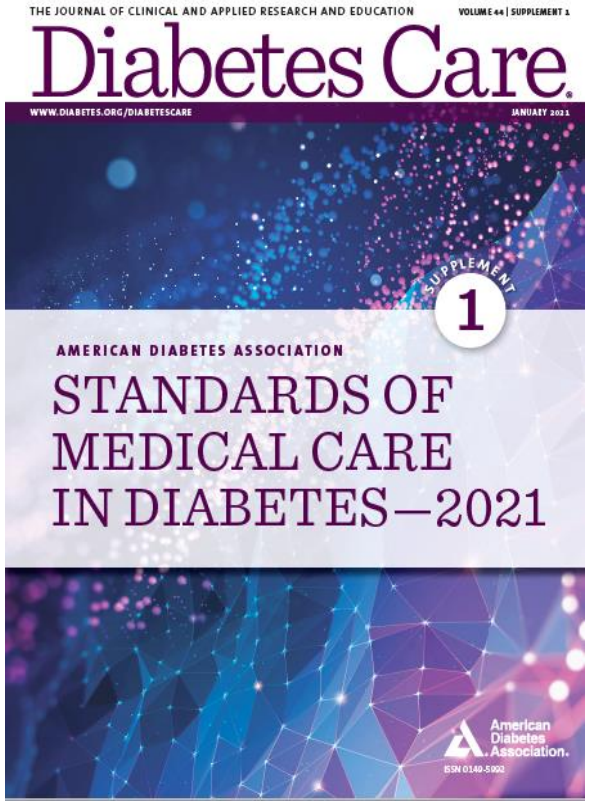
HỘI NGHỊ TĂNG HUYẾT ÁP VIỆT NAM LẦN THỨ IV

Cần Thơ, ngày 16 - 17 tháng 10 năm 2021

World Health Organization

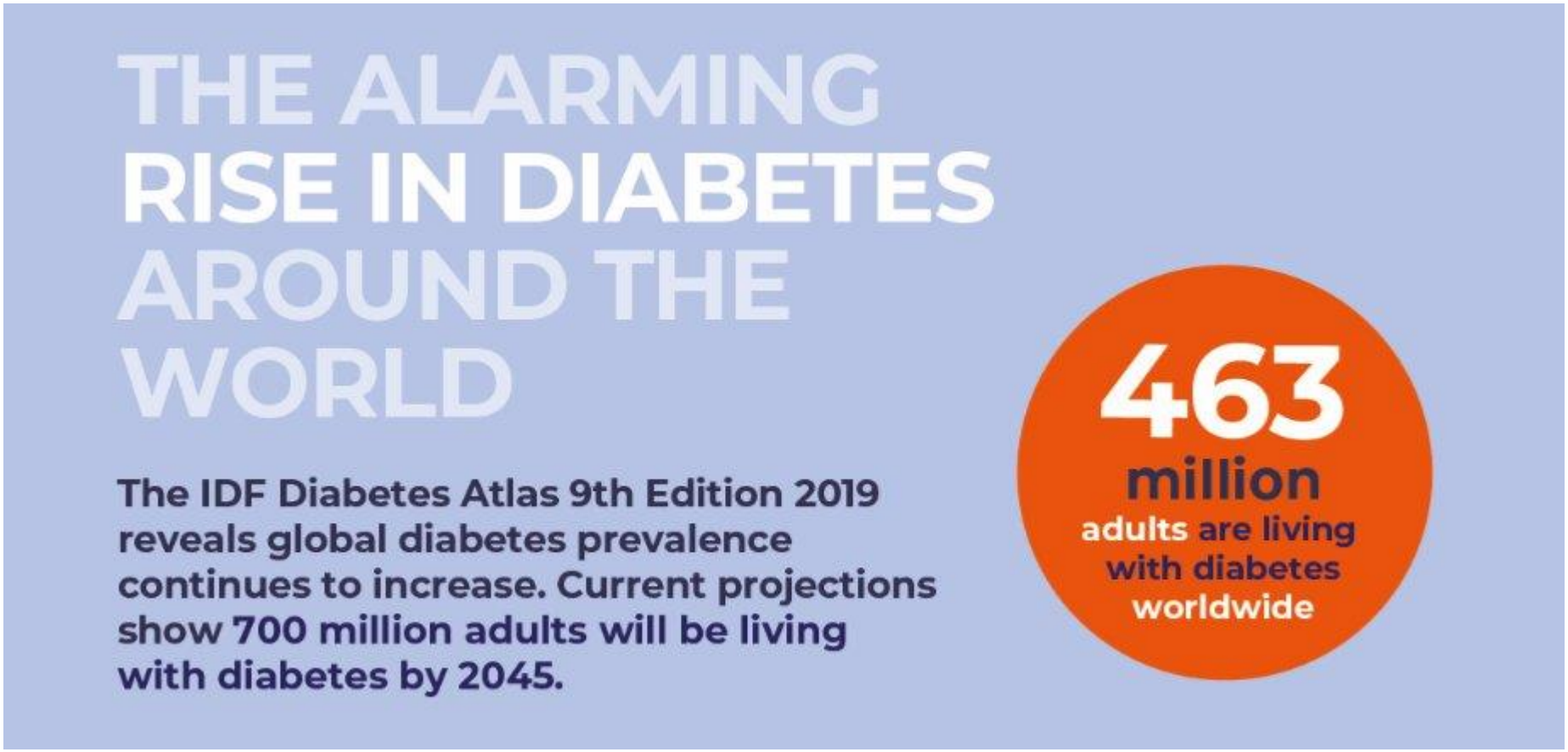


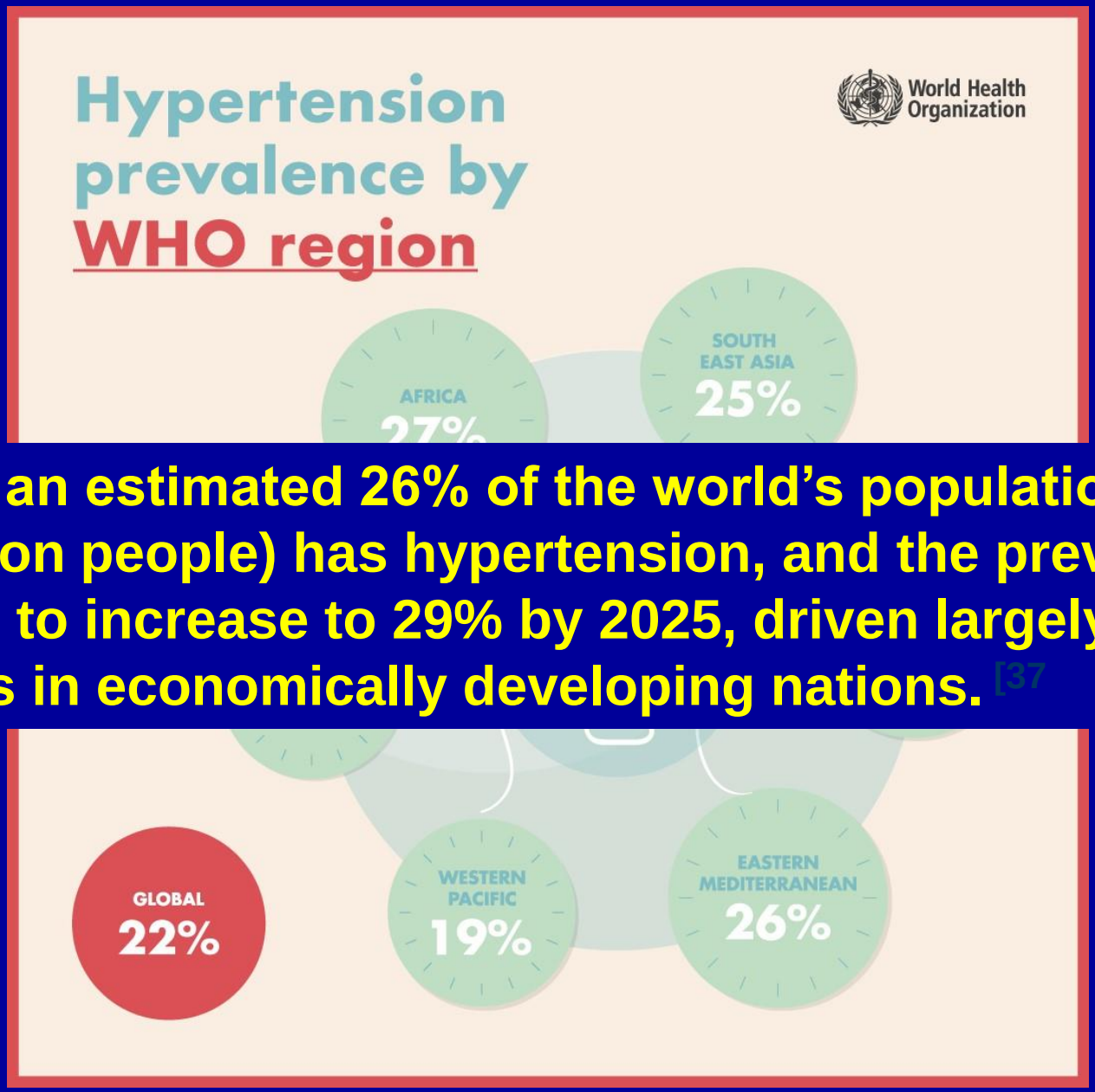
CẬP NHẬT
ĐIỀU TRỊ TĂNG HUYẾT ÁP TRÊN BỆNH NHÂN ĐÁI THÁO ĐƯỜNG TÍP 2
ADA 2021 & WHO 2021

GS.TS.NGUYỄN HẢI THUỶ
PCT Hội Nội Tiết – ĐTĐ Việt Nam

1.Đái Tháo Đường và Tăng Huyết Áp

ĐTĐ ngày càng có khuynh hướng gia tăng

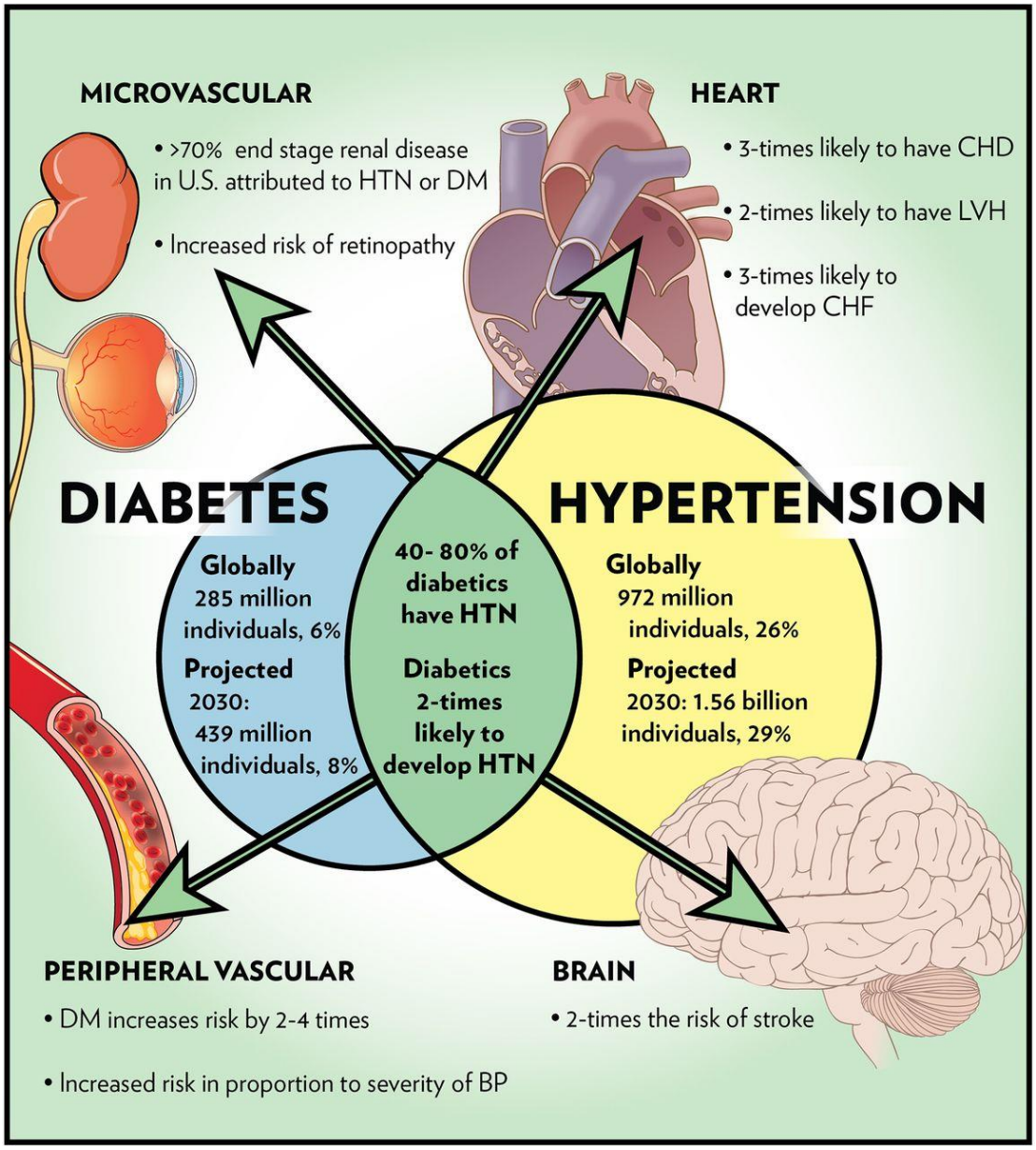




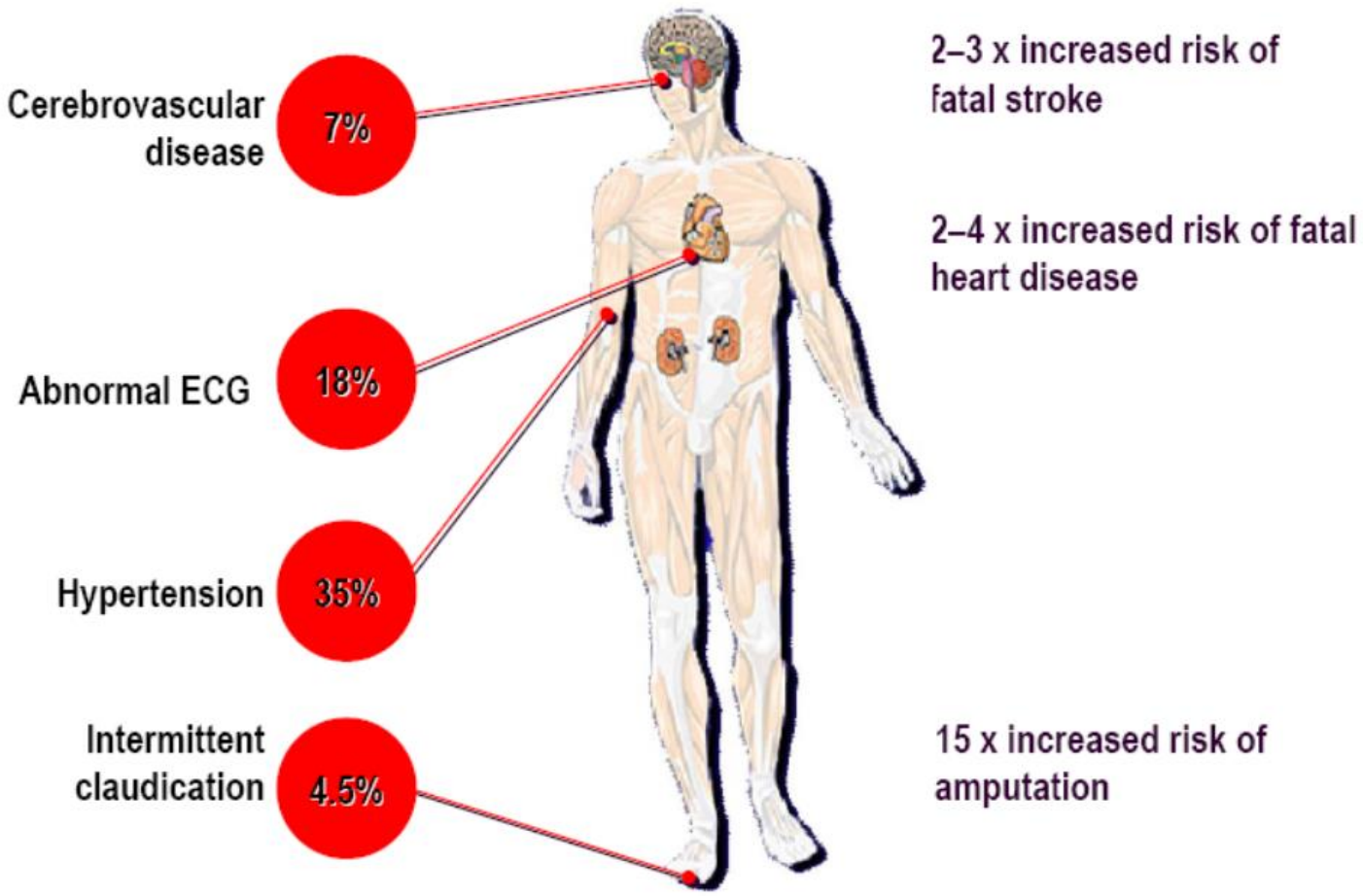
Globally, an estimated 26% of the world's population (972 million people) has hypertension, and the prevalence is expected to increase to 29% by 2025, driven largely by increases in economically developing nations. [37

World Hypertension Day 2019

ĐTĐ và THA thường song hành trên cùng bệnh nhân

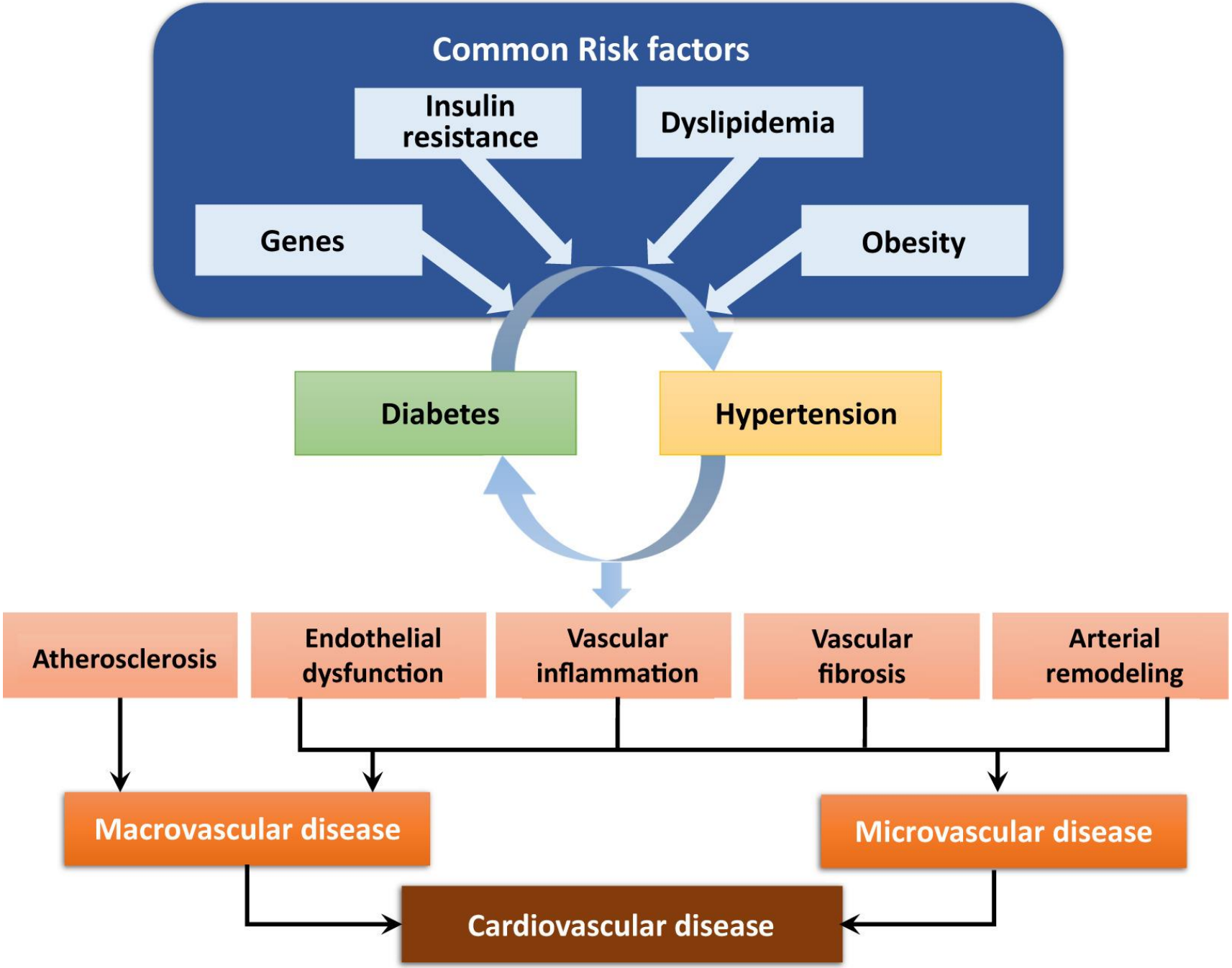


Macrovascular diseases in type 2 diabetes

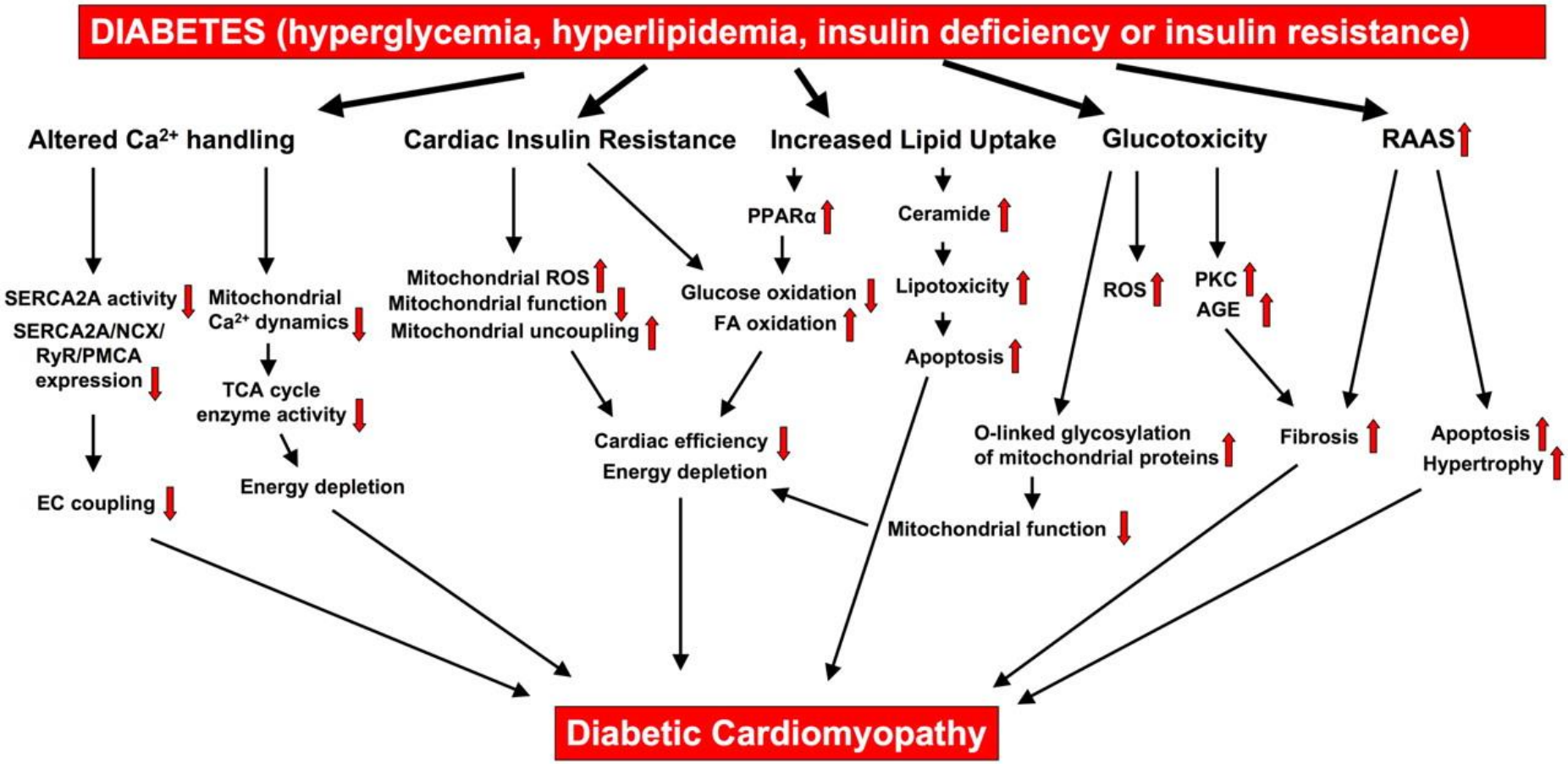


35% bn ĐTĐ có THA ngay khi phát hiện bệnh ĐTĐ


Hypertension
Diabetes
Microvascular damage, ↑ SNS, antihypertensive drugs
Obesity
Insulin resistance
↑ ROS
↑ RAAS
↑ SNS
Altered renal
Na handling
Altered immune
responses
↑ inflammation
Arterial stiffness, nephroparenchymal hypertension


Common Risk factors
Insulin resistance
Dyslipidemia
Genes
Obesity
Diabetes
Hypertension
Atherosclerosis
Endothelial dysfunction
Vascular inflammation
Vascular fibrosis
Arterial remodeling
Macrovascular disease
Microvascular disease
Cardiovascular disease

Bệnh cơ tim ĐTĐ



Bệnh tim tăng áp là biến Chứng Tăng Huyết Áp

COMPLICATIONS OF HYPERTENSION

"THE 5C'S"

C — CORONARY ARTERY DISEASE

Can lead to narrowing of blood vessels making them more likely to block from blood clots.

C — CHRONIC RENAL FAILURE

Constant high blood pressure can damage small blood vessels in the kidneys making it not to function properly.

C — CONGESTIVE HEART FAILURE

Pumping blood against the higher pressure in the vessels causes the heart muscles to thicken.

C — CARDIAC ARREST

High blood pressure can cause CAD, damaged arteries cannot deliver enough oxygen to other parts of the body eventually leading to heart attack.

