# Bệnh Cơ Tim Đái Tháo Đường

GS.TS.Nguyễn Hải Thủy

# 1. Định Nghĩa Bệnh cơ tim đái tháo đường

"Diabetic Cardiomyopathy has been defined as a distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension and significant valvular disease"

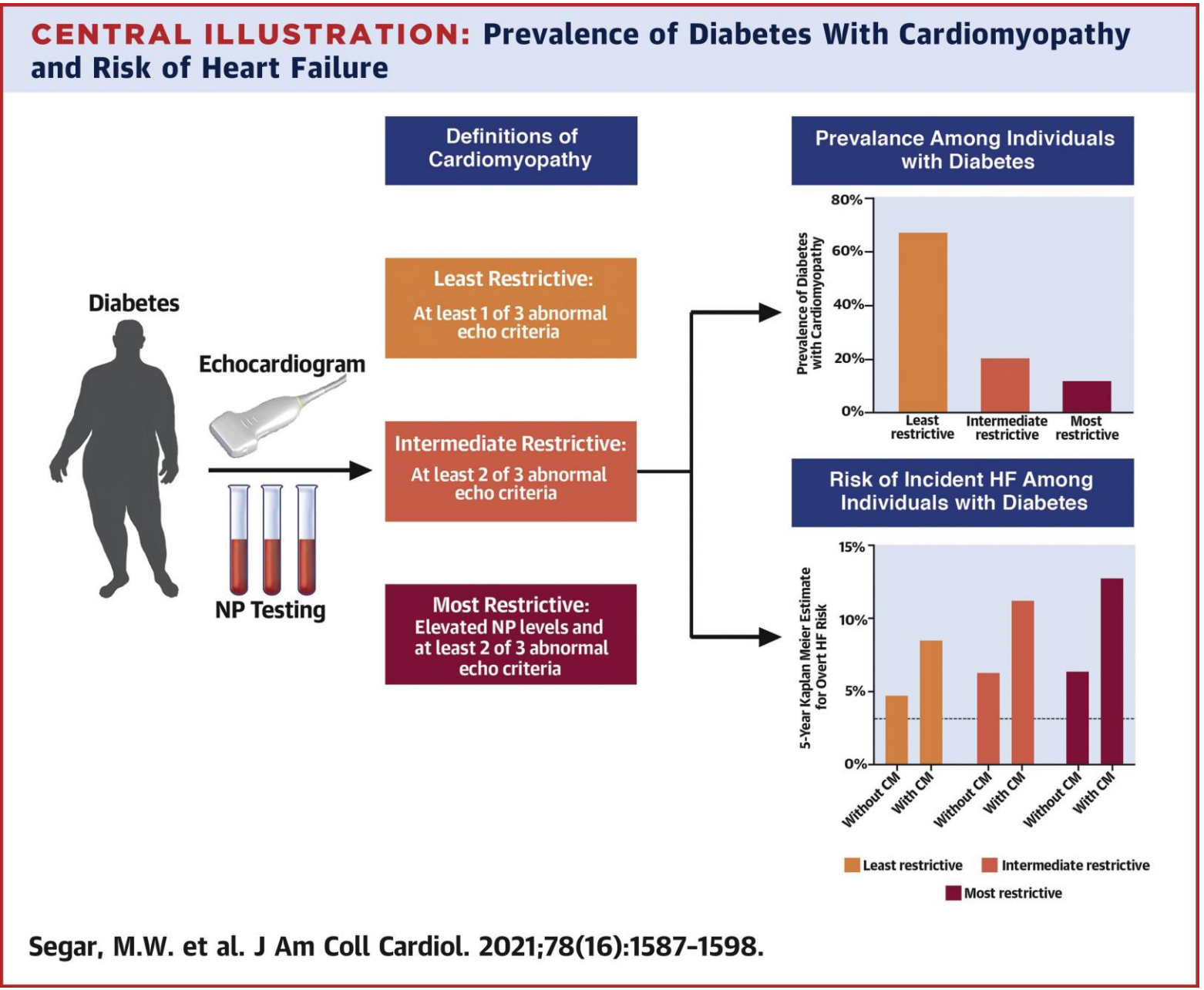
Refs.Aneja, Tang, Bansilal et al. Am Jnl of Med 121. 2008

Diabetic cardiomyopathy is defined as myocardial disease in patients with diabetes, not attributable to HTA, CAD or other cardiac disease

Maisch B, Alter P and Pankuweit S. Diabetic cardiomyopathy–fact or fiction? *Herz* 2011; 36: 102–115

Bệnh cơ tim đái tháo đường là sự bất thường cấu trúc và chức năng tim trên bệnh nhân ĐTĐ khi không có các yếu tố nguy cơ tim mạch nào khác chẳng hạn như bệnh mạch vành, tăng huyết áp và bệnh van tim

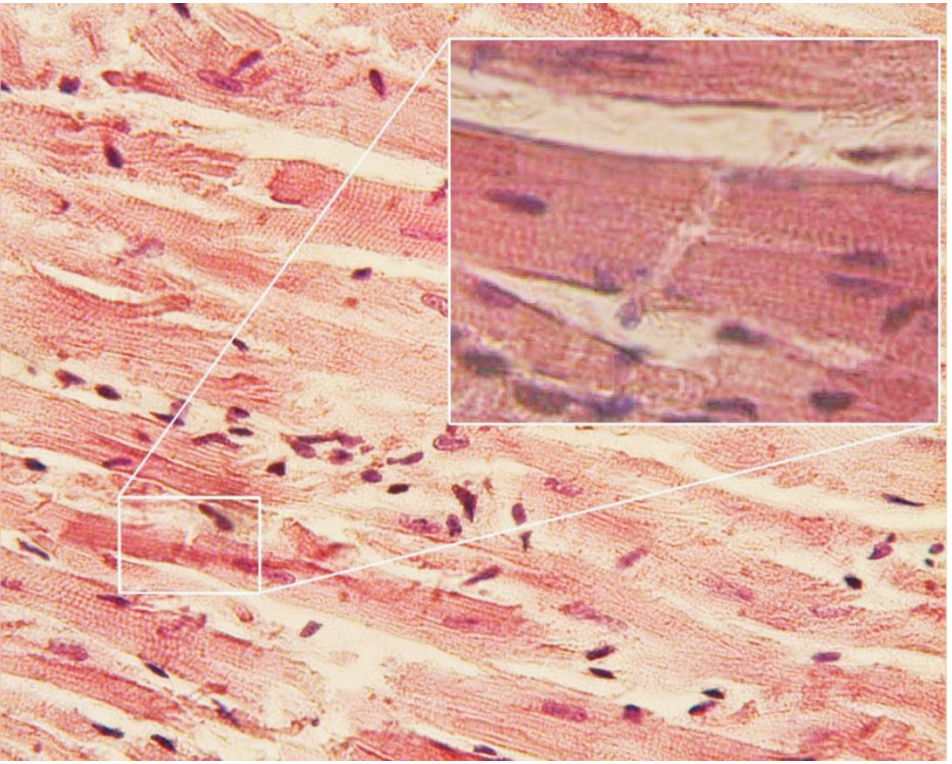
Guanghong Jia et al. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity Circ Res . 2018 February 16; 122(4): 624–638

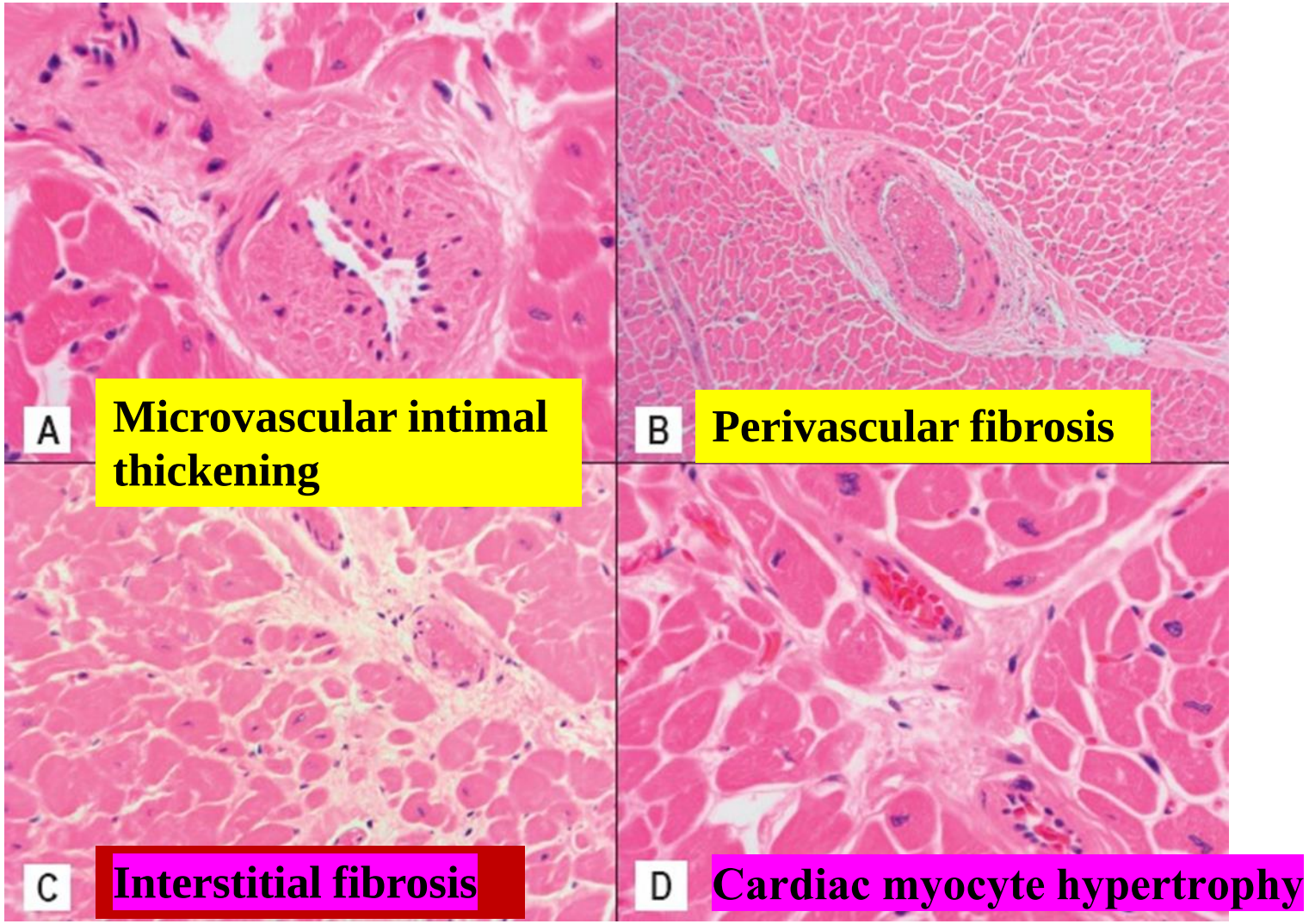



Among individuals with diabetes (2,900 of 10,208 included), the prevalence of DbCM ranged from 67.0% to 11.7% in the least and most restrictive criteria, respectively. Higher fasting glucose, body mass index, and age as well as worse kidney function were associated with higher risk of DbCM. The 5-year incidence of HF among participants with DbCM ranged from 8.4%-12.8% in the least and most restrictive definitions, respectively. Compared with euglycemia, DbCM was significantly associated with higher risk of incident HF with the highest risk observed for the most restrictive definition of DbCM (HR: 2.55 [95% CI: 1.69-3.86]; least restrictive criteria HR: 1.99 [95% CI: 1.50-2.65]). A similar pattern of results was observed across cohort studies, across sex and race subgroups, and among participants without hypertension or obesity.

# MÔ BỆNH HỌC
# Bệnh cơ tim đái tháo đường

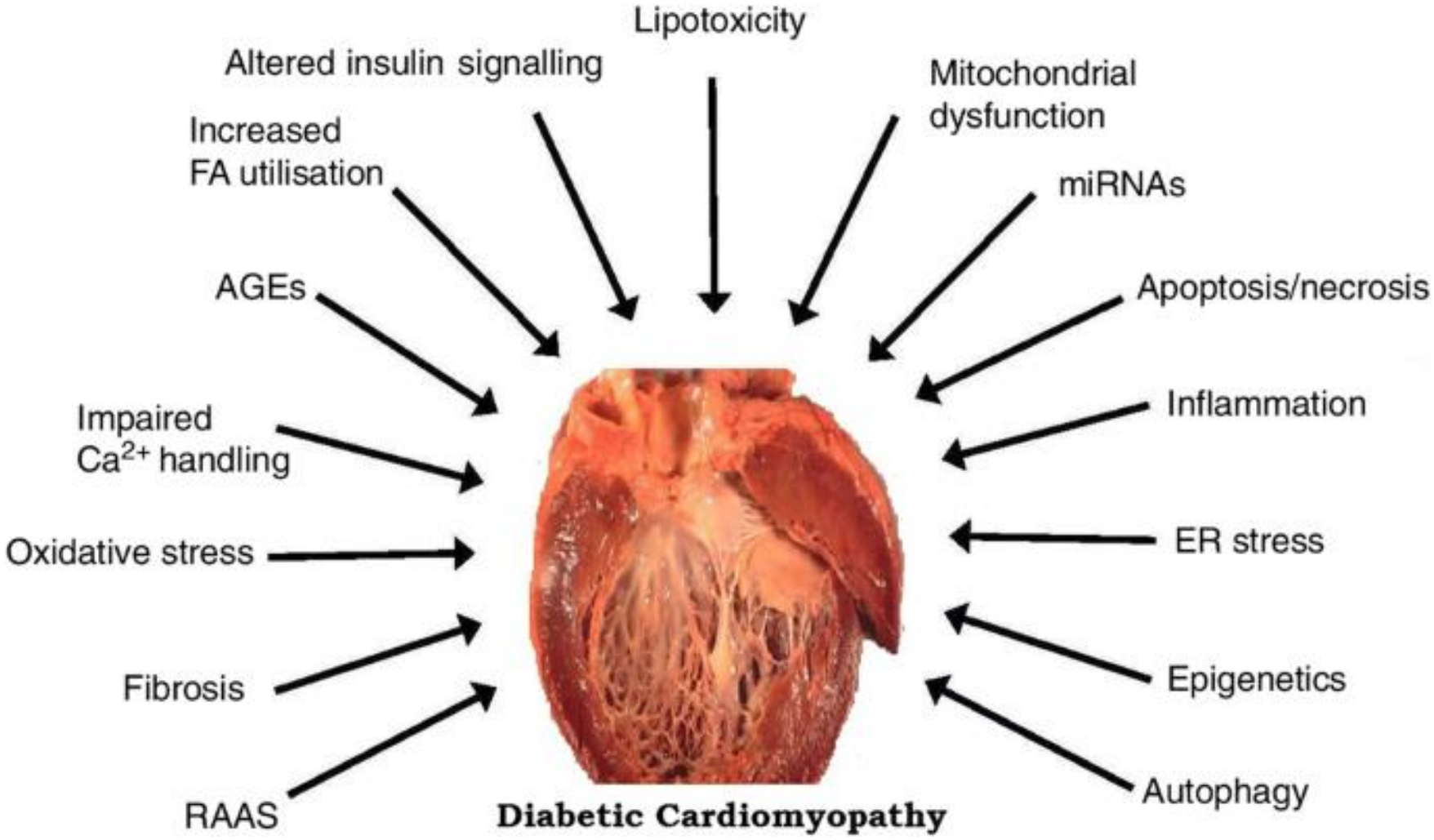
Tế bào Cơ Tim bình thường



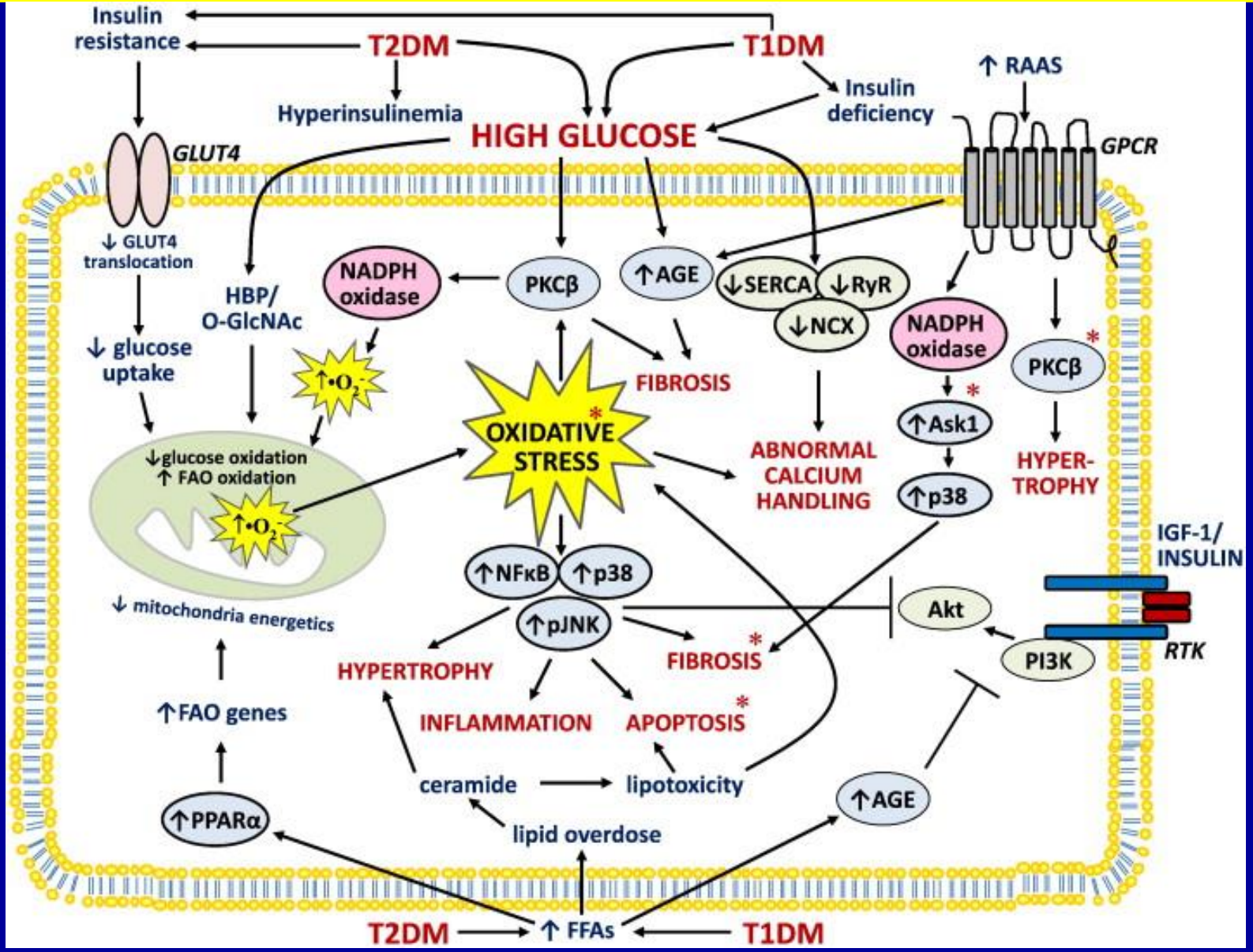


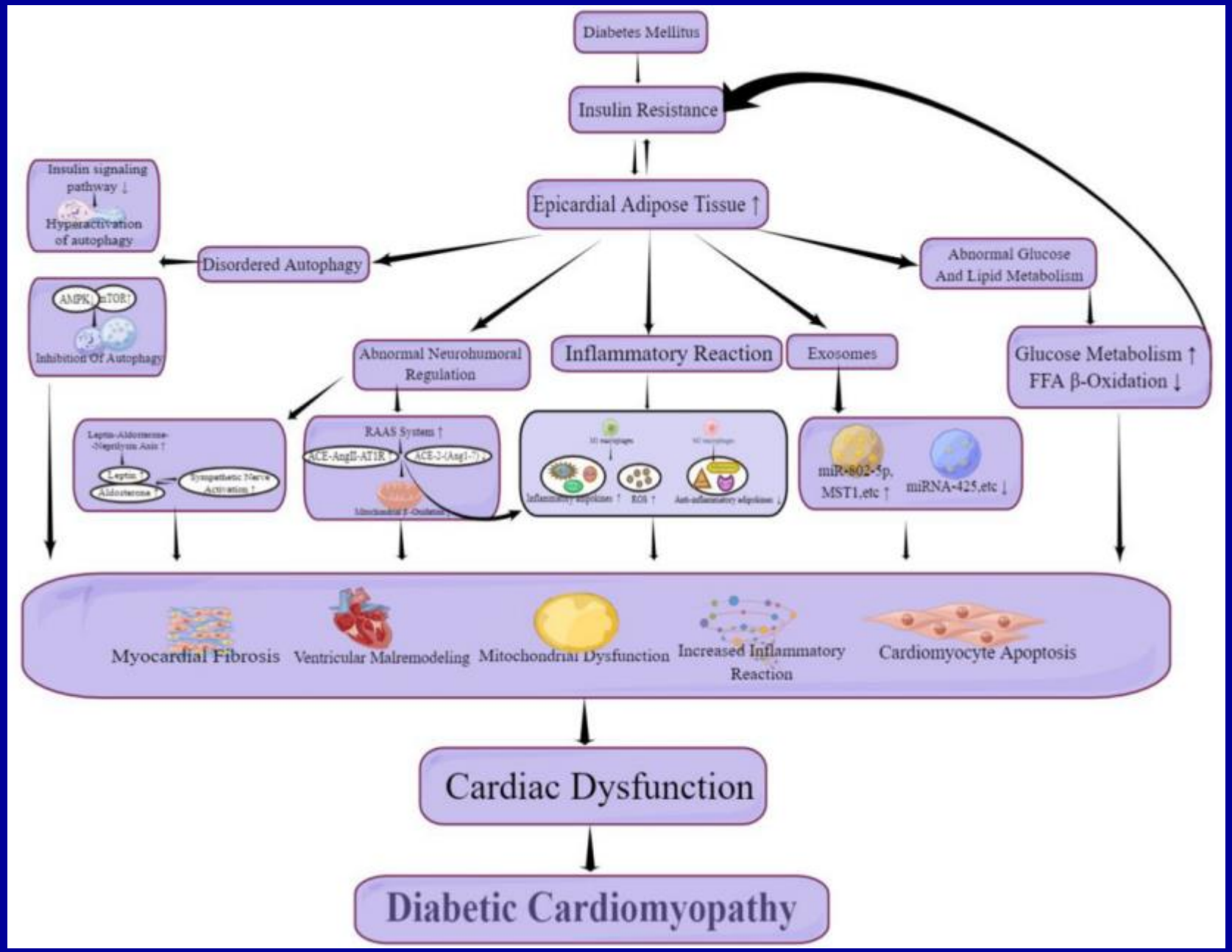

**15-year-old male with diabetes**
**no history of hypertension, congenital or valvular disease,**
**and no coronary artery atherosclerosis at autopsy.**

# Bệnh nguyên
# Bệnh cơ tim đái tháo đường



# Cơ chế bệnh sinh bệnh cơ tim ĐTĐ theo típ ĐTĐ






**Pathogenesis of diabetic cardiomyopathy.**
The relationship of diabetes mellitus, epicardial adipose tissue and cardiac dysfunction.

Biomedicines 2023, 11, 662. https://doi.org/10.3390/biomedicines11030662

# Epicardial Adipose Tissue and Diabetic Cardiomyopathy

Journal of Cardiovascular Pharmacology and Therapeutics
2023, Vol. 28 1-10
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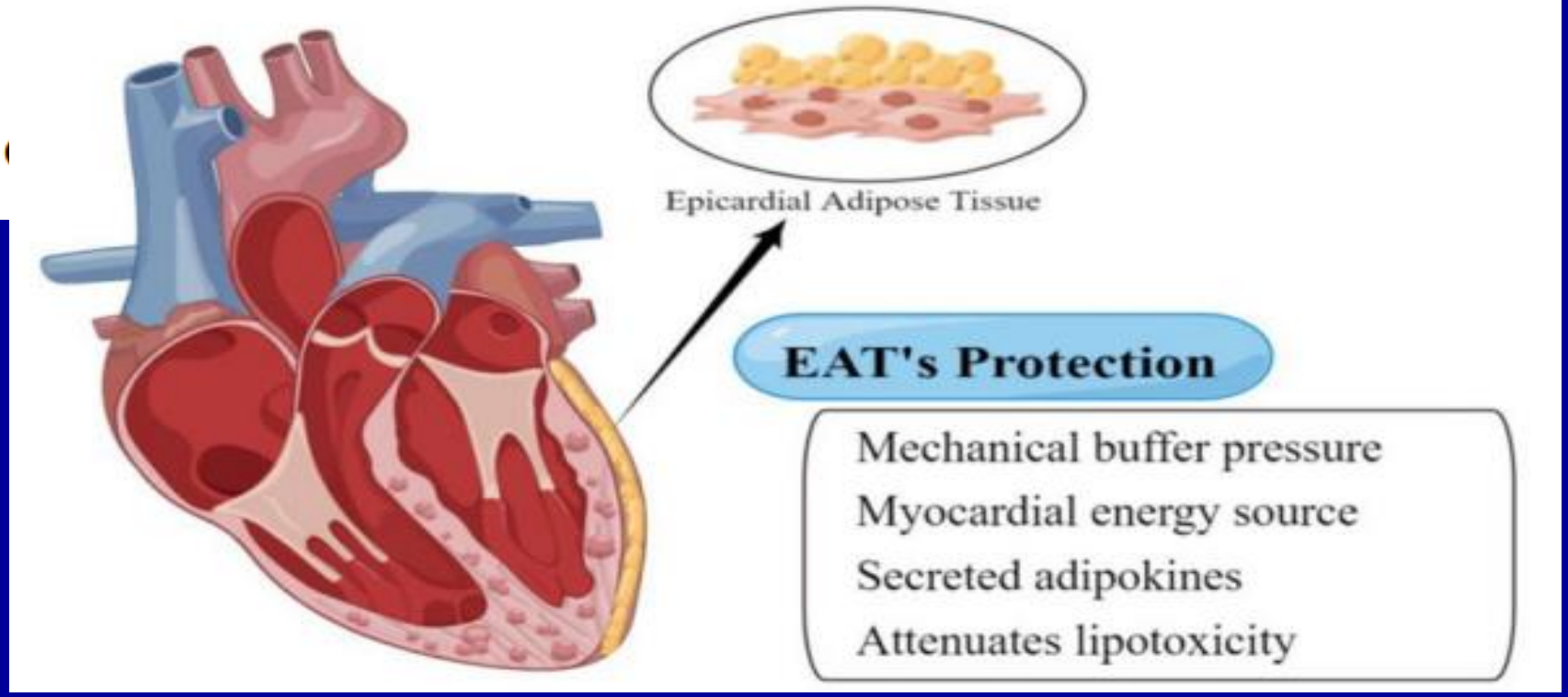
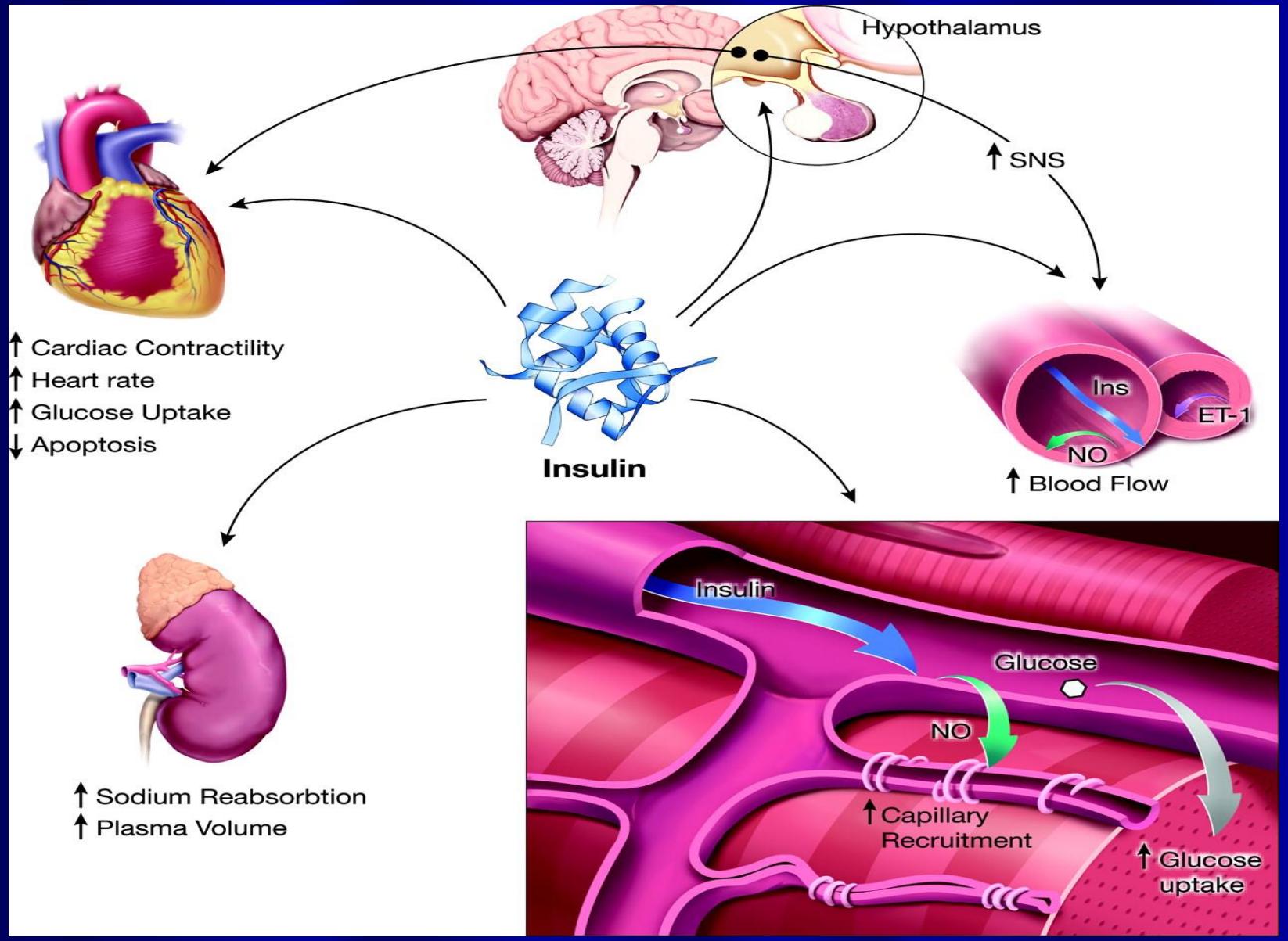
Xueyuan Yang, MM[1]




Epicardial fat, as the heart fat bank, functions as fatty tissue and is the heart's endocrine organ. The existence of diabetes affects the distribution of heart fat and promotes the secretion of adipokine. In different pathological conditions, it can promote the secretion of pro-inflammatory adipokine, reactive oxygen species, oxidative stress, and even autophagy, thus affecting cardiac function.

# Kháng Insulin Và Tim Mạch




Muniyappa R et al. Endocrine Reviews 2007;28:463-491

ENDOCRINE REVIEWS

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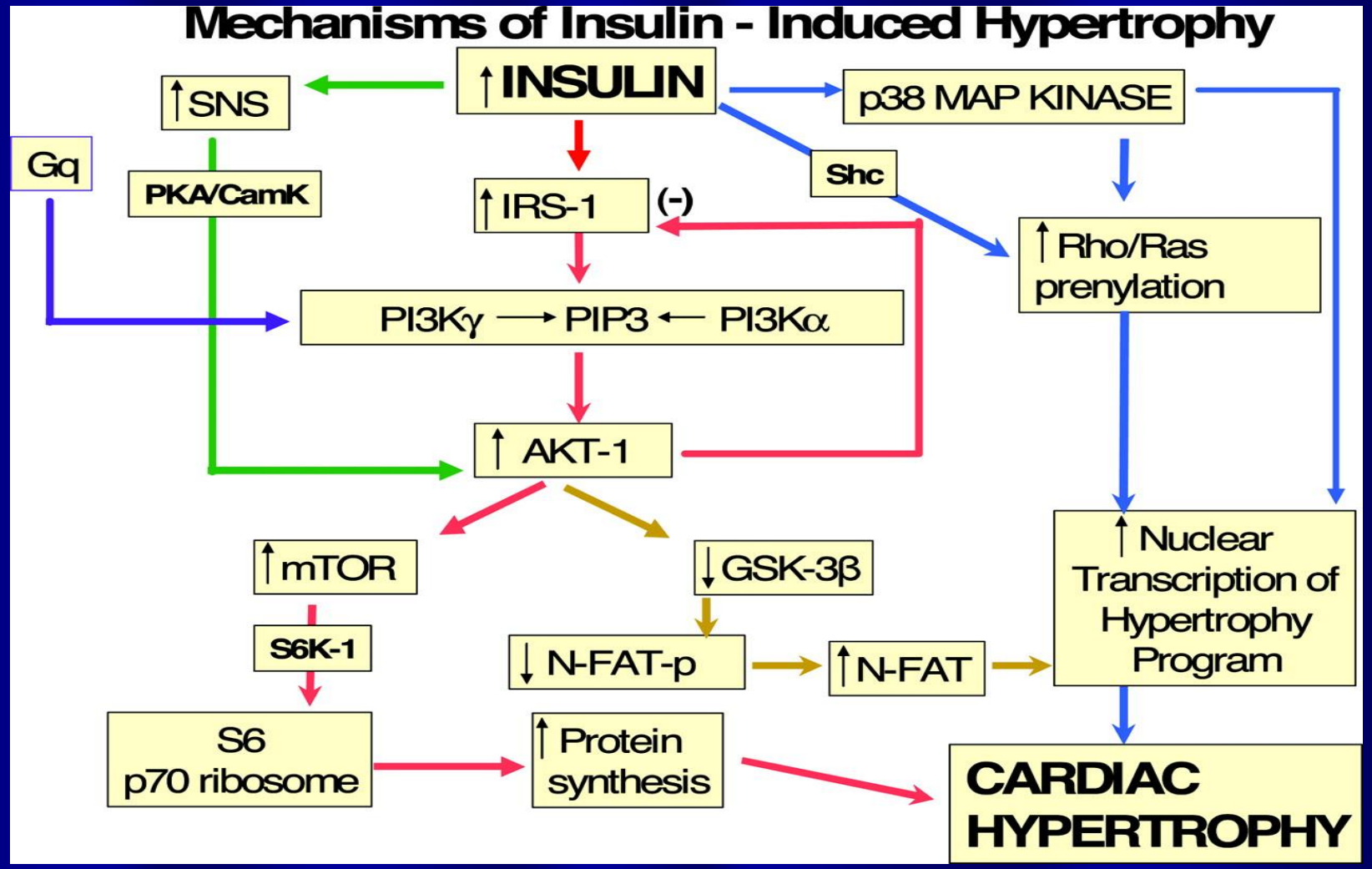
**Figure 3. Alternative pathways whereby compensatory hyperinsulinemia contributes to myocyte hypertrophy through the sympathetic nervous system activation and MAP kinase/ERK pathways at a time when insulin receptor mediated Akt-1 activation is impaired.**




Poornima I et al. Circulation Research 2006;98:596-605

American Heart Association

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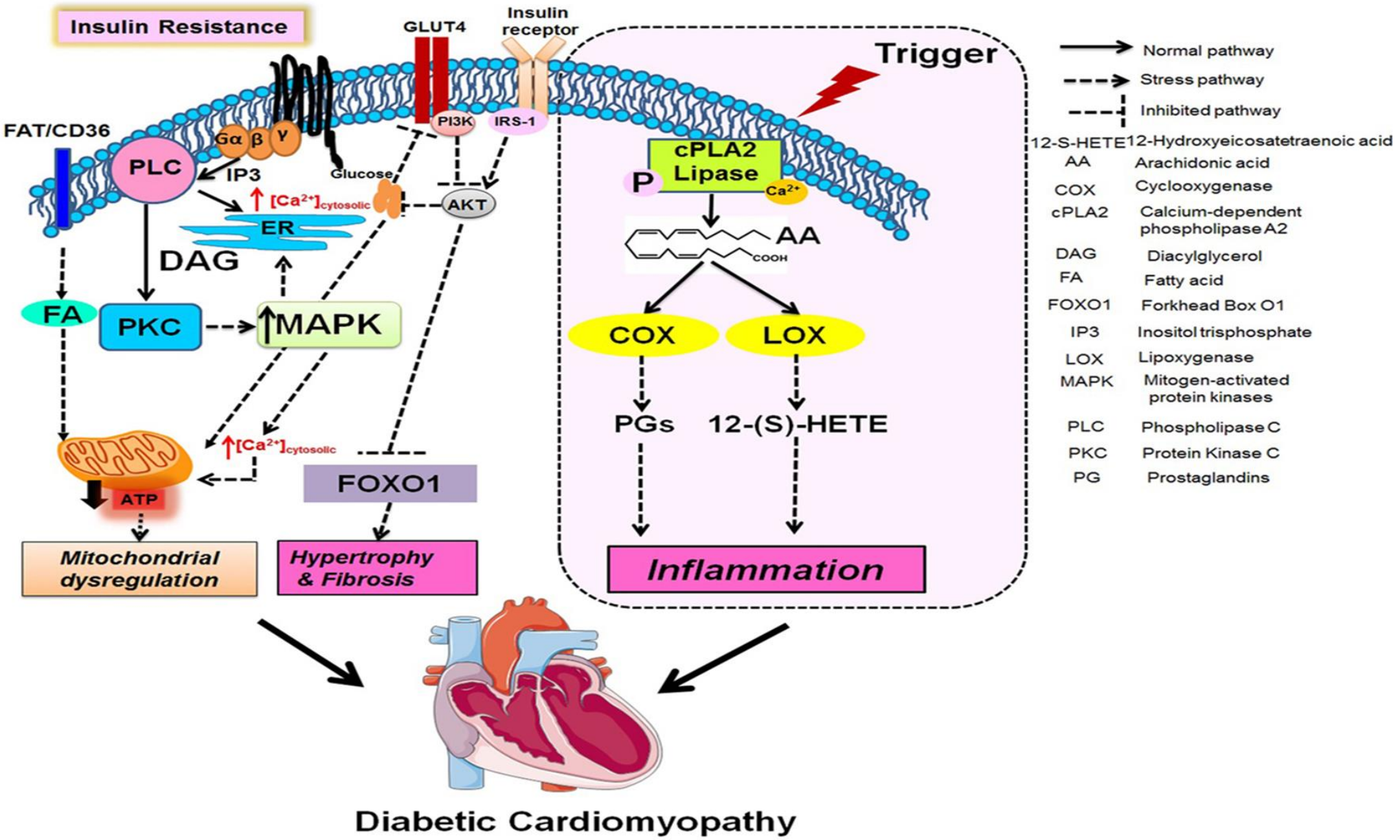
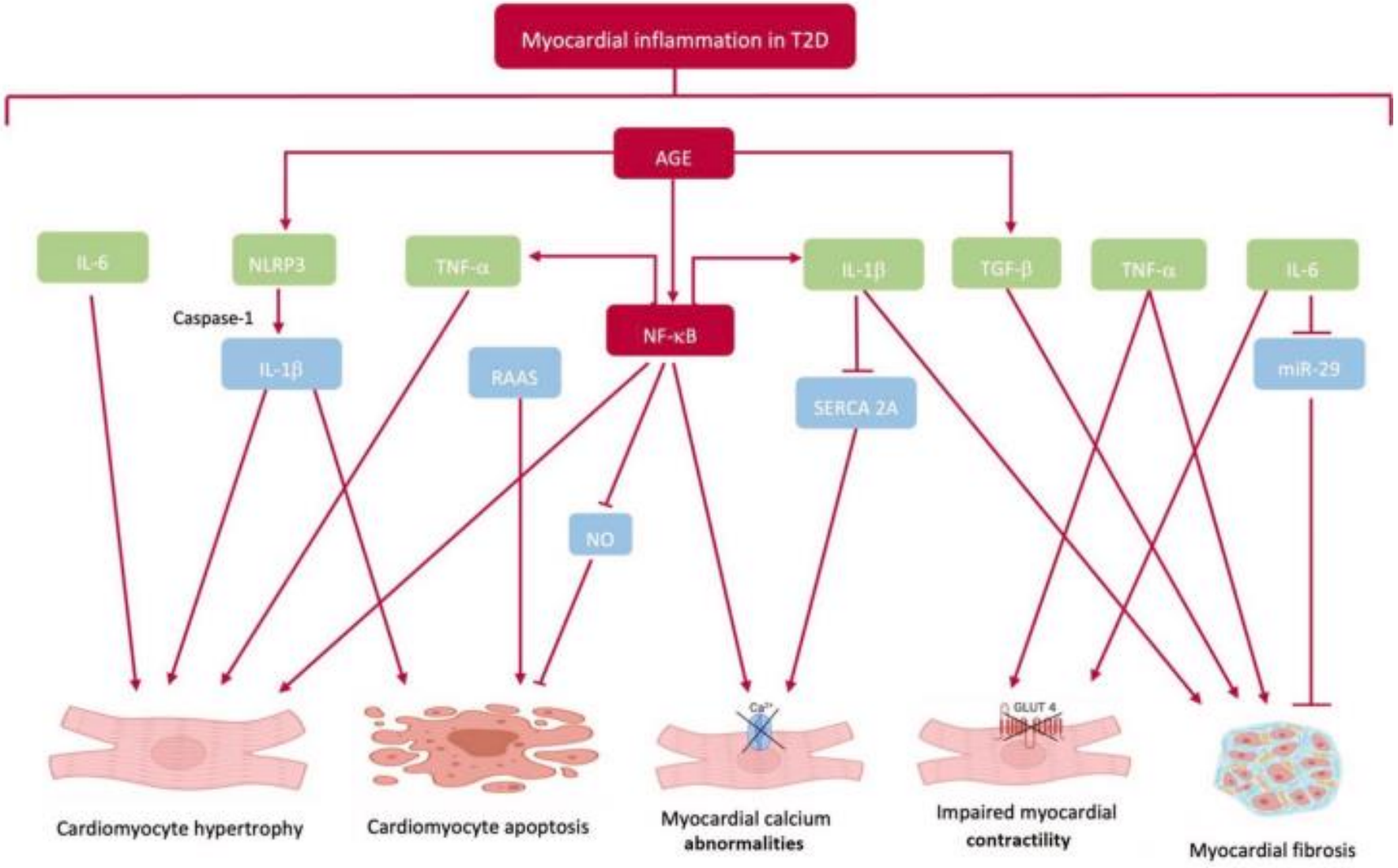
# Kháng Insulin và Phản ứng Viêm



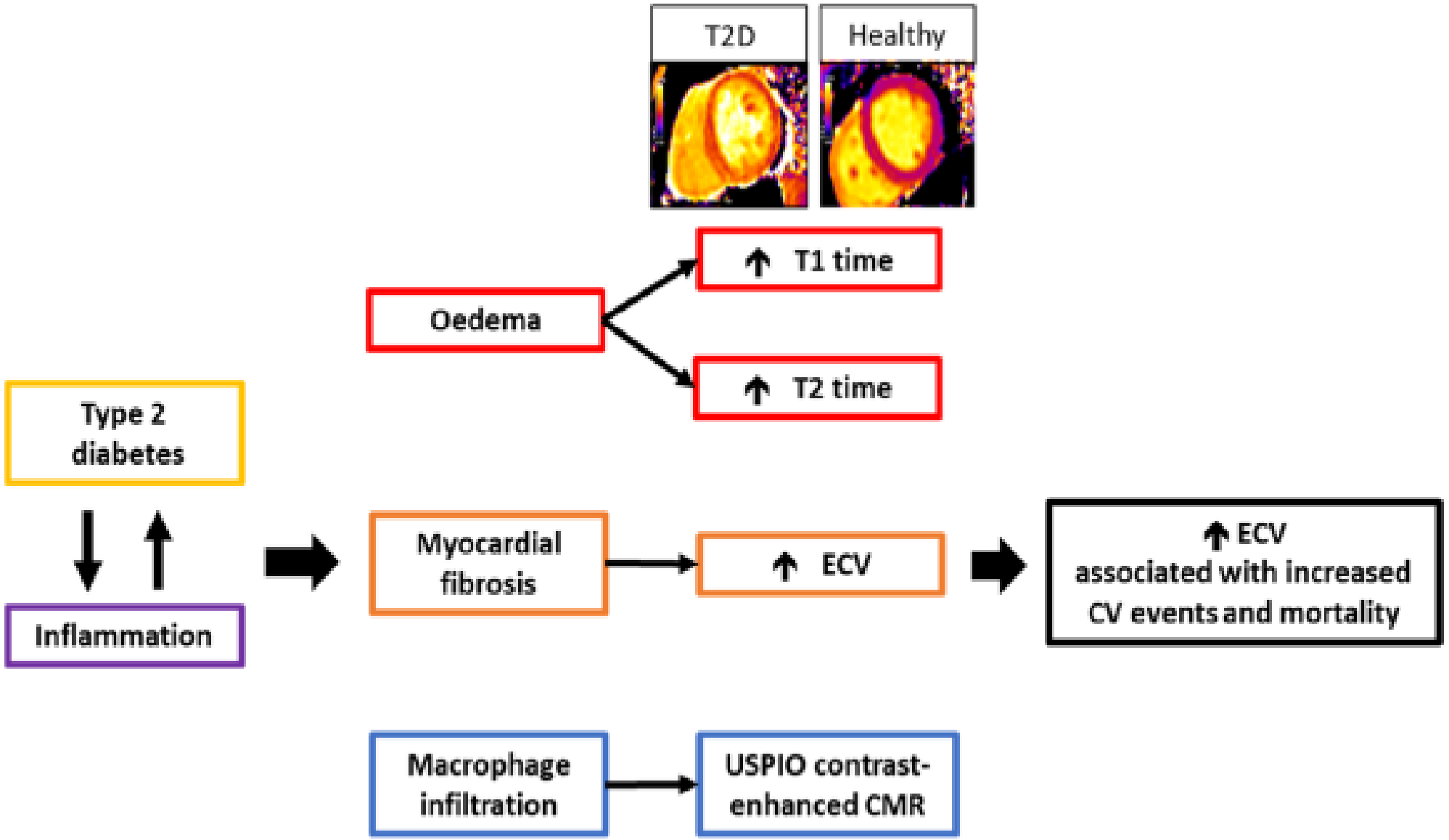



Tóm tắt các con đường viêm dẫn đến rối loạn tái tạo và rối loạn chức năng tim trong bệnh CTĐTĐ.
Sự phóng thích cytokine liên quan đến ĐTĐ chủ yếu thông qua hai cơ chế: kích hoạt NF-κB và tích lũy AGE.
Các chất trung gian trực tiếp kích thích các nguyên bào sợi dẫn đến xơ hóa, ức chế sự vận chuyển của calci gây suy giảm khả năng co bóp và trực tiếp kích thích quá trình chết và phì đại tế bào cơ tim.

