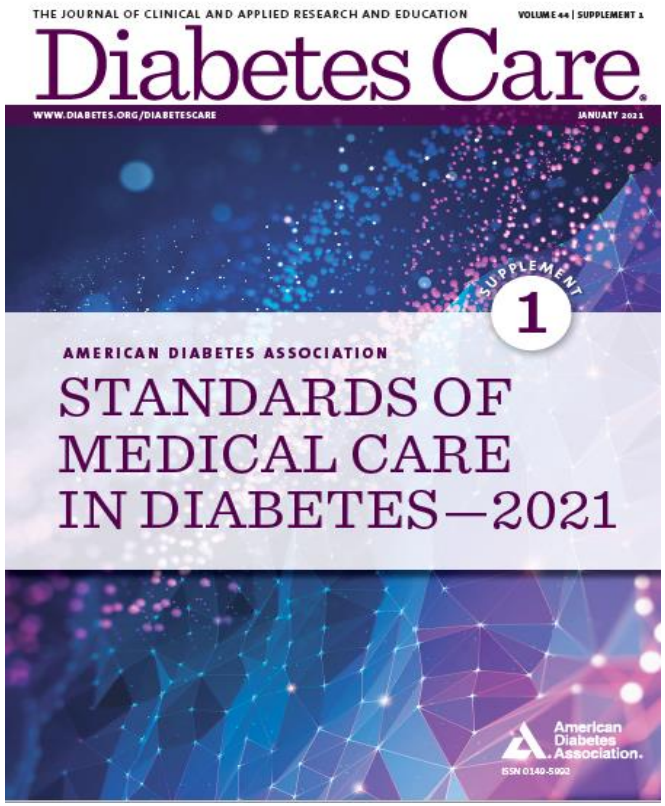
HỘI NGHỊ TĂNG HUYẾT ÁP VIỆT NAM LẦN THỨ IV

Cần Thơ, ngày 16 - 17 tháng 10 năm 2021

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

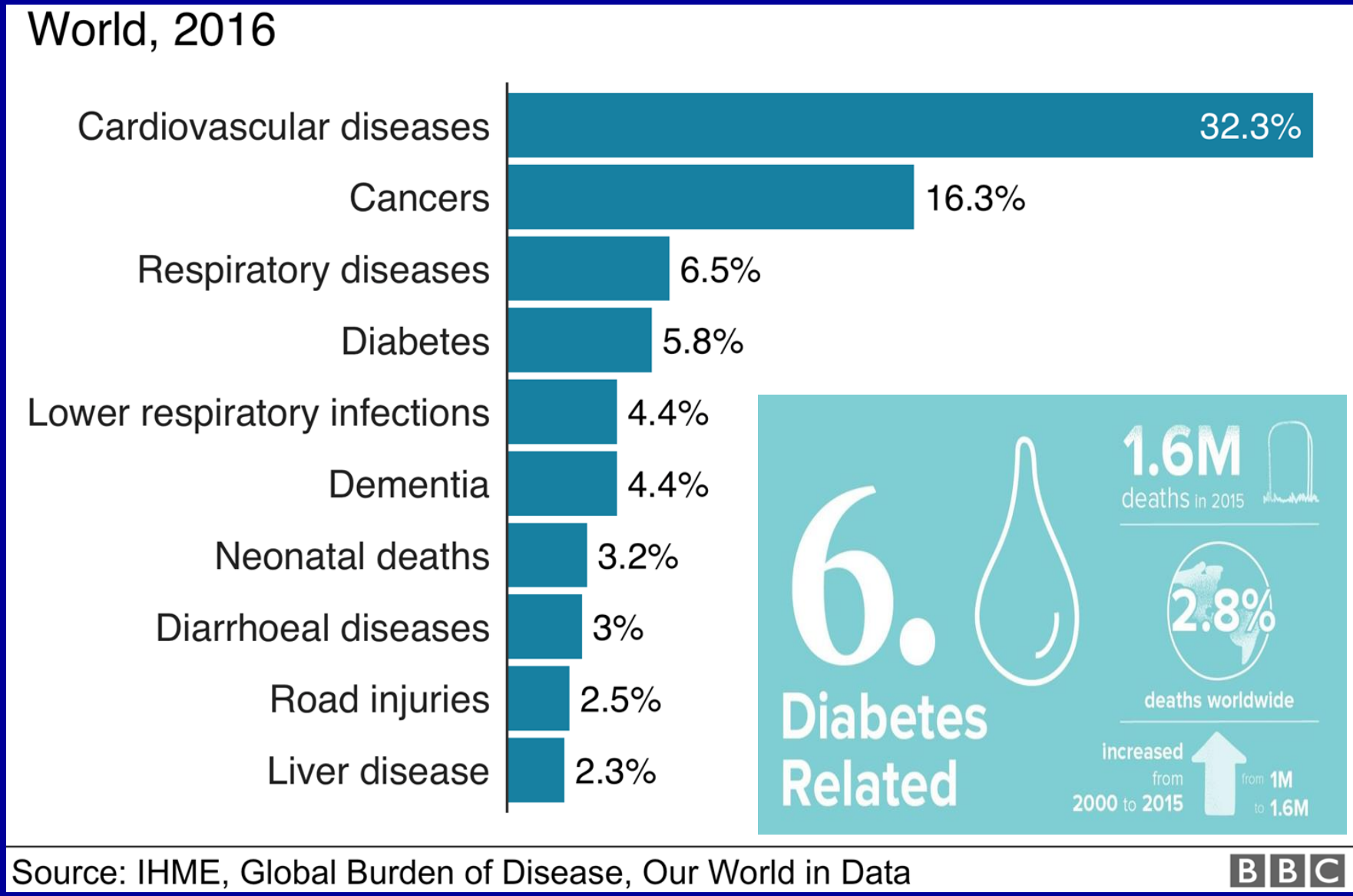


Vai Trò Bảo Vệ Tim Mạch Của Nhóm Ức Chế SGLT2 Trên Bệnh Nhân ĐTĐ Típ 2 (ADA 2021 và ESC 2021)

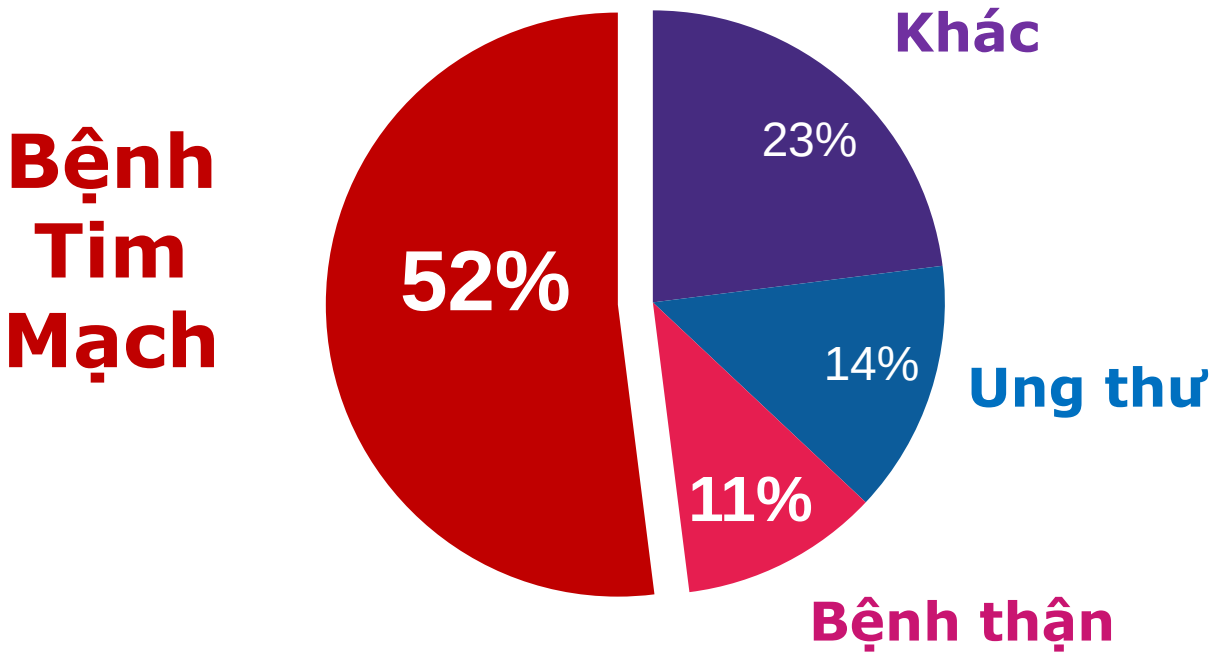
GS.TS.Nguyễn Hải Thủy
PCT Hội Nội Khoa Việt Nam

1. Đề xuất nhóm Ức chế SGLT2 theo các khuyến cáo ADA 2021 và ESC 2021

ĐTĐ là một trong 10 căn bệnh gây tử vong cao nhất trên toàn thế giới



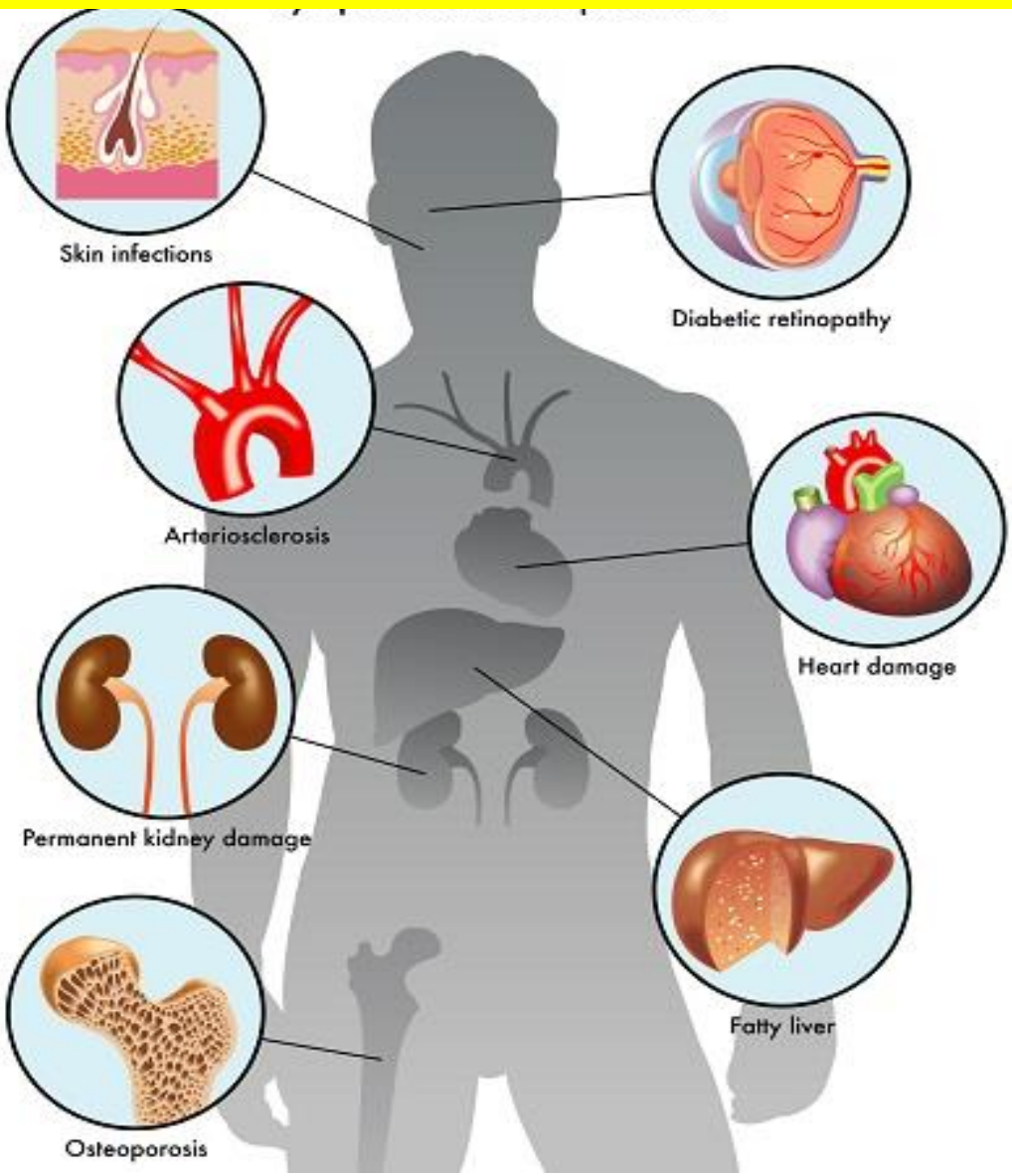
Nguyên nhân tử vong ở bn ĐTĐ típ 2 chủ yếu là tim mạch[2]



Mean follow-up was 9.4 years for men and 9.8 years for women; N=709

1. International Diabetes Federation. IDF Diabetes Atlas. 7th edn. 2015. www.idf.org/diabetesatlas (accessed June 2017);
2. Morrish NJ et al. Diabetologia 2001;44(Suppl. 2):S14

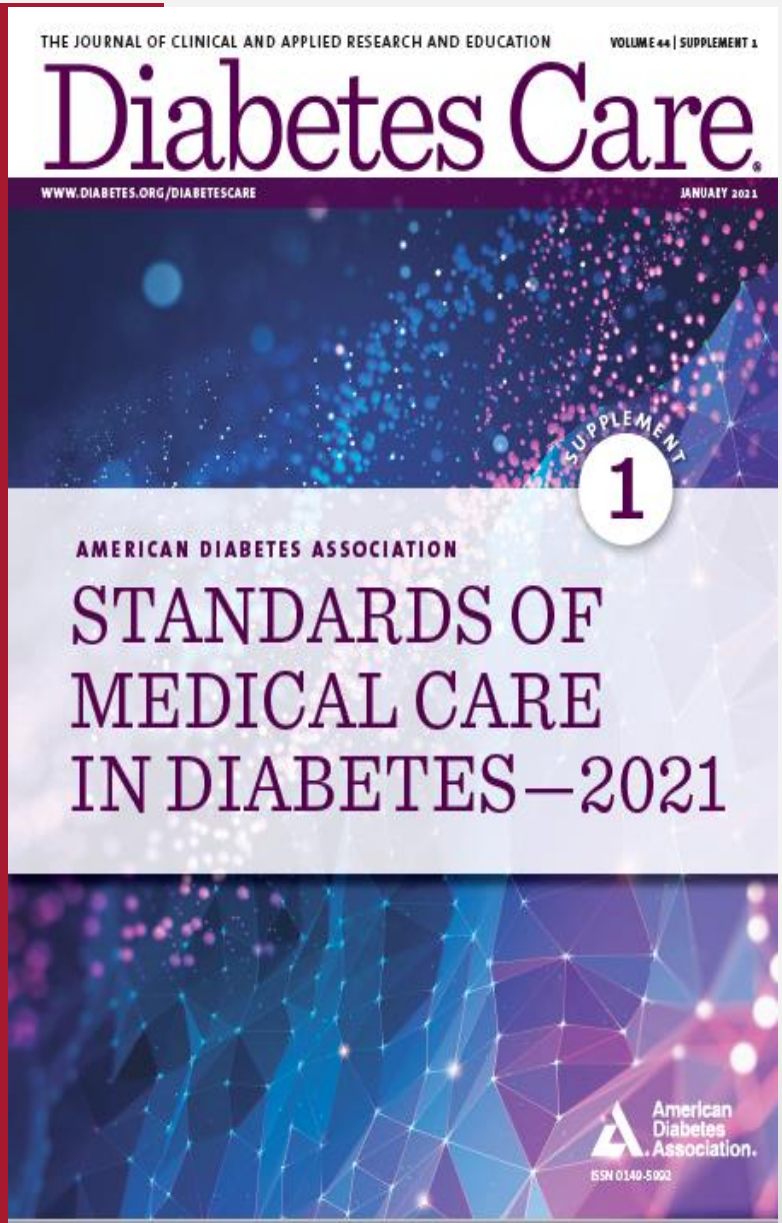
Khi nói đến Đái tháo đường Típ 2 người ta liên tưởng đến biến chứng Tim Mạch.



Standards of Medical Care in Diabetes—2021

Section 9. Pharmacologic Approaches to Glycemic Treatment

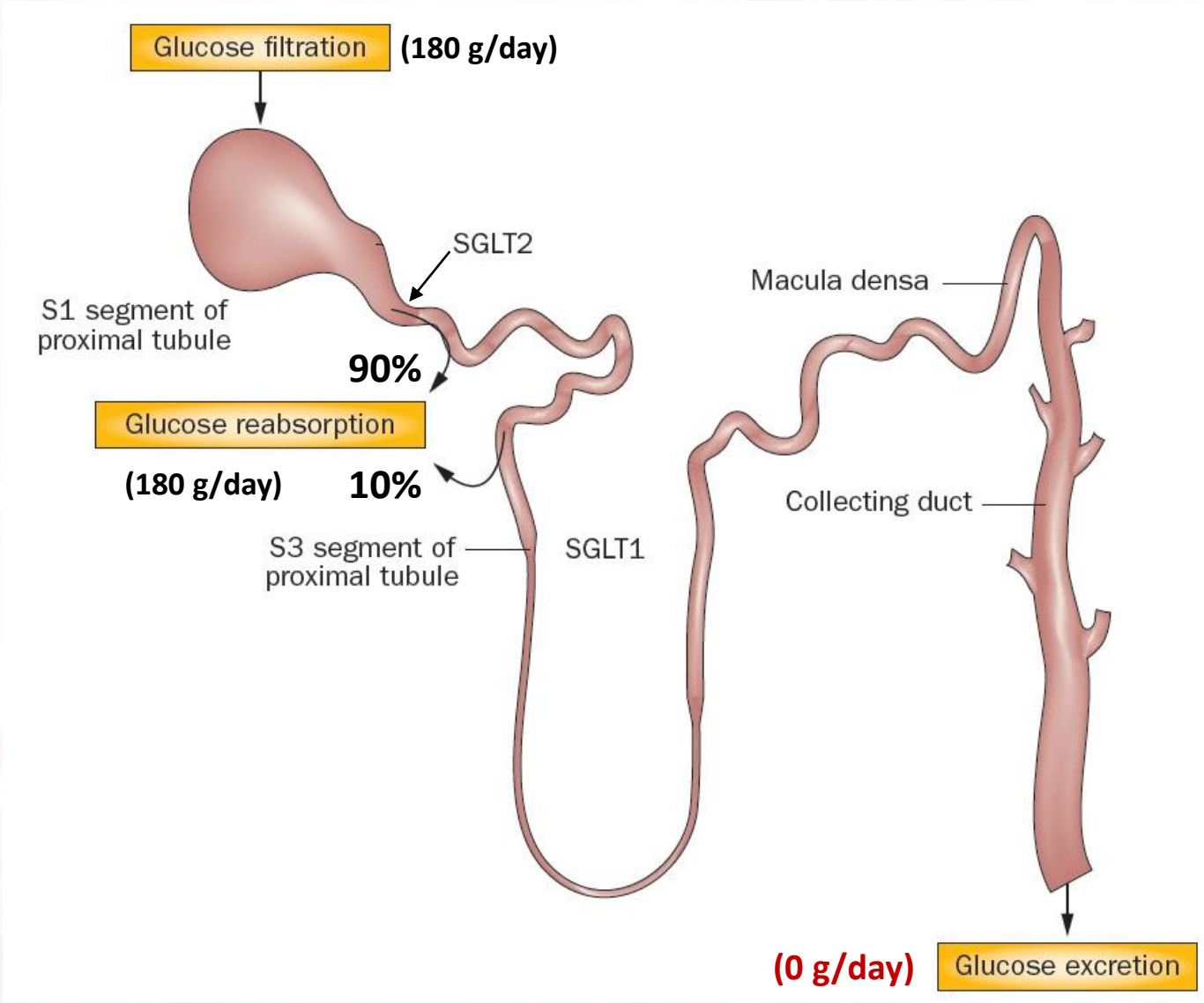
Section 10. Cardiovascular Disease and Risk Management



American Diabetes Association.
Connected for Life

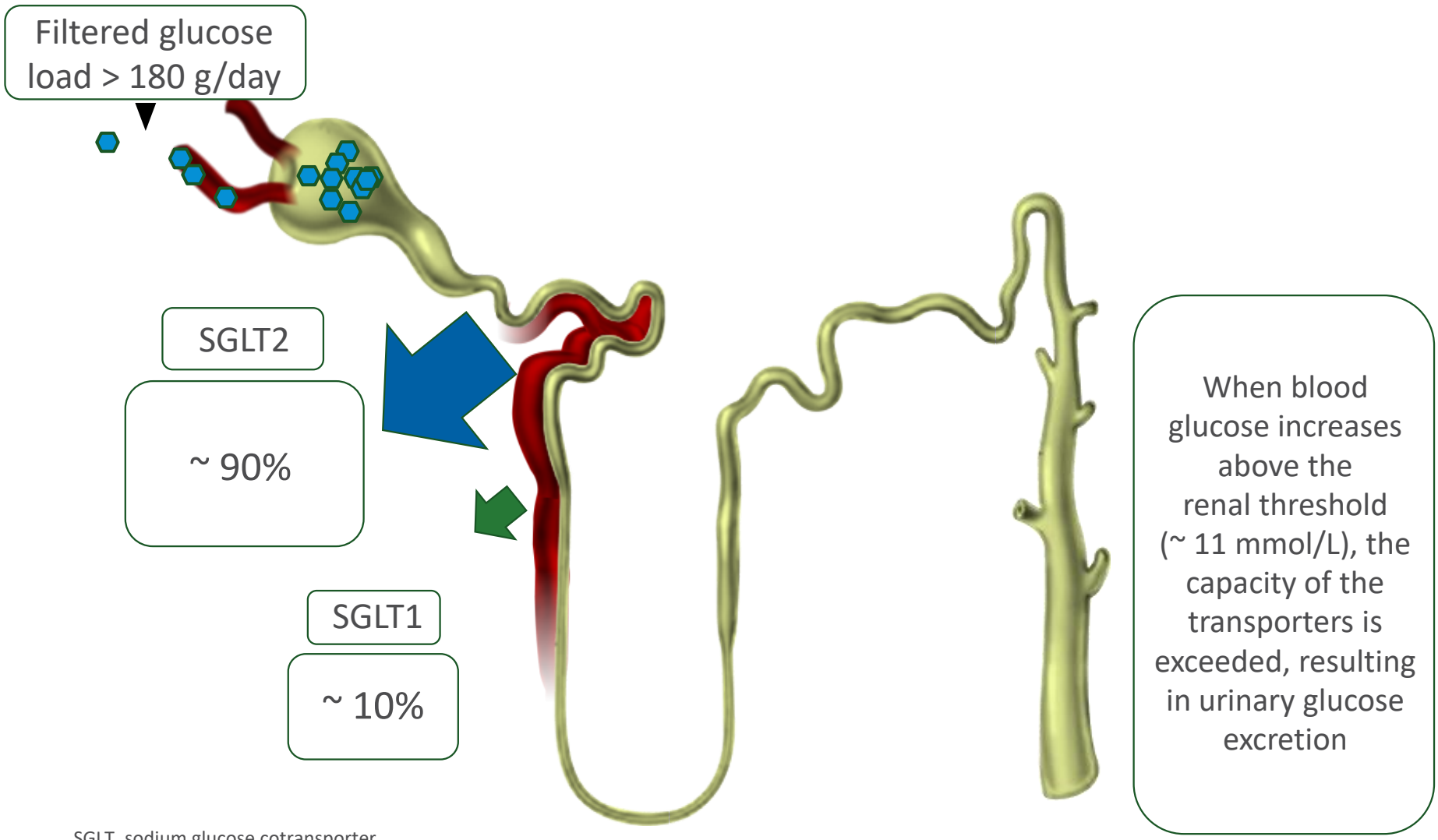
In 1835, French chemists first isolated a substance known as **phlorizin** from the bark of apple trees, and in 1886, German physician and early diabetes pioneer **Joseph von Mering** demonstrated that the ingestion of high doses of phlorizin caused people to expel glucose in their urine (glucosuria)….

SGLT2 inhibitors, also called **Gliflozins**



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

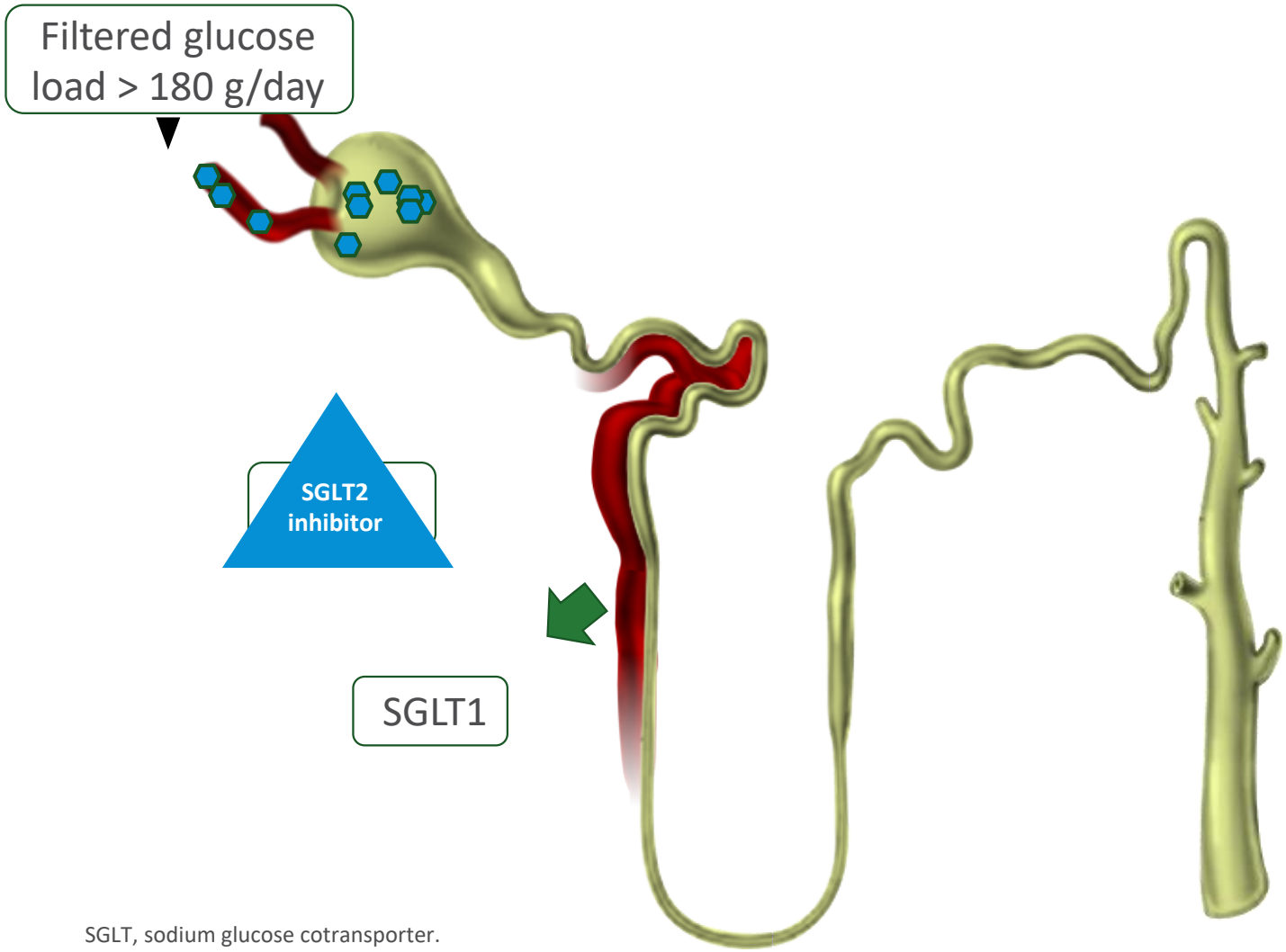
Renal glucose re-absorption in patients with diabetes[1,2]



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]



SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

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.

Một số thông tin liên quan SGLT và Ức chế SGLT

Hiện diện SGLTs

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.

Thành viên nhóm Gliflozin

1.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.[22][23]

2.Dapagliflozin is the first SGLT2 inhibitor approved anywhere in the world by the EU in **2012**.[24] It was approved for use in the United States under the brand name Farxiga by the Food and Drug Administration in January 2014.[25] the first oral treatment in combination with insulin to treat type 1 diabetes mellitus in UK and EU.

3.Empagliflozin, approved in the United States in August **2014**, under the brand name Jardiance by Boehringer Ingelheim.[26] Of the gliflozins, empagliflozin and tofogliflozin have the highest specificity for SGLT2 inhibition.[1] It is the only oral medicine for type 2 diabetes that has been shown to reduce the risk of cardiovascular death.[27][*needs update*]

4.Ertugliflozin was approved in the United States under the brand name Steglatro in December **2017**.[28]

5.Ipragliflozin, produced by the Japanese company Astellas Pharma Inc. under the brand name Suglat, approved in Japan January **2014**.[29][30]

6.Luseogliflozin was approved in Japan March **2014** under the brand name Lusefi and was developed by Taisho Pharmaceutical.[31]

7.Remogliflozin etabonate was commercially launched first in India by Glenmark in May **2019**.