C — CEREBROVASCULAR ACCIDENT

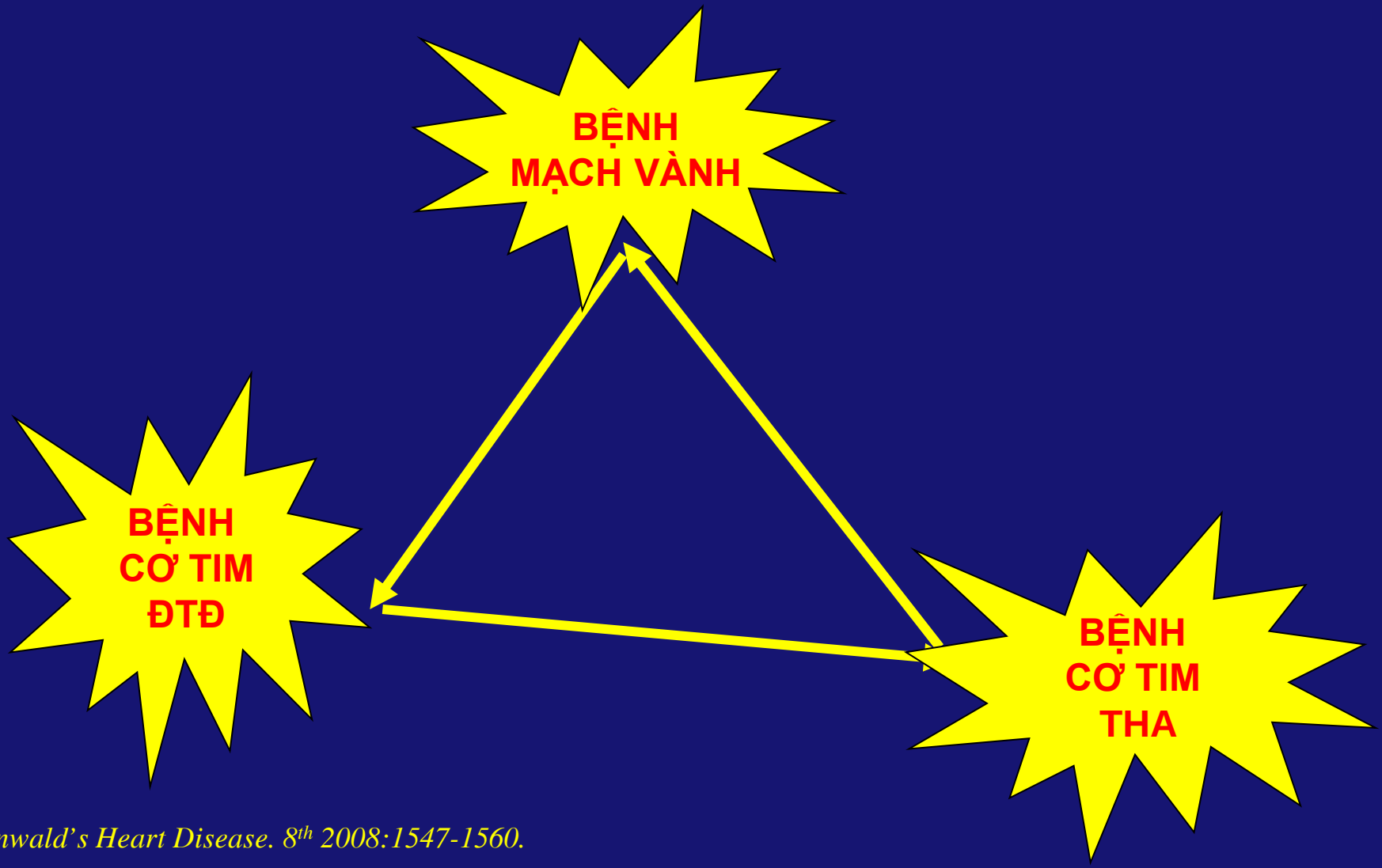
Hypertension leads to atherosclerosis and hardening of the large arteries. This, in turn, can lead to blockage of small blood vessels in the brain.

LEARN MORE: **HYPERTENSION COMPLICATIONS**

The excessive pressure on the artery walls caused by hypertension or high blood pressure can damage the blood vessels, as well as organs in the body. The higher the blood pressure and the longer it goes uncontrolled, the greater the damage. With time, hypertension increases the risk of heart disease, kidney disease, and stroke.

NCLEXQuiz.com

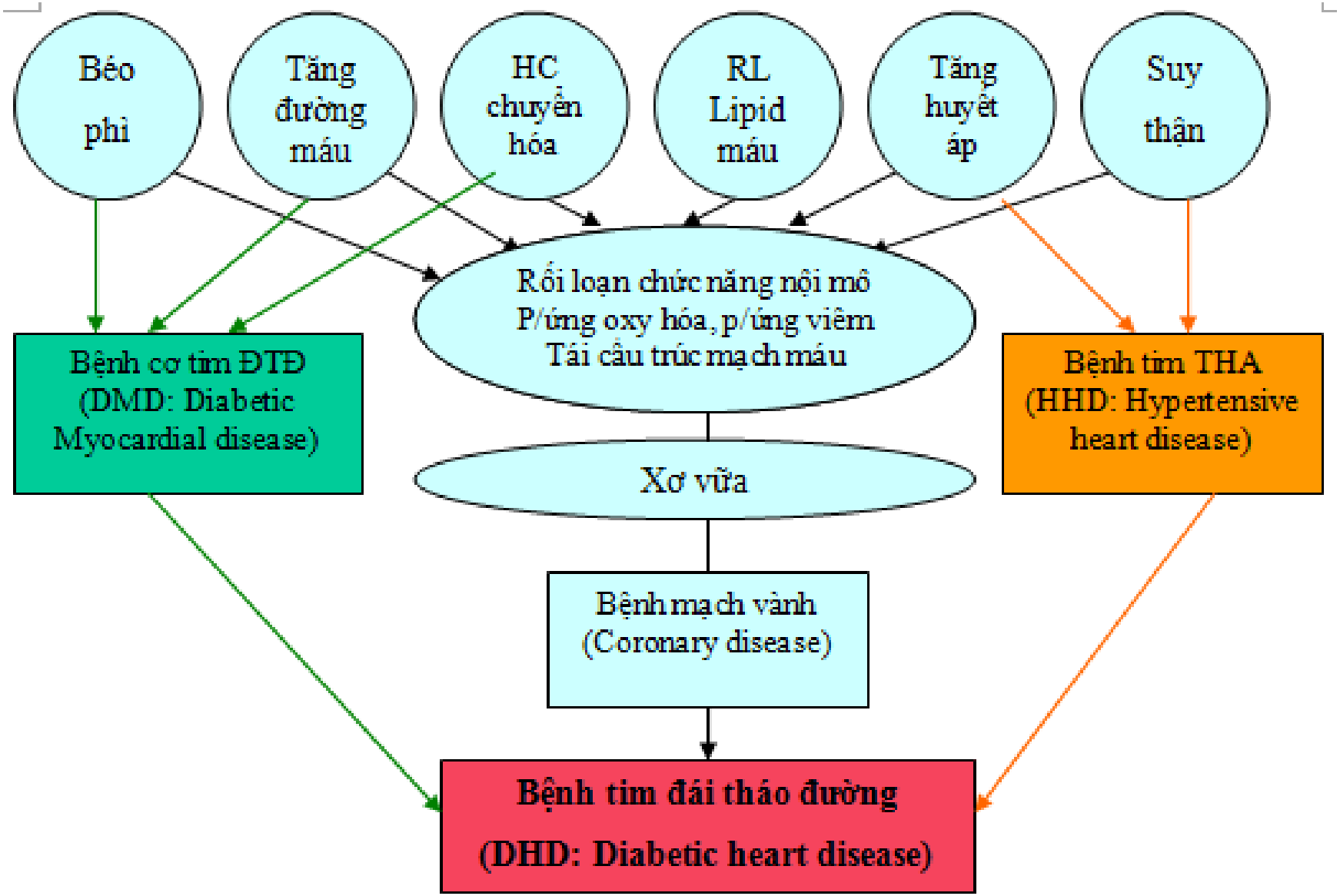
Tam chứng nhiễm độc tim (Cardiotoxic Triad) trên bệnh nhân ĐTĐ



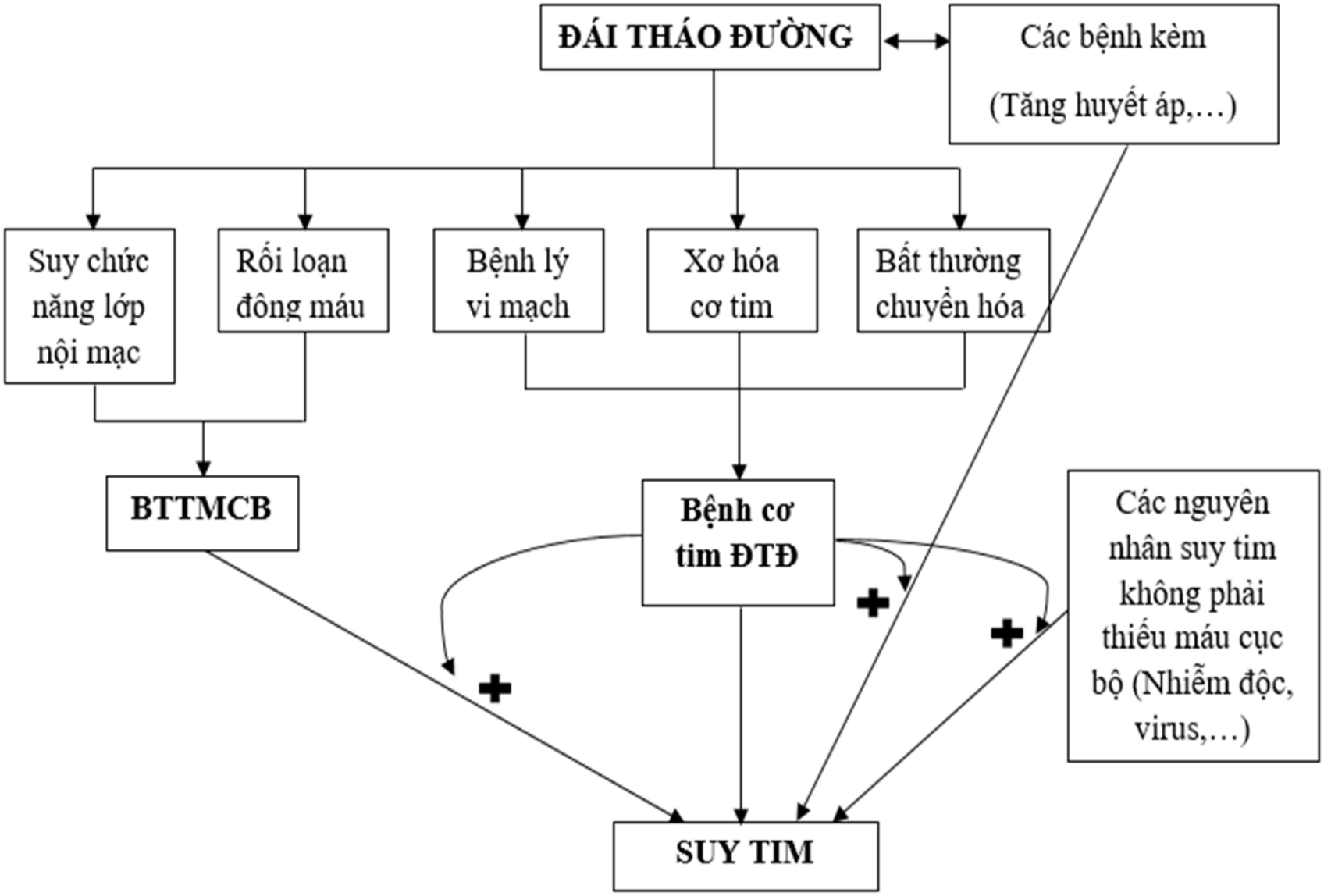
Braunwald's Heart Disease. 8th 2008:1547-1560.

Crawford.MH: Cardiology clinics: heart failure. 2007, vol 25, num 4: p 523-536.

Bệnh tim đái tháo đường

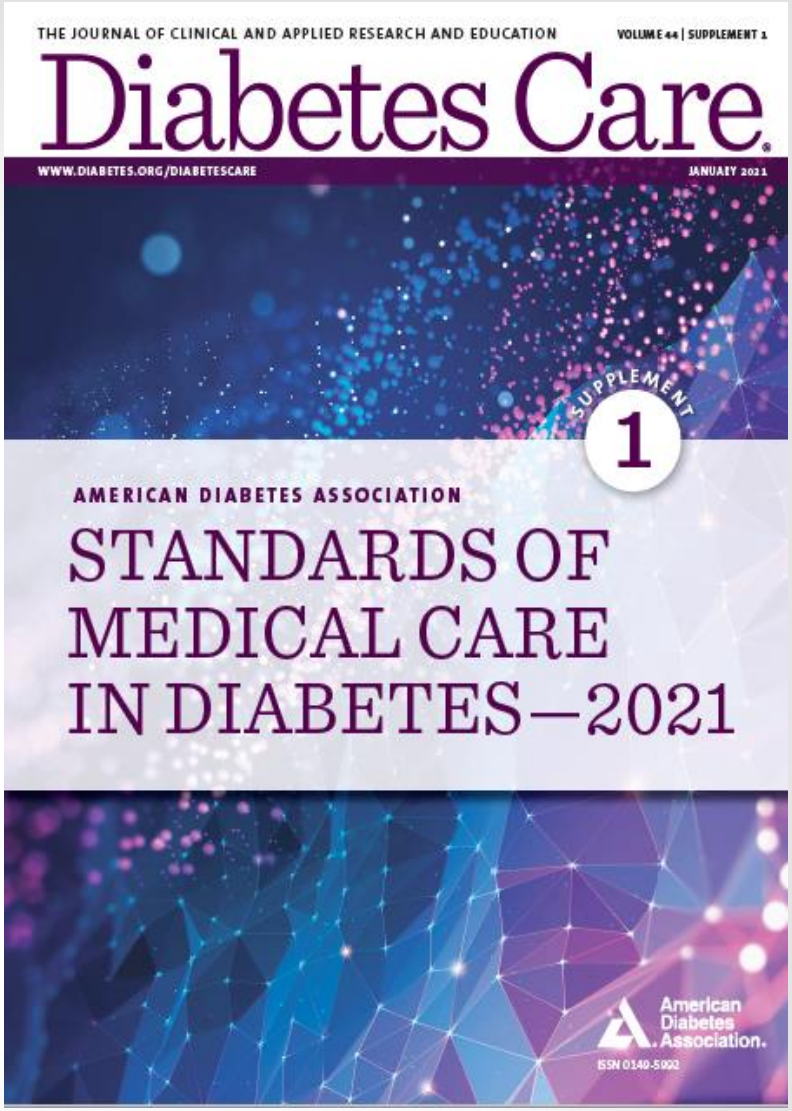


Suy tim đái tháo đường



Section 10.

Cardiovascular Disease and Risk Management



American Diabetes Association.
Connected for Life

10.1 Blood pressure should be measured at every routine clinical visit. Patients found to have elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**

10.2 All hypertensive patients with diabetes should monitor their blood pressure at home. **B**

10.5 For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a blood pressure target of <140/90 mmHg. **A**

10.7 For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. **A**

10.8 Patients with confirmed office-based blood pressure ≥140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. **A**

10.9 Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. **A**

10.10 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes. **A** ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A**

10.11 Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. **A**

10.12 An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**

12. Older Adults: *Standards of Medical Care in Diabetes—2021*

Diabetes Care 2021;44(Suppl. 1):S168–S179 | https://doi.org/10.2337/dc21-s012

status	Rationale	Blood pressure
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<140/90 mmHg
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<140/90 mmHg
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<150/90 mmHg

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

Initial BP >140/90 and <160/100 mmHg

Initial BP ≥160/100 mmHg

Start one agent

Lifestyle management

Start two agents

Albuminuria or CAD*

Albuminuria or CAD*

No

Yes

No

Yes

Start one drug:
- ACEi
- ARB
- CCB***
- Diuretic**

Start:
- ACEi or ARB

Start drug from 2 of 3 options:
- ACEi or ARB
- CCB***
- Diuretic**

Start:
- ACEi or ARB and
- CCB*** or Diuretic**

Assess BP Control and Adverse Effects

Treatment tolerated and target achieved

Not meeting target

Adverse effects

Continue therapy

Add agent from complementary drug class:
- ACEi or ARB
- CCB***
- Diuretic**

Consider change to alternative medication:
- ACEi or ARB
- CCB***
- Diuretic**

Not meeting target on two agents

Adverse effects

Assess BP Control and Adverse Effects

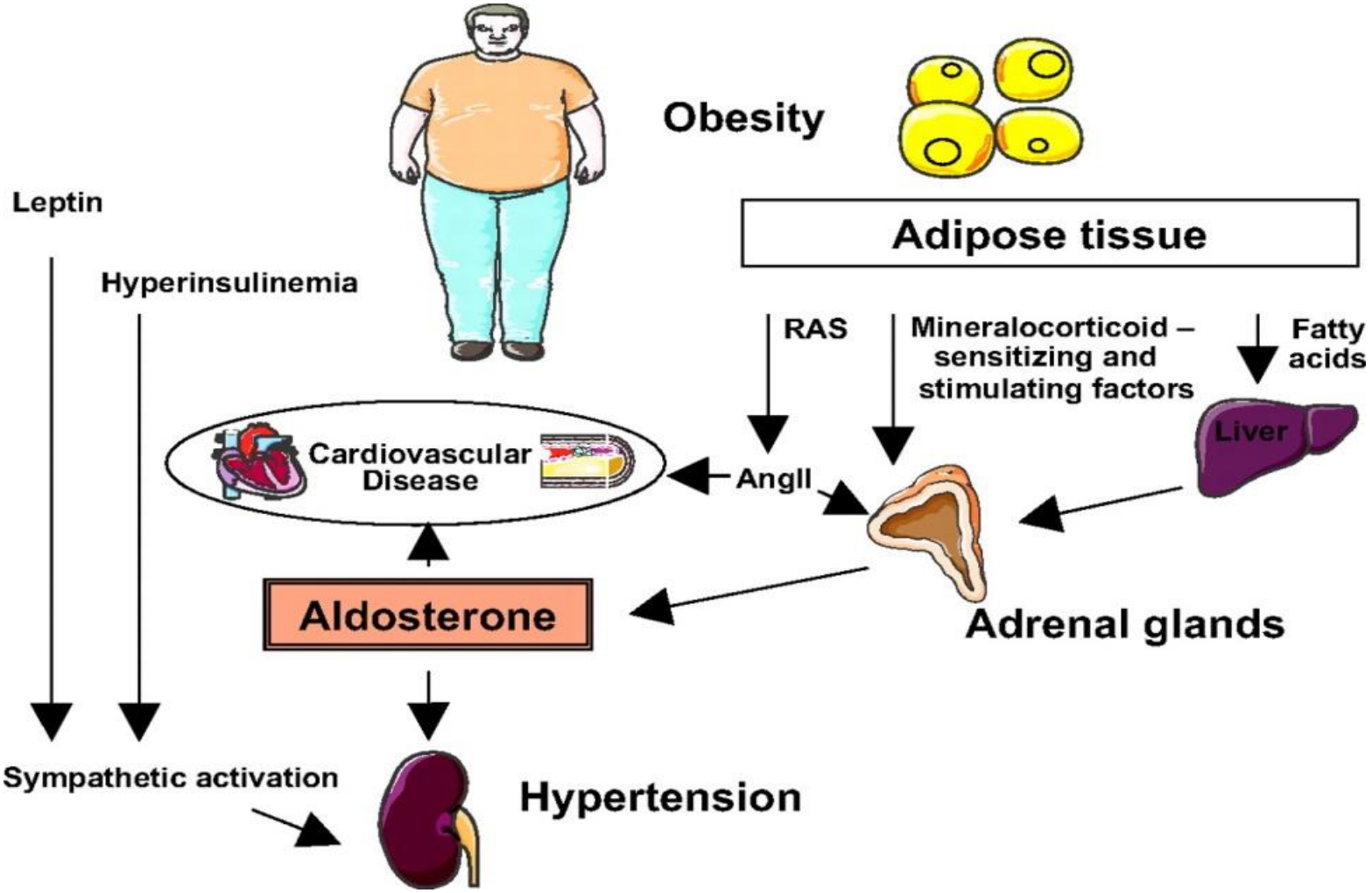
Treatment tolerated and target achieved

Not meeting target or adverse effects using a drug from each of three classes

Continue therapy

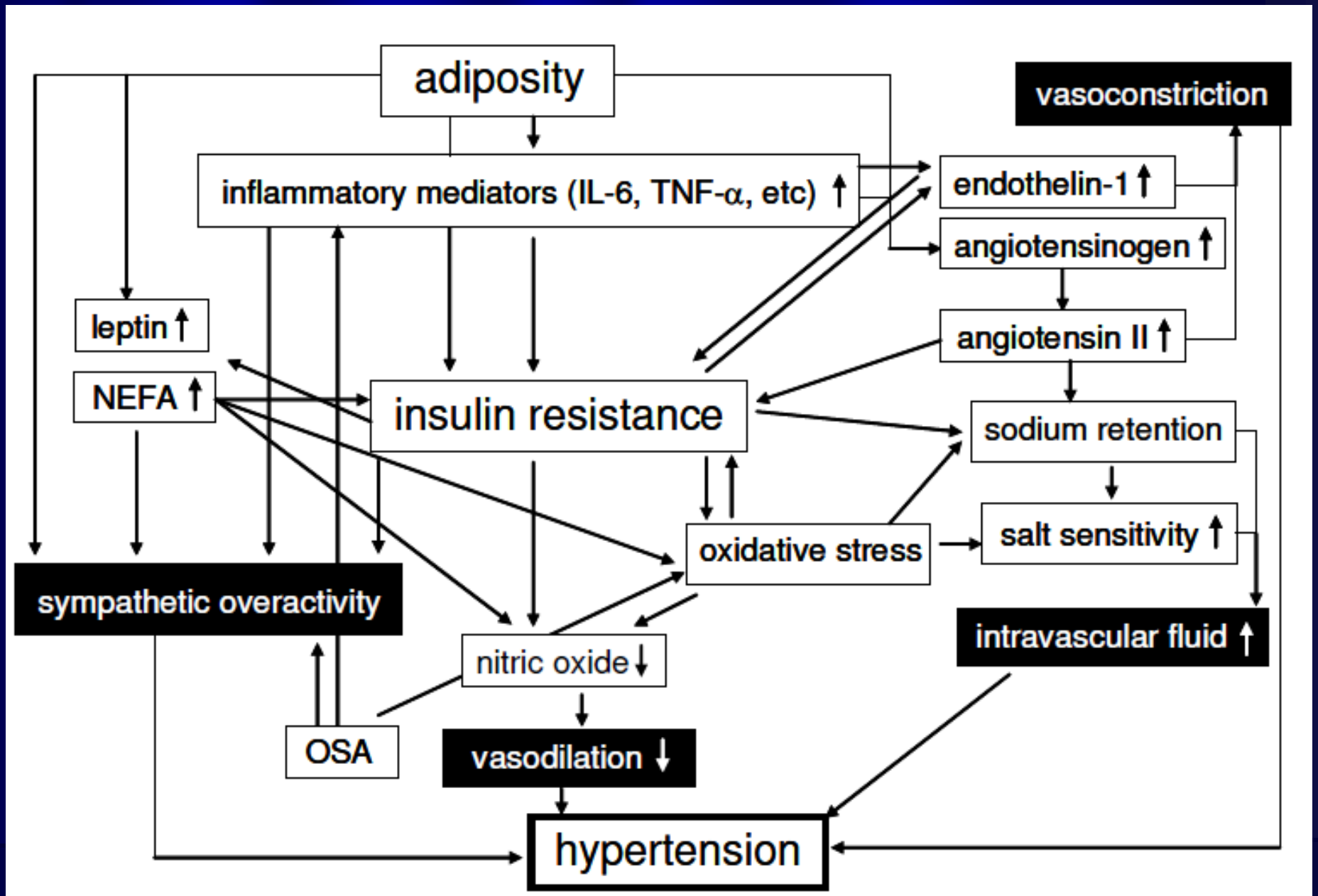
Consider Addition of Mineralocorticoid Receptor Antagonist; Refer to Specialist With Expertise in BP Management

2. Vì sao ACEis và ARBs được chọn ưu tiên trong điều trị THA ở bn ĐTĐ típ 2 (ADA 2021)

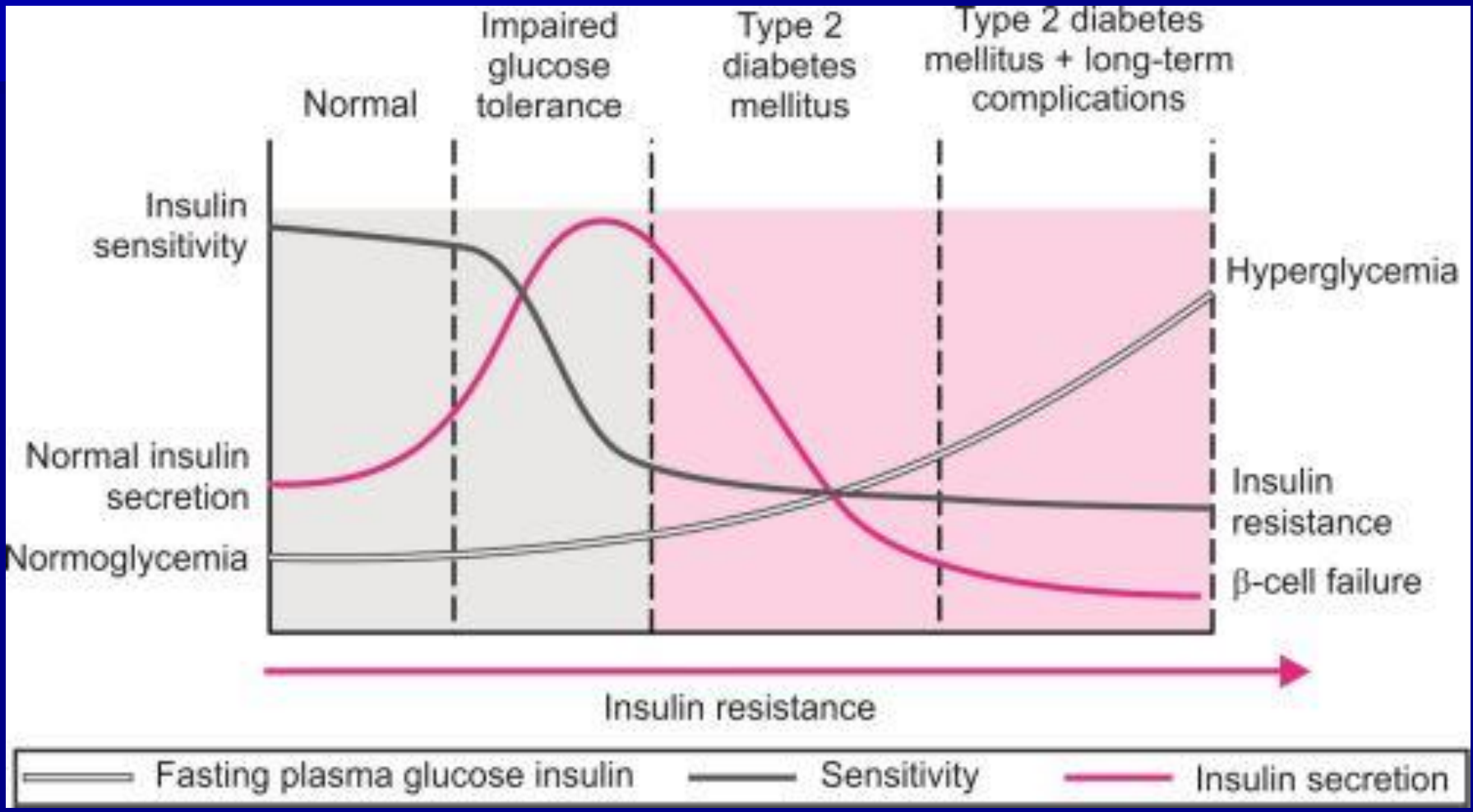


Diabetes and hypertension often occur together and may share some common causes. These include: Obesity, inflammation , oxidative stress và insulin resistance