**Table 1.** A summary of clinical studies evaluating the predictive values of serum biomarkers for CVD in T2D.

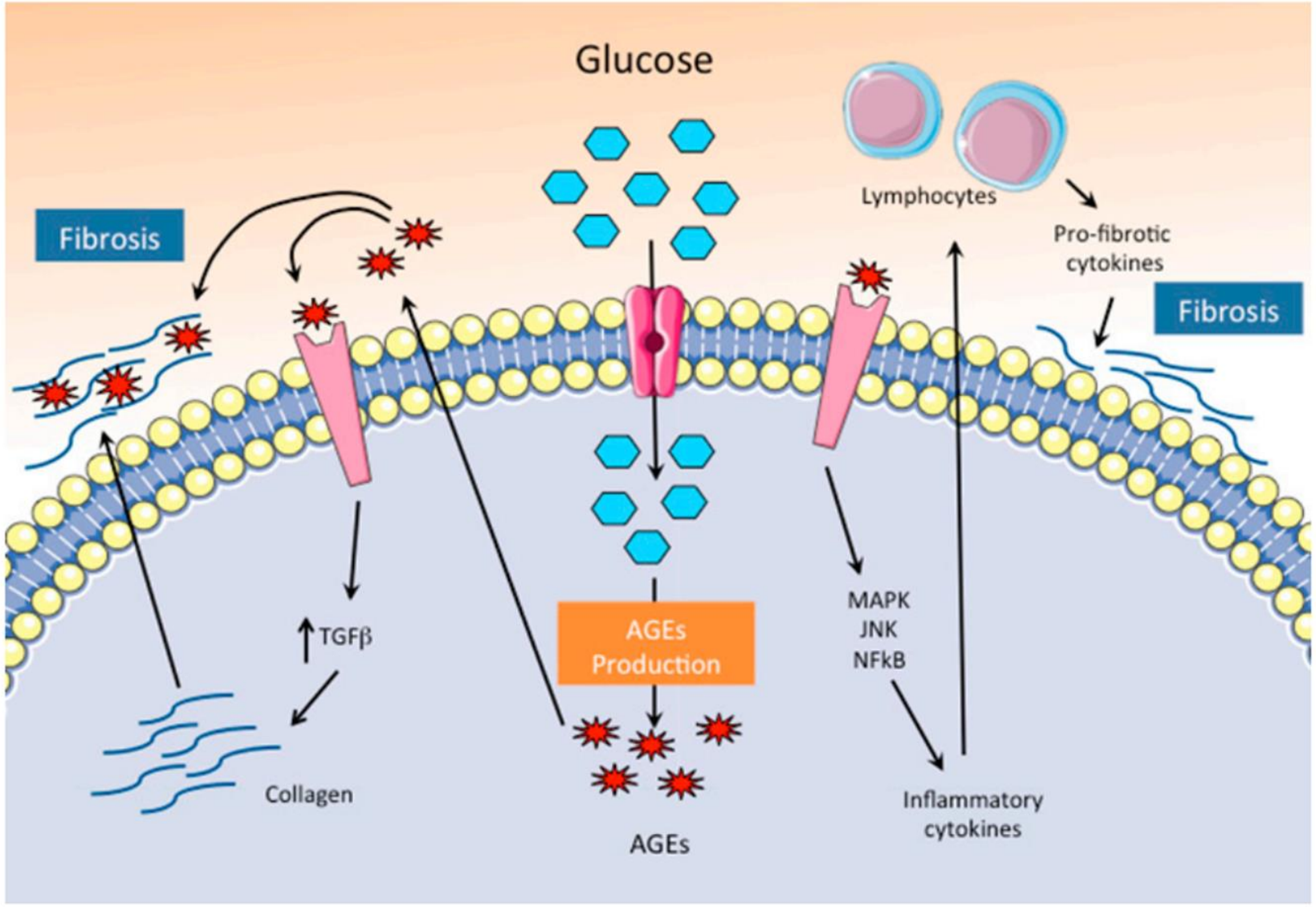
| Author | Biomarker | Sample details | Main findings |
|---|---|---|---|
| Soinio *et al.*[57] | CRP | $N = 1059$<br>All T2D (mean age 57 years; 55% male) | ↑ CRP associated with ↑ CHD mortality [RR 1.72 (1.23–2.41), $p < 0.002$] |
| Bruno *et al.*[58] | | $N = 2381$<br>All T2D (mean age 68 years; 50% males) | ↑ CRP (>4.4 mg/dl) associated with ↑ 5-year CV mortality [RR 1.76 (1.09–2.82), $p < 0.015$] |
| Herder *et al.*[59] | IL-6 | $N = 1072$<br>All T2D (median age 65 years; 54% males) | ↑ IL-6 (>7.44 pg/ml) associated with ↑ risk for CV events [a] [HR 1.90 (1.07–3.40), $p = 0.009$; follow-up of 5 years] |
| Ofstad *et al.*[60] | | $N = 135$<br>All T2D (mean age 59 years; 65% males) | ↑ IL-6 (>0.6 pg/ml) associated with ↑ risk of MACE [b] [HR 15.8 (2.2–115.8), $p = 0.007$; mean follow-up of 8.6 years] |
| Kilhovd *et al.*[61] | AGE | $N = 87$<br>61% T2D (mean age 59 years; 60% males) | ↑ AGE in T2D *versus* controls (7.4 *versus* 4.2 U/ml, $p < 0.0001$)<br>↑ AGE in those with T2D and CHD *versus* those without CHD (8.1 *versus* 7.1 U/ml, $p = 0.03$) |
| Kiuchi *et al.*[62] | | $N = 83$<br>51% T2D (mean age 64 years; 76% males) | ↑ AGE in those with T2D and obstructive CAD *versus* those without CAD (5.5 *versus* 2.8 mU/ml)<br>↑ AGE concentrations in those with more severe arteriosclerosis (7.2 *versus* 3.4 mU/ml) |
| Tuttle *et al.*[63] | TNF-α | $N = 63$<br>51% T2D (mean age 60 years; all females) | No significant difference in TNF-α concentrations between those with T2D and CVD |
| Dinh *et al.*[64] | | $N = 41$<br>67% T2D (mean age 65 years; 70.7% males) | ↑ TNF-α levels in those with LV diastolic dysfunction (E/e' ratio > 15) *versus* those without (7.2 *versus* 3.1 pg/ml, $p < 0.001$) |
| Hotta *et al.*[65] | Adiponectin | $N = 265$<br>69% T2D and prior MI (mean age 60 years; 69% males) | ↓ Adiponectin levels in T2D *versus* controls (5.7 *versus* 7.9 μg/ml, $p < 0.001$, in men)<br>↓ Adiponectin levels in those with T2D and CAD *versus* those with T2D without CAD (4.0 *versus* 6.6 μg/ml) |
| Mehta *et al.*[66] | | $N = 906$<br>21% T2D (mean age 55 years; 54% males) | ↓ Adiponectin levels associated with coronary artery calcification in women [OR 0.32 (0.13–0.81)], but not men |

**Các nghiên cứu lâm sàng các chất chỉ điểm sinh học về tim mạch trong ĐTĐ típ 2**

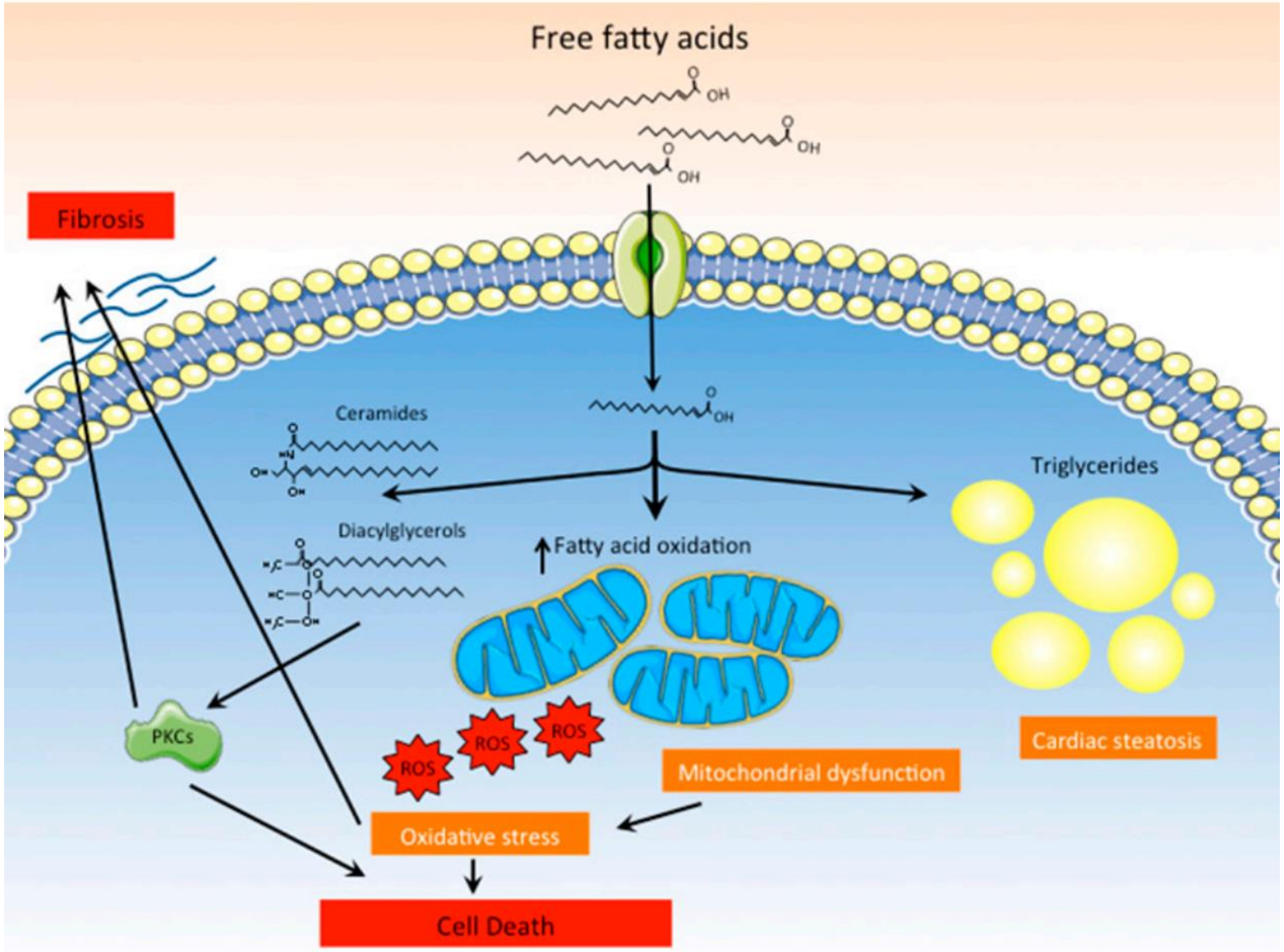


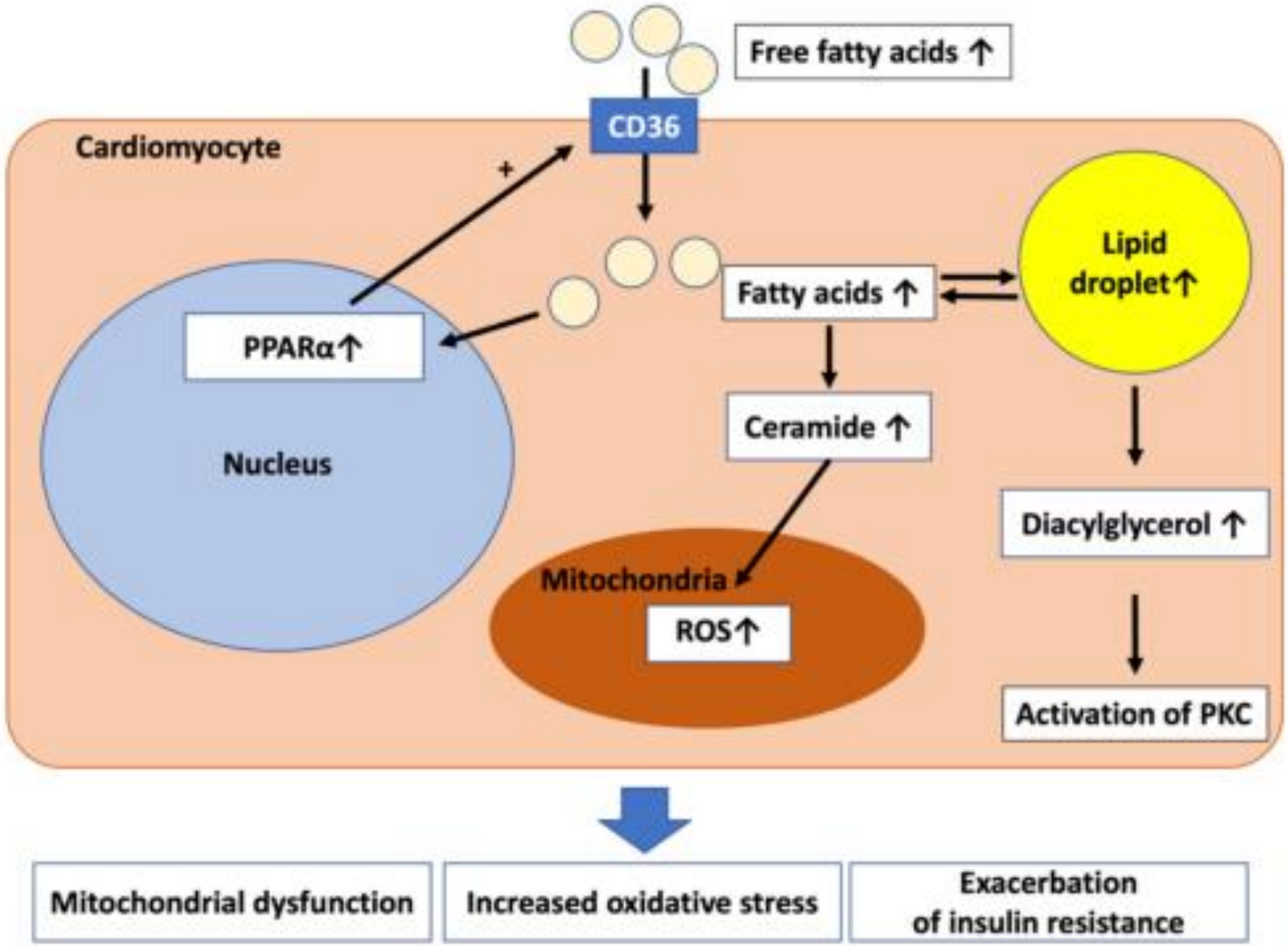

Bệnh ĐTĐ típ 2 kèm hiện tương viêm gây phù nề, xơ hóa cơ tim và thâm nhiễm đại thực bào phát hiện qua CMR. Tăng thể tích ngoại bào (ECV) liên quan các biến cố và tử vong tim

# Tăng glucose máu và Bệnh Cơ Tim ĐTĐ



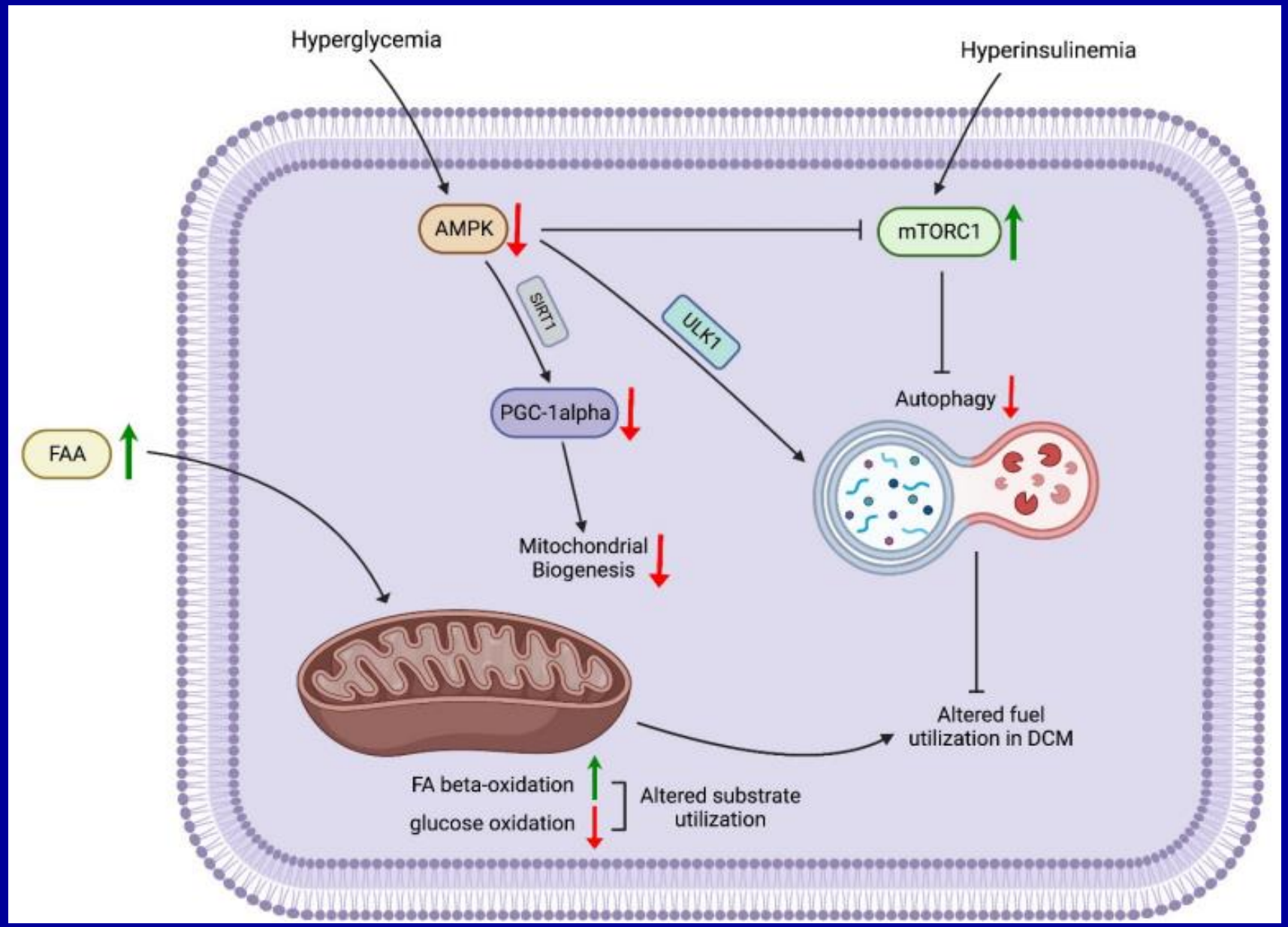
# Tăng Acid béo tự do (FFA) và Bệnh CTĐTĐ






Sơ đồ nhiễm độc lipid tại cơ tim trong bệnh cơ tim đái tháo đường

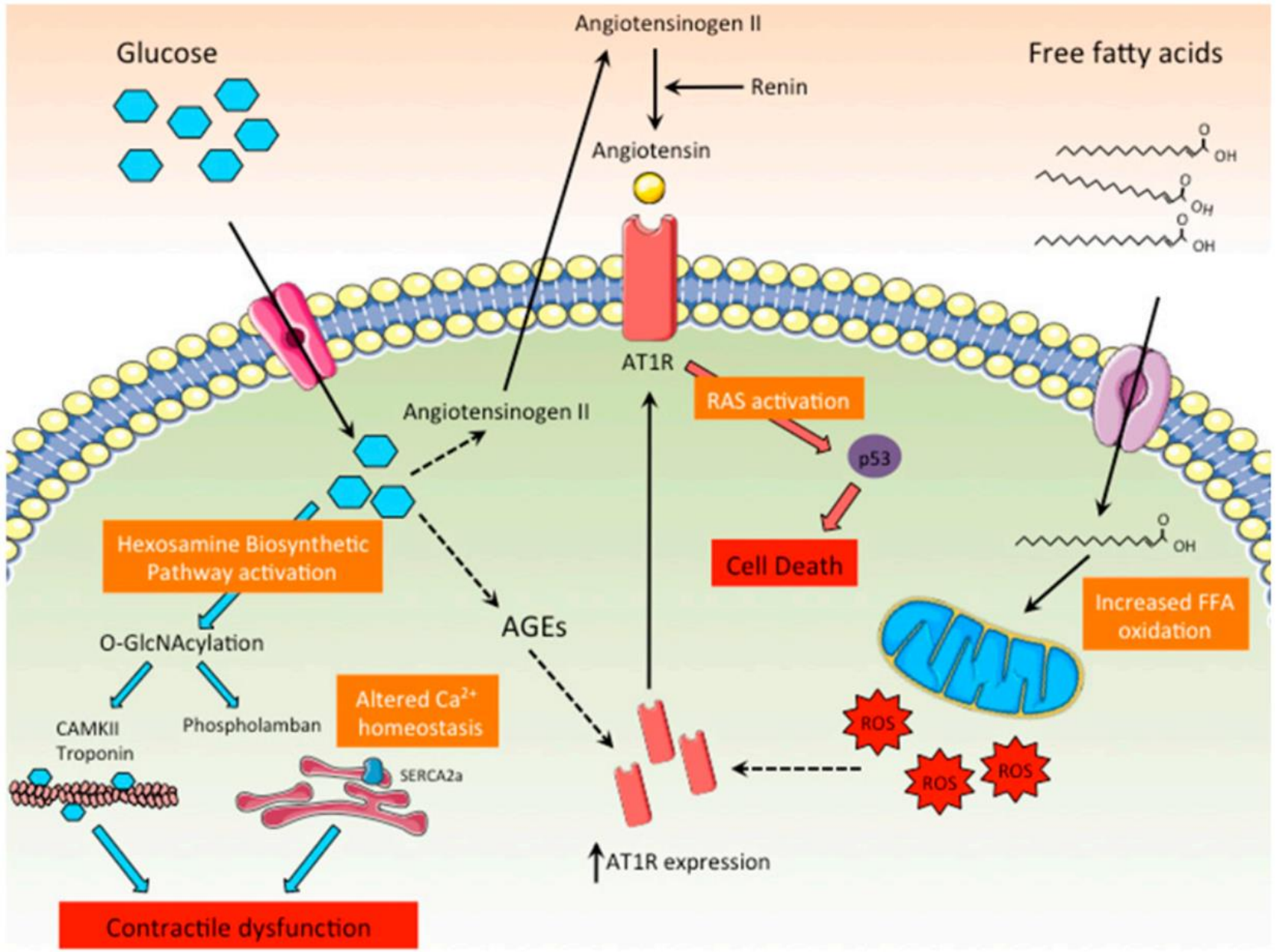
Int. J. Mol. Sci. 2022, 23, 3587. https://doi.org/10.3390/ijms23073587

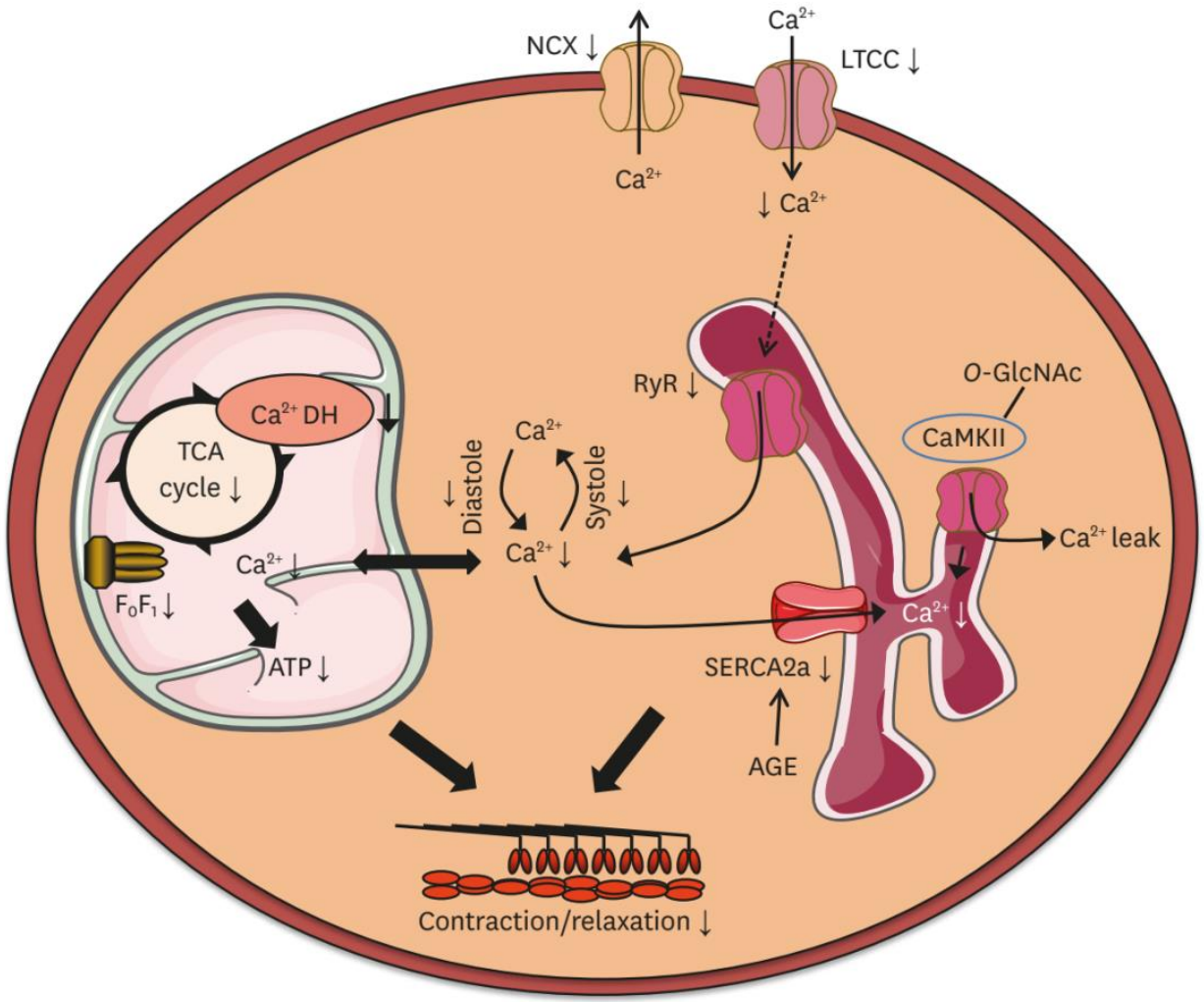



Impaired nutrient-sensing signaling, dysregulated autophagy, impaired mitochondrial energetics, and altered fuel utilization in the pathogenesis of diabetic cardiomyopathy

Biomedicines 2023, 11, 662.https://doi.org/10.3390/biomedicines11030662

# RAAS và Bệnh Cơ Tim ĐTĐ





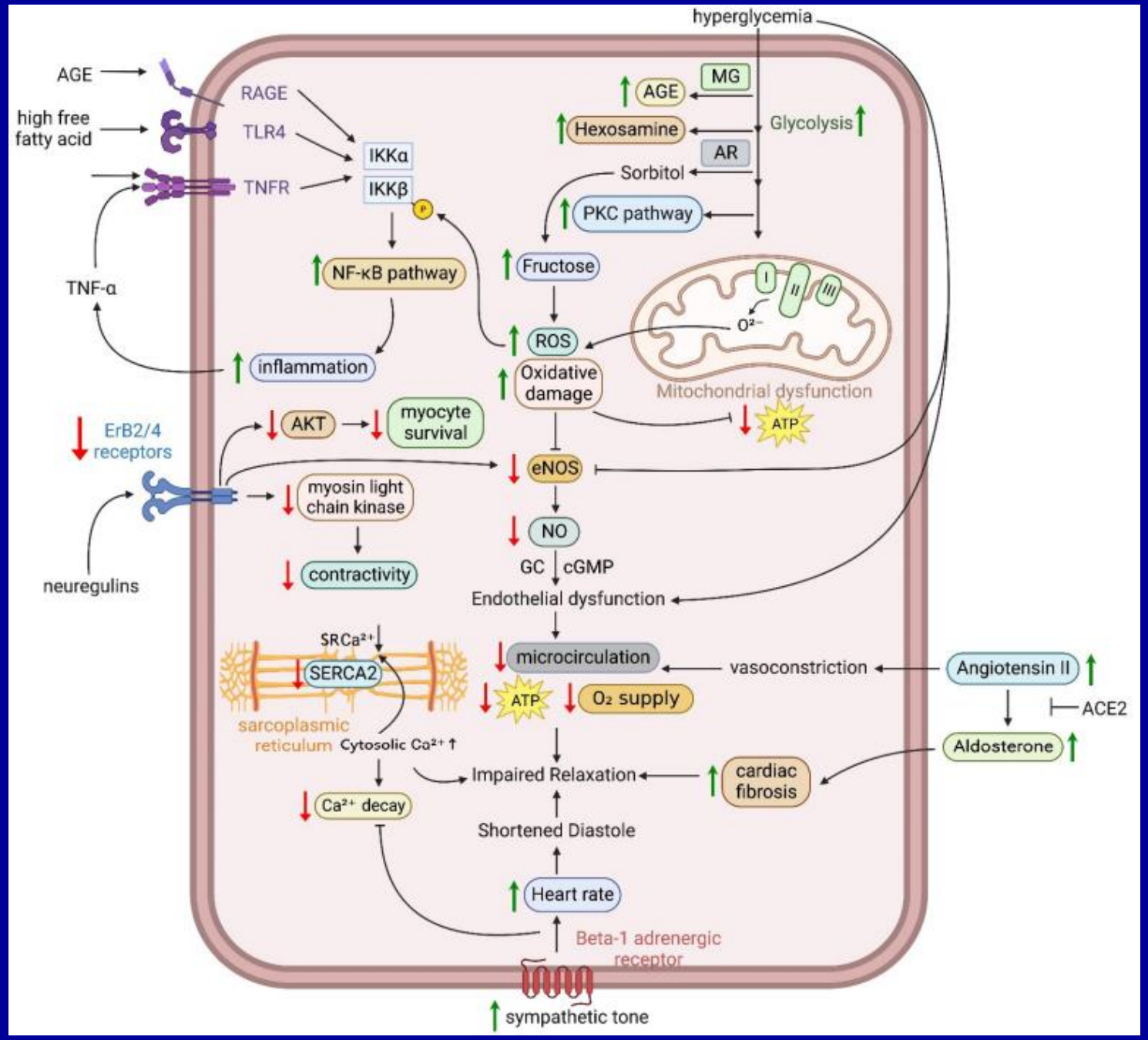

# BẤT THƯỜNG TRAO ĐỔI CALCI CƠ TIM

Suy giảm luồng Ca 2+ vào và ra TB cơ tim

Suy giảm phóng thích và tái hấp thu Ca 2+ của hệ vỏng trạng nội mô

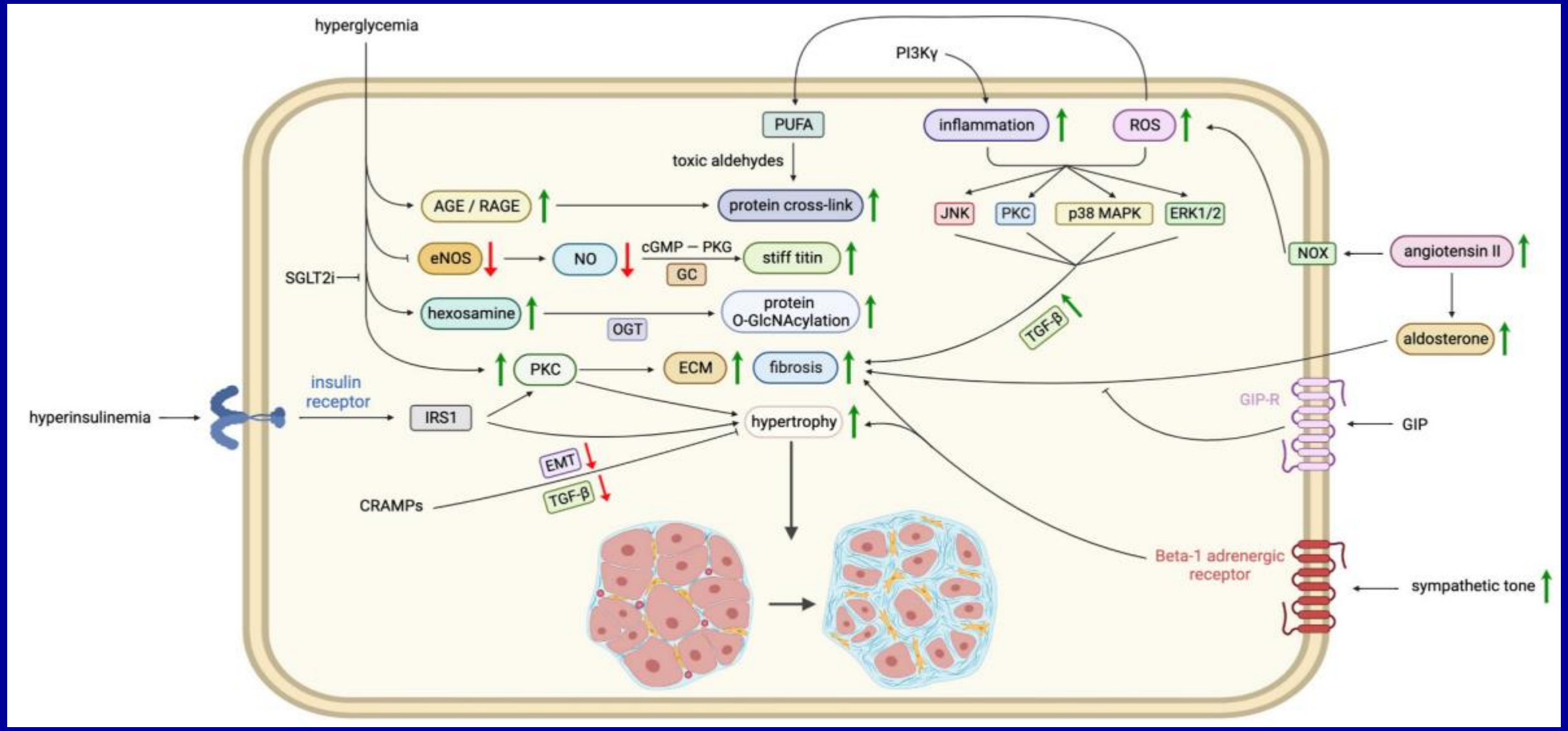
Suy giảm hấp thu Ca 2+ của ty thể, sau đó làm

Suy giảm khả năng tái tạo ATP và góp phần gây RLCN tâm trương & tâm thu ở bệnh cơ tim ĐTĐ.



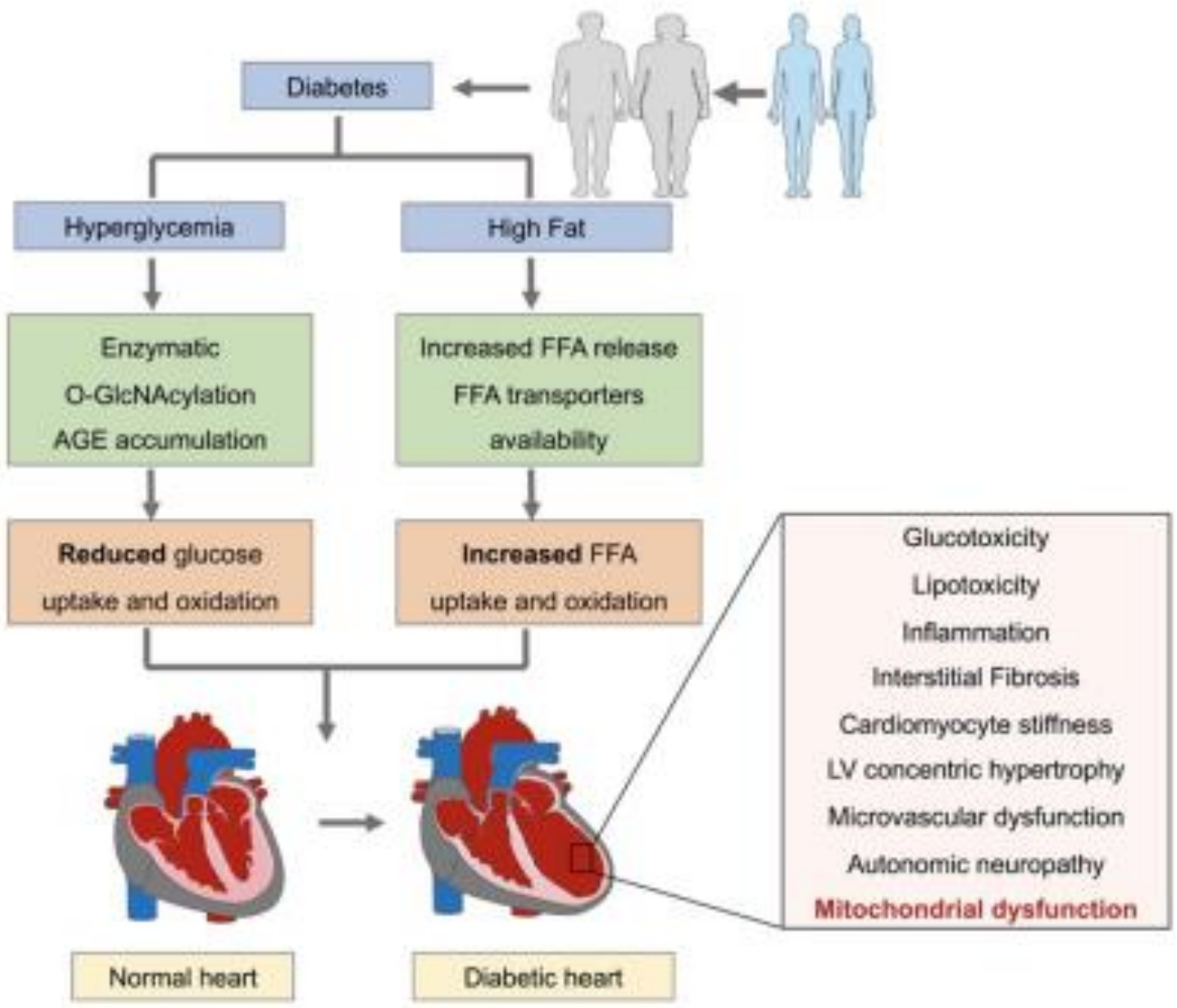

Oxidative stress, inflammation, impaired calcium homeostasis, abnormal endothelial function and nitric oxide production, aberrant epidermal growth factor receptor singling, and activation of the renin–angiotensin–aldosterone and sympathetic systems in the pathogenesis of diabetic cardiomyopathy

Biomedicines 2023, 11, 662. https://doi.org/10.3390/biomedicines11030662




The pathogenesis of extracellular matrix (ECM) accumulation and fibrosis in diabetic cardiomyopathy

Biomedicines 2023, 11, 662. https://doi.org/10.3390/biomedicines11030662



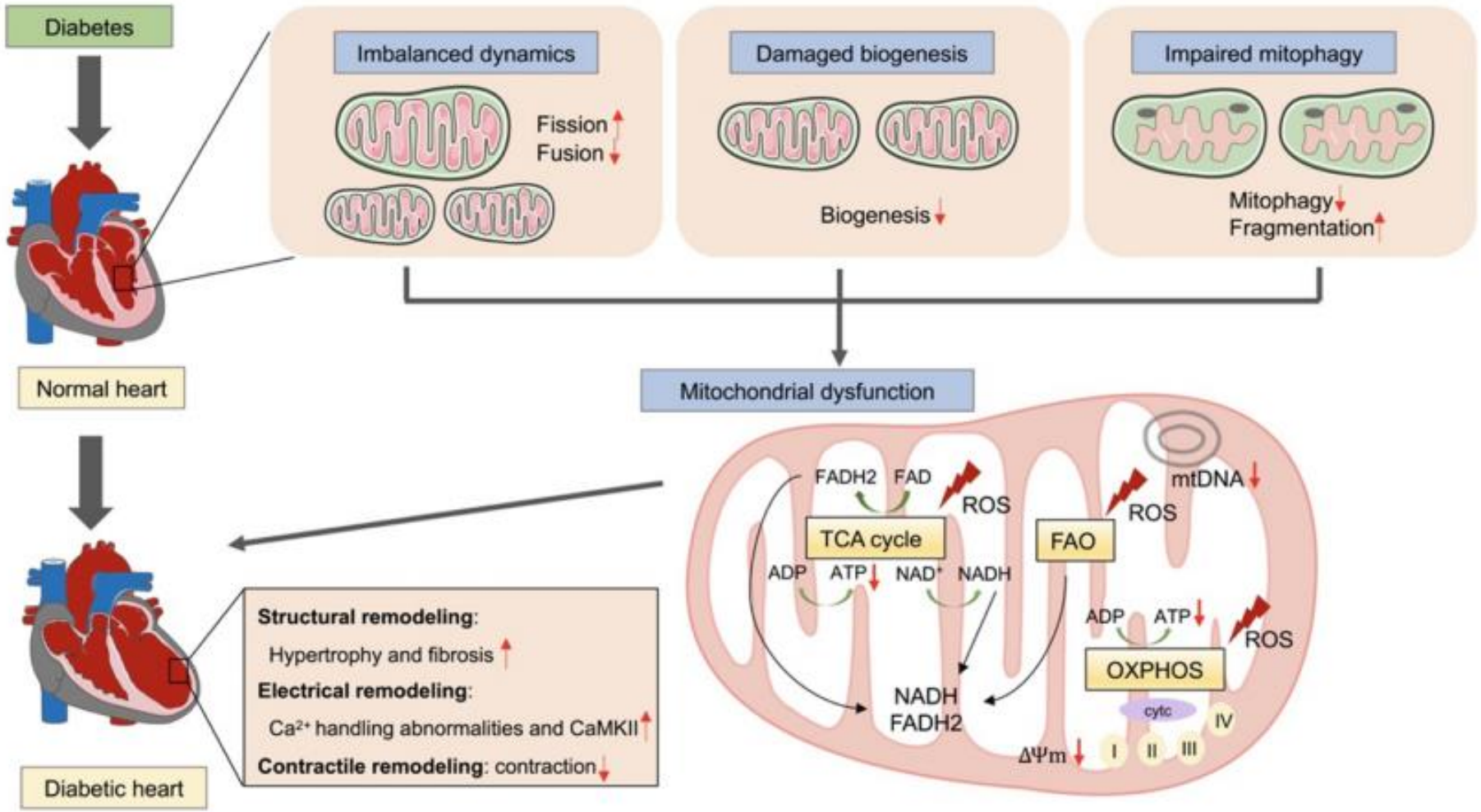

## Tái tạo chuyển hóa TB cơ tim để đáp ứng với bệnh ĐTĐ.

Gia tăng nồng độ G và FFA trên tim ĐTĐ dẫn đến

1.Giảm thu nhận và oxy hóa Glucose

2. Tăng thu nhận và oxy hóa FFA.

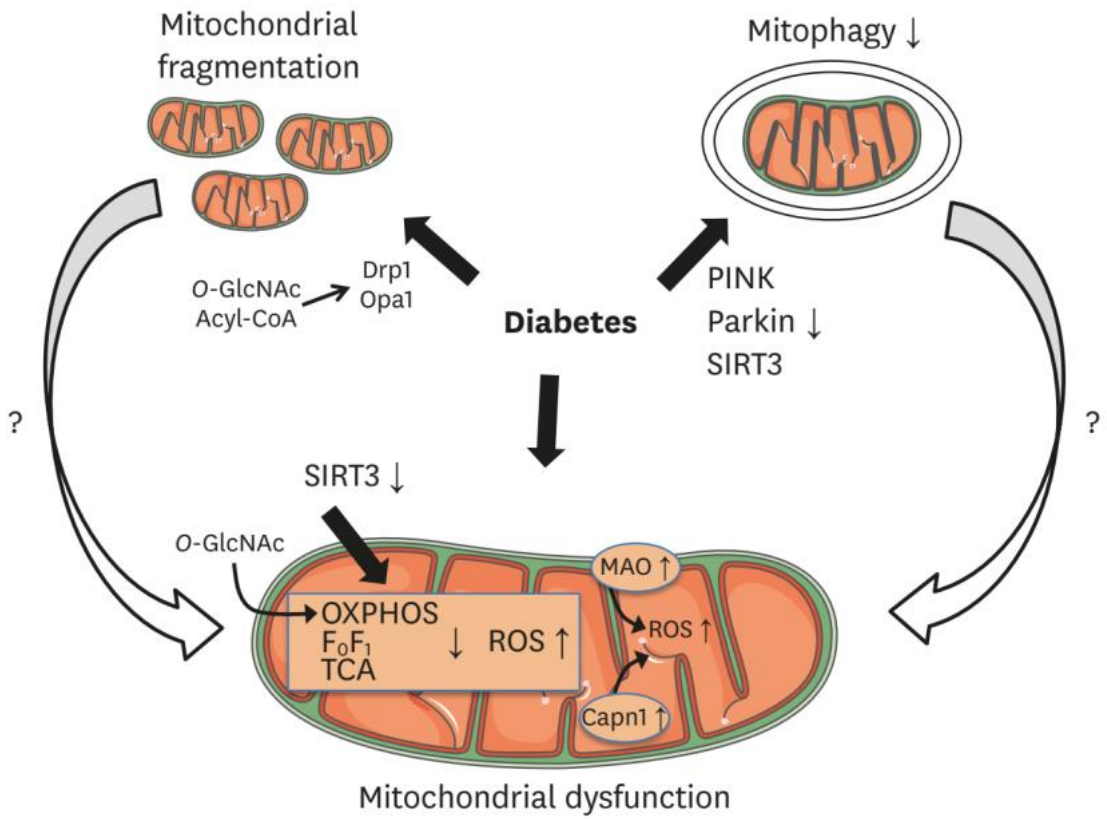
Sự rối loạn chuyển hóa này sau cùng góp phần gây ra các Rối loạn về cấu trúc, điện học và chức năng cơ Tim.