8.Sergliflozin etabonate discontinued after Phase II trials.[32]

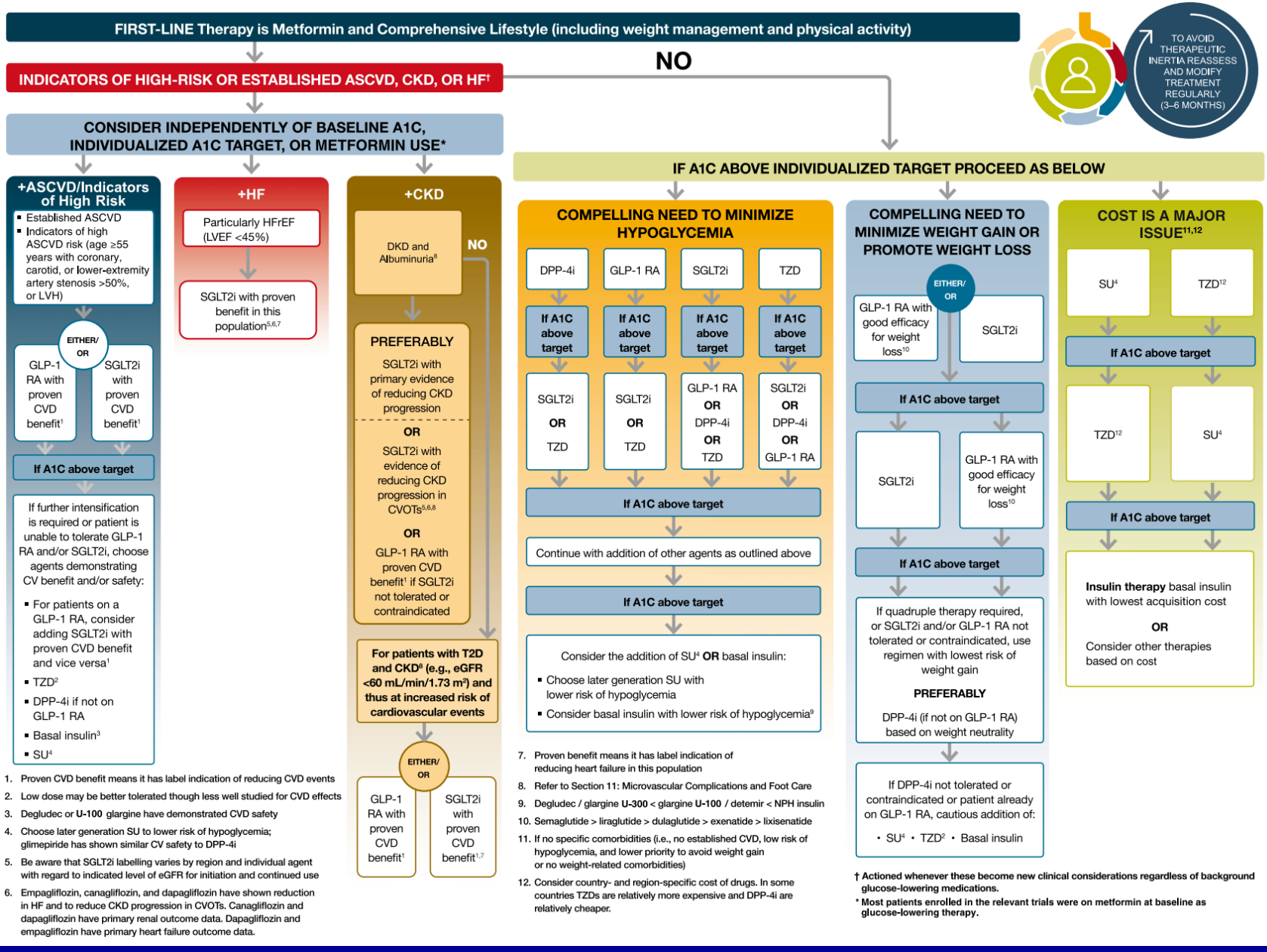
9.Sotagliflozin is a dual SGLT1/SGLT2 inhibitor in phase III trials under the brand name Zynquista. Developed by Lexicon pharmaceuticals. It was planned to be the first oral treatment in combination with insulin to treat type 1 diabetes mellitus.[33] The Food and Drug Administration refused its approval for use in combination with insulin for the treatment of type 1 diabetes.[34][35]

10. Tofogliflozin was approved in Japan in March **2014**, under the brand names Apleway and Deberza developed by Sanofi and Kowa Pharmaceutical.[36]

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.



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or **U-100** glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine **U-300** < glargine **U-100** / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

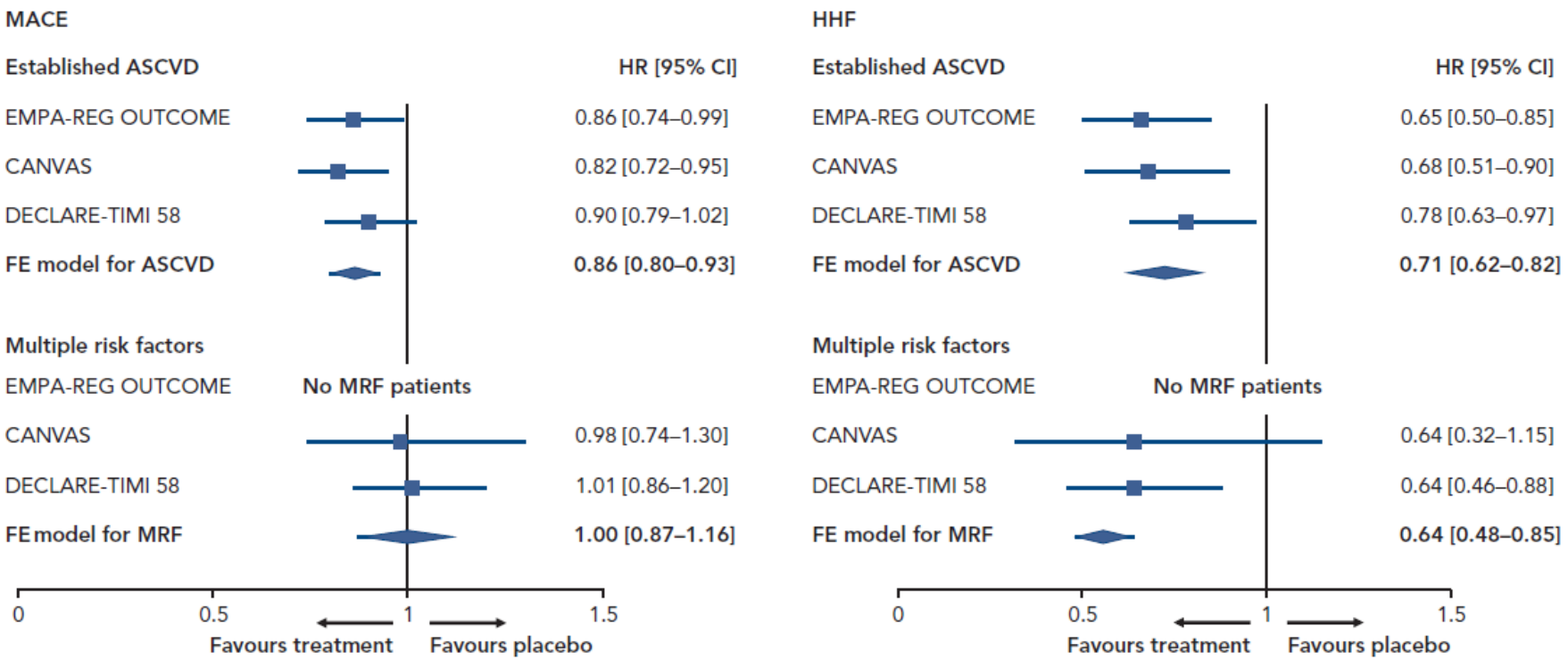
† **Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.**

* **Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.**

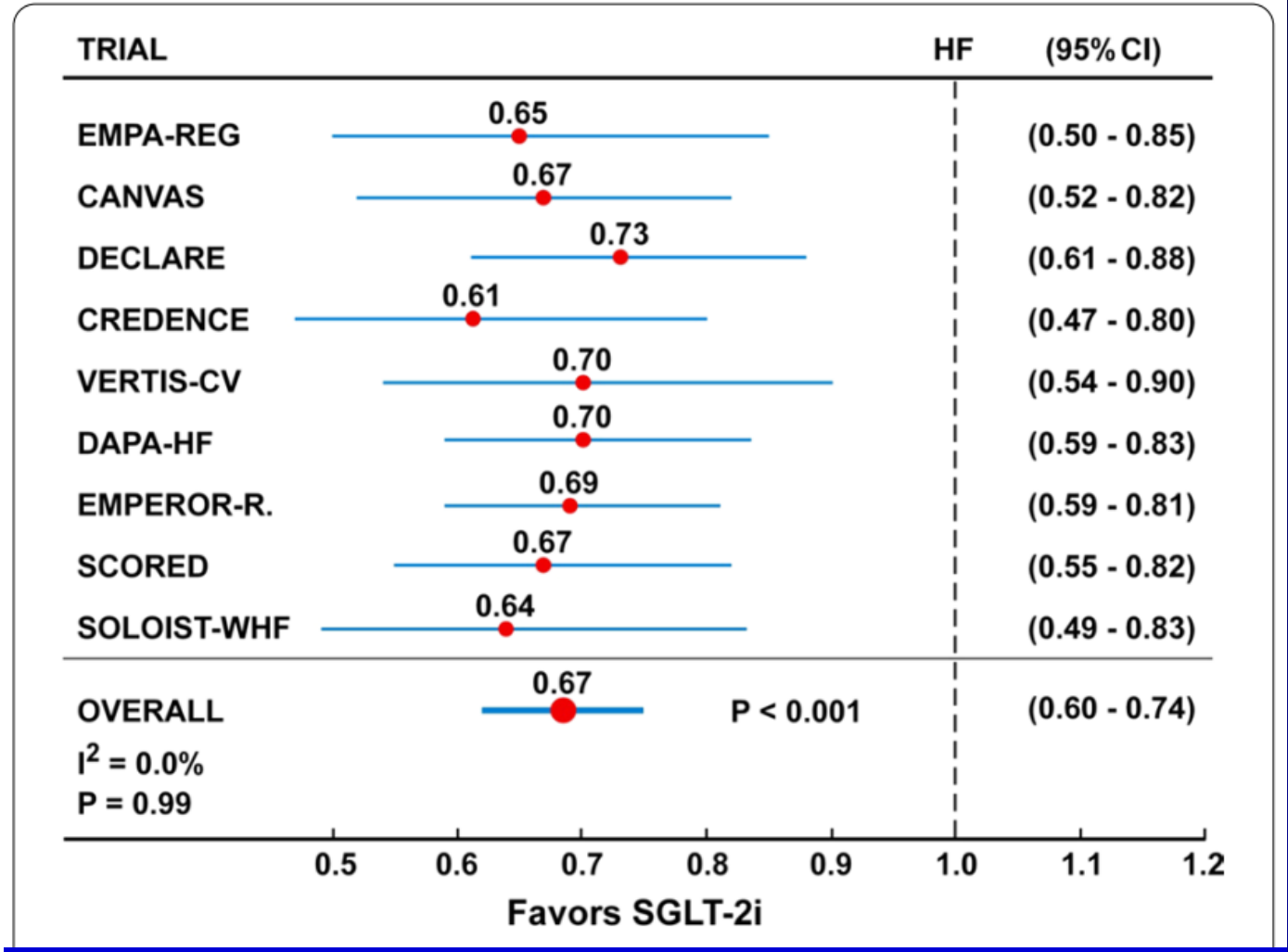
TABLE 9.1 Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	▪ Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m^2 ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – Analogs						High	SQ			

Kết quả nghiên cứu nhóm ức chế SGLT2 trên Kết cục Tim Mạch ở ĐTĐ típ 2



ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HHF = hospitalisation for heart failure; FE = fixed effects; MACE = major adverse cardiovascular events; MRF = multiple risk factors; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes. Source: Zelniker et al. 2019.[12] Reproduced with permission from Elsevier.



Đánh giá 9 thử nghiệm nhóm ức chế SGLT2
Suy tim trên bn có và không ĐTĐ típ 2
Nhóm Bn có và không có Suy tim

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 suy tim ở bệnh nhân ĐTĐ

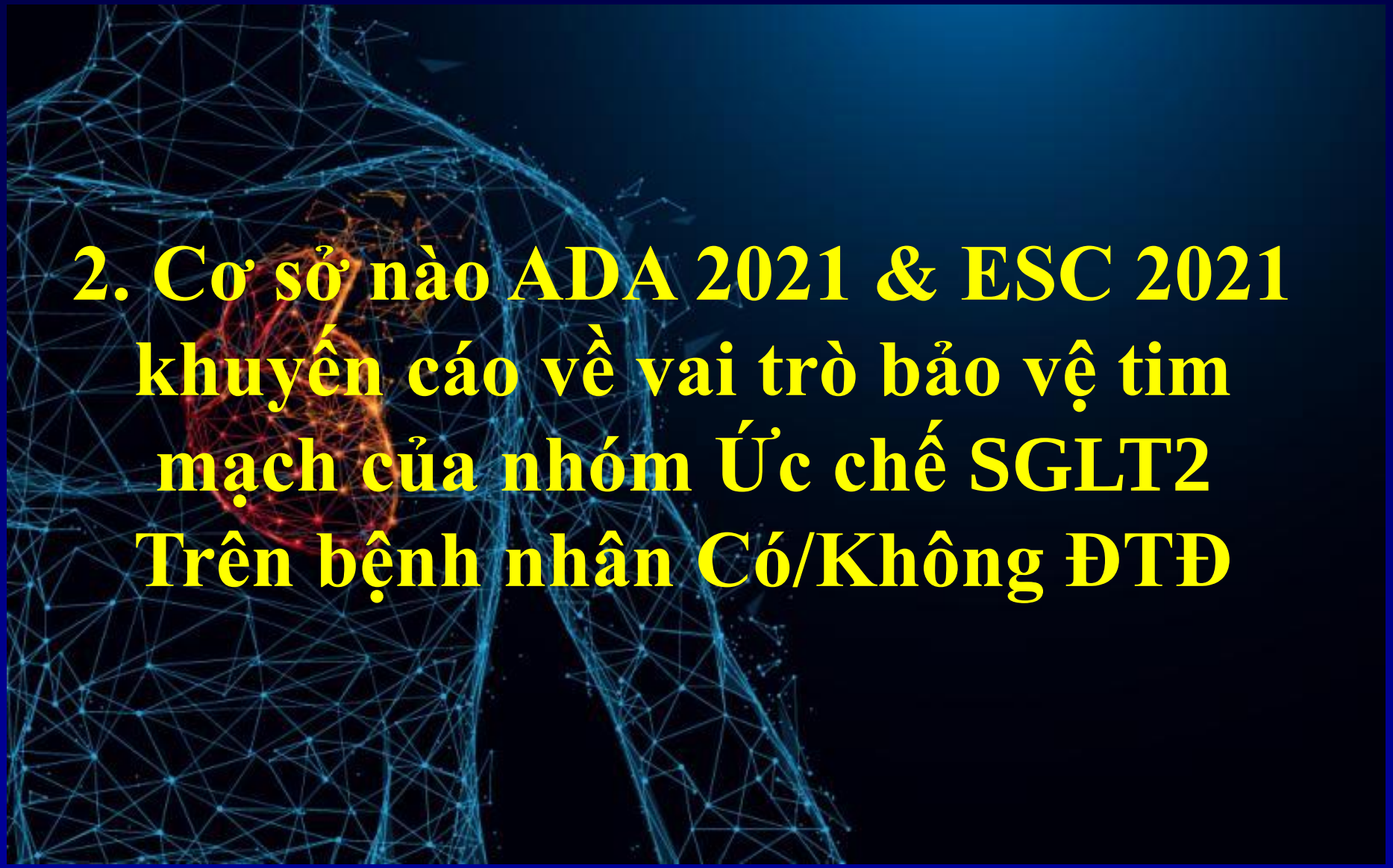
Recommendation	Class[a]	Level[b]
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.[293–297]	I	A
SGLT2 inhibitors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

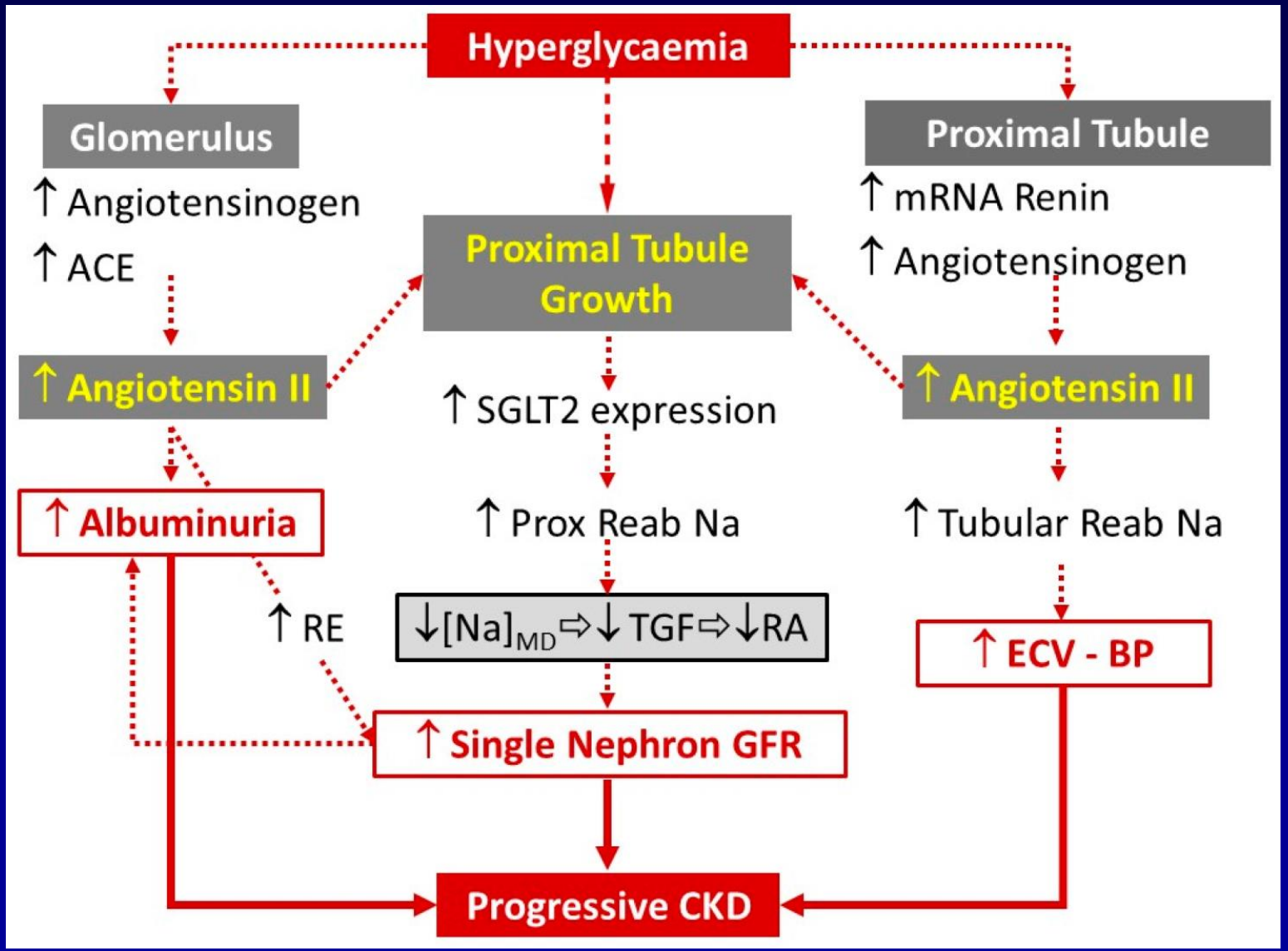
Khuyến cáo điều trị ở bệnh nhân Suy tim (NYHA II-IV) với EF ≤ 40%

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

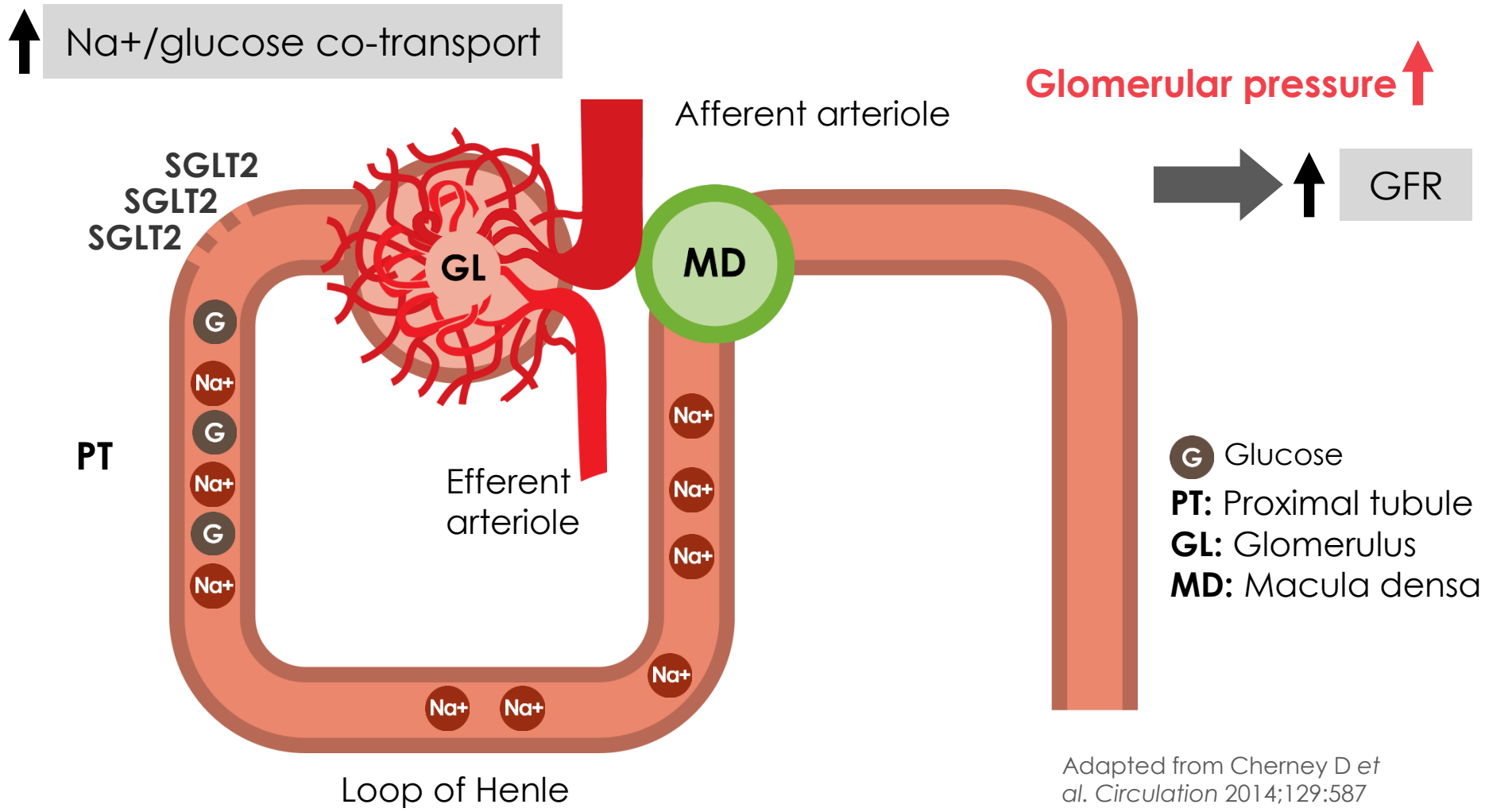


2. Cơ sở nào ADA 2021 & ESC 2021 khuyến cáo về vai trò bảo vệ tim mạch của nhóm Ức chế SGLT2 Trên bệnh nhân Có/Không ĐTĐ

1.Ức chế SGLT2 & Bảo vệ Thận



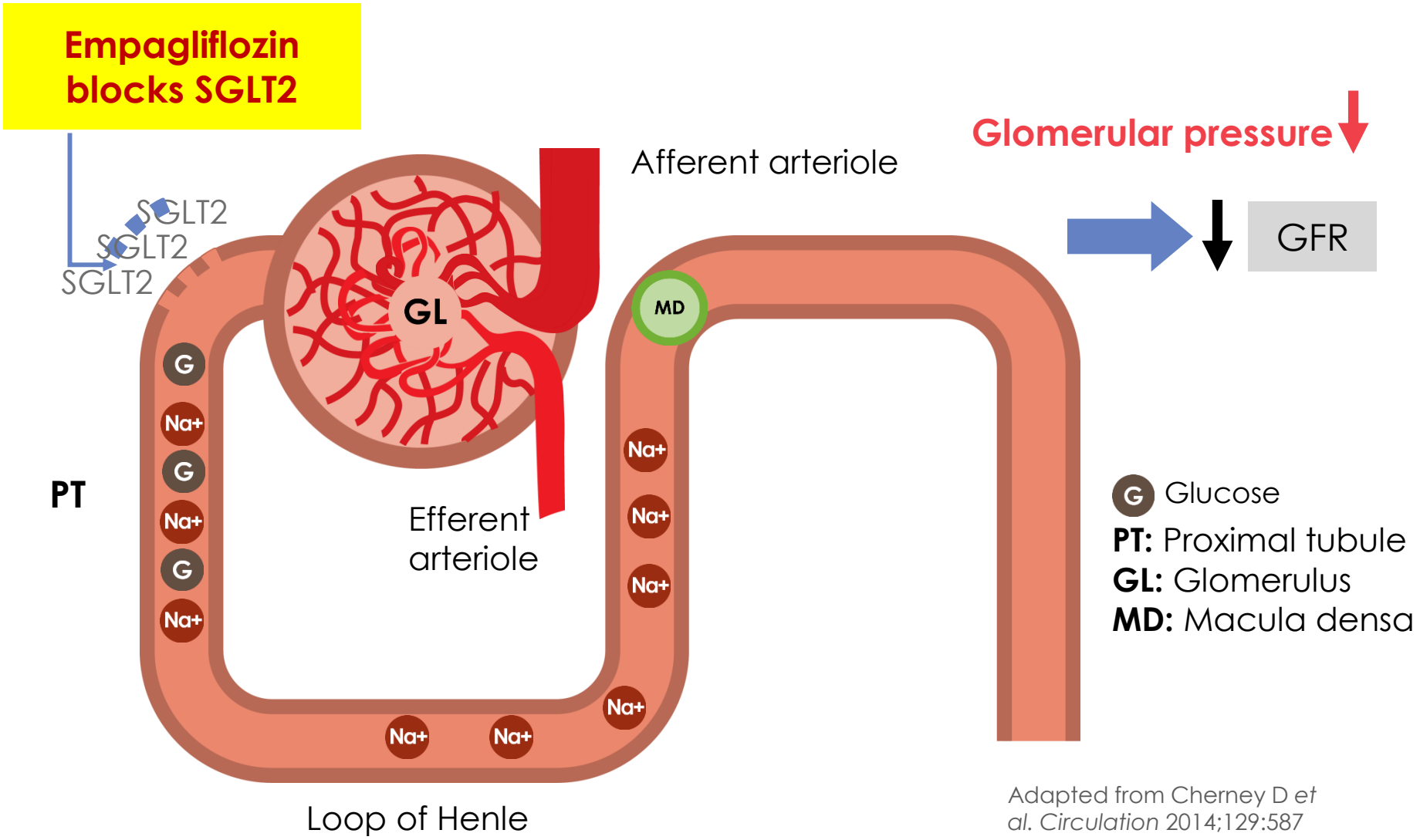
Diabetes Causes Glomerular Hypertension



Renal hemodynamics under hyperglycemia

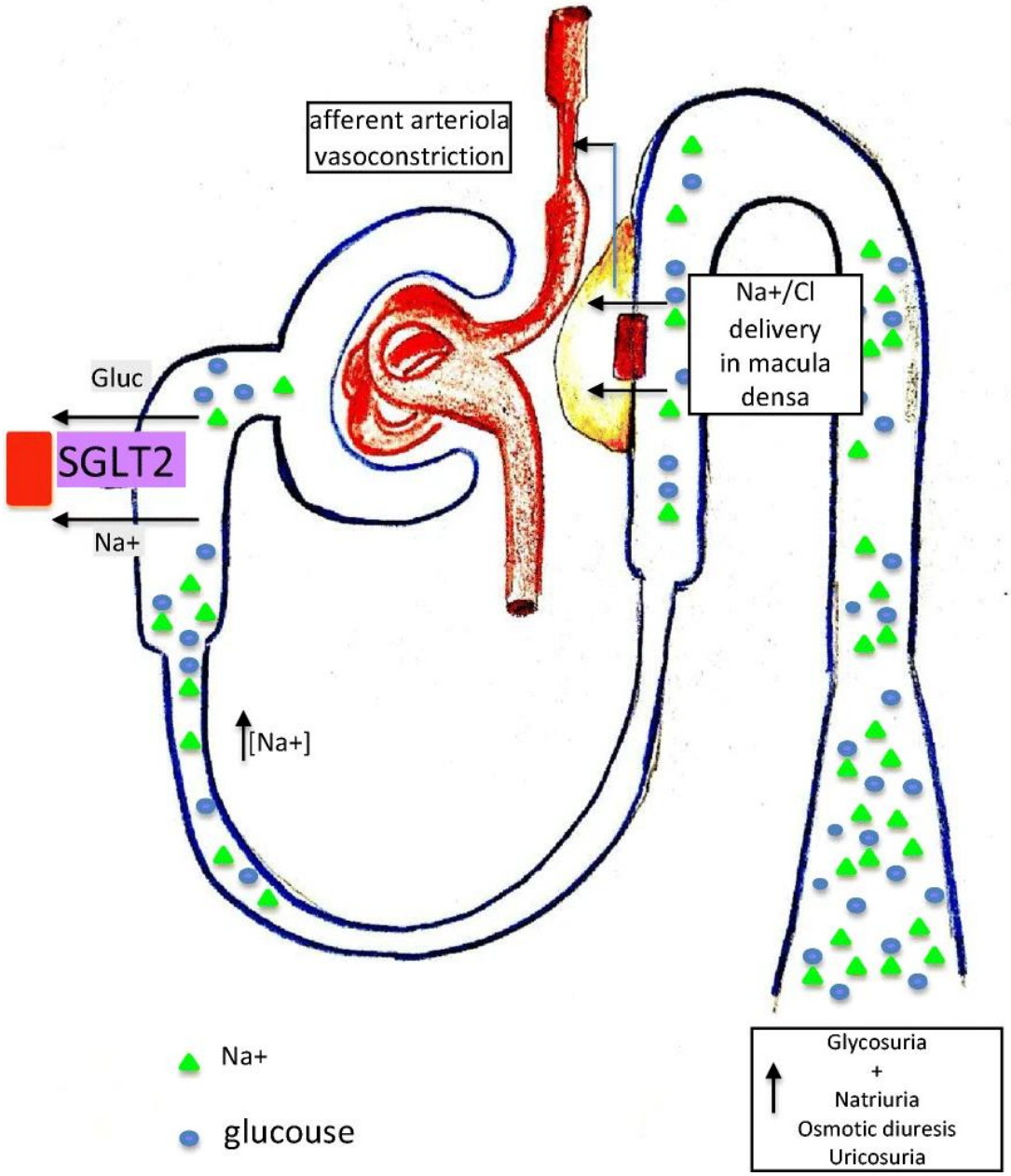
Adapted from: Cherney D et al. Circulation 2014;129:587