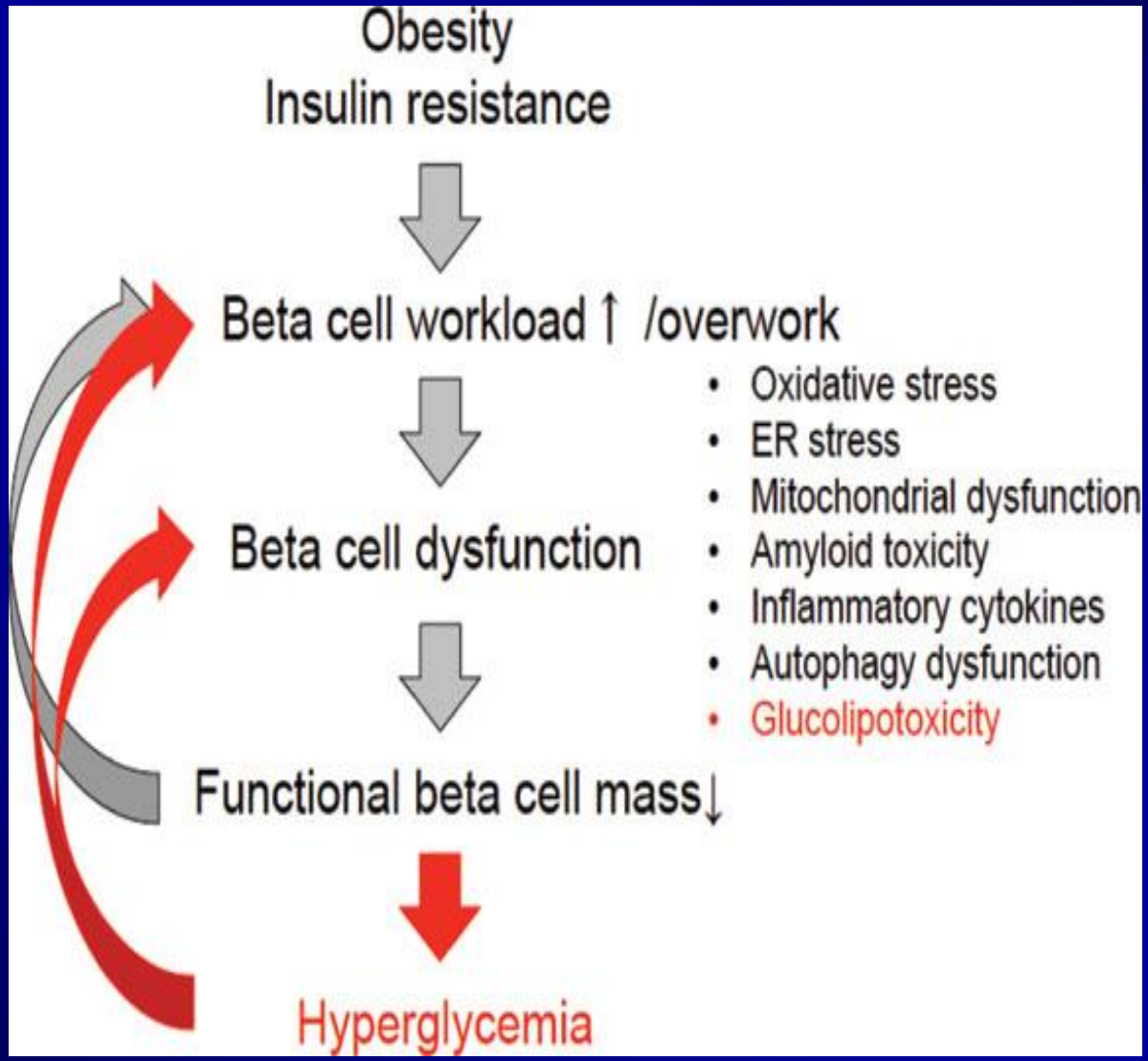
Cơ chế bệnh sinh THA trong ĐTĐ típ 2



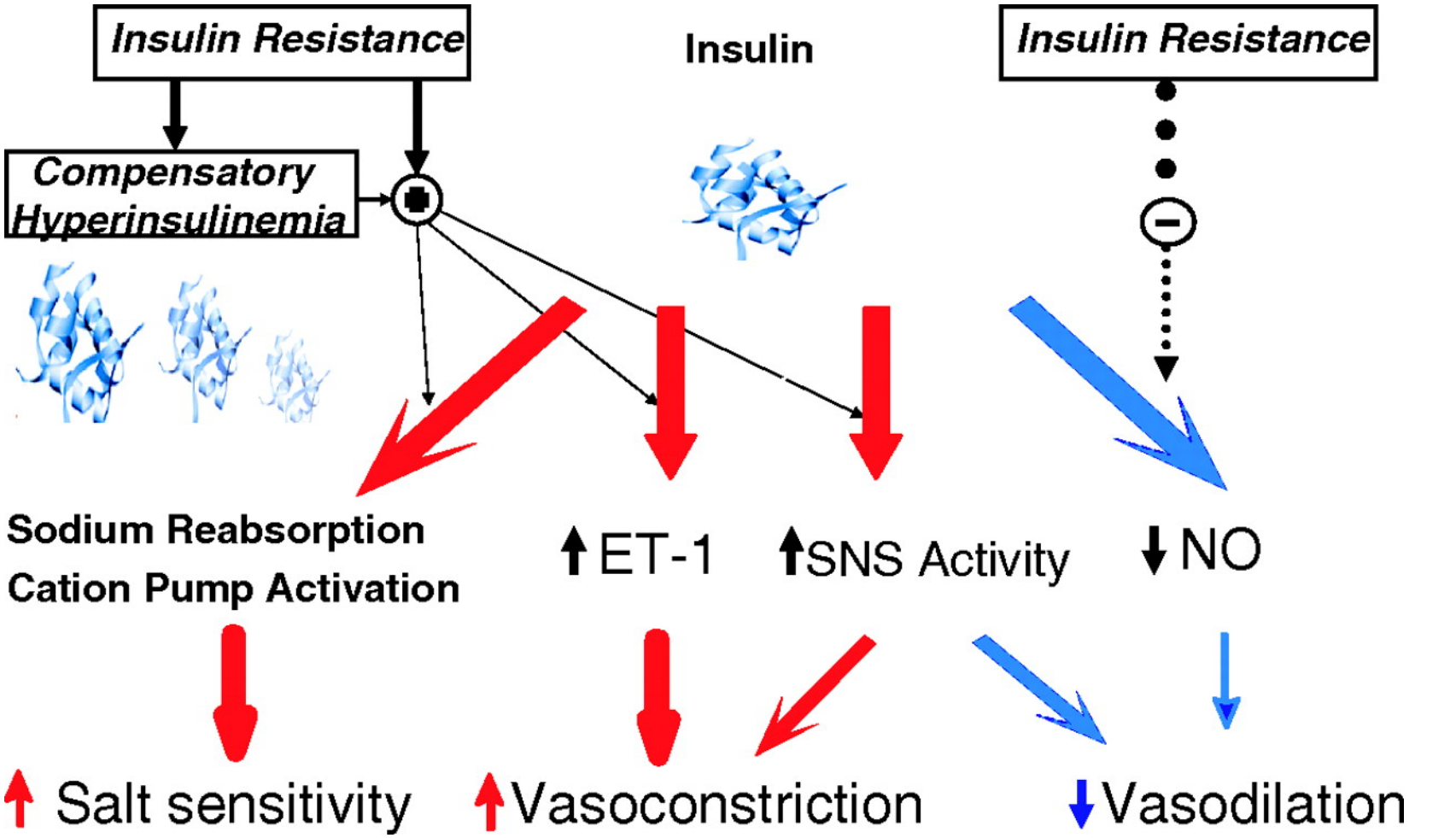
Kháng insulin trong ĐTĐ típ 2



Kháng insulin và chức năng tế bào beta



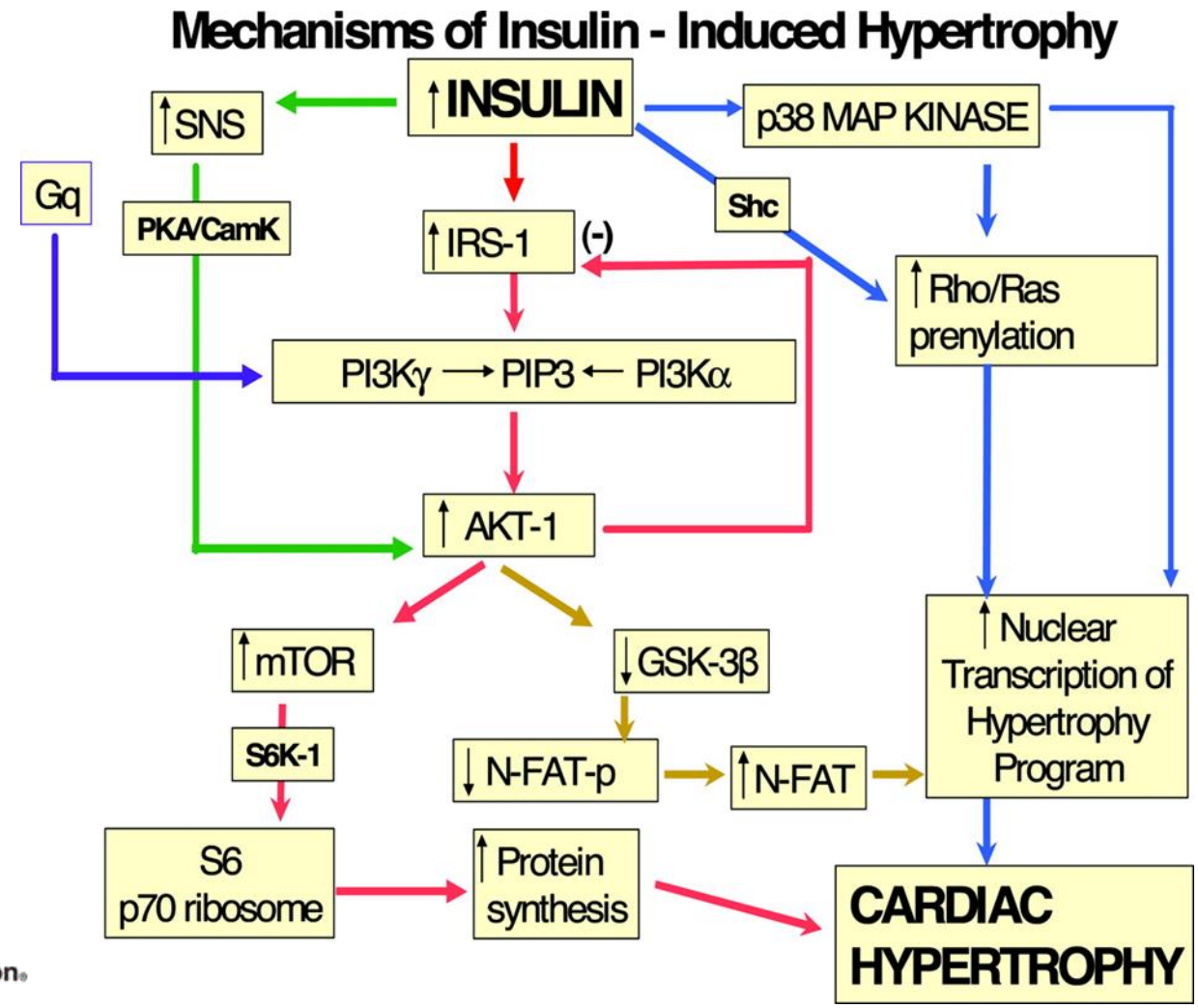
Pathway-selective insulin resistance in PI3K signaling creates imbalance between prohypertensive and antihypertensive vascular actions of insulin exacerbated by compensatory hyperinsulinemia.



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

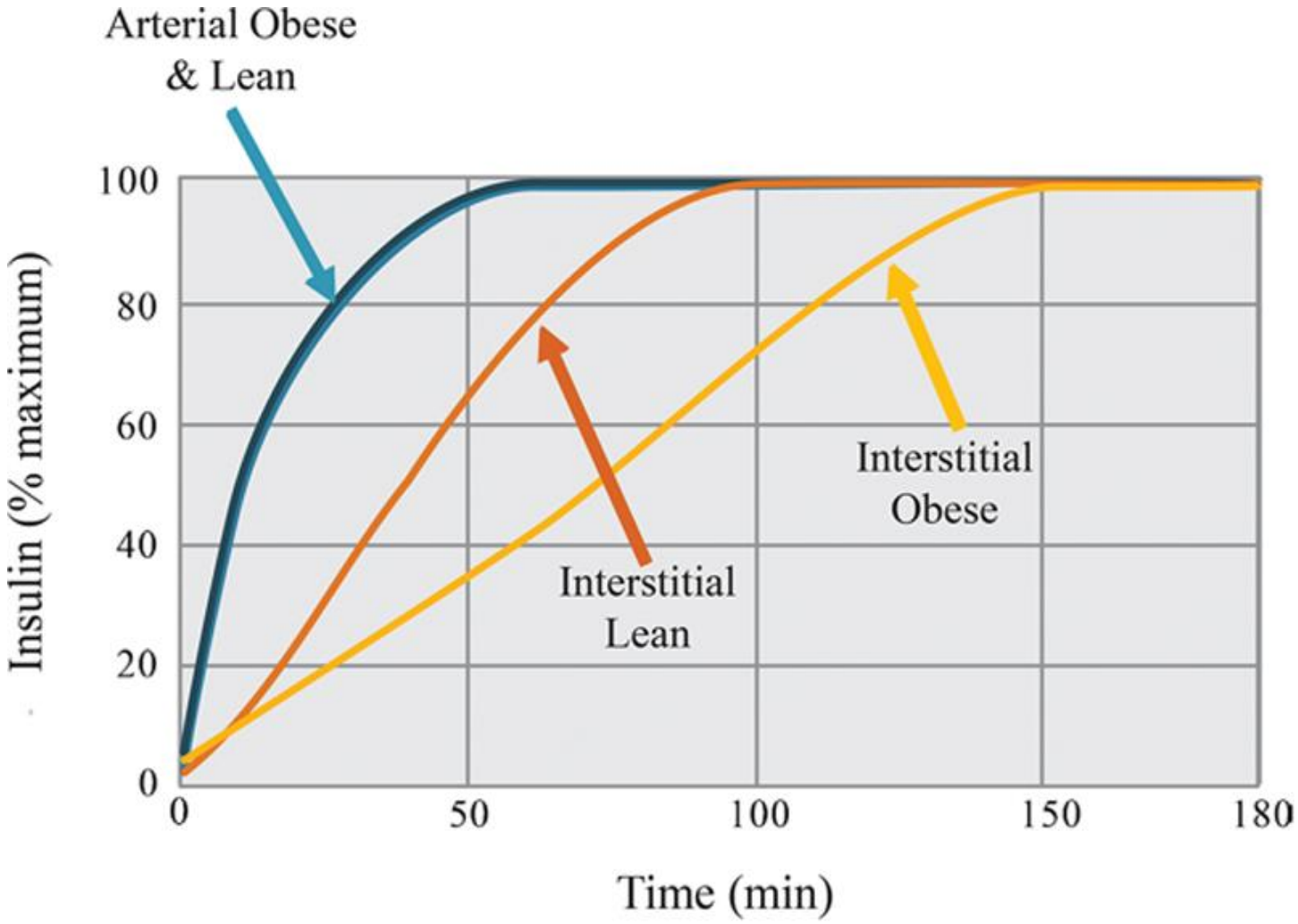
ENDOCRINE REVIEWS

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.

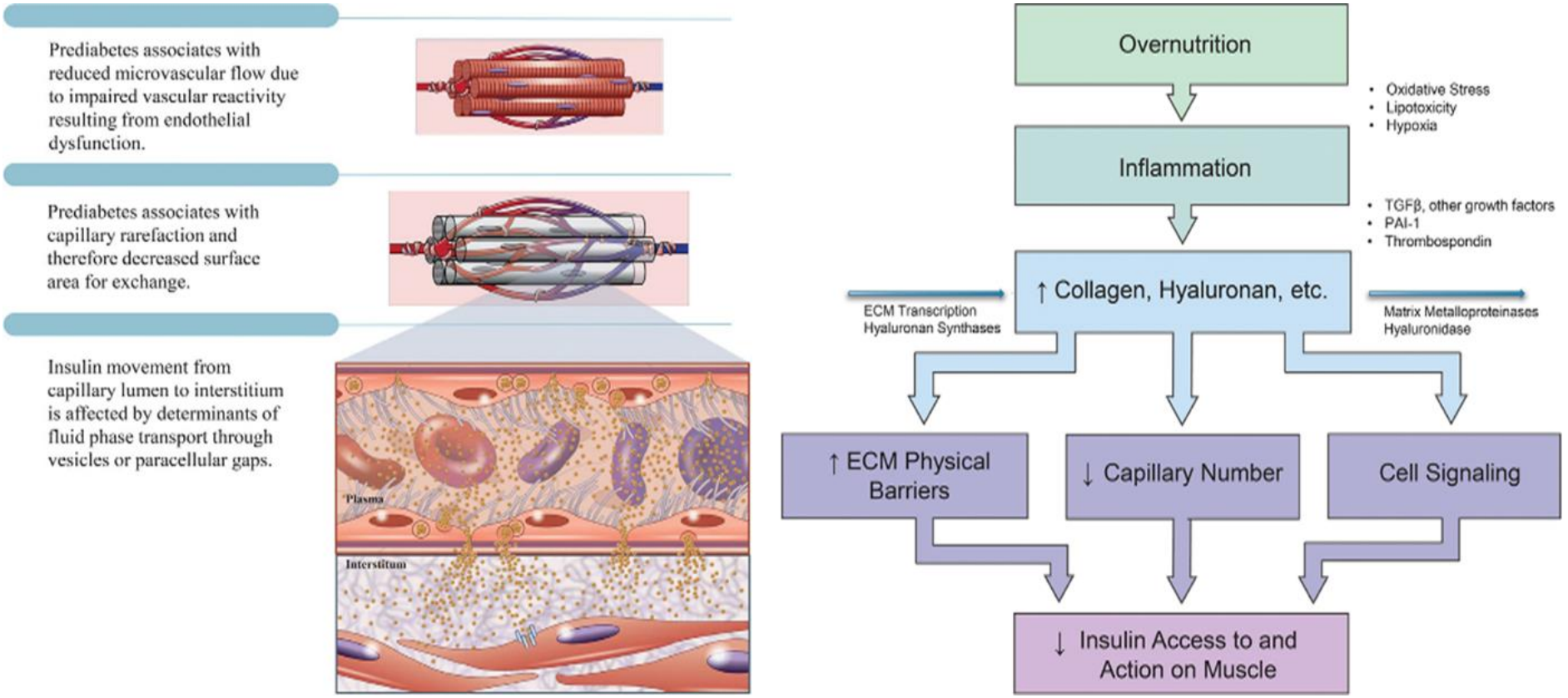


American Heart Association

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



Trên Bn béo phì vi tuần hoàn là một rào cản đối với việc tiếp cận insulin của cơ vân, vốn bị chậm. Nồng độ insulin ở tổ chức kẽ tăng chậm hơn so với nồng độ insulin trong máu động mạch vì insulin đi vào mao mạch thời gian này kéo dài trong bệnh béo phì.



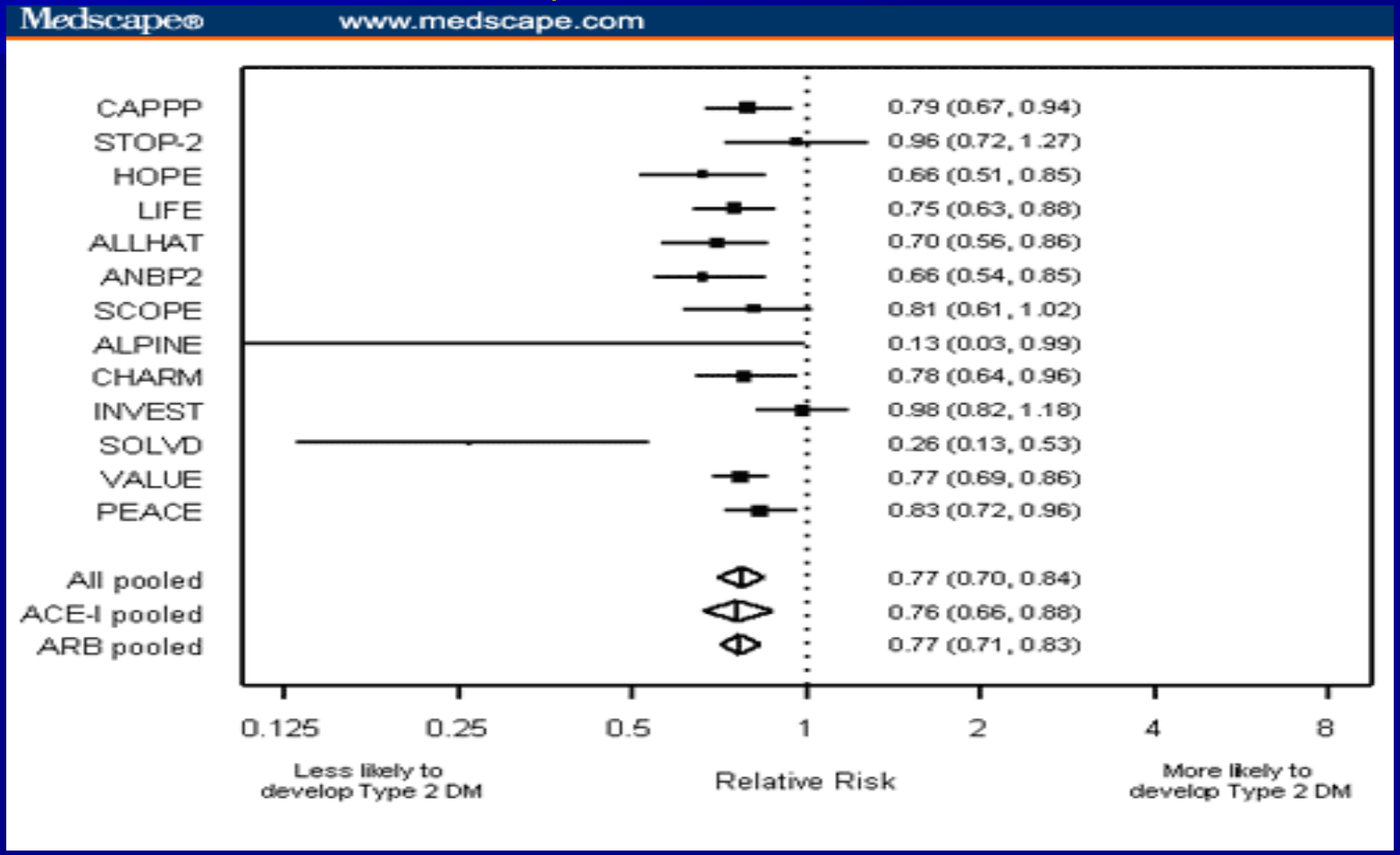
Insulin access is determined by (1) vascular reactivity; (2) microcirculatory hemodynamics; and (3) capillary insulin permeability (determined by vesicular or paracellular fluid phase transport). Vascular reactivity and microcirculatory hemodynamics are determined by endocrine factors, paracrine factors, cytokines, and microcirculatory architecture. Capillary insulin efflux is determined by the balance between hydrostatic and oncotic pressures. The extracellular matrix (ECM) in the sequelae of prediabetes. Inflammation results in ECM remodeling which creates endothelial dysfunction, capillary regression, spatial barriers, and increased ECM component interaction with cell surface receptors, including the integrin receptor family. These result in a decrease in tissue insulin access and, consequently, insulin action

- **Cơ là mục tiêu chính cho hoạt động của insulin và là yếu tố quyết định điểm cuối của việc thu nhận glucose.**
- **ACEis và ARBs cải thiện lưu lượng máu đến cơ**
- **Liệu pháp này có hiệu quả làm tăng diện tích bề mặt để trao đổi glucose giữa giường mao mạch và cơ và một phần có thể góp phần làm giảm bệnh nhân đái tháo đường típ 2 mới khởi phát khi bệnh nhân được điều trị ACEs và ARBs**

ACE Inhibitors or ARBs for Prevention of Type 2 Diabetes
A Meta-analysis of Randomized Clinical Trials.

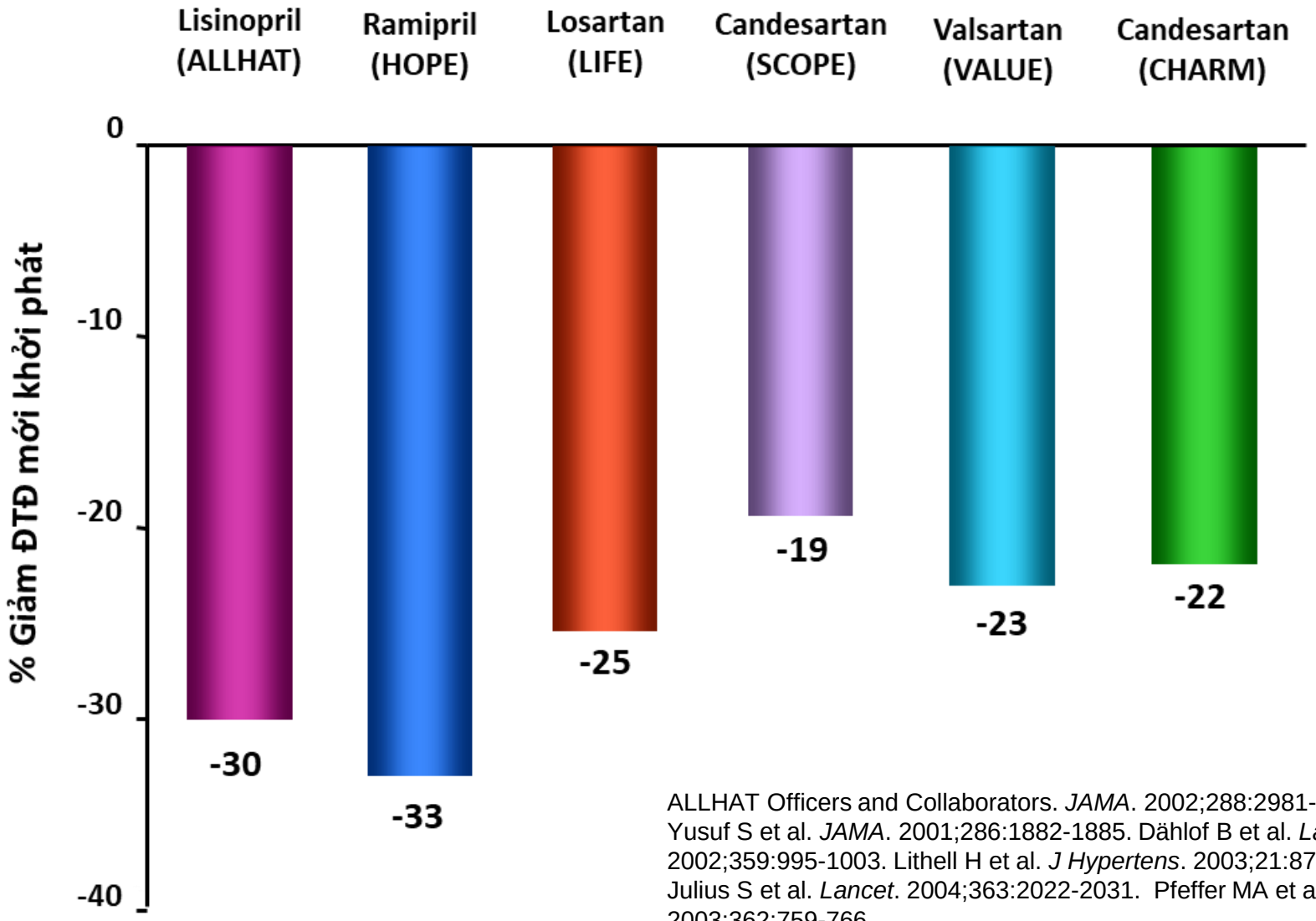
James H. O'Keefe Jr, MD, FACC ; Hussam Abuissa, MD...

Of the 13 studies that met criteria for entering the meta-analysis, 6 used ACE inhibitors and 7 used ARBs. These trials involved 125,356 patients, of whom 90,474 did not have diabetes at baseline.