**Vai trò của RLCN ty thể trong sự phát triển của bệnh cơ tim ĐTĐ.**

Trên tim Bn ĐTĐ, ty thể bị mất Cân bằng về động lực học, quá trình sinh học bị hư hỏng và suy giảm chức năng. Ngược lại, RLCN ty thể có thể do giảm sản xuất ATP và tổn thương do ROS, dẫn đến RL cấu trúc, điện học và chức năng tim.

# Cơ chế mới về ty thể góp phần vào bệnh tim đái tháo đường

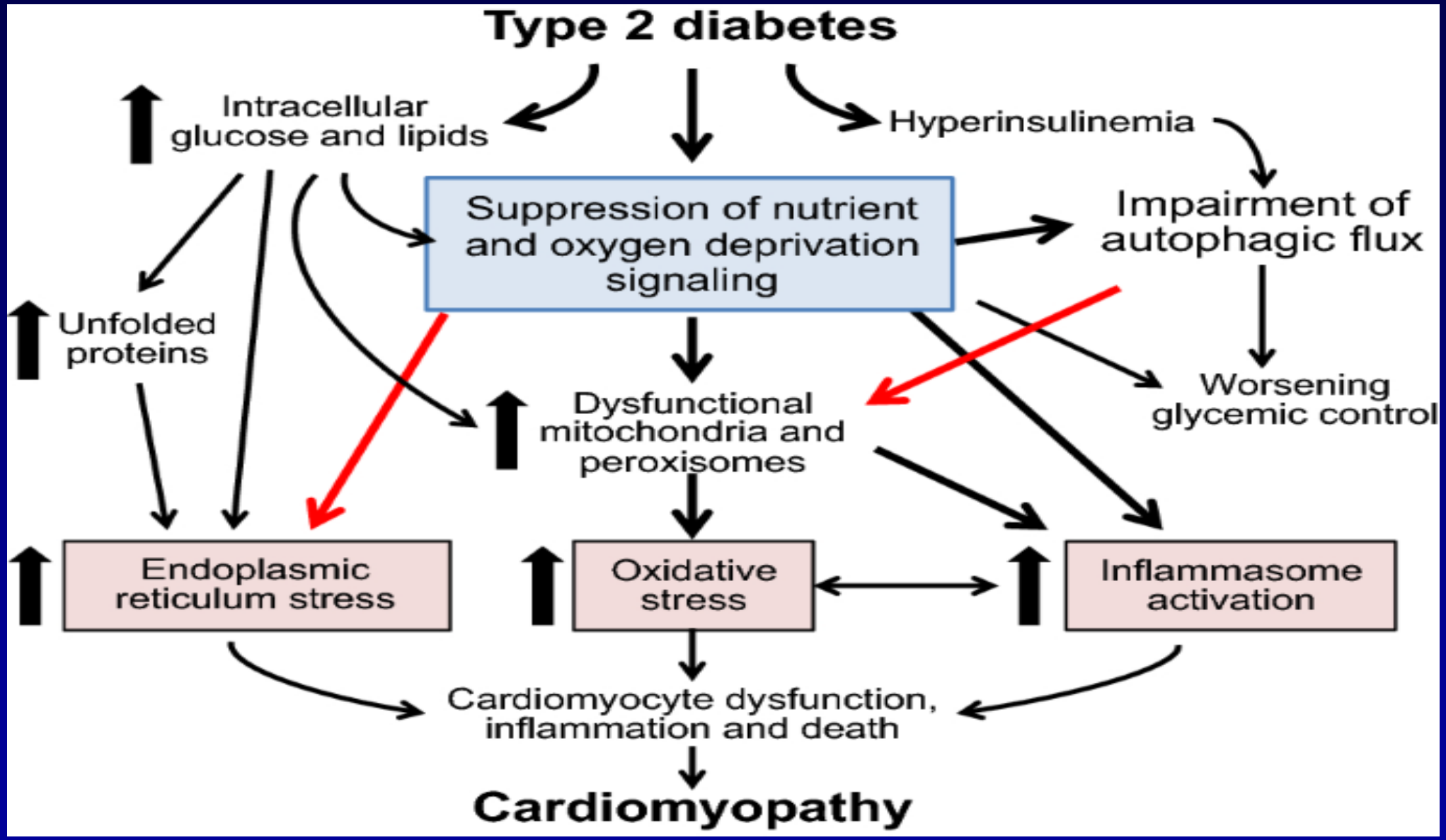


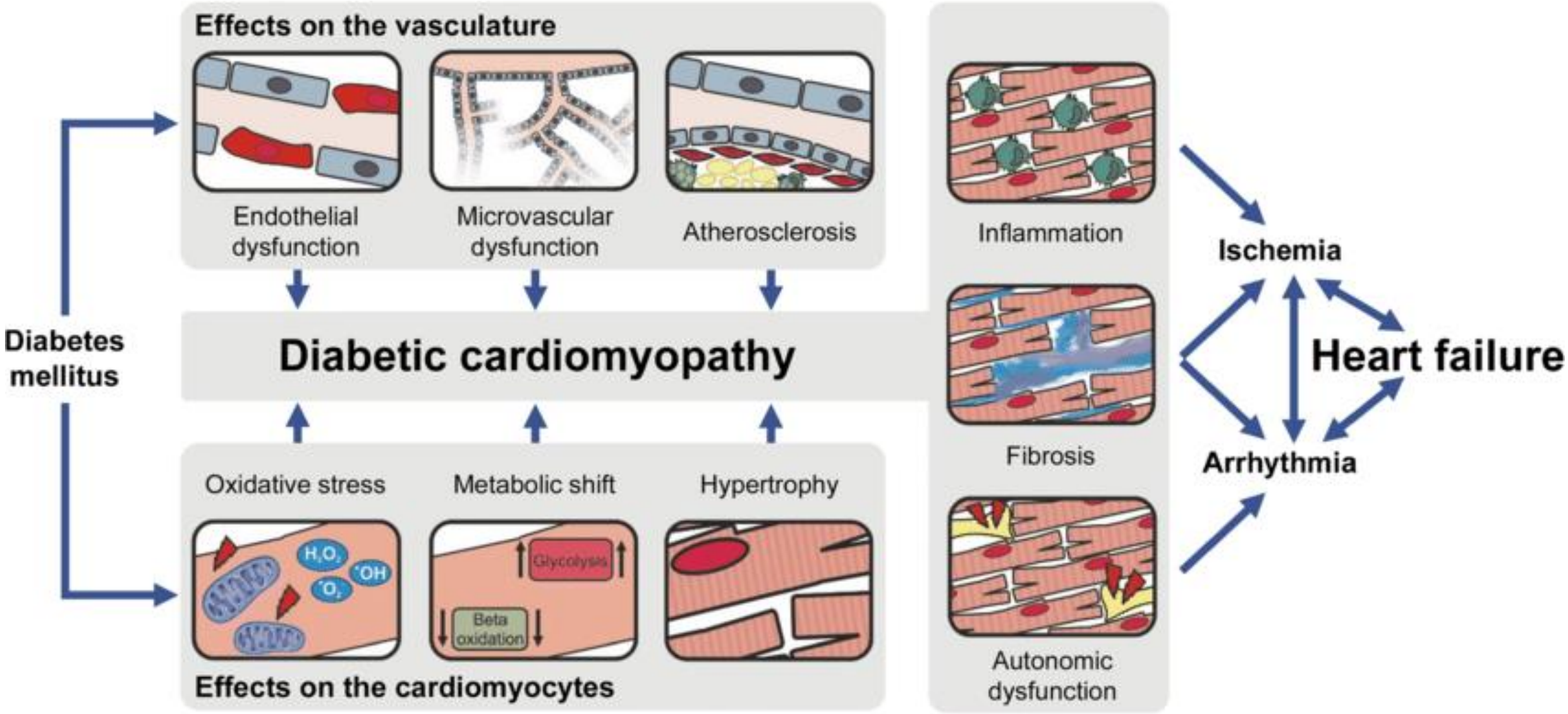

Hoạt động **SIRT3** bị giảm trong cơ tim ĐTĐ có thể góp phần làm suy giảm khả năng tái tạo ATP do oxy hóa, tăng sản xuất ROS và **ức chế tự thực bào**.

MAO và calpain 1 có thể góp phần làm tăng ROS ty thể. O-GlcNAcylation và sự thay đổi sau chuyển dịch do acyl-CoA điều khiển của Drp1 và Opa1 có thể góp phần vào sự phân mảnh ty thể. Mức độ giảm của PINK và Parkin có thể ngăn chặn quá trình tự thực bào trong cơ tim ĐTĐ.

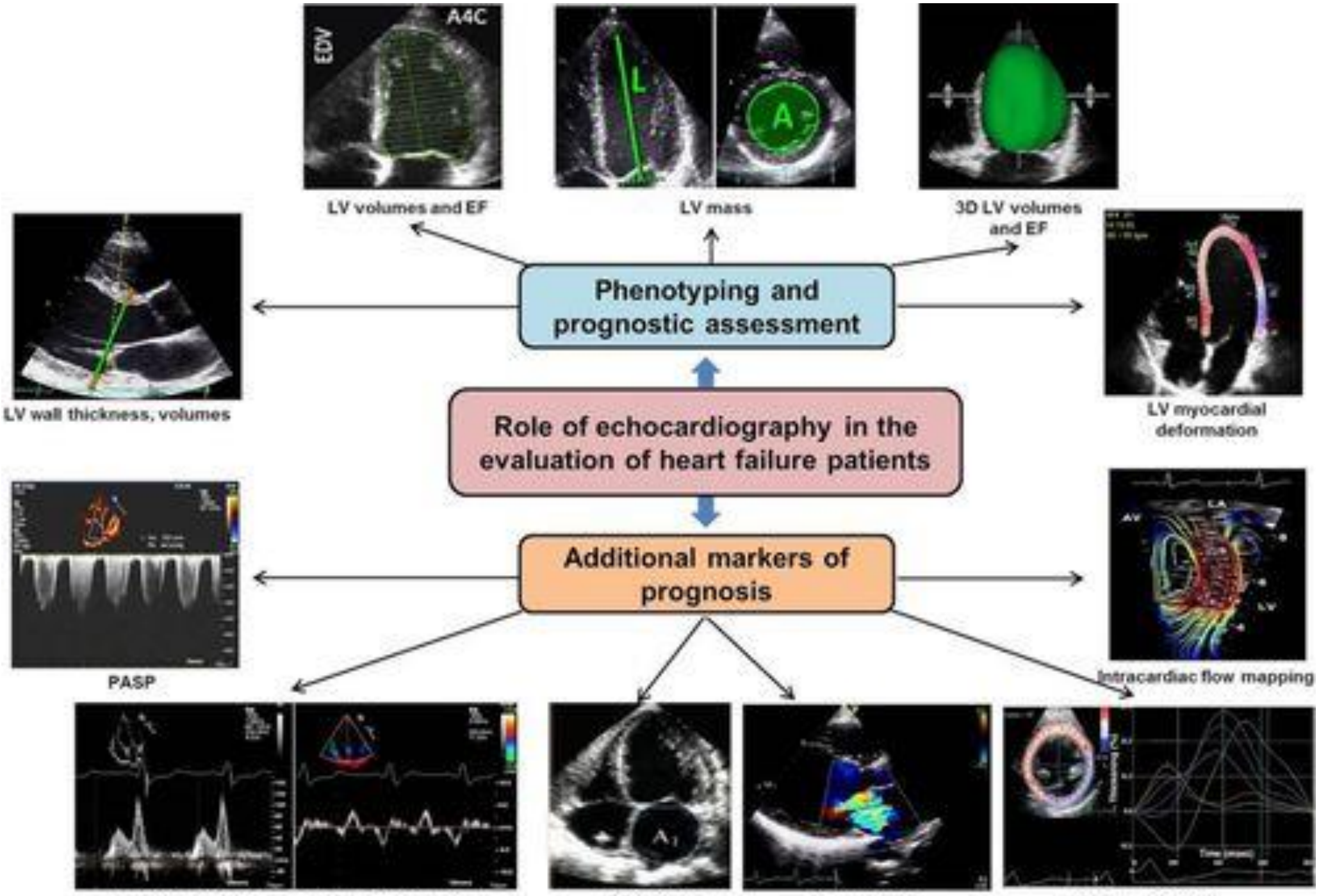
Sự phân mảnh ty thể và ức chế tự thực bào có thể tiếp tục khuếch đại RLCN ty thể trong cơ tim ĐTĐ.

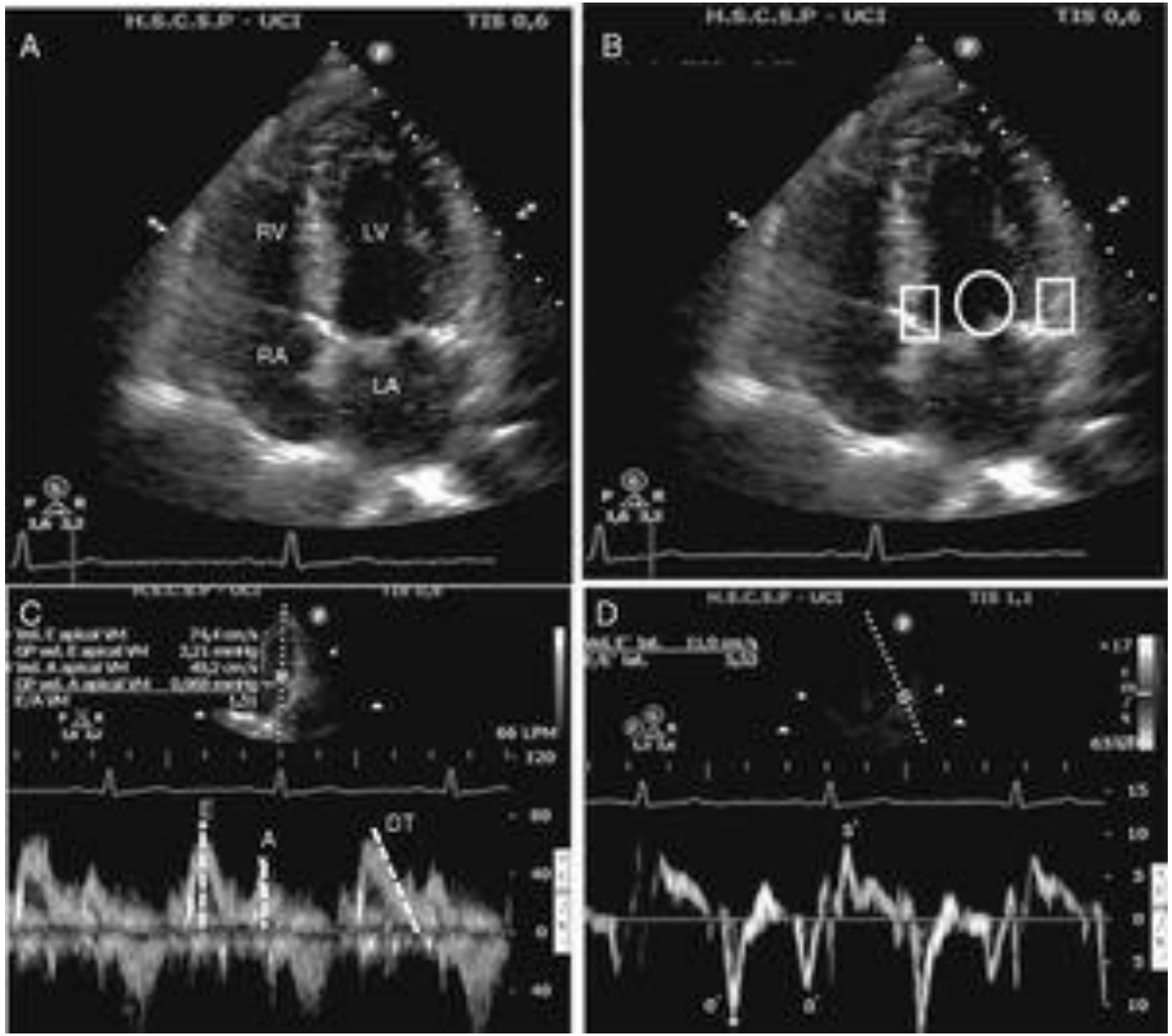
# Tự thực tế bào (Autophagy) và ĐTĐ Típ 2




Effects on the vasculature
Endothelial dysfunction
Microvascular dysfunction
Atherosclerosis
Diabetes mellitus
Diabetic cardiomyopathy
Oxidative stress
Metabolic shift
Hypertrophy
Glycolysis
Beta oxidation
Effects on the cardiomyocytes
Inflammation
Fibrosis
Autonomic dysfunction
Ischemia
Heart failure
Arrhythmia

# Làm thế nào phát hiện
# Bệnh Cơ Tim Đái Tháo Đường

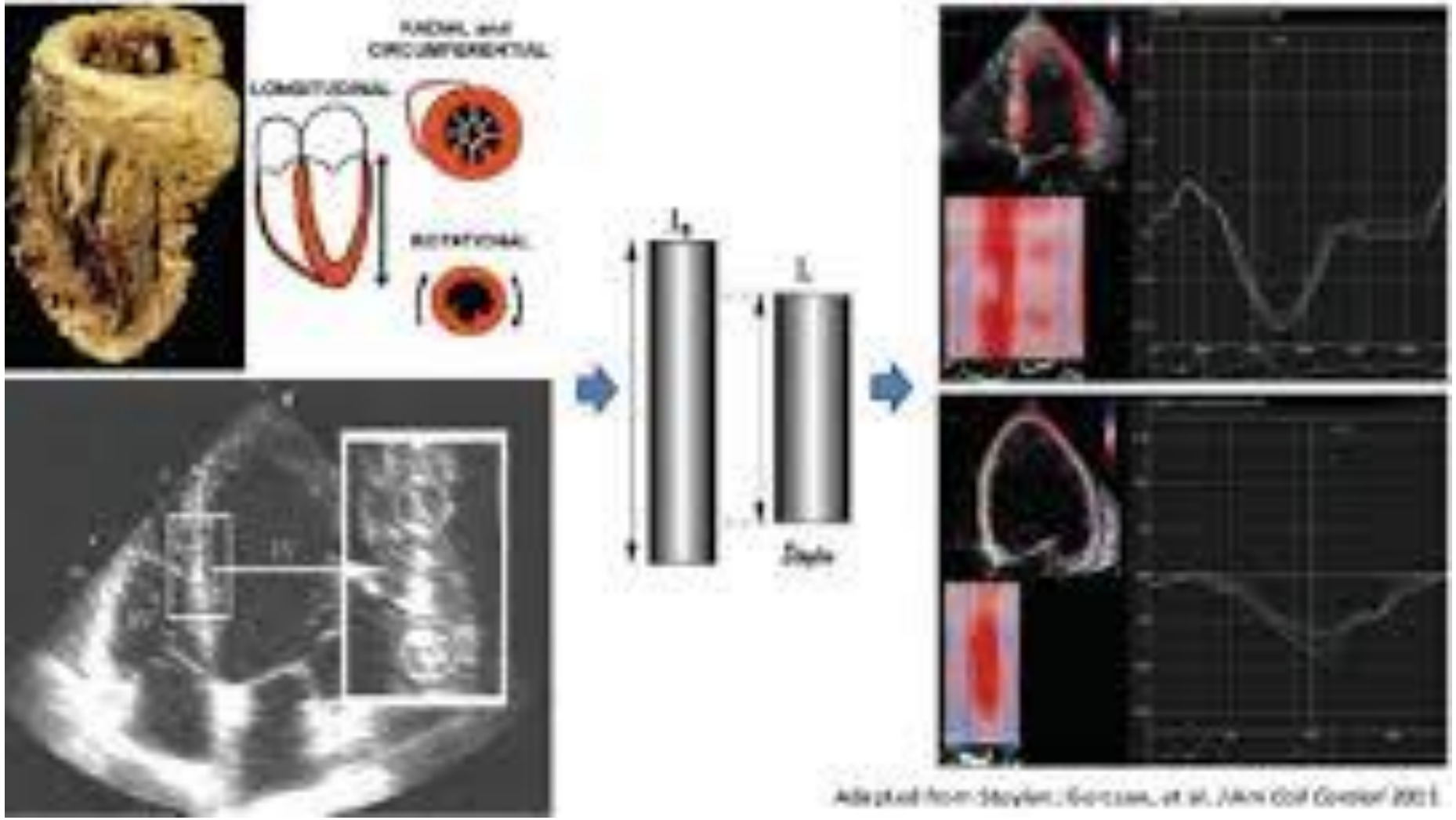

A4C
EDV
LV volumes and EF
L
A
LV mass
3D LV volumes and EF
LV wall thickness, volumes
Phenotyping and prognostic assessment
LV myocardial deformation
Role of echocardiography in the evaluation of heart failure patients
PASP
Additional markers of prognosis
Intracardiac flow mapping



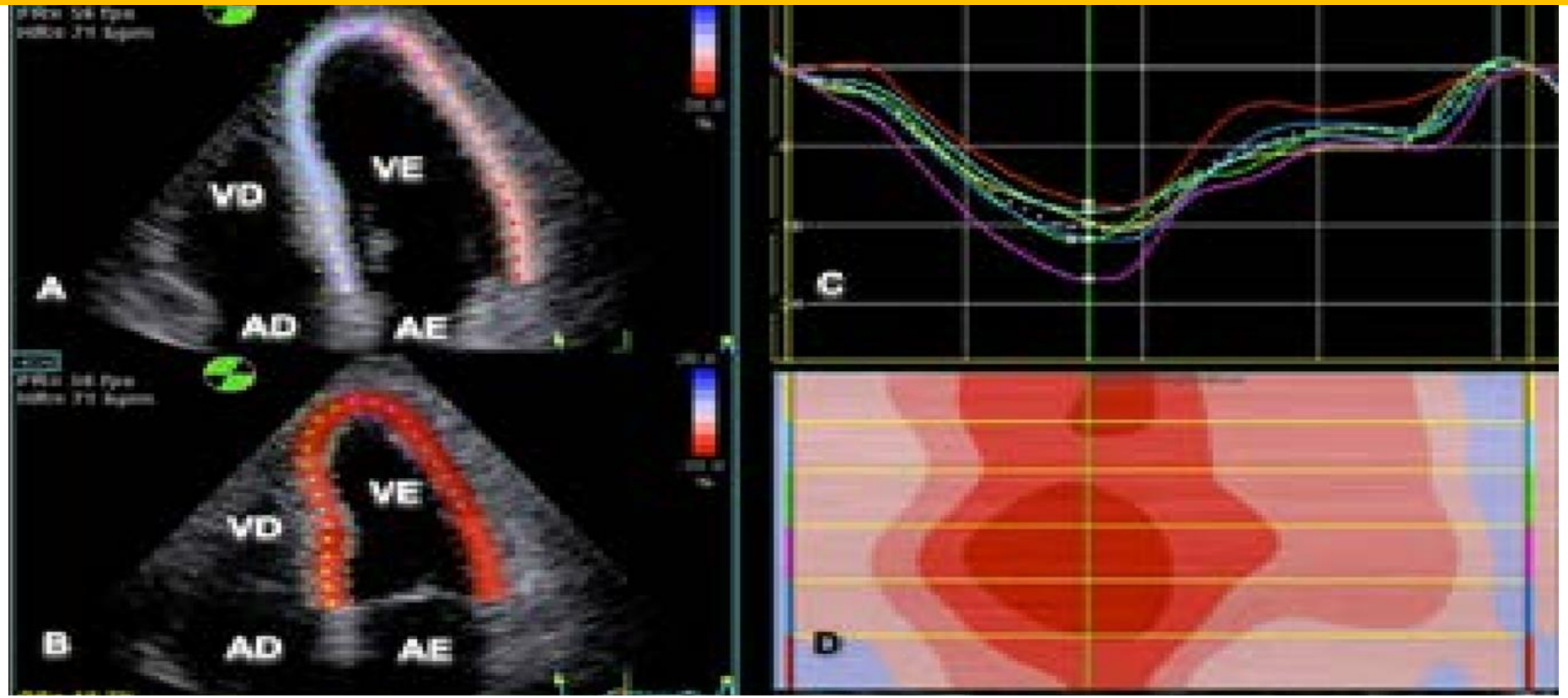

Echocardiographic assessment of left ventricular diastolic function

# Siêu âm đánh dấu mô tim

## Speck Tracking Echocardiography

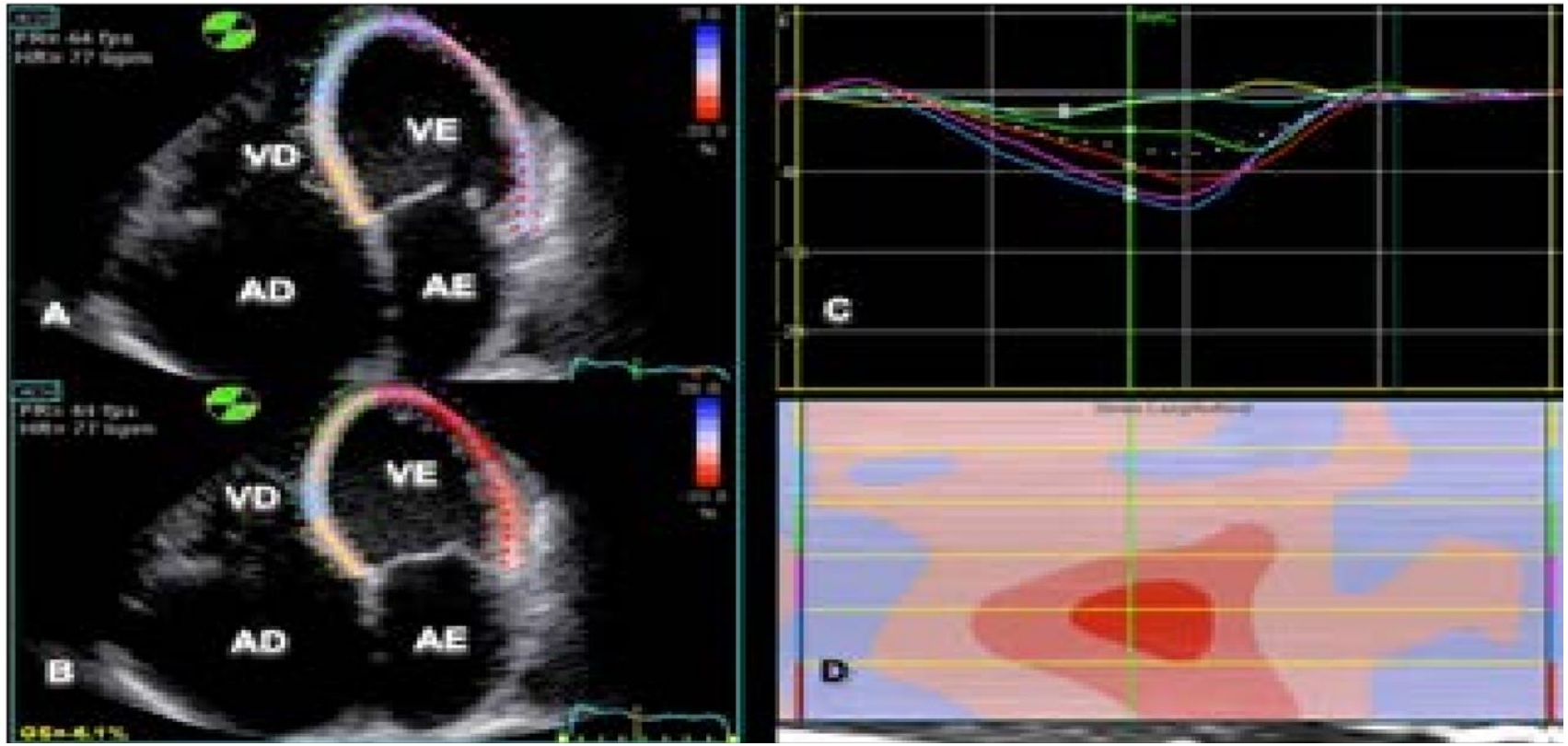


# Siêu âm đánh dấu mô tim
# Suy tim EF bảo tồn




Panel A: left ventricle in diastole. Panel B: left ventricle in systole. Panel C: LV myocardial systolic longitudinal deformation, where each line represents a segment (Y axis) along the cardiac cycle. Panel D: anatomic M mode of the LV in the four-chamber window: the systolic deformation of each segment (y-axis) is represented by color over time (x-axis),darker red tones are considered normal and abnormal, light tones

# Siêu âm tim đánh dấu mô
# Suy tim phân suất tống máu giảm (HFREF).

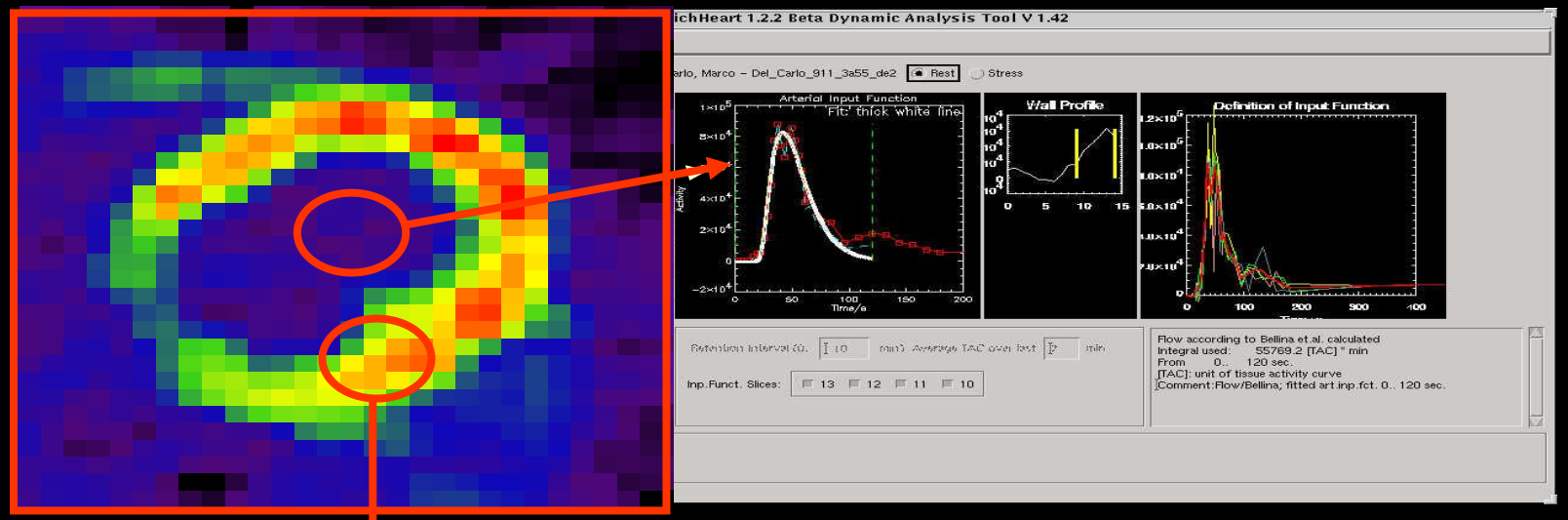



Panel A: left ventricle in diastole. Panel B: left ventricle in systole. Panel C: LV myocardial systolic longitudinal deformation, where each line represents a segment (Y axis) along the cardiac cycle. Panel D: anatomic M mode of the LV in the four-chamber window: the systolic deformation of each segment (y-axis) is represented by color over time (x-axis), darker red tones are considered normal and abnormal, light tones.

# Positron Emission Tomography

*"Technology of choise to assess microvascular function"*

Quantitative Imaging of Microvascular Function
(Myocardial Blood Flow → MBF)




MBF (ml/min/g)

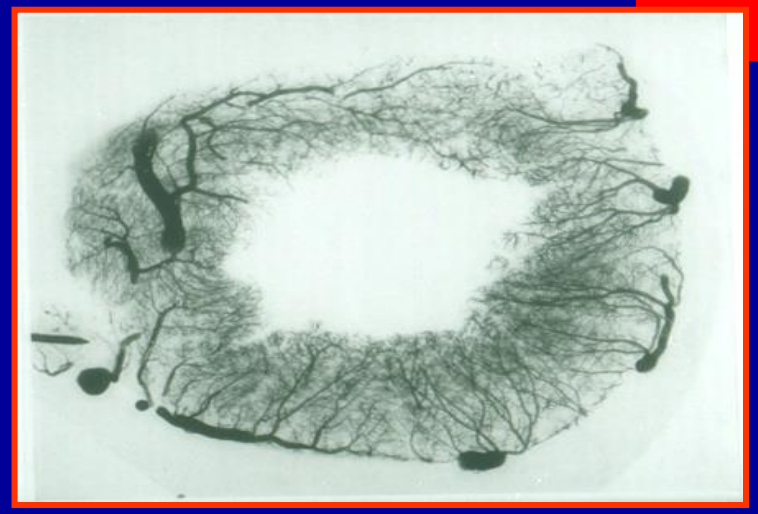
*Bellina et al., J Nucl Med 1990*

# Rối loạn chức năng vi mạch vành và cấu trúc trong BCTĐTĐ

MACRO vessels

In the absence of stenosis

MICRO vessels

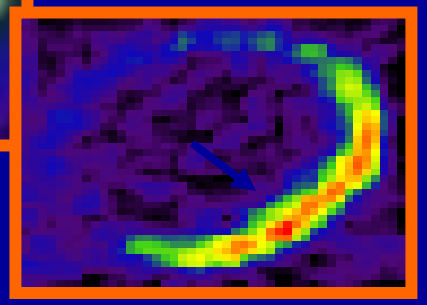


… blood flow can be reduced by Microvascular Dysfunction

TISSUE perfusion/metabolism

*<< Flow*

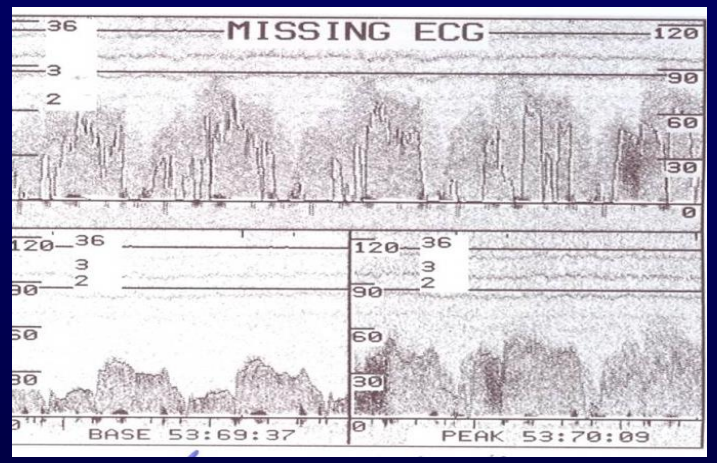
*>> Glucose*

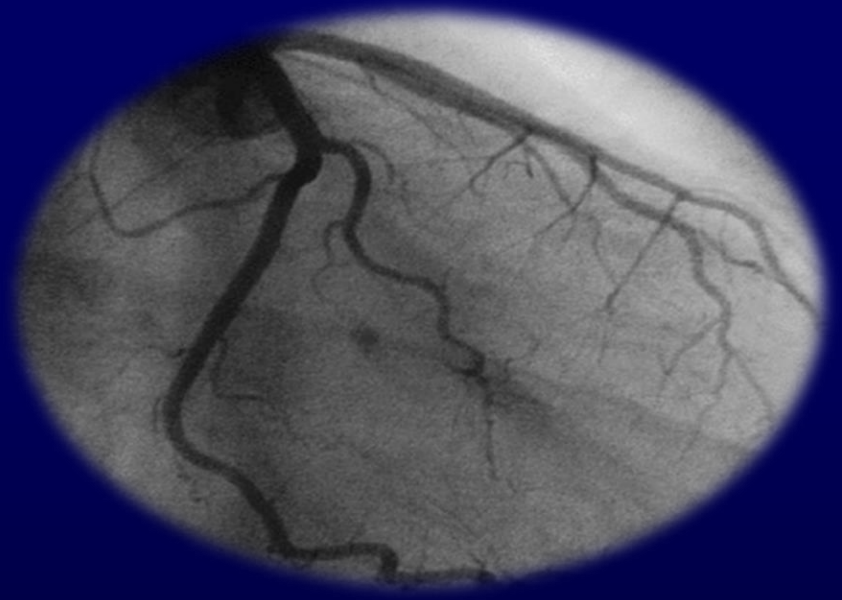


… causing ischemic metabolism and Tissue Dysfunction

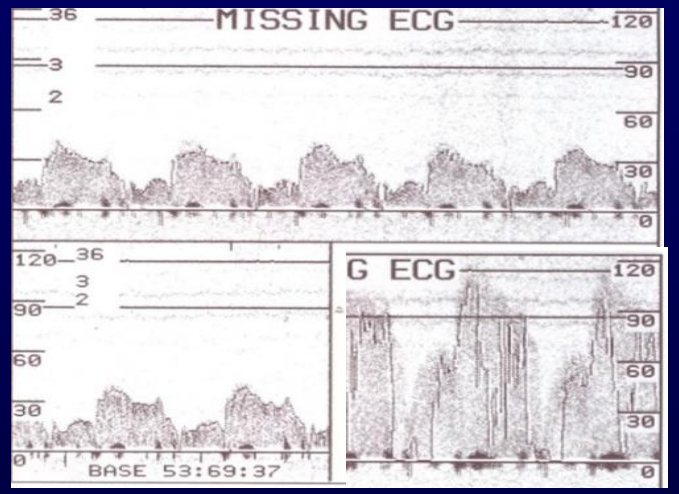
# Coronary Flow Reserve (CFR)

## Acetilcolina CFR 1.5

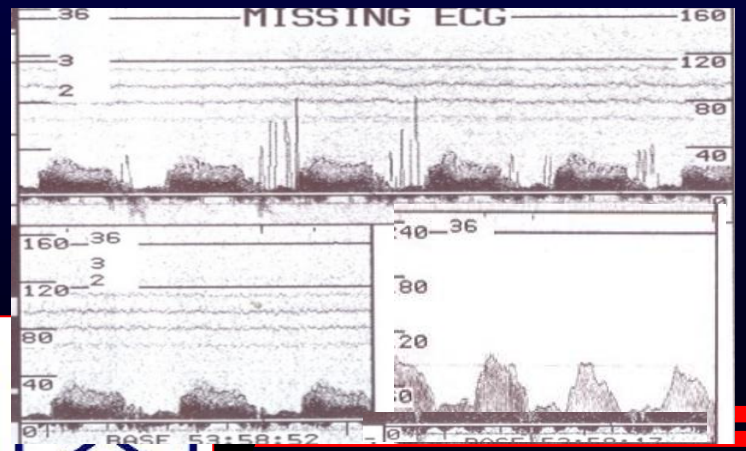


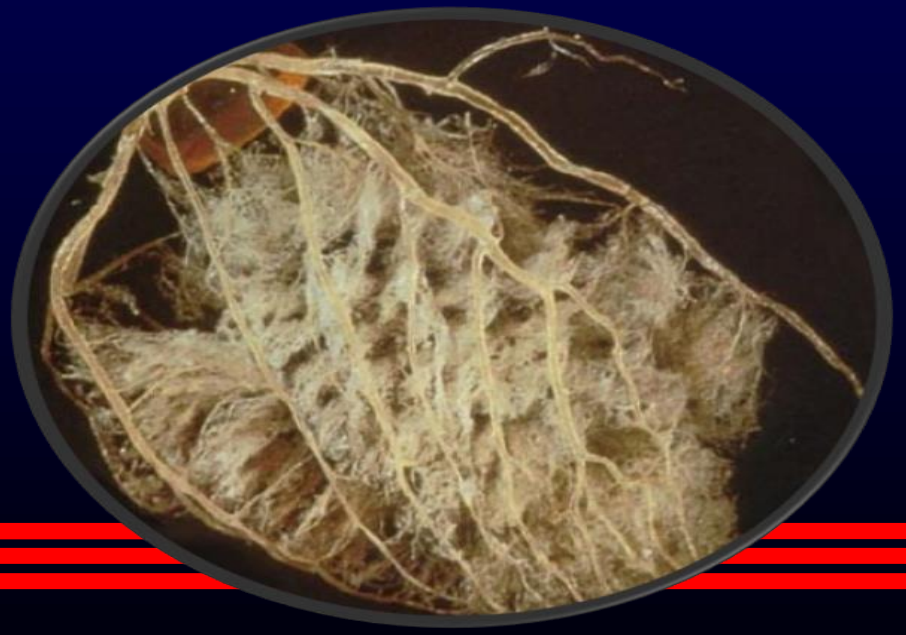



## Adenosina CFR 3.0

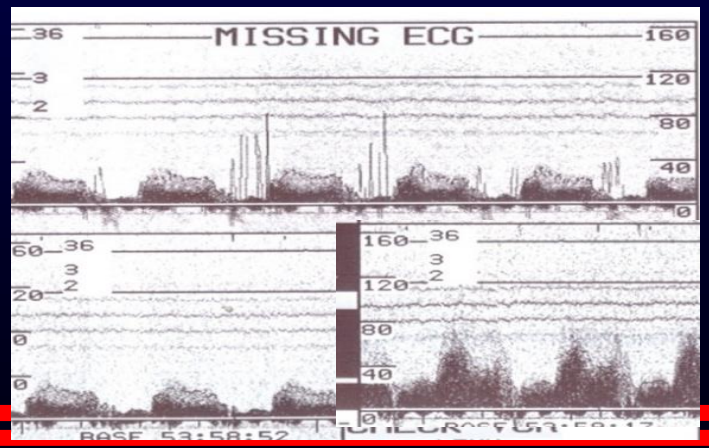


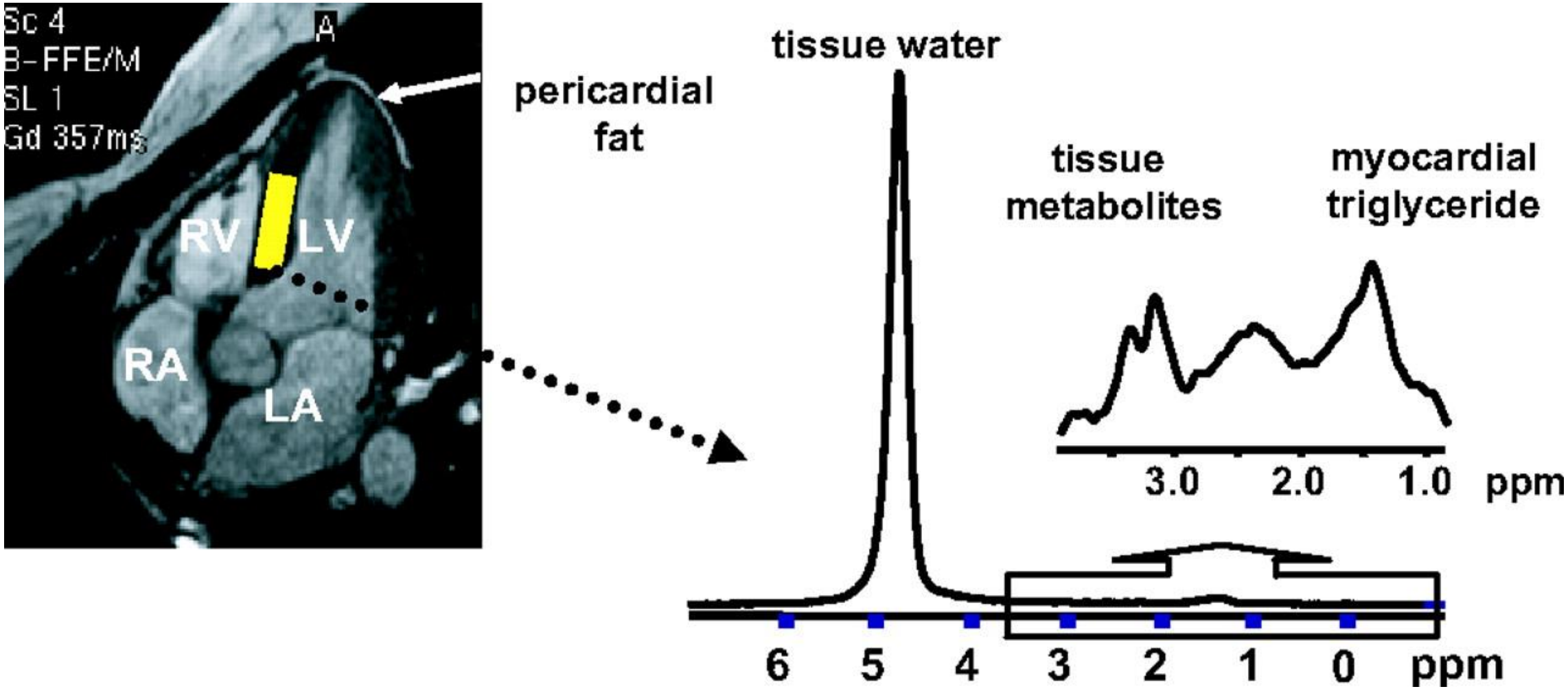

## Acetilcolina CFR 1.5



## Adenosina CFR 2.17






Đo lượng TG cơ tim bằng cộng hưởng từ phổ học (MRS) . Hình ảnh 4 buồng tim . Cơ tim có màu xám đen; máu trong các buồng cơ tim và màng ngoài tim và mỡ mỡ có màu xám nhạt. Thể tích để kiểm tra hàm lượng TG của cơ tim được đặt trong vách liên thất (hình chữ nhật màu vàng). Phổ từ mô cơ tim được thu thập đồng thời trong quá trình kích thích cuối thở ra và cuối tâm thu đồng thời bằng đo chức năng hô hấp và ECG.