SGLT2.I Lowers Intra-Glomerular Pressure



Renal hemodynamics with empagliflozin

Adapted from: Cherney D et al. Circulation 2014;129:587



Direct Renal Effects

1. Osmotic diuresis—> intestitial pressure
2. Reduction of oxigen consumption
3. Reduction of oxidative stress and inflammation
4. Reduction of intragolmerular ipertension

Indirect Renal Effects

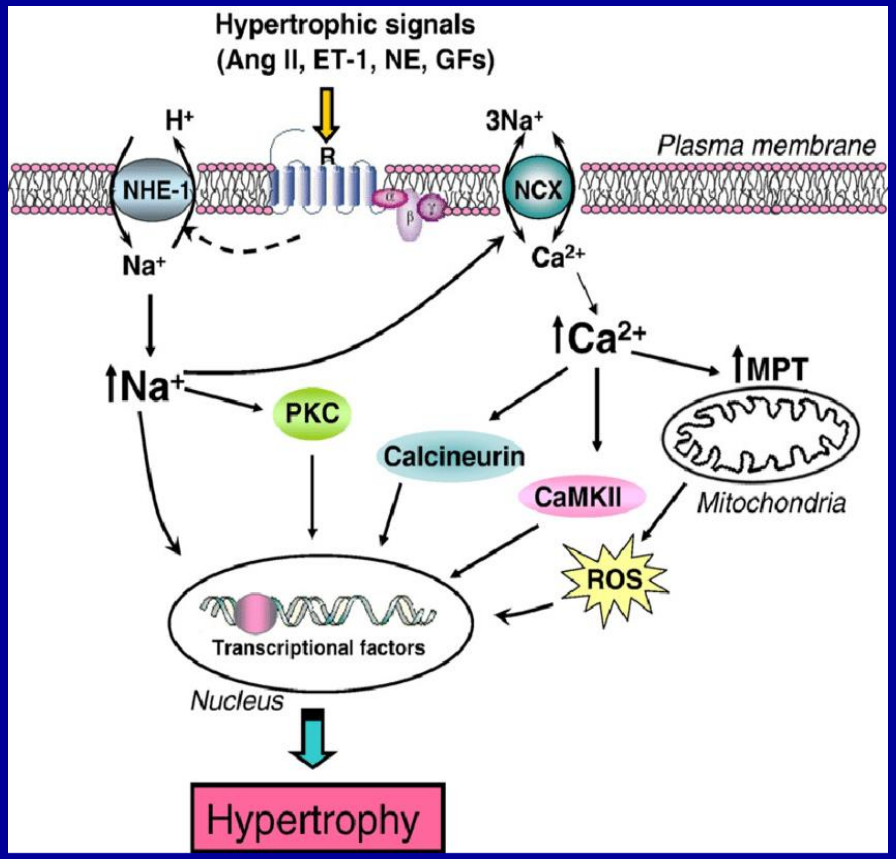
1. Reduction of blood pressure
2. Reduction of body fat and body weight
3. Reduction of oxidative stress and inflammation
4. Uricosuria
5. Reduction of plasma volume
6. Activation of AT2 type 2
7. Sympathetic system modulation

Mostly due to glycosuria

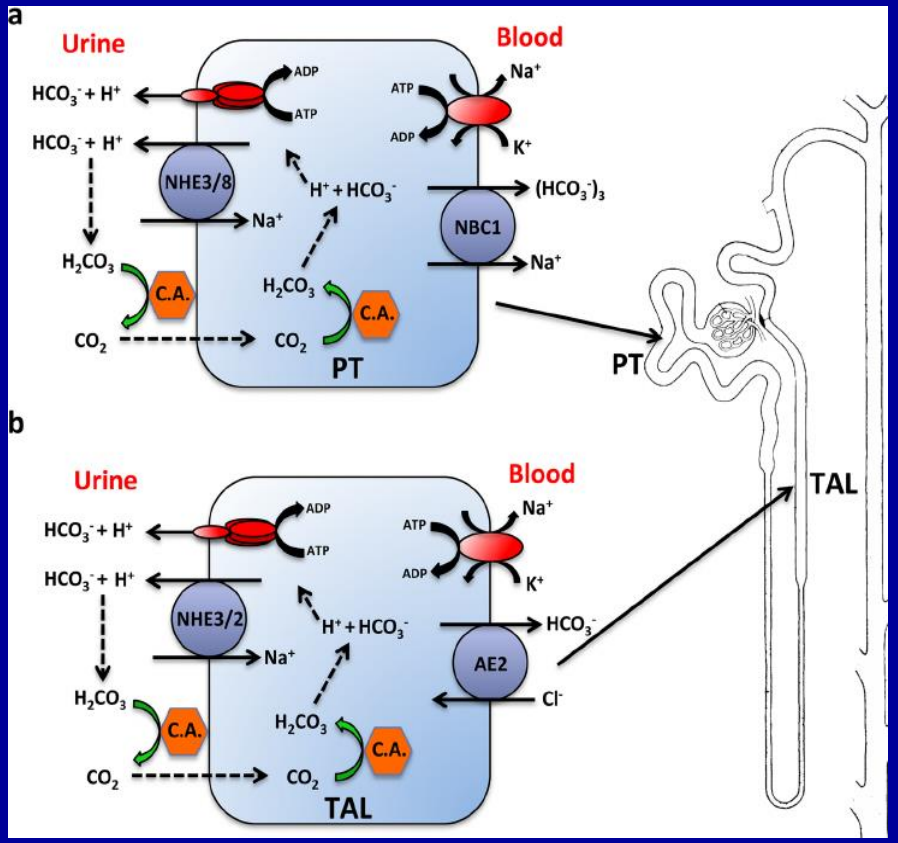
Mostly due to natriuresis

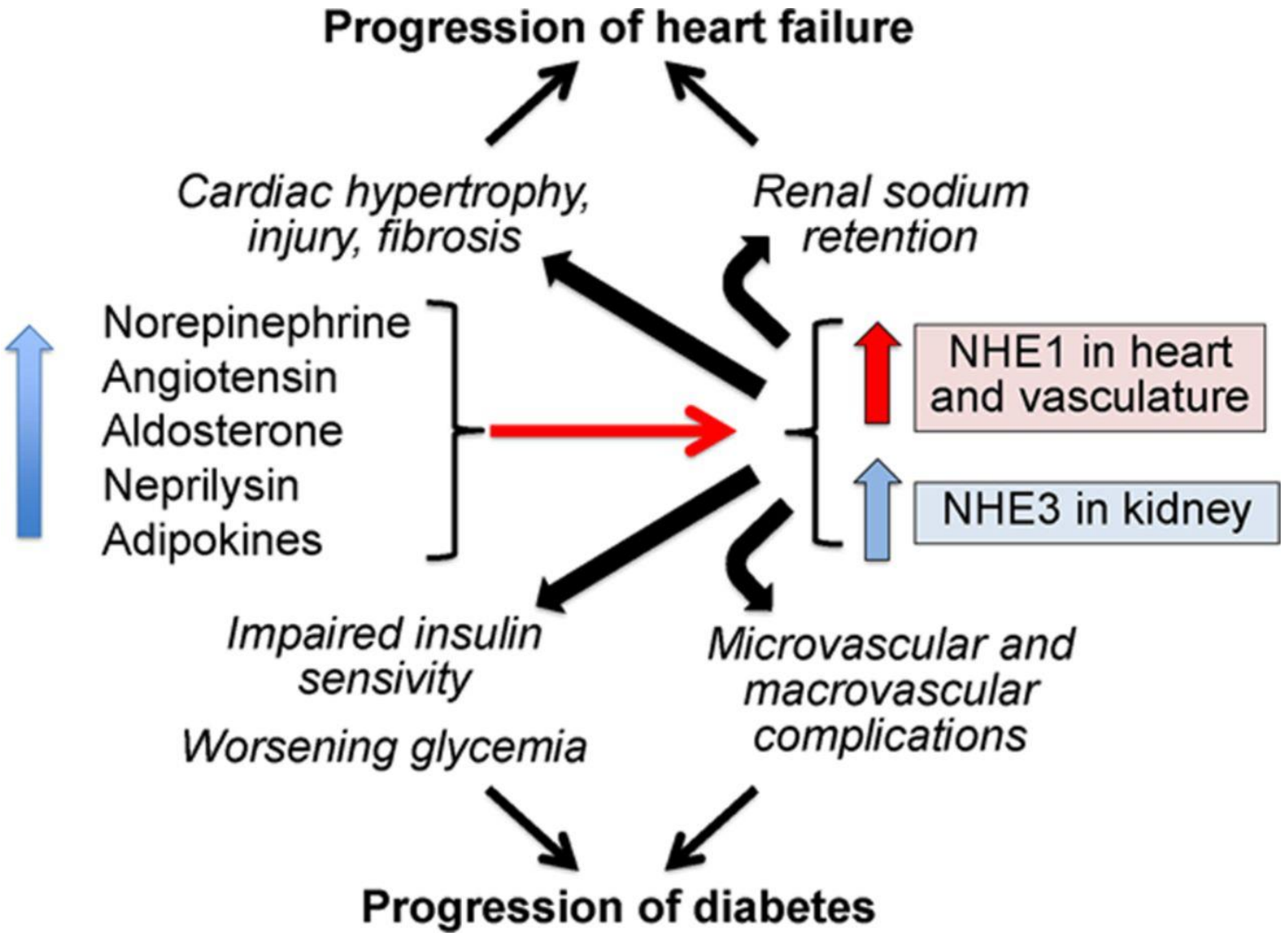
2.Ức chế & SGLT2Hệ thống trao đổi Natri–Hydro (Sodium-Hydrogen Exchanger-NHE)

NHE1 (tim)

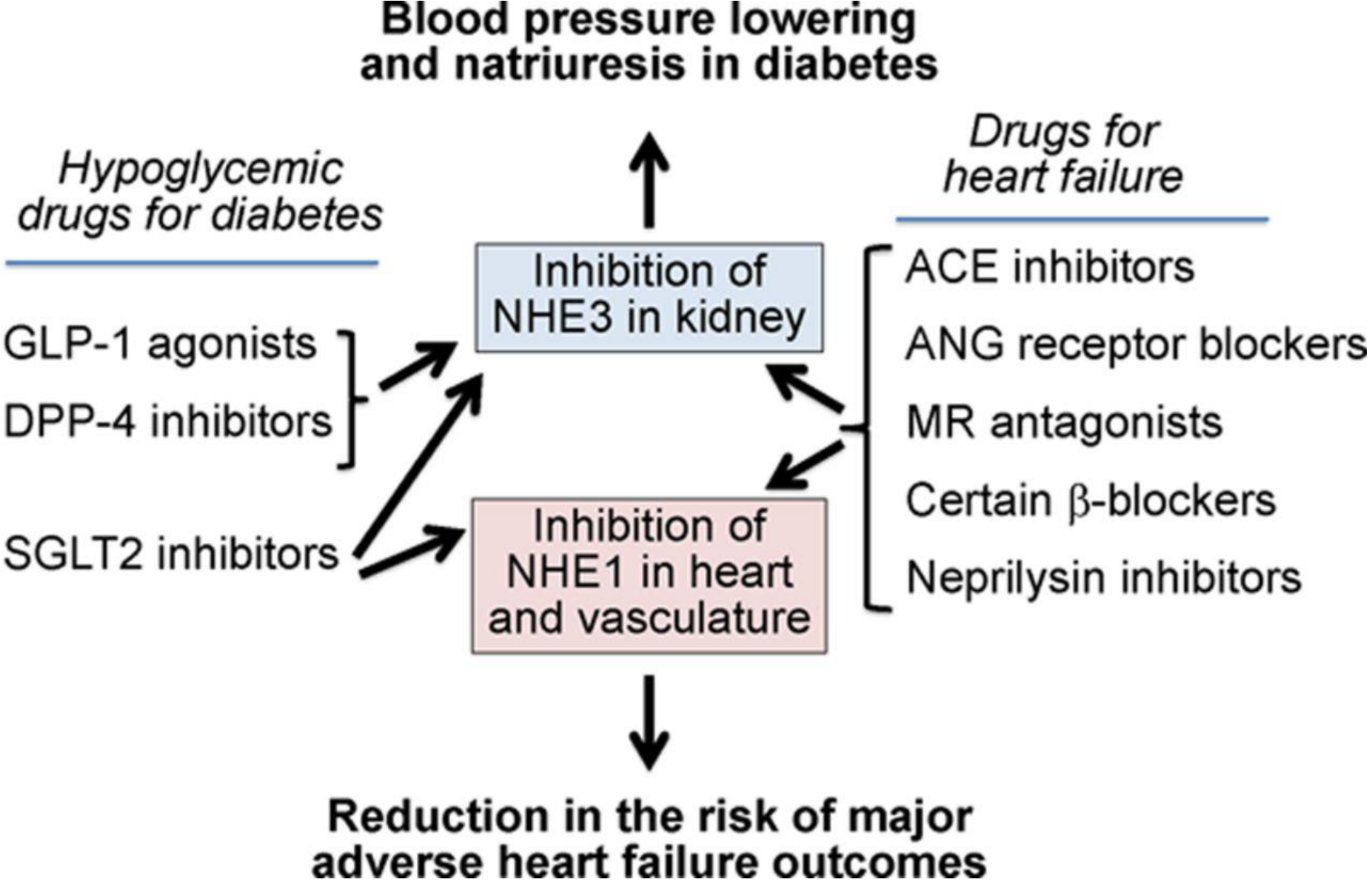


NHE3 (thận)





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.

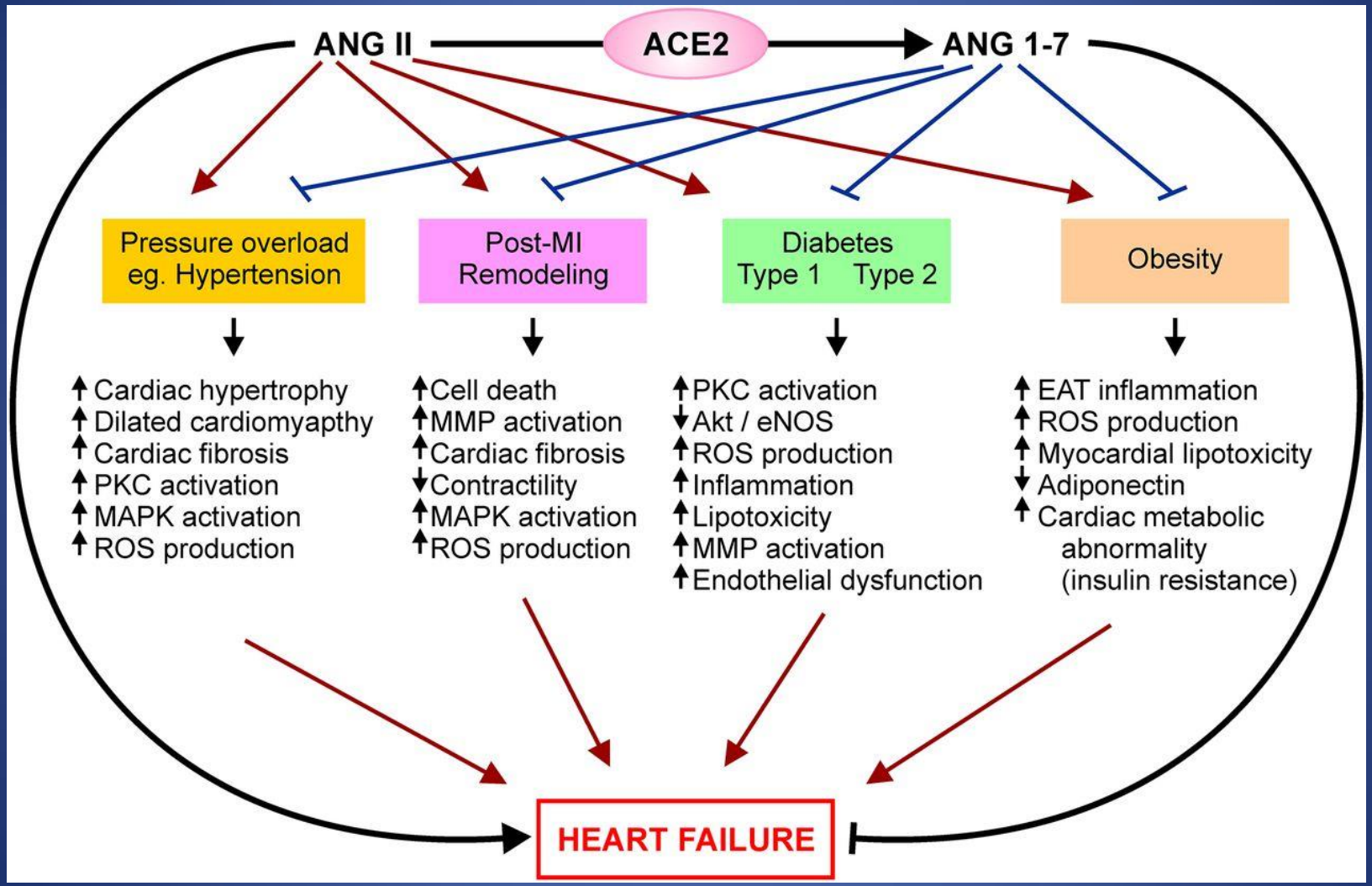


Packer M.(2017) Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With That of Heart Failure. Circulation. 2017 Oct 17;136(16):1548-1559.

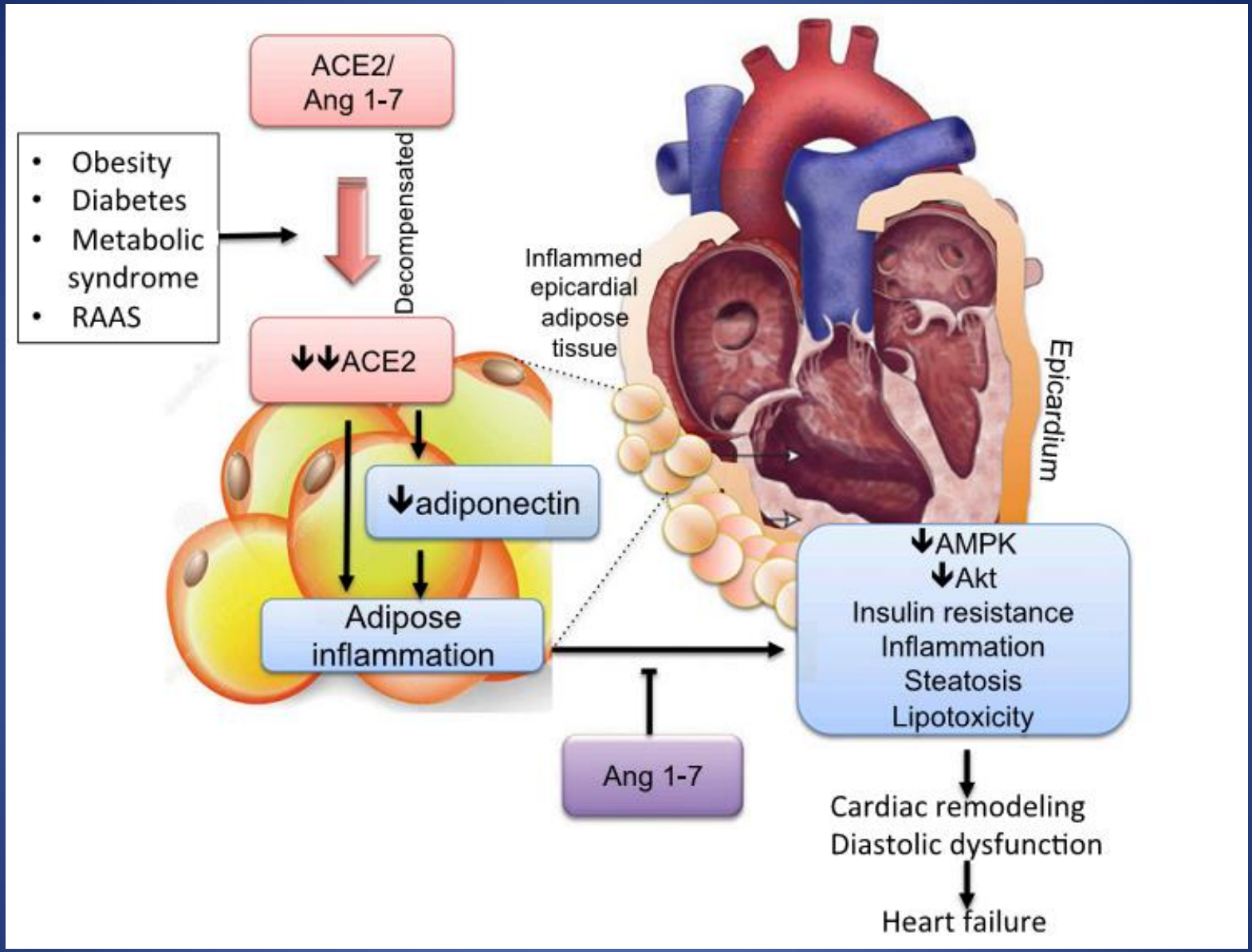
3. ỨC CHẾ SGLT2 & ACE2

- Angiotensin-Converting Enzyme 2 (ACE2) là enzyme mới được tìm thấy chủ yếu ở tim và thận.
- ACE2 tách một dư lượng duy nhất từ Ang I chuyển Ang 1-9 thành chất giãn mạch Ang 1-7 và
- làm giảm Ang II , tác nhân chính của RAS.
  ACE2 có thể hoạt động theo cách điều hòa ngược với ACE, điều chỉnh sự cân bằng giữa co mạch và thuốc giãn mạch trong tim và thận, và đóng một vai trò quan trọng trong việc điều hòa chức năng tim mạch và thận

Protecting the Heart in Obesity: Role of ACE2 and Its Partners



Rhian M. Touyz. (2016) Protecting the Heart in Obesity: Role of ACE2 and Its Partners. DiabetesVolume 65, January 2016



Rhian M. Touyz. (2016) Protecting the Heart in Obesity: Role of ACE2 and Its Partners. DiabetesVolume 65, January 2016

3. Ức chế SGLT2 và Magnesium máu

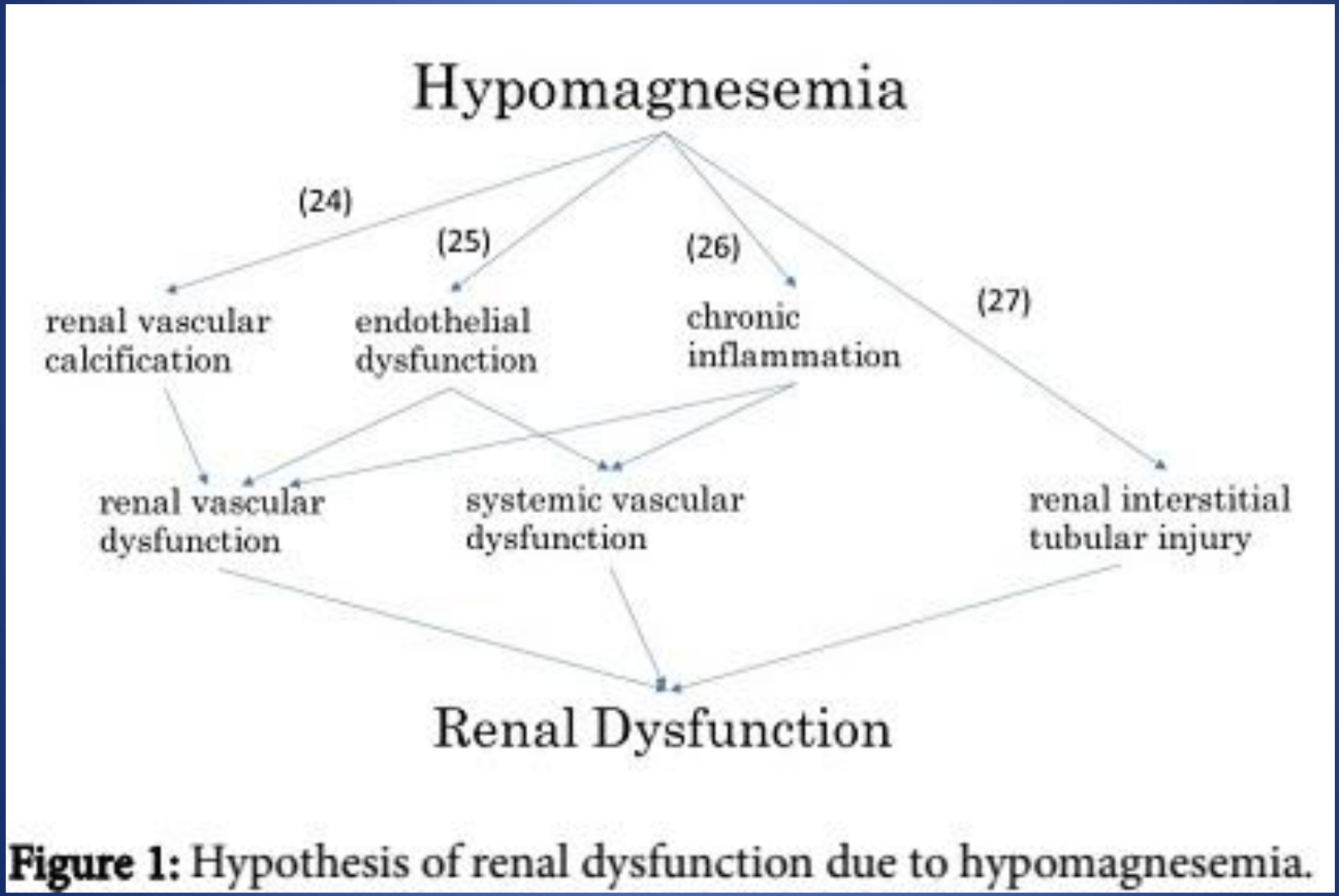
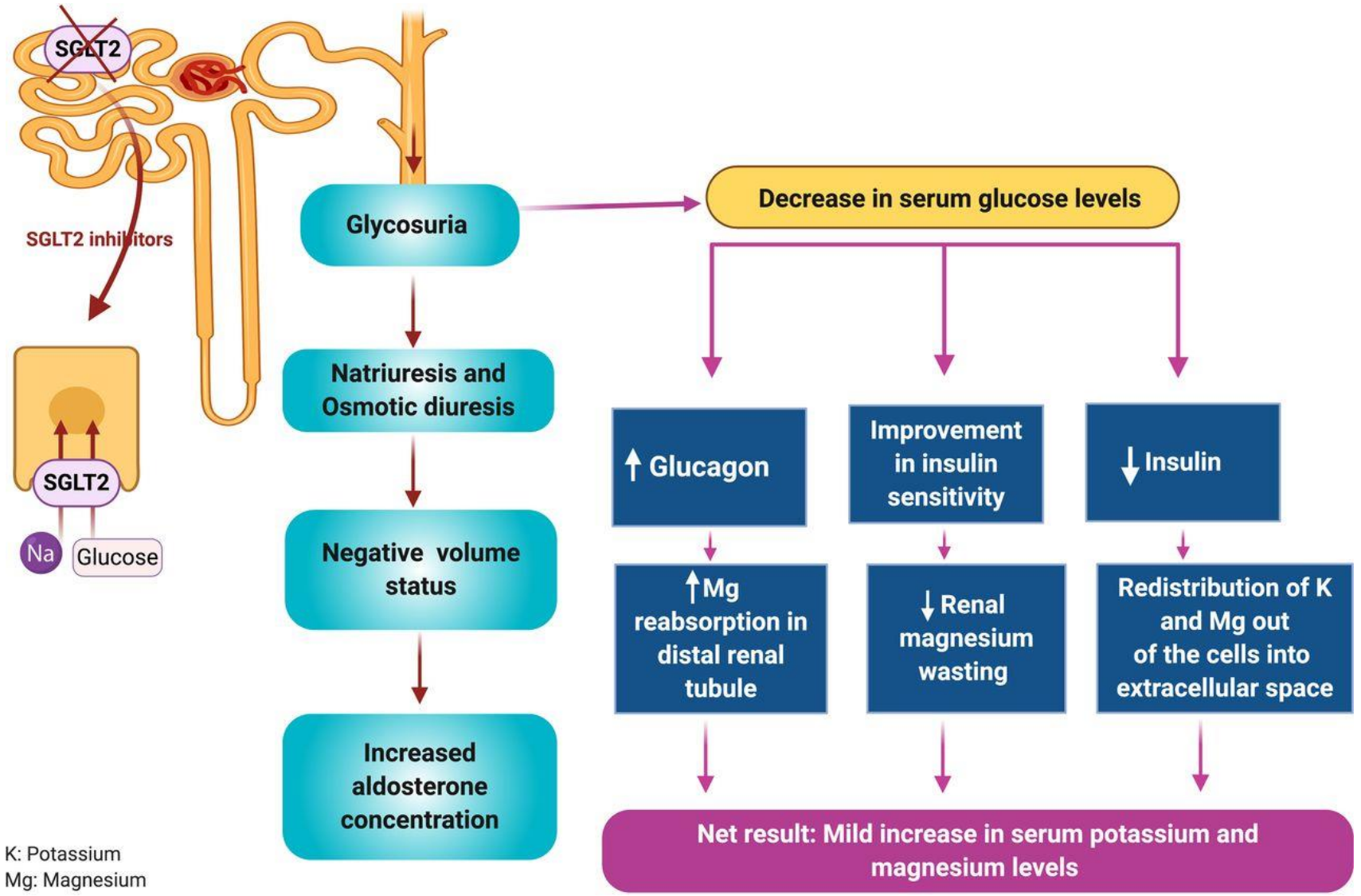


Figure 1: Hypothesis of renal dysfunction due to hypomagnesemia.