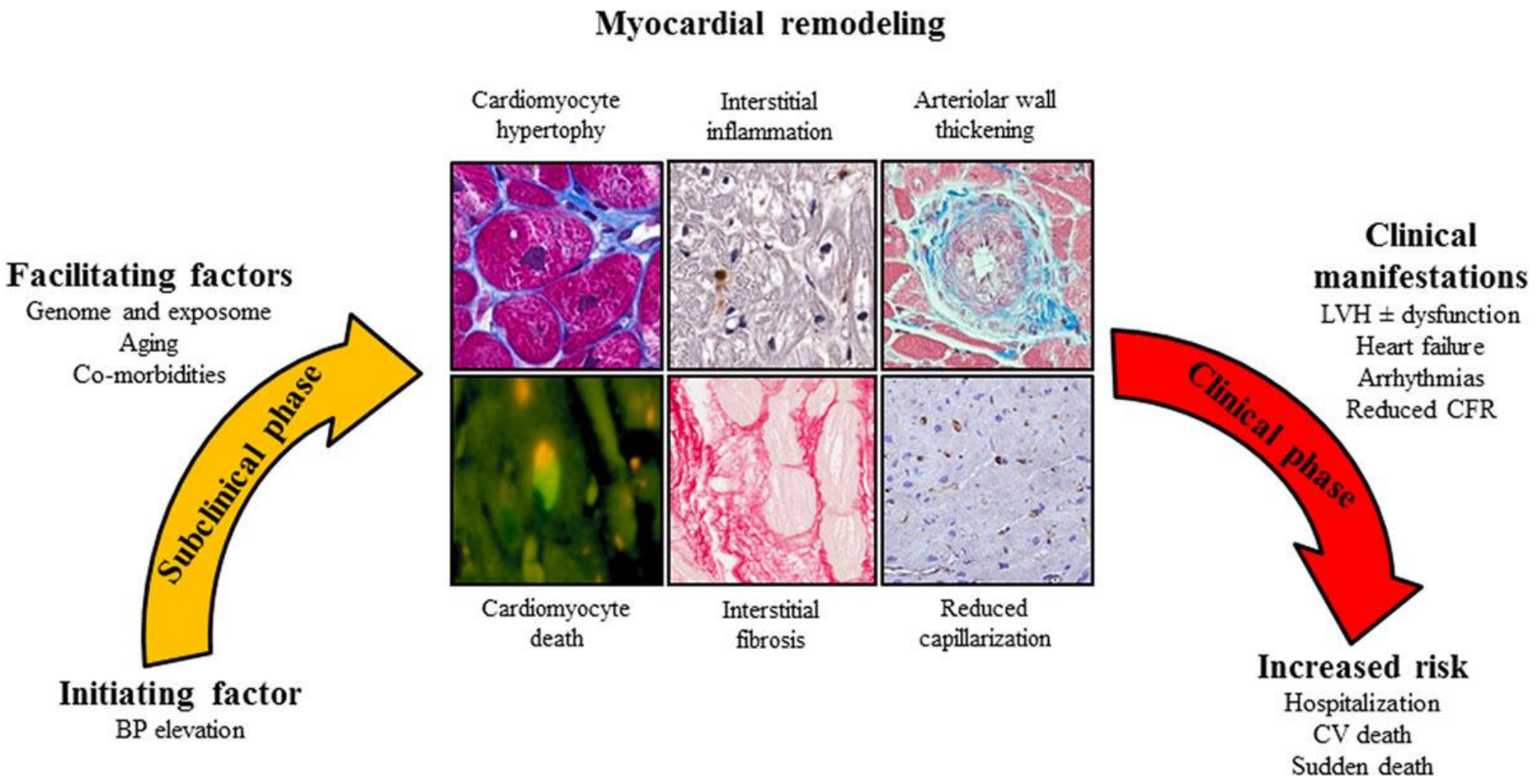
Pooled risk estimates of ACE inhibitor (ACE-I) and ARB trials. ACE inhibitor or ARB therapy resulted in a 23% reduction in new-onset type 2 diabetes.

Nhóm ức chế hệ ARBs giảm tỷ lệ ĐTĐ mới mắc

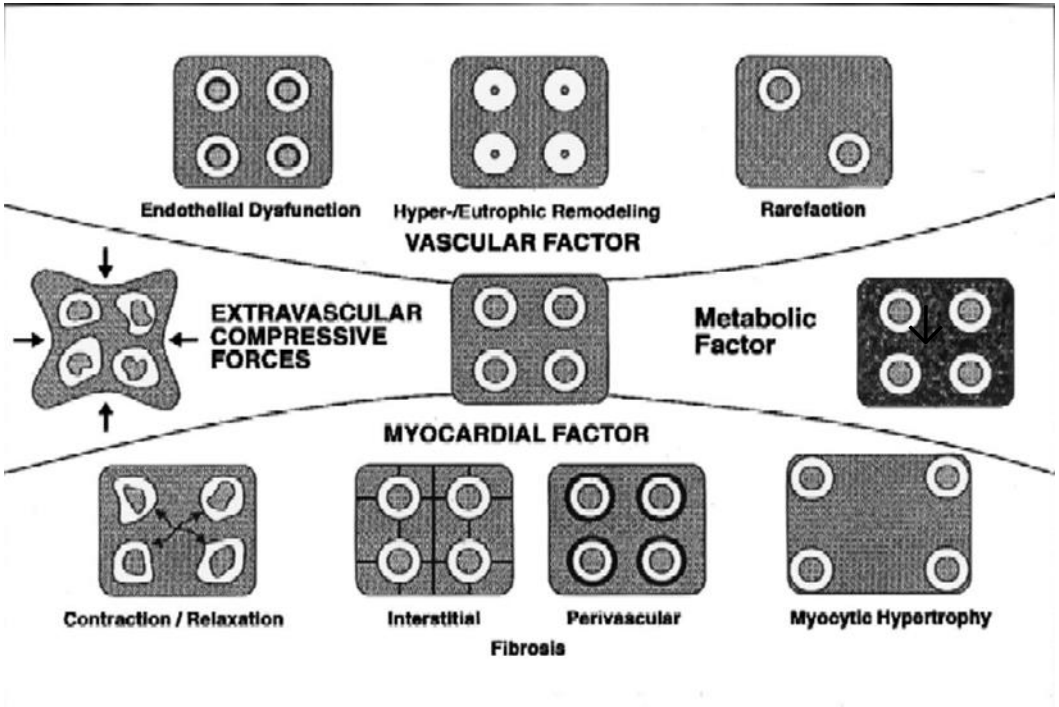


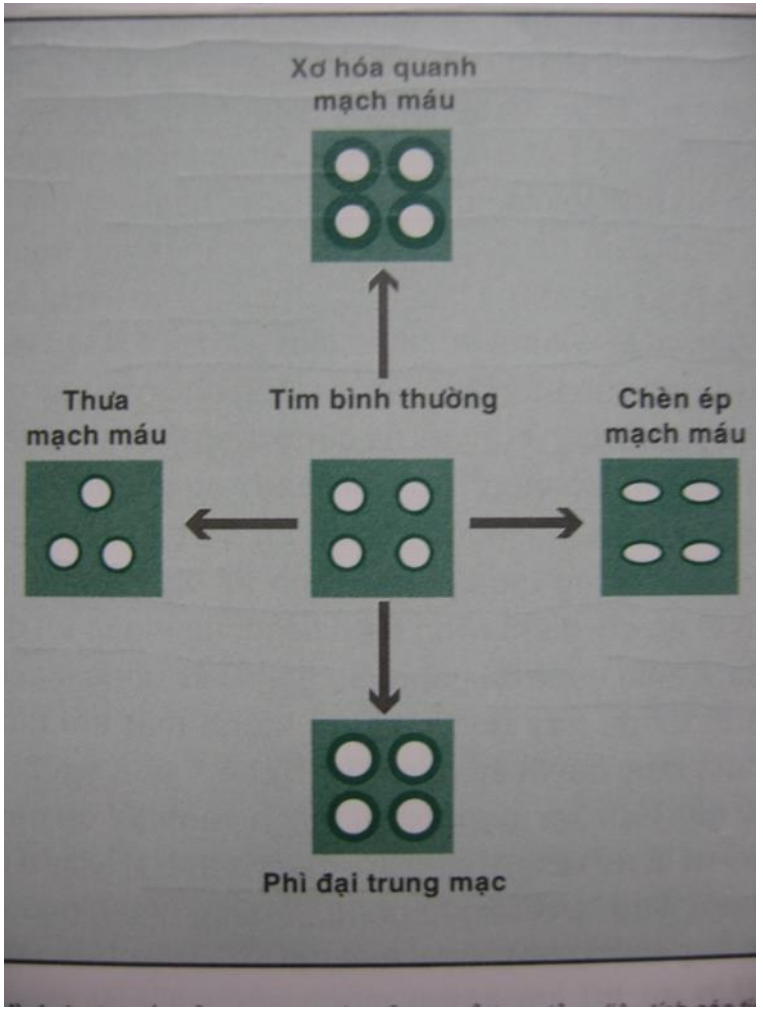
ALLHAT Officers and Collaborators. *JAMA*. 2002;288:2981-2997. Yusuf S et al. *JAMA*. 2001;286:1882-1885. Dählof B et al. *Lancet*. 2002;359:995-1003. Lithell H et al. *J Hypertens*. 2003;21:875-886. Julius S et al. *Lancet*. 2004;363:2022-2031. Pfeffer MA et al. *Lancet.* 2003;362:759-766.

Phì đại thất trái trong ĐTĐ và THA

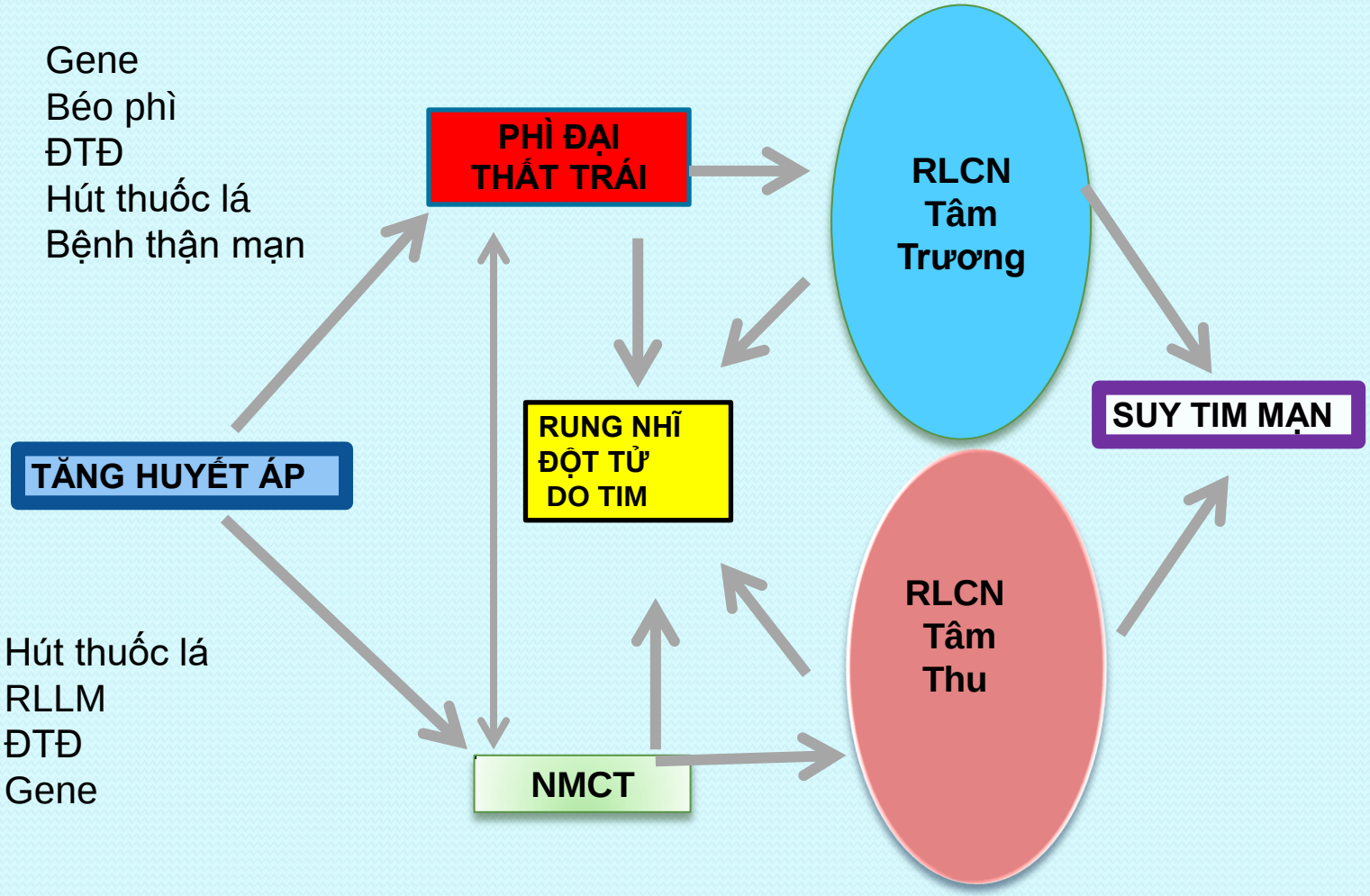


Cơ tim ở bệnh nhân ĐTĐ có THA liên quan đến tiểu và vi mạch vành



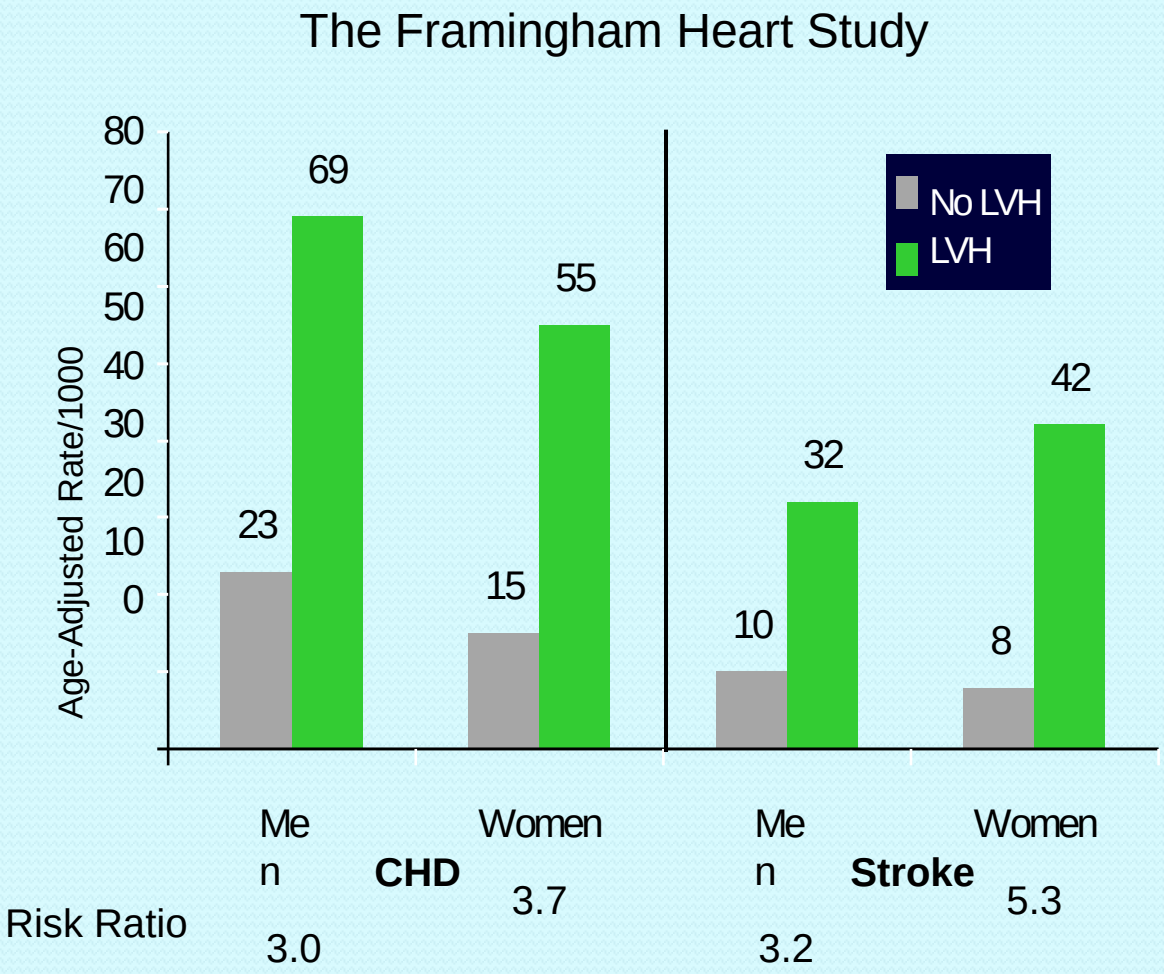


Hậu quả của Phì đại thất trái



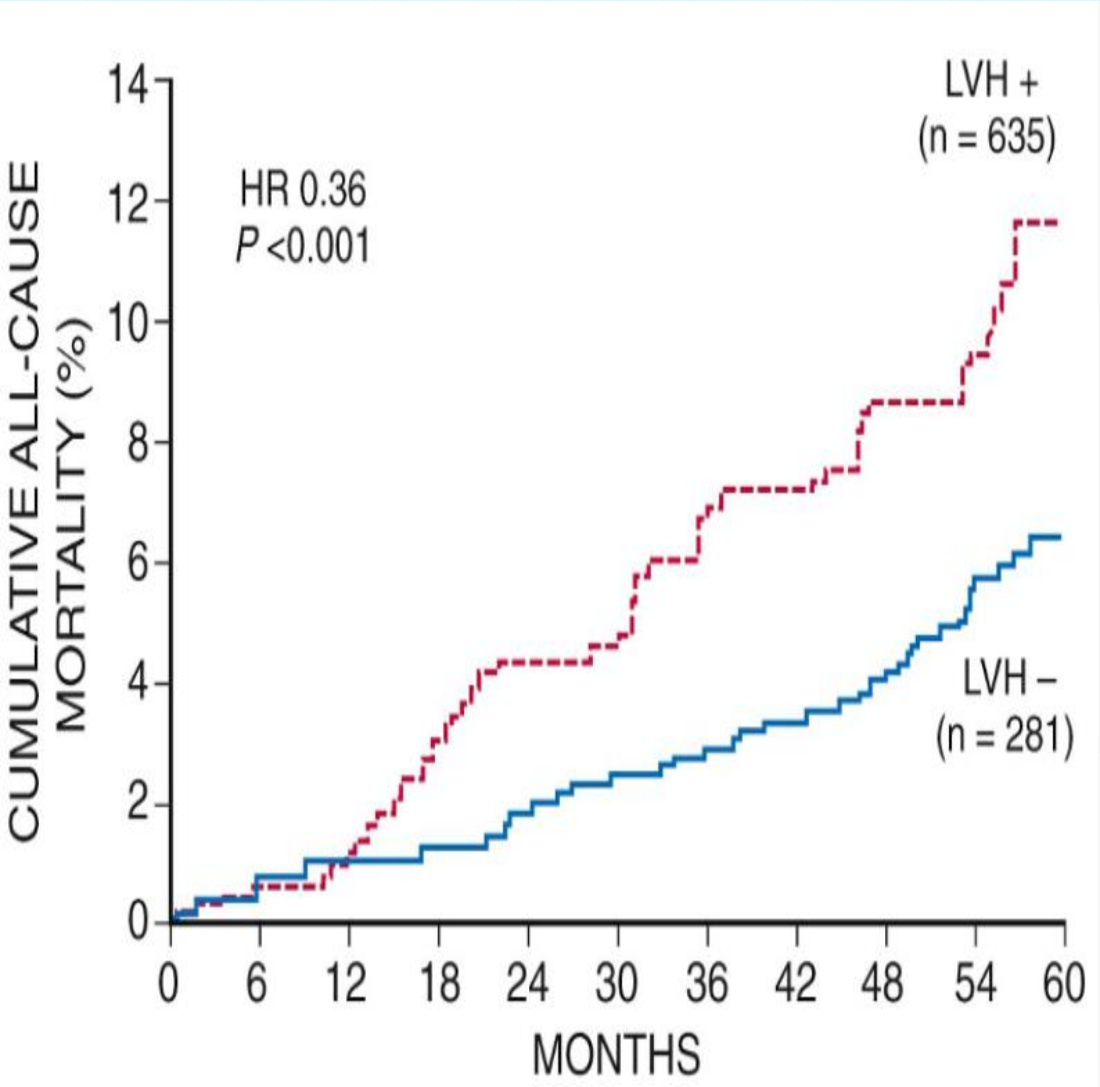
Rader F, Victor RG. In Heart failure: A Companion to Braunwald's Heart Disease; 3rd ed, 2016, Elsevier, p 361-372

Phì đại thất trái tăng nguy cơ biến cố tim mạch



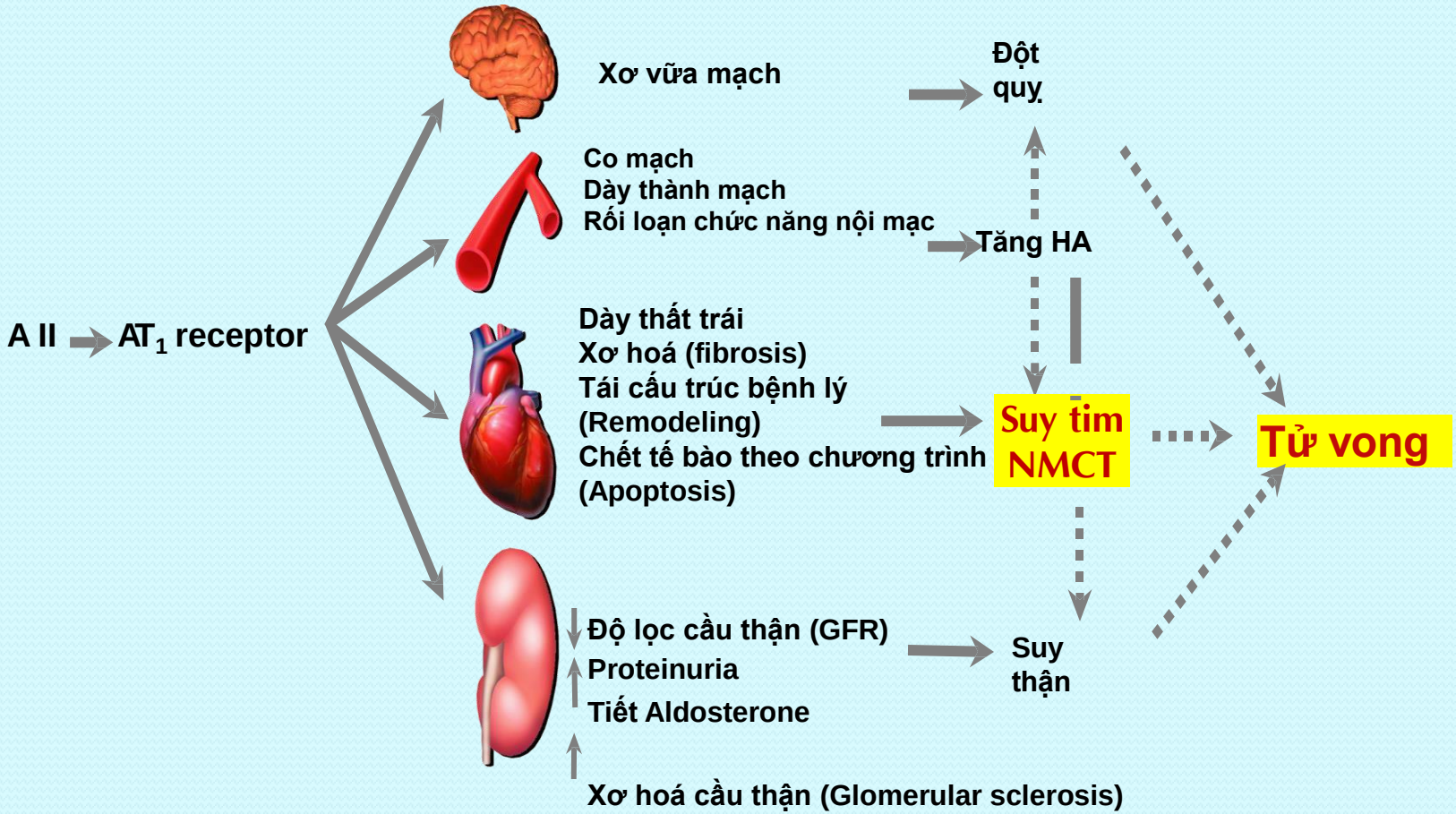
Cupples LA, D'Agostino RB. *NIH Publication No 87-2703*, Feb 1987.