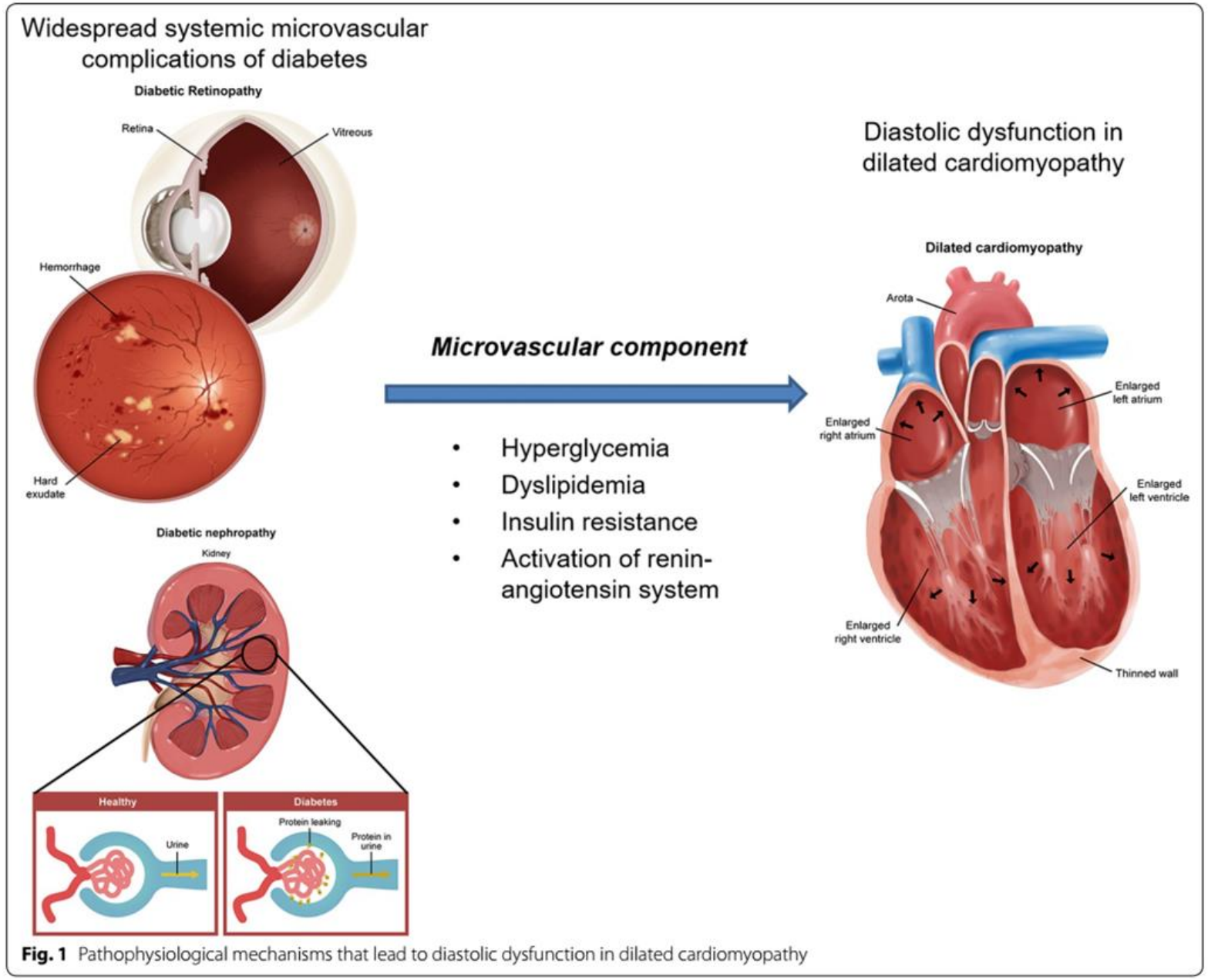



**Fig. 1** Pathophysiological mechanisms that lead to diastolic dysfunction in dilated cardiomyopathy

**Bệnh võng mạc ĐTĐ có liên quan RLCN tâm trương ở bệnh nhân ĐTĐ típ 2 có bệnh cơ tim dãn không do thiếu máu cục bộ .**

Chung *et al. Cardiovasc Diabetol (2017) 16:82*

# Chỉ điểm sinh học bệnh cơ tim đái tháo đường

| Promising Biomarkers | |
|---|---|
| sST2 | An interleukin-33 (IL-33) decoy receptor that ameliorates the Th2 inflammatory response. Increased plasma levels of sST2 have been linked to a worse prognosis of HF. |
| Galectin-3 | A lectin family protein that has been associated with fibrosis and inflammation in heart failure. It is elevated in diabetic patients with a mild depressed ejection fraction and is associated with a diminished global longitudinal strain. It is an easy and reproducible tool for the evaluation and follow-up of diabetic cardiomyopathy. It was approved by the FDA as a novel biomarker for predicting adverse cardiovascular events. |
| lncRNAs | Long noncoding RNAs (lncRNAs)are a diverse subgroup of noncoding RNAs that are epigenetic regulators of gene expression. Circulating lncRNA serum levels are associated with cardiac remodeling and are positively correlated with cardiac diastolic dysfunction. |
| GDF-15 | Expressed in response to oxidative stress and inflammation. GDF-15 levels predict diabetic cardiomyopathy. |
| TGF-β | A fibrogenic cytokine that promotes extracellular matrix accumulation. Higher plasma levels of TGF-β are associated with both DM and diastolic dysfunction. |
| IGFBP7 | Regulates the IGF signaling pathway and is related to insulin resistance. IGFBP7 is correlated with DM with diastolic dysfunction. |

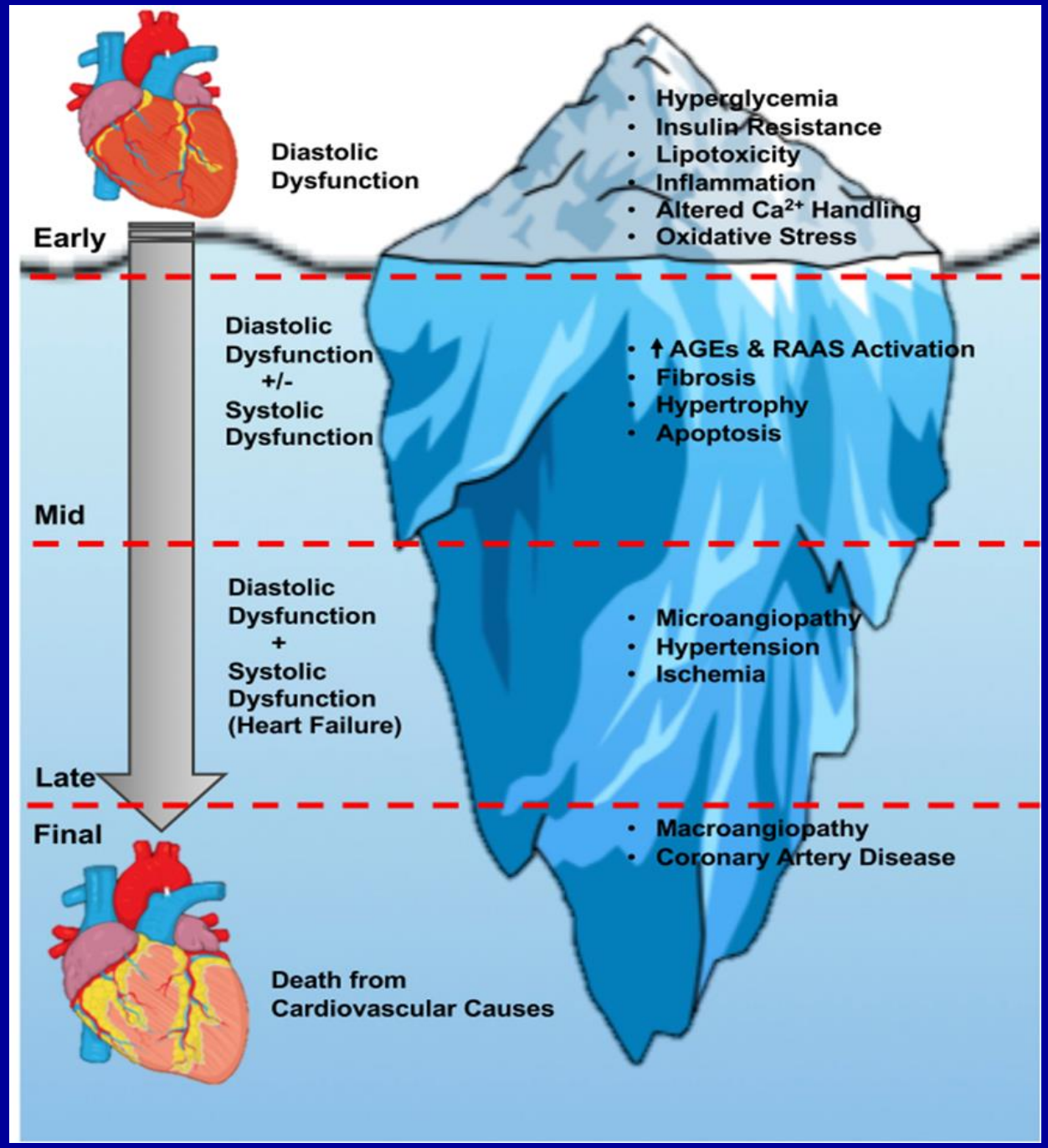
Biomedicines 2023, 11, 662. https://doi.org/10.3390/biomedicines11030662

# Chỉ điểm sinh học bệnh cơ tim đái tháo đường

| Promising Biomarkers | |
|---|---|
| **Other candidate biomarkers** | |
| Activin A | A protein produced by epicardial adipose tissue. It is correlated with both myocardial glucose metabolism abnormality and left ventricular remodeling. |
| H-FABP | It has an independent association with outcomes in patients with HF. It enables the detection of early myocardial injuries in patients with metabolic syndrome or DM. |
| TNF-α | The level was increased in diabetic patients with diastolic dysfunction. It might be used for the early detection of diabetic cardiomyopathy. |
| ICTP and PIIINP | Circulating collagen turnover biomarkers are associated with adverse cardiac outcomes and can be used to predict HF progression. |
| Cardiotrophin-1 | A glycoprotein 130 and a potent inducer of myocardial hypertrophy. It is correlated with blood glucose and ventricular hypertrophy. It is less specific for dilated cardiomyopathy. |

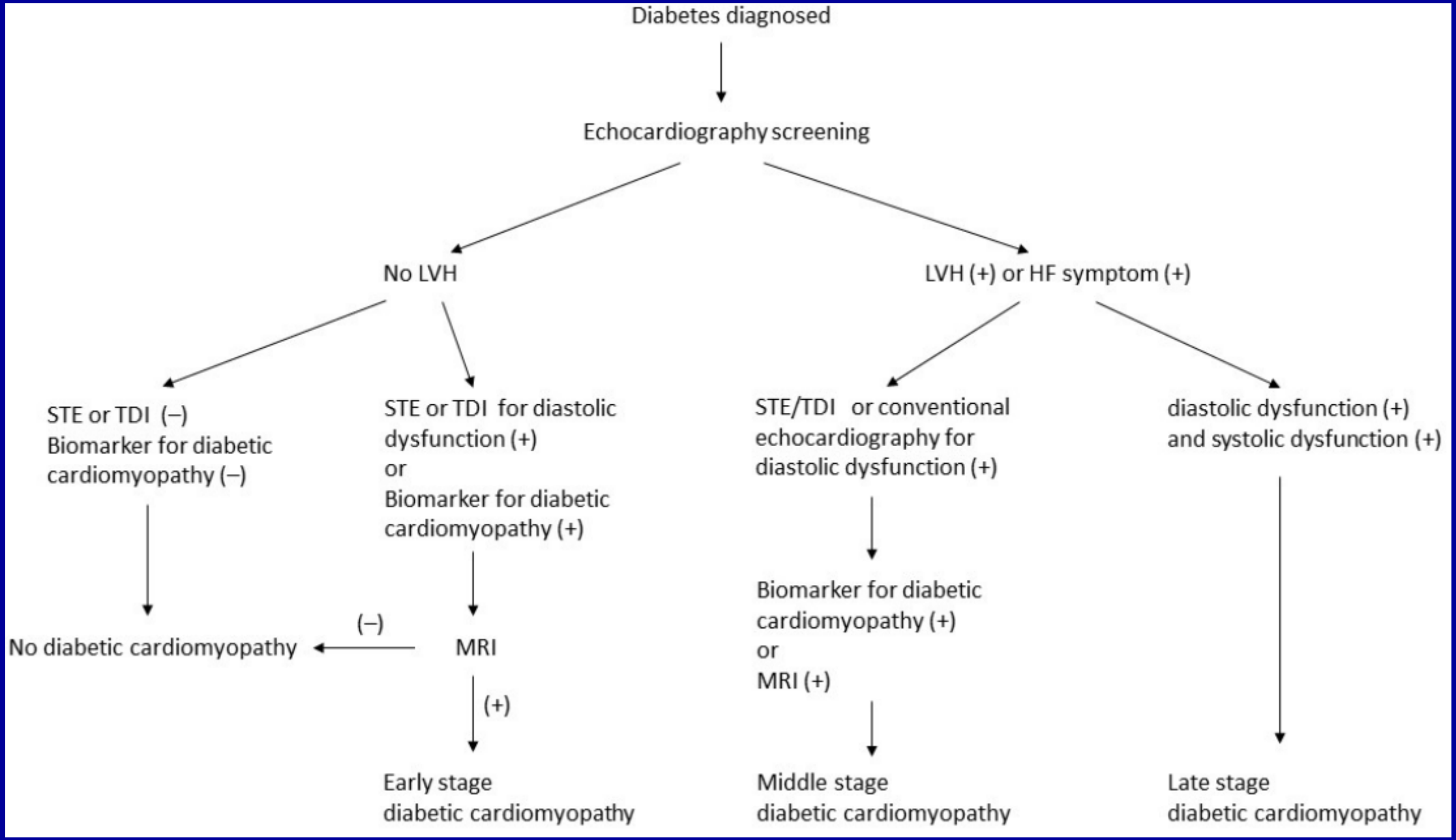
Biomedicines 2023, 11, 662. https://doi.org/10.3390/biomedicines11030662

# 4. Chẩn Đóan
# Bệnh Cơ Tim Đái Tháo Đường




Stages of diabetic cardiomyopathy. An overview of the current understanding of the stages of diabetic cardiomyopathy progression, from the initial onset of hyperglycemia and diastolic dysfunction, through the later stages of hypertrophy, angiopathy, ischemia, and heart failure with systolic and diastolic dysfunction.

The initial diastolic dysfunction that characterizes the early stages of diabetic cardiomyopathy can be viewed as just the tip of the iceberg if left untreated in people with T2DM.




Đề xuất sơ đồ chẩn đoán bệnh cơ tim đái tháo đường

# Chẩn đoán Bệnh Cơ Tim ĐTĐ dựa trên rối loạn cấu trúc-chức năng-chuyển hoá

Structural changes

- LV hypertrophy assessed by 2D echocardiography or CMR
- Increased integrated backscatter in the LV (septal and posterior wall)
- Late Gd-enhancement of the myocardium in CMR

Functional changes

- LV diastolic dysfunction assessed by pulsed Doppler echocardiography and TDI
- LV systolic dysfunction demonstrated by TDI/SRI
- Limited systolic and/or diastolic functional reserve assessed by exercise TDI

Metabolic changes

- Reduced cardiac PCr/ATP detected by $^{31}$P-MRS
- Elevated myocardial triglyceride content detected by $^{1}$H-MRS

# Chẩn đoán bệnh cơ tim ĐTĐ qua chẩn đoán hình ảnh

| | | METHODOLOGY | DCM Evolution: Early | Middle | Late | DRAWBACKS |
|---|---|---|---|---|---|---|
| Echocardiography | Conventional Döppler | Conventional 2D echocardiography with addition of Doppler filter to detect anomalous flows | | ↓E/A ratio (incl. pseud. filling)<br>↑LV mass ↓diameter<br>↑Decc. time (diastolic dysf.) | ↓EF (systolic dysf.) | Inter/intraobserver variab.<br>Angle dependence<br>Noise interference |
| | TDI | Excludes high velocities and low-intensity reflectors to quantify velocities through myocardial tissue | | E/E' ratio > 15 (diastolic dysf.) | Strain rate, global/regional ventricular strains (systolic dysf.) | Non-discrimination between pasive and active motion. Segments or contractility may interfere with radial measurements. |
| | STE | Quantitative and qualitative analysis of tissue deformation and motion by speckle based on interference patterns and acoustic reflections, and 2D/3D Echo | Longitudinal and circumferential strains (left ventricle dysf.) | Strain and strain rate for diastolic dysf. | Strain and strain rate for systolic dysf. | Irregular ventricular remodeling and wall thinning |
| MRI | Phase | Detects changes of blood flow by changes in signal intensity through valves | Metabolic changes | Velocities and ventricular filling (diastolic dysf.) | ↑LV mass | Claustrophobia<br>Pacemakers<br>Understimation of diastolic dysf. |
| | Gradient | Cine display by radiofrequency combined with electrocardiogram | | Ventricular filling (diastolic dysf.) | | |
| | Tagged | Cardiac deformation through radiofrequency pulses | | ↑LV mass and volume | Regional contractility of the LV (systolic dysf.) | |
| MsCT | | Computer-processed combinations of X-ray images, reconstructed for cross-sectional tomography | | | Myocardial ischemia<br>Calcification<br>Systolic dysf. | Radiation<br>Contrast media |
| Nuclear Imaging | G-Spect | A γ-emitting radioisotope guides acquisition of images coupled electrocardiogram | Metabolic changes | | Perfusion alterations | High complexity<br>Radiation |
| | PET | Detects pairs of γ-rays emitted indirectly by a positron-emitting radionuclide (tracer) and construct 3D-images by CT analysis. | Metabolic changes | | Perfusion alterations | High complexity<br>Radiation<br>Impairment tracer uptake |

Lorenzo-Almorós *et al. Cardiovasc Diabetol (2017) 16:28*

# Phân loại Bệnh cơ tim ĐTĐ theo giai đoạn

**Pathophysiological Mechanisms**

- Insulin resistance
- Hyperglycemia
- Inflammation
- RAAS overactivation
- Oxidative stress
- Myocardial energy substrate alteration
- Epigenetics
- AGEs
- Autoimmunity*

**Intermediate Mechanisms**

- Myocardial fibrosis
- Cardiomyocyte hypertrophy
- Lipotoxicity
- Mitochondrial dysfunction
- ER Stress
- Impaired calcium handling
- Endothelial dysfunction
- Microvascular dysfunction
- Impaired myocardial perfusion
- Apoptosis

**Subclinical Abnormalities**

- LV hypertrophy
- LV Systolic dysfunction
- LV Diastolic dysfunction
- Right ventricular dysfunction
- Left atrial enlargement and myopathy

**Clinical Manifestation**

- Asymptomatic CMP
- HF with preserved EF
- HF with reduced EF

# Phân loại Bệnh cơ tim ĐTĐ theo giai đoạn

**TABLE 1** | Stages of DMCM.

| Classification | Stage 1 DMCM (early stage) | Stage 2 DMCM (middle stage) | Stage 3 DMCM (middle- late stage) | Stage 4 DMCM (late stage) |
|---|---|---|---|---|
| Symptoms of heart failure/dyspnoea | NYHA I (asymptomatic) | NYHA II | NYHA II - III | NYHA II - IV |
| Function (echo) | Diastolic dysfunction (HFpEF) normal systolic function | Diastolic and systolic dysfunction (HFpEF and HFrEF), EF < 50%, low flow | Worsening diastolic and systolic dysfunction (HFpEF and HFrEF), EF < 50%, low flow | Worsening diastolic and systolic dysfunction (HFpEF and HFrEF), EF < 50%, low flow |
| Morphology | Increased LV mass (hypertrophy), | Increased LV mass (hypertrophy), dilatation, fibrosis | Dilatation, fibrosis, microangiopathy | Dilatation, fibrosis, micro and macro angiopathy (CAD) |
| Cellular mechanisms | Cardiac steatosis with increased FFA, shift of substrate metabolism | AGE formation, IR, cell death (apoptosis), necrosis, fibrosis, mild CAN, increased RAAS | Features from early and middle stages + hypertension and microvascular changes, severe CAN | Features from early and middle stages + hypertension and microvascular changes, severe CAN and CAD |
| Metabolism | Prediabetes, metabolic syndrome | Early diabetes, hyperglycaemia | Overt diabetes, IR | Overt diabetes, IR |
| Biomarkers of diabetes | Hyperglycaemia and elevated HbA1C | Hyperglycaemia and elevated HbA1C | Hyperglycaemia and elevated HbA1C | Hyperglycaemia and elevated HbA1C |

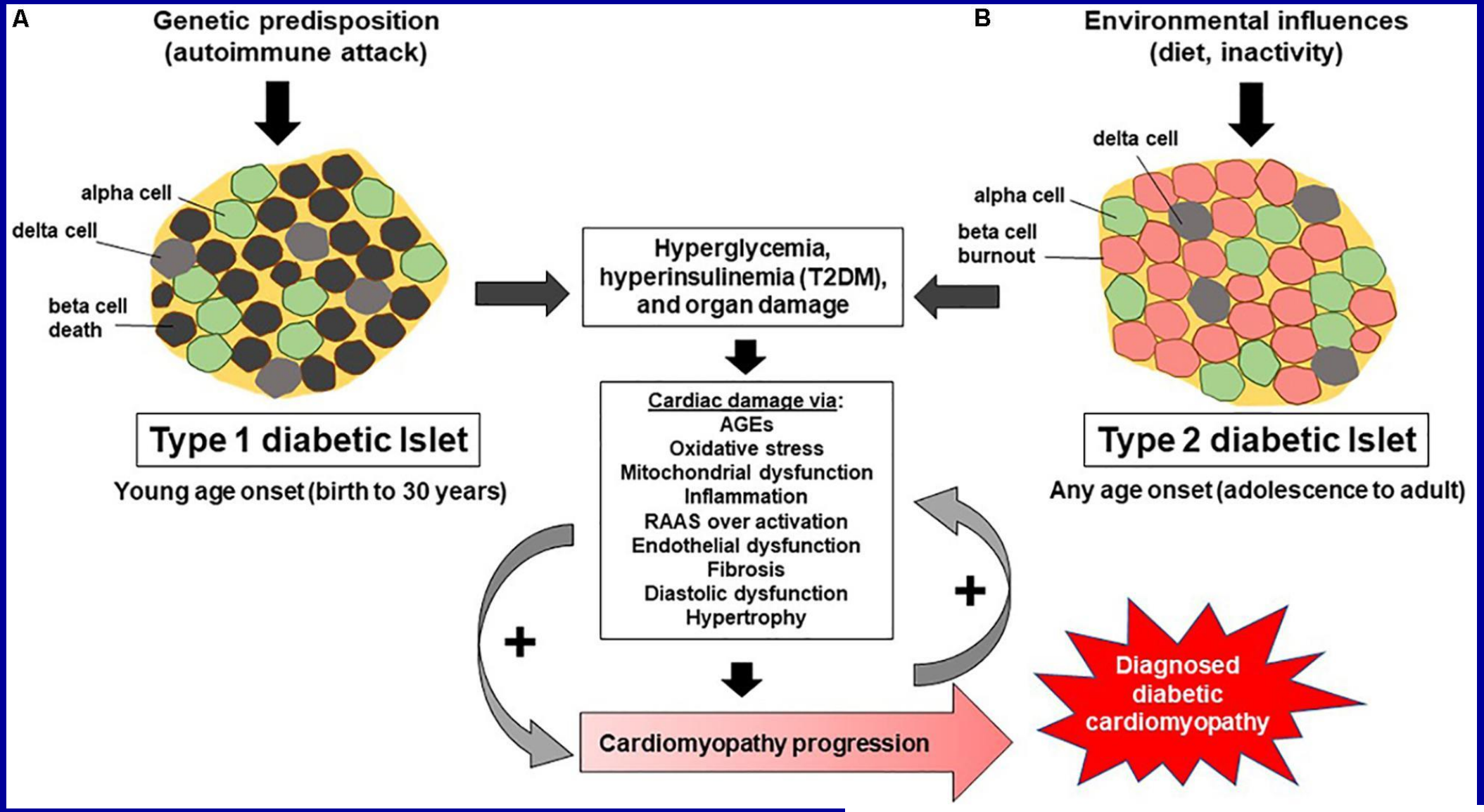
*CAD, coronary artery disease; NYHA, New York Heart Association functional classification of HF; EF, ejection fraction; CAN, cardiovascular autonomic neuropathy; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction.*

# Các giai đoạn bệnh cơ tim ĐTĐ

| Stages | Stage 1 (Early) | Stage 2 (Middle) | Stage 3 (Late) | Stage 4 (Late) |
|---|---|---|---|---|
| Morphological features | Normal LV wall thickness, size, and mass | Slightly increased LV wall thickness, size, and mass | Significantly increased LV wall thickness, size, and mass | Significantly increased LV wall thickness, size, and mass |
| Functional changes | Normal or slightly diastolic dysfunction | Diastolic dysfunction with normal or slightly systolic dysfunction | Diastolic and systolic dysfunction | Diastolic and systolic dysfunction |
| Cellular and metabolic abnormalities | Insulin resistance with reduced glucose uptake<br>Increased circulating free fatty acids and fatty acid utilization<br>$Ca^{2+}$ homeostasis impairment | AGE formation<br>Cardiomyocyte death<br>Myocardial fibrosis<br>Increased oxidative stress and inflammation<br>Reduced nitric oxide<br>Activated RAAS<br>Mild CAN | Extensive myocardial fibrosis<br>Microvascular changes<br>Severe CAN | Extensive myocardial fibrosis<br>Microvascular changes<br>Severe CAN<br>CAD |
| Echocardiographic methods for diagnosis | Sensitive echocardiographic techniques such as speckle-tracking echocardiography and tissue Doppler imaging | Conventional echocardiography with sensitive echocardiographic techniques | Conventional echocardiography | Conventional echocardiography |

Biomedicines 2023, 11, 662. https://doi.org/10.3390/biomedicines11030662

# Phân loại Bệnh CTĐTĐ theo típ ĐTĐ

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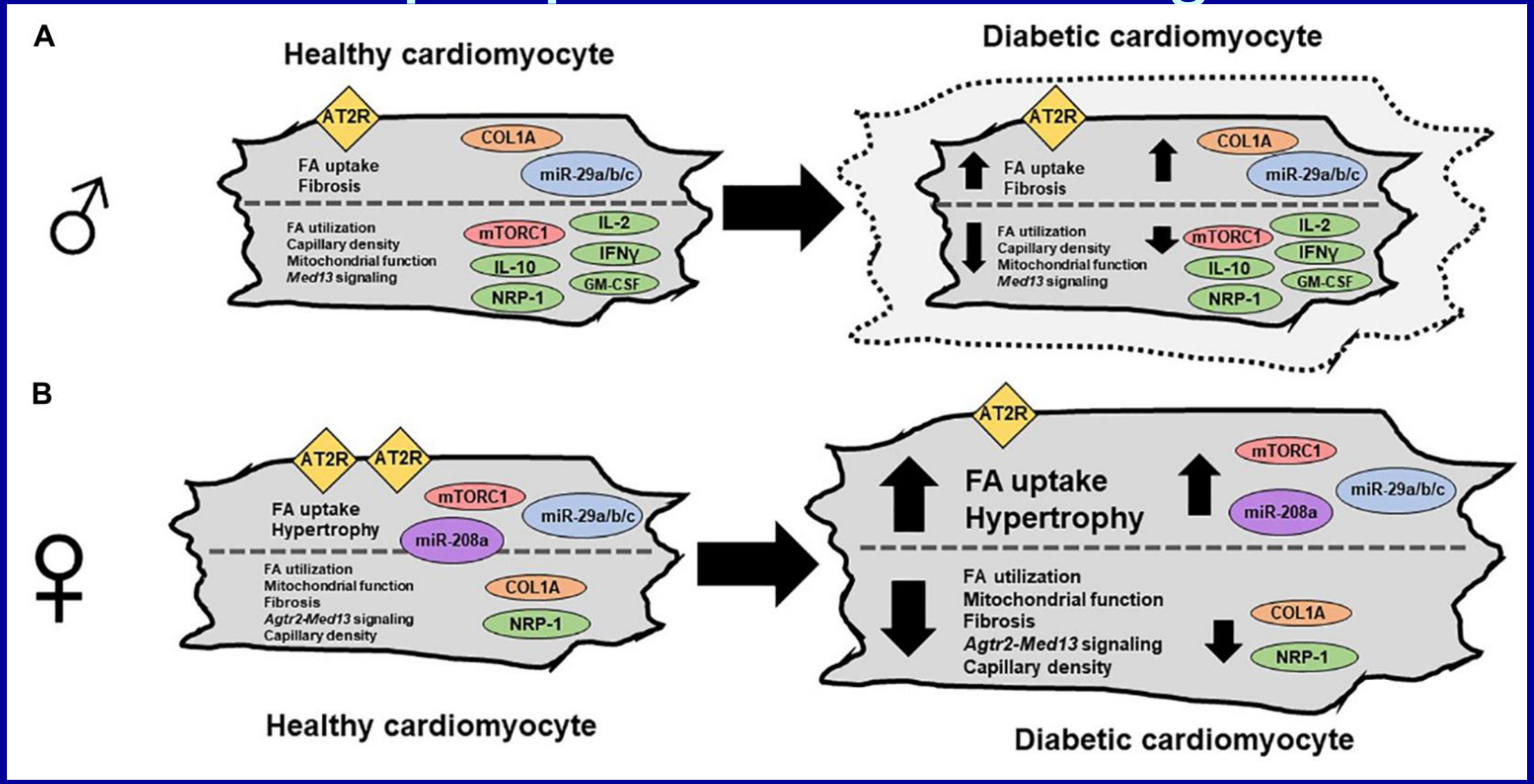
# Phân loại Bệnh CTĐTĐ theo giới tính

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# Phân loại Bệnh CTĐTĐ theo phân suất tống máu(EF).

## Thể hạn chế/EF bảo tồn

**DMCMP**
**Restrictive/HFPEF Phenotype**

1) Presence of DM
2) Exclusion of CAD, valvular or congenital heart disease
3) Exclusion of hypertensive heart disease (=DBP<90mmHg)
4) Exclusion of infiltrative heart disease by endomyocardial biopsy
5) LVEF>50%; LVEDVI<97ml/m²
6) E/E'>15 or
   8<E/E'<15+LAVI>40ml/m² or
   8<E/E'<15+BNP>200pg/ml or
   8<E/E'<15+atrial fibrillation or
   8<E/E'<15+LVH (LVMI♀ >122g/m²; LVMI♂>149g/m²)

## Thể dãn / EF giảm

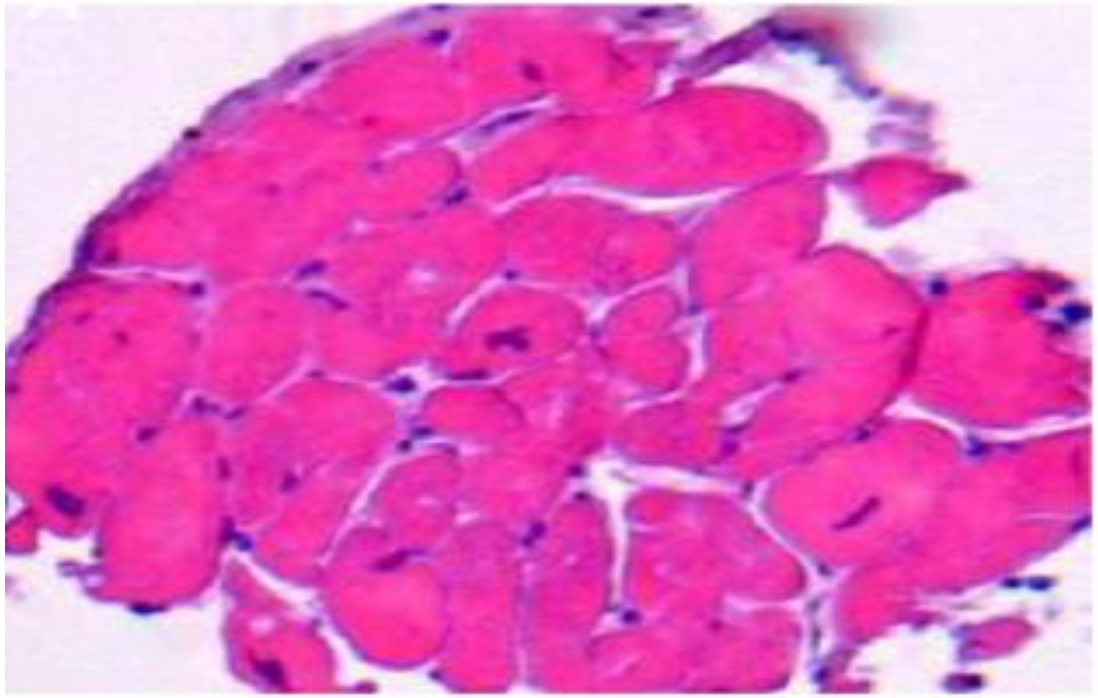
**DMCMP**
**Dilated/HFREF Phenotype**

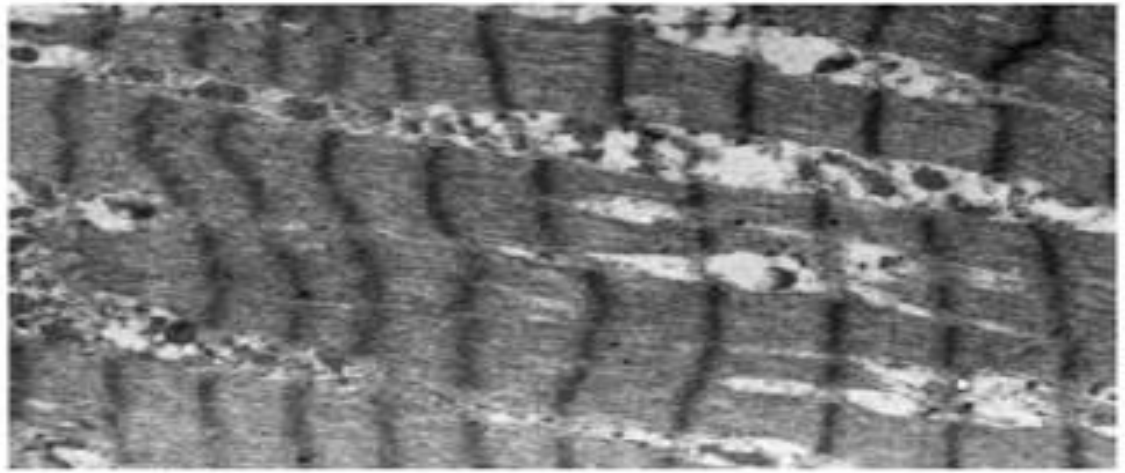
1) Presence of DM
2) Exclusion of CAD, valvular or congenital heart disease
3) Exclusion of hypertensive heart disease (=DBP<90mmHg)
4) Exclusion of viral myocarditis by endomyocardial biopsy
5) LVEF<50%; LVEDVI>97ml/m²

Petar M. Seferović. Eur Heart J 2015.

# Thể cơ tim hạn chế / suy tim phân suất tống máu bảo tồn (HFPEF):

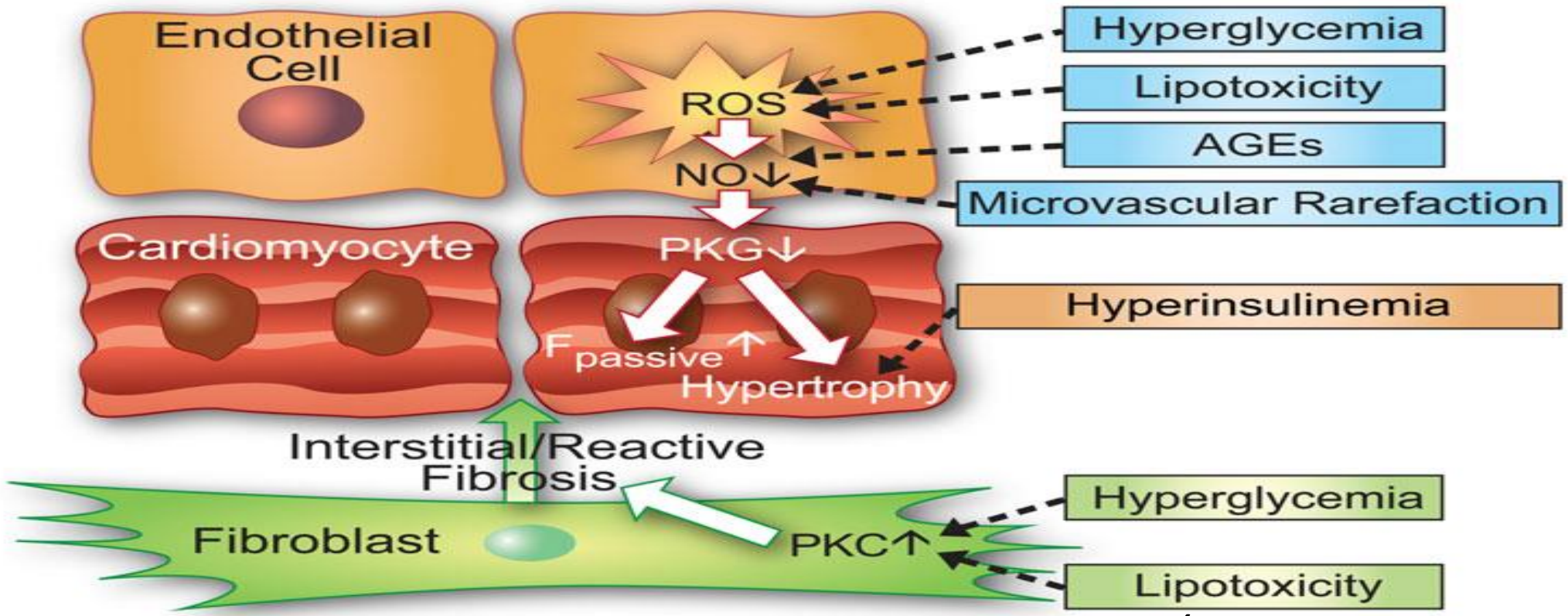
Restrictive/HFPEF phenotype





Cơ tim phì đại , collagen nằm giữa tế bào cơ tim (phản ứng xơ hóa) (bên trái) và cấu trúc bao cơ còn bảo tồn (bên phải).