Ức chế SGLT2I với Kali và Magnesium máu



K: Potassium
Mg: Magnesium

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

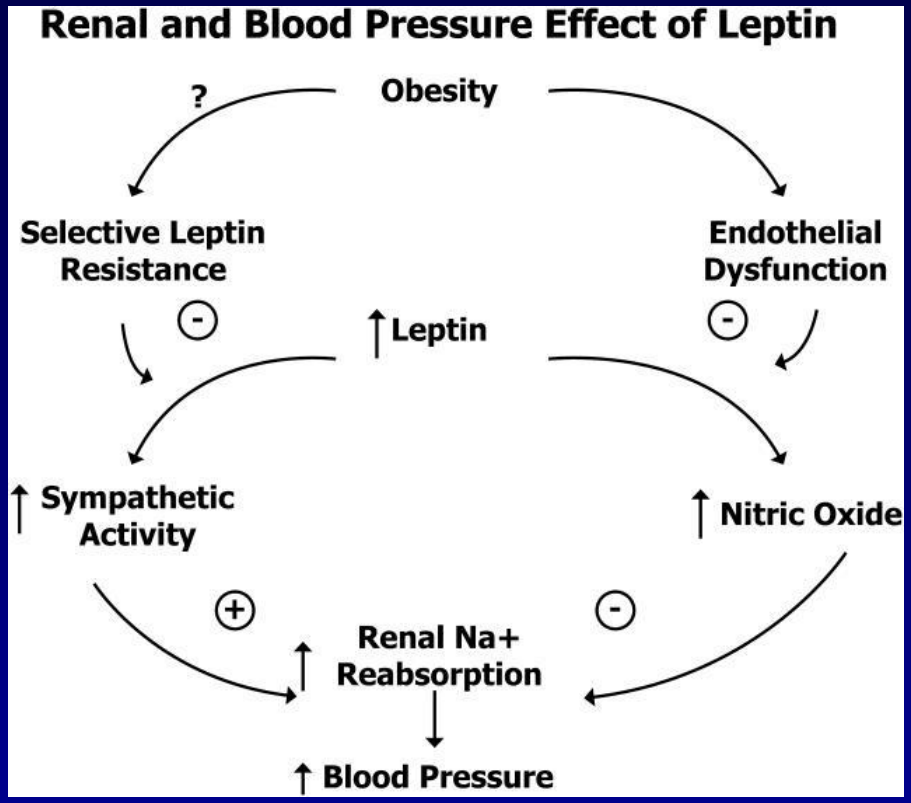
Mg Concentration Increases with SGLT2 Inhibitor Treatment

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.

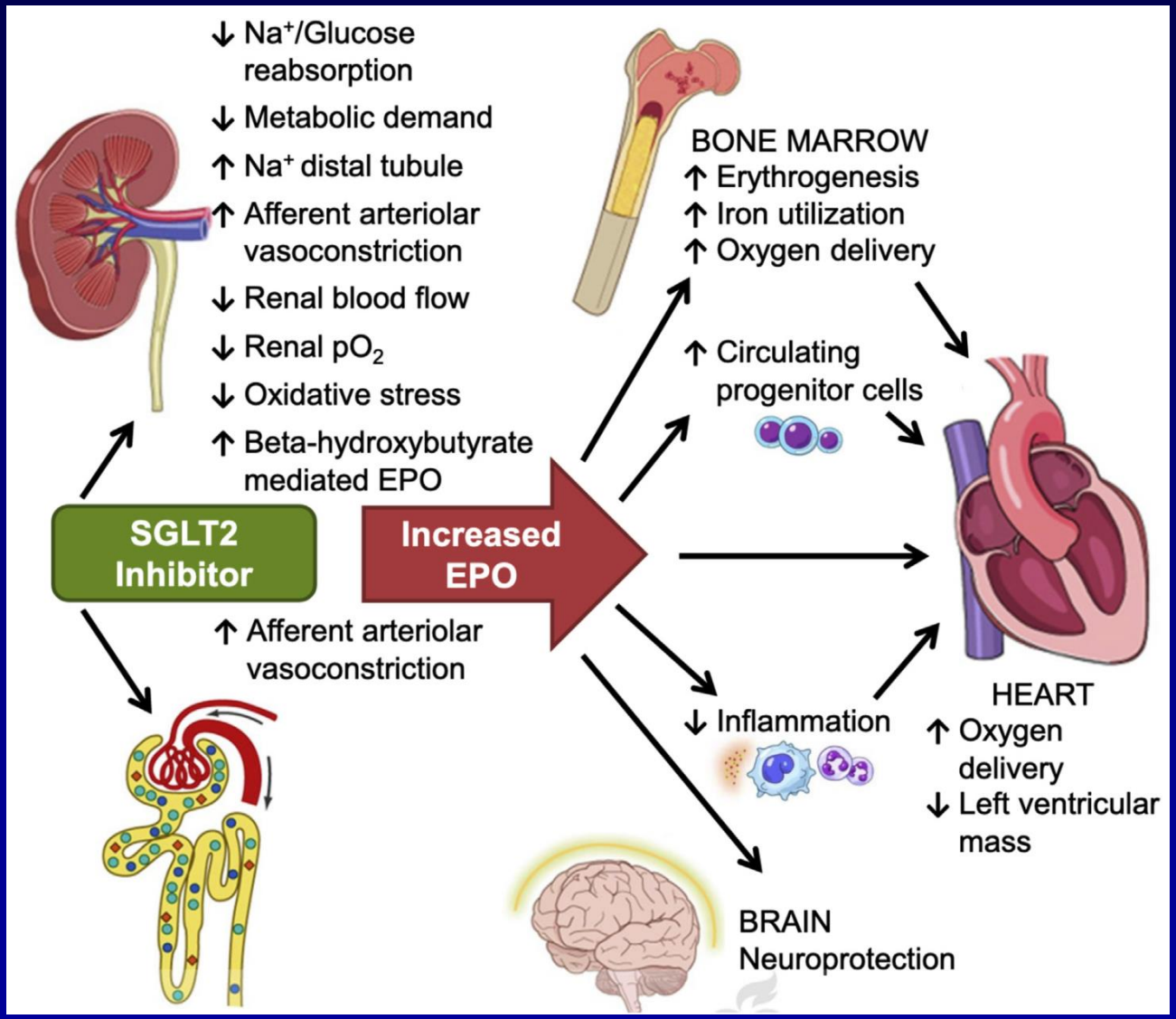
4. Ức chế SGLT2 và Leptin

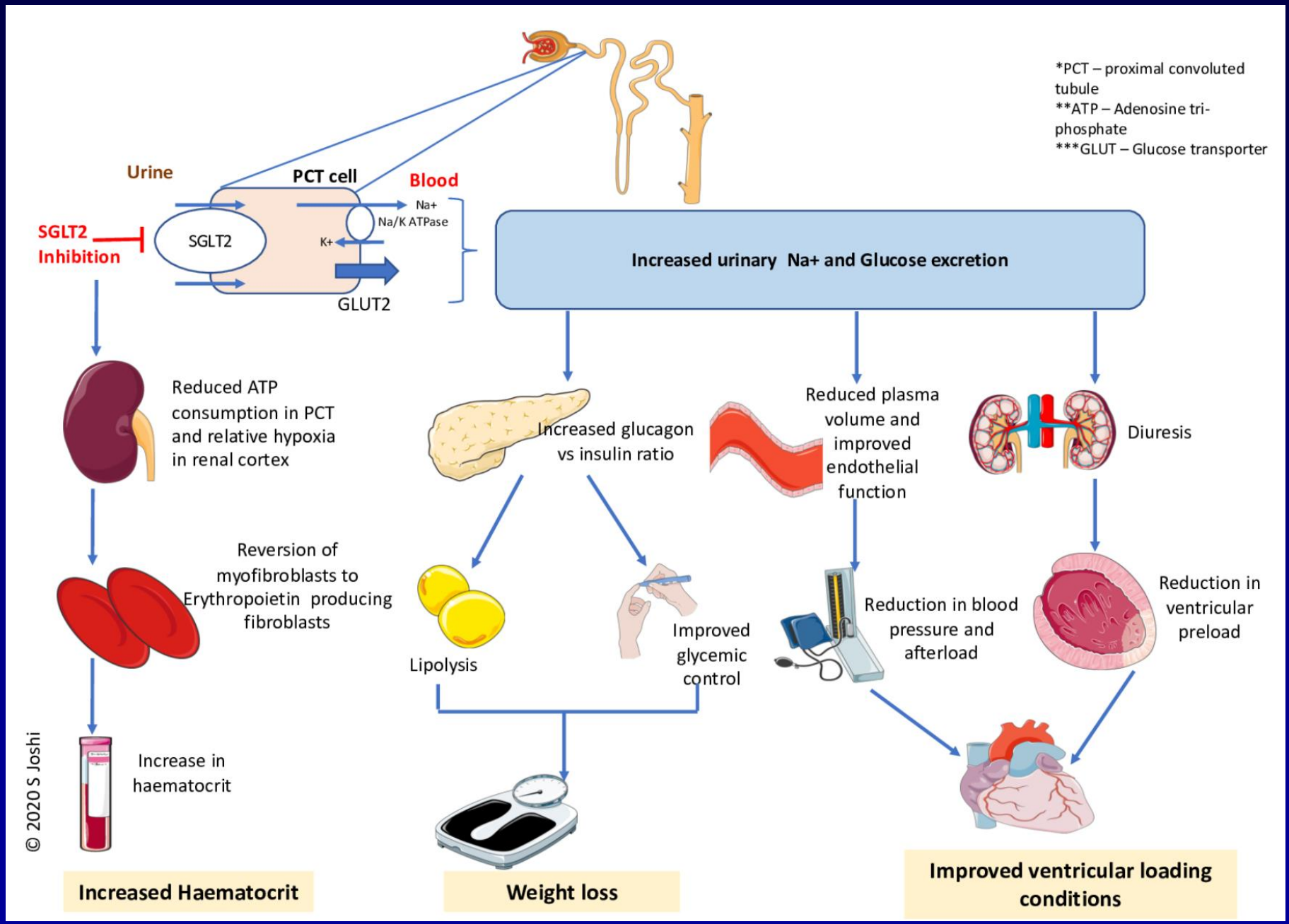


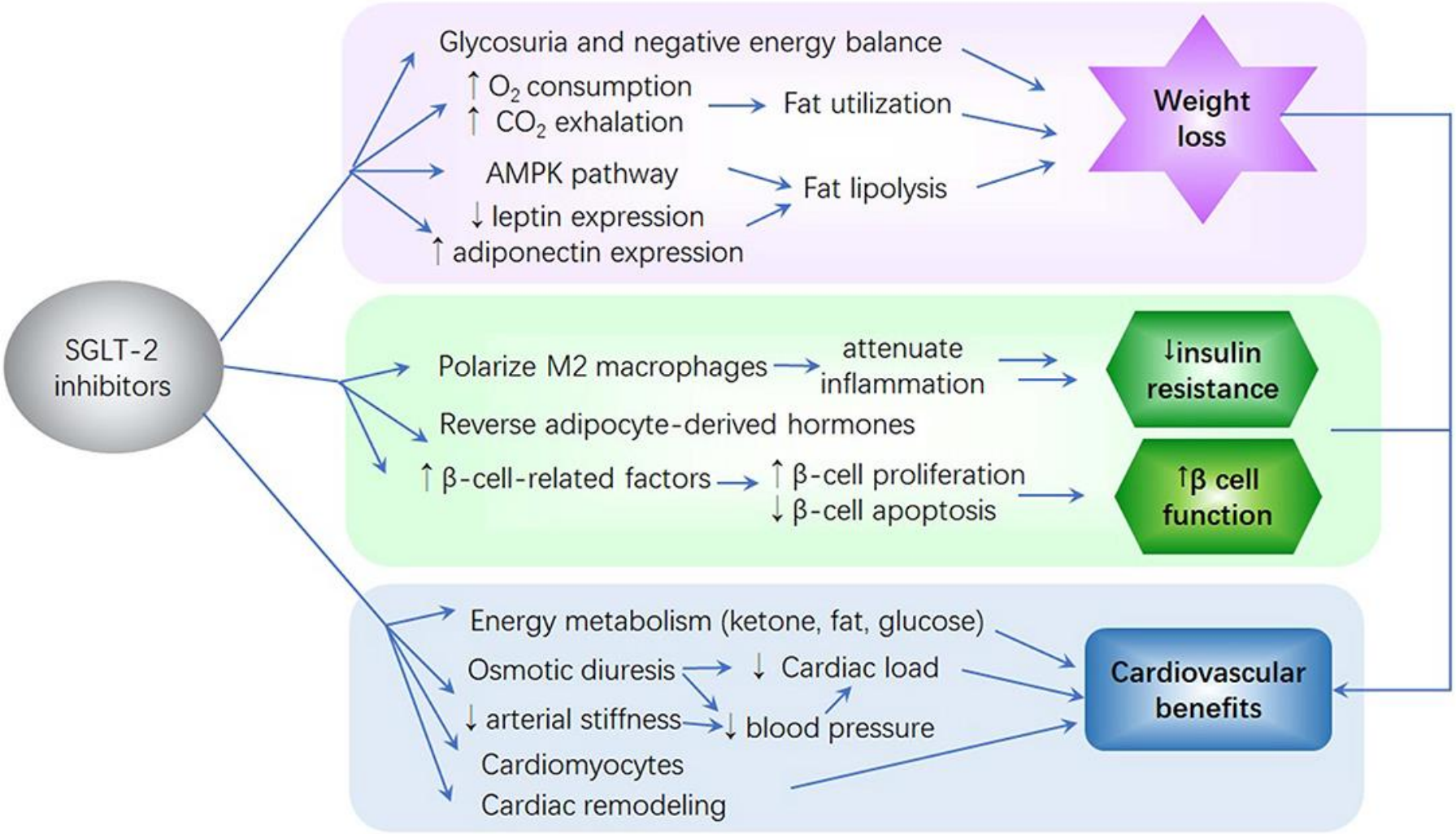
SGLT2 inhibitors reduce the accumulation and inflammation of perivisceral adipose tissue, thus minimizing the secretion of leptin and its paracrine actions on the heart and kidneys to promote fibrosis. Such fibrosis probably contributes to the impairment of cardiac distensibility and glomerular function that characterizes obesity-related HFpEF.

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

5.Ức chế SGLT2 và EPO




*PCT – proximal convoluted tubule
**ATP – Adenosine tri-phosphate
***GLUT – Glucose transporter
Urine
PCT cell
Blood
SGLT2 Inhibition
SGLT2
Na+
Na/K ATPase
K+
GLUT2
Increased urinary Na+ and Glucose excretion
Reduced ATP consumption in PCT and relative hypoxia in renal cortex
Increased glucagon vs insulin ratio
Reduced plasma volume and improved endothelial function
Diuresis
Reversion of myofibroblasts to Erythropoietin producing fibroblasts
Lipolysis
Improved glycemic control
Reduction in blood pressure and afterload
Reduction in ventricular preload
Increase in haematocrit
Increased Haematocrit
Weight loss
Improved ventricular loading conditions
© 2020 S Joshi


SGLT-2 inhibitors
Glycosuria and negative energy balance
↑ O_2 consumption
↑ CO_2 exhalation
Fat utilization
AMPK pathway
↓ leptin expression
↑ adiponectin expression
Fat lipolysis
Weight loss
Polarize M2 macrophages
attenuate inflammation
Reverse adipocyte-derived hormones
↓insulin resistance
↑ β-cell-related factors
↑ β-cell proliferation
↓ β-cell apoptosis
↑β cell function
Energy metabolism (ketone, fat, glucose)
Osmotic diuresis
↓ Cardiac load
↓ arterial stiffness
↓ blood pressure
Cardiomyocytes
Cardiac remodeling
Cardiovascular benefits

Cơ chế cải thiện chức năng tim của ức chế SGLT2

Potential Mechanisms
1. Stimulation of natriuresis
2. Stimulation of osmotic diuresis
3. Cardiomyocyte Na^+/H exchanger inhibition
4. Increased myocardial energetics (via altered myocardial substrate metabolism)
5. Reduction in left ventricular mass
6. Improved systolic and diastolic function
7. Improved cardiac filling conditions secondary to reductions in preload and afterload
8. Increased circulating proangiogenic progenitor cells
9. Increased erythropoietin
10. Improved endothelial function
11. Reduction in myocardial CaM kinase II activity
12. Improved myocardial autophagy
13. Inhibition of cardiac fibrosis
14. Increased cardiac output, HR, O_2 consumption, coronary blood flow mediated by increased levels of circulating glucagon

CaM indicates Ca^{2+}/calmodulin-dependent protein; HR, heart rate; SGLT-2, sodium-glucose cotransporter-2.

Cập nhật tác dụng
Nhóm ức chế SGLT2 trên Tim Mạch
bệnh nhân có và không ĐTĐ

Một số cơ chế bảo vệ sớm Tim-Thận của Ức chế SGLT2

International Journal of
Molecular Sciences

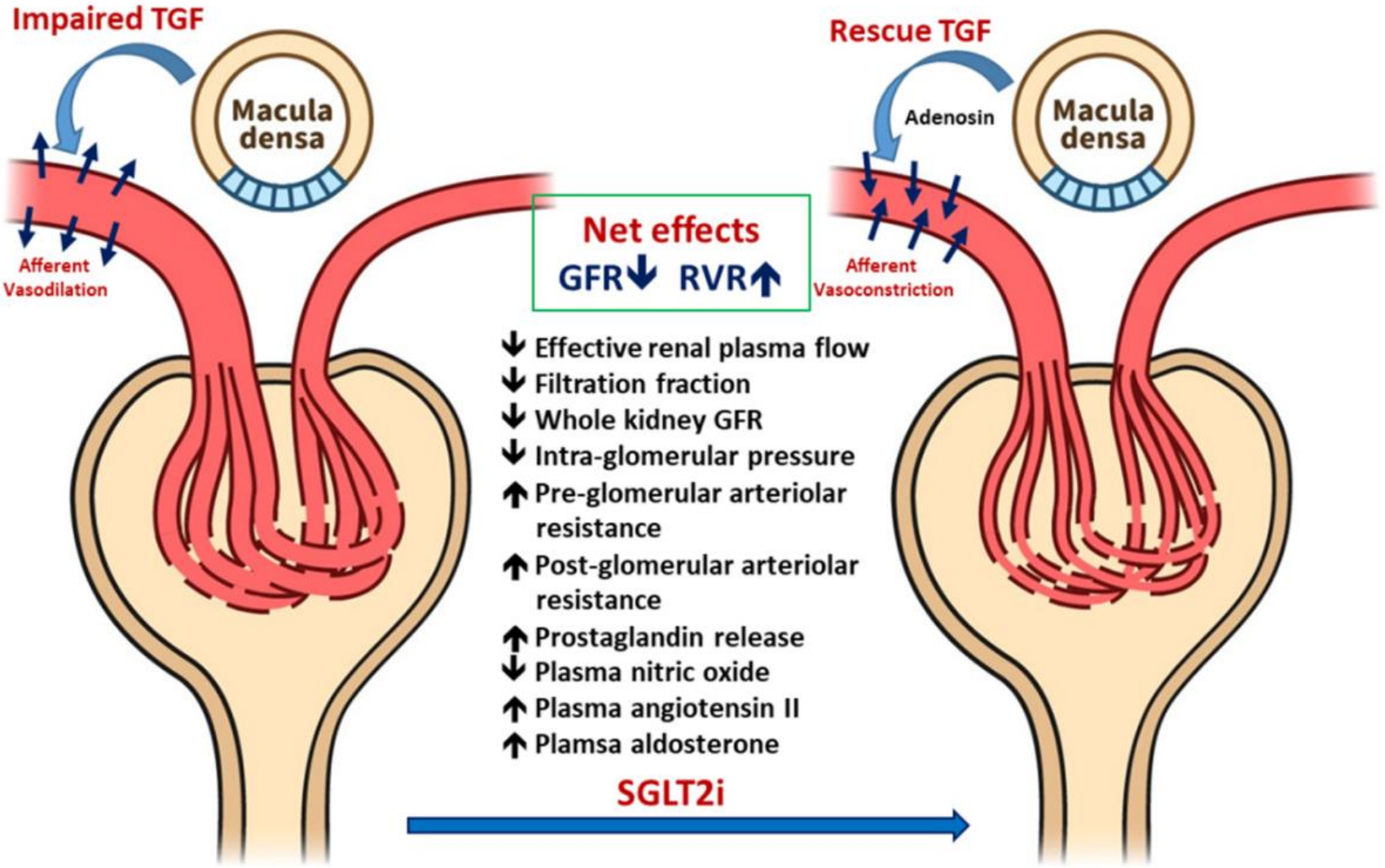
MDPI

Review

Molecular Mechanisms of SGLT2 Inhibitor on Cardiorenal Protection

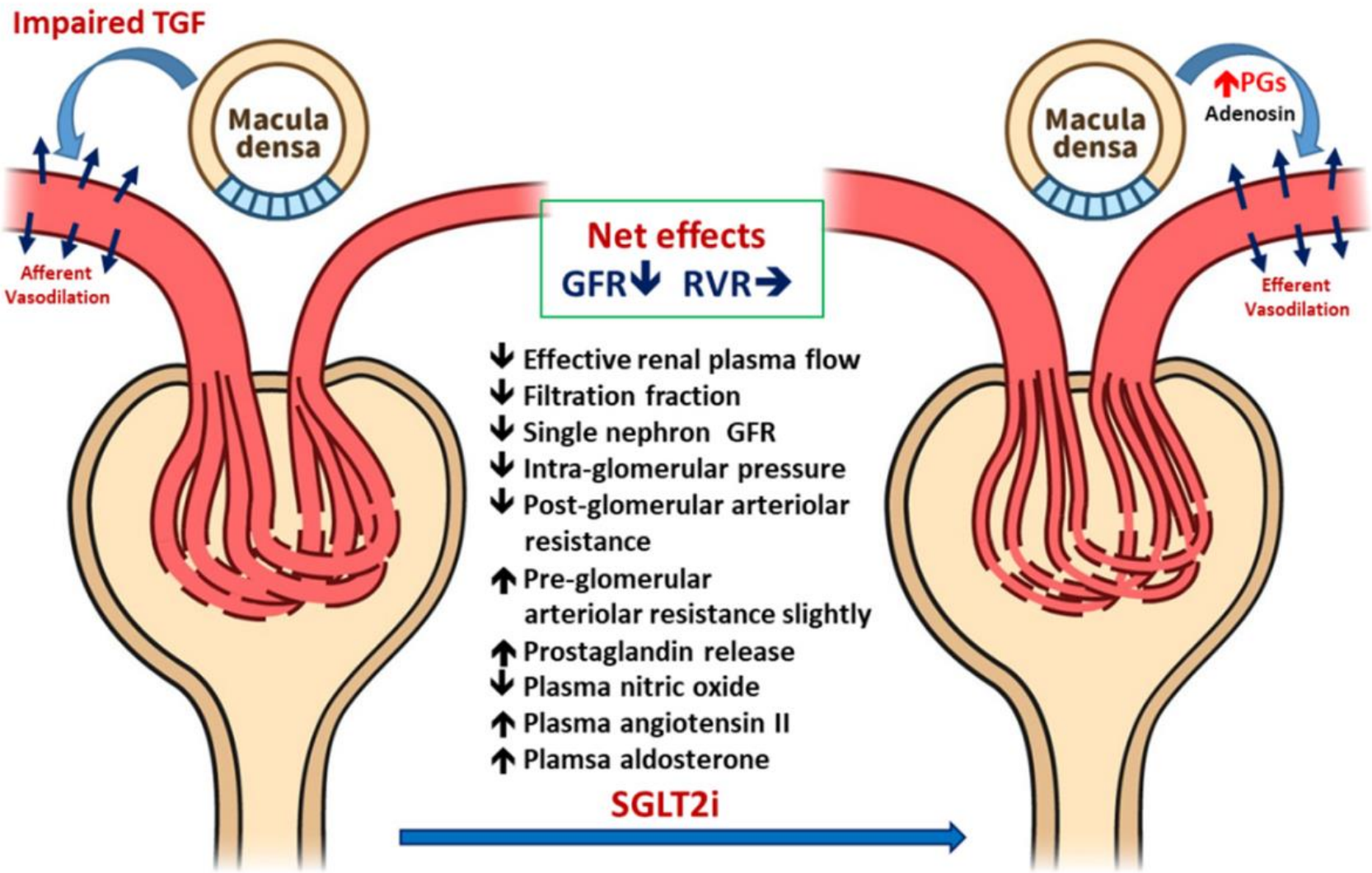
Yi-Chou Hou [1,2], Cai-Mei Zheng [3,4,5], Tzung-Hai Yen [6,7] and Kuo-Cheng Lu [8,*]

Int. J. Mol. Sci. **2020**, *21*, 7833; doi:10.3390/ijms21217833



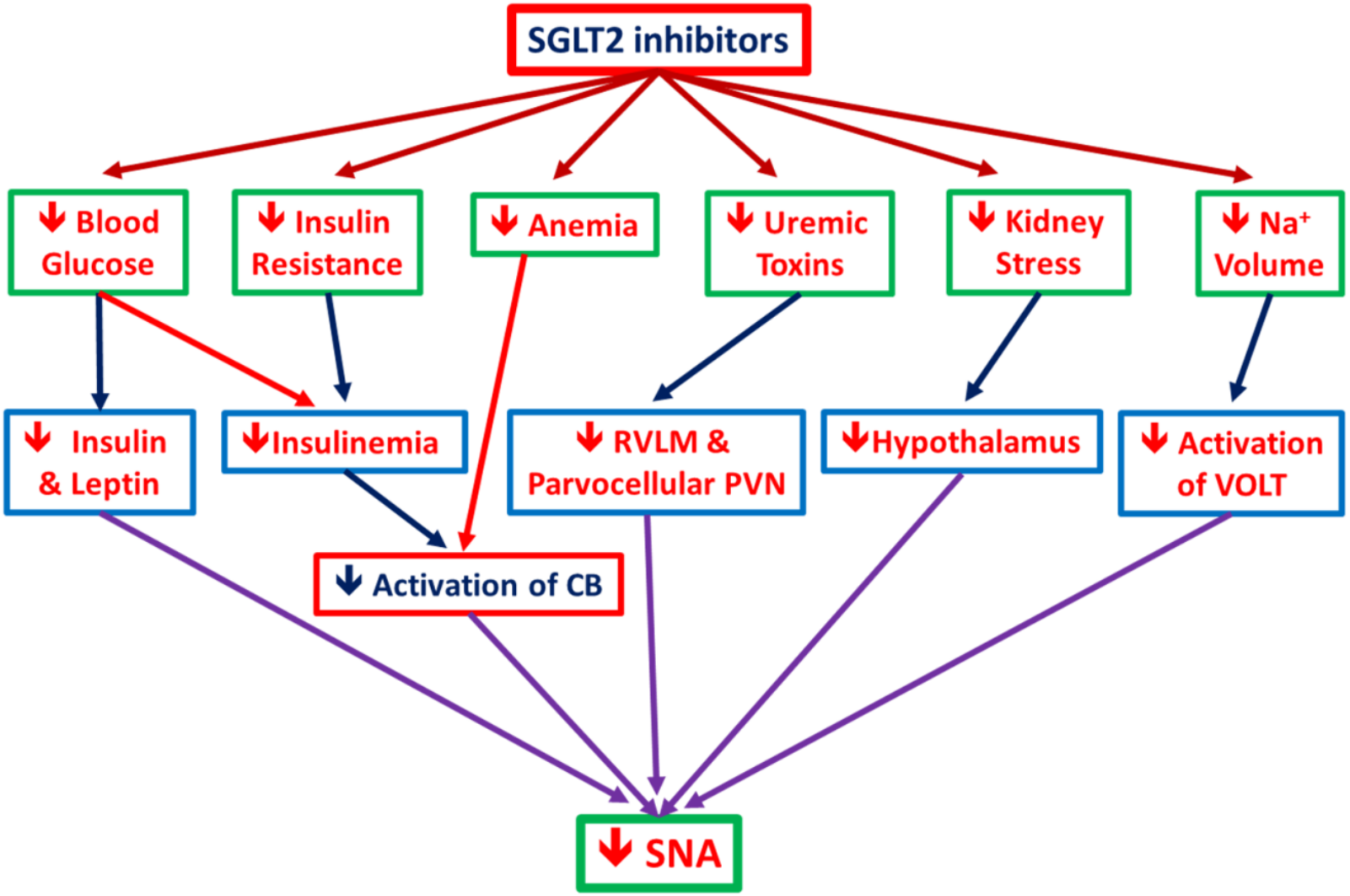
Đáp ứng của ức chế SGLT2 ở giai đoạn sớm bệnh nhân ĐTĐ típ 1