LVH cũng là 1 YTNC tim mạch trên BN THA



Adapted from Devereux RB, Wachtell K, Gerdts E, et al: Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA 292:2350–2356, 2004

Angiotensin II tác động trên các cơ quan đích

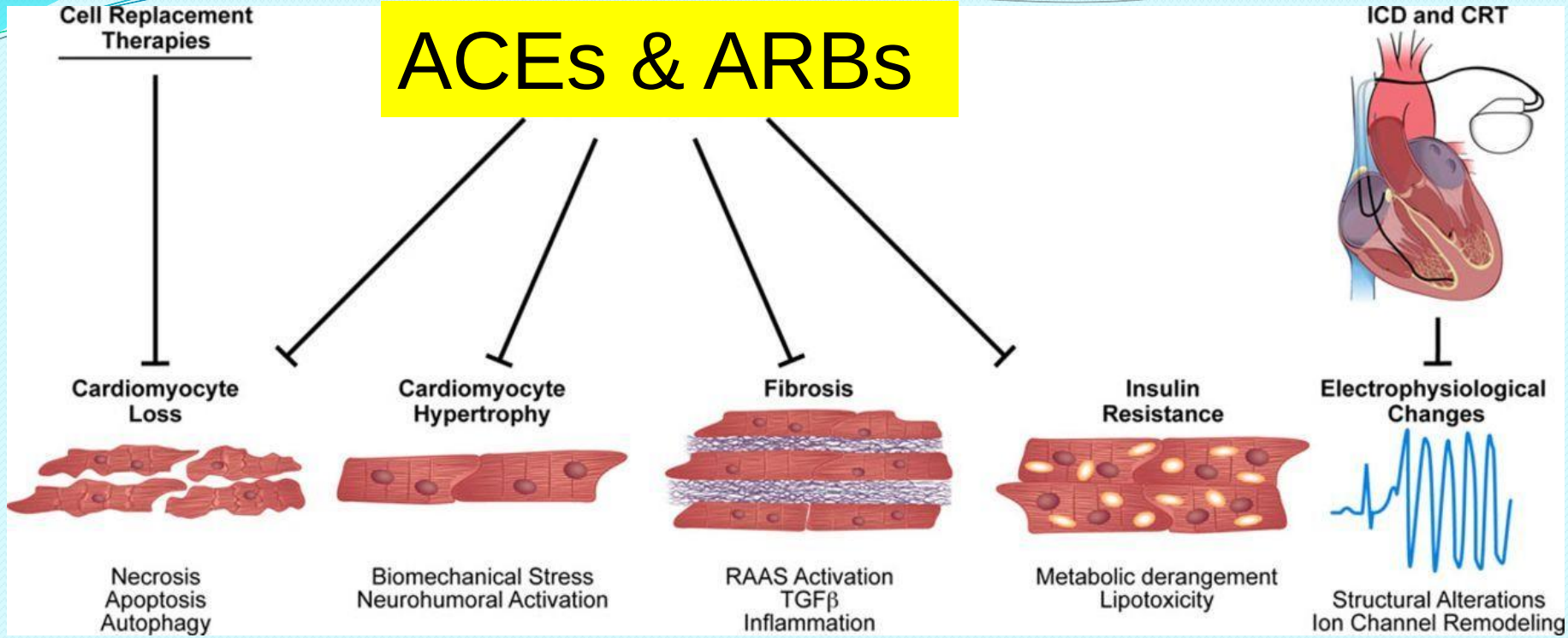


*preclinical data

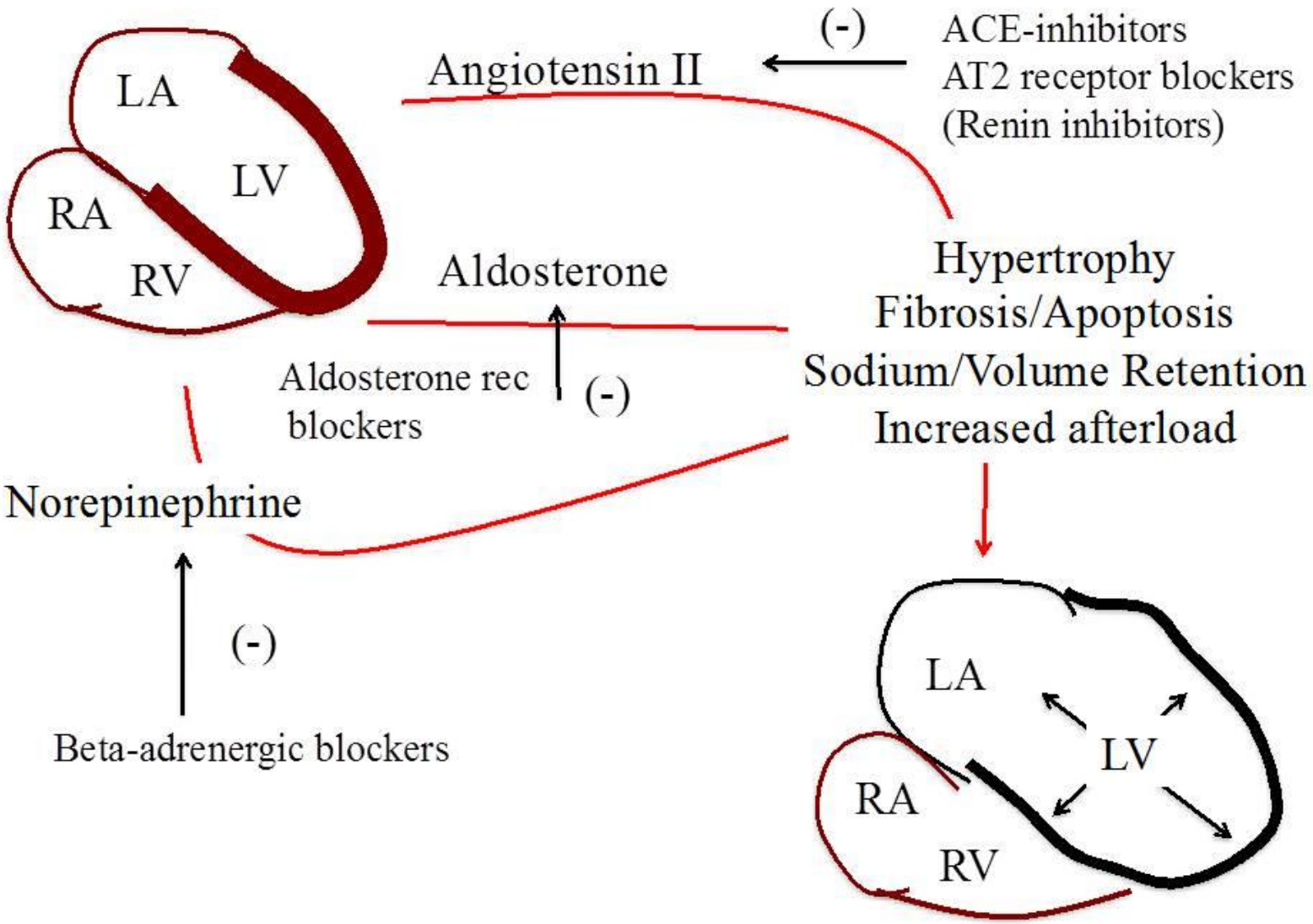
LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

Adapted from Willenheimer R et al *Eur Heart J* 1999; 20(14): 997□1008, Dahlöf B *J Hum Hypertens* 1995; 9(suppl 5): S37□S44, Daugherty A et al *J Clin Invest* 2000; 105(11): 1605□1612, Fyhrquist F et al *J Hum Hypertens* 1995; 9(suppl 5): S19□S24, Booz GW, Baker KM *Heart Fail Rev* 1998; 3: 125□130, Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy*. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories 1999: 1682□1704, Anderson S *Exp Nephrol* 1996; 4(suppl 1): 34□40, Fogo AB *Am J Kidney Dis* 2000; 35(2):179□188

ACEs & ARBs

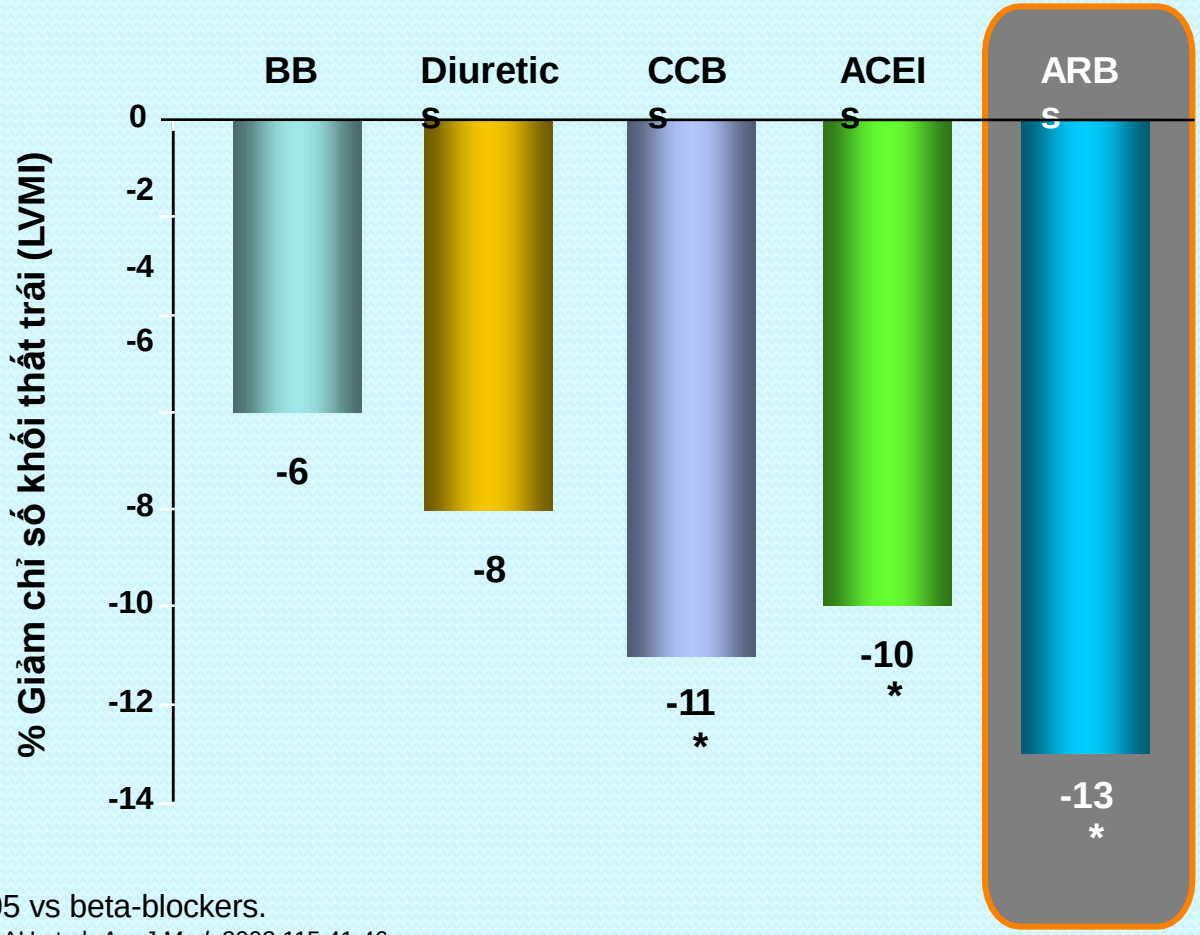


Pharmacological agents reduce morbidity and mortality, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs by reducing cell death, hypertrophy, insulin resistance and fibrosis….


LA
LV
RA
RV
(-)
ACE-inhibitors
AT2 receptor blockers
(Renin inhibitors)
Angiotensin II
Aldosterone
Aldosterone rec blockers
(-)
Hypertrophy
Fibrosis/Apoptosis
Sodium/Volume Retention
Increased afterload
Norepinephrine
(-)
Beta-adrenergic blockers
LA
LV
RA
RV

So sánh hiệu quả các thuốc hạ huyết áp trên sự thoái triển Phì đại thất trái

Phân tích gộp 80 nghiên cứu liên quan 3767 bệnh nhân
mức giảm huyết áp tương đương

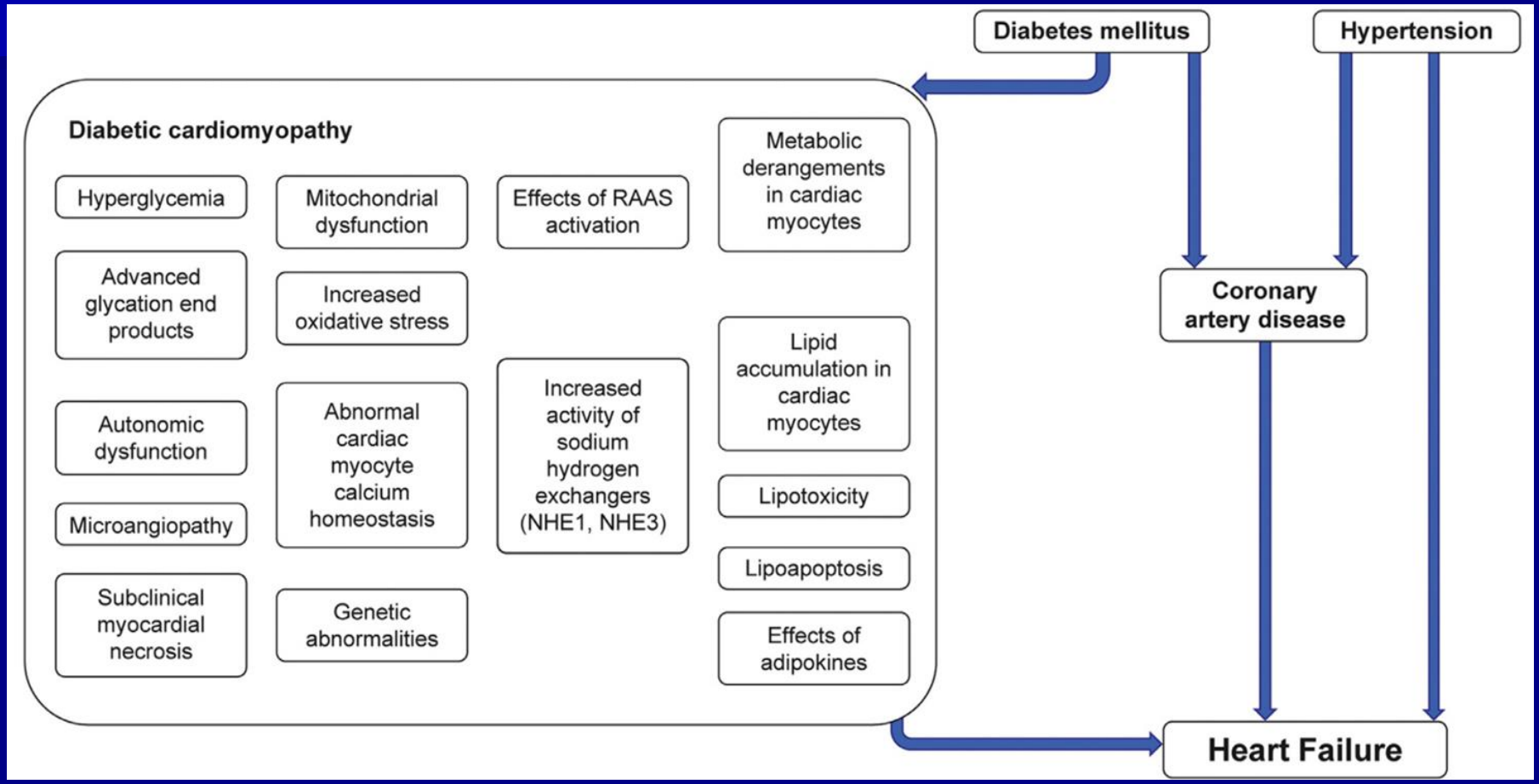


**P*<0.05 vs beta-blockers.

Klingbeil AU et al. *Am J Med.* 2003;115:41-46.

Heart Failure and Diabetes Mellitus: Defining the Problem and Exploring the Interrelationship

Michael J. Wilkinson, MD, Adena Zadourian, BS, Pam R. Taub, MD



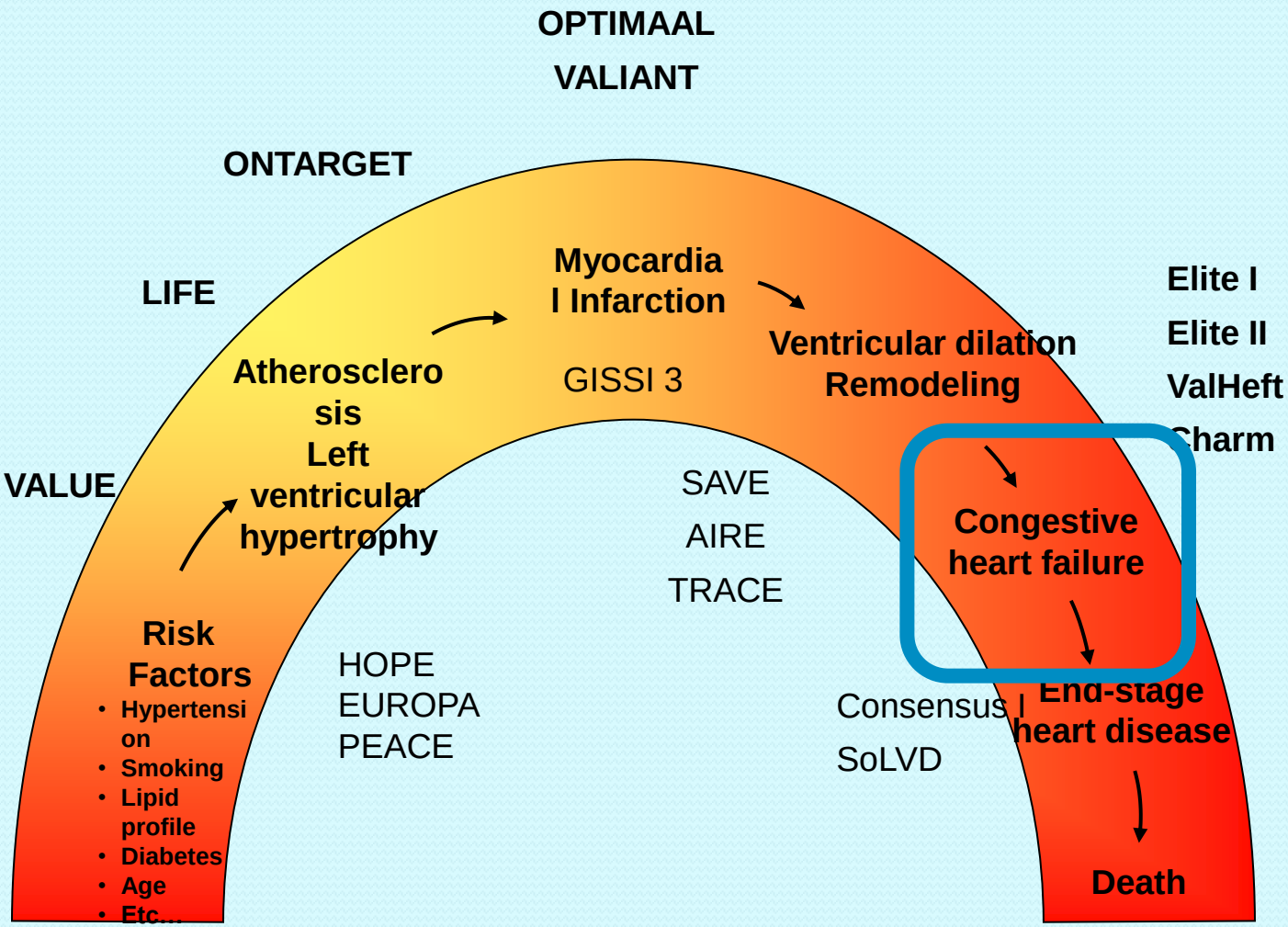
The American Journal of Medicine, Vol 132, No 10S, October 2019

ARBs giúp giảm biến cố ở các Bn Suy tim

Trial	Primary/Secondary End Points	Results	ΔBP Syst/Diast mm Hg
CHARM-Added	Primary: cardiovascular death and CHF hospitalization Secondary: cardiovascular morbidity and mortality composite	15% RRR in primary end point 17% RRR in CV death 17% RRR in CHF admission	4.6/3.0 mm Hg lower in combined arm
Val-HeFT	Primary: all-cause mortality and cardiovascular combined morbidity and mortality	No difference in mortality 13% RRR in morbidity and mortality, driven by CHF reduction	5.2/1.3 mm Hg lower in combined arm
CHARM-Alternative	Primary: cardiovascular mortality or CHF hospitalization Secondary: composite cardiovascular morbidity and mortality	23% RRR in primary end point 15% RRR in CV death 32% RRR in CHF admission	4.4/3.9 mm Hg lower with ARB
ELITE-II	Primary: all-cause mortality Secondary: sudden death/arrest Tertiary: admissions for cardiovascular cause/all-cause mortality	No difference in any end point No difference in CHF admissions	No difference
OPTIMAAL	Primary: all-cause mortality Secondary: sudden death/arrest Tertiary: fatal/nonfatal MI	All outcomes favored captopril Primary: 13% RRR ($p = 0.07$) Secondary: 19% RRR ($p = 0.07$) Tertiary: no difference CV death: 17% RRR ($p = 0.03$) CHF admit: 16% RRR ($p = 0.07$)	No difference
VALIANT	Primary: all-cause mortality Secondary: CV morbidity and mortality	No difference in primary or secondary end point	By treatment arm (in mm Hg): ACE: 127/76 ARB/ACE: 125/75 ARB: 127/75
ATLAS	Primary: all-cause mortality Secondary: 1) cardiovascular mortality; 2) cardiovascular hospitalizations; 3) all-cause mortality + cardiovascular hospitalization; 4) Cardiovascular mortality + cardiovascular hospitalization	All results favored high-dose therapy Primary: 8% RRR ($p = 0.128$) Secondary: 1) CV mortality: 10% RRR ($p = 0.07$); 2) CV hospitalizations: 16% RRR; 3) mortality/CV hospitalization: 8% RRR; 4) CV mortality/CV hospitalization: 9% RRR, CHF hospitalization: 24% RRR	4.4/2.3 mm Hg reduction favoring high-dose therapy

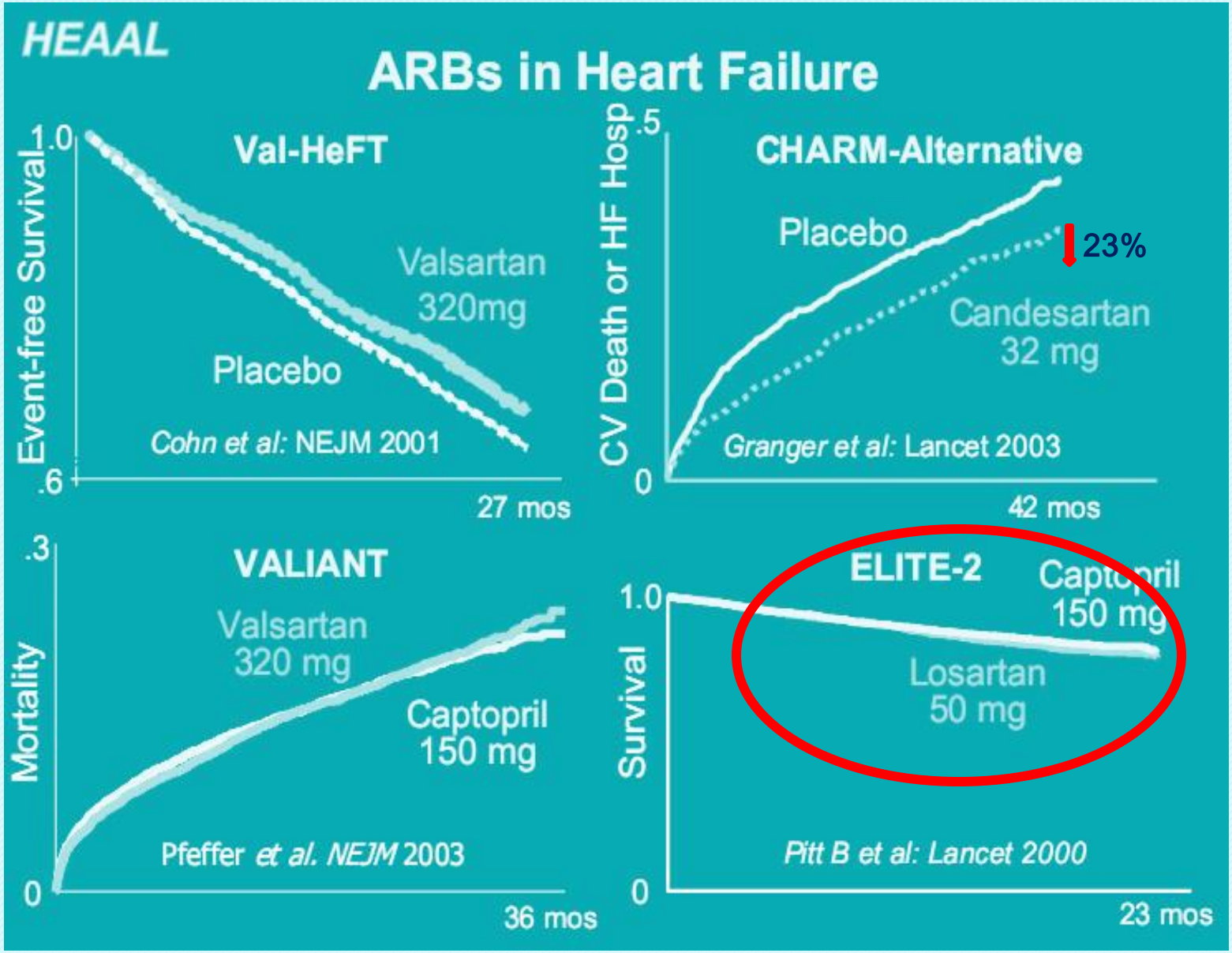
BP = blood pressure; CHF = congestive heart failure; CV = cerebrovascular; Diast = diastolic; MI = myocardial infarction; RRR = relative risk reduction; Syst = systolic. Other abbreviations as in Table 2.

Các nghiên cứu ACEi & ARBs trên Suy tim



Adapted from Dzau V, et al. Am Heart J 1991; 121:1244-63.

Kết quả nghiên cứu của ACEi & ARBs trong suy tim



Tuy nhiên, ACEI / ARB chưa được tối ưu hóa liều trên Bệnh nhân suy tim

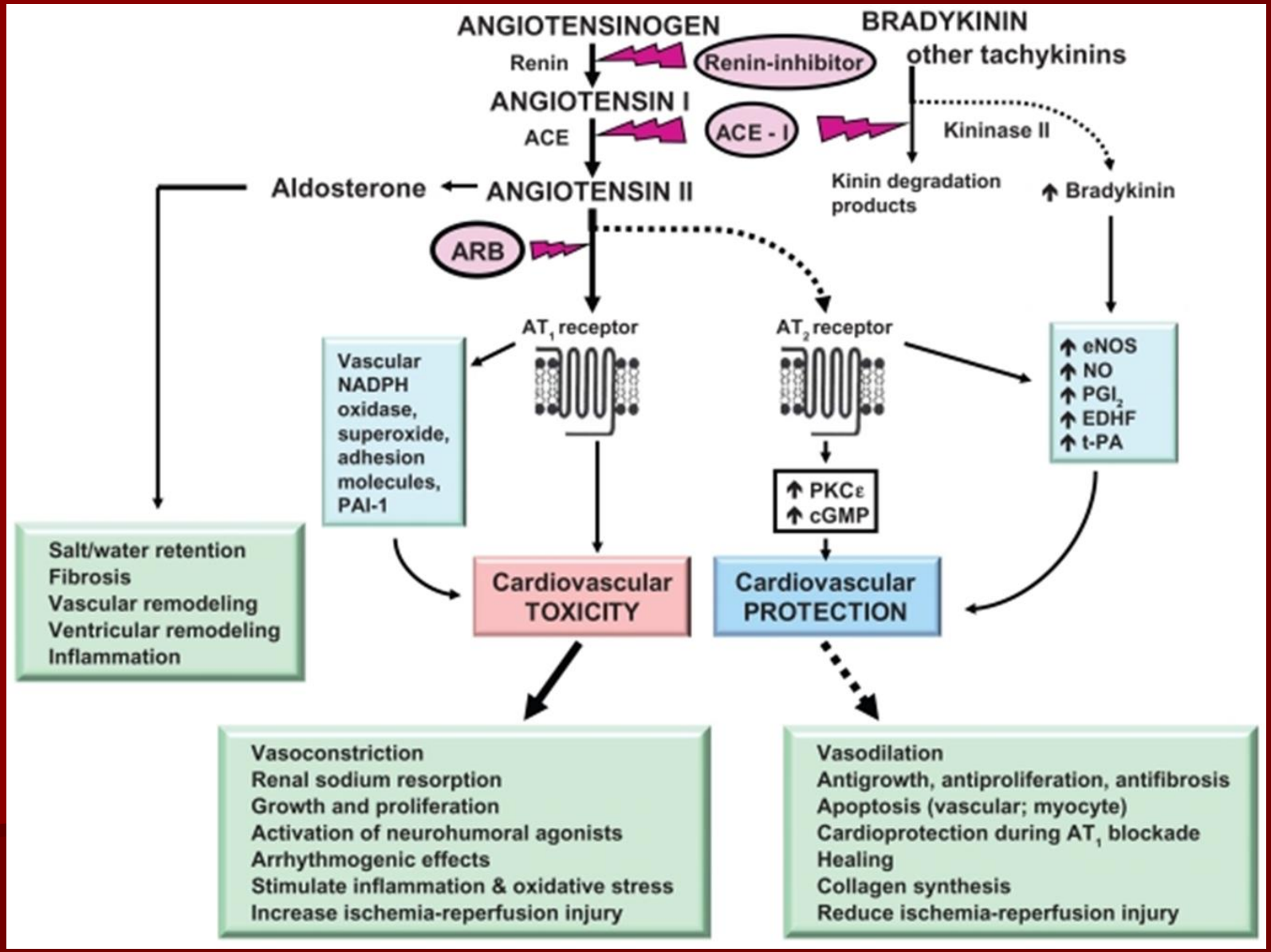
- Phân tích trên 43,405 BN (≥65t), được kê ACEI hoặc ARB khi mới được chẩn đoán Suy tim mạn.
- **29% BN được kê ACEI/ARB liều thấp**
- Tiêu chí: tử vong do mọi nguyên nhân
- ACEI:
  - Low dose: HR 1.16 (95% CI 1.12-1.2)
  - **High dose:HR 0.90 (95% CI 0.86-0.94**)
- ARB:
  - Low dose: HR 1.15 (95% CI 1.06-1.24)
  - **High dose: HR 0.93 (95% CI 0.86-1.00)**

→Kết luận**: Ở BN suy tim mạn, hiệu quả giảm tử vong do mọi nguyên nhân của ACEI/ARB là phụ thuộc vào liều**

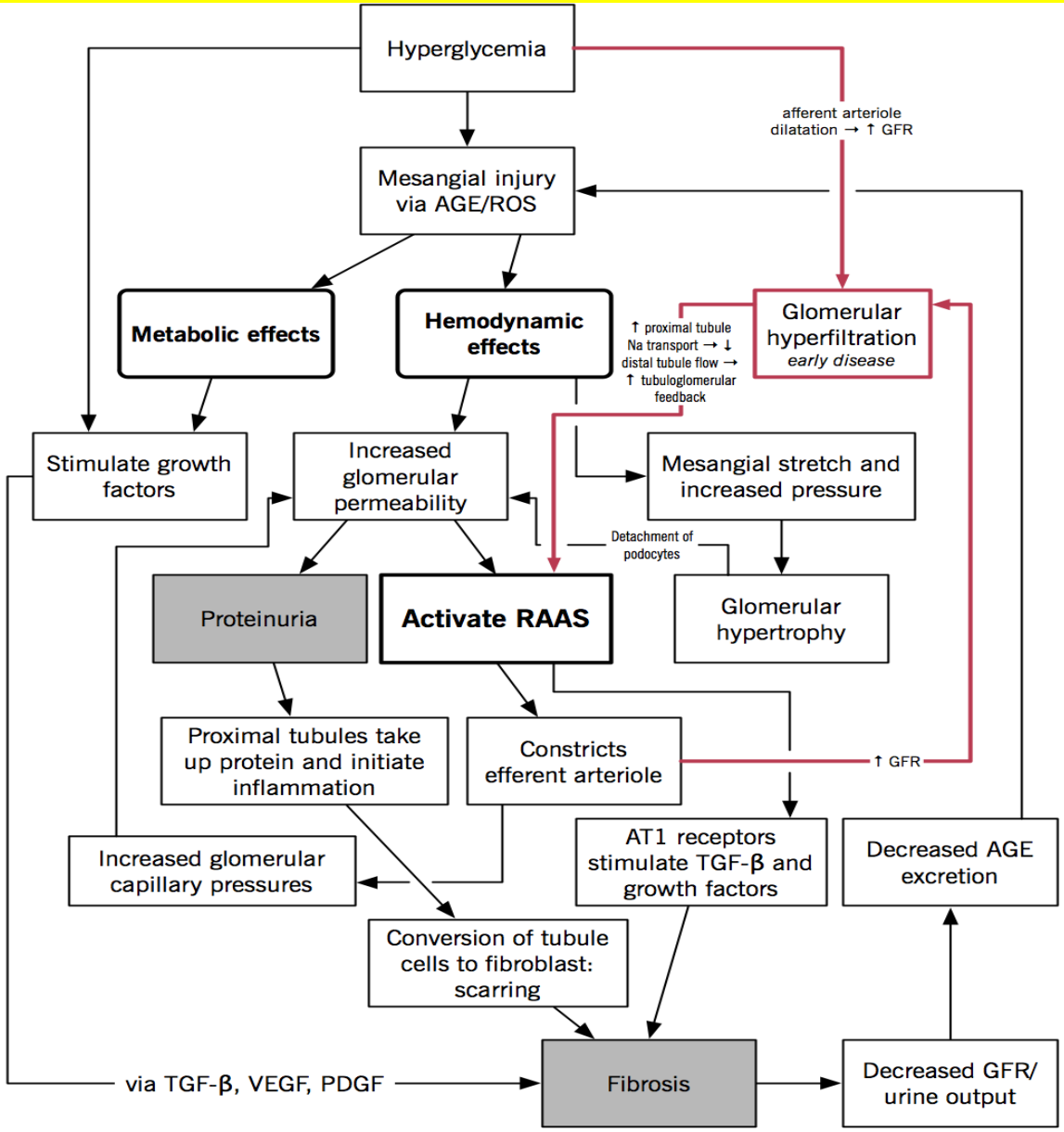
→ **tuy nhiên gần 1/3 BN chỉ được kê đơn liều thấp**.