# Thể cơ tim hạn chế / suy tim phân suất tống máu bảo tồn (HFPEF):

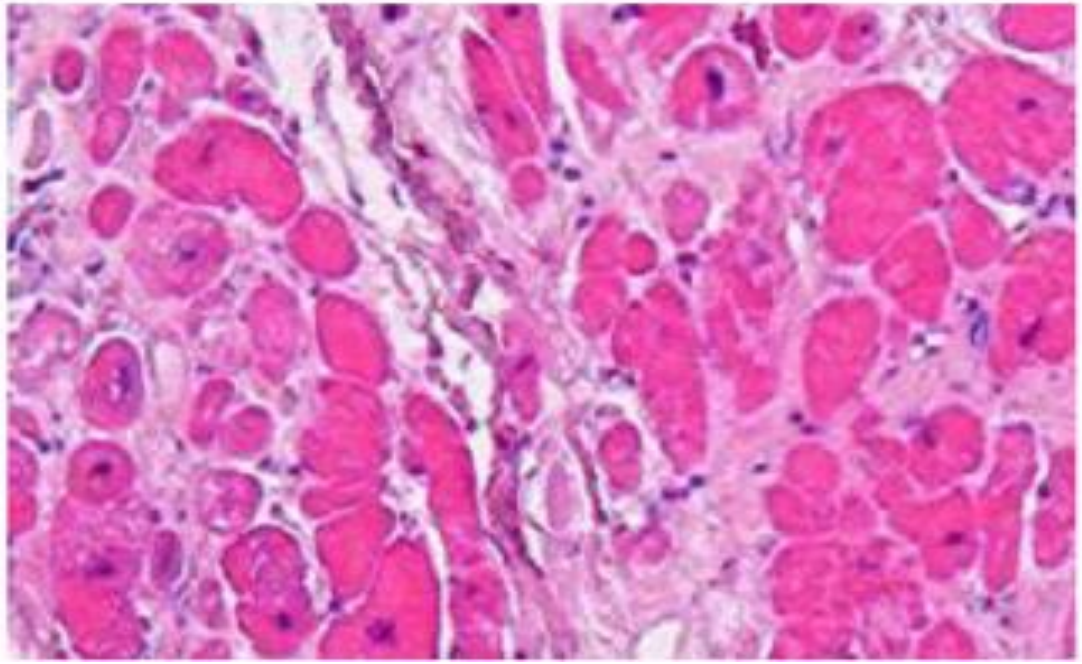


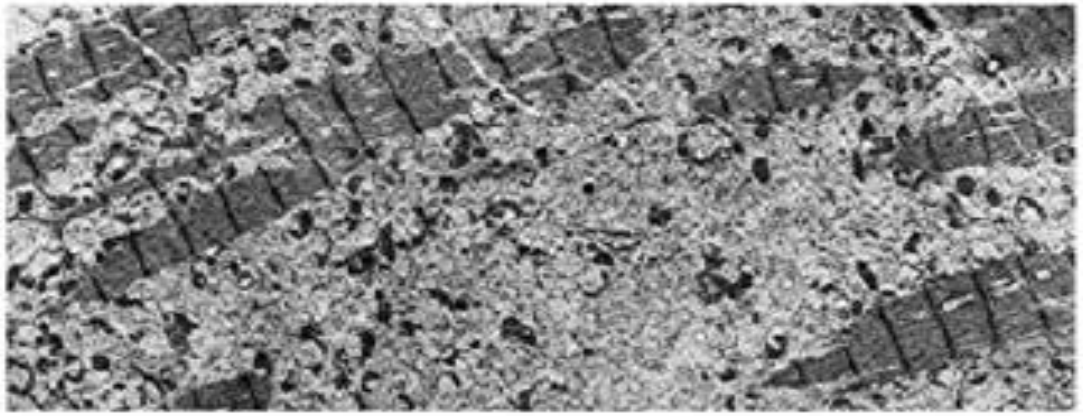

RLCN nội mạc vi mạch vành do tăng G máu, nhiểm độc lipid và lắng đọng AGEs. Thưa vi mạch góp phần giảm sinh tổng hợp NO và cường insulin gây phì đại cơ tim. Tăng G máu và nhiểm độc lipid làm tăng PKC trong nguyên bào sợi và tăng lắng đọng collagen tổ chức kẻ .

RLCN nội mạc vi mạch vành dẫn đến rối loạn và tái cấu trúc cơ thất trái liên quan giảm sinh tổng hợp NO cơ tim và giảm hoạt động PKG. Điều này tác động phì đại cơ tim và xơ hóa tổ chức kẻ phản ứng.

# Thể cơ tim giãn / suy tim kèm giảm phân suất tống máu (HFREF).

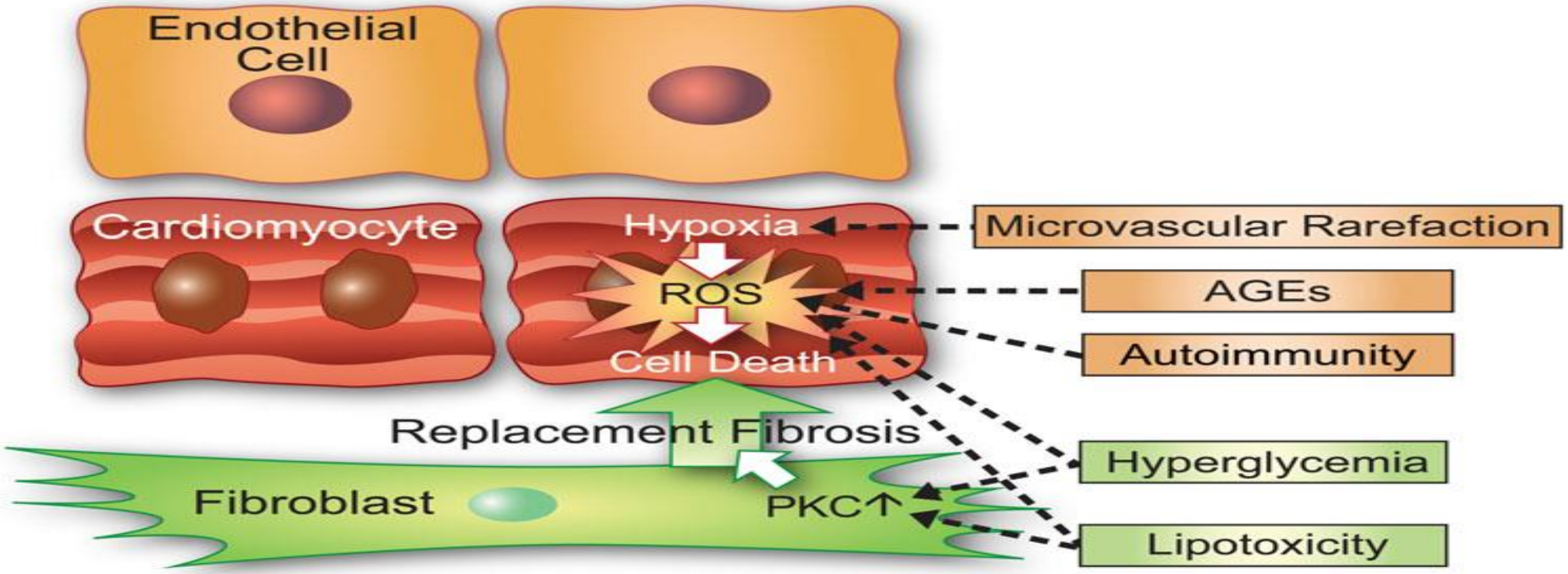
Dilated/HFREF phenotype





Tế bào cơ tim nhỏ lại  và hư hại, collagen hiện diện lớn (thay thế tổ chức xơ ) (bên trái ) và màng bao cơ mất (bên phải ).

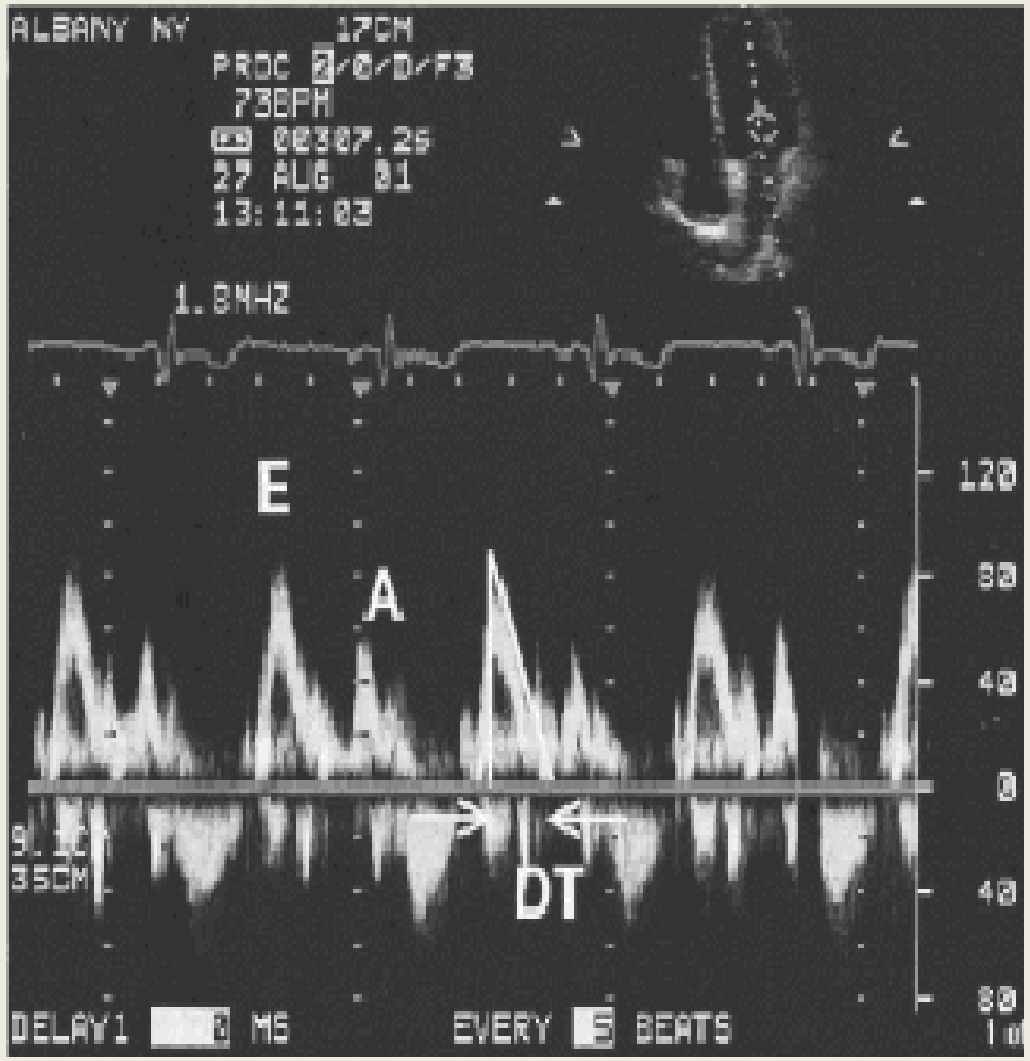
# Thể cơ tim giãn / suy tim kèm giảm phân suất tống máu (HFREF).



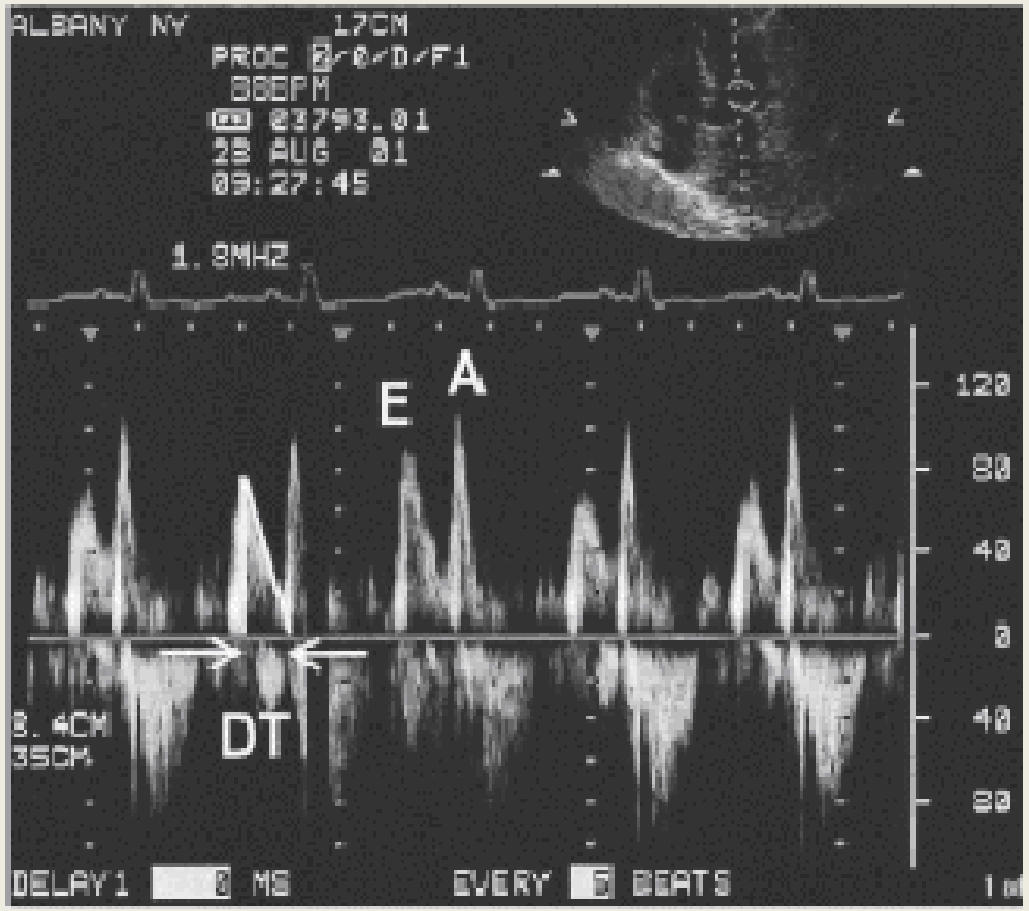

- TB cơ tim chết dẫn đến tái tạo và RLCN thất trái. TB cơ tim chết do stress oxy hóa trong ngăn TB cơ tim  do tổ chức thiếu khí gây ra bởi thưa mao mach, hiện diện TB viêm liên quan tự miễn, lắng đọng AGEs và khả năng do tăng G máu và nhiểm độc lipid . Do TB cơ tim chết có sự thay thế tổ chức xơ được hổ trợ bởi nồng độ PKC trong nguyên bào sợi do tăng G máu và nhiểm độc lipid

# Bệnh cơ tim đái tháo đường
# dưới góc nhìn Nội Tiết Tim Mạch Học Việt Nam

# Rối Loạn chức năng tâm trương trên Bn ĐTĐ không THA

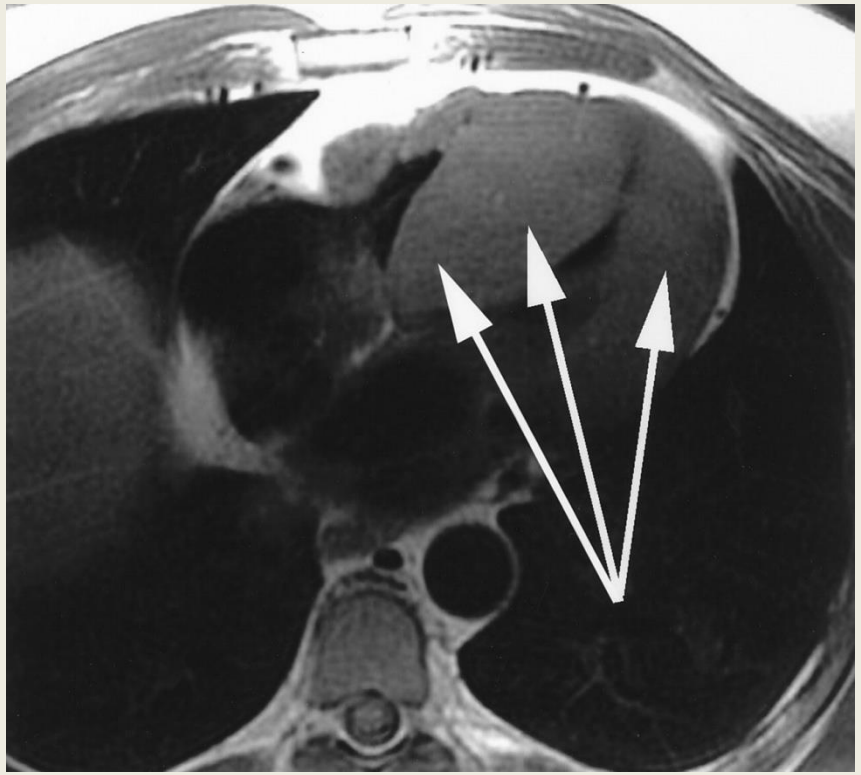


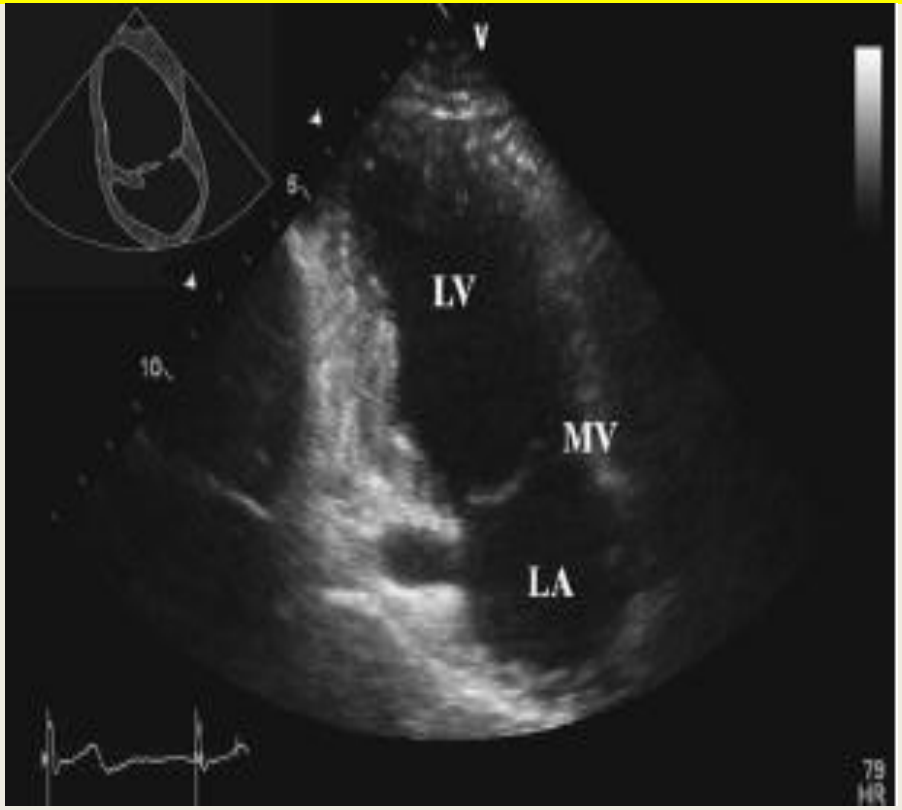

Normal




- Echocardiography study of 48 non-hypertensive type 2 diabetic patients
- **Prevalence of diastolic dysfunction was 81,25% and first degree was 70,83%**
- (Nguyen Quoc Viet- Nguyen Hai Thuy, Nguyen Anh Vu 2003)

# LVMI in type 2 diabetic patients without HTN
# Tran Thi Van Anh,Nguyen Hai Thuy, Nguyen Anh Vu (2006-2007)






**Prevalence of LVH (with LVMI in male >125g/m2 and female > 110 g/m2) was 40%**

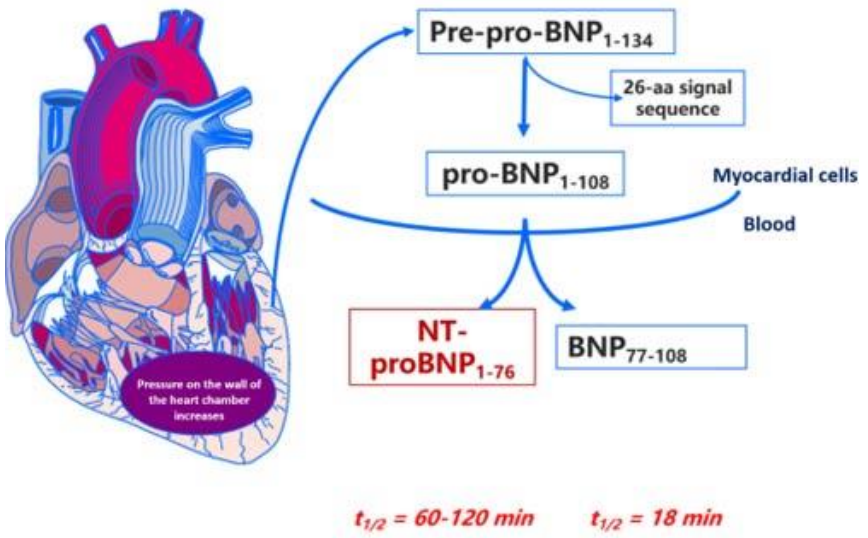
# Tỷ lệ bất thường LVMI, EF và CNTTr trên 130 bệnh nhân Tiền Đái Tháo Đường

Trần Thị Như Hảo Nguyễn Hải Thủy,Nguyễn Anh Vũ (2009-2010)

| Giới / Thông số | Nam n=62 | | Nữ n=68 | | Chung n (%) |
|---|---|---|---|---|---|
| | n | % | N | % | |
| ↑ LVMI | 23 | 37,09 | 27 | 39,70 | 50 (38,46) |
| EF ≤ 55% | 7 | 11,29 | 3 | 4,41 | 10 (7,69) |
| RLCNTTr | 24 | 38,71 | 34 | 50 | 58 (44,61) |

## Liên quan giữa Nồng độ NT-proBNP huyết thanh và một số chỉ số SÂ Tim Trên 104 bênh nhân ĐTĐ típ 2

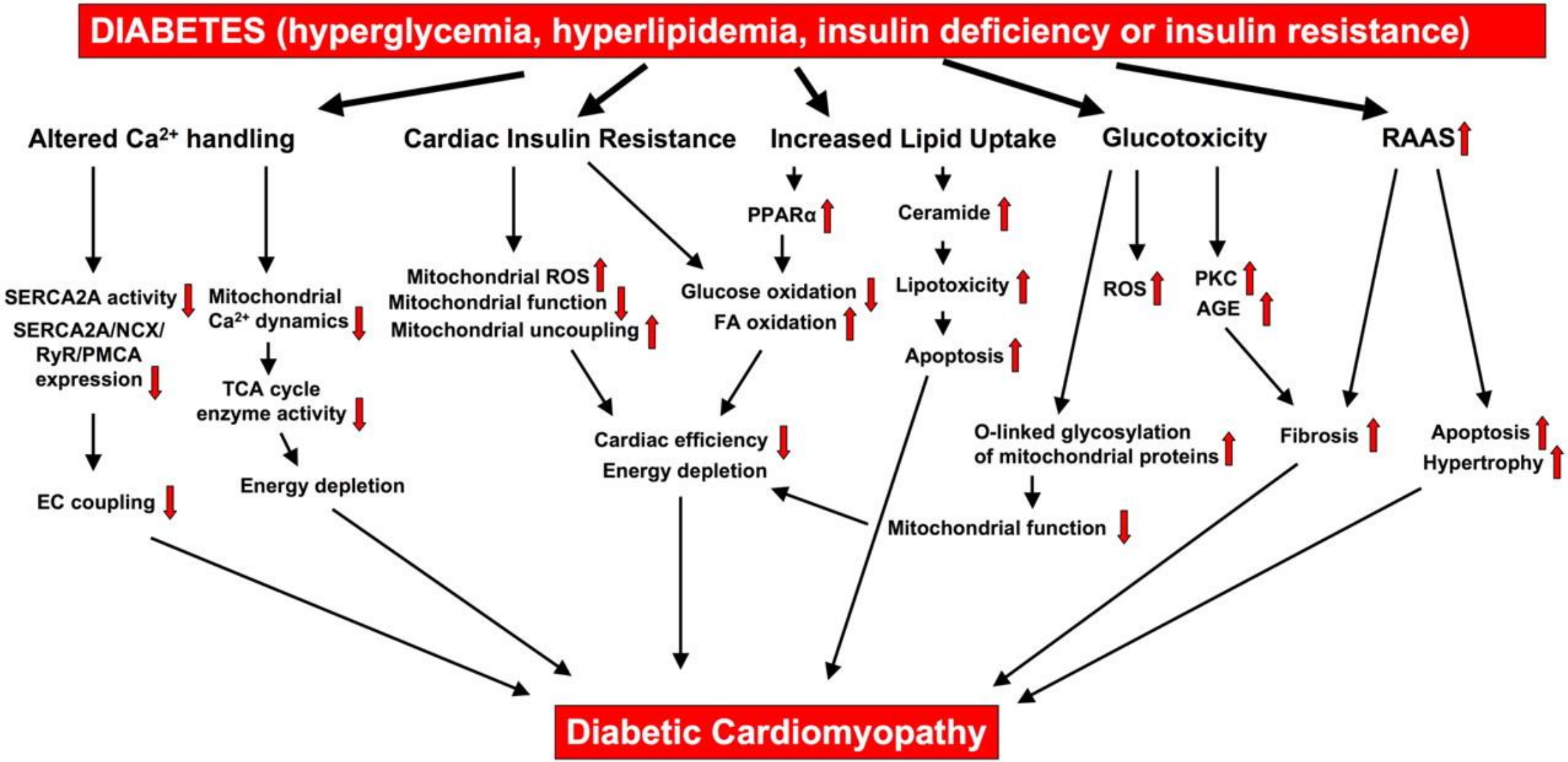
**(Lê Thanh Tùng, Nguyễn Hải Thủy, 2010)**

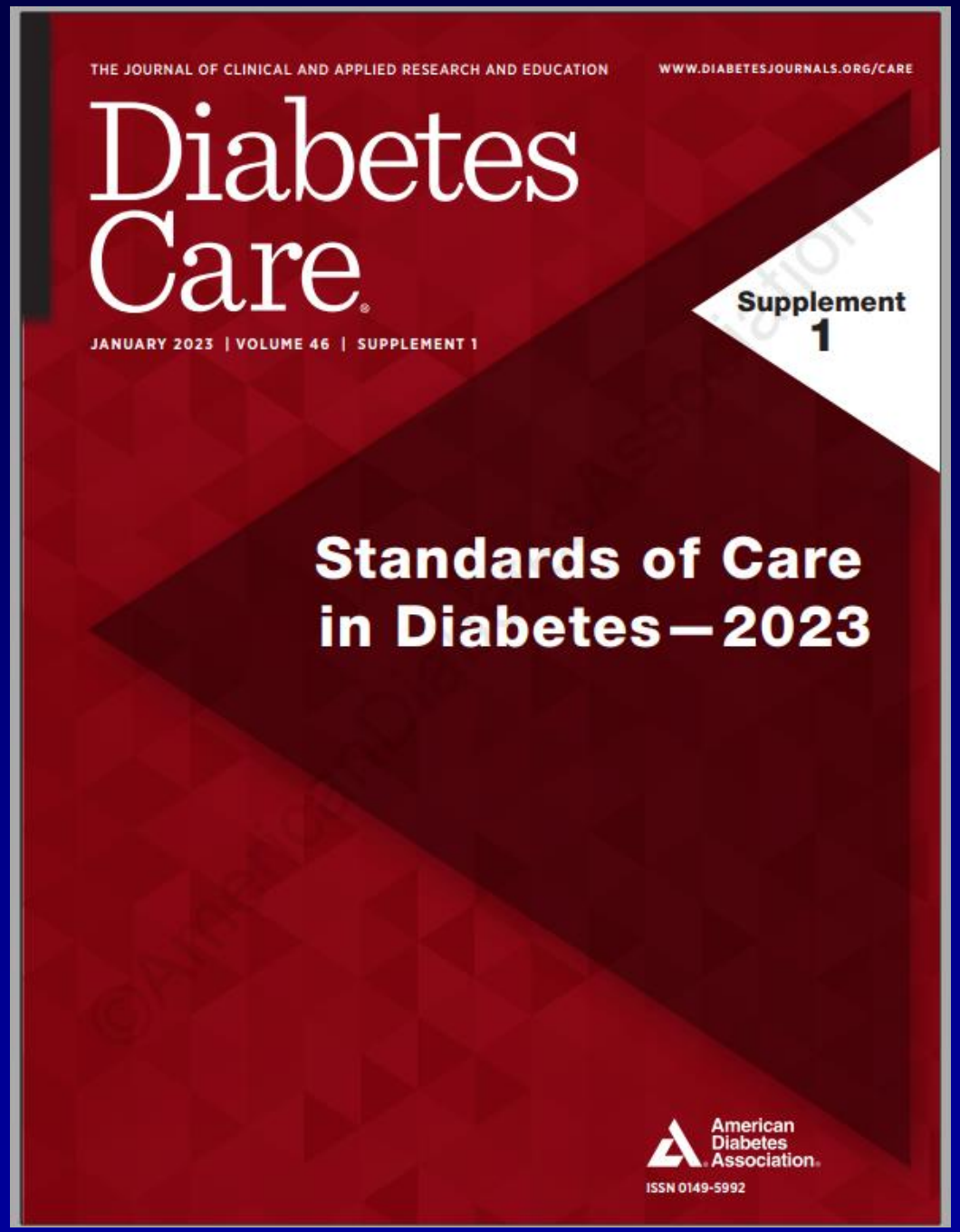



| Chỉ số siêu âm Tim | Bệnh lý | NTproBNP ( pg/ml ) | p |
|---|---|---|---|
| RLCN tâm Trương | Có | 286,19 ± 230,34 | p < 0,001 |
| | Không | 48,44 ± 34,53 | |
| Phì đại Thất Trái | Có | 279 ± 227,2 | p < 0,001 |
| | Không | 45,72 ± 31,5 | |
| RLCN tâm Thu | Có | 376,69 ± 299,4 | p < 0,001 |
| | Không | 89,75 ± 91,8 | |

# 5.Điều Trị
# Bệnh Cơ Tim Đái Tháo Đường

# Điều trị Bệnh CTĐTĐ nên dựa theo cơ chế bệnh sinh






**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

**10.41b** In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. A

10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*

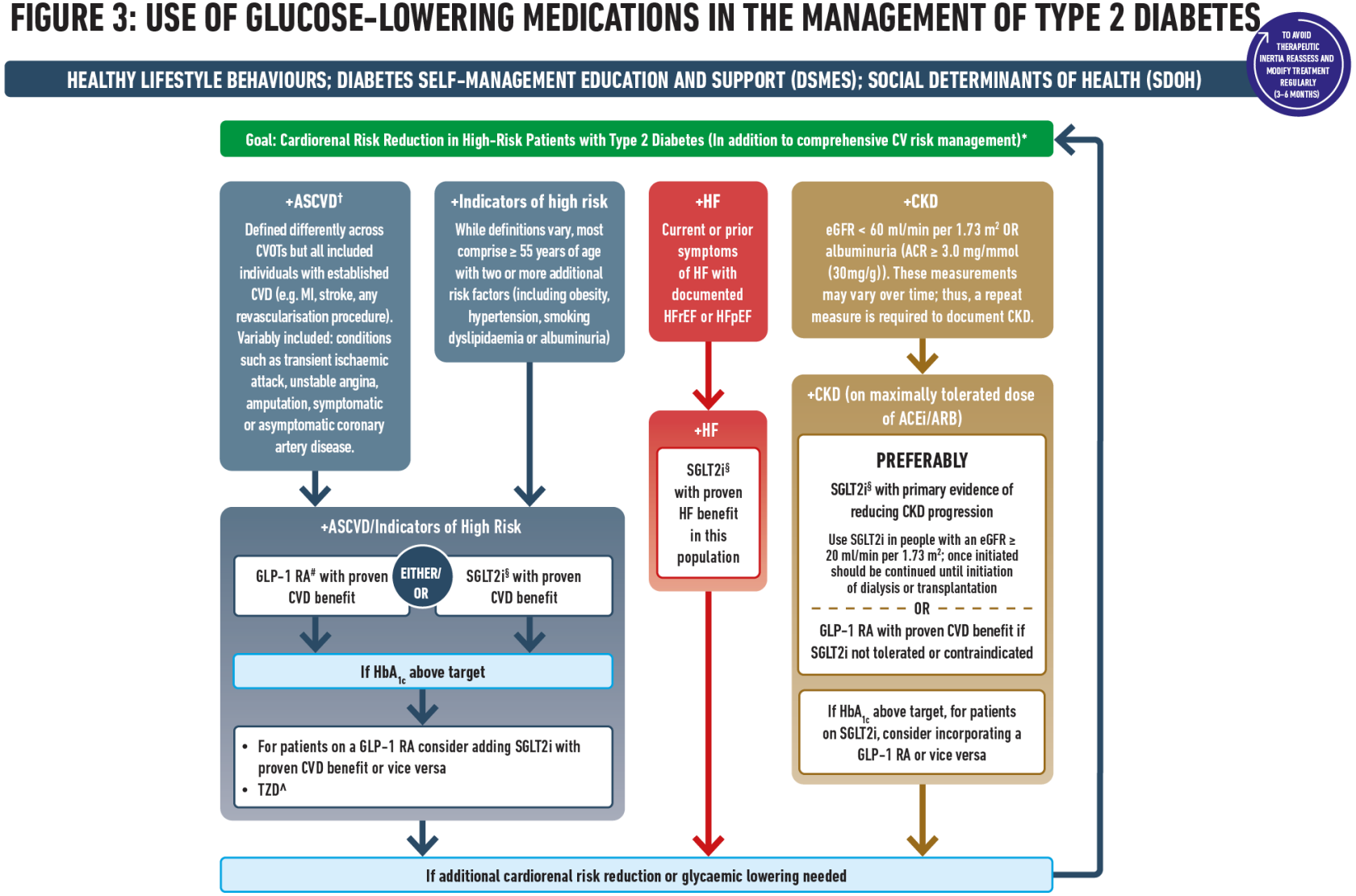
*Diabetes Care 2023;46(Suppl. 1):S158–S190 | https://doi.org/10.2337/dc23-S010*

**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**

# FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES




ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

American Diabetes Association®

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

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

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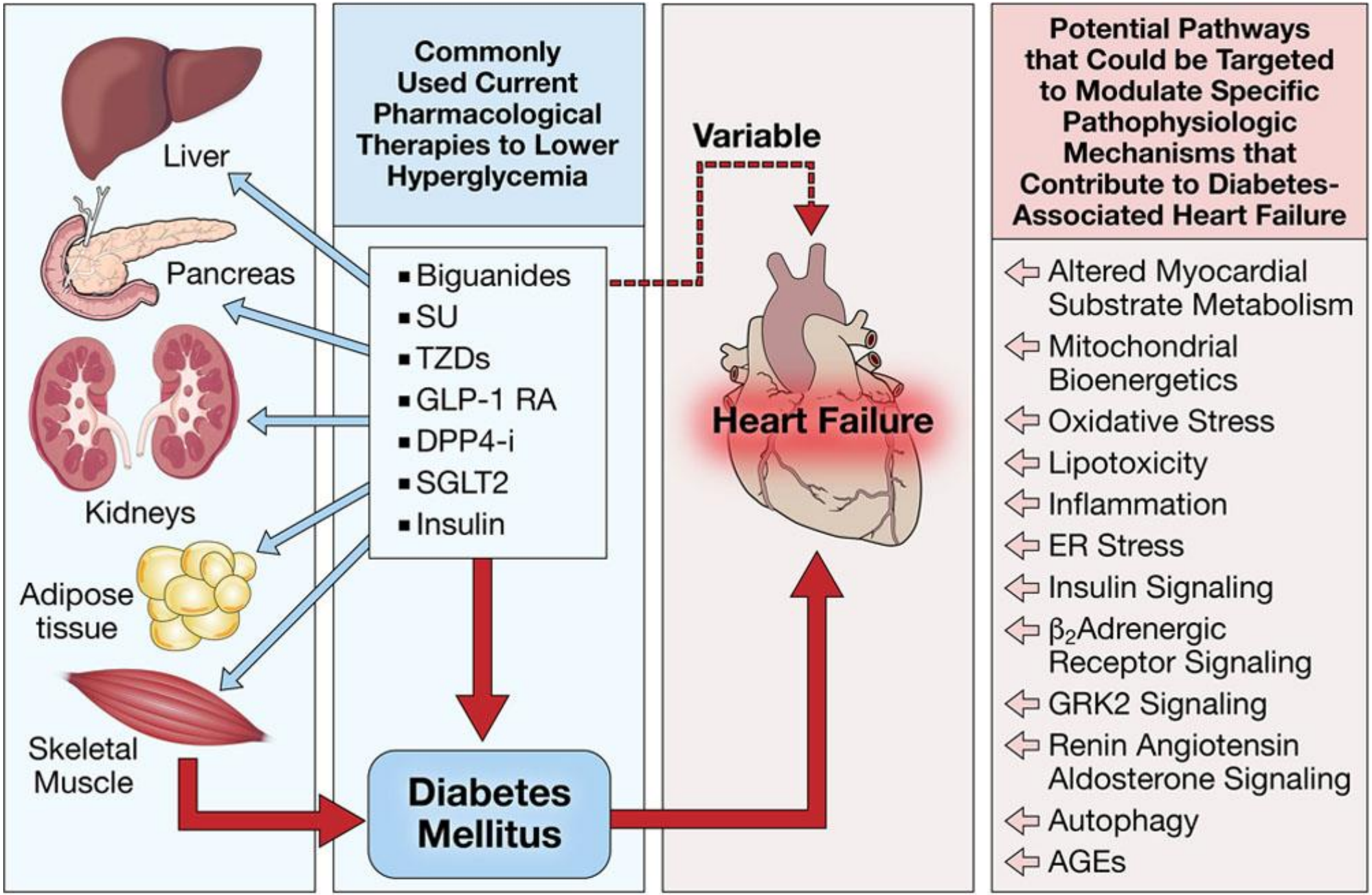
EASD European Association for the Study of Diabetes


Liver
Pancreas
Kidneys
Adipose tissue
Skeletal Muscle
Commonly Used Current Pharmacological Therapies to Lower Hyperglycemia
Biguanides
SU
TZDs
GLP-1 RA
DPP4-i
SGLT2
Insulin
Diabetes Mellitus
Variable
Heart Failure
Potential Pathways that Could be Targeted to Modulate Specific Pathophysiologic Mechanisms that Contribute to Diabetes-Associated Heart Failure
Altered Myocardial Substrate Metabolism
Mitochondrial Bioenergetics
Oxidative Stress
Lipotoxicity
Inflammation
ER Stress
Insulin Signaling
β2Adrenergic Receptor Signaling
GRK2 Signaling
Renin Angiotensin Aldosterone Signaling
Autophagy
AGEs

Laksono S, Hosea GT, Nurusshofa Z. Diabetic Cardiomyopathy: Pathophysiology and Novel Therapies. *Brown J Hosp Med*. 2022;1(3). doi:10.56305/001c.37850

Brief Reviews

# Diabetic Cardiomyopathy: Pathophysiology and Novel Therapies

Sidhi Laksono, MD[1], Grace T. Hosea, MD[2], Zahra Nurusshofa, MD[3]

[1] Siloam Diagram Heart Hospital, Cinere, Indonesia; Faculty of Medicine, Universitas Muhammadiyah Prof Dr Hamka, Tangerang, Indonesia, [2] Faculty of Medicine, Pelita Harapan University, Tangerang, Indonesia, [3] Faculty of Medicine, Universitas Muhammadiyah Prof Dr Hamka, Tangerang, Indonesia

- GLP-1 analog and SGLT2i have been shown to reduce cardiovascular mortality and improve glycemic control.However, the treatment of T2DM patients with HF using GLP-1 analogs remains controversial. Several studies in DM patients have found that GLP-1 analogs did not affect any major adverse cardiovascular event (MACE). Other trials showed that GLP-1 analogs have a significantly lower cardiovascular mortality rate, nonfatal myocardial infarction, or nonfatal stroke, improve lipotoxicity, and also protects cardiac function in T2DM patients.
- On the other hand, there are also studies that concluded the liraglutide (a GLP-1 analog) worsened the cardiac outcomes and significantly increase MACE.