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



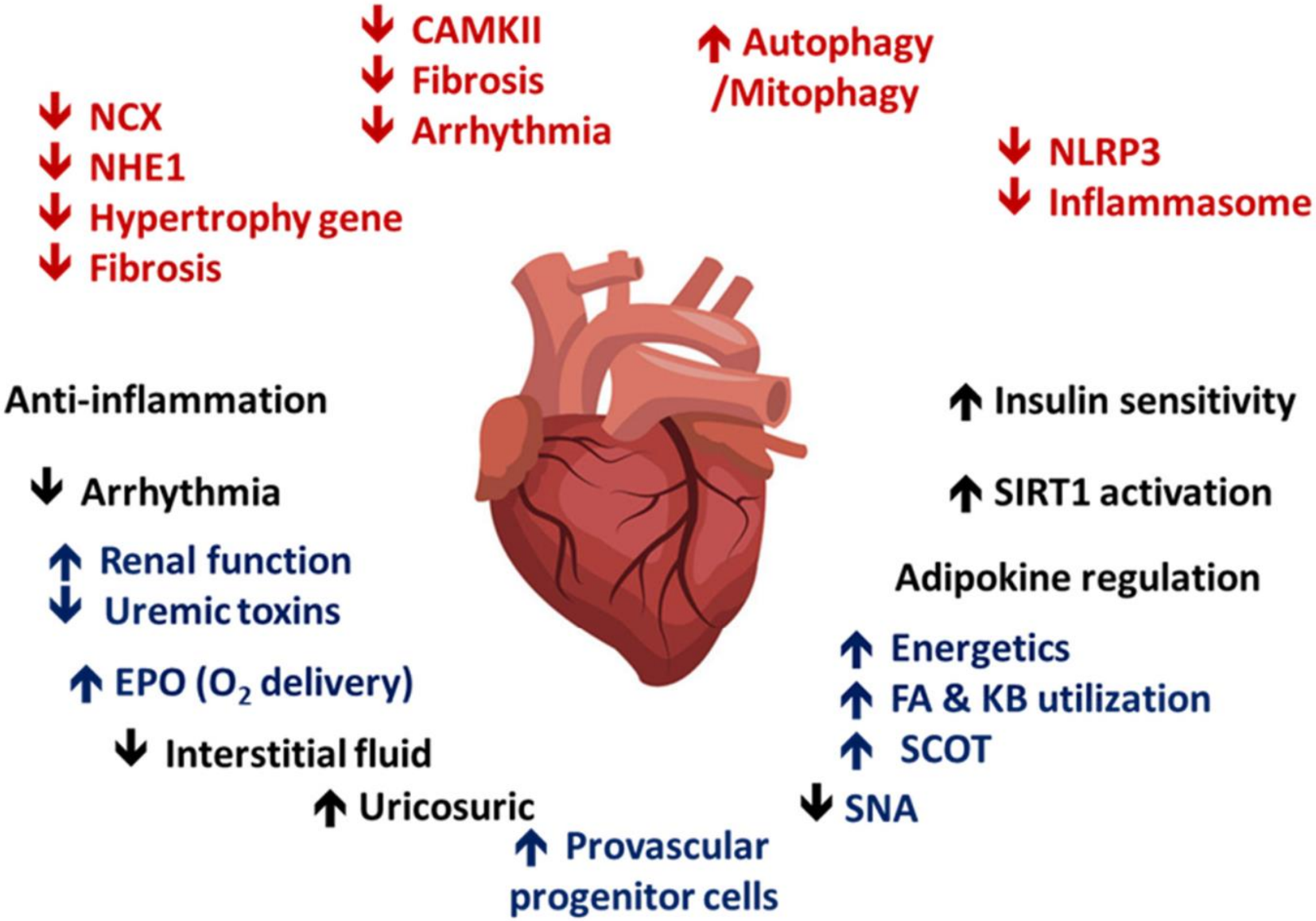
Đáp ứng của ức chế SGLT2 ở giai đoạn sớm bệnh nhân ĐTĐ típ 2

Hemodynamic responses to SGLT2i in patients with early stage T2DM:



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

Possible mechanisms of SGLT2 inhibitors on reducing sympathetic nervous activity (SNA)



Tác dụng trực tiếp và gián tiếp trên cơ tim của Ức chế SGLT2

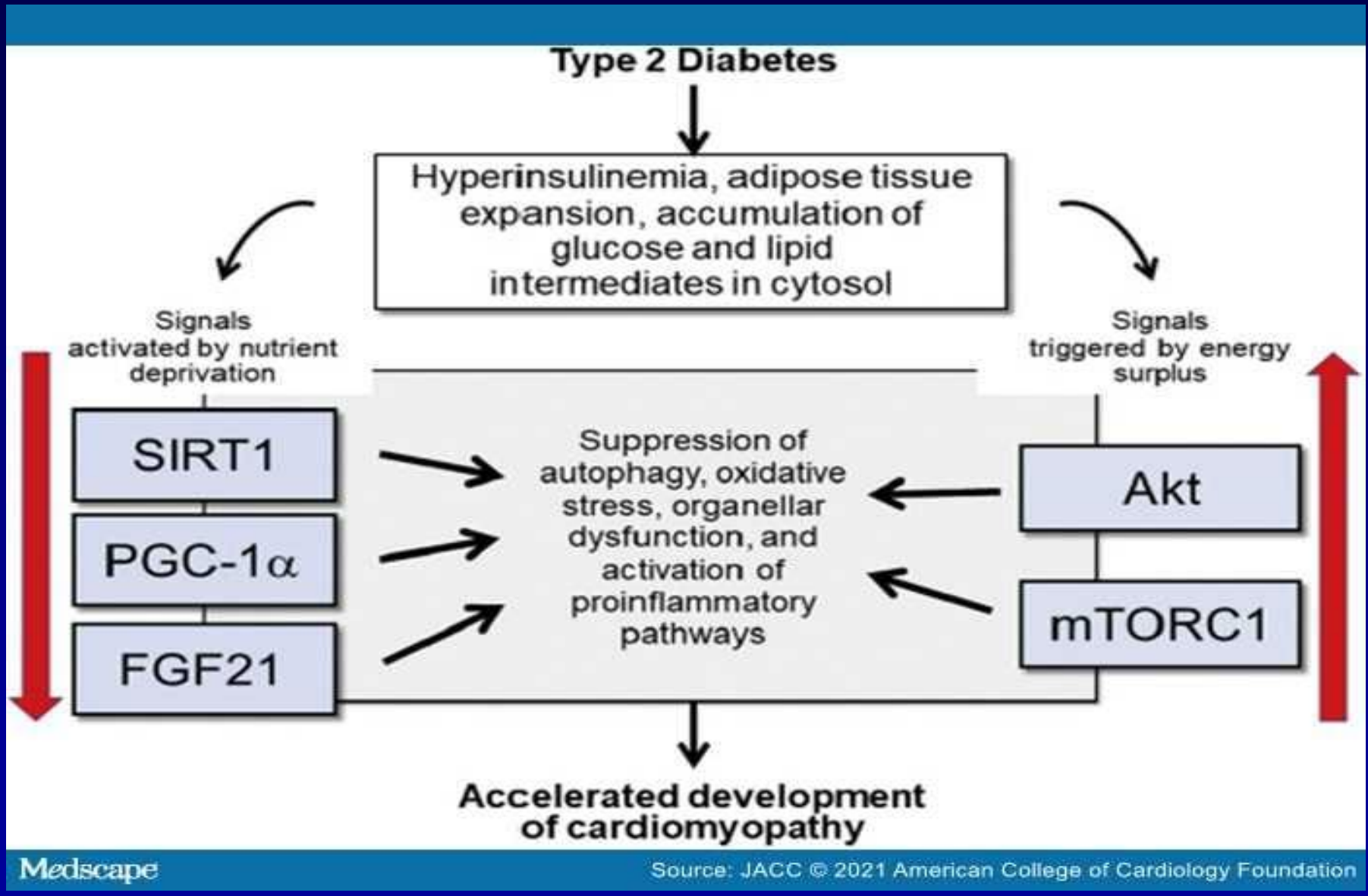
Direct (red) myocardial and indirect/systemic (blue) effects of SGLT2i:

Cơ chế bảo vệ chức năng Tim của Ức chế SGLT2

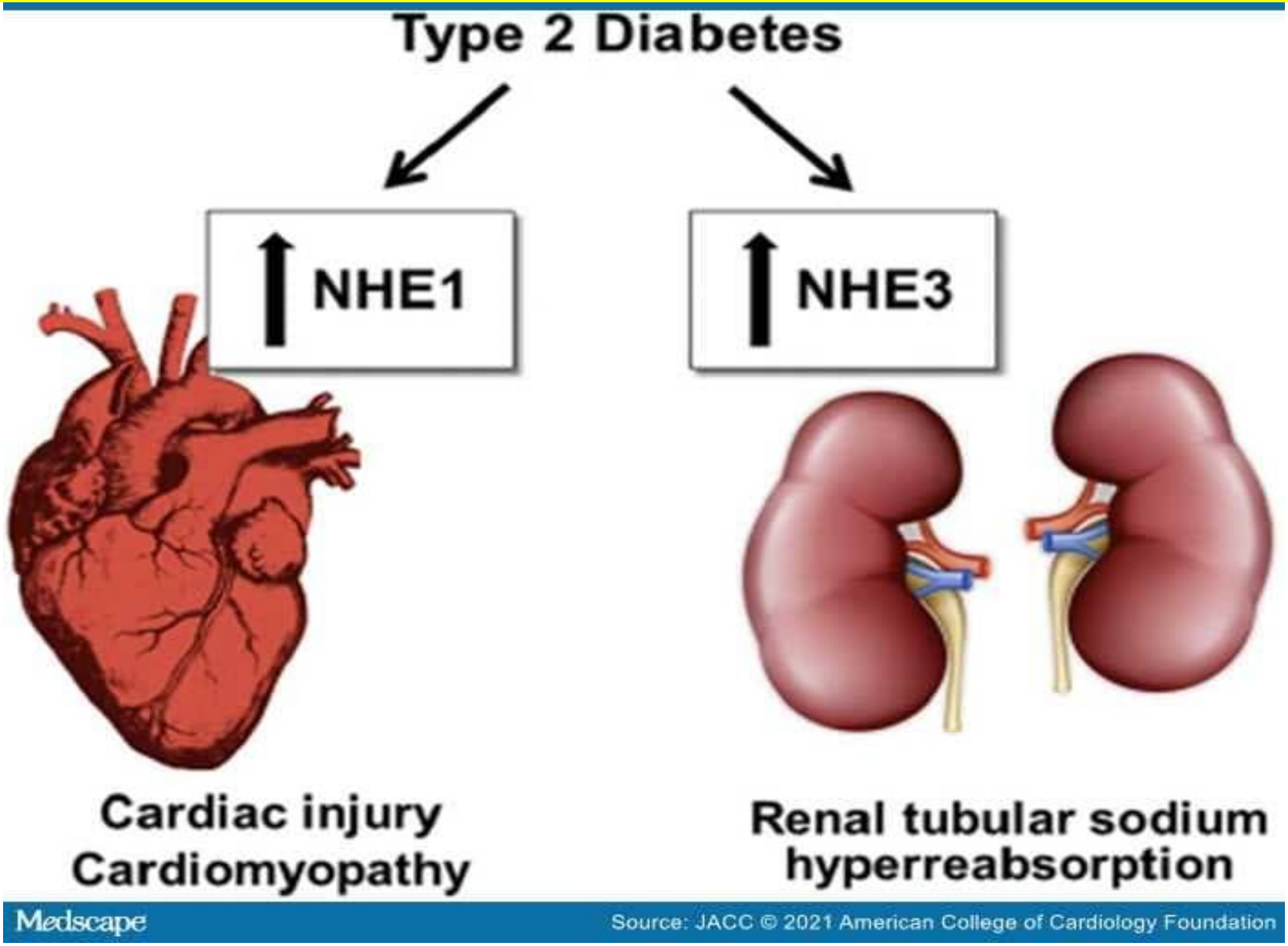
Differential Pathophysiological Mechanisms in Heart Failure With a Reduced or Preserved Ejection Fraction in Diabetes

Milton Packer, MD. JACC Heart Fail. 2021;9(7):535-549.

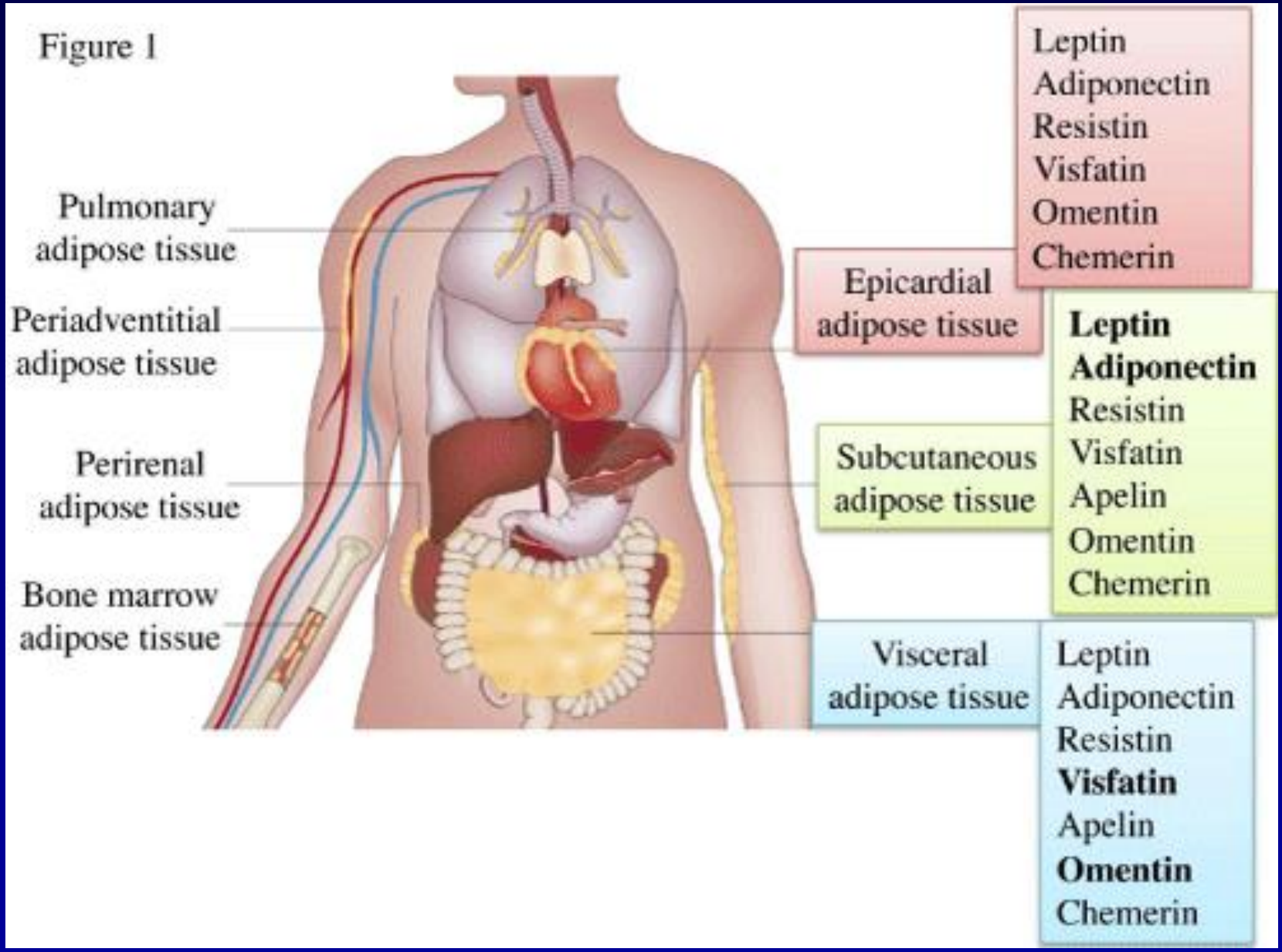
Rối Loạn cảm biến về dinh dưỡng



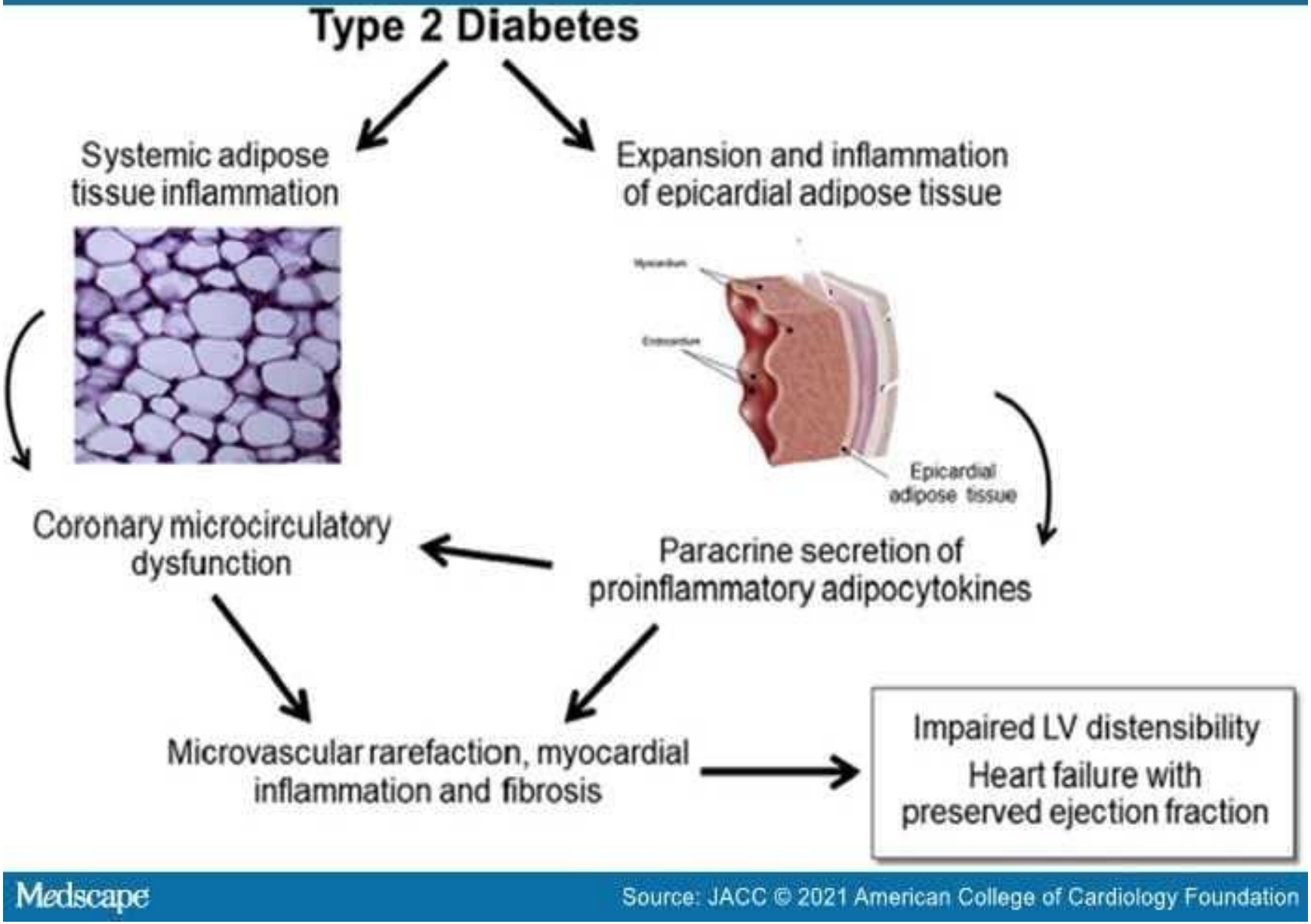
Gia tăng hệ thống trao đổi Natri–Hydro (NHE)



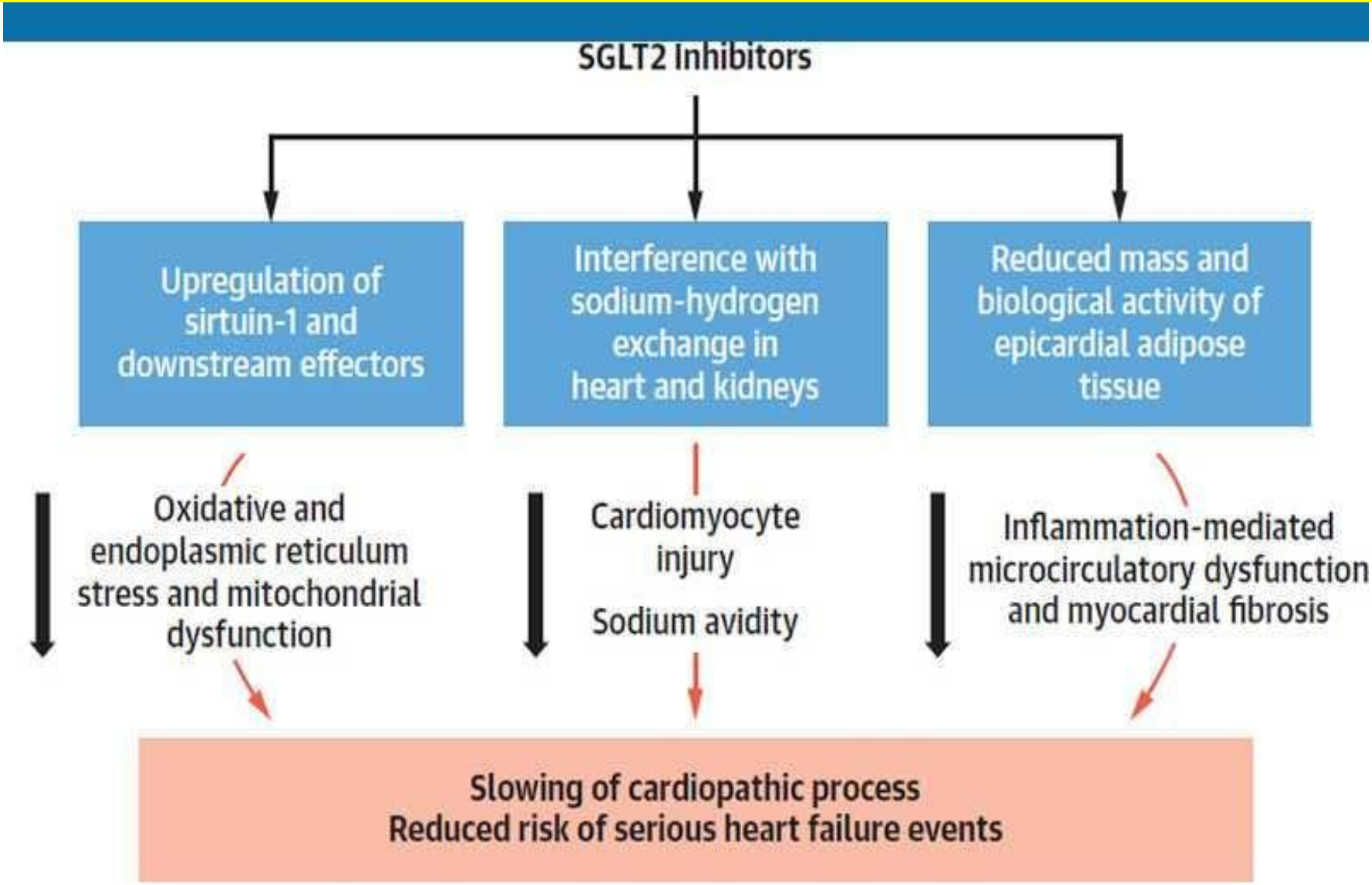
Cytokine viêm tại các tổ chức mỡ



Tác dụng Cytokine viêm tại các tổ chức cơ tim



Cơ chế bảo vệ Tim Mạch

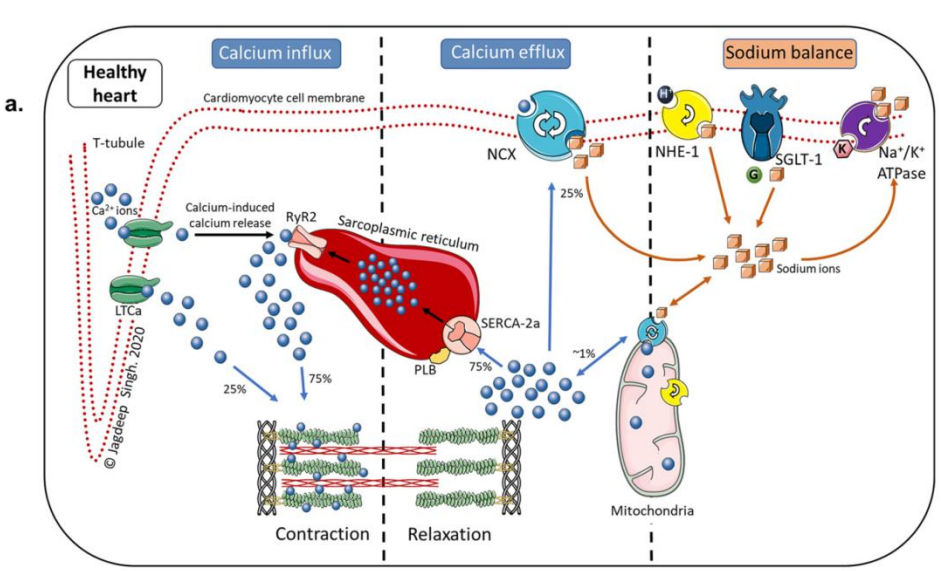


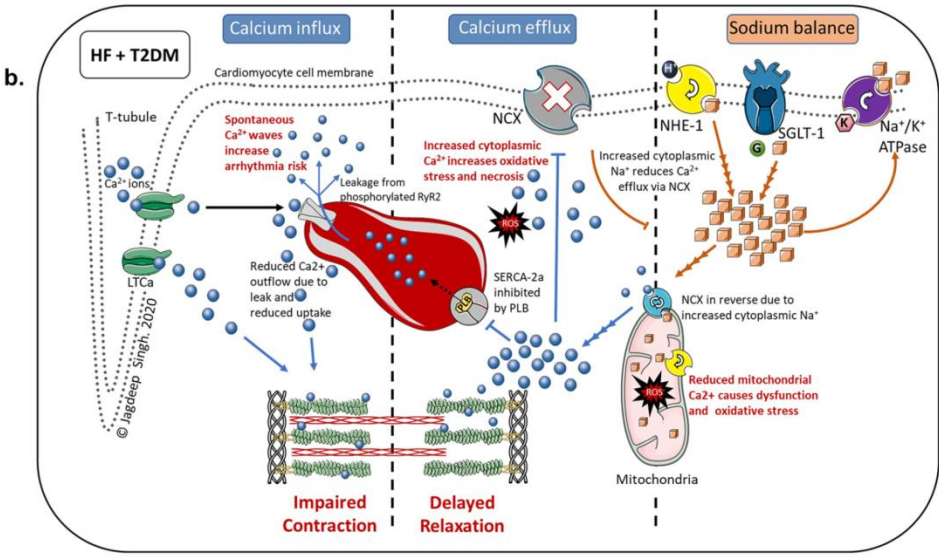
Packer, M. J Am Coll Cardiol HF. 2021;9(8):535-549.