Dose comparison of ACE inhibitors and angiotensin ii receptor Blockers in congestive heart failure – G.egiziano, H behlouli, L pilote, SS daskalopoulou . https://doi.org/10.1016/j.cjca.2011.07.228

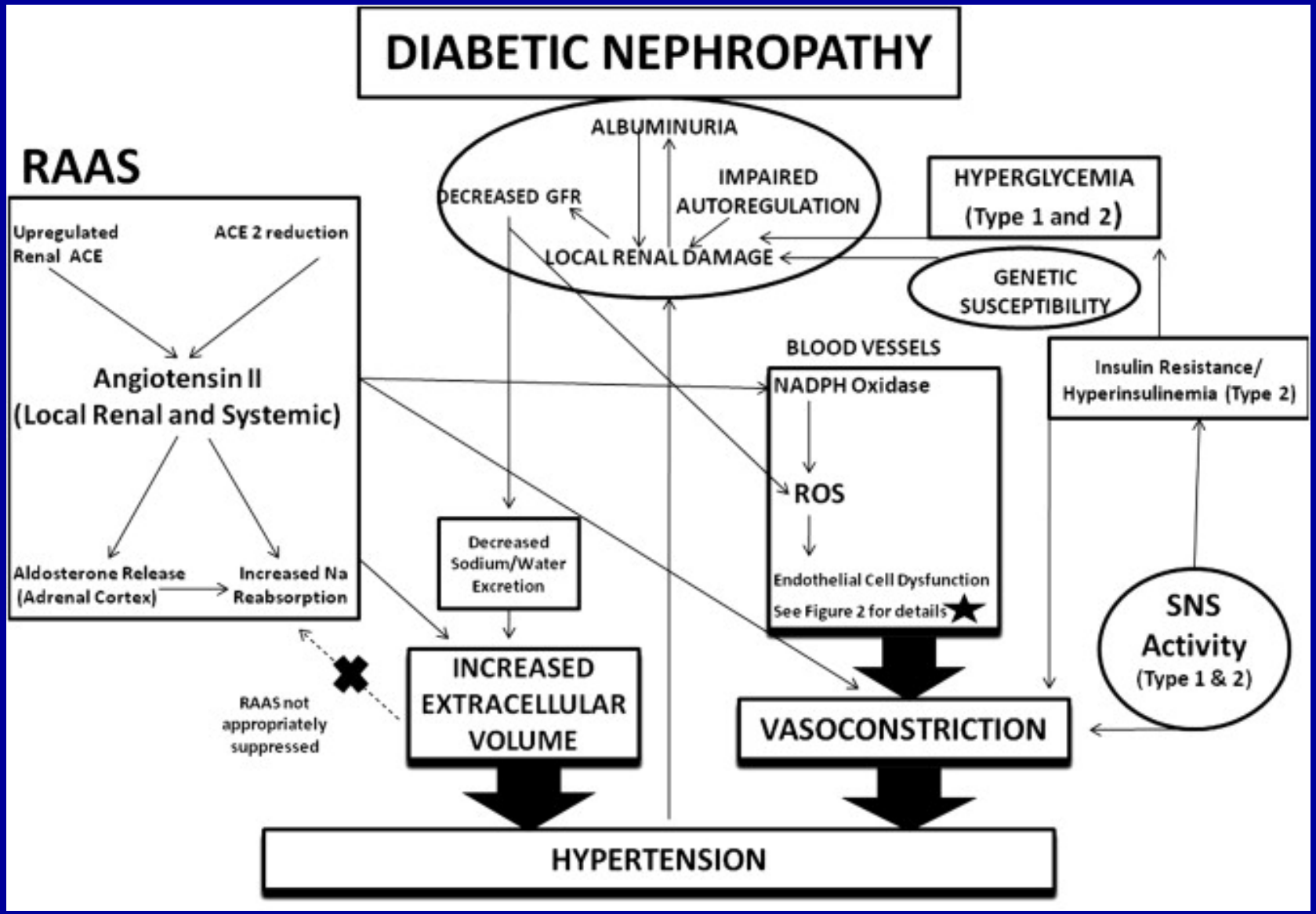
Vai trò bảo vệ Tim mạch của ACEi & ARBs



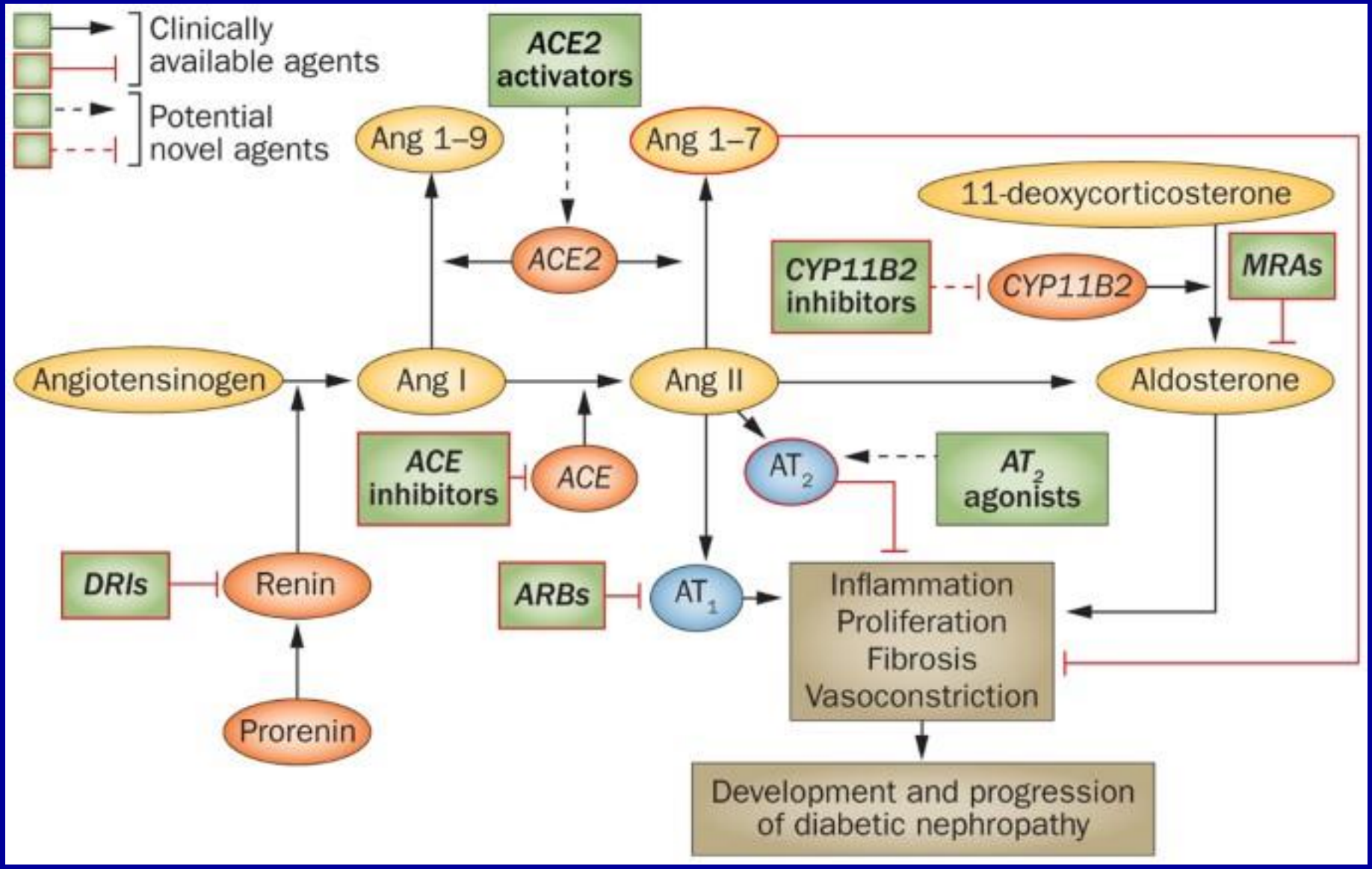
Bệnh Thận Đái Tháo Đường



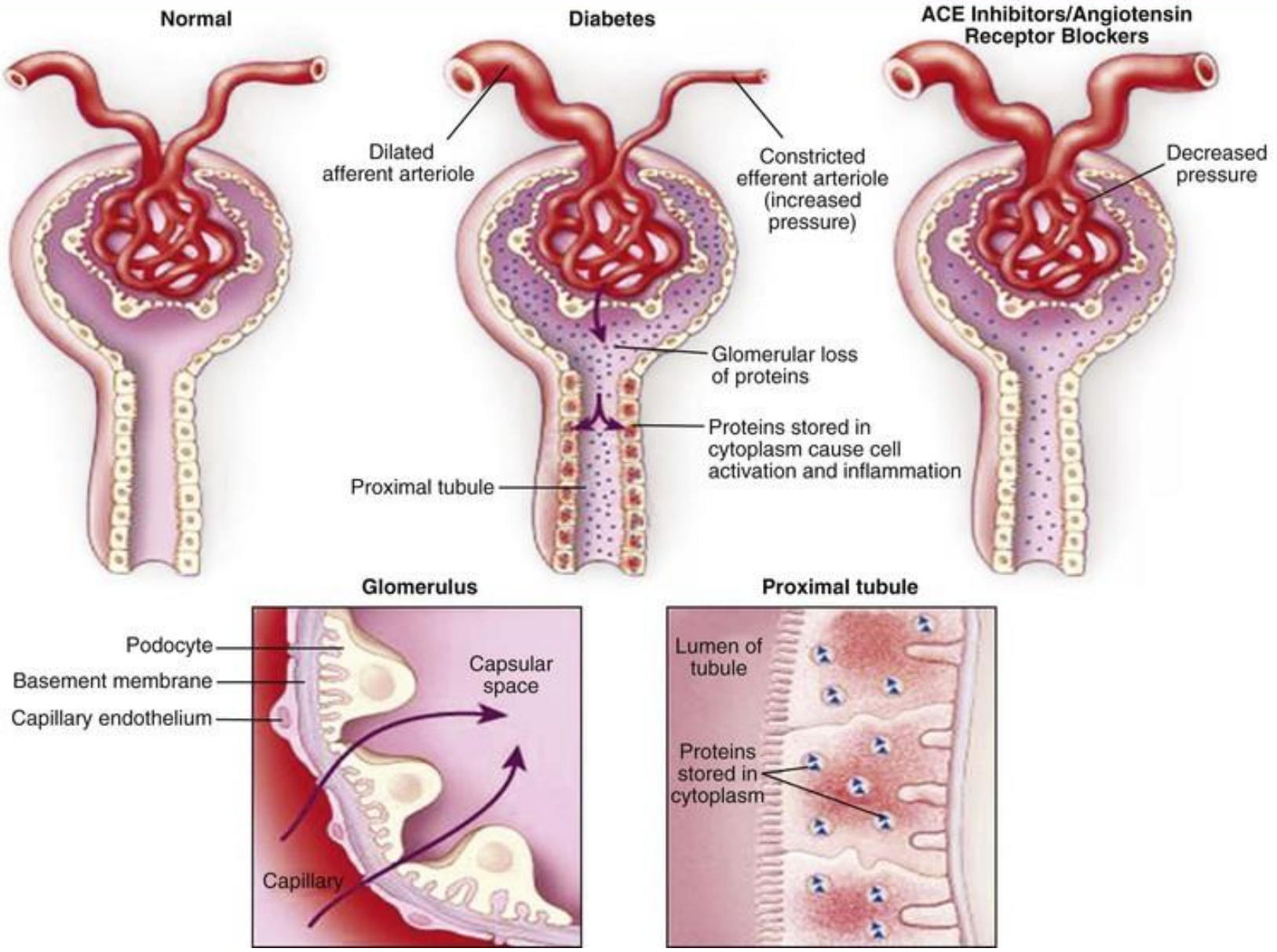
Cơ chế THA trong Bệnh Thận ĐTĐ

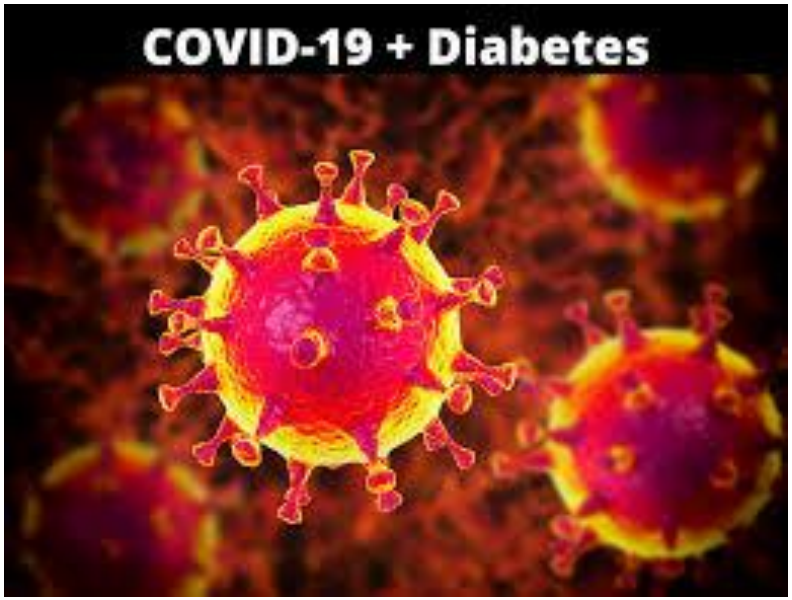


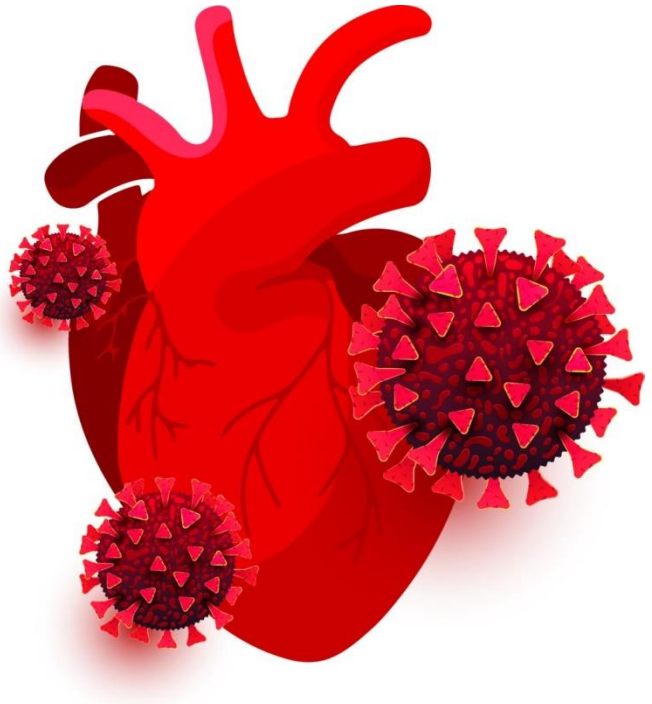
Tác dụng của ACEi & ARBs trên bệnh thận ĐTĐ



Nephron Changes in Diabetes and After Administration of an ACE Inhibitor or Angiotensin Receptor Blocker







3.Bệnh nhân ĐTĐ và THA trong Đại dịch COVID-19 thì sao ?

World Health Organization

COVID-19 Weekly E l Update

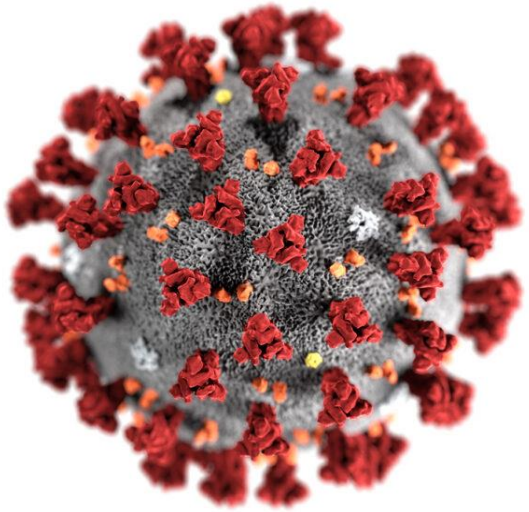
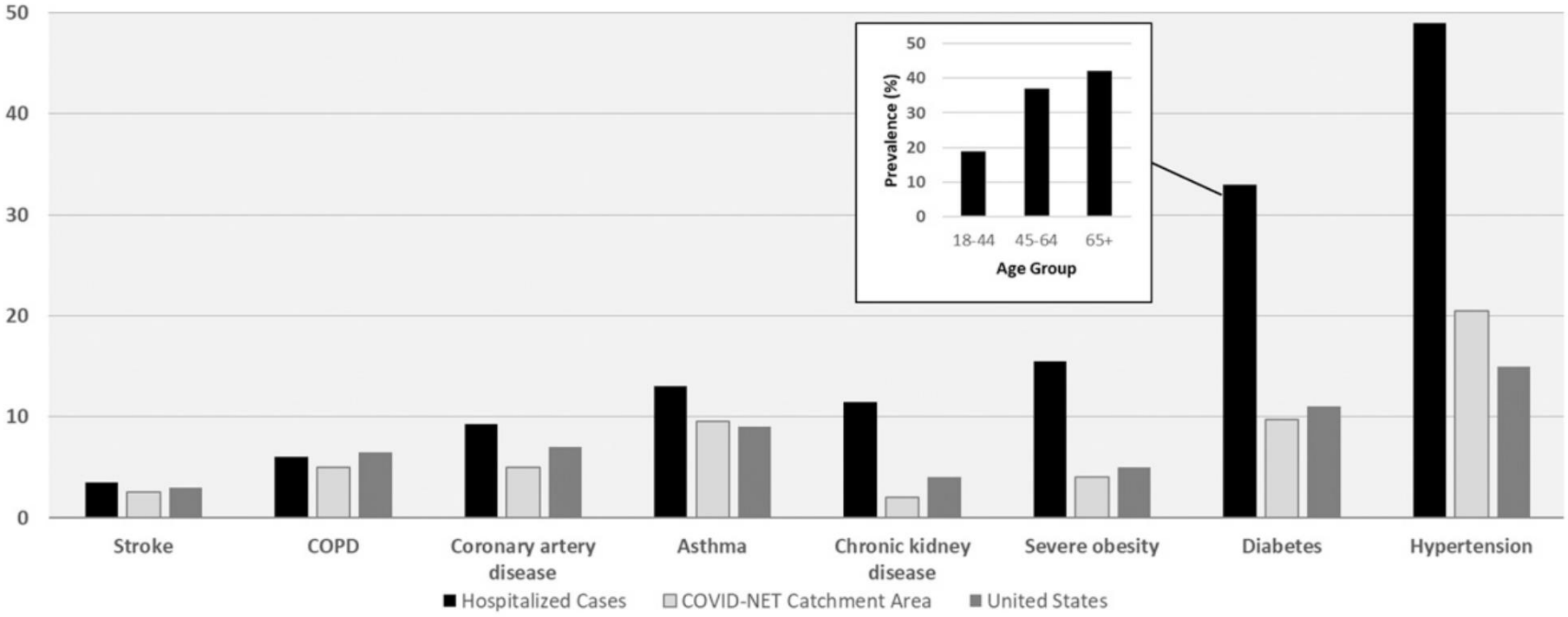


Table 1. Newly reported and cumulative COVID-19 ca 3 October 2021**

WHO Region	New cases in last 7 days (%)	Change in new cases in last 7 days *			e in new s in last 7 days *	Cumulative deaths (%)
Americas	1 120 999 (36%)	-12%	90 357 809 (39%)	24 311 (45%)	2%	2 220 453 (46%)
Europe	1 164 750 (37%)	5%	70 589 709 (30%)	15 403 (28%)	2%	1 342 600 (28%)
South-East Asia	278 657 (9%)	-19%	43 121 902 (18%)	4 318 (8%)	-18%	678 035 (14%)
Eastern Mediterranean	166 068 (5%)	-21%	15 825 445 (7%)	3 567 (7%)	-17%	290 562 (6%)
Western Pacific	338 603 (11%)	-12%	8 609 714 (4%)	4 725 (9%)	-10%	117 705 (2%)
Africa	49 333 (2%)	-43%	6 048 196 (3%)	1 897 (3%)	-25%	146 854 (3%)
Global	**3 118 410 (100%)**	**-9%**	**234 553 539 (100%)**	**54 221 (100%)**	**-4%**	**4 796 222 (100%)**

THA & Đái Tháo Đường chiếm tỷ lệ cao trong nhóm bệnh nhân nhiễm COVID-19



Diabetes and COVID-19: Population Impact 18 Months Into the Pandemic

Edward W. Gregg,[1] Marisa K. Sophiea,[1] and Misghina Weldegiorgis[1,2]

Diabetes Care 2021;44:1–8 | https://doi.org/10.2337/dci21-0001

PREVALENCE OF COMORBIDITIES IN COVID 19 INFECTION

Meta analysis of **8 studies** with **46,248** COVID-19 patients showed the most prevalent comorbidity:

- **Hypertension** 17±7 (95% CI 14-22%)
- **Diabetes** 8±6 (95% CI 6-11%)
- **Cardiovascular diseases** 5±4 (95% CI 4-7%)
- **Respiratory system disease** 2±0 (95% CI 1-3%)

Yang J et al. Int J Infect Dis. S1201-9712(20)30136-3. doi: 10.1016/j.ijid.2020.03.017.