# Vai trò bảo vệ Tim Mạch của Đồng vận GLP1

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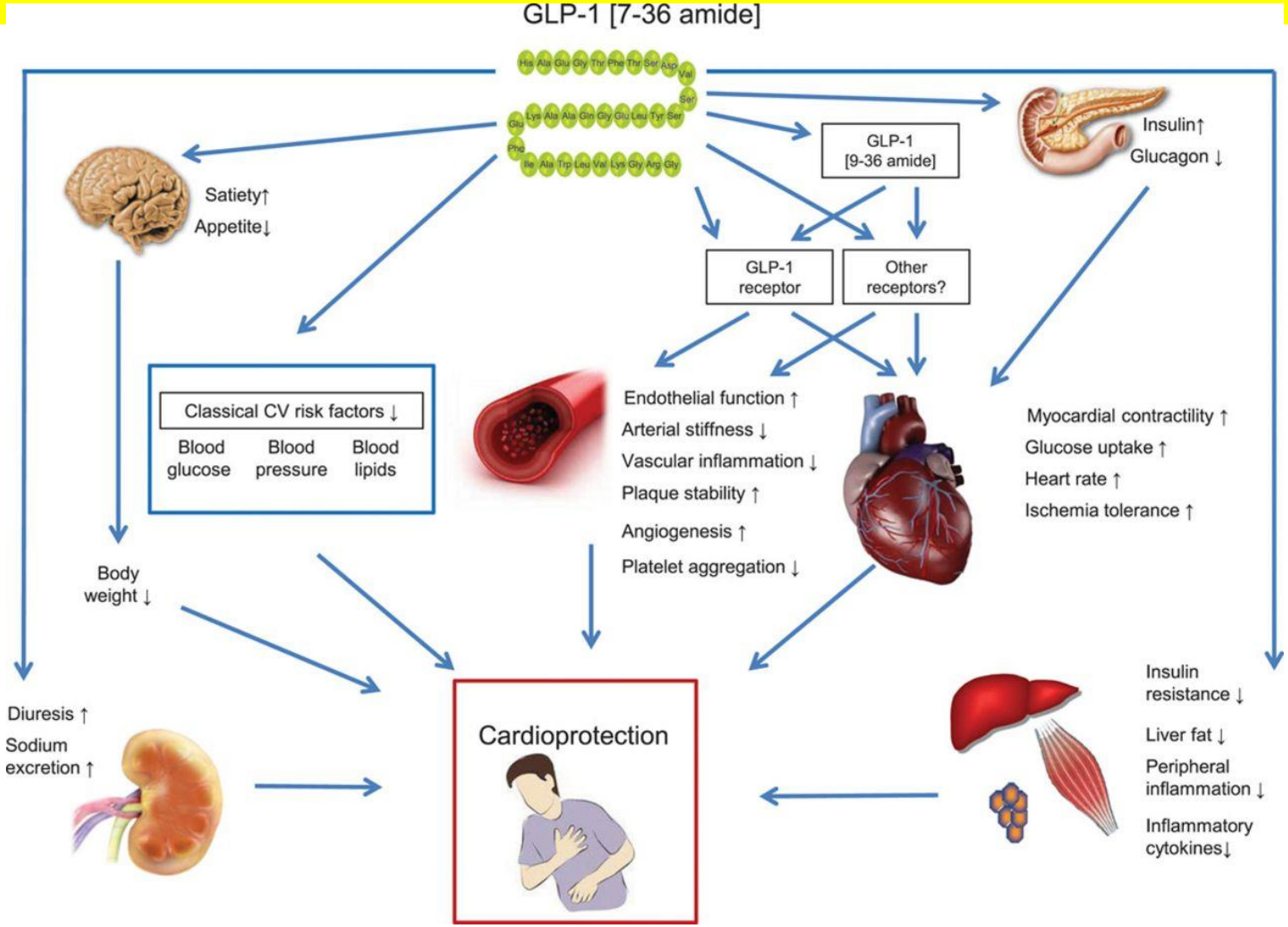
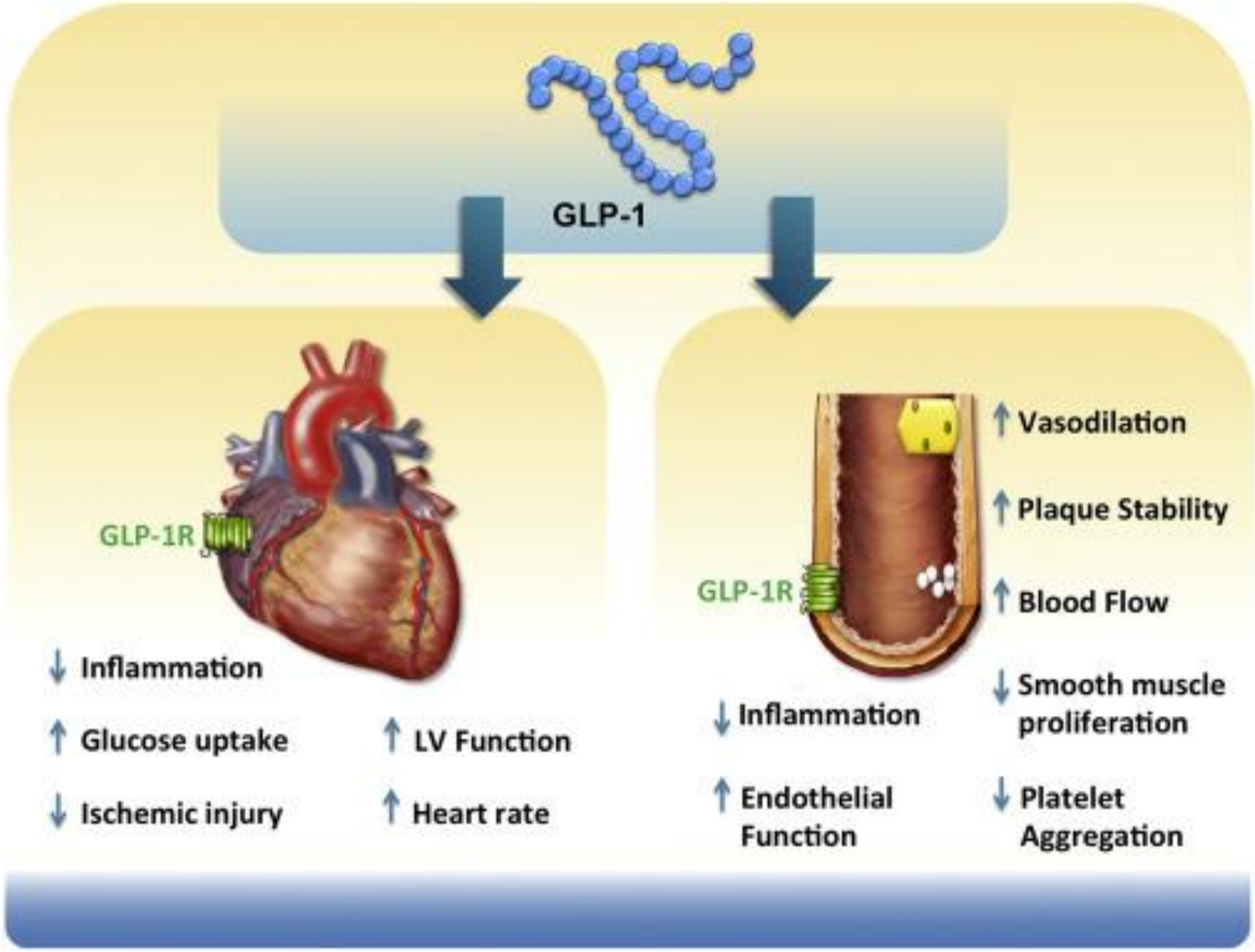
# Bảo vệ Tim của nhóm đồng vận Thụ thể GLP1



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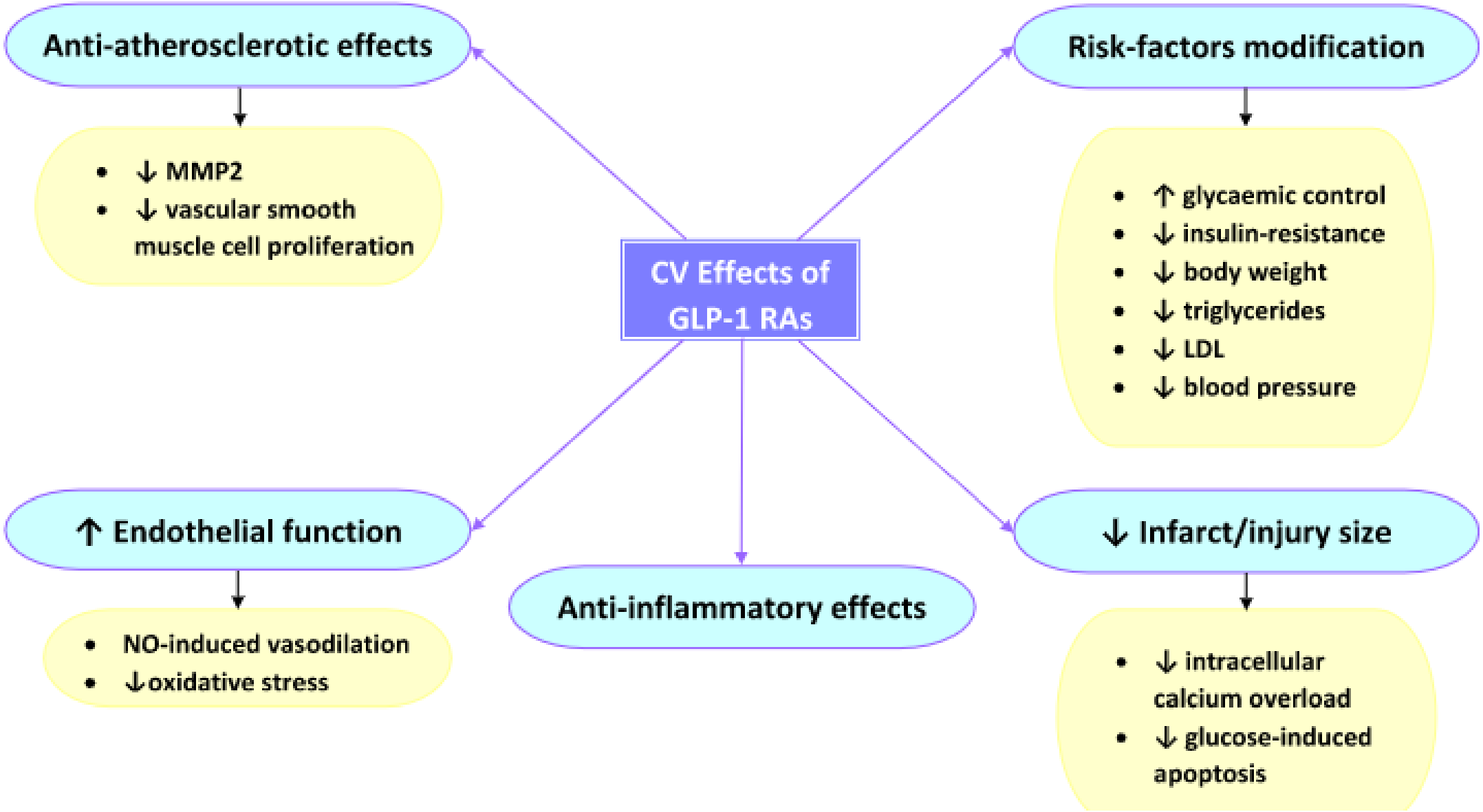


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| GLP-1R agonist | Study model | GLP-1R agonist mediated outcome |
|---|---|---|
| Liraglutide (uptitrated to 1.8 mg once daily) | Subjects with T2DM and no history of cardiovascular disease treated with liraglutide for 6-months | • Increased e′<br>• Decreased LV end diastolic volume |
| Liraglutide (uptitrated to 1.8 mg once daily) | Subjects with T2DM and no history of acute coronary disease treated with liraglutide for 6-months | • Increased e′<br>• Increased e′/a′ ratio<br>• Decreased E/e′ ratio |
| Exenatide (10 μg twice daily) | Subjects with T2DM treated with exenatide for 3-months | • Decreased pulse wave velocity<br>• Decreased E/e′ ratio |
| Liraglutide (uptitrated to 1.8 mg once daily) | Subjects with T2DM and 65% having ≥1 cardiovascular risk factor treated with liraglutide for 6-months | • No difference in circumferential peak early diastolic strain rate |
| Liraglutide (30 μg once daily) | Male C57BL/6J mice subjected to T2DM and TAC surgery, treated with liraglutide for 15-weeks | • Liraglutide treatment prevented a decline in the LVEF in response to TAC |
| Liraglutide (30 μg twice daily) | Male C57BL/6J mice subjected to T2DM and treated with liraglutide for 2-weeks | • Increased mitral E/A ratio<br>• Decreased E/e′ ratio |
| Exendin-4 (100 μg/kg once daily SQ) | Male C57BL/6 mice subjected to T2DM and treated with exendin-4 for 8-weeks | • Increased mitral E/A ratio<br>• Increased LVEF |
| Liraglutide (75 μg once daily) | Male Sprague-Dawley rats subjected to T2DM treated with liraglutide for 4-weeks. | • Decreased oxidative stress and cardiac myocyte apoptosis |
| Exenatide (24 nmol/kg once daily IP) | Male C57BL/6J mice subjected to experimental obesity and treated with exenatide for 4-weeks. | • Decreased oxidative stress<br>• Increased mitral E/A ratio |

The impact of GLP-1R agonists on diabetic cardiomyopathy.

Front. Physiol. 11:603247. doi: 10.3389/fphys.2020.603247

# Vai trò bảo vệ Tim Mạch của Ức chế SGLT2

1.**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.

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.[22][23]

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]


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

**8.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]

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

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



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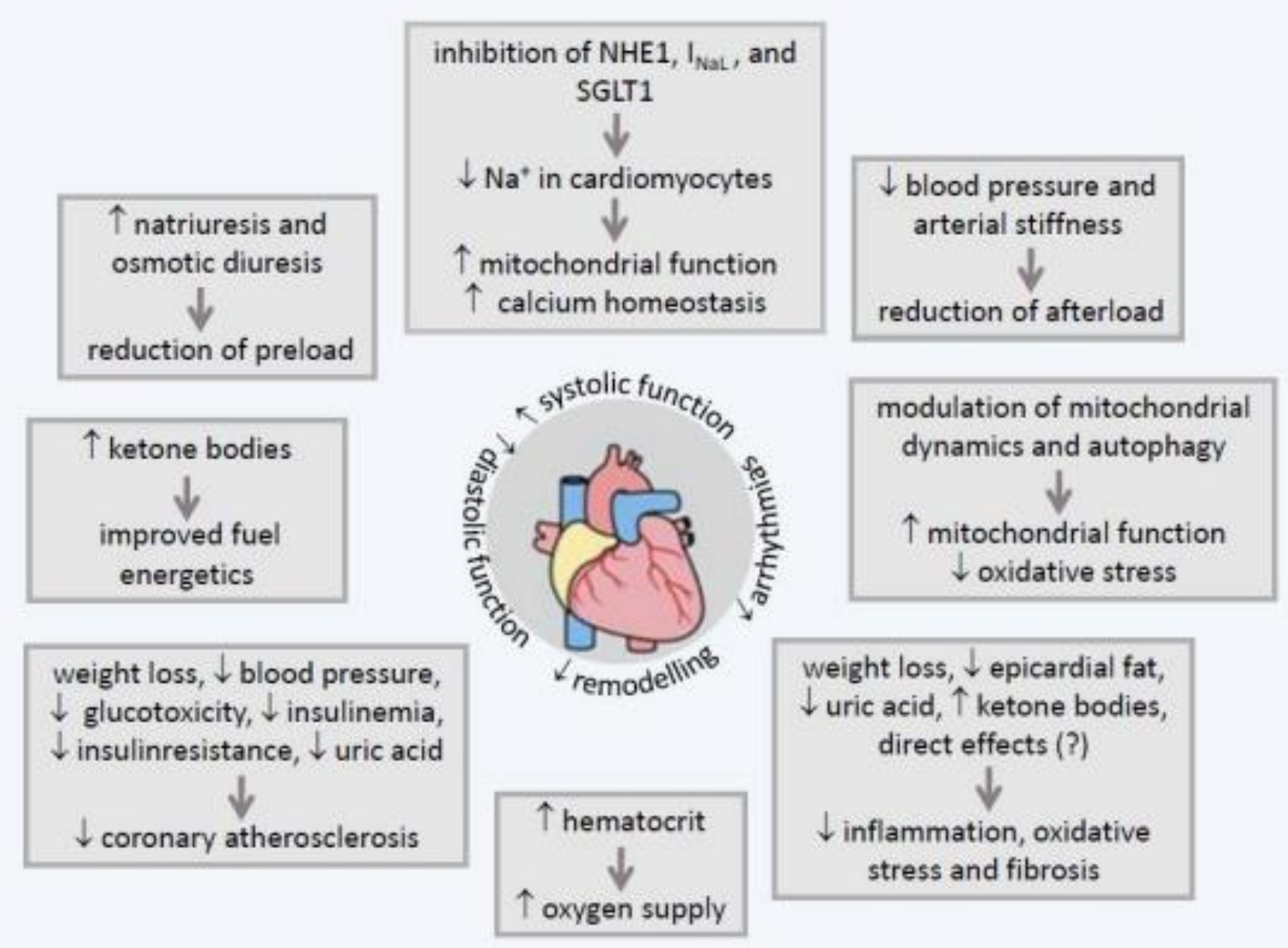
# Tóm tắt cơ chế bảo vệ tim của ức chế SGLT2

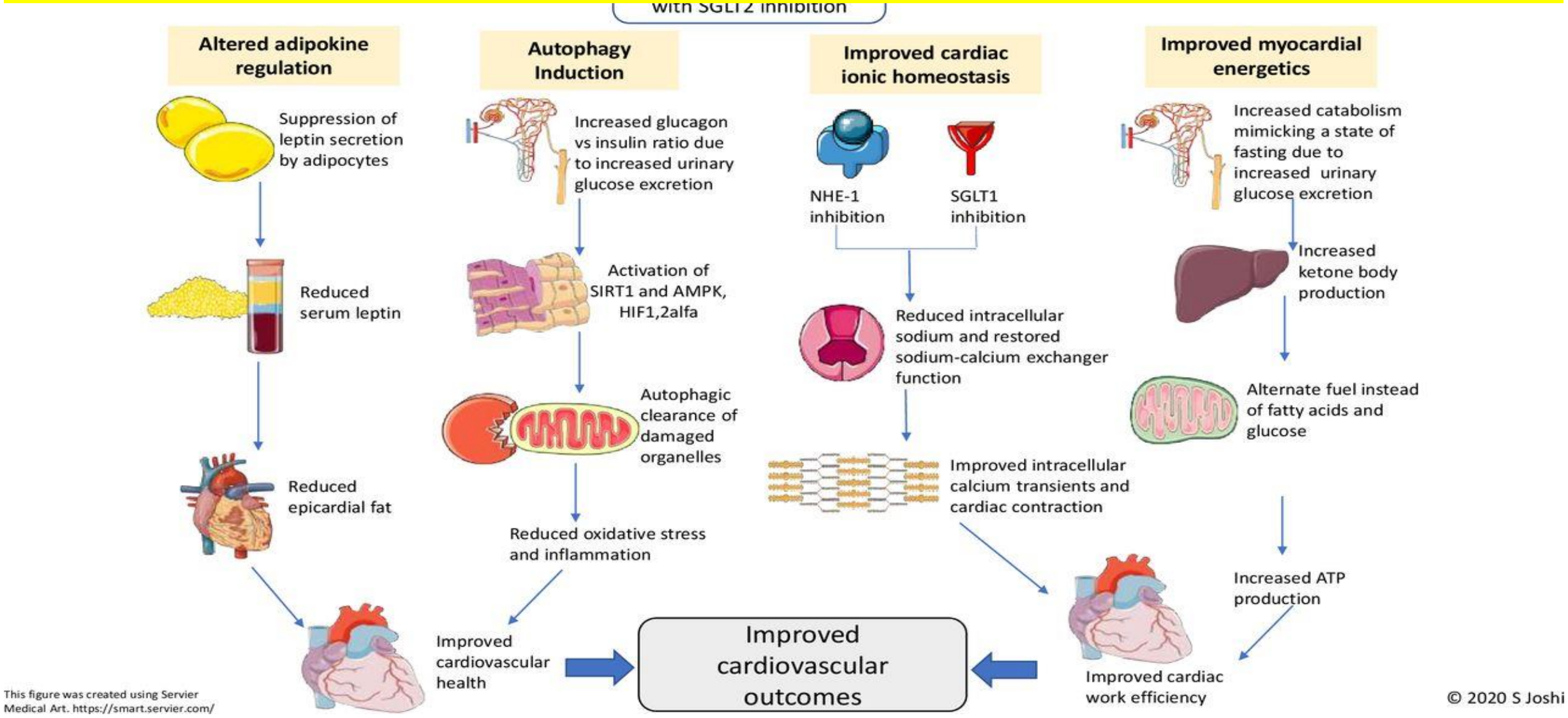
| Potential Mechanisms |
|---|
| 1. Stimulation of natriuresis |
| 2. Stimulation of osmotic diuresis |
| 3. Cardiomyocyte $Na^+/H$ exchanger inhibition |
| 4. Increased myocardial energetics (via altered myocardial substrate metabolism) |
| 5. Reduction in left ventricular mass |
| 6. Improved systolic 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.

# Tác dụng chính bảo vệ Tim của ức chế SGLT2

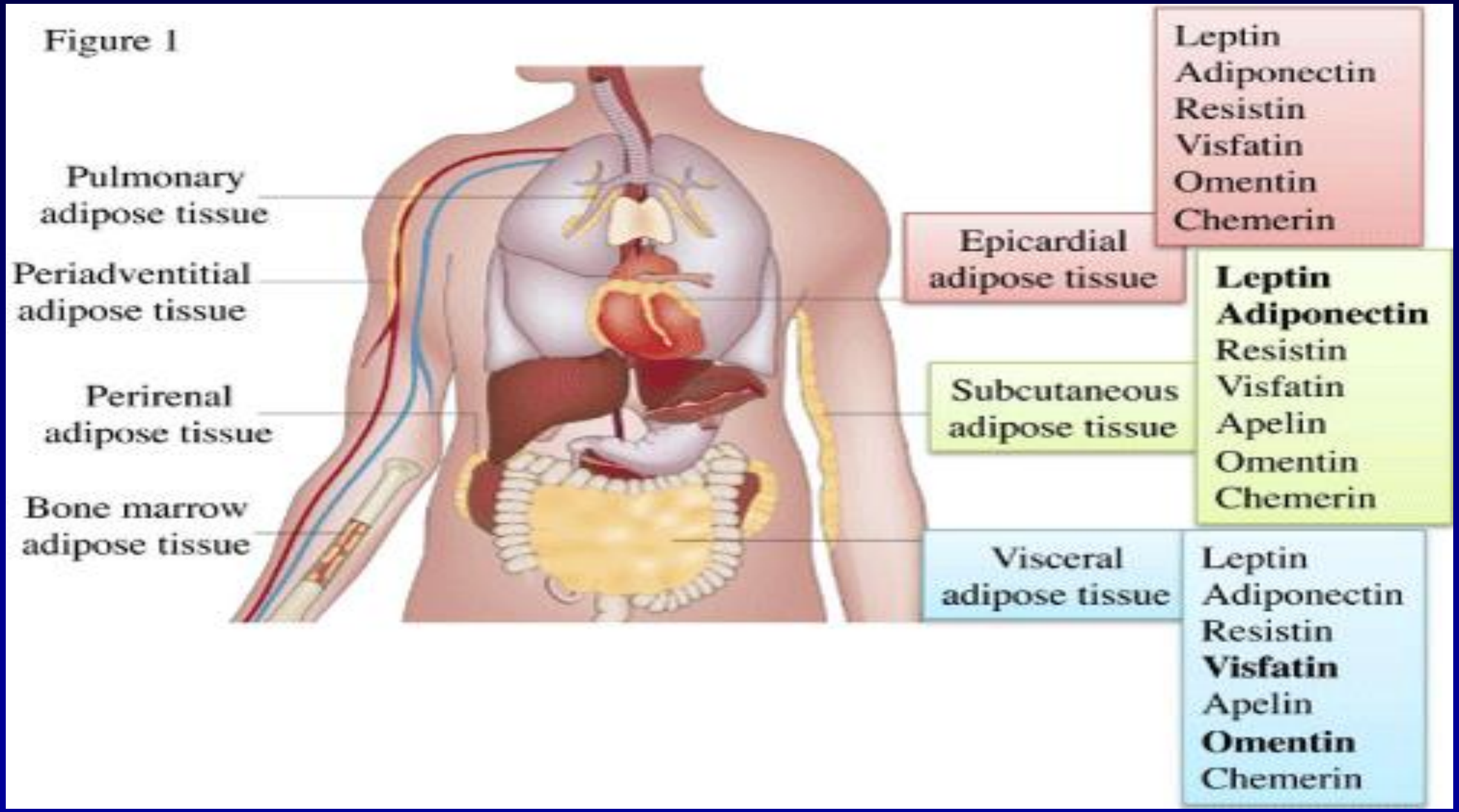


# Các cơ chế mới tác dụng trên suy tim của ức chế SGLT2

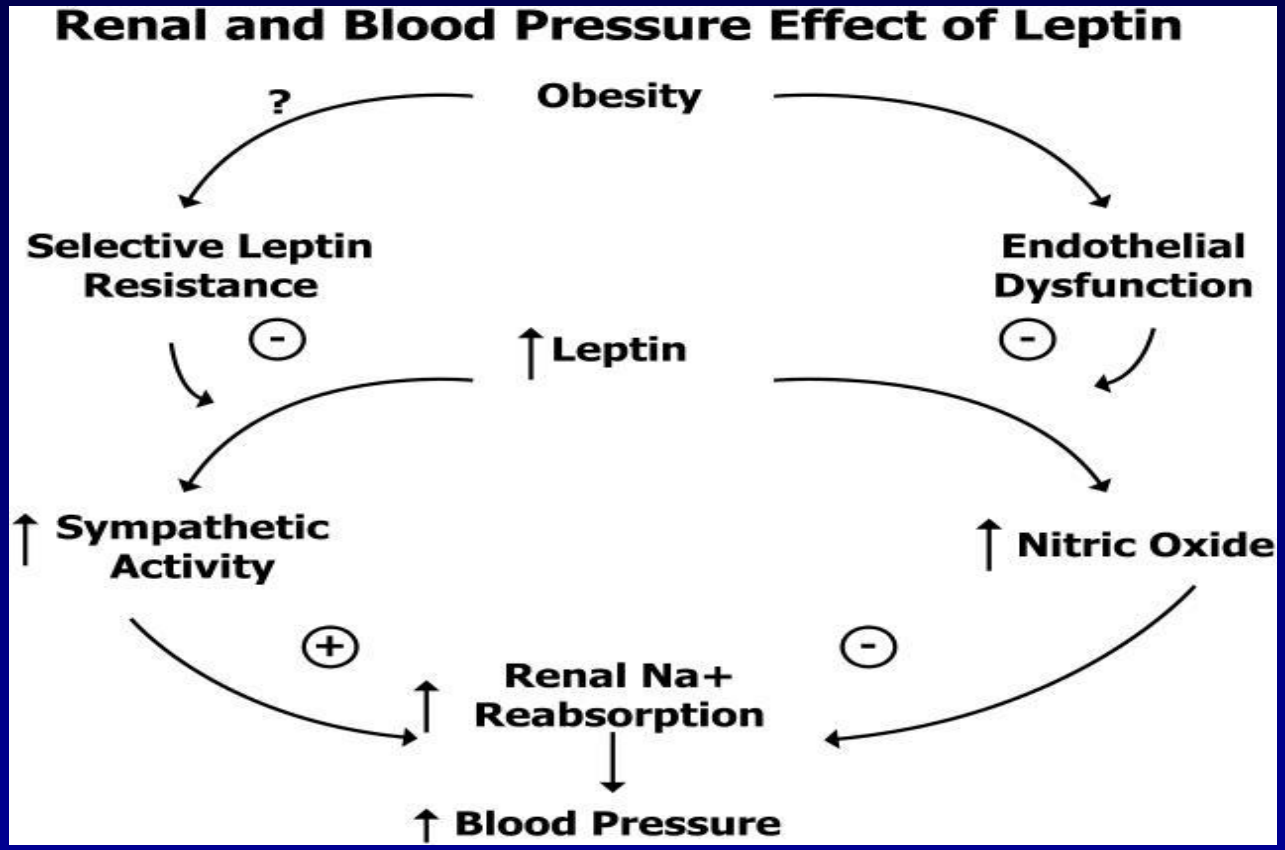



**Novel mechanisms of action of SGLT2 inhibitors in heart failure. AMPK, adenosine monophosphate-activated protein kinase; HIF, hypoxia-inducible factor; SIRT, sirtuin.**

# Cytokine viêm tại các tổ chức mỡ



# Ức chế SGLT2 và Điều hoà Adipokine

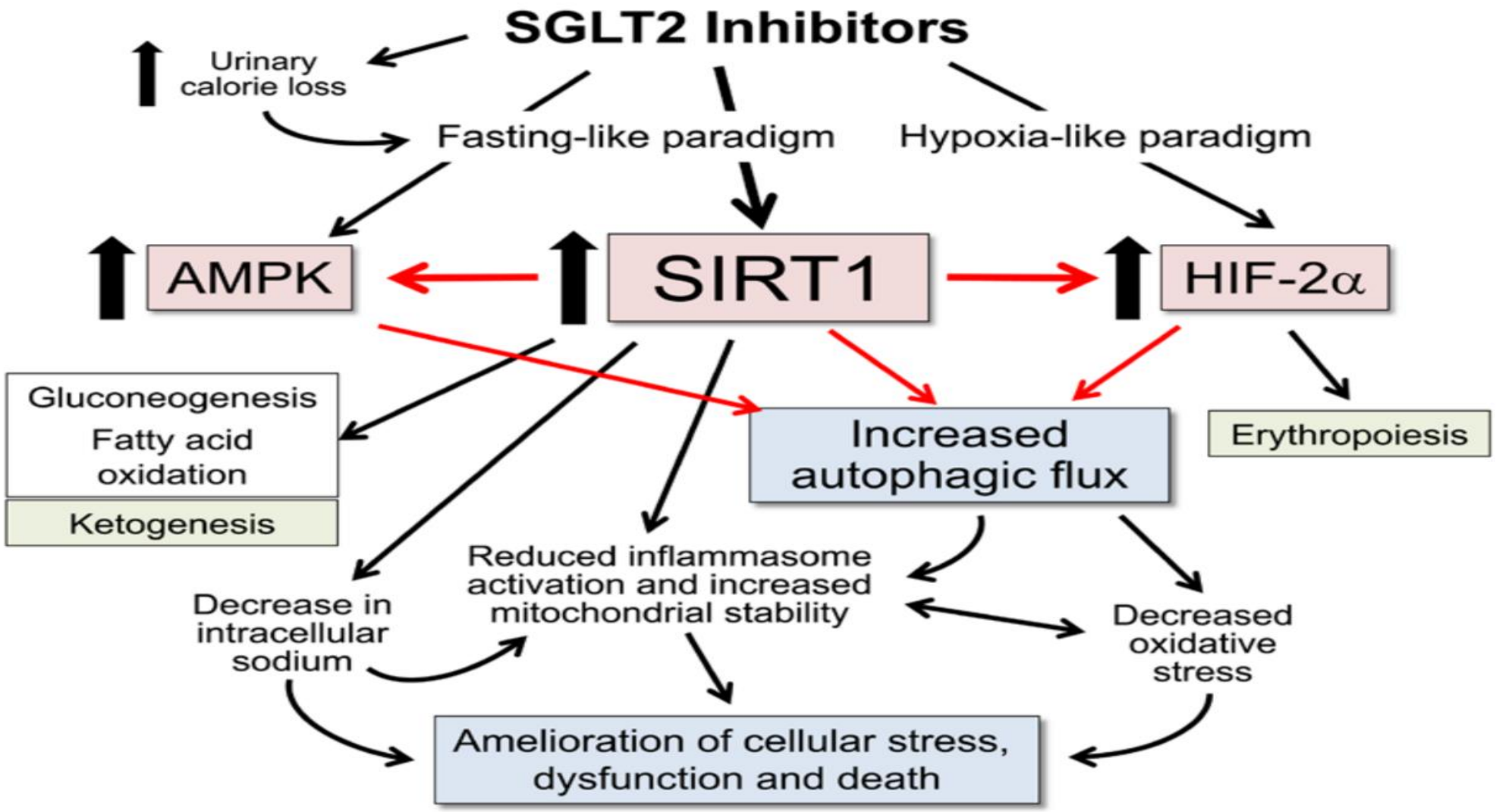



Ức chế SGLT2 và Leptin

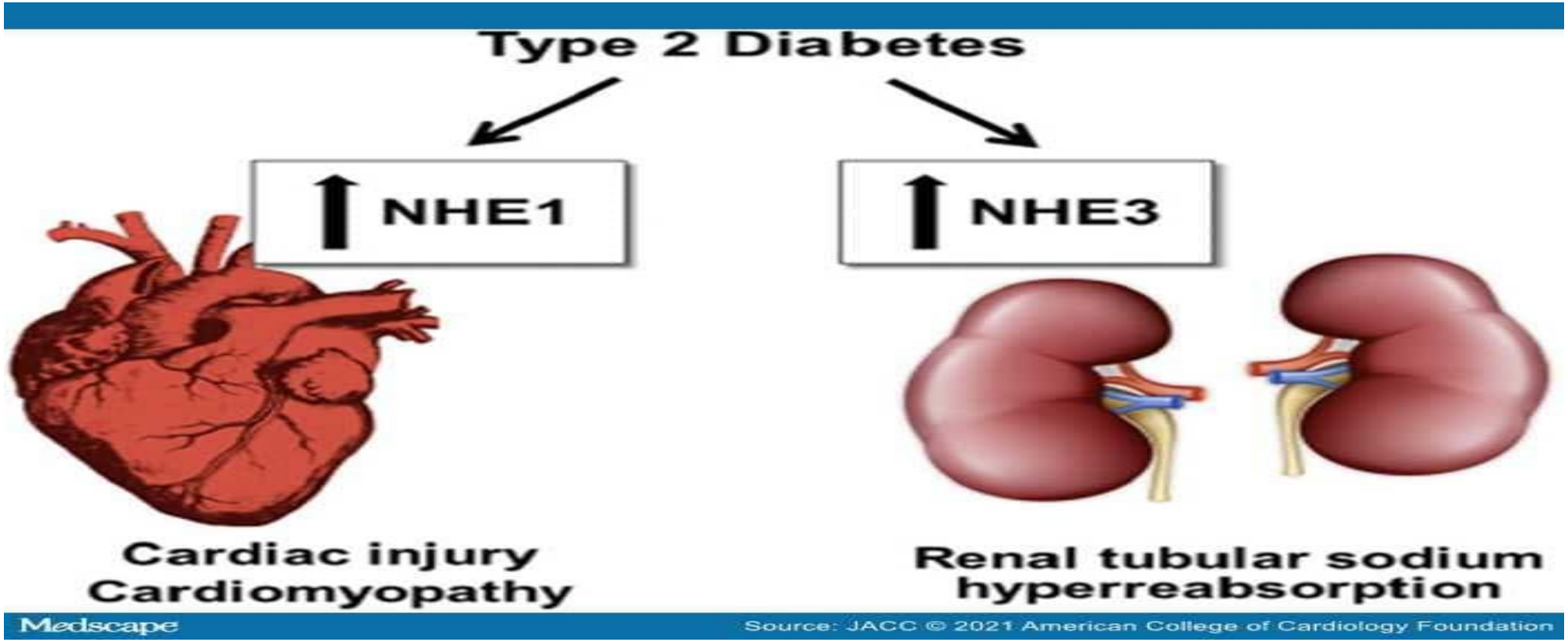
SGLT2 inhibitors reduce the accumulation and inflammation of perivisceral adipose tissue, thus minimizing the secretion of leptin and its paracrine actions on the heart and kidneys to promote fibrosis. Such fibrosis probably contributes to the impairment of cardiac distensibility and glomerular function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

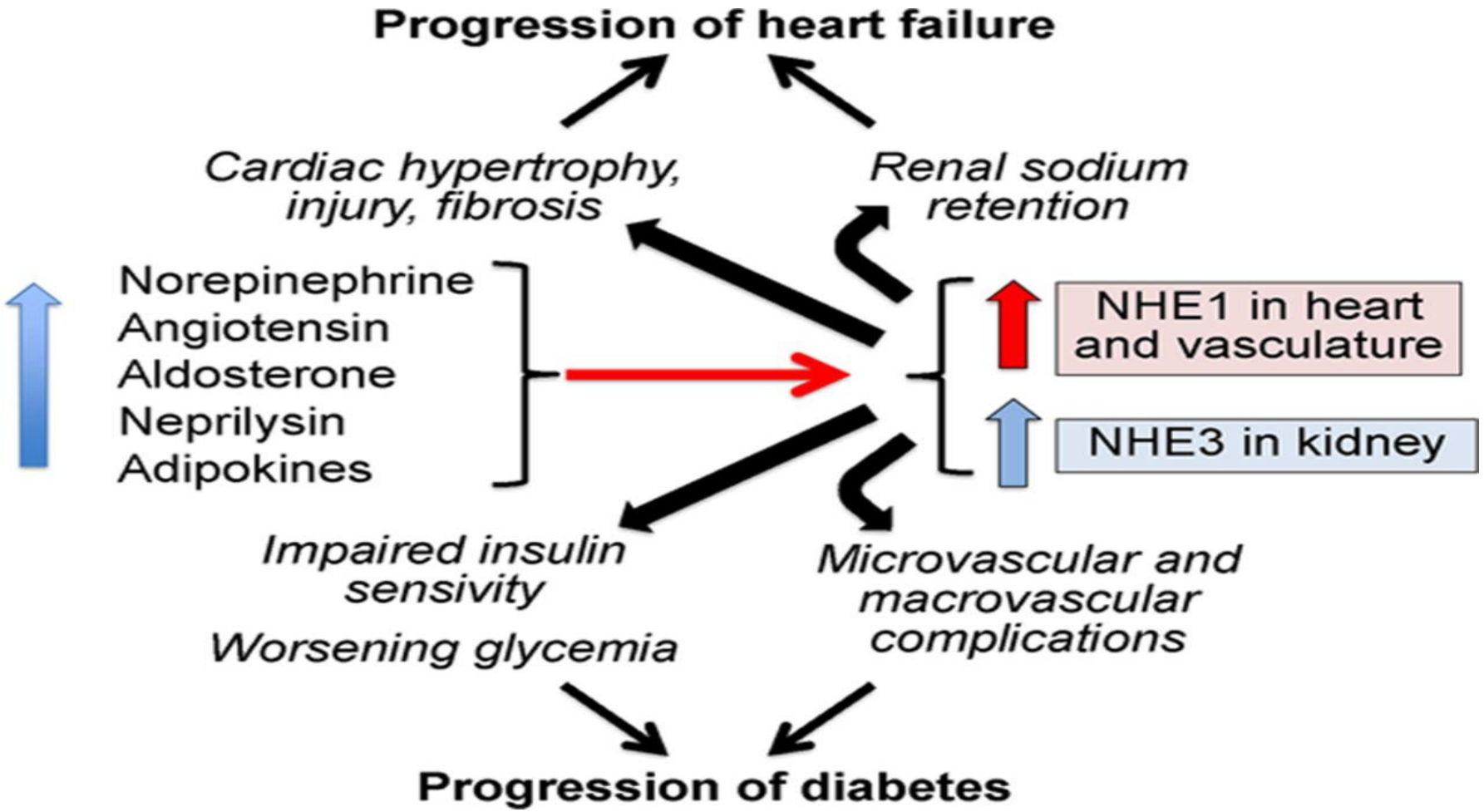
# Ức chế SGLT2 và Tự thực tế bào ( Autophagy)



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

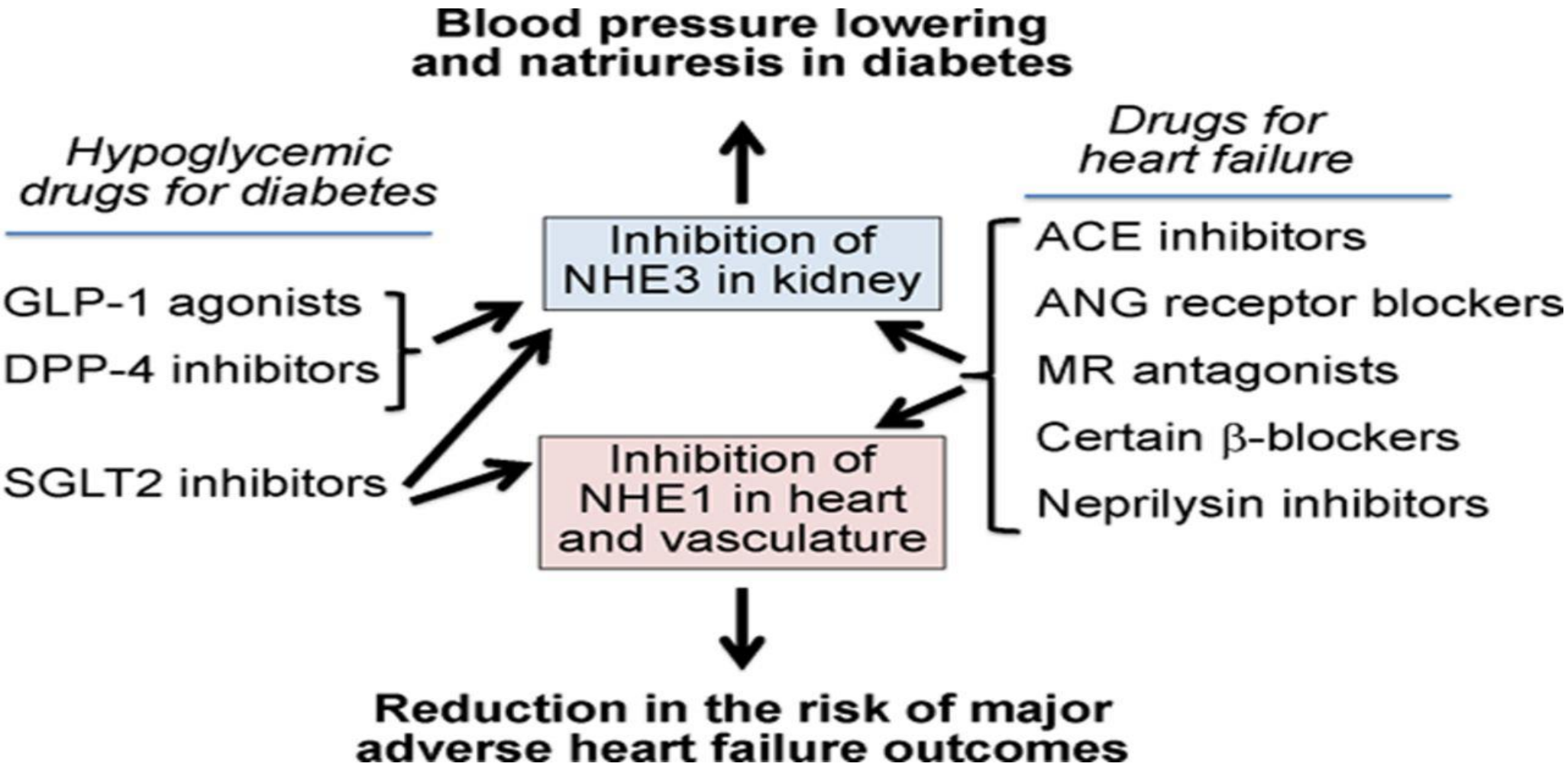


# Ức chế SGLT2 & Hệ thống trao đổi Natri–Hydro



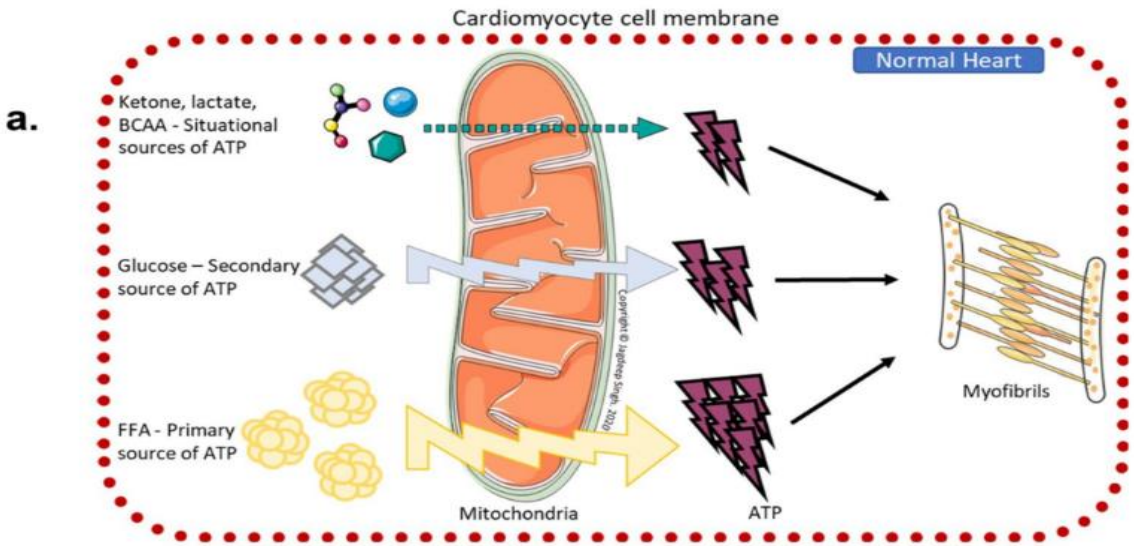

Packer M. (2017) Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With That of Heart Failure. Circulation. 2017 Oct 17;136(16):1548-1559.