Medscape

Ức chế SGLT2 và năng lượng cơ tim trên bn suy tim và ĐTĐ típ 2

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

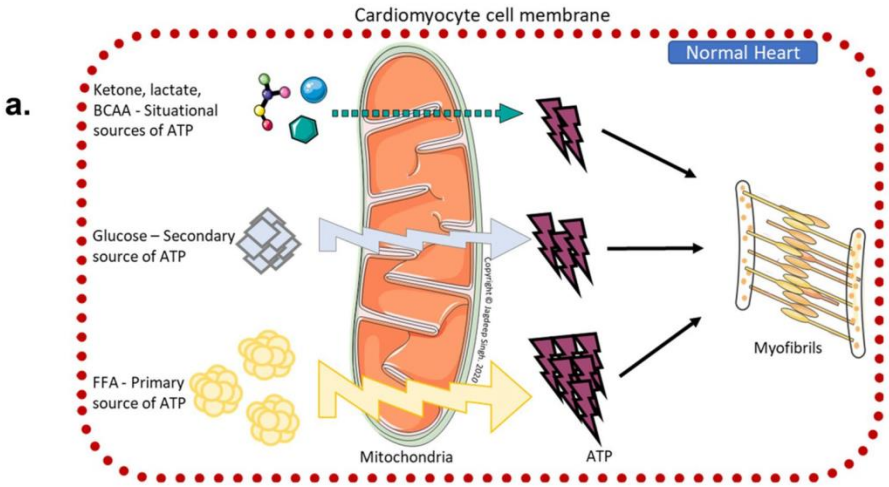


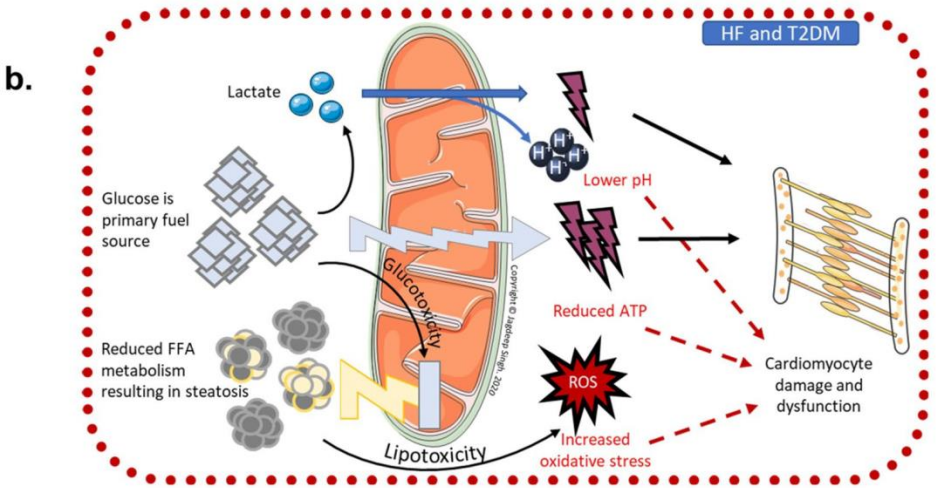


2a: Cân bằng Natri và Calci trong cơ tim trên người bình thường

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

So sánh
Năng lượng cơ tim tiêu thụ trên người không và ĐTĐ

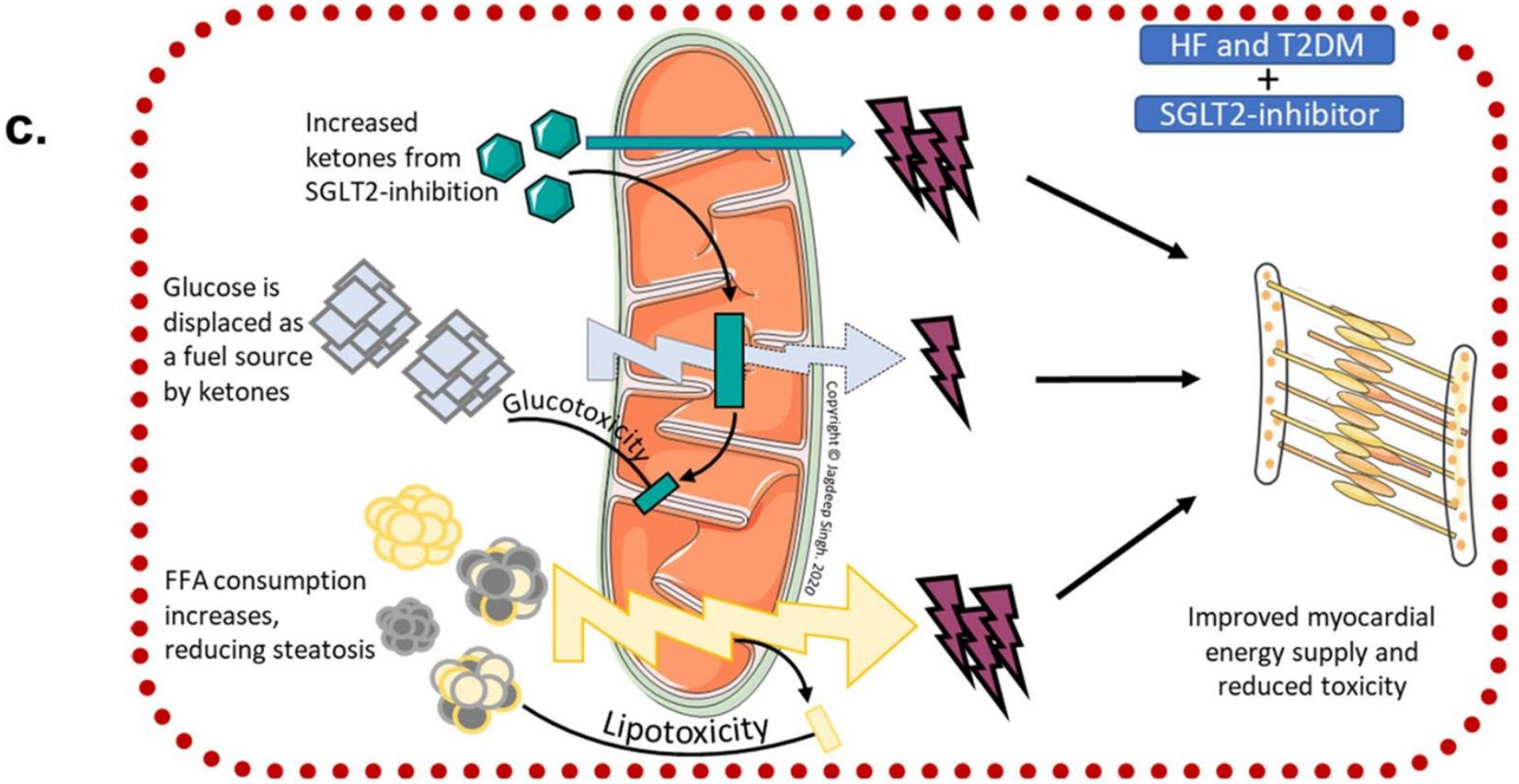


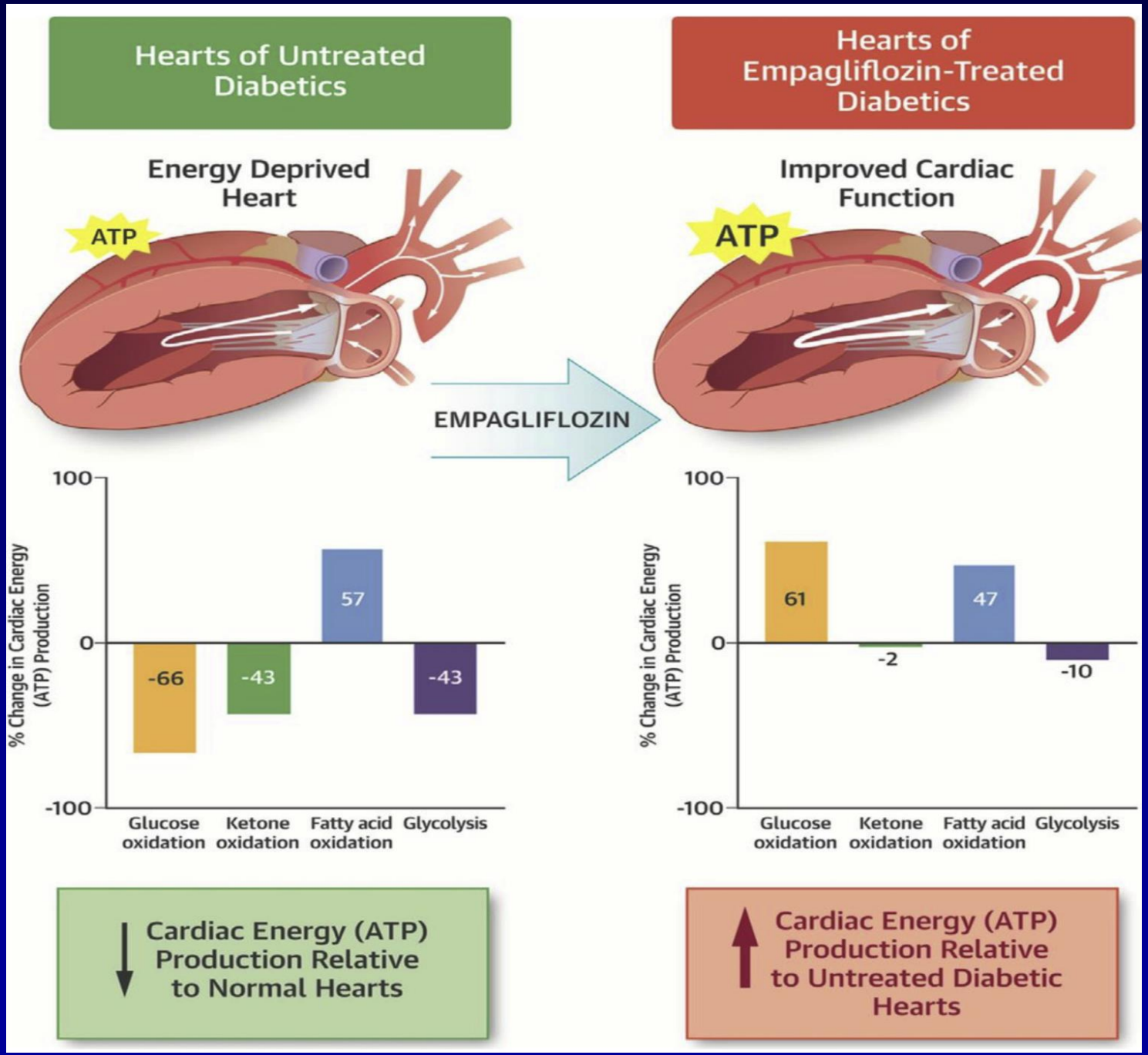


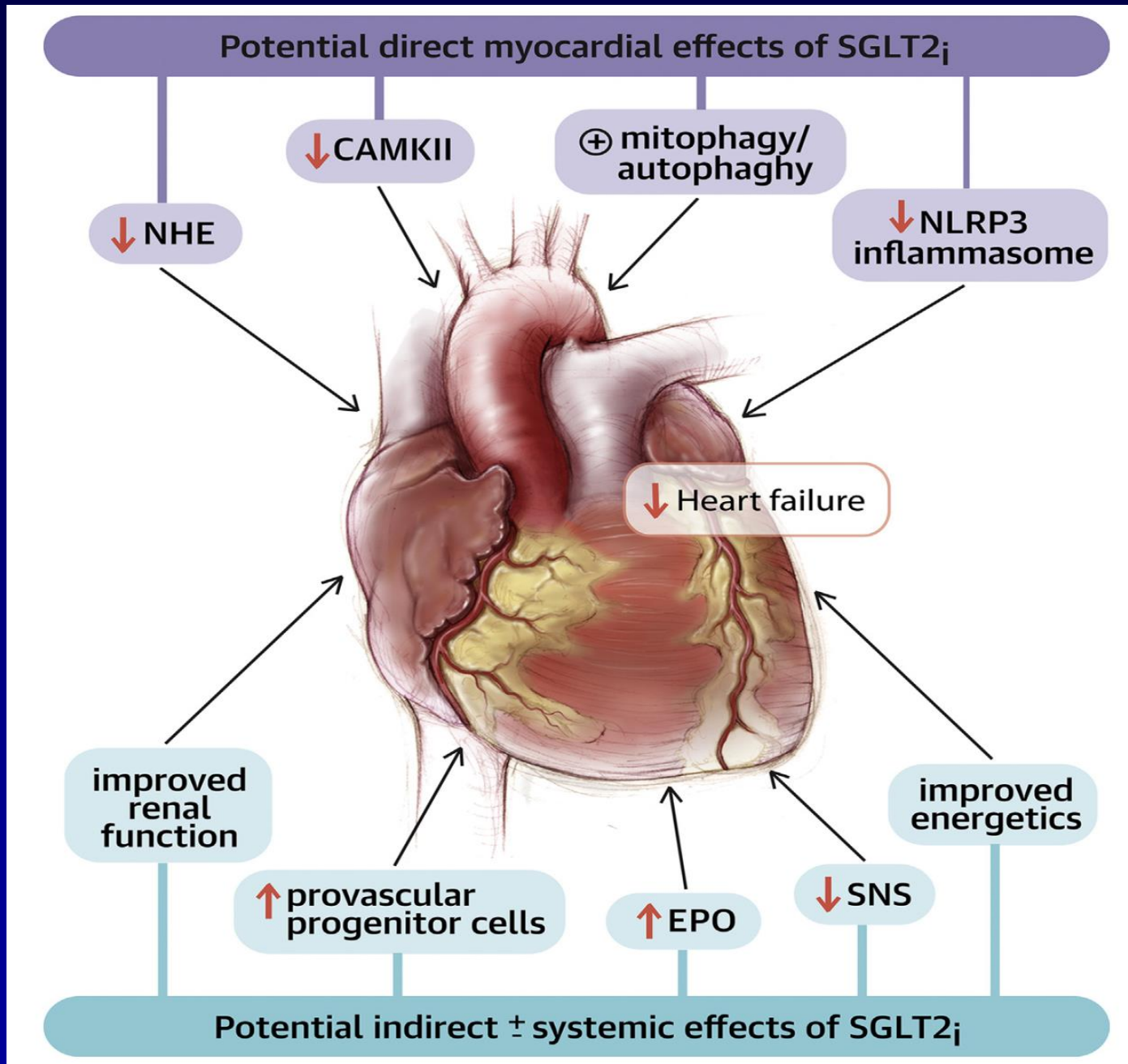
3a: Năng lượng cơ tim ở người khỏe mạnh trong khi nghi ngơi

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

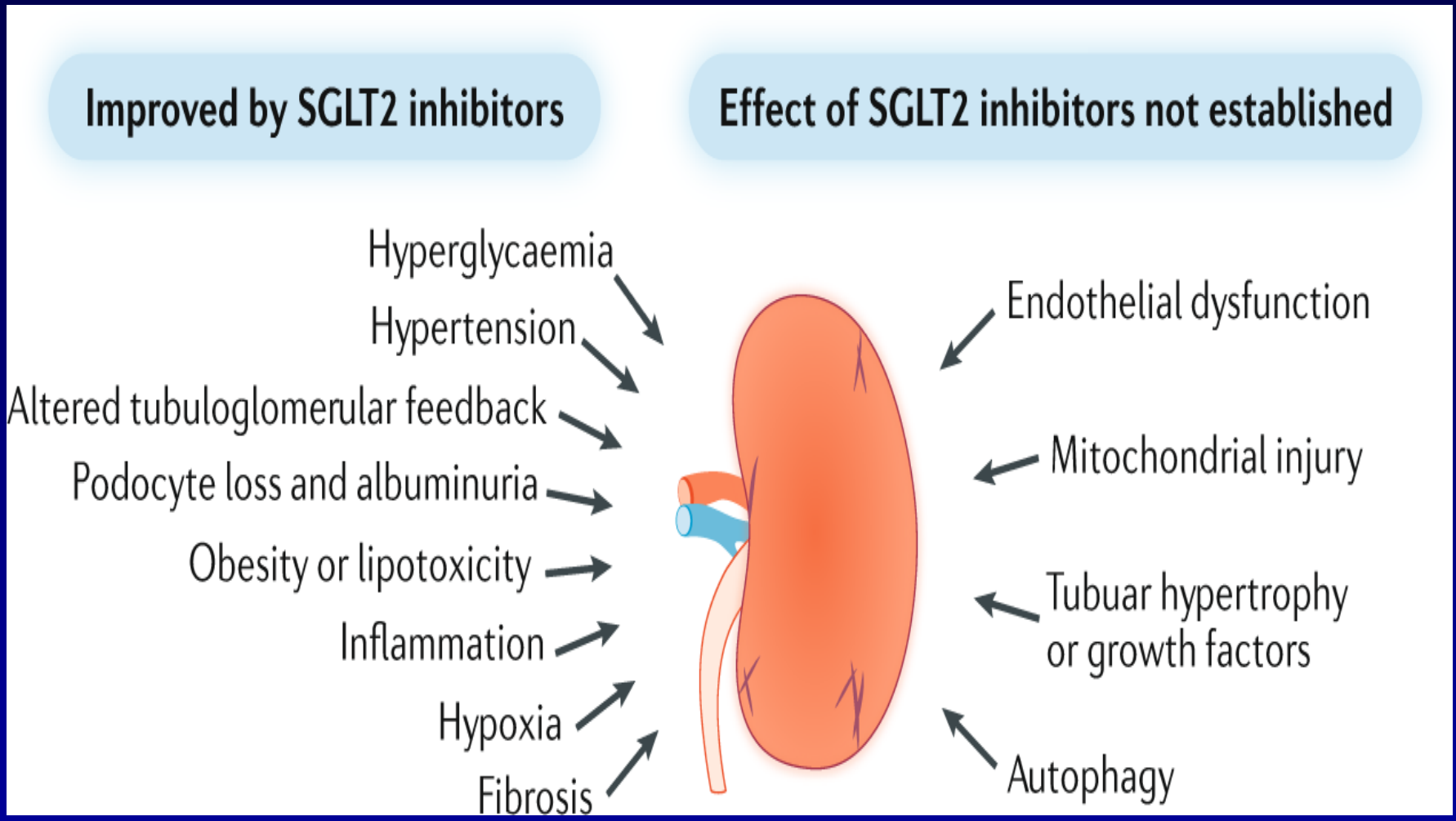
Sự thay đổi về năng lượng cơ tim (myocardial energetics) khi sử dụng ức chế SGLT2 trên bn suy tim và ĐTĐ típ 2



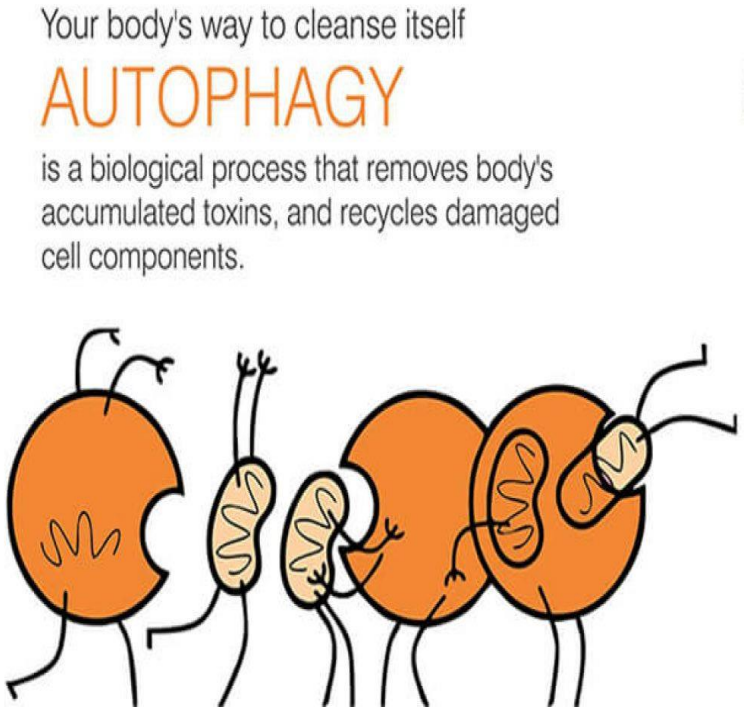

Hearts of Untreated Diabetics
Hearts of Empagliflozin-Treated Diabetics
Energy Deprived Heart
ATP
Improved Cardiac Function
ATP
EMPAGLIFLOZIN
100
0
-100
% Change in Cardiac Energy (ATP) Production
-66
-43
57
-43
Glucose oxidation
Ketone oxidation
Fatty acid oxidation
Glycolysis
100
0
-100
% Change in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


Potential direct myocardial effects of SGLT2i
↓CAMKII
⊕ mitophagy/ autophaghy
↓NHE
↓NLRP3 inflammasome
↓ Heart failure
improved renal function
↑provascular progenitor cells
↑EPO
↓SNS
improved energetics
Potential indirect ± systemic effects of SGLT2i

Ức chế SGLT2 và Tự thực tế bào (Autophagy)



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.

Prof. Yoshinori Ohsumi & Prof. Mariko Ohsumi

"Wife & husband research team"

Prof. Yoshinori Ohsumi, from Institute of Innovative research, Tokyo institute of Technology, who won the Nobel prize in Medicine, in 2016, discovered the mechanisms of Autophagy

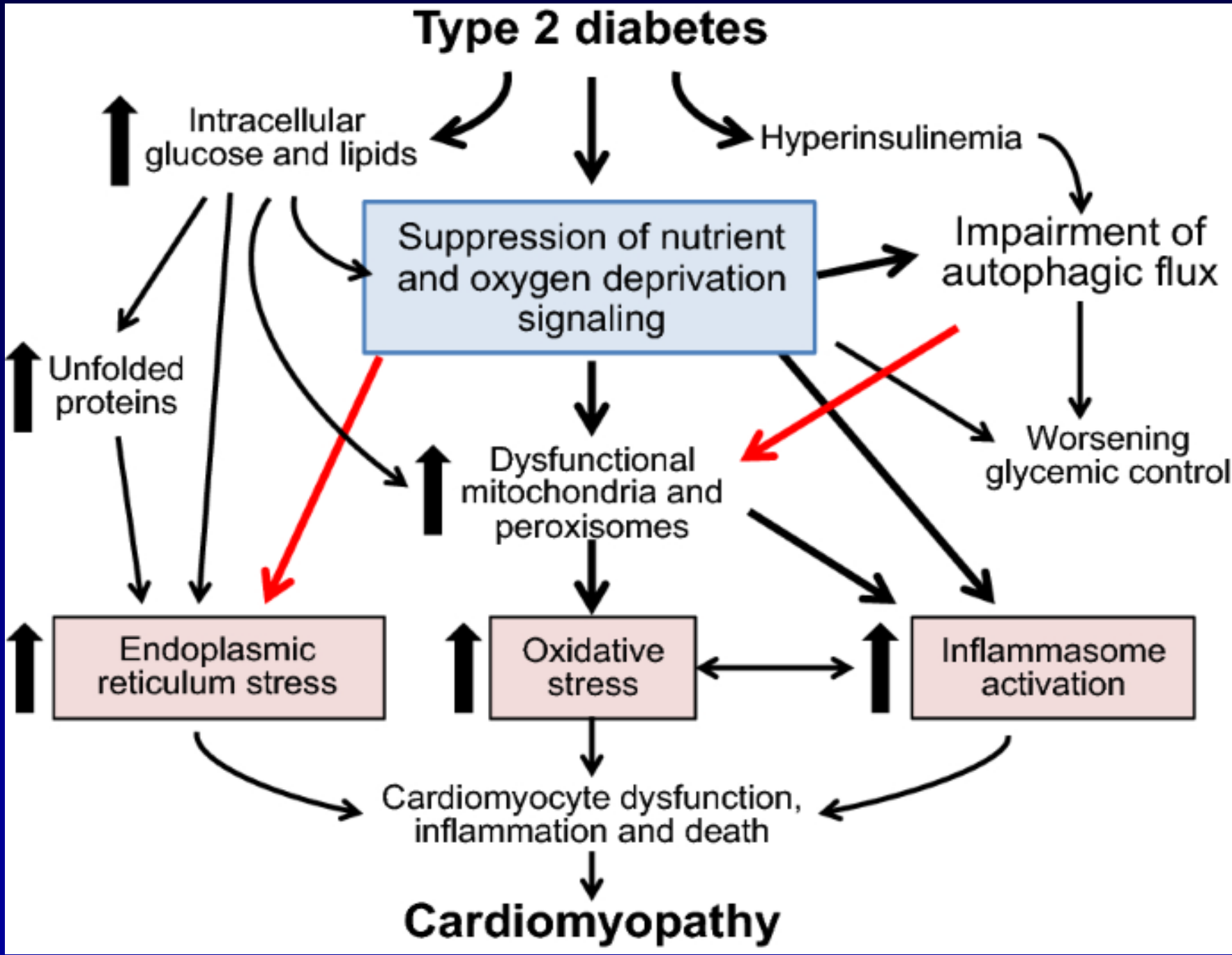
Pitavastatin, Ursolic acid, Maresin, DIM, Ursolic acid Lutein, Maresin, Cholecalciferol, Catalpol, Isoliquiritigenin (PUMDULMCCI)

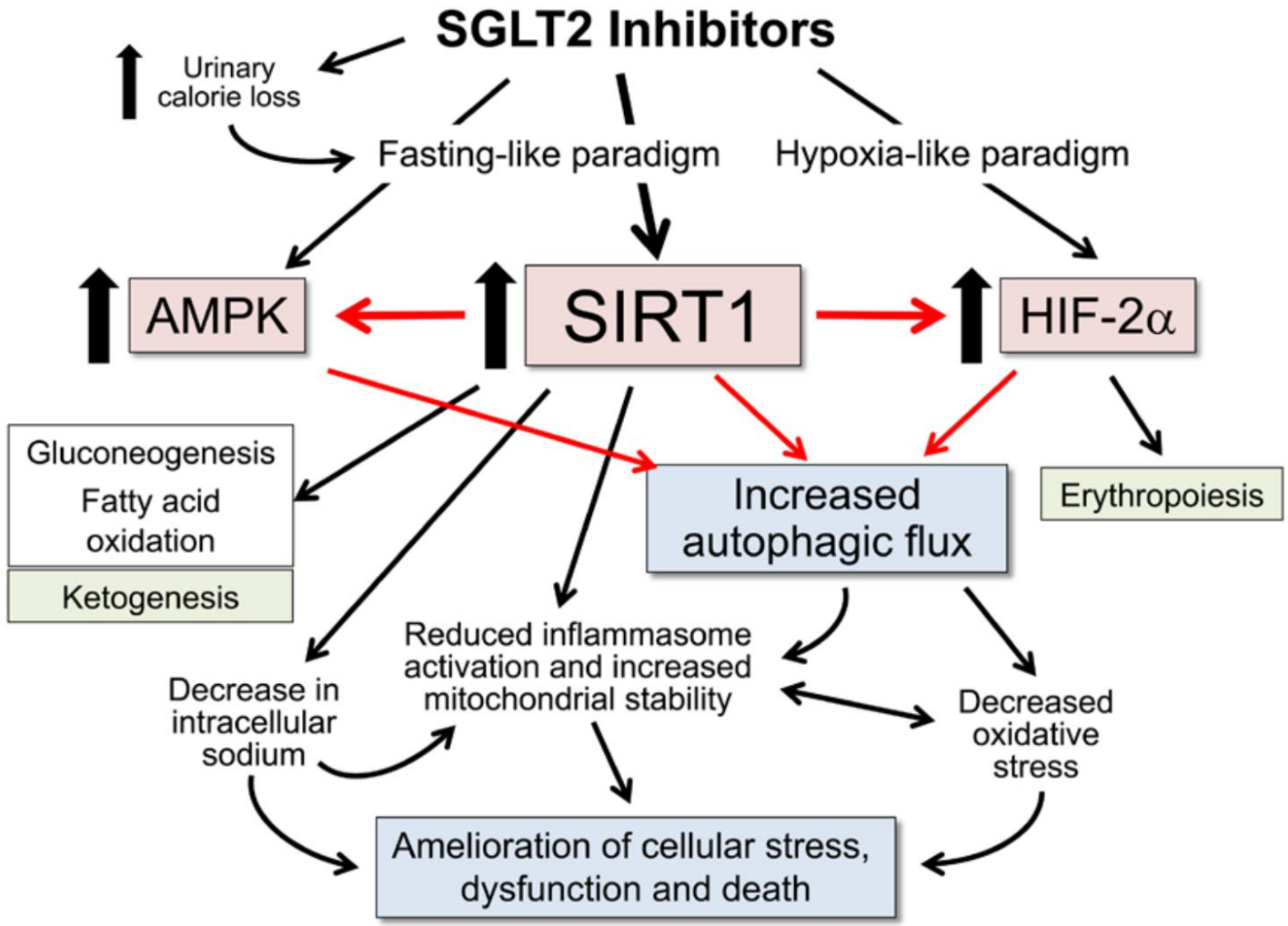
+

ATG5 ATG5 ATG5 ATG5 ATG5

Longevity

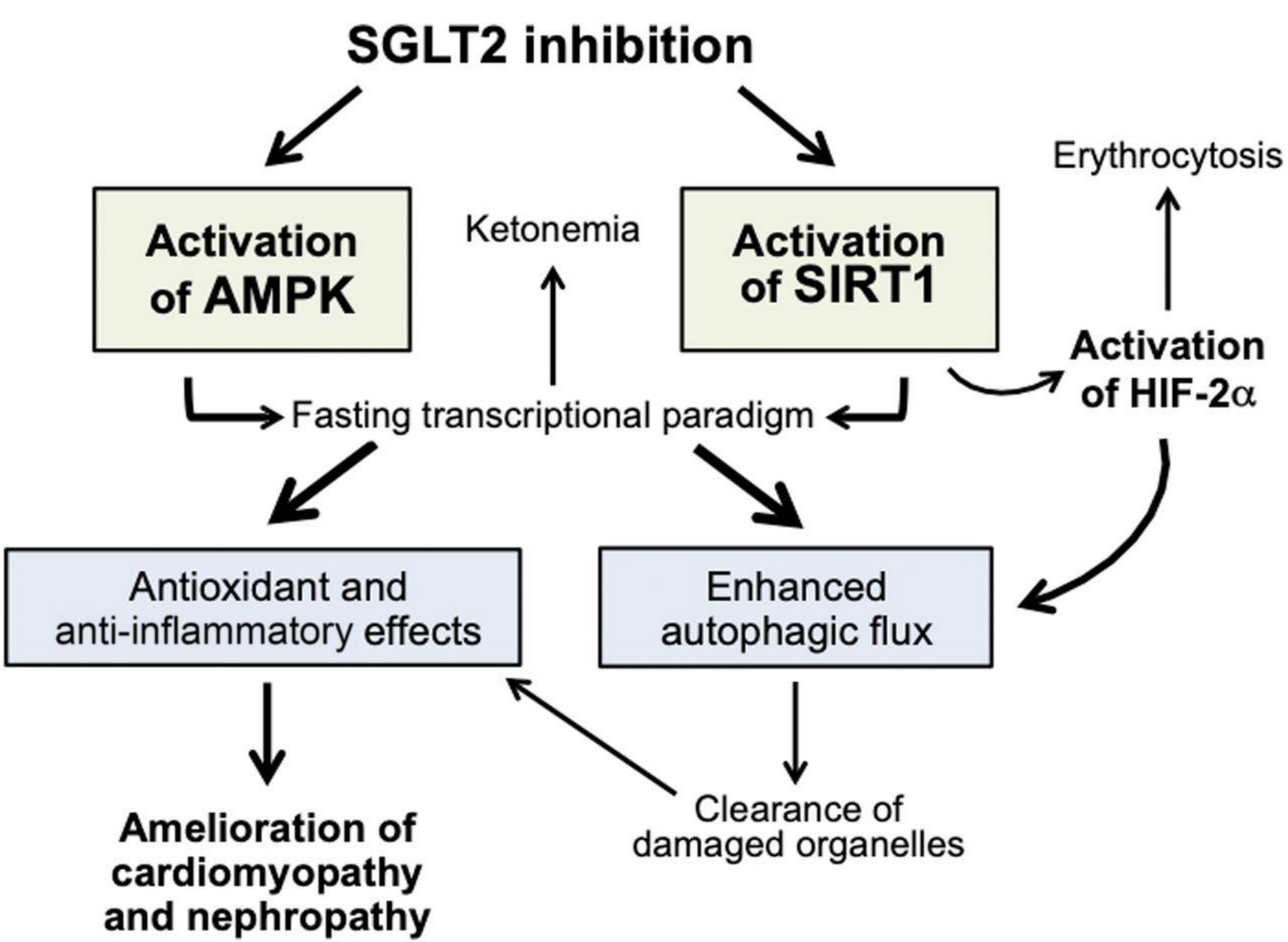
A therapeutic mix encompassing Pitavastatin, Ursolic acid, Maresin, DIM, Ursolic acid Lutein, Maresin, Cholecalciferol, Catalpol, Isoliquiritigenin (PUMDULMCCI) promotes leanness, insulin sensitivity, motor function and longevity through up regulation of ATG5 (Autophagy-related protein-5)