Prevalence estimates of comorbidities among adults with COVID-19

	Newer estimate	Early estimate
Diabetes	12%	14.3%
Hypertension	17%	26%-30%

Healio

vs 2.0%

; 323 (11): 1061-69

Nee…

0.8-9%

Cheng Y, et al. Kidney Int 2020; doi.org/10.1016/j.ki…

Guan W, et al. NEJM 2020; doi:10.1056/NEJMoa2002032

Urinary abnormalities

Albuminuria 34%
Proteinuria 63%
Hematuria 26.7%
Both 44%

Naicker S, et al. Kidney Int 2020; doi.org/10.1016/j.kint.2020.03.001

…omorbidities

Arentz M, et al. JAMA 2020; doi:10.1001/jama.20204326
Chen H, et al. Lancet 2020; 395 (10226): 809-15
Cheng Y, et al. Kidney Int 2020; doi.org/10.1016/j.kint.2020.03.005
Guan W, et al. NEJM 2020; doi:10.1056/NEJMoa2002032
Huang C, et al. Lancet 2020; 395 (10223); 497-506

CVD	CKD	Diabetes	Hypertension
40%	0.7-48%	7.4-20%	15-33%

ISN 1960 — 60 years 1960-2020

Rolando Claure-Del Granado, MD
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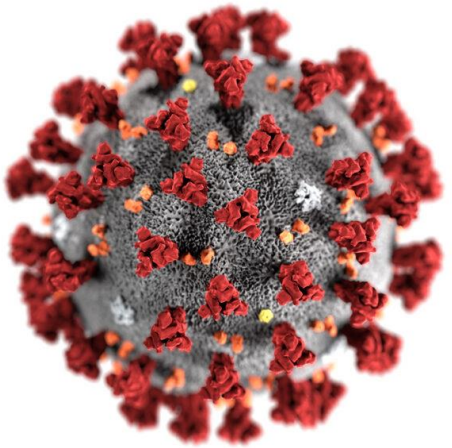
Edgar V. Lerma, MD @edgarvlermamd

Prevalence of Diabetes and Hypertension and Their Associated Risks for Poor Outcomes in Covid-19 Patients

Francisco J. Barrera,[1,2,3,*] Skand Shekhar,[4,5,*] Rachel Wurt[illegible],[4] [illegible],[2] Oscar J. Ponce,[3,6] Michelle Hajdenberg,[7] Neri A. Alvarez-Vi[illegible]ll,[5] Ernesto L. Schiffrin,[9] Graeme Eisenhofer,[10] Forbes P[illegible] Stefan R. Bornstein,[12,13,14] Constantine A. Stratakis,[4] José Ge[illegible]z,[1,2,8] René Rodríguez-Gutiérrez,[1,2,3,8] and Fady Har[illegible]

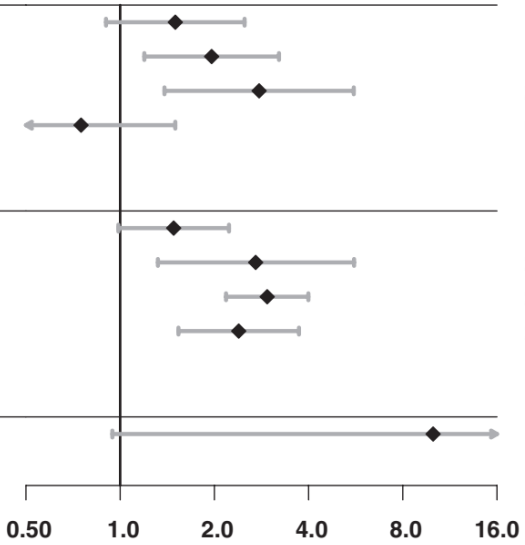


Coronavirus disease 2019 (Covid-19) has affected millions of pec[illegible]ately affect those with hypertension and diabetes. Because of inadequat[illegible]stem-atic reviews, the prevalence of diabetes and hypertension and assc[illegible]es in Covid-19 patients are unknown. We searched databases from Dec[illegible]2020, and selected observational peer-reviewed studies in English of pati[illegible]ident reviewers extracted data on study participants, interventions, and outcomes and assessed risk of bias, and the certainty of evidence. We included 65 (15 794 participants) observational studies at moderate to high risk of bias. Overall prevalence of diabetes and hypertension was 12% (95% confidence interval [CI], 10-15; n = 12 870; I^2: 89%), and 17% (95% CI, 13-22; n = 12 709; I^2: 95%), respectively. In severe Covid-19, the prevalence of diabetes and hypertension were 18% (95% CI, 16-20; n = 1099; I^2: 0%) and 32% (95% CI, 16-54; n = 1078; I^2: 63%), respectively. Unadjusted relative risk for intensive

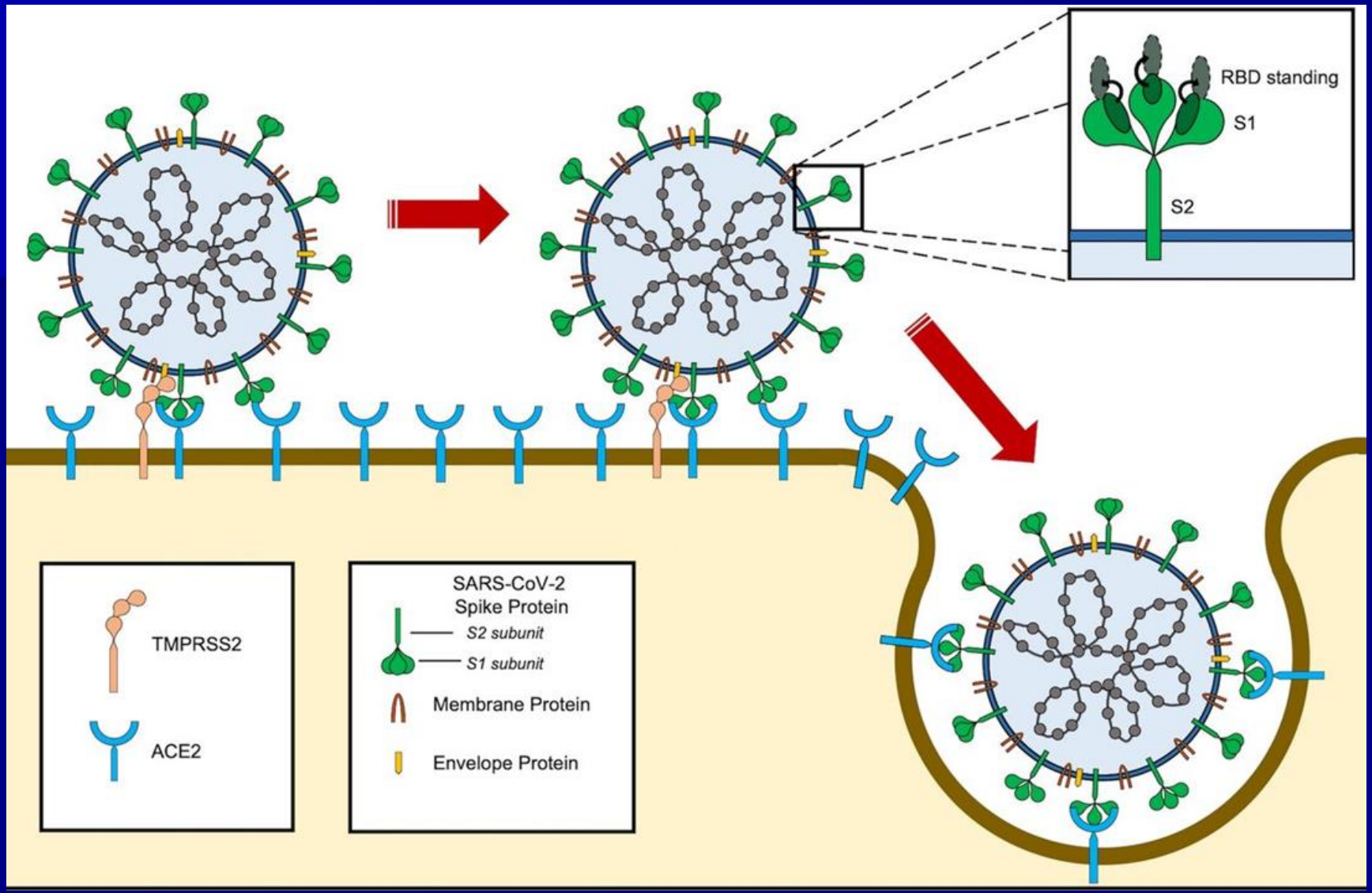
September 2020 | Vol. 4, Iss. 9
doi: 10.1210/jendso/bvaa102 | Journal of the Endocrine Society | 1–16

Risk estimates for severe Covid-19, intensive care unit admission, and mortality.

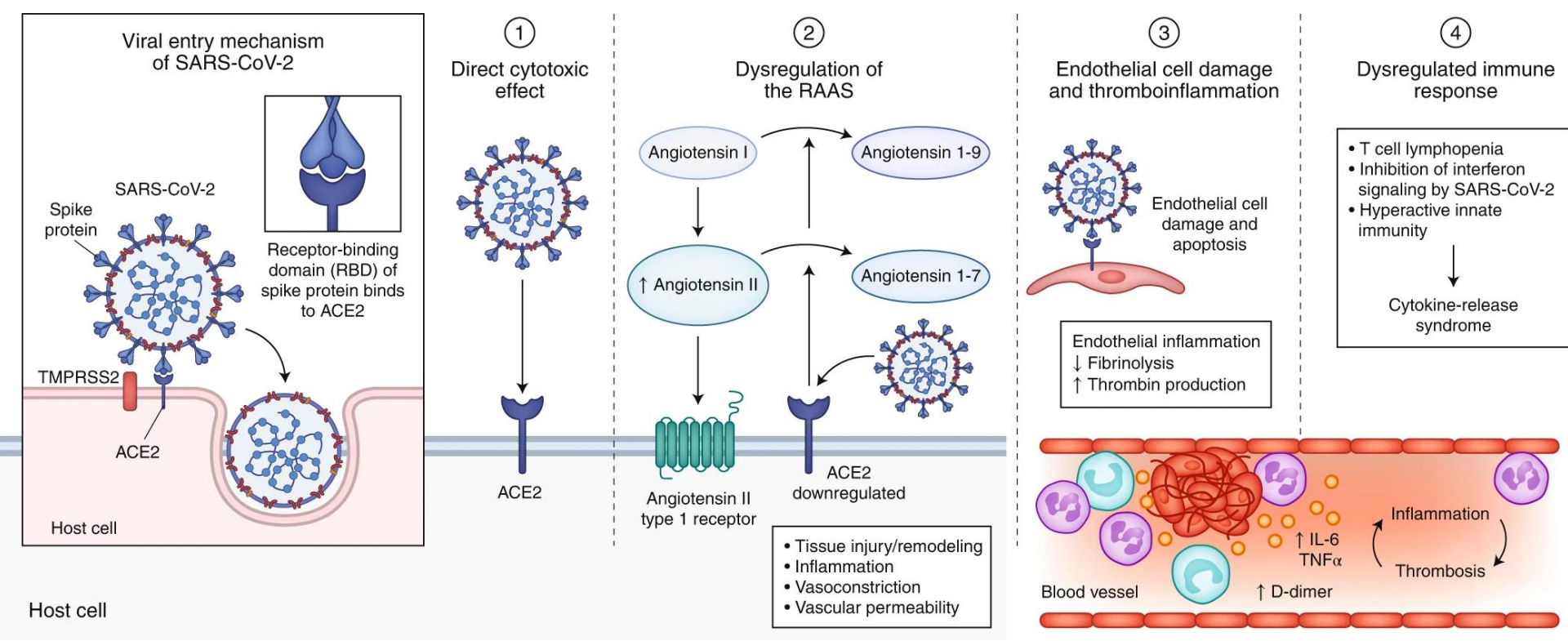
Disease and outcome	Effect estimate	N of Studies	Total N	I^2	Effect size (95%CI)	p value
Diabetes						
Severe COVID–19	Unadjusted (RR)	6	1991	74 %	1.50 (0.90 – 2.50)	0.119
ICU admission	Unadjusted (RR)	3	8890	80 %	1.96 (1.19 – 3.22)	0.008
Mortality	Unadjusted (RR)	4	2058	75 %	2.78 (1.39 – 5.58)	0.004
	Adjusted (HR)*	1	416	na	0.75 (0.38 – 1.50)	0.420
Hypertension						
Severe COVID–19	Unadjusted (RR)	8	2023	69 %	1.48 (0.99 – 2.23)	0.058
	Adjusted (OR)**	1	487	na	2.71 (1.32 – 5.59)	0.007
ICU admission	Unadjusted (RR)	4	1737	0 %	2.95 (2.18 – 3.99)	<0.001
Mortality	Unadjusted (RR)	8	3107	66 %	2.39 (1.54 – 3.73)	<0.001
Diabetes and Hypertension						
Severe COVID–19	Unadjusted (RR)	1	22	na	10.00 (0.94 – 105.92)	0.056



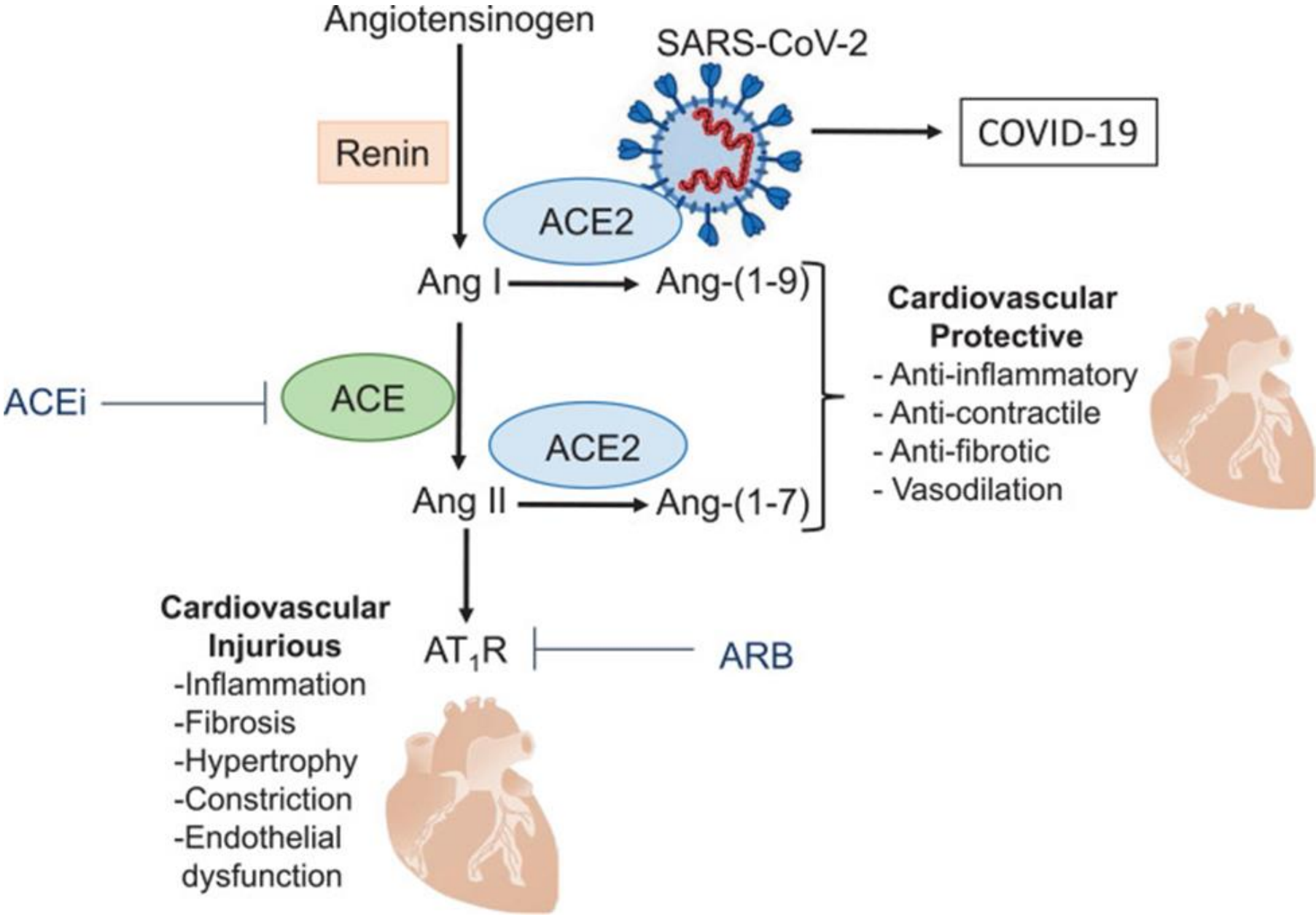
n = 2023; I^2: 69%; P = .058) was associated with severe Covid-19. In conclusion, the risk of intensive care unit admission and mortality for patients with diabetes or hypertension who developed Covid-19 is increased compared with those without these comorbidities.



SARS-CoV-2 entry into the cell. SARS-CoV-2 binds to ACE2 through the receptor-binding domain (RBD) of spike protein.

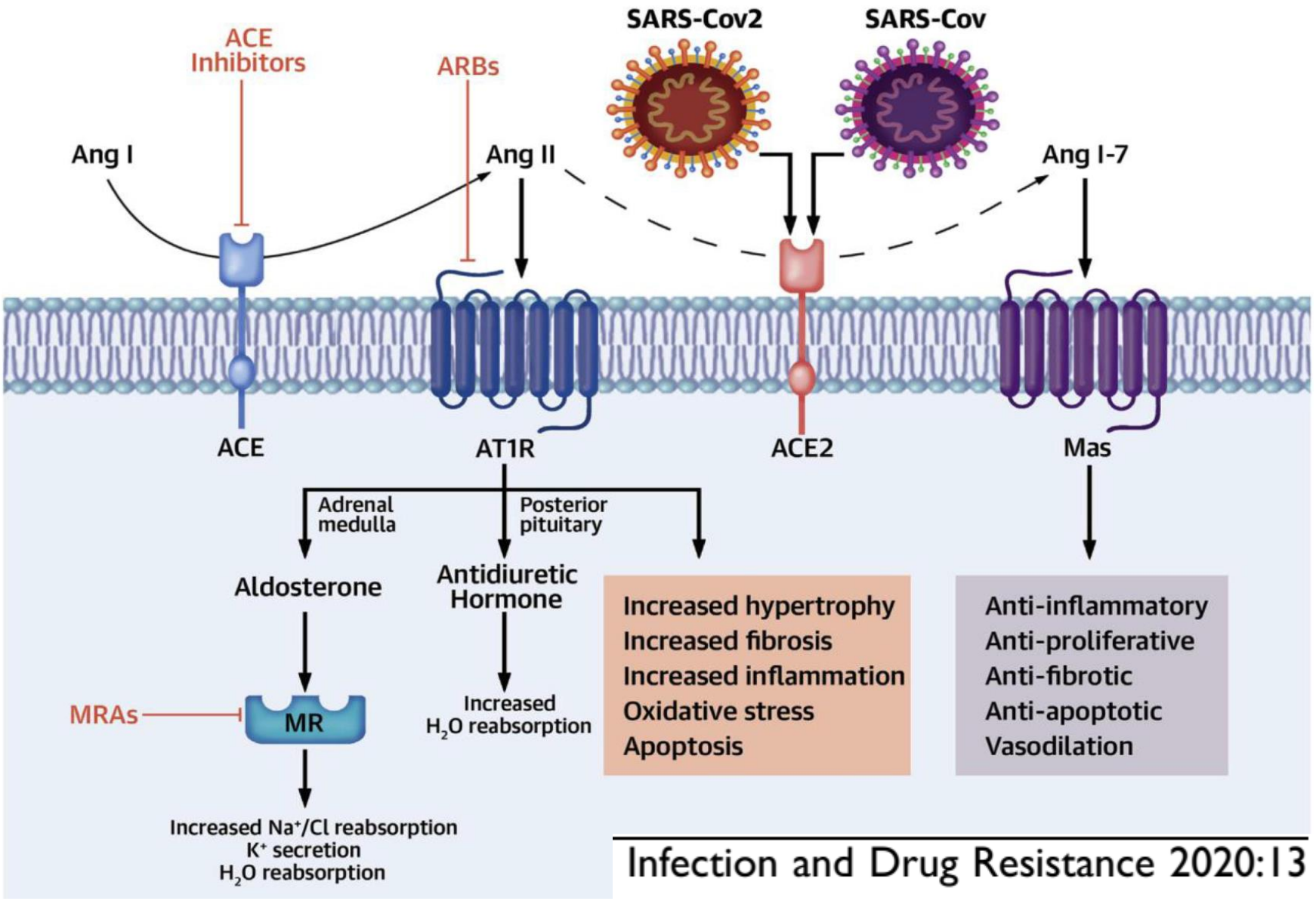


SARS-CoV-2 xâm nhập vào tế bào chủ thông qua sự tương tác của protein đột biến của nó với thụ thể xâm nhập ACE2 với sự hiện diện của TMPRSS2 (ngoài cùng bên trái). Các cơ chế đề xuất đối với COVID-19 do nhiễm SARS-CoV-2 bao gồm (1) tổn thương tế bào trực tiếp qua trung gian vi rút; (2) rối loạn điều hòa RAAS do hậu quả của việc giảm điều hòa ACE2 liên quan đến sự xâm nhập của virus, dẫn đến giảm sự phân cắt của angiotensin I và angiotensin II; (3) tổn thương tế bào nội mô và viêm huyết khối; và (4) rối loạn điều hòa phản ứng miễn dịch và quá trình viêm do vi rút ức chế tín hiệu interferon, sự suy giảm lympho bào T, và sản xuất các cytokine tiền viêm, đặc biệt là IL-6 và TNFα.


Angiotensinogen
SARS-CoV-2
Renin
COVID-19
ACE2
Ang I
Ang-(1-9)
Cardiovascular
Protective
- Anti-inflammatory
- Anti-contractile
- Anti-fibrotic
- Vasodilation
ACEi
ACE
ACE2
Ang II
Ang-(1-7)
Cardiovascular
Injurious
-Inflammation
-Fibrosis
-Hypertrophy
-Constriction
-Endothelial
dysfunction
AT1R
ARB

ACEIs and ARBs and Their Correlation with COVID-19: A Review

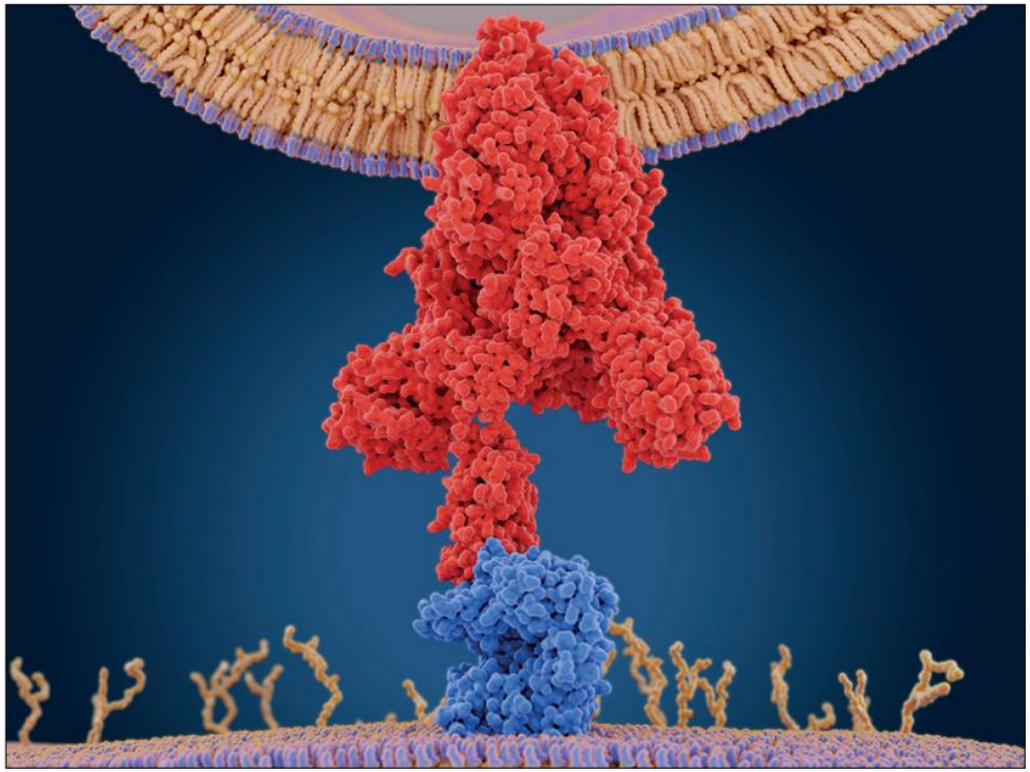
Yehualashet and Belachew



Infection and Drug Resistance 2020:13

ACE2 polymorphism.

We suggest that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection and, therefore, should be monitored for ACE2-modulating medications, such as ACE inhibitors or ARBs. Based on a PubMed search on Feb 28, 2020, we did not find any evidence to suggest that antihypertensive calcium channel blockers increased ACE2 expression or activity, therefore these could be a suitable alternative treatment in these patients.



Juan Gaertner/Science Photo Library

Lei Fang, George Karakiulakis,*Michael Roth . **Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?** Published **Online.**March 11, 2020.https://doi.org/10.1016/S2213-2600(20)30116-8