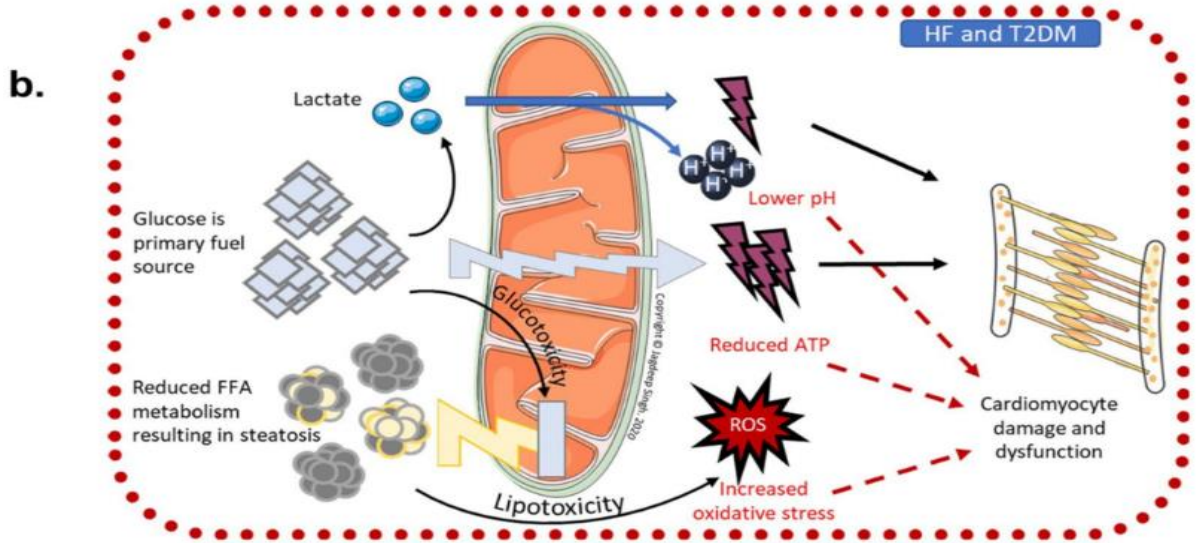
# Ức chế SGLT2 & Hệ thống trao đổi Natri–Hydro




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 Năng Lượng cơ tim
# Năng lượng cơ tim tiêu thụ người bình thường và Suy tim ĐTĐ

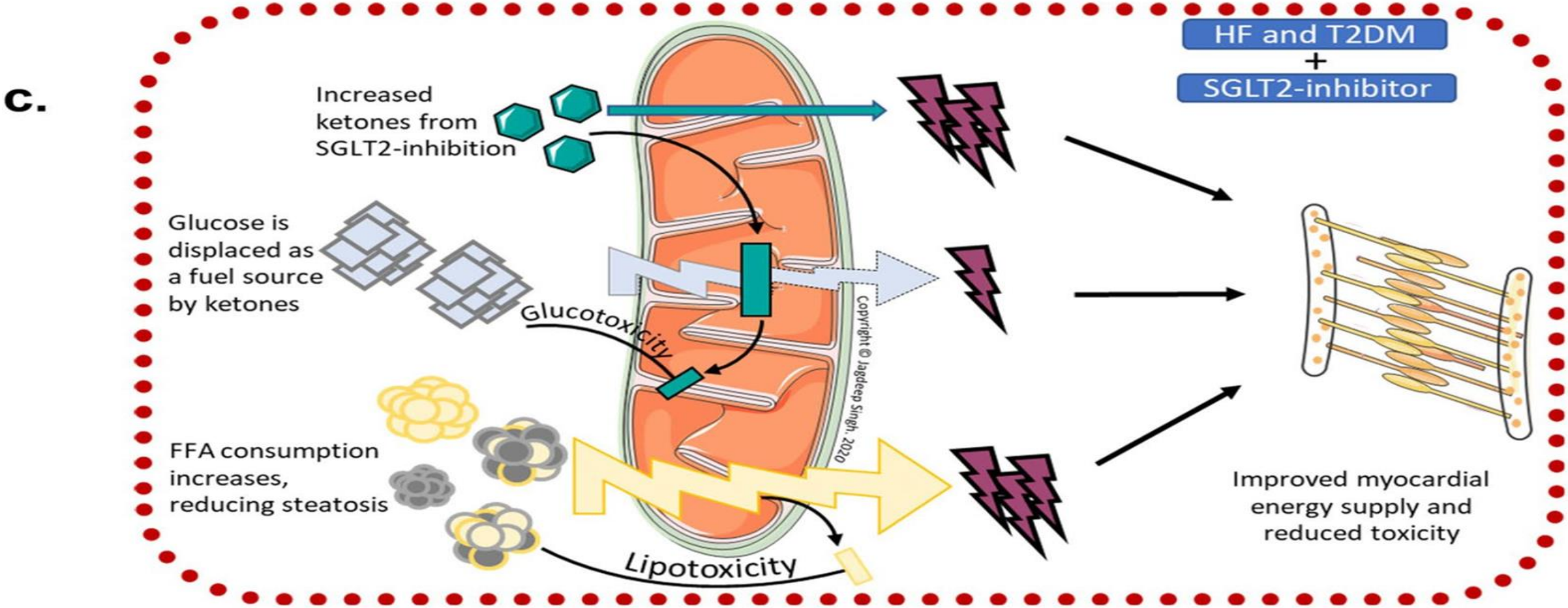


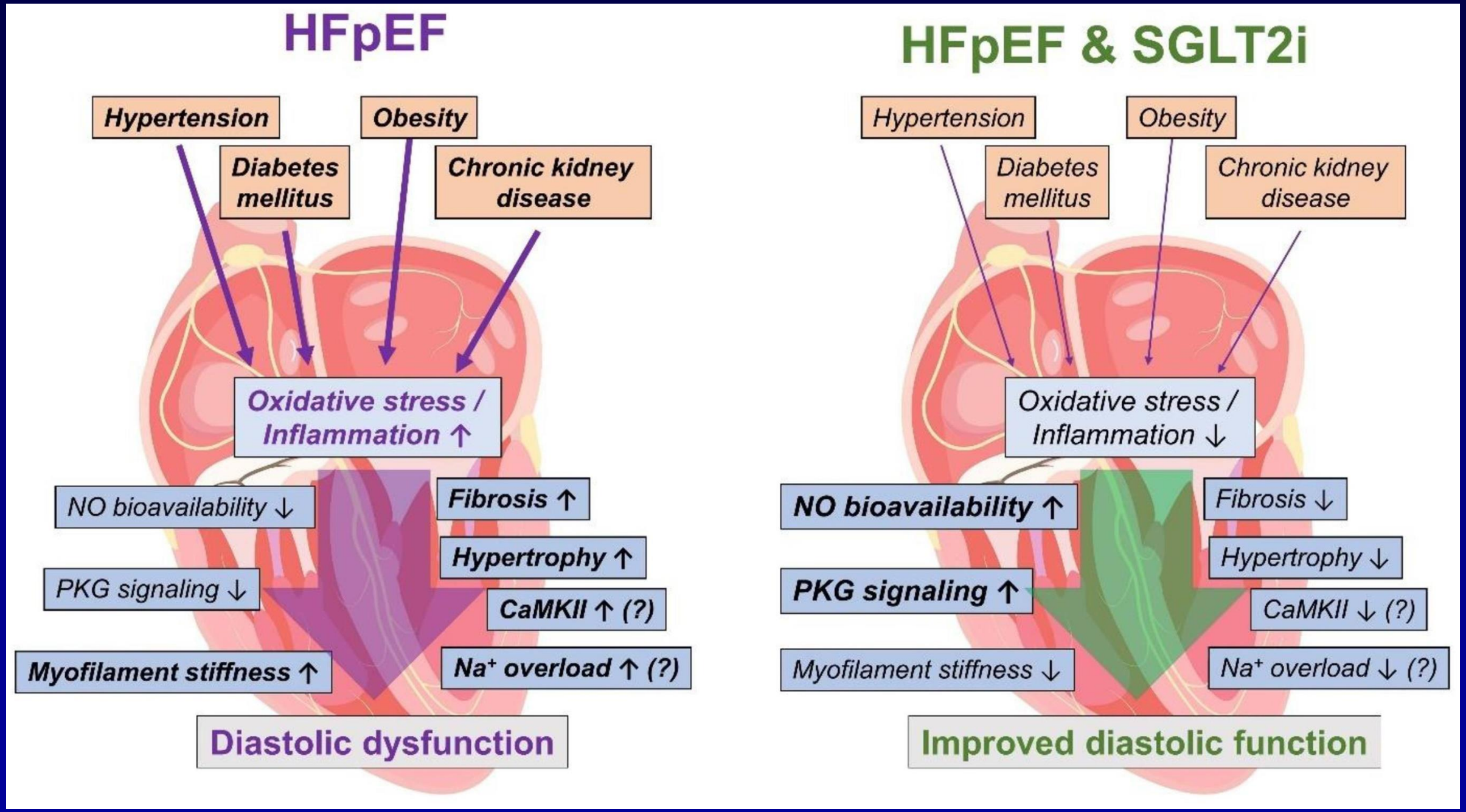




3a: Năng lượng cơ tim ở người khỏe mạnh trong khi nghi ngơi

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




HFpEF
Hypertension
Obesity
Diabetes mellitus
Chronic kidney disease
Oxidative stress / Inflammation ↑
NO bioavailability ↓
Fibrosis ↑
Hypertrophy ↑
PKG signaling ↓
CaMKII ↑ (?)
Myofilament stiffness ↑
Na+ overload ↑ (?)
Diastolic dysfunction
HFpEF & SGLT2i
Hypertension
Obesity
Diabetes mellitus
Chronic kidney disease
Oxidative stress / Inflammation ↓
NO bioavailability ↑
Fibrosis ↓
Hypertrophy ↓
PKG signaling ↑
CaMKII ↓ (?)
Myofilament stiffness ↓
Na+ overload ↓ (?)
Improved diastolic function

| SGLT2 inhibitor | Study model | SGLT2 inhibitor mediated outcome |
|---|---|---|
| Empagliflozin (10 mg once daily) | Subjects with T2DM and history of cardiovascular disease treated with empagliflozin for 3-months | • Decreased LVMI<br>increased e′ |
| Empagliflozin (10 mg once daily) | Subjects with T2DM (20% with cardiovascular disease) treated with empagliflozin for 6-months | • Decreased LV end diastolic volume |
| Canagliflozin (100 mg once daily) | Subjects with T2DM (32% with cardiovascular disease) treated with canagliflozin for 3-months | • Decreased LVMI<br>• Decreased E/e′ ratio |
| Dapagliflozin (5 mg once daily) | Subjects with T2DM and stable heart failure treated with dapagliflozin for 6-months | • Decreased LVMI<br>• Decreased E/e′ ratio<br>• Increased global Longitudinal strain |
| Tofogliflozin (20 mg once daily) | Subjects with T2DM without cardiovascular disease treated with tofogliflozin for ~8-months | • Decreased E/e′ ratio |
| Empagliflozin (60 mg per kg of chow) | Female *db/db* mice treated with empagliflozin for 5-weeks | • Decreased E/e′ ratio<br>• Increased e′/a′ ratio |
| Empagliflozin (25 mg/kg intravenously) | ZDF rats treated acutely with empagliflozin | • Decreased IVRT<br>• Increased mitral E/A ratio |
| Empagliflozin (10 mg/kg/day) | Male *db/db* mice treated with empagliflozin for 8-weeks | • Decreased IVRT<br>• Increased mitral E/A ratio |
| Empagliflozin (10 mg/kg/day) | Male Dahl salt-sensitive rats fed a high-salt diet and treated with empagliflozin for 2-weeks | • Decreased E/e′ ratio |
| Empagliflozin (10 mg/kg/day in the chow) | Male *db/db* mice treated with empagliflozin for 4-weeks | • No effect on the E/e′ ratio |

The impact of SGLT2 inhibitors on diabetic cardiomyopathy.



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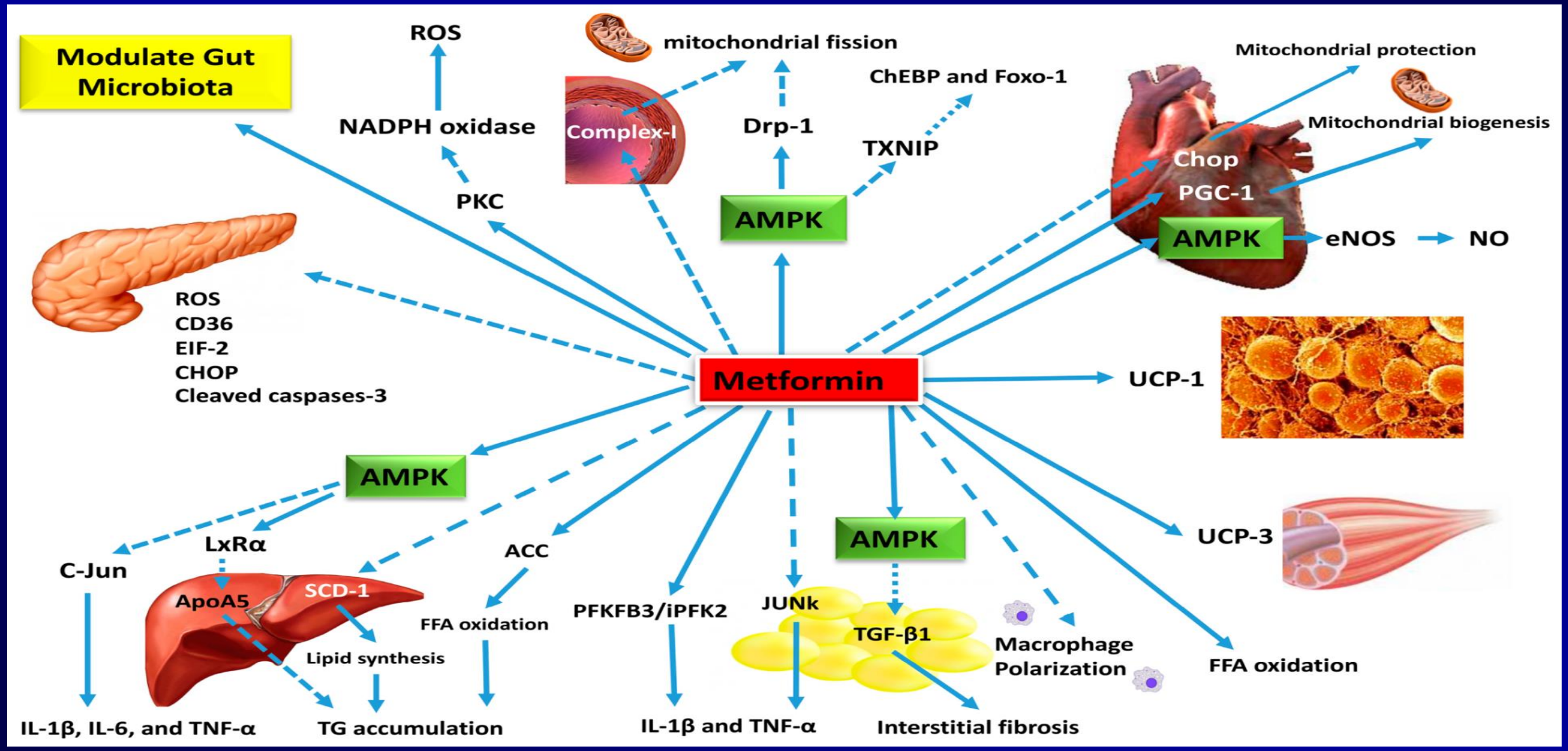
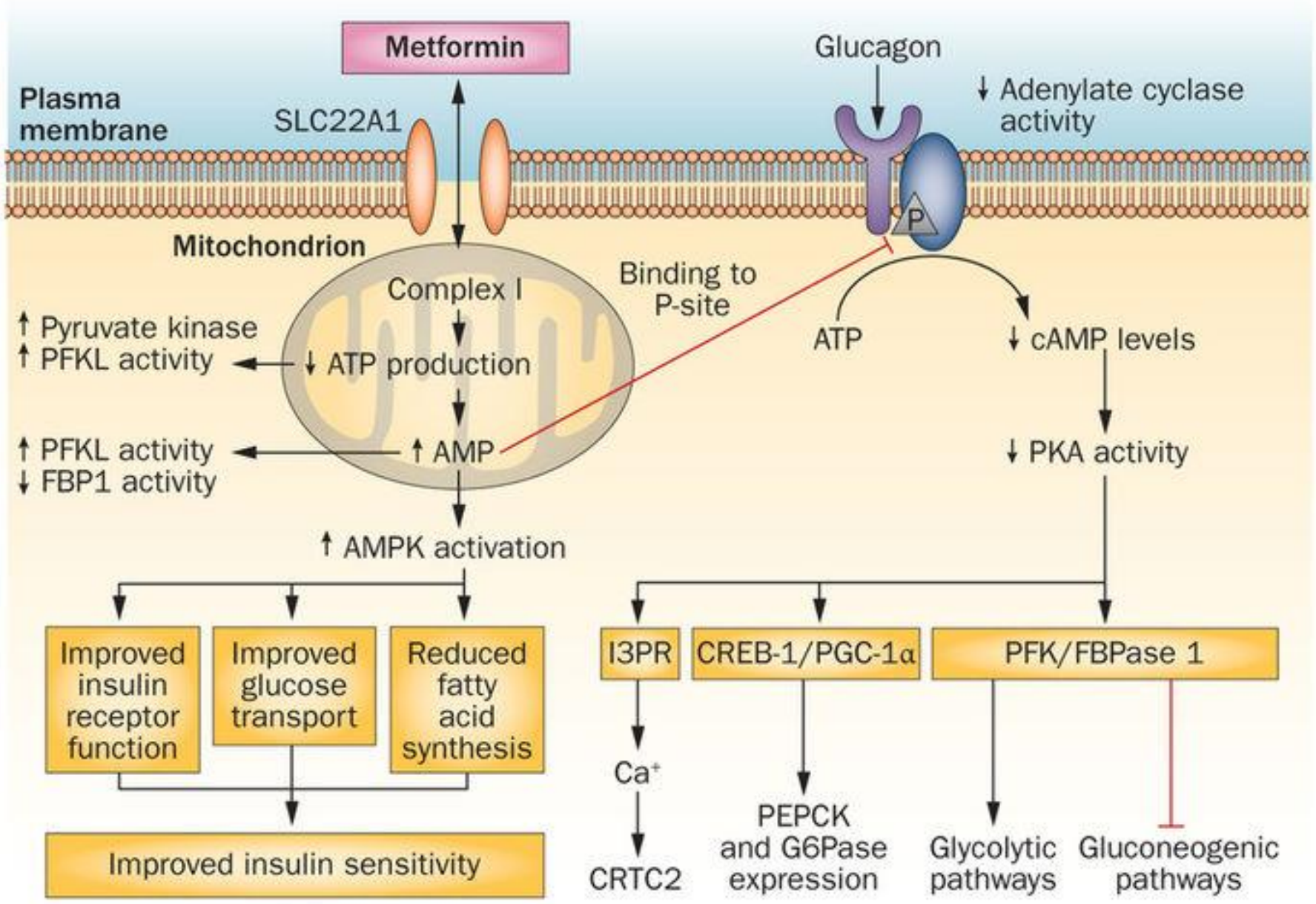
# Vai trò bảo vệ Tim Mạch của Metformin

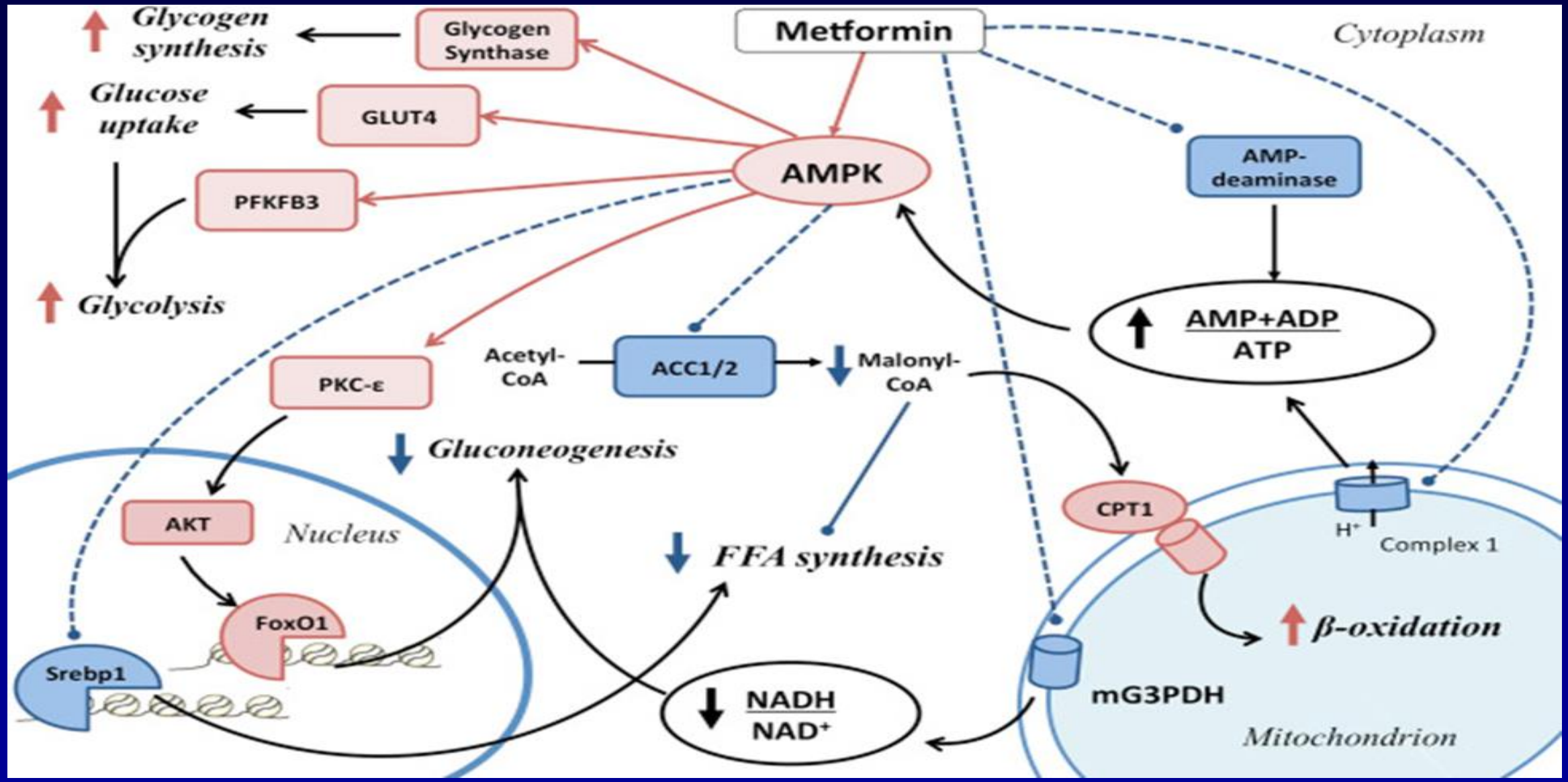
# Cơ chế Bảo vệ Tim của Metformin

- VN_GM-DIA_29
- Exp:26/09/2020

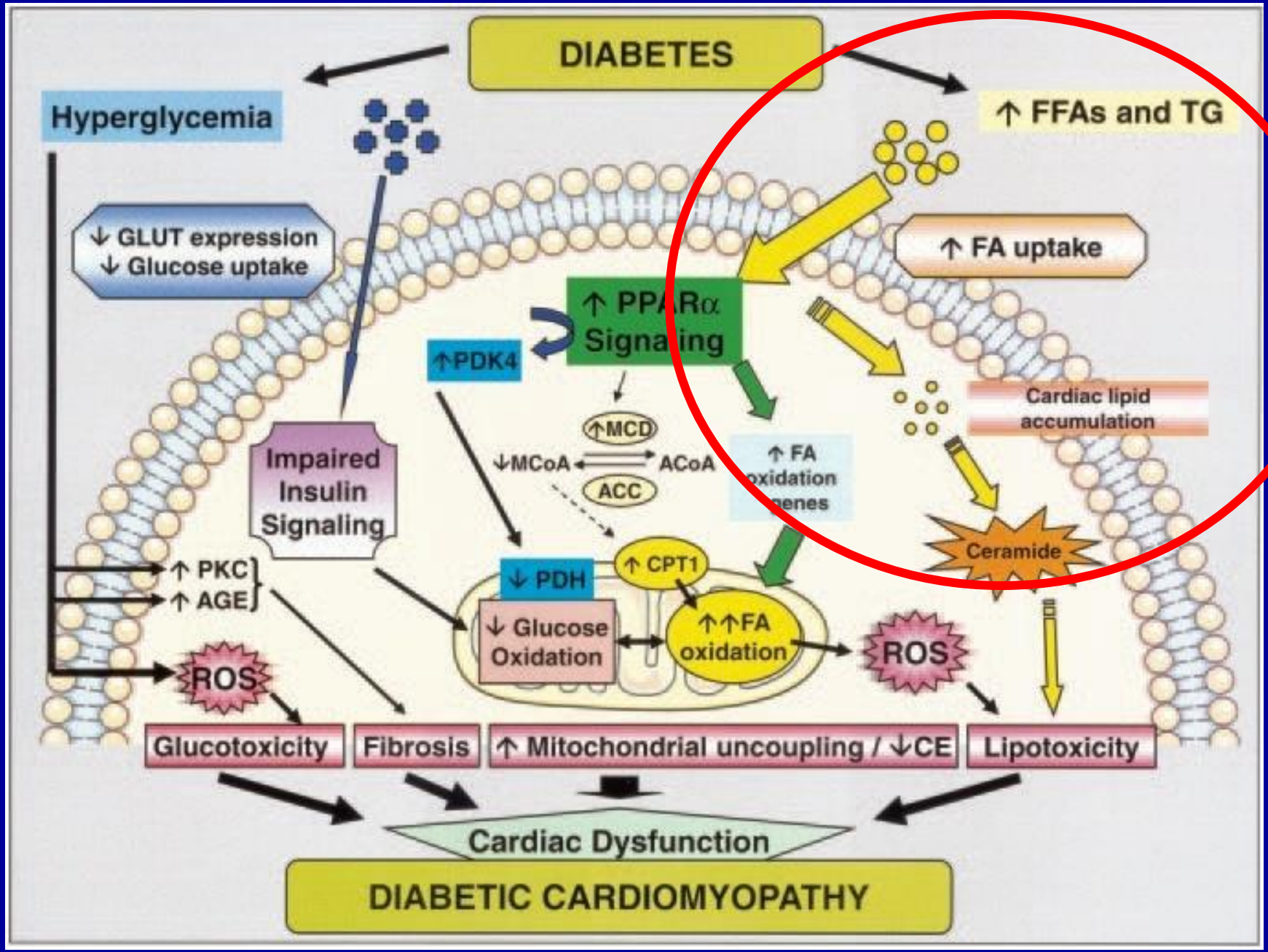


# Metformin và Kháng insulin

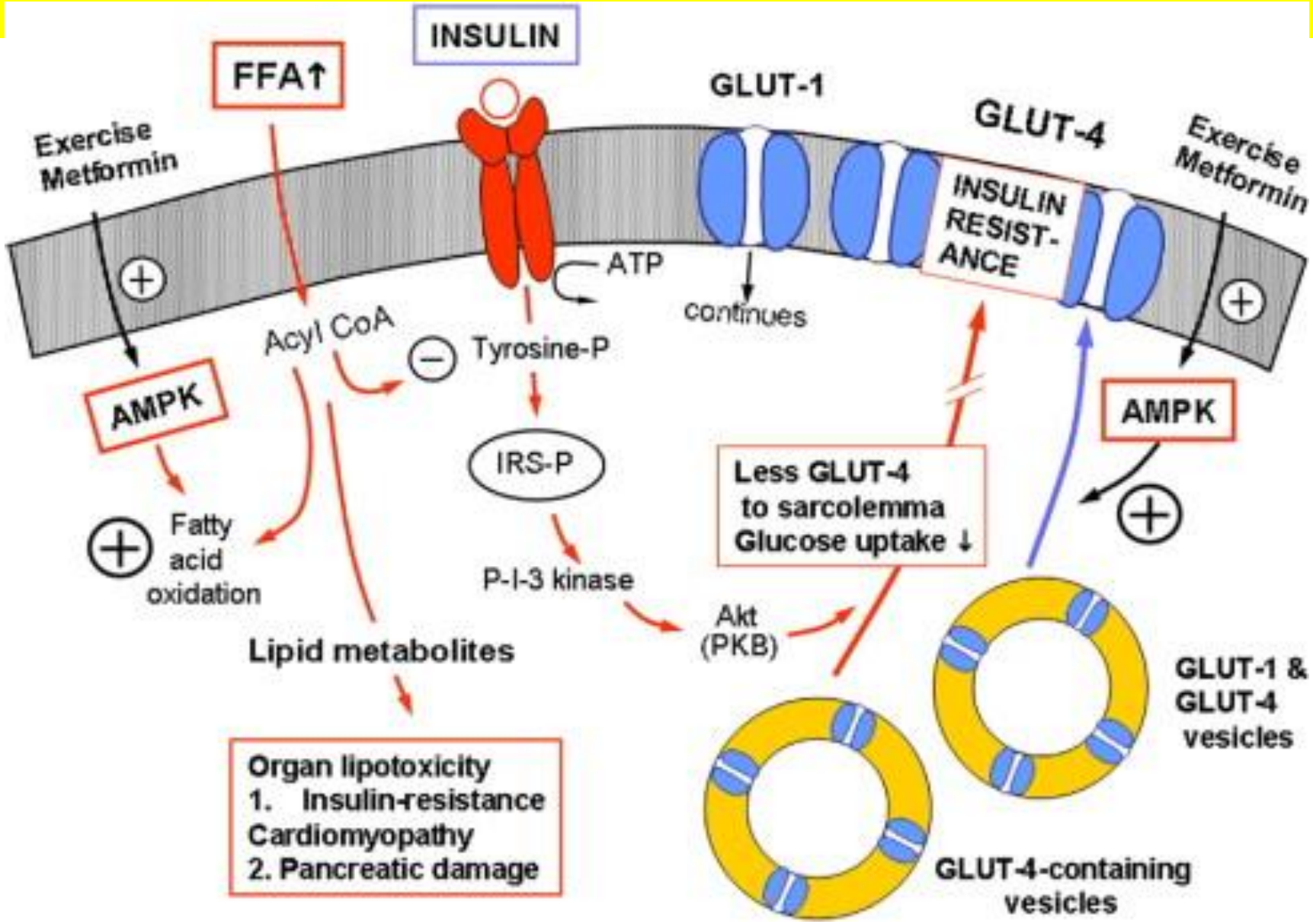




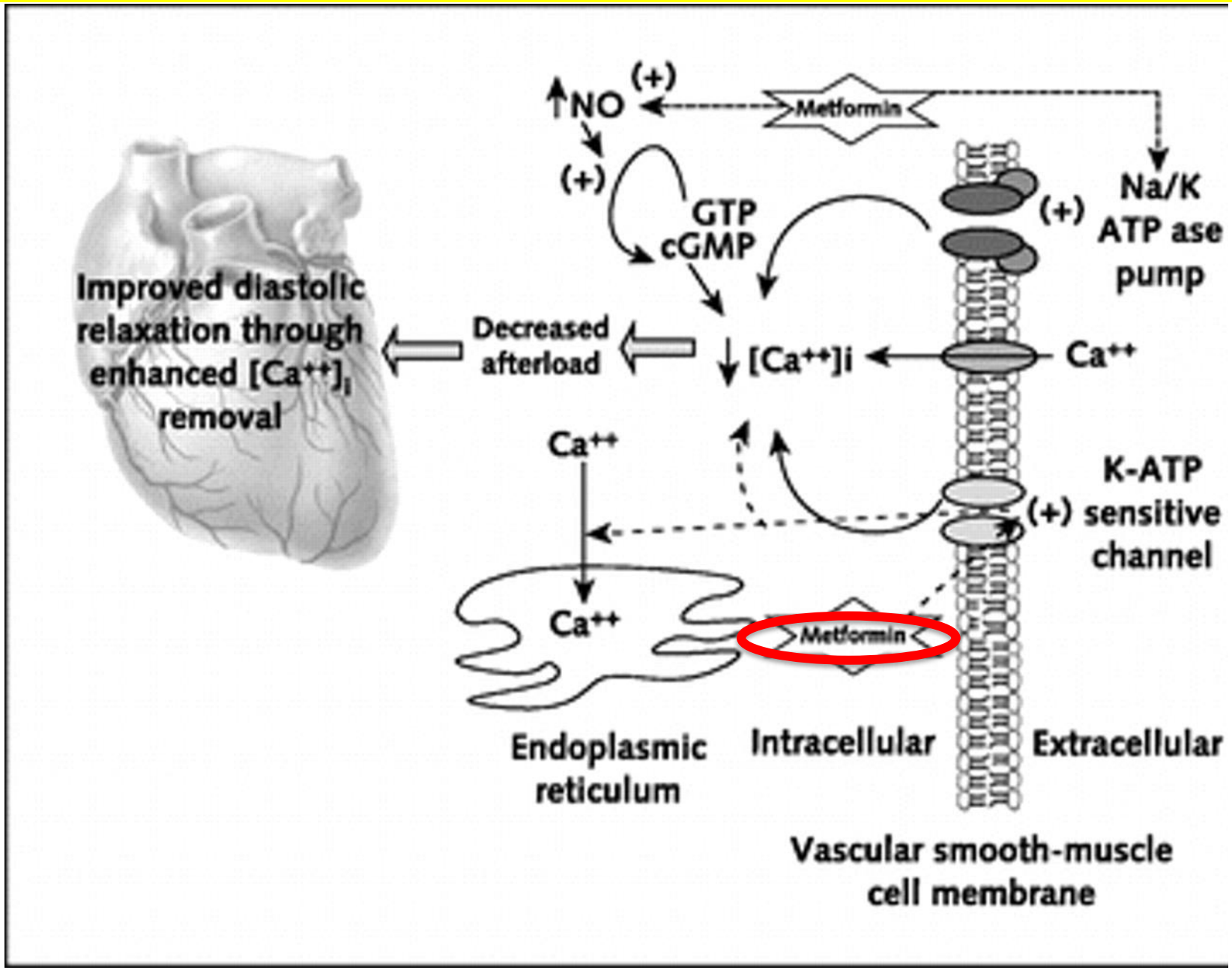

- VN_GM-DIA_29
- Exp:26/09/2020


DIABETES
Hyperglycemia
↑ FFAs and TG
↓ GLUT expression
↓ Glucose uptake
↑ FA uptake
↑ PPARα Signaling
↑PDK4
Cardiac lipid accumulation
↑MCD
↓MCoA
ACoA
ACC
↑ FA oxidation genes
Impaired Insulin Signaling
Ceramide
↑ PKC
↑ AGE
↓ PDH
↑ CPT1
↓ Glucose Oxidation
↑↑FA oxidation
ROS
ROS
Glucotoxicity
Fibrosis
↑ Mitochondrial uncoupling / ↓CE
Lipotoxicity
Cardiac Dysfunction
DIABETIC CARDIOMYOPATHY

# Metformin cải thiện chuyển hóa tế bào cơ tim

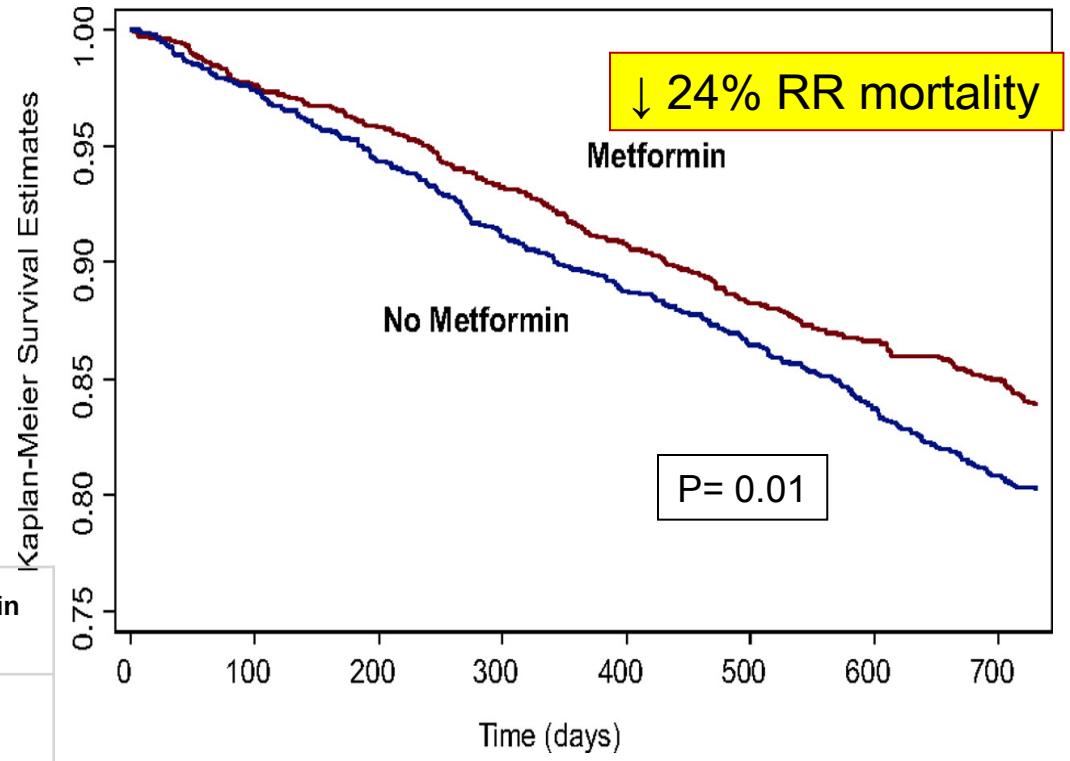


# Metformin và chức năng tâm trương



# Metformin trên bn ĐTĐ suy tim

Veterans Affairs
- 6185 bn ĐTĐ + suy tim
- NC tỷ lệ tử vong trong 2 năm
- Thời gian nhập viện do suy tim và nhập viện do mọi nn
- Phân nhóm :
  - có Metformin (1561bn #25%)
  - không Metformin
- NC cohort 2 năm (propensity score–matched cohort)




| Outcome | Metformin (n=1437) | No Metformin (n=1437) |
|---|---|---|
| Tử vong HR (95% CI) | **0.76 (0.63–0.92, *P*<0.01)** | Reference |
| Nhập viện ST HR (95% CI) | **0.93 (0.74– 0.18, *P*=0.56)** | Reference |
| Nhập viện HR (95% CI) | **0.94 (0.83–1.07, *P*= 0.35)** | Reference |

**David Aguilar et al. Circ Heart Fail. 2011;4:53-58**

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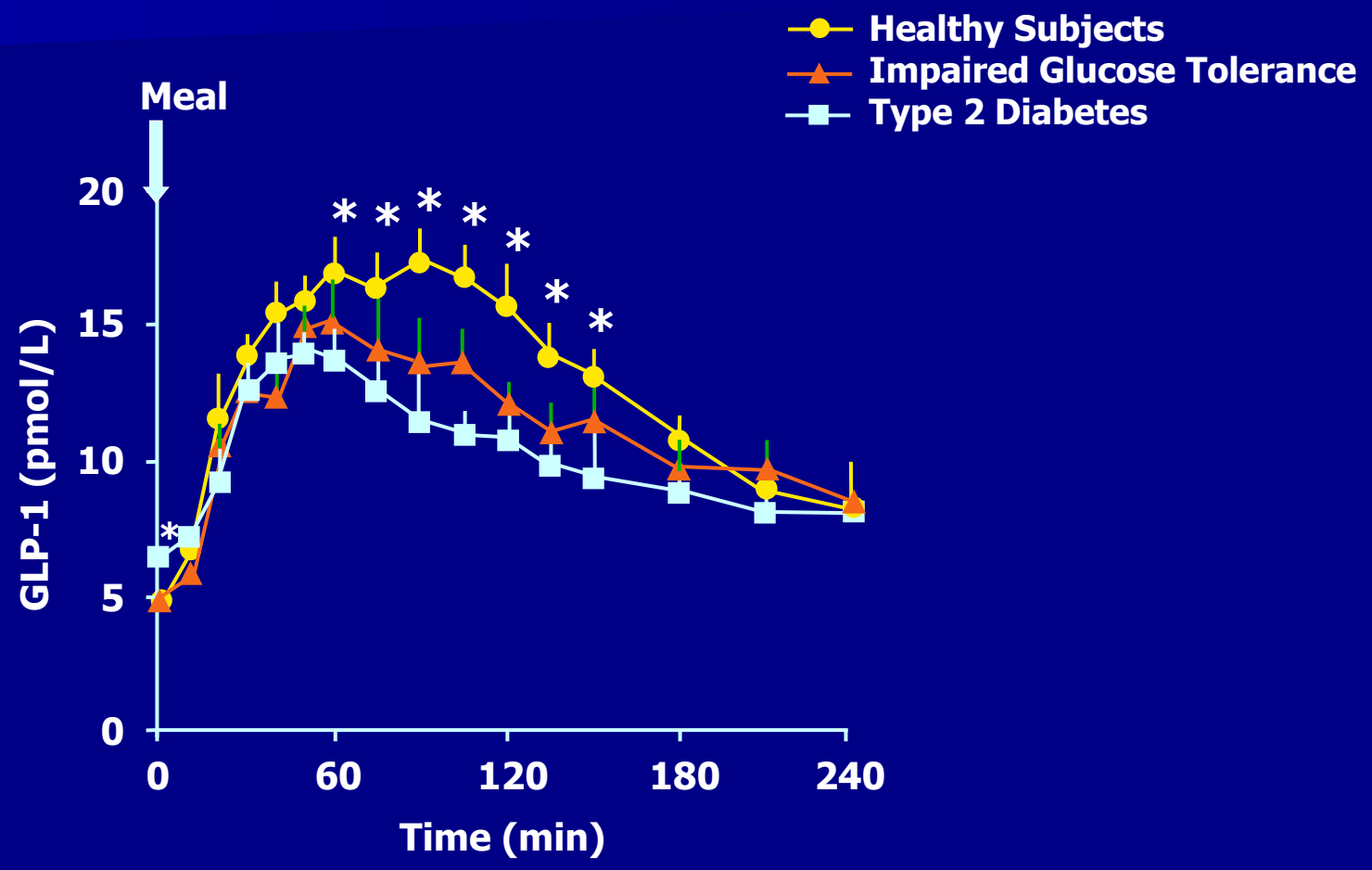
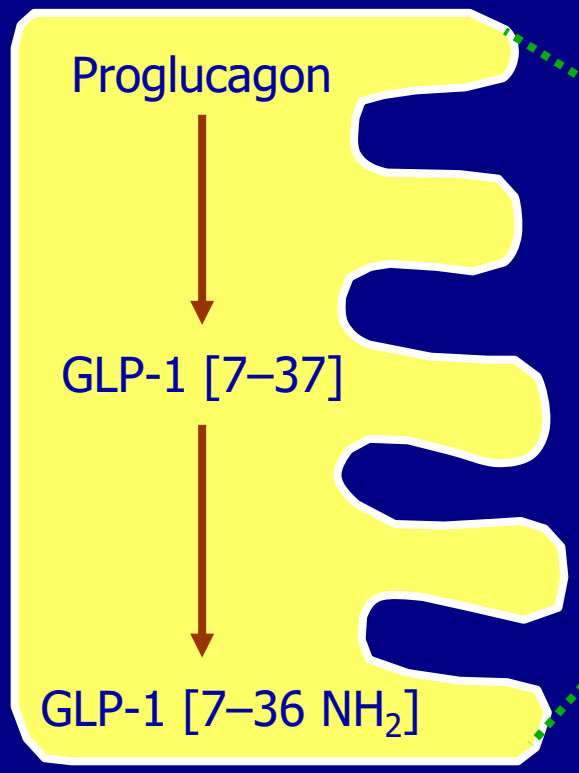
# Suy giảm nồng độ GLP-1 sau ăn đã xãy ra từ tiền ĐTĐ típ 2




VN_GM_PRE-DIA_71

N = 102; Mean (SE); * *P*<0.05 between type 2 diabetes and healthy subjects
Data from Toft-Nielsen MB, et al. J Clin Endocrinol Metab 2001;86:3717-3723.

Tế bào L
(hồi tràng)




Metformin has been found to increase the plasma levels of the incretin hormone GLP-1. it is known that metformin has no effect on DPP-IV which degrades GLP-1. Possible effect on GLP-1 secreting L cells

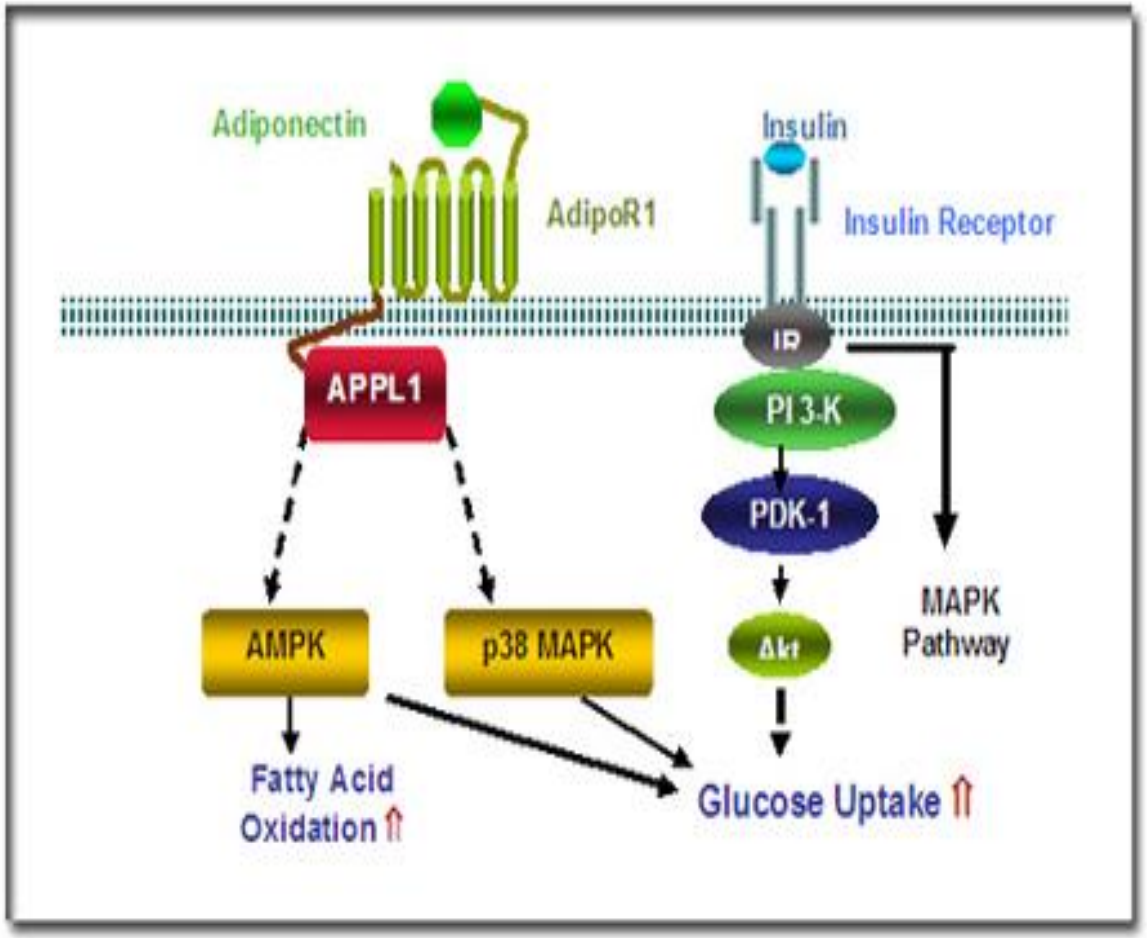
ProGIP

GIP [1–42]

**GIP=glucose-dependent insulinotropic peptide;**
**GLP-1=glucagon-like peptide-1**
Adapted from Drucker DJ. *Diabetes Care.* 2003; 26: 2929–2940.