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

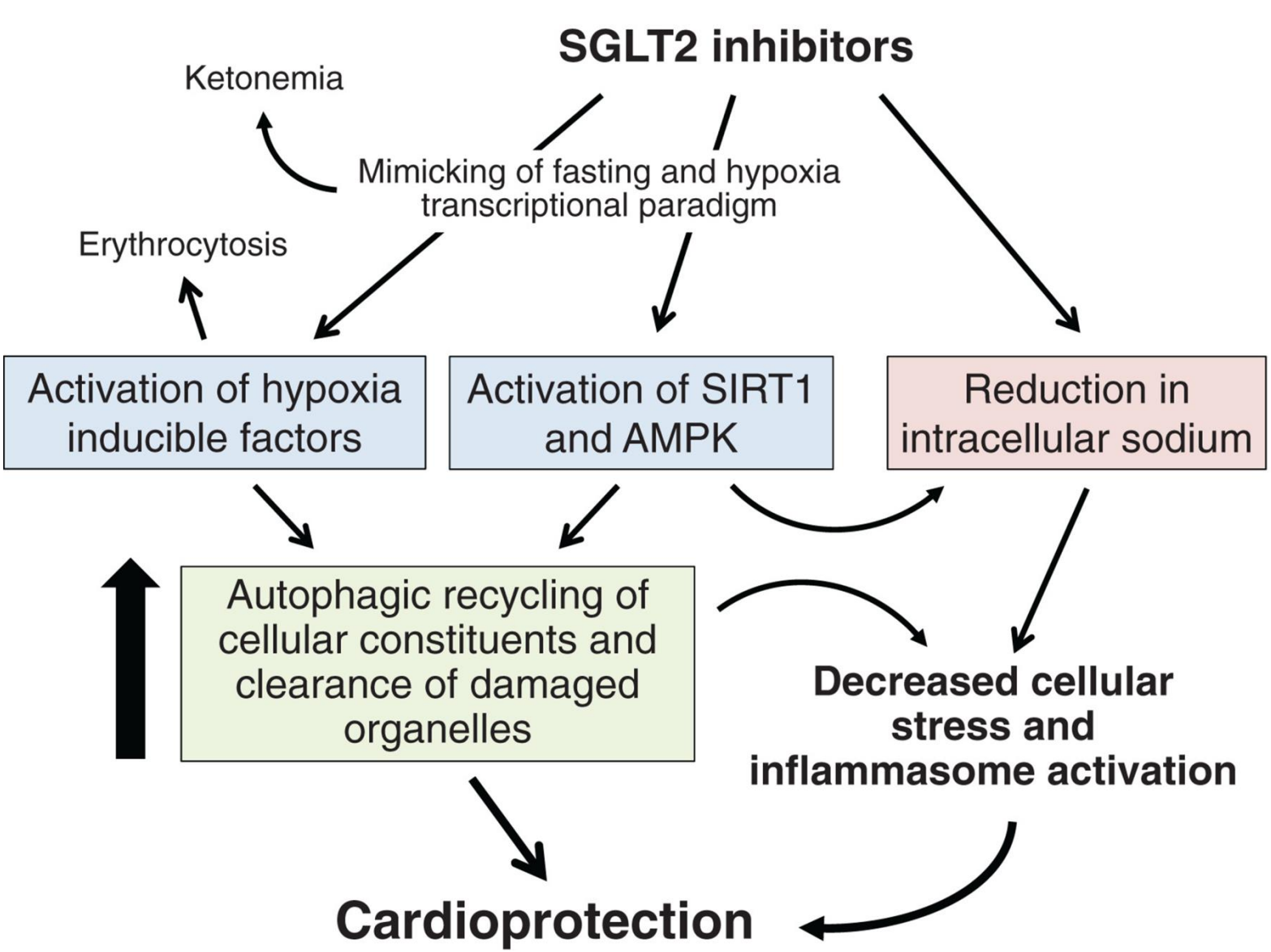


Proposed conceptual framework to explain the molecular mechanisms underlying the effect of SGLT2 inhibitors to reduce serious heart failure and adverse renal events.

The activation of nutrient and oxygen deprivation sensors is designated in pink, whereas the clinical biomarkers of this activation (ketonemia and erythrocytosis) are highlighted in green. AMPK indicates AMP-activated protein kinase; HIF-2α, hypoxia inducible factor isoform 2α; SGLT2, sodium-glucose cotransporter 2; and SIRT1, sirtuin-1



Induction of fasting transcriptional paradigm by SGLT2 inhibitors underlies their action to reduce heart failure and serious adverse renal events.

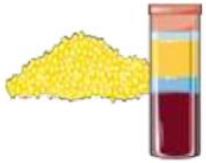


Potential pathways mediating a cardioprotective effect of SGLT2 inhibitors. AMPK, (3) adenosine 5’ monophosphate-activated protein kinase; SIRT1, sirtuin-1.

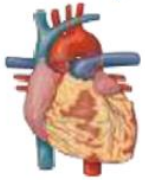
Novel mechanisms of benefit in heart failure with SGLT2 inhibition

Altered adipokine regulation

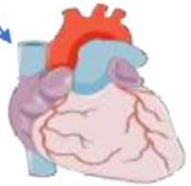
Suppression of leptin secretion by adipocytes



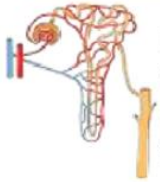
Reduced serum leptin



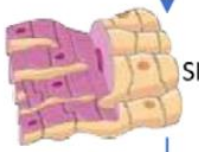
Reduced epicardial fat



Autophagy Induction



Increased glucagon vs insulin ratio due to increased urinary glucose excretion



Activation of SIRT1 and AMPK, HIF1,2alfa

Autophagic clearance of damaged organelles

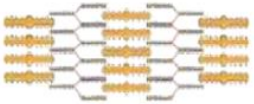
Reduced oxidative stress and inflammation

Improved cardiac ionic homeostasis

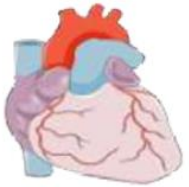
NHE-1 inhibition

SGLT1 inhibition

Reduced intracellular sodium and restored sodium-calcium exchanger function

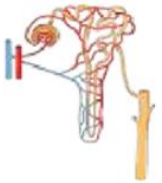


Improved intracellular calcium transients and cardiac contraction



Improved cardiac work efficiency

Improved myocardial energetics



Increased catabolism mimicking a state of fasting due to increased urinary glucose excretion

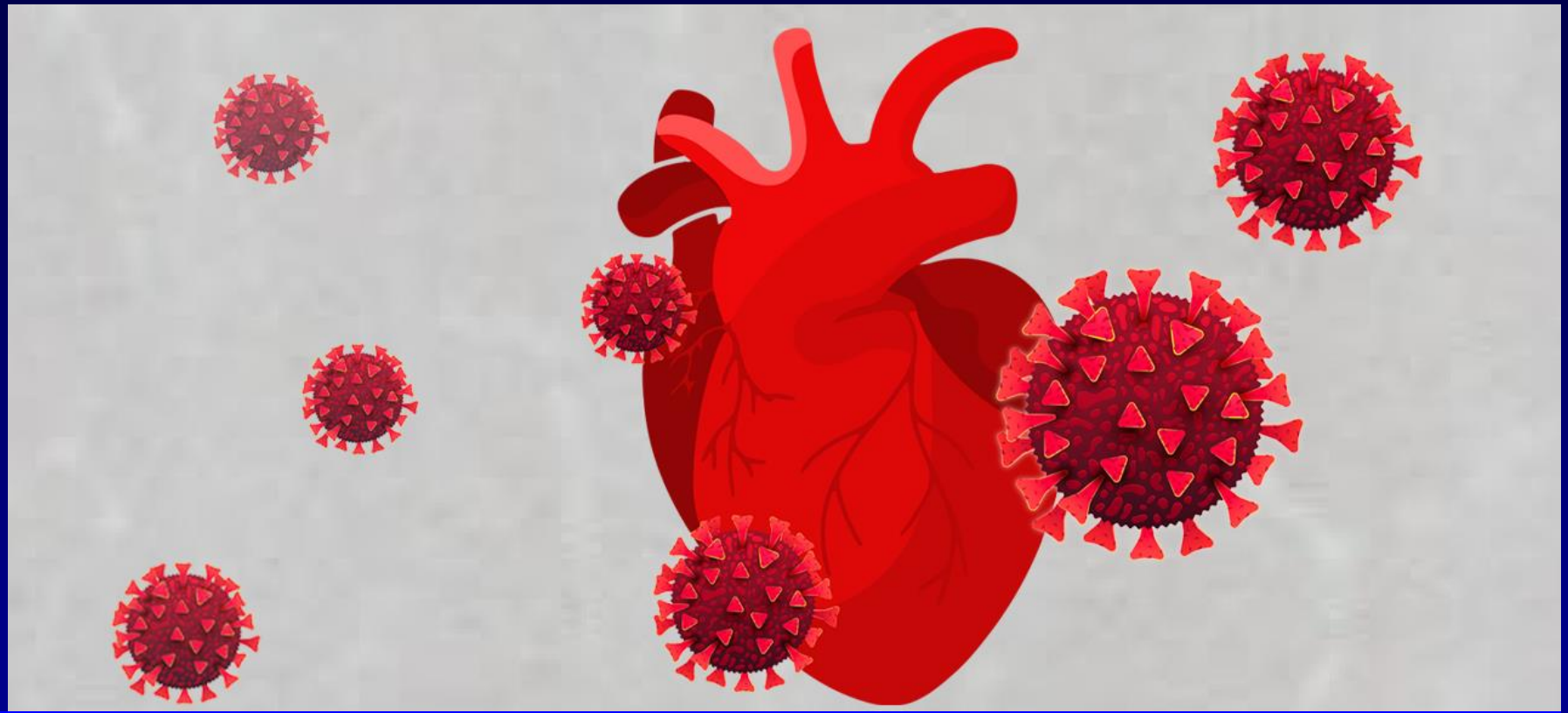
Increased ketone body production

Alternate fuel instead of fatty acids and glucose

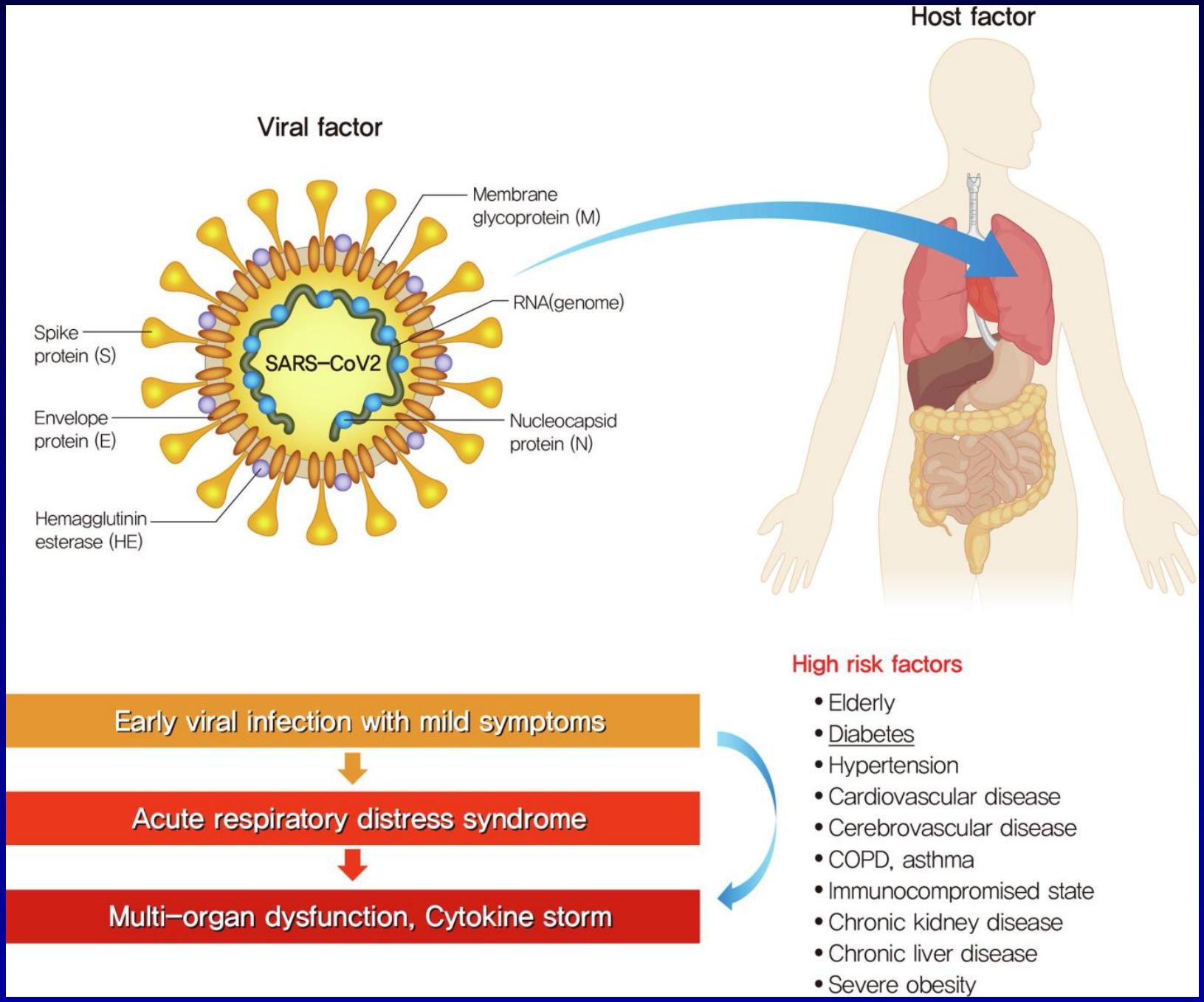
Increased ATP production

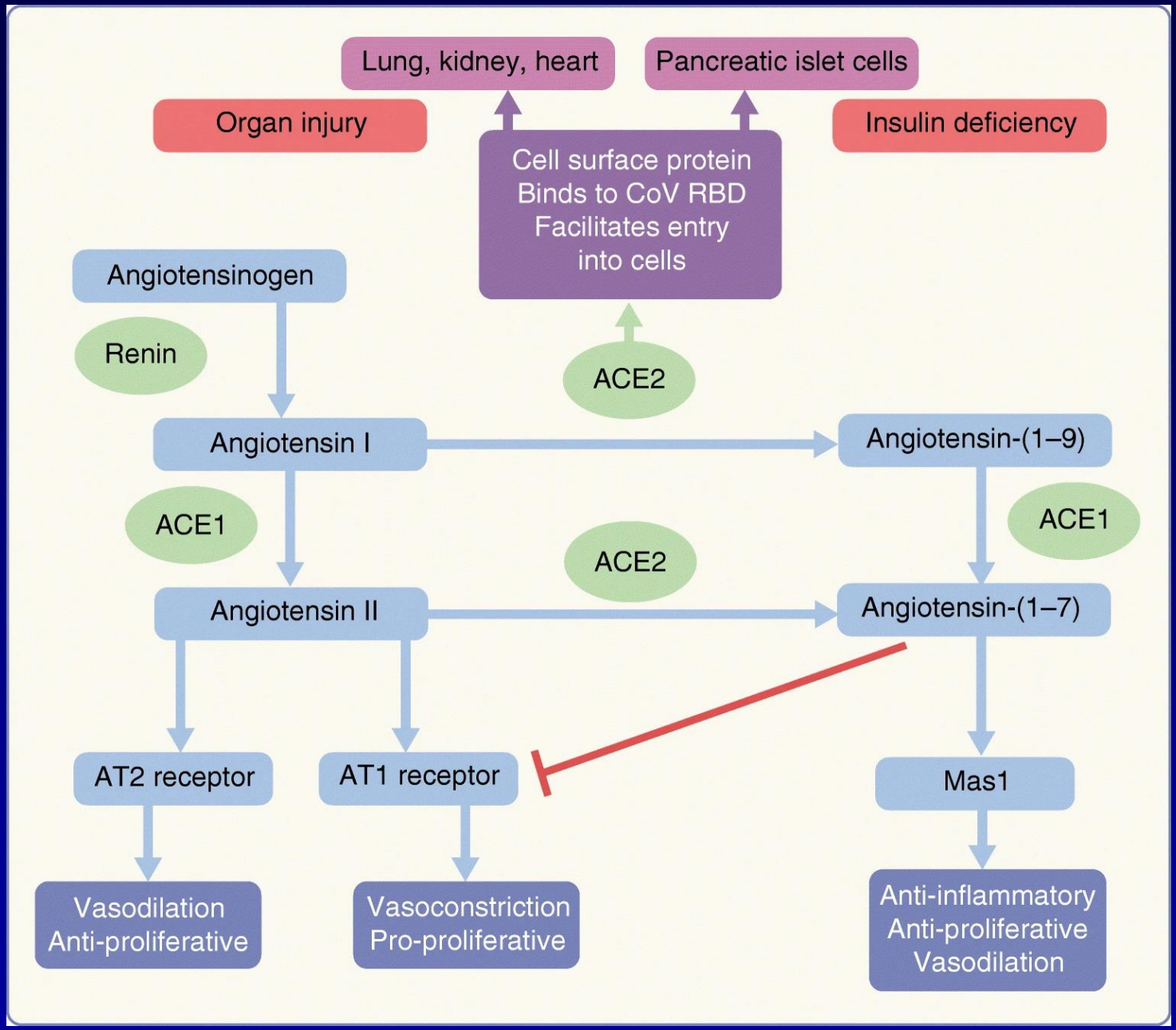
Improved cardiovascular health

Improved cardiovascular outcomes

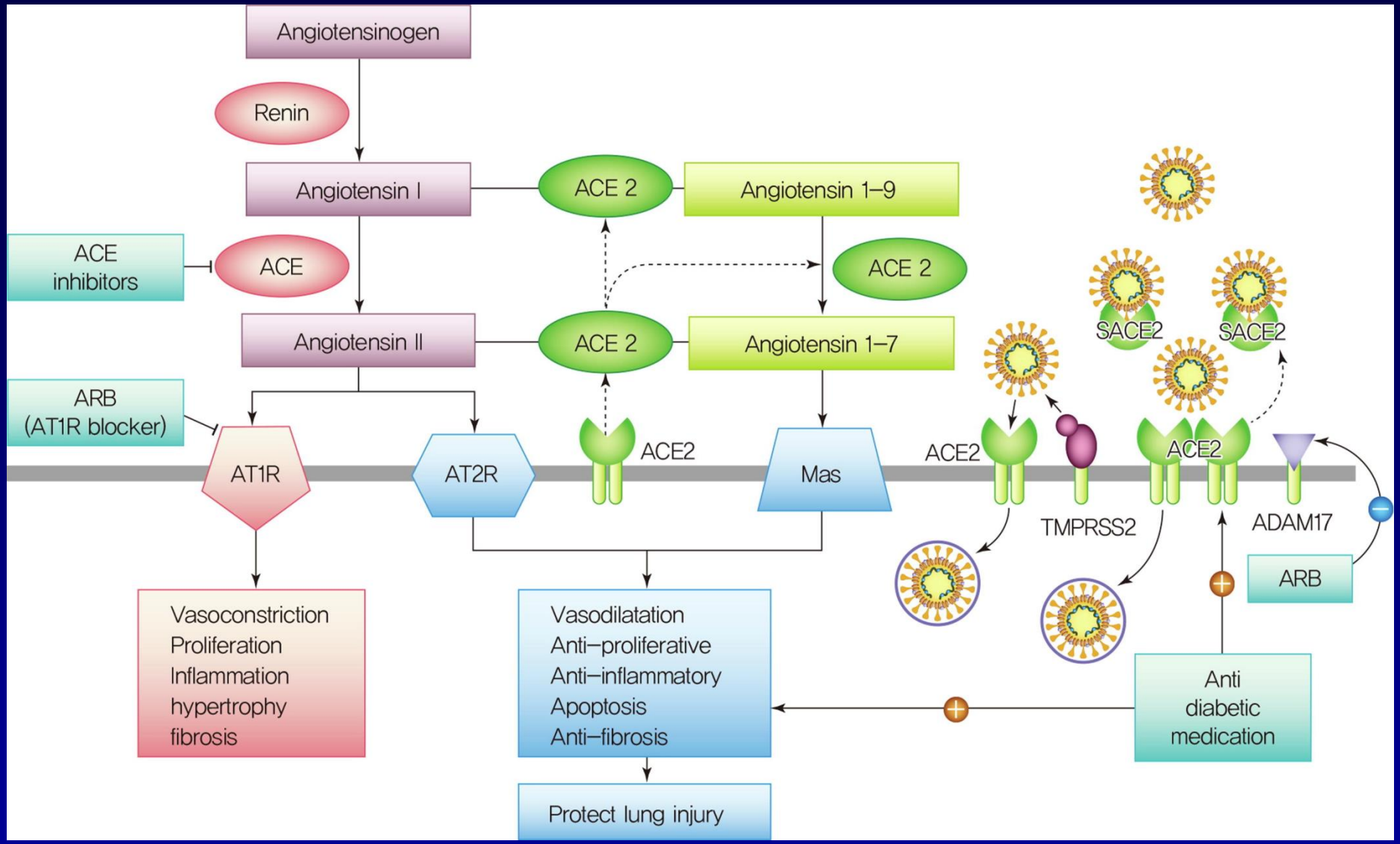


Ức chế SGLT2 và COVID-19


Host factor
Viral factor
Membrane glycoprotein (M)
RNA(genome)
Spike protein (S)
SARS-CoV2
Envelope protein (E)
Nucleocapsid protein (N)
Hemagglutinin esterase (HE)
Early viral infection with mild symptoms
Acute respiratory distress syndrome
Multi-organ dysfunction, Cytokine storm
High risk factors
• Elderly
• Diabetes
• Hypertension
• Cardiovascular disease
• Cerebrovascular disease
• COPD, asthma
• Immunocompromised state
• Chronic kidney disease
• Chronic liver disease
• Severe obesity


Lung, kidney, heart
Pancreatic islet cells
Organ injury
Insulin deficiency
Cell surface protein
Binds to CoV RBD
Facilitates entry
into cells
Angiotensinogen
Renin
ACE2
Angiotensin I
Angiotensin-(1–9)
ACE1
ACE1
ACE2
Angiotensin II
Angiotensin-(1–7)
AT2 receptor
AT1 receptor
Mas1
Vasodilation
Anti-proliferative
Vasoconstriction
Pro-proliferative
Anti-inflammatory
Anti-proliferative
Vasodilation

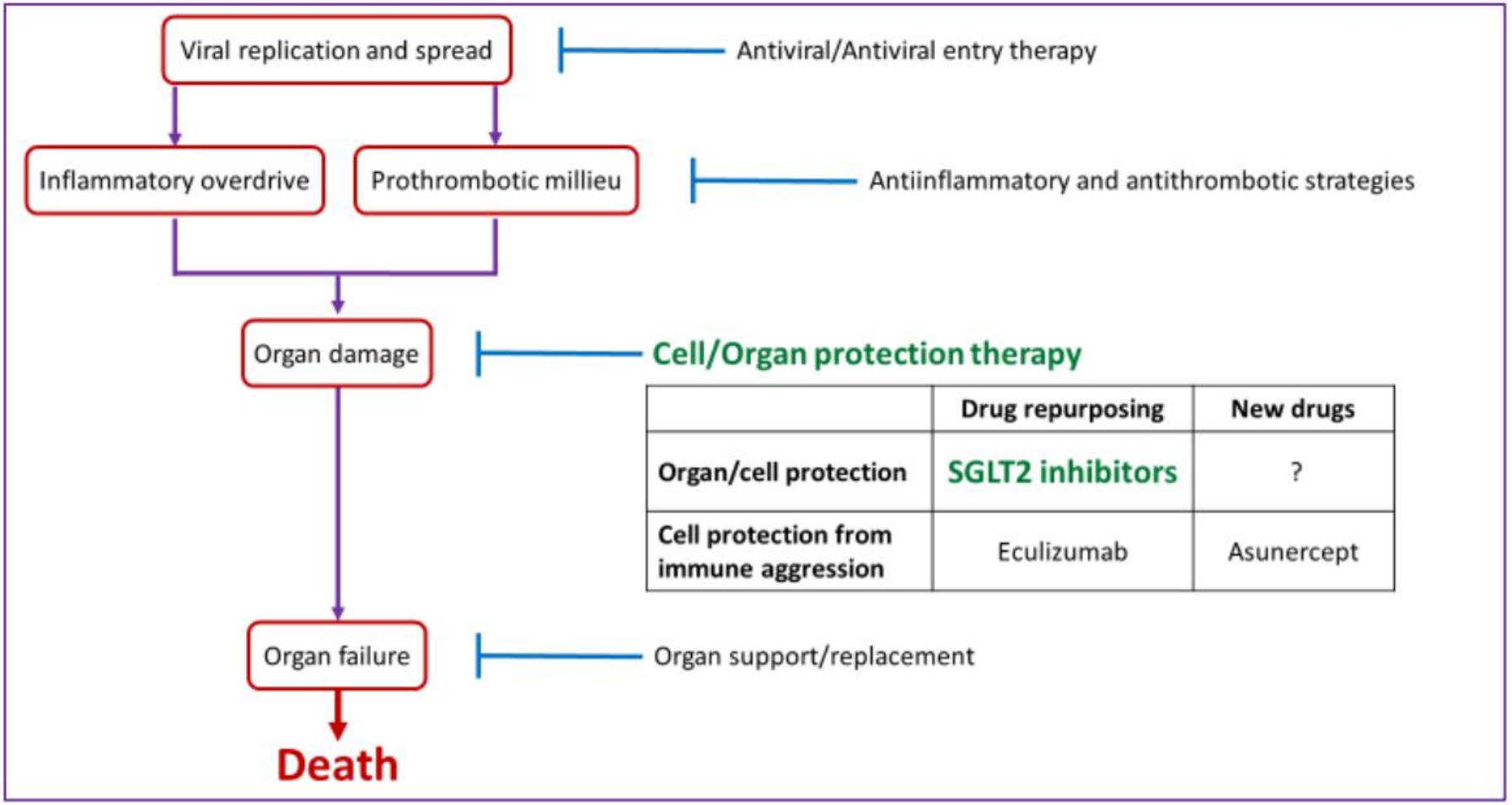
- Role of ACE2 in the pathogenesis of coronavirus diseases.
- ACE2 converts angiotensin I and angiotensin II to angiotensin-(1–9) and angiotensin-(1–7), respectively.
- ACE2 is also expressed in the lung, kidney, heart and pancreas and acts as a facilitator for CoV entry into cells.
- Use of ACEI/ARBs increases angiotensin I levels and upregulates *ACE2* gene expression. This facilitates excess viral entry into host cells causing organ injury and insulin deficiency, contributing to hyperglycaemia.
- Upregulated ACE2 may convert angiotensin II to angiotensin-(1–7). The latter acts on the Mas1 receptor to trigger anti-inflammatory effects and inhibits the AT1 receptor to cause vasodilation.
- However, at least in ACEI users, angiotensin II levels will be low and the net benefit of ACE2 upregulation is uncertain. CoV infection downregulates ACE2 expression, thereby reducing angiotensin-(1–7) levels, which reduces its anti-inflammatory effects and potentially worsens organ vulnerability to infection. AT, angiotensin; RBD, receptor binding domain