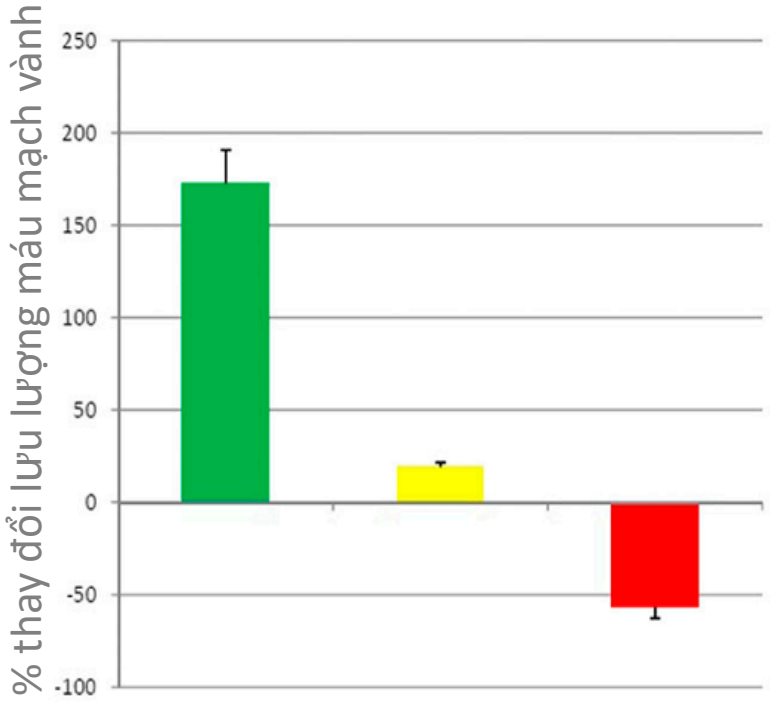
Recently published data indicate that metformin treatment is associated with a significant increase in serum adiponectin [12], which plays an important role in insulin sensitivity, inflammation, lipid metabolism and atherogenesis [13–15].
Marina Shargorodsky1 Relation between augmentation index and adiponectin during one-year metformin treatment for nonalcoholic steatohepatosis: effects beyond glucose lowering? Cardiovascular Diabetology 2012, 11:61

Metformin regulates adiponectin signalling in epicardial adipose tissue and reduces atrial fibrillation vulnerability.
Biao Li et al (2020). Metformin regulates adiponectin signalling in epicardial adipose tissue and reduces atrial fibrillation vulnerability. J Cell Mol Med. 2020;24:7751–7766.

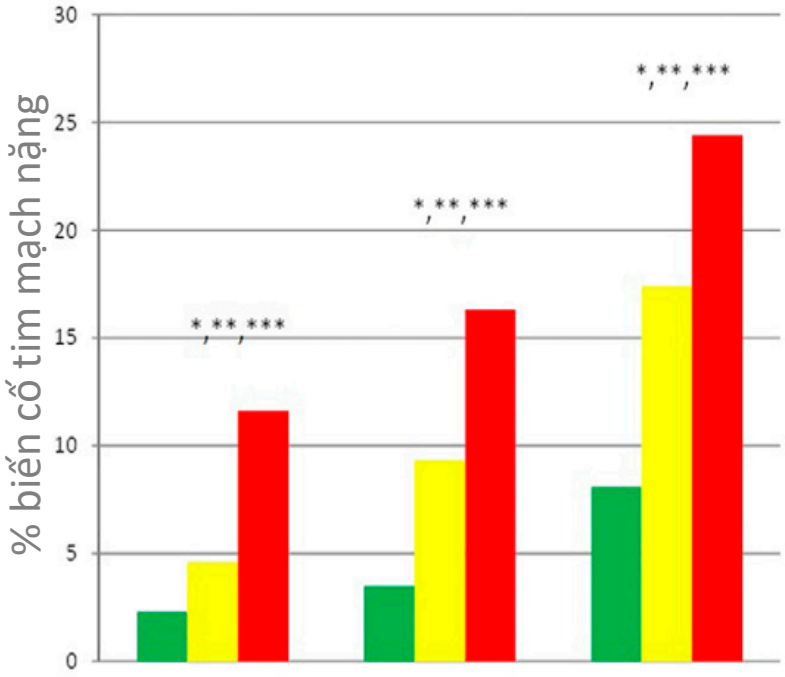


# Metformin giảm nguy cơ cao biến cố tim mạch ở BN tiền ĐTĐ

**hiên cứu CODYCE 2 năm (N=25**



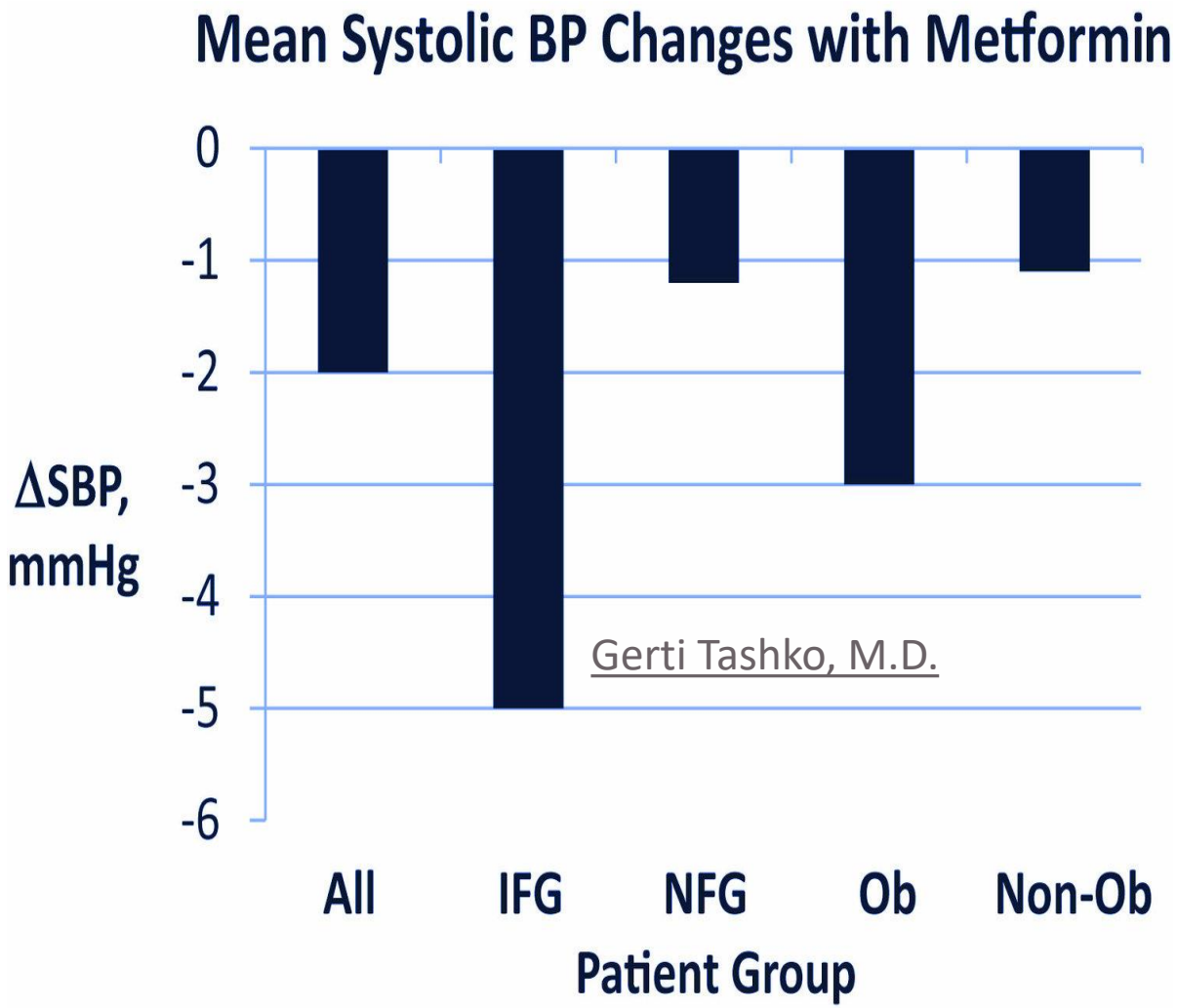

% thay đổi trung bình lưu lượng máu mạch vành ở 3 nhóm




MACE tại tháng thứ 6, 12 và 24 theo dõi.

*p<0,05, ĐH bình thường so với nhóm tiền ĐTĐ
**p<0,05, nhóm tiền ĐTĐ so với nhóm tiền ĐTĐ sử dụng metformin
***p<0,05, ĐH bình thường so với nhóm tiền ĐTĐ sử

Sardu et al. Diabetes Care 2019;42:1946–1955




**28 studies** from **26 articles** consisting of **4113 participants** were included. This meta-analysis suggested that **metformin** could effectively **lower SBP** in nondiabetic patients, especially in those with **impaired glucose tolerance** or **obesity**.

Gerti Tashko . **JOURNAL OF HYPERTENSION, META-ANALYSIS, JANUARY 2017**

# Vai trò bảo vệ Tim Mạch của Ức chế DPP4



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| DPP-4 inhibitor | Study model | DPP-4 inhibitor mediated outcome |
|---|---|---|
| Sitagliptin (100 mg once daily) | Subjects with poorly controlled T2DM, on metformin plus glyburide, randomized to receive bedtime NPH insulin or sitagliptin for 24-weeks. | • 46.7 vs. 35.7% of subjects experienced a decrease in the E/e′ ratio with sitagliptin vs. NPH insulin treatment |
| Sitagliptin (50 or 100 mg once daily) | Subjects with poorly controlled T2DM despite lifestyle interventions and/or pharmacotherapy were randomized to sitagliptin vs. placebo for 2-years | • Decreased E/e′ ratio |
| Sitagliptin (50 mg once daily) | Subjects with T2DM treated with sitagliptin for 24-weeks. | • No changes in both the e′ and E/e′ ratio<br>• Increased e′ and decreased E/e′ ratio in subjects also treated with pioglitazone |
| Linagliptin (5 mg once daily) | Subjects with T2DM and asymptomatic impaired LV systolic function treated with linagliptin for 48-weeks. | • No changes in e′ or the mitral E/A and E/e′ ratios |
| Sitagliptin (16 mg/day in the chow) | Male *db/db* mice treated with sitagliptin for 3-weeks | • Reduced relaxation time constant (Tau) |
| Linagliptin (83 mg per kg of chow) | Female C57BL/6J mice supplemented with a high-fat /high sucrose/high-fructose corn syrup diet treated with linagliptin for 4-months. | • Increased e′/a′ ratio<br>• Reduced IVRT<br>• Decreased cardiac interstitial fibrosis |
| Linagliptin (83 mg per kg of chow) | Male Zucker obese rats treated with linagliptin for 8-weeks | • Increase in the e′/a′ ratio<br>• Decrease in the E/e′ ratio, e′, and IVRT |
| MK-0626 (3 mg/kg/day) | Male C57BL/6J mice subjected to T2DM and TAC surgery, treated with MK-0626 for 15-weeks | • Exacerbation of cardiac hypertrophy and reduced LVEF |
| Vildagliptin (10 mg/kg/day in the chow) | Male Dahl salt-sensitive rats fed a high-salt diet and treated with vildagliptin for 9-weeks | • Decrease in LVEDP<br>• Increase in the mitral E/A ratio |

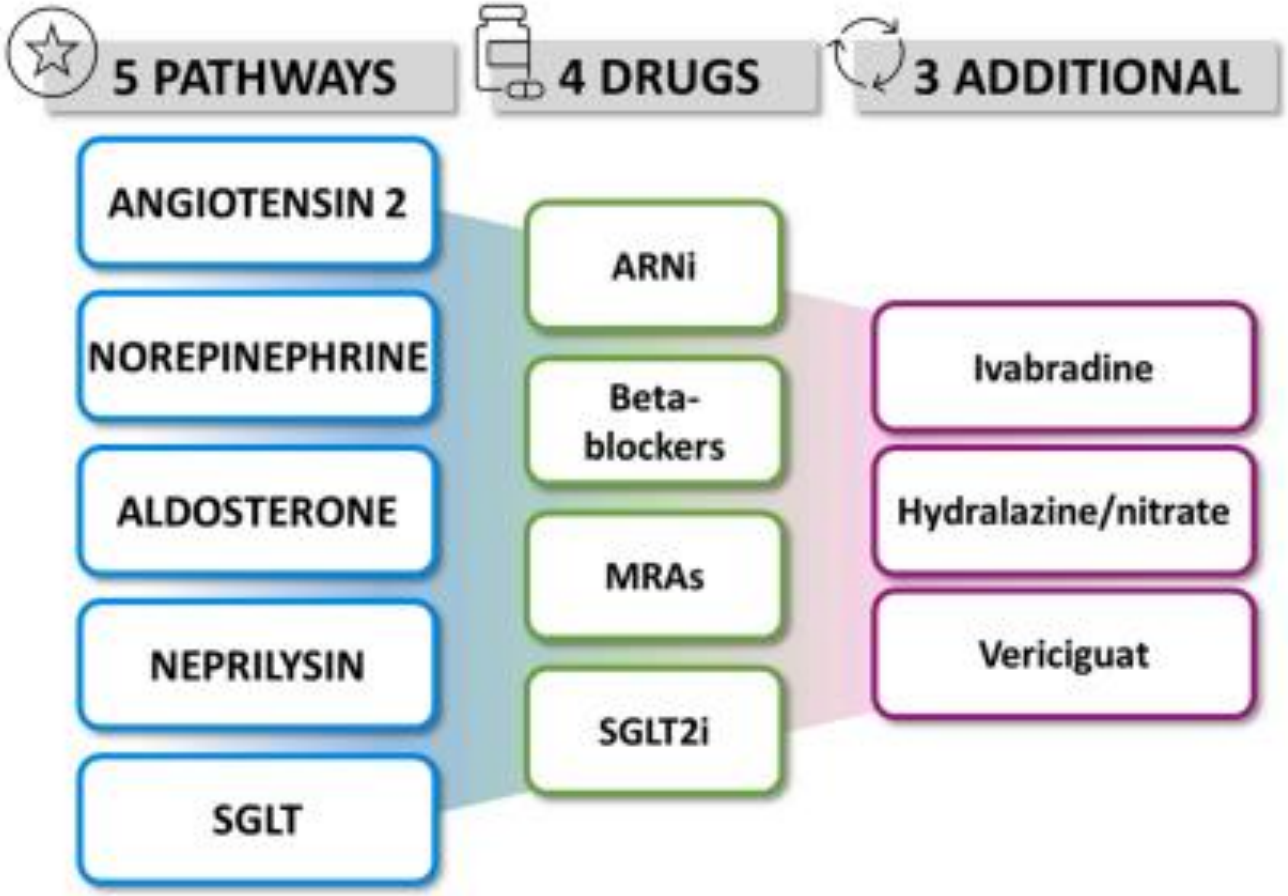
**The impact of DPP-4 inhibitors on diabetic cardiomyopathy**

Front. Physiol. 11:603247. doi: 10.3389/fphys.2020.603247

# NOVEL TARGETED THERAPIES FOR DIABETIC CARDIOMYOPATHY

- MicroRNA (miRNA) is reported to have a role in the pathophysiology of diabetic cardiomyopathy, such as increase ROS production and promote cardiomyocyte apoptosis.
- Anti-miRNA and miRNA mimics are actively studied and developed to treat cardiomyopathy.
- Antioxidant therapies can be used for prevention and intervention for diabetic cardiomyopathy.

- Phenolic acids are beneficial for mitochondrial dysfunction as the protective agent of the heart against mitochondrial dysfunction and are obtained from plants such as nuts and fruits and thus can be added to the diets.
- Bile Acids are synthesized by cholesterol, bind and activate Farnesoid X Receptor (FXR) that leads to reduction of inflammation and have a regulatory effect on autophagy and mitochondrial function and can also suppress oxidative stress that showing a potential therapeutic effect.




**Điều trị HFrEF**

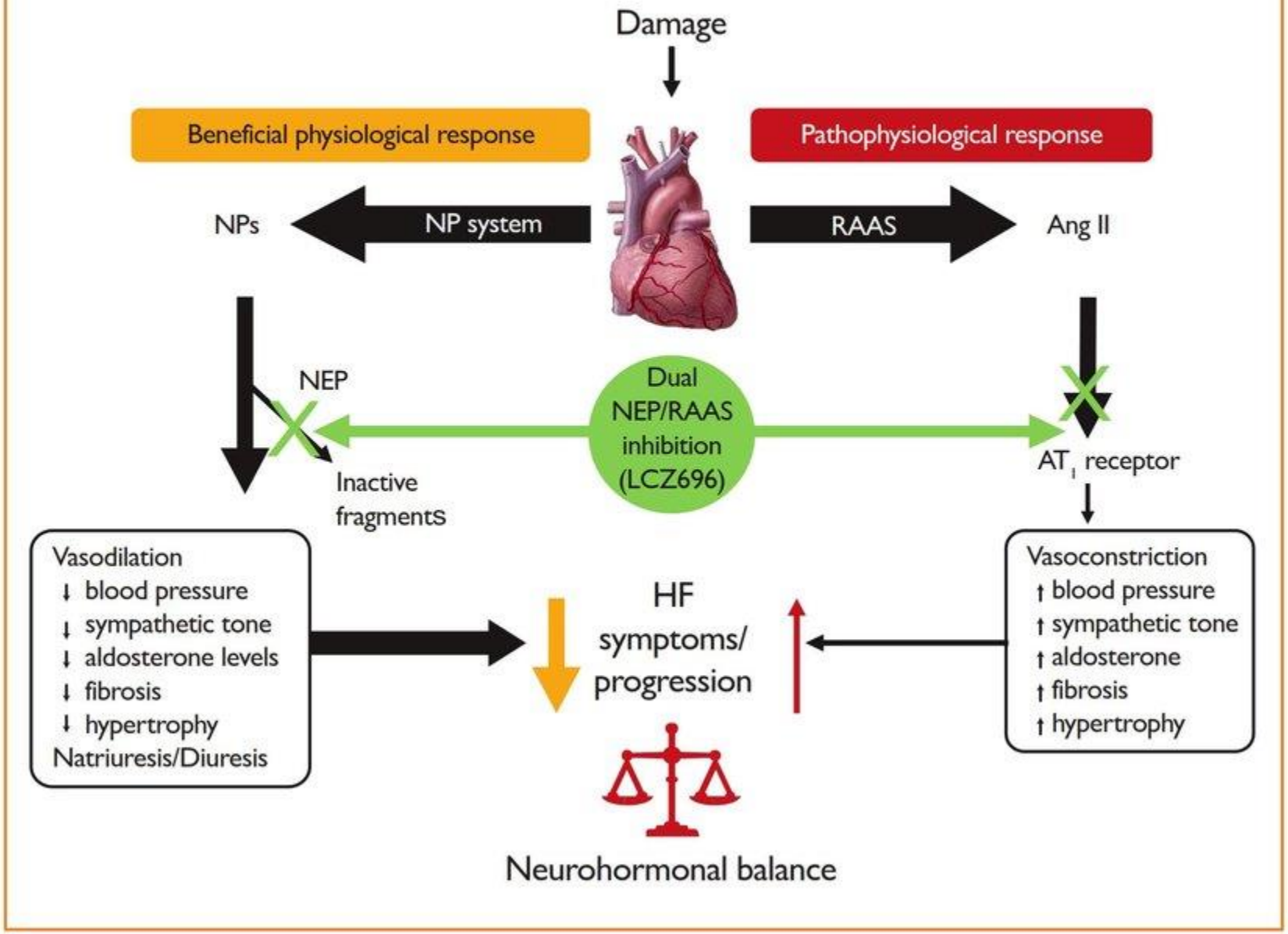
Cách tiếp cận mới 5–4–3

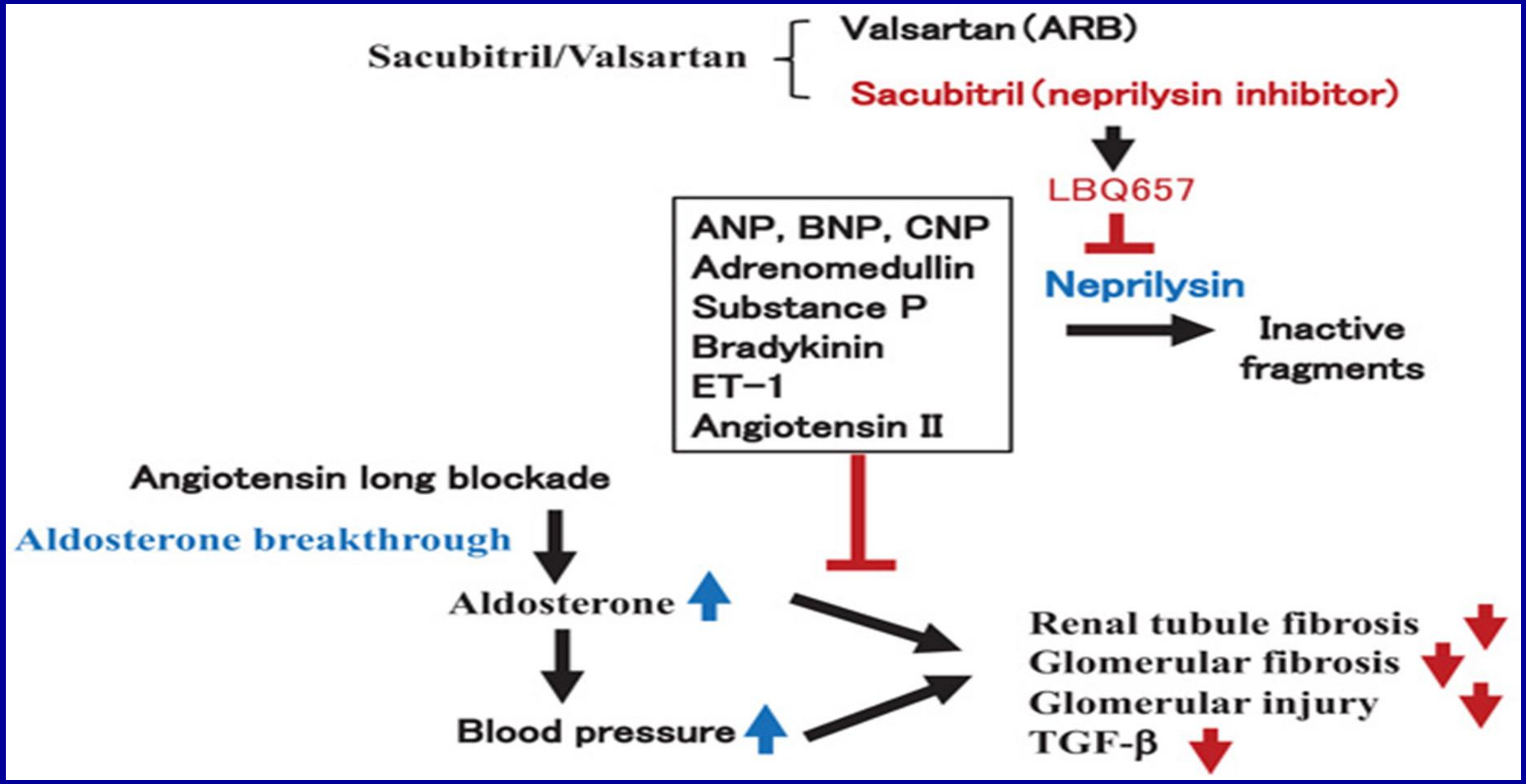
Năm con đường bao gồm điều hoà angiotensin 2, norepinephrine, aldosterone, neprilysin và SGLT.

Bốn loại thuốc được khuyến cáo là chất ức chế thụ thể angiotensin-neprilysin (ARNi), thuốc chẹn beta, ức chế thụ thể mineralocorticoid và chất ức chế SGLT2.

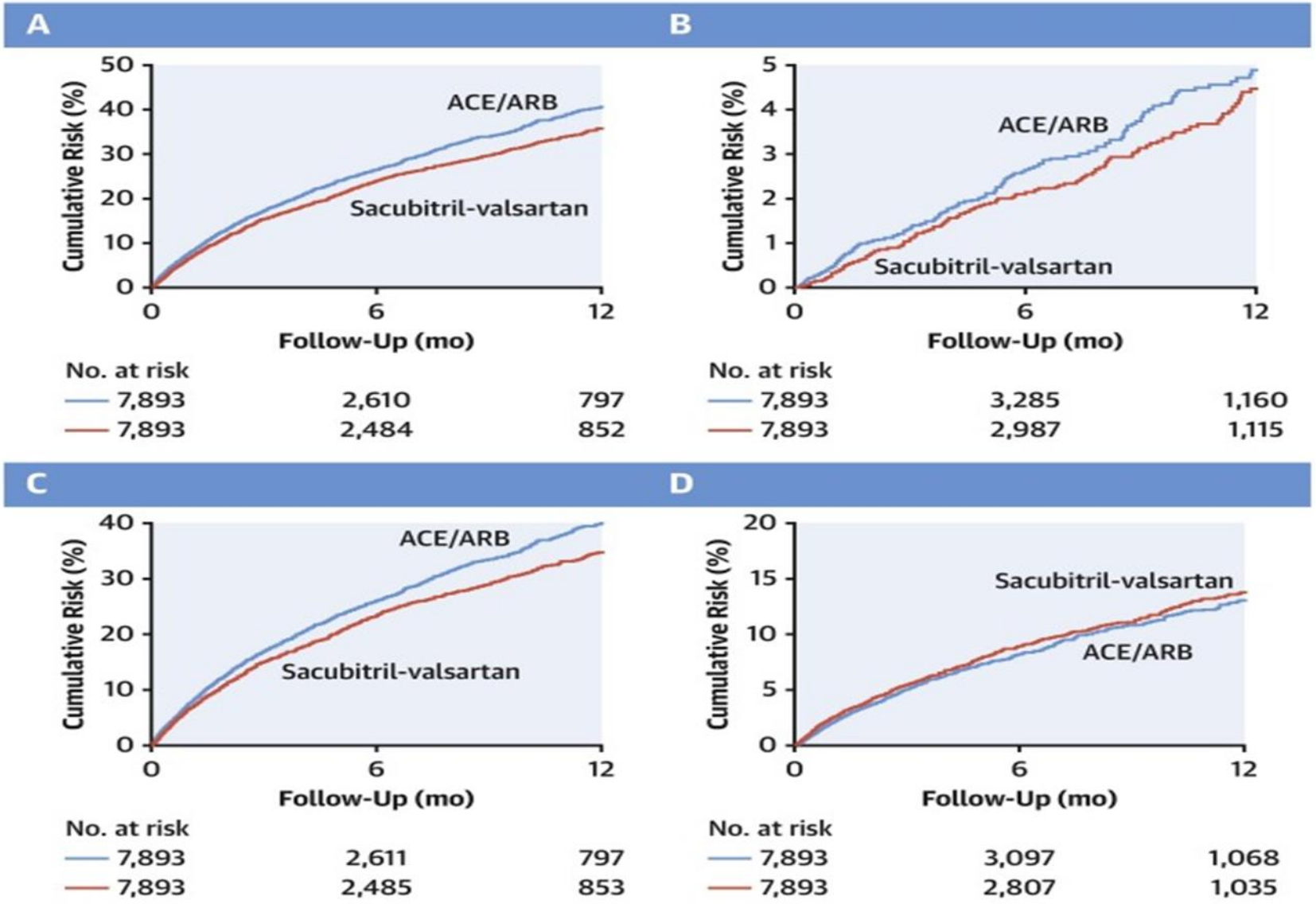
Ba con đường bổ sung sử dụng ivabradine, hydralazine / nitrate, và vericiguat.

# Mechanism of action of LCZ696

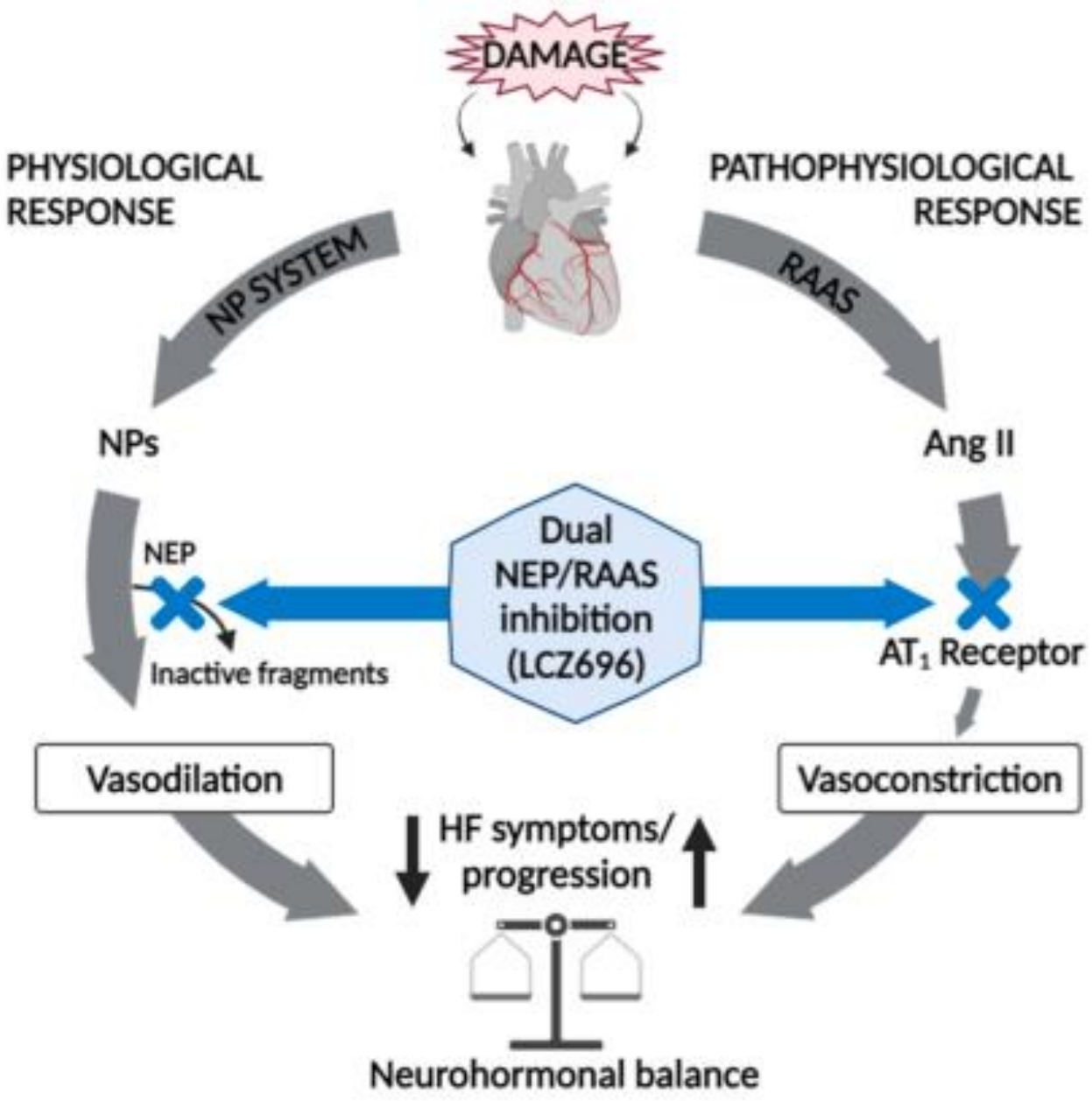



Sacubitril/Valsartan
Valsartan (ARB)
Sacubitril (neprilysin inhibitor)
LBQ657
Neprilysin
Inactive fragments
ANP, BNP, CNP
Adrenomedullin
Substance P
Bradykinin
ET-1
Angiotensin II
Angiotensin long blockade
Aldosterone breakthrough
Aldosterone
Blood pressure
Renal tubule fibrosis
Glomerular fibrosis
Glomerular injury
TGF-β

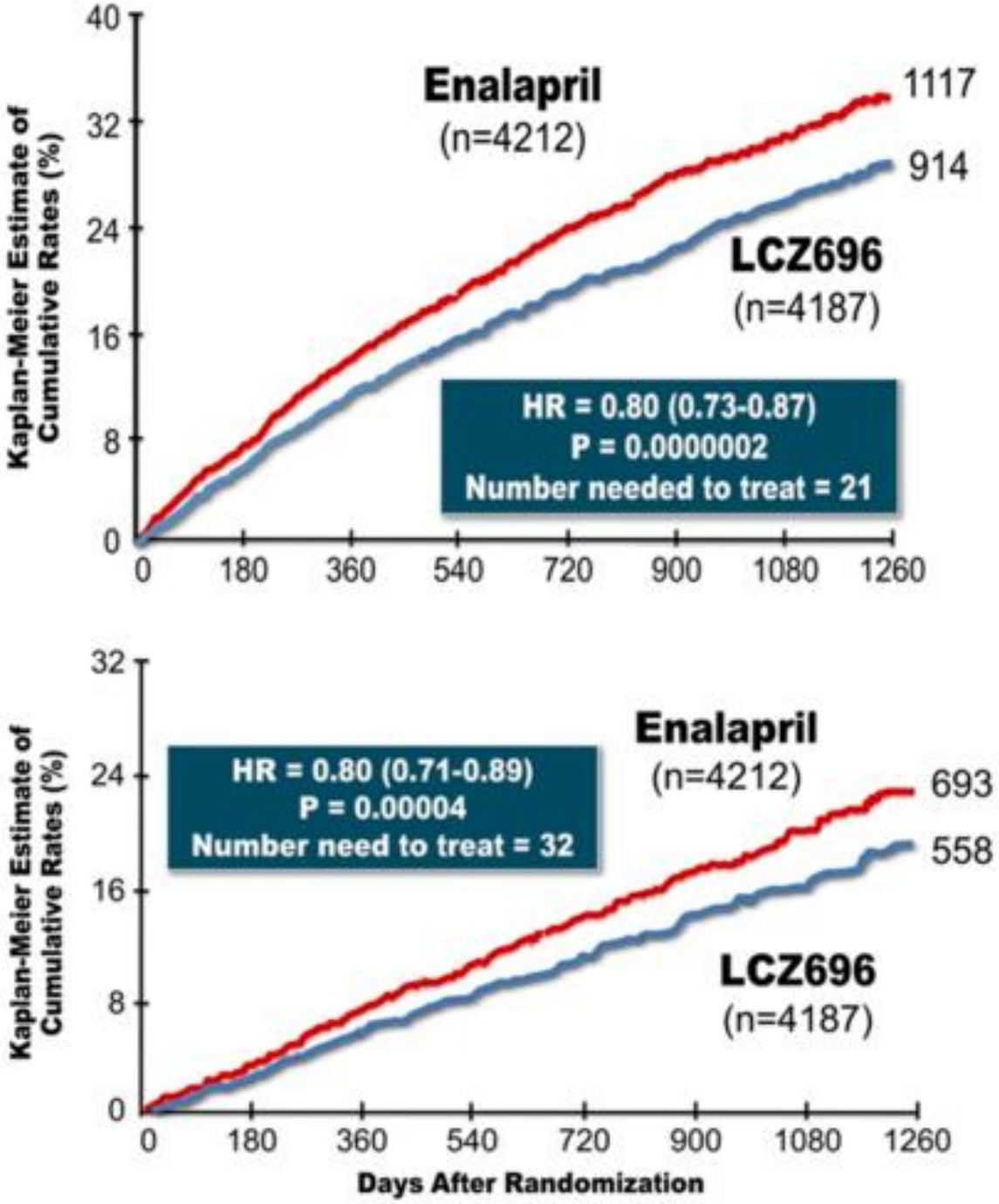
**CENTRAL ILLUSTRATION: Cumulative Risk of Outcomes in Patients Treated With Sacubitril-Valsartan or ACE/ARB**




Tan, N.Y. et al. J Am Coll Cardiol HF. 2020;8(1):43–54.

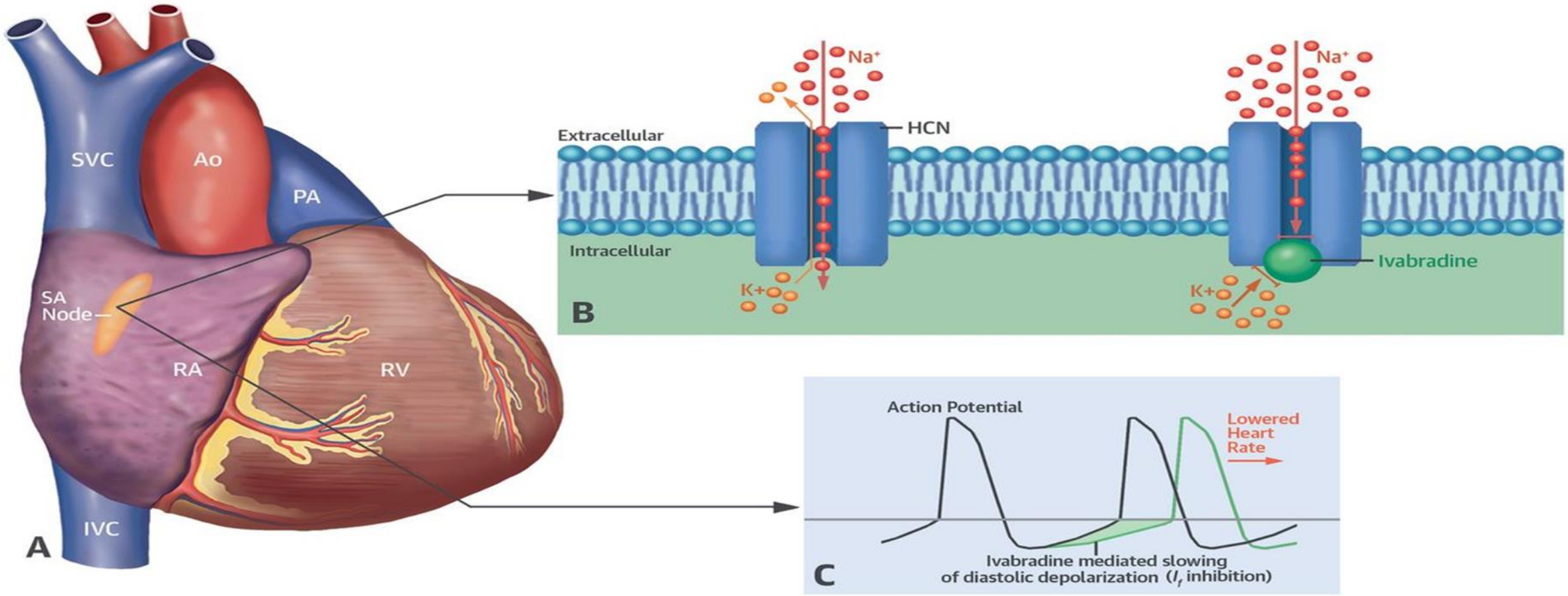



Sơ đồ cơ chế tác dụng của Sacubitril/Valsartan (LCZ696). Khi bị tổn thương, tim sẽ phản ứng thông qua phản ứng sinh lý và sinh lý bệnh hệ thống peptide lợi tiểu natri và hệ thống Renin-angiotensin-aldosterone. Sacubitril và valsartan khi được sử dụng kết hợp như một liệu pháp ức chế kép NEP/RAAS , sẽ hoạt động cùng nhau để duy trì sự cân bằng hormon thần kinh.




So sánh kết quả giữa ACEi (Enalapril) và ARNI (LCZ696) liên quan đến Tử vong do tim mạch hoặc nhập viện do suy tim được đặt làm tiêu chí chính (trên) và
Kết cục tử vong do tim mạch (dưới)

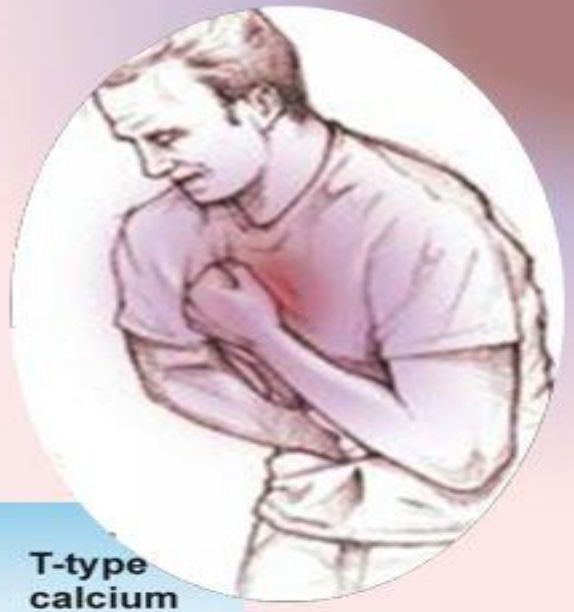
## CENTRAL ILLUSTRATION: Mechanism of Action of Ivabradine




Koruth, J.S. et al. J Am Coll Cardiol. 2017;70(14):1777–84.

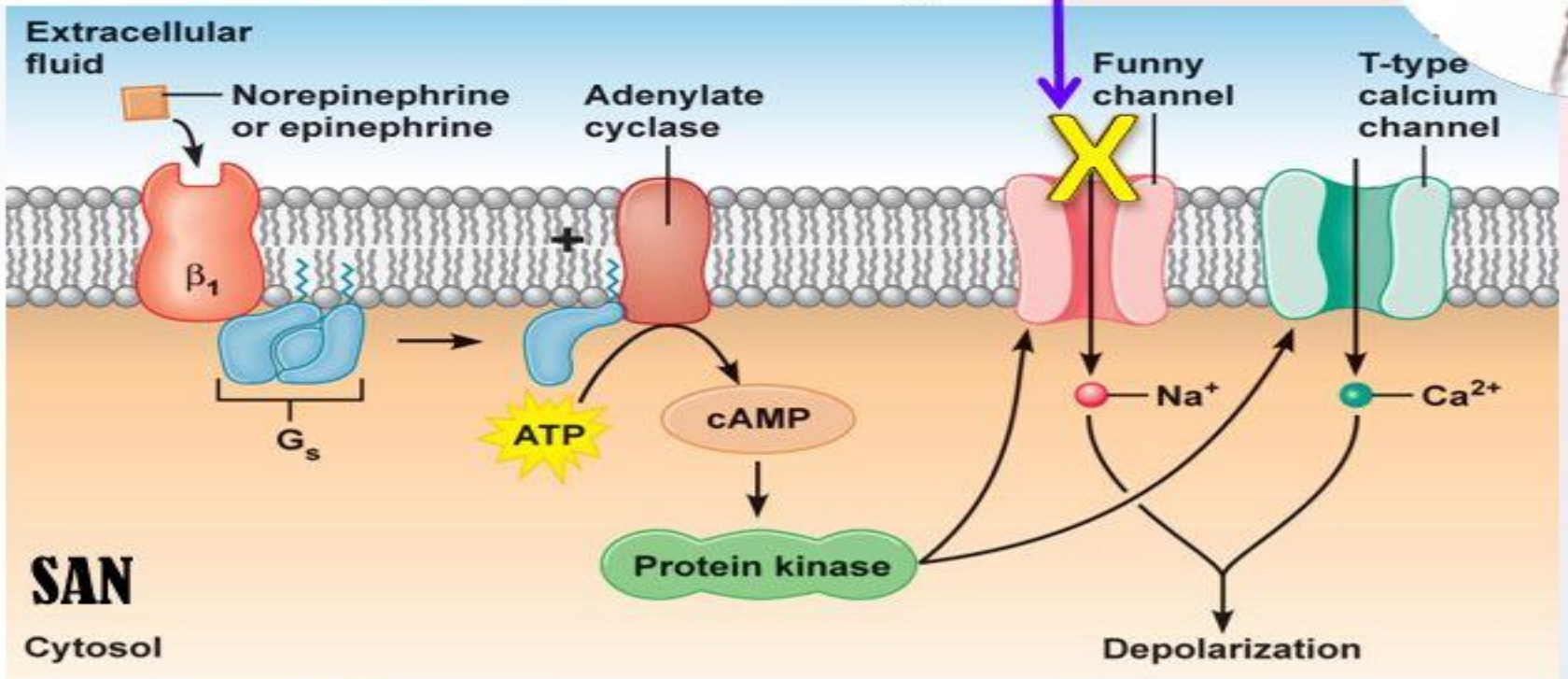
# DRUGS USED IN TREATMENT OF ANGINA

## OTHERS



**Ivabradine**

Not classified ➔ claimed to be *CARDIOTONIC agent*




Acts on the " Funny Channel" a special Na channel in SAN

➔ ↓HR ➔ ↓myocardial work ➔ ↓**Myocardial $O_2$ demand**

OTHERS

**Chân thành cảm ơn**
**sự theo dõi của quý đồng nghiệp**

# Kính mời quý đồng nghiệp tham dự Hội nghị
# Nội Tiết – Đái Tháo Đường – Rối Loạn Chuyển Hoá
# Tại Thành Phố Đà Nẵng ngày 16 và 17/6/2023