Diabetes and COVID-19: Global and regional perspectives In-Kyung Jeong a , Kun Ho Yoon b, * , Moon Kyu Lee c, *diabetes research and clinical practice 166 (2020) 108303

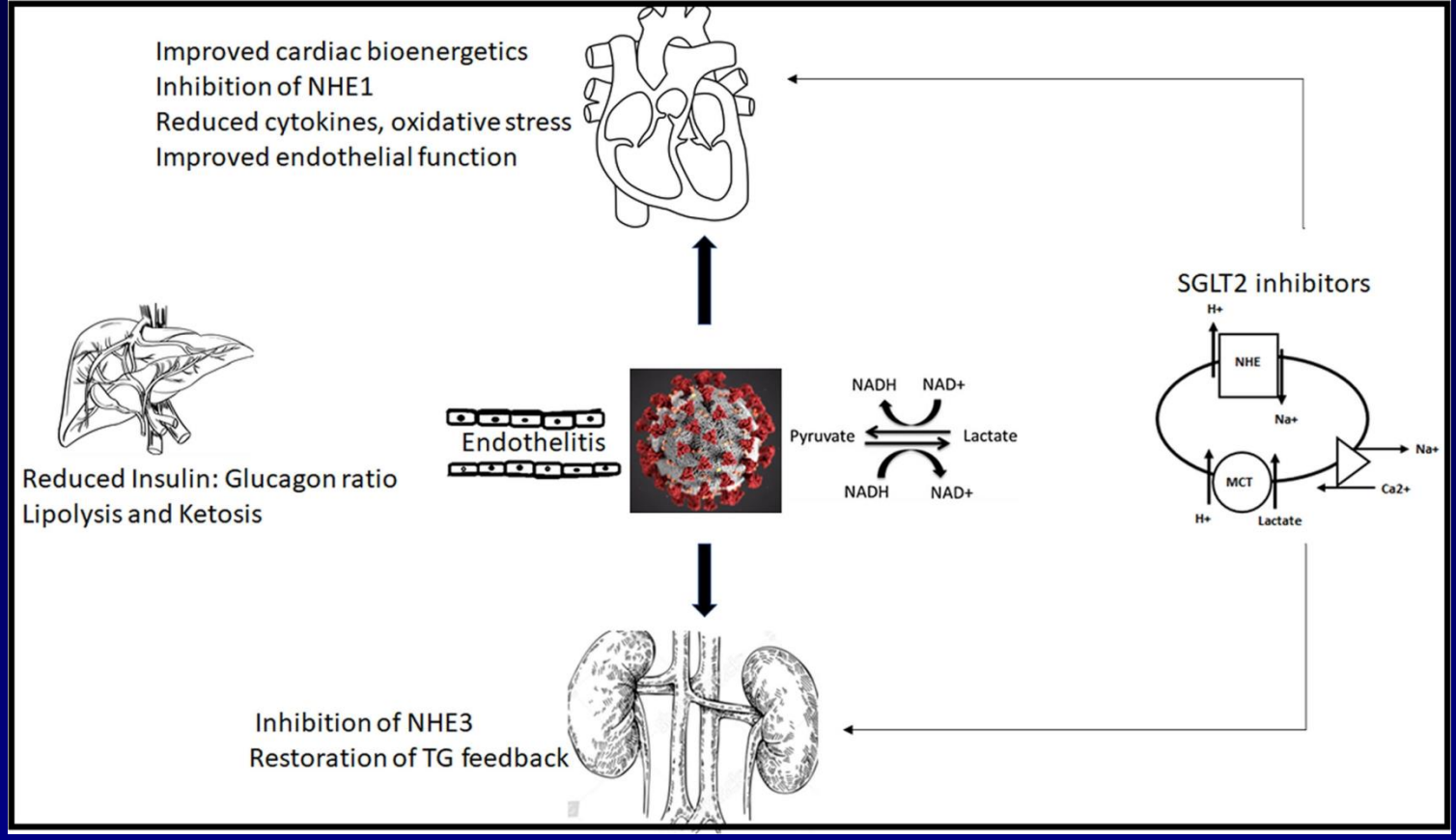
The role of angiotensin-converting enzyme 2 (ACE2) on the cardiovascular system and entry of SARS-CoV-2. ACE2 converts Ang I to Ang-(1–9) and Ang II (angiotensin II) to Ang-(1–7), which acts on the Mas receptor (MasR) to lower blood pressure through vasodilation but also to attenuate inflammation and fibrosis. ACE1 converts Ang I into Ang II, which acts at the angiotensin II type 1 receptor (AT1R) to increase blood pressure by inducing vasoconstriction, increasing kidney reabsorption of sodium and water, and increasing oxidative stress to promote inflammation and fibrosis. ACE2 also binds to and internalizes SARS-CoV-2 after priming by the serine protease TMPRSS2 (transmembrane protease, serine-2). Shedding of membrane-bound ACE2 by a disintegrin and metalloprotease 17 (ADAM17) results in the occurrence of soluble ACE2, which can no longer mediate SARS-Cov-2 entry and might even prevent such entry by keeping the virus in solution. AT1R (Ang II type 1 receptor) upregulates ADAM17, and AT1R blockers (ARBs) would prevent this. However, diminishing production of Ang II with an ACE inhibitor or blocking Ang II–AT1R actions with an ARB can enhance the ACE2-Ang-(1–7)-MasR pathway, which attenuates inflammation, fibrosis, and lung injury. Anti-diabetic medication increased the expression of ACE2 in animal study. However, anti-diabetic medications that enhance immune modulation and effectively control hyperglycemia may have a beneficial effect on the outcomes of patients with COVID-19.

Exploring Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors for Organ Protection in COVID-19



Pathogenic basis of current therapeutic approaches to COVID-19 and potential place of SGLT2 inhibitors.

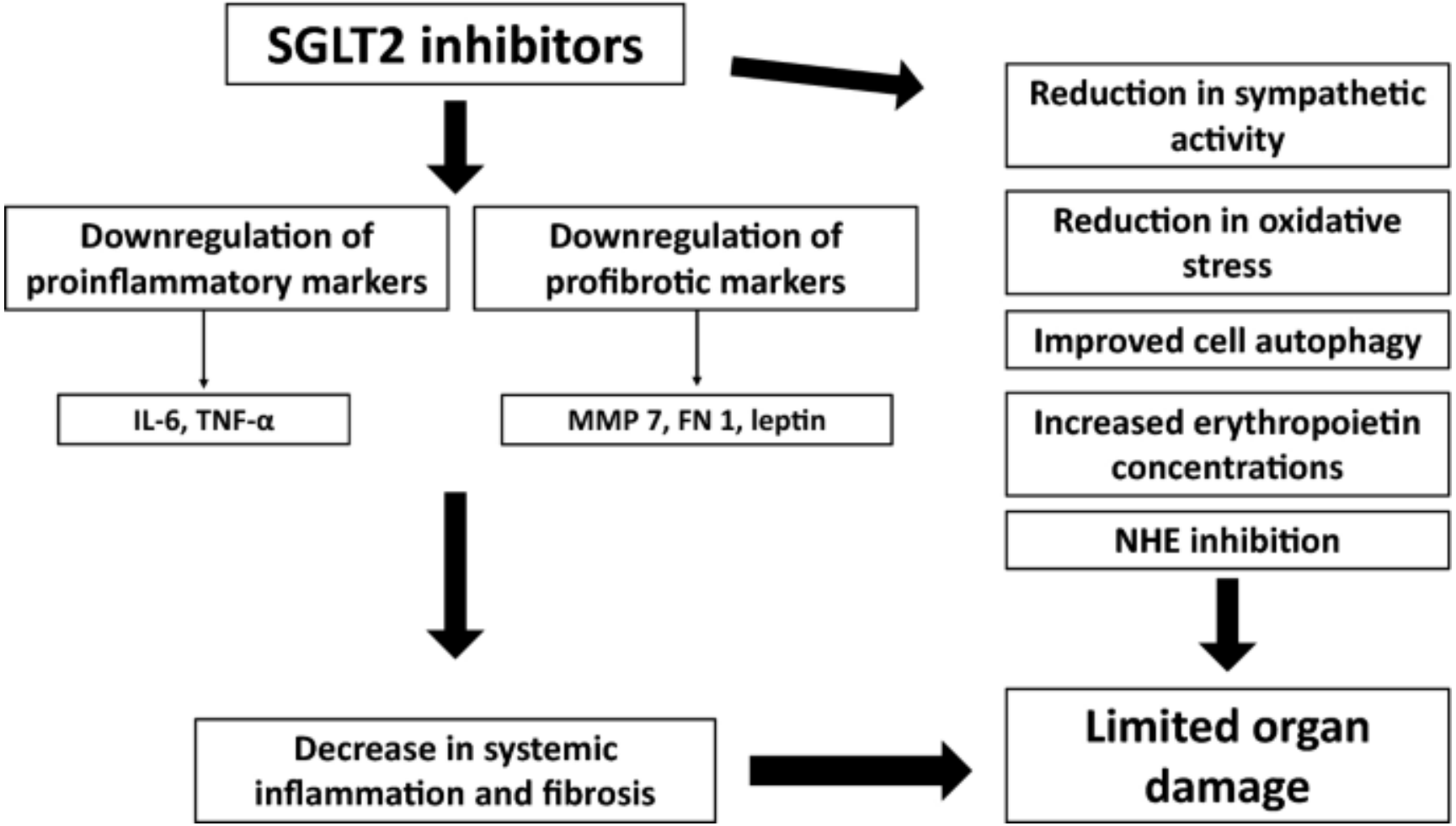
J. Clin. Med. **2020**, *9*, 2030



Schematic representation of the proposed pathophysiology of COVID-19 induced cardiac and renal dysfunction induced by endothelitis and increased lactate production under conditions of impaired tissue oxygenation induced anaerobic glycolysis which leads to increased cellular entry of H+along with lactate, leading to activation of the NHE, sodium accumulation and cell oedema and destruction. SGLT2 inhibitors, apart from having beneficial effects on multiple cardiovascular risk factors (diabetes, hypertension and obesity) which predispose to adverse outcomes in COVID-19, may possibly have benefits in acute decompensated states by inhibiting the NHE, decreasing lactate and improving endothelial function. MCT, Monocarboxylate transporter (H+lactate symporter); TG, Tubuloglomerular feedback

Sodium-glucose co-transporter 2 inhibitors in COVID-19: meeting at the crossroads between heart, diabetes and infectious diseases

Theocharis Koufakis[1] · Antonis N. Pavlidis[2] · Symeon Metallidis[3] · Kalliopi Kotsa[1]



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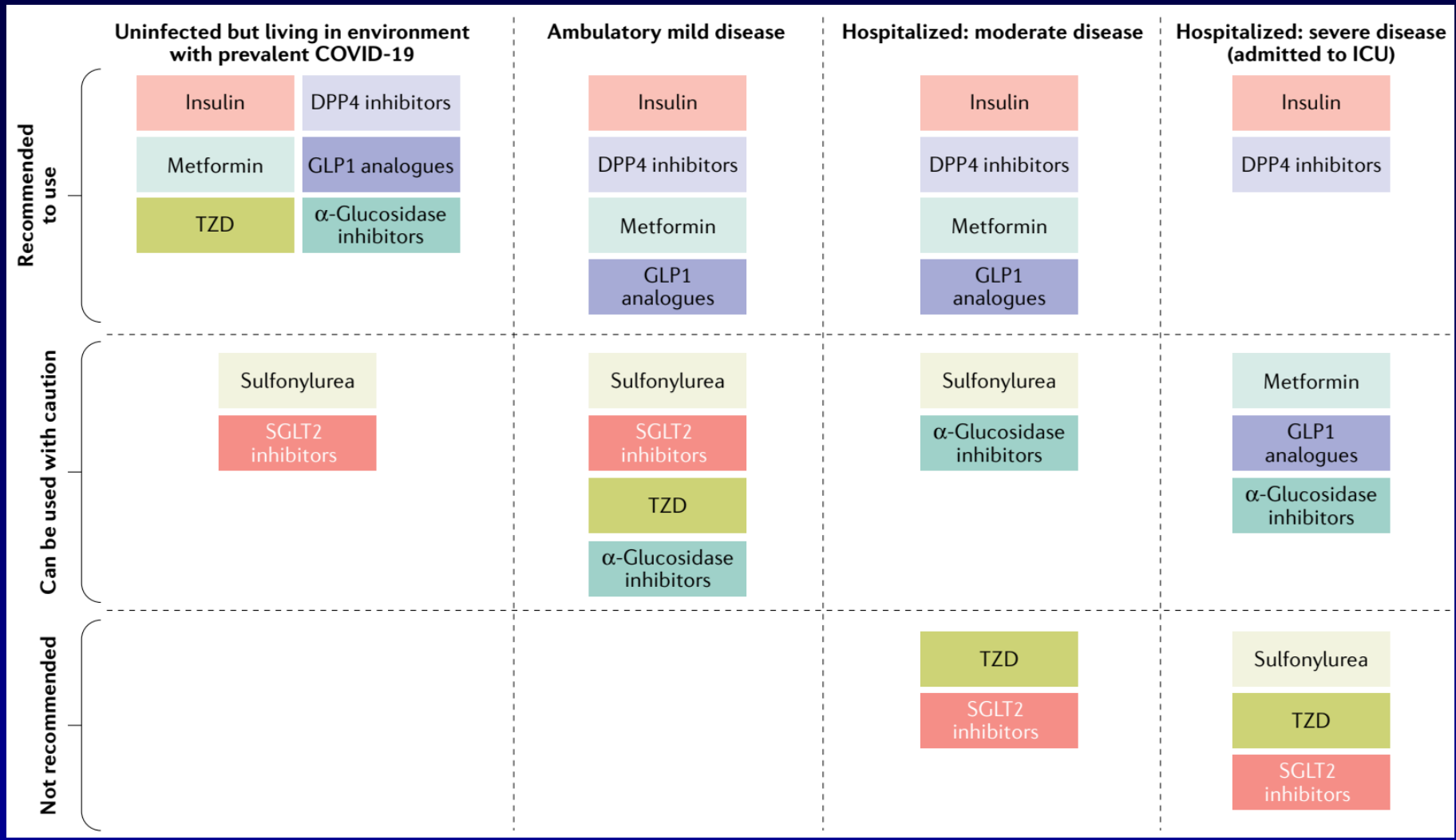
International Journal of Clinical Pharmacy



COVID-19 and diabetes mellitus: from pathophysiology to clinical management

Soo Lim[1,5]✉, Jae Hyun Bae[2,5], Hyuk-Sang Kwon[3] and Michael A. Nauck[4]✉

NATURE REVIEWS | ENDOCRINOLOGY

24 | JANUARY 2021 | VOLUME 17

SGLT-2 inhibitors for COVID-19 — A miracle waiting to happen or just another beat around the bush?

Rationality of using dapagliflozin in COVID-19.

A. Reduced serum lactate level
1. Reduces oxygen consumption in tissues and channelizes glucose towards the aerobic pathway, thus diminishing lactate production
2. Reduces lactate release from adipose tissue
3. Increased renal excretion of lactate
B. Inhibition of NHE
C. Organ protective effective (heart, vasculature, kidney)
D. Activation of alternative RAAS pathway by activating ACE2
E. Decreased proinflammatory cytokines
F. Glycemic control

Primary Care Diabetes 14 (2020) 564–565

Ức chế SGLT2

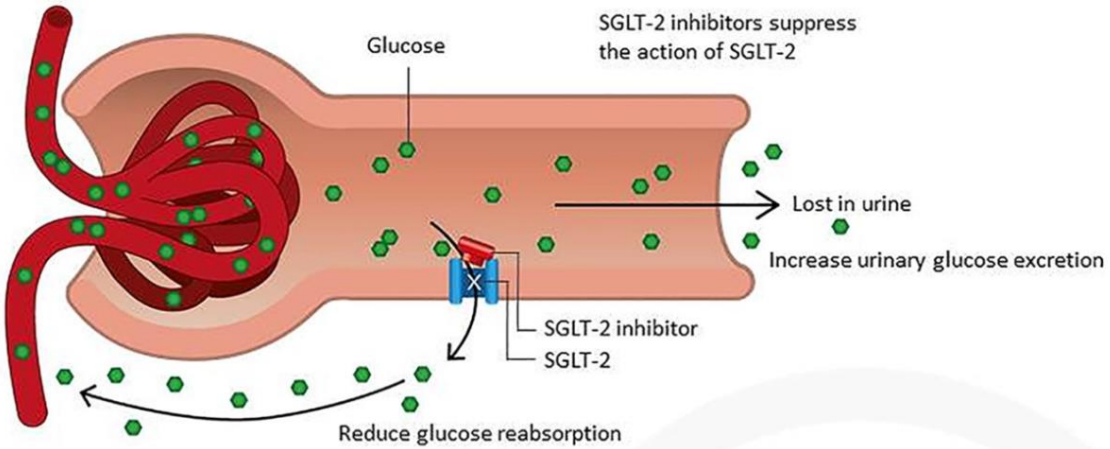
Mechanism of Drug Action	Possible Influence on the Course of COVID-19
- inhibition of renal glucose reuptake in proximal renal tubes - increased expression of ACE2 [79] - increased production of angiotensin (1–7) [91] - reduction of cardiovascular and renal complications [92,97] - anti-inflammatory properties [92] - decreased production of tumour necrosis factor, IL-6, monocyte chemoattractant protein 1 [93,94] - decreased lactic acidosis, influencing the acid–base balance inside a cell [95]	- increased susceptibility to the infection [79] - anti-oxidative and anti-fibrotic properties [91] - prevention of ARDS development [91] - prevention of cell injury during the infection [95] - protection from the severe course of the disease [95]

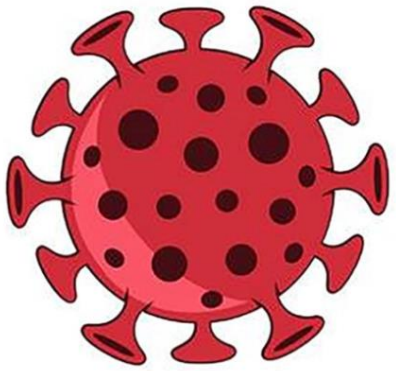
Weronika Bielka, Agnieszka Przezak and Andrzej Pawlik * Therapy of Type 2 Diabetes in Patients with SARS-CoV-2 Infection. *Int. J. Mol. Sci.* 2021, *22*, 7605

Ức chế SGLT2

Table 4. Putative Beneficial and Harmful Effects, and Clinical Outcomes of SGLT2 Inhibitors in Glycemic Control Among COVID-19 Patients

Putative beneficial effects	Putative harmful effects	Clinical outcomes
No applicable data	Owing to their pharmacological characteristics, SGLT2 inhibitors might cause adverse effects in patients with COVID-19 and so cannot be recommended [25].	A 52-year-old male with type 2 diabetes on empagliflozin and no history of diabetic ketoacidosis (DKA) presented with symptoms of COVID-19 as well as laboratory findings consistent with euglycemic DKA. SGLT2 inhibitors should be held as early as possible in COVID-19 patients due to the risk of euglycemic DKA [28].
	People with diabetes should be encouraged to continue medication prescribed for hypertension, diabetes or dyslipidemia. Furthermore, patients with diabetes and COVID-19 infection should follow their usual antidiabetic treatment with the exception of SGLT2 inhibitors [26].	The patient of euglycemic DKA due to empagliflozin use was initially suspected to be a case of COVID-19 [29].
	Avoidance of diabetic ketoacidosis associated with SGLT2 inhibitors is of particular medical importance during the COVID-19 pandemic [27].	





SGLT2i

- ↑ Endothelial function
- ↓ Oxidative stress
- ↓ Inflammation
- ↓ Insulin/insulin resistance and glucose

SGLT2i improve:

- Hypertension
- Hyperglycemia/T2D
- HF
- CKD
- Obesity

Common mechanisms?

Extravascular volume: pulmonary edema

Inflammation: Cytokines, e.g. IL-6

COVID-19

- ↓ Endothelial function
- ↑ Oxidative stress
- ↑ Inflammation
- ↑ Insulin resistance

Morbidity/Mortality increased by:

- Hypertension
- Hyperglycemia/T2D
- HF
- CKD
- Obesity

Loss of glucose is balanced by increased endogenous glucose production. The new homeostasis may be responsible for the favourable effects of dapagliflozin on the cardiovascular, renal and immune functions. The effects on glucose control, including insulin demand, endothelial function, oxidative stress, oxygen delivery capacity, congestion and inflammation are probably most important to protect from worsening of organ function in hospitalized patients with COVID-19 and medical history with risk factors, including hypertension, T2D, HF, CKD and obesity. CKD, HF…

Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19)

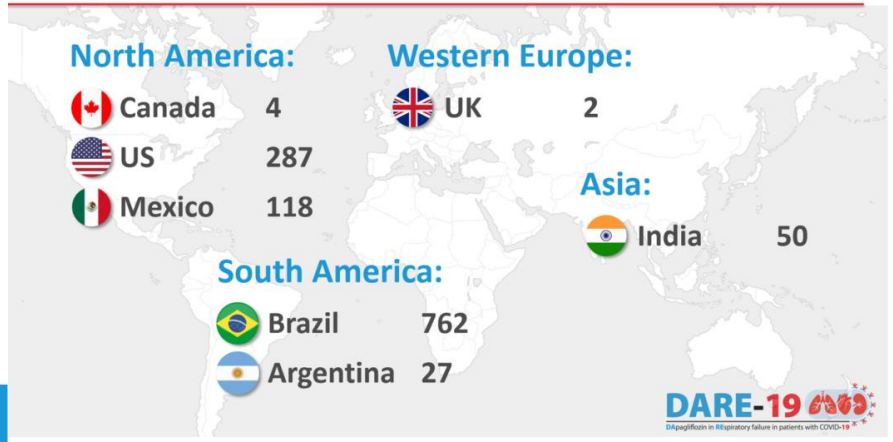
Primary Outcome of Prevention: Organ Failure or Death from Any Cause

DARE-19
DApagliflozin in REspiratory failure in patients with COVID-19

AstraZeneca | Saint Luke's | George Clinical

DARE-19 Trial

1250 Patients – 7 Countries – 95 Sites



Objectives

- We hypothesized that dapagliflozin may reduce the risk of multi-organ failure and death, and improve recovery in patients that are hospitalized with Covid-19 and have cardiometabolic risk factors

Background and Rationale

- Patients hospitalized with Covid-19 and cardiometabolic risk factors are at high risk for multi-organ failure and death
- There is a dearth of efficacious therapies that reduce the risk of major clinical events, and large unmet clinical need for additional treatment options
- SGLT2i provide organ protection in patients with chronic cardiometabolic conditions (T2D, HF, CKD) and favorably affect a number of pathophysiologic pathways disrupted during acute illness, such as Covid-19

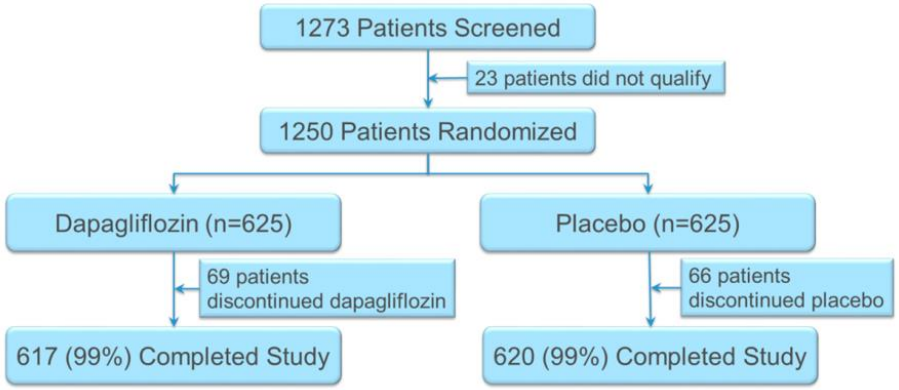
DARE-19

CKD, chronic kidney disease; HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.

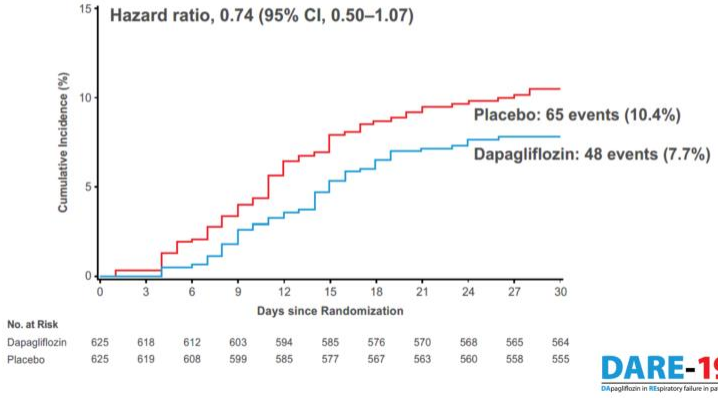
DARE-19

Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19)

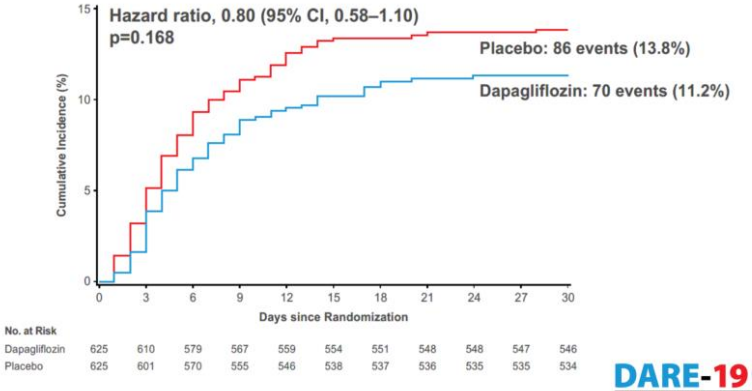
Patient Disposition



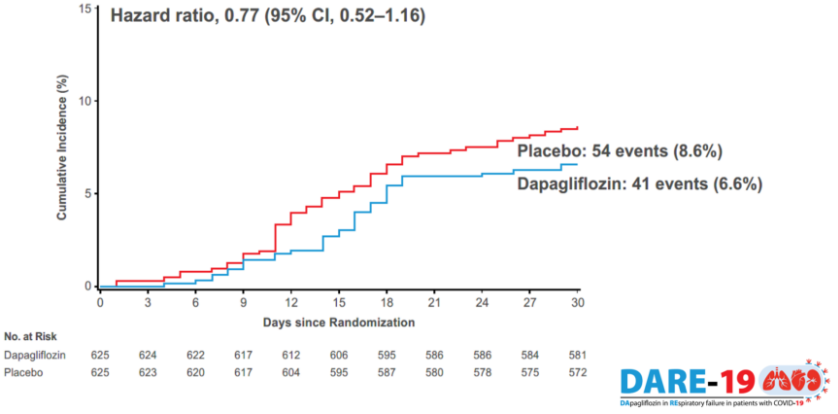
Composite Kidney Endpoint



Time to Organ Failure or Death



All-cause Mortality



Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19)

Practice Implications

- DARE-19 - first trial that evaluated SGLT2i in patients with acute illness, patient population with the highest risk ever tested with this class
- Given the lack of data, there were concerns that using SGLT2i in Covid-19 could increase the risk of AKI and ketoacidosis
- This fueled recommendations from some groups to stop SGLT2i in patients with Covid-19, even if they had conditions in which this class has been proven to produce substantial benefits (T2D, HF)
- In DARE-19, rates of serious adverse events (including AKI) were numerically lower with dapagliflozin than placebo, and only two non-severe events of DKA were reported
- Our results do not support discontinuation of SGLT2i in a setting of Covid-19, as long as patients are monitored

AKI, acute kidney injury; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.

DARE-19
DApagliflozin in REspiratory failure in patients with COVID-19

Chân thành cám ơn sự theo dõi của quý đồng nghiệp