4. Liệu có nên tiếp tục sử dụng ACEis và ARBs trong điều trị Bệnh nhân COVID-19 có ĐTĐ kèm THA ?
(WHO 2021)

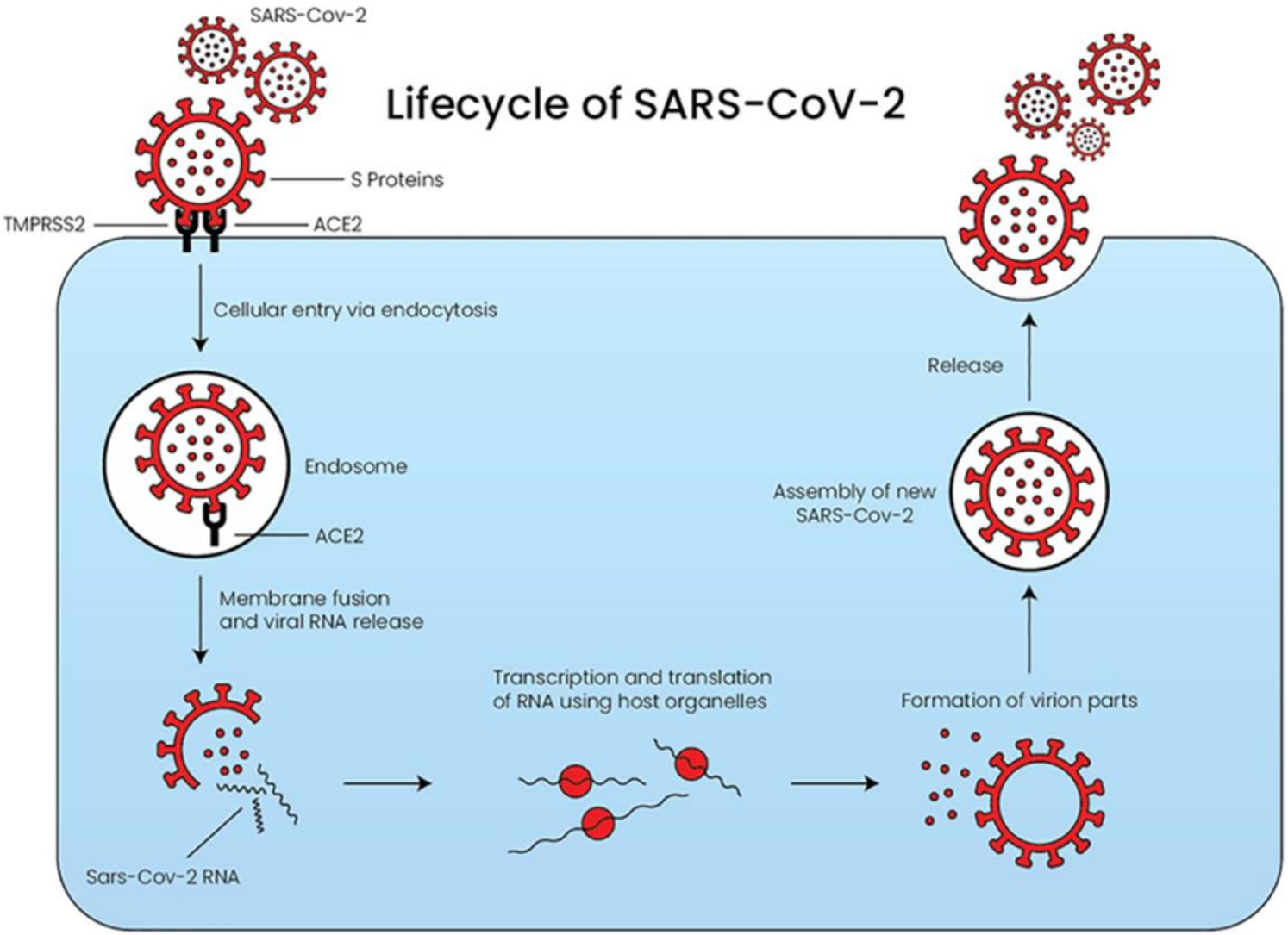
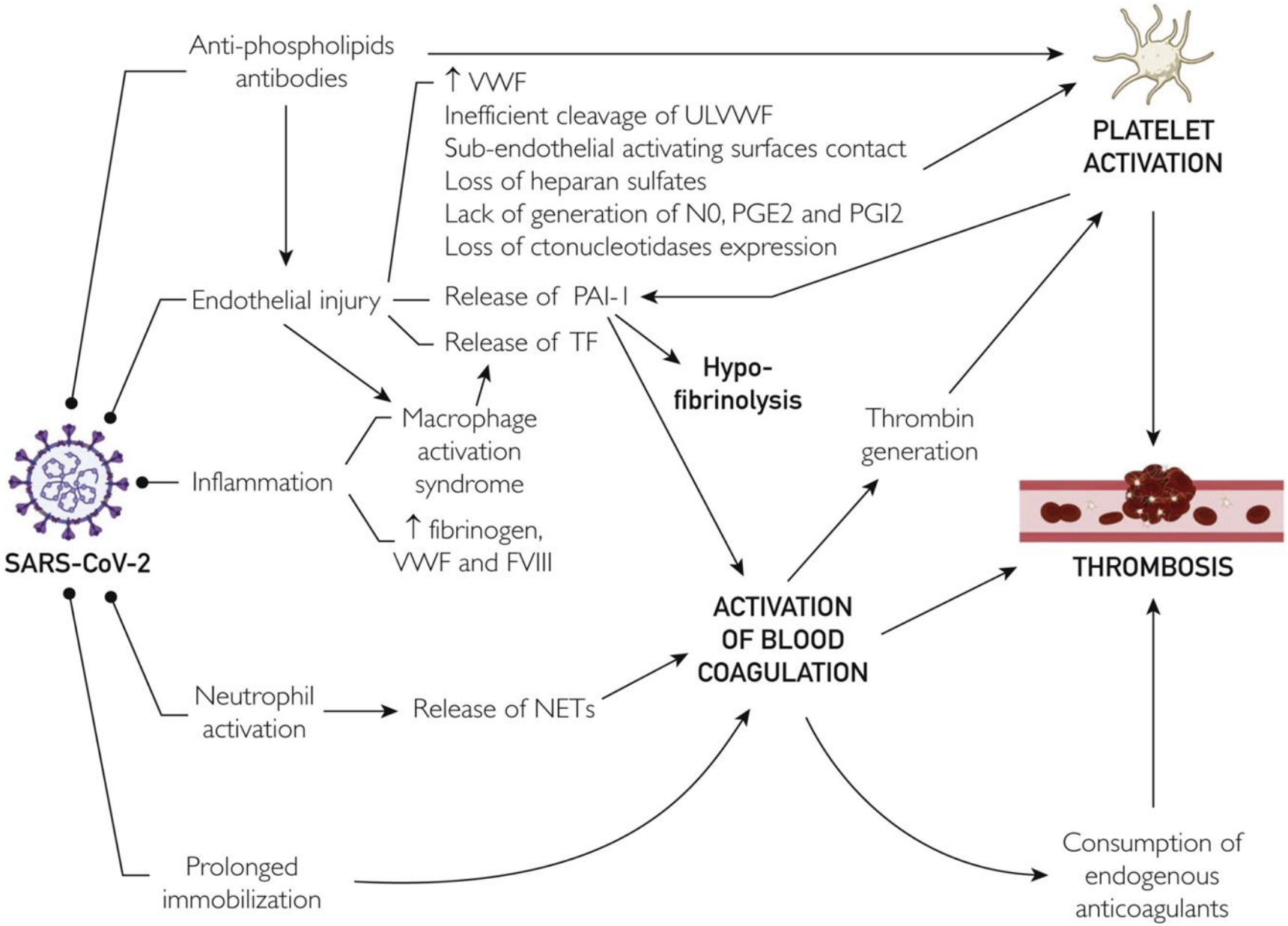
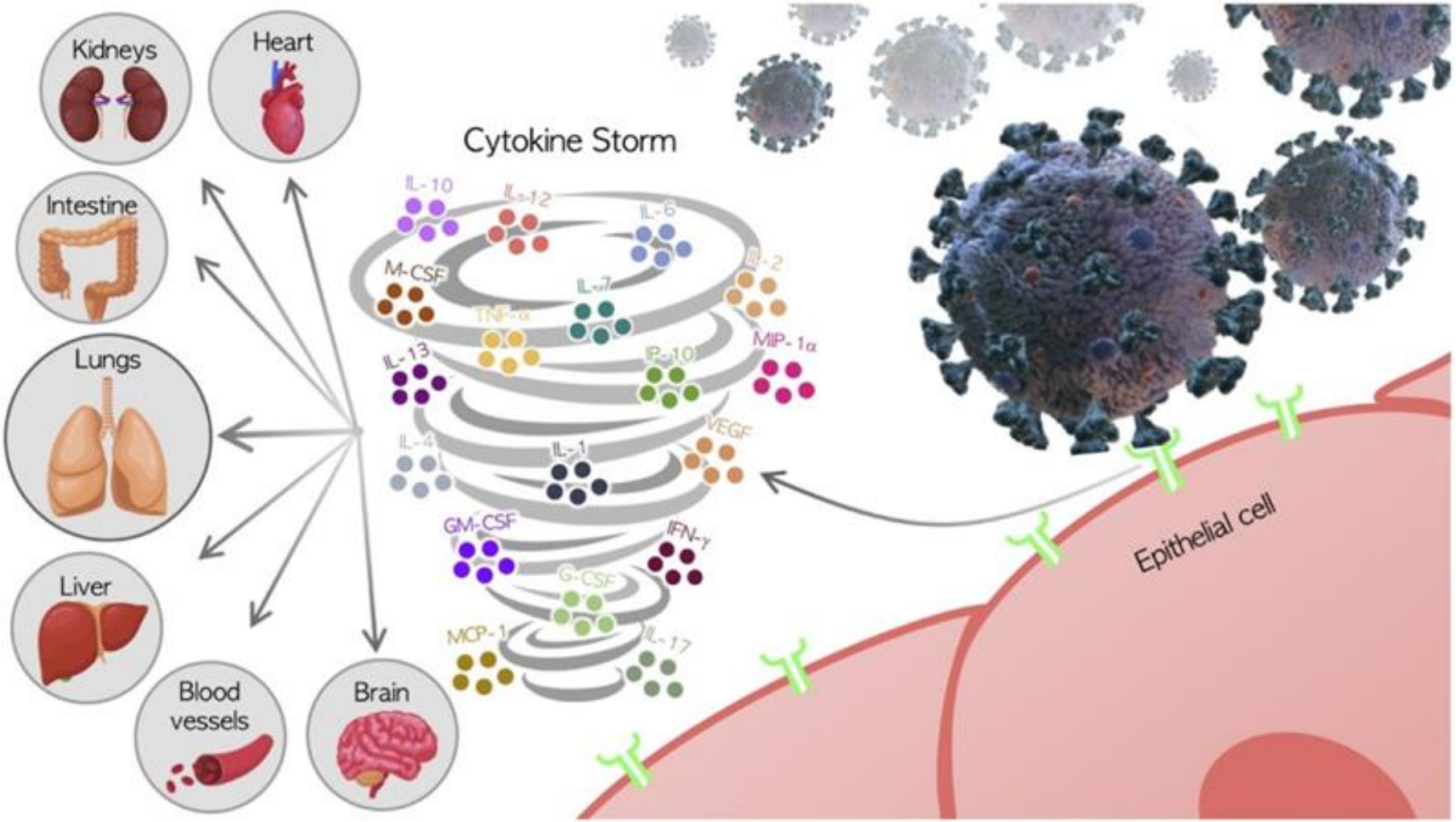
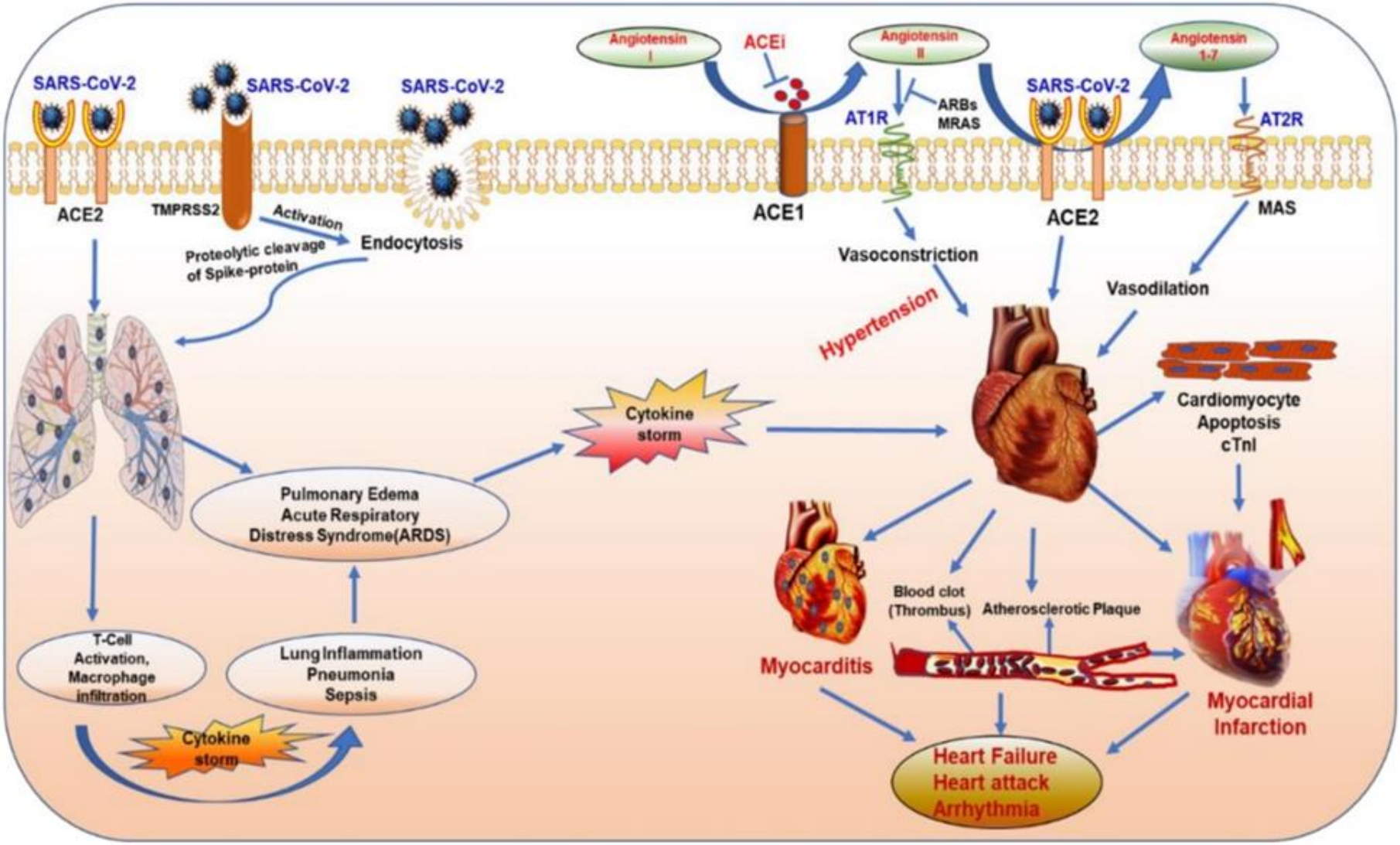


FIGURE 2 | The lifecycle of SARS-CoV-2 starting from the penetration of the virus into the cell until its release. The virus requires both ACE2 and TMPRSS2 to facilitate its entry. ACE: angiotensin converting enzyme, TMPRSS2: transmembrane protease serine 2.


Anti-phospholipids antibodies
↑ VWF
Inefficient cleavage of ULVWF
Sub-endothelial activating surfaces contact
Loss of heparan sulfates
Lack of generation of N0, PGE2 and PGI2
Loss of ctonucleotidases expression
PLATELET ACTIVATION
Endothelial injury
Release of PAI-1
Release of TF
Hypo-fibrinolysis
Thrombin generation
Macrophage activation syndrome
Inflammation
↑ fibrinogen, VWF and FVIII
SARS-CoV-2
THROMBOSIS
ACTIVATION OF BLOOD COAGULATION
Neutrophil activation
Release of NETs
Prolonged immobilization
Consumption of endogenous anticoagulants


Kidneys
Heart
Intestine
Lungs
Liver
Blood vessels
Brain
Cytokine Storm
IL-10
IL-12
IL-6
M-CSF
IL-7
IL-2
TNF-α
MIP-1α
IL-13
IP-10
VEGF
IL-4
IL-1
GM-CSF
IFN-γ
G-CSF
MCP-1
IL-17
Epithelial cell


SARS-CoV-2
SARS-CoV-2
SARS-CoV-2
ACE2
TMPRSS2
Activation
Proteolytic cleavage of Spike-protein
Endocytosis
Angiotensin I
ACEi
ACE1
Angiotensin II
AT1R
ARBs
MRAS
Vasoconstriction
SARS-CoV-2
ACE2
Angiotensin 1-7
AT2R
MAS
Vasodilation
Hypertension
Cytokine storm
Pulmonary Edema
Acute Respiratory Distress Syndrome(ARDS)
T-Cell Activation, Macrophage infiltration
Lung Inflammation
Pneumonia
Sepsis
Cytokine storm
Cardiomyocyte Apoptosis
cTnI
Myocarditis
Blood clot (Thrombus)
Atherosclerotic Plaque
Myocardial Infarction
Heart Failure
Heart attack
Arrhythmia

Pathological Role of Angiotensin II in Severe COVID-19

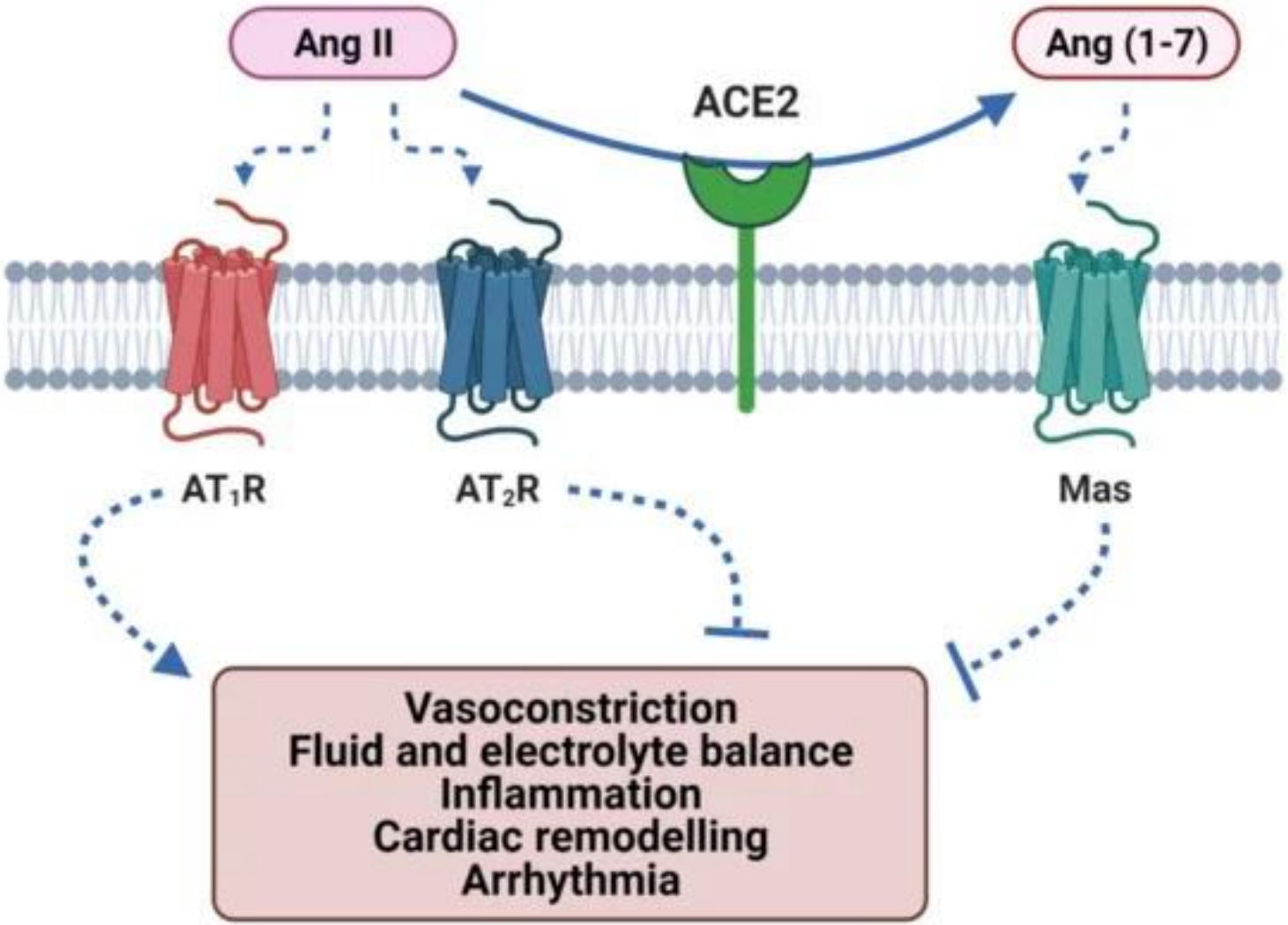
Wolfgang Miesbach[1]

Table 2 Possible effects of angiotensin II on clinical symptoms of COVID-19

Clinical COVID-19 symptom	Sepsis	ARDS	Organ injury (cardiac, kidney)	Thrombosis
Ang II-induced inflammation	Increase of IL-6 (59–61)			Increase of IL-6 (59–61)
Ang II-induced vasculopathy and thrombosis		Vasoconstriction[16] Increased hydrostatic pressure[41] Fibroproliferation[20,24,48] Vascular smooth muscle cells[60,61]	Vasoconstriction[16] Fibroproliferation[20,24,48] Vascular smooth muscle cells[60,61]	Vasoconstriction[16] Fibroproliferation[20,24,48] Vascular smooth muscle cells[60,61]
Ang II-induced coagulopathy				Increase of TF[49] and PAI-1[54,55] Increased platelet aggregation[50,67] and increase of PDGF[50]

Role of the Renin–Angiotensin–Aldosterone and Kinin–Kallikrein Systems in the Cardiovascular Complications of COVID-19 and Long COVID

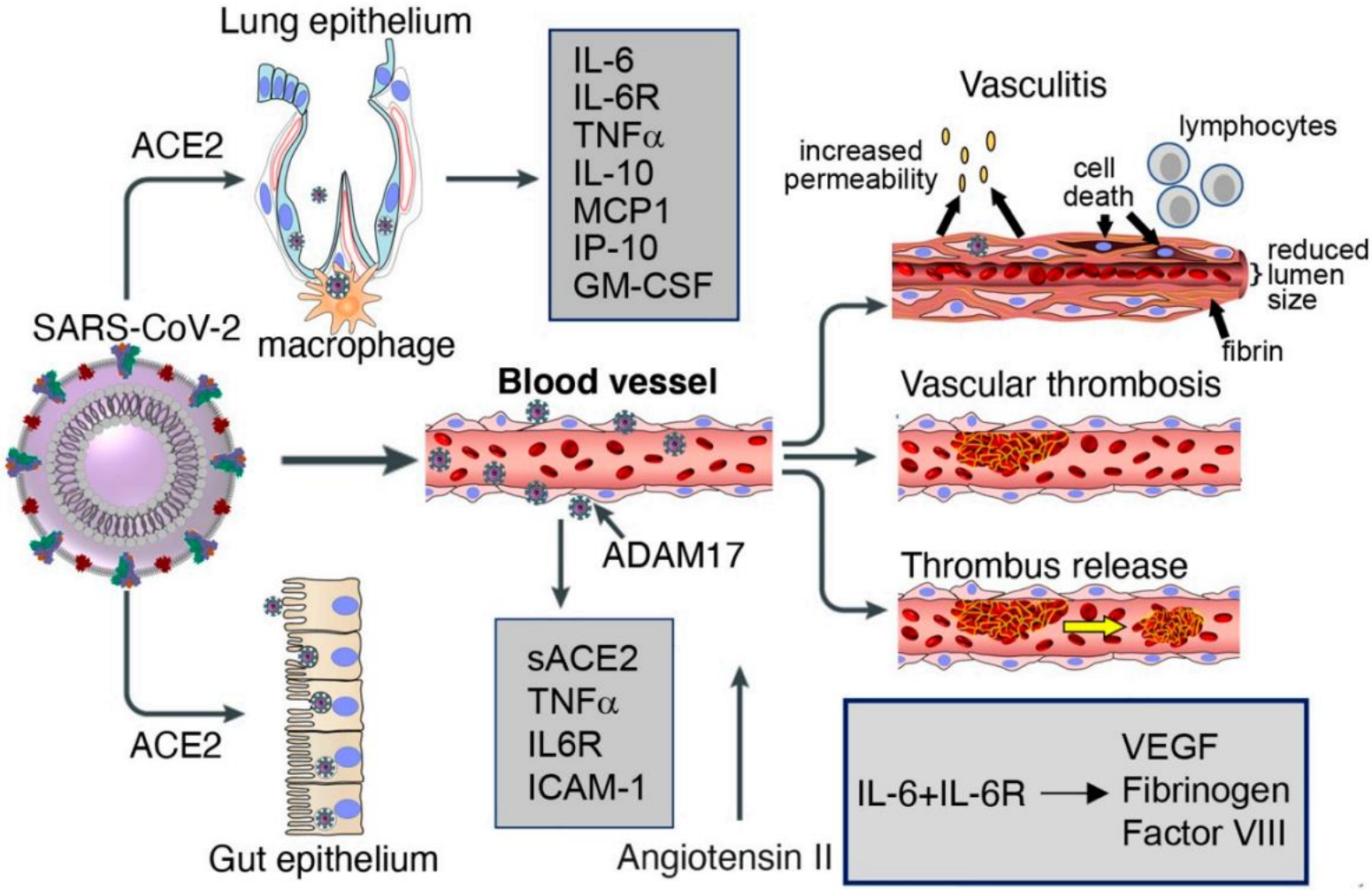
Samantha L. Cooper [1,2,*], Eleanor Boyle [3], Sophie R. Jefferson [3], Calum R. A. Heslop [3], Pirathini Mohan [3], Gearry G. J. Mohanraj [3], Hamza A. Sidow [3], Rory C. P. Tan [3], Stephen J. Hill [1,2] and Jeanette Woolard [1,2,*]



Int. J. Mol. Sci. **2021**, *22*, 8255. https://doi.org/10.3390/ijms22158255

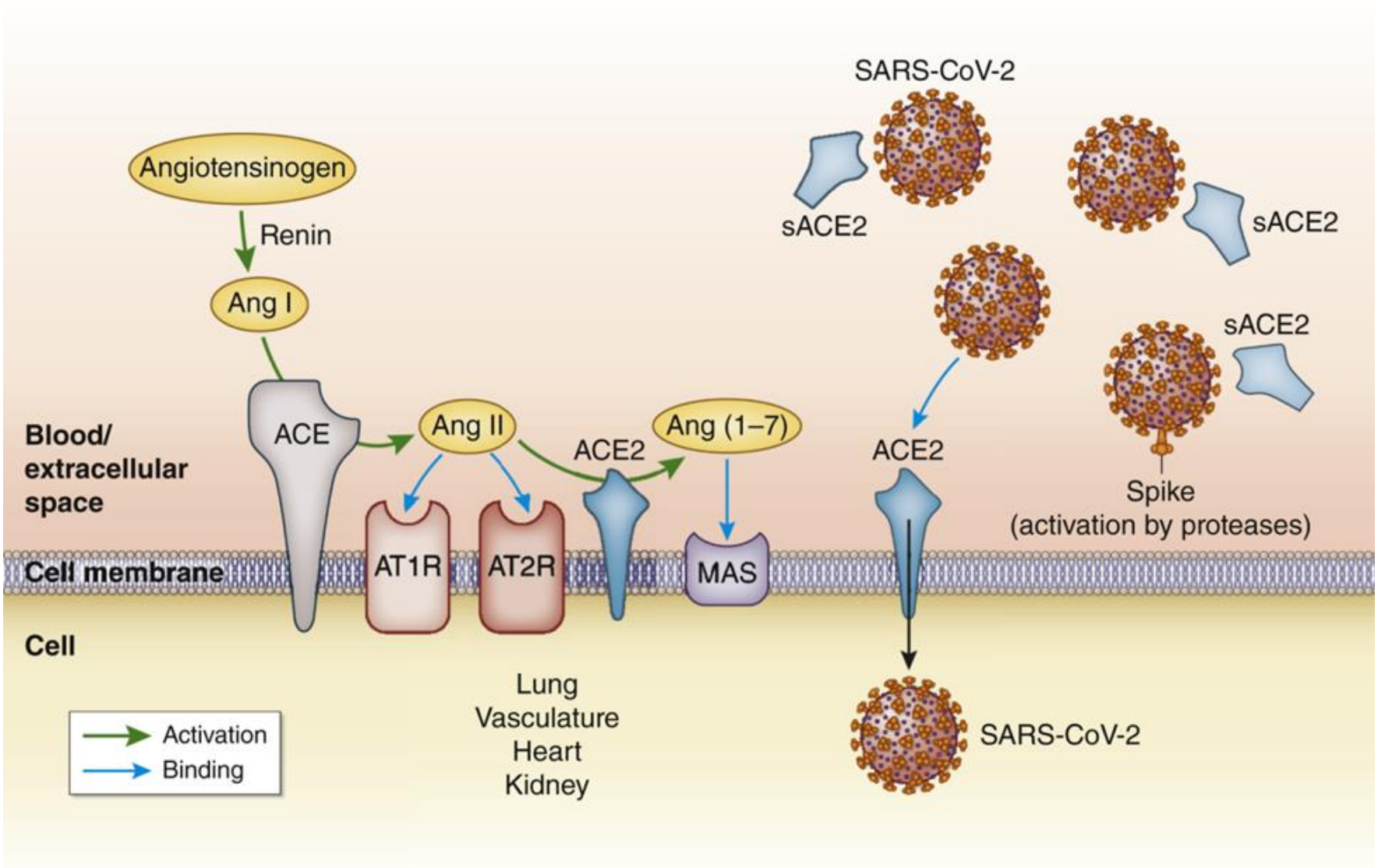
Vasculopathy and Coagulopathy Associated with SARS-CoV-2 Infection

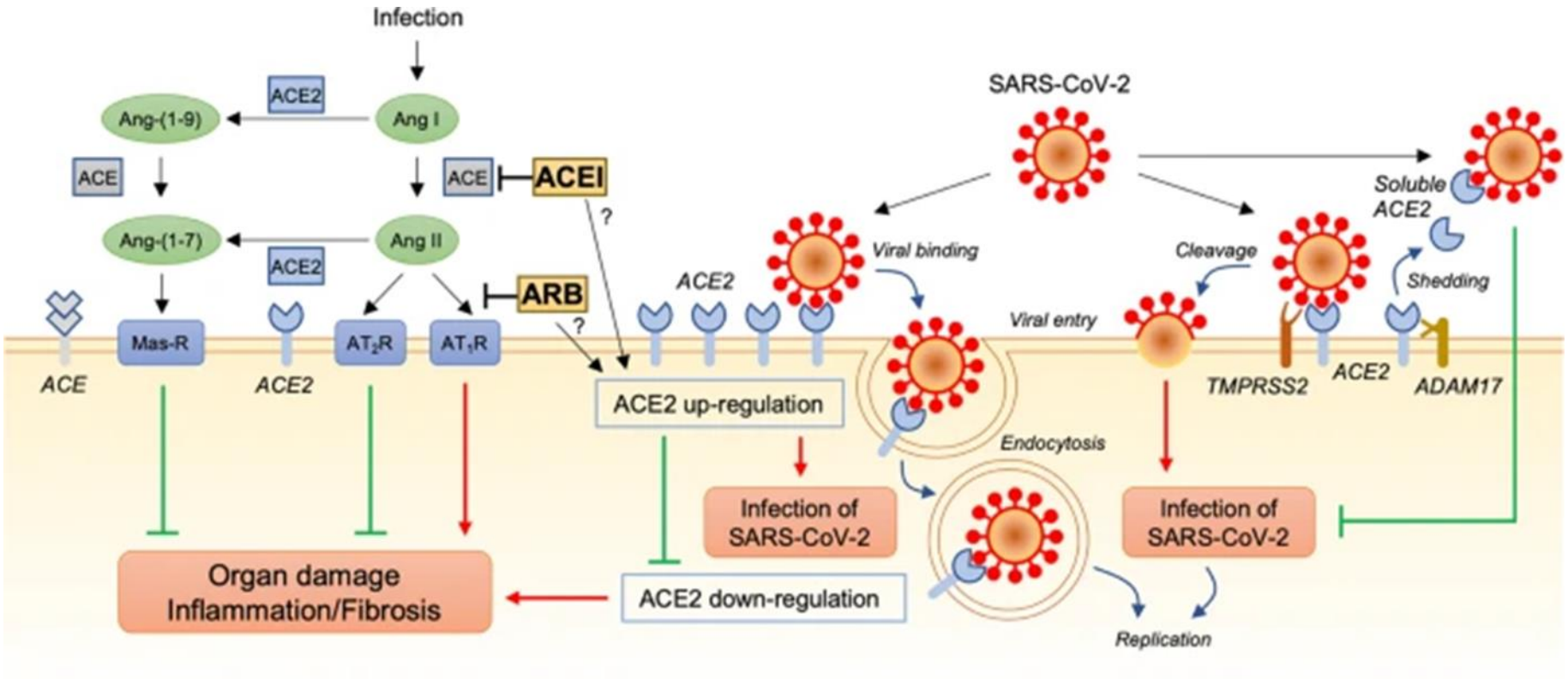
Nazzarena Labò [1], Hidetaka Ohnuki [2] and Giovanna Tosato [2,*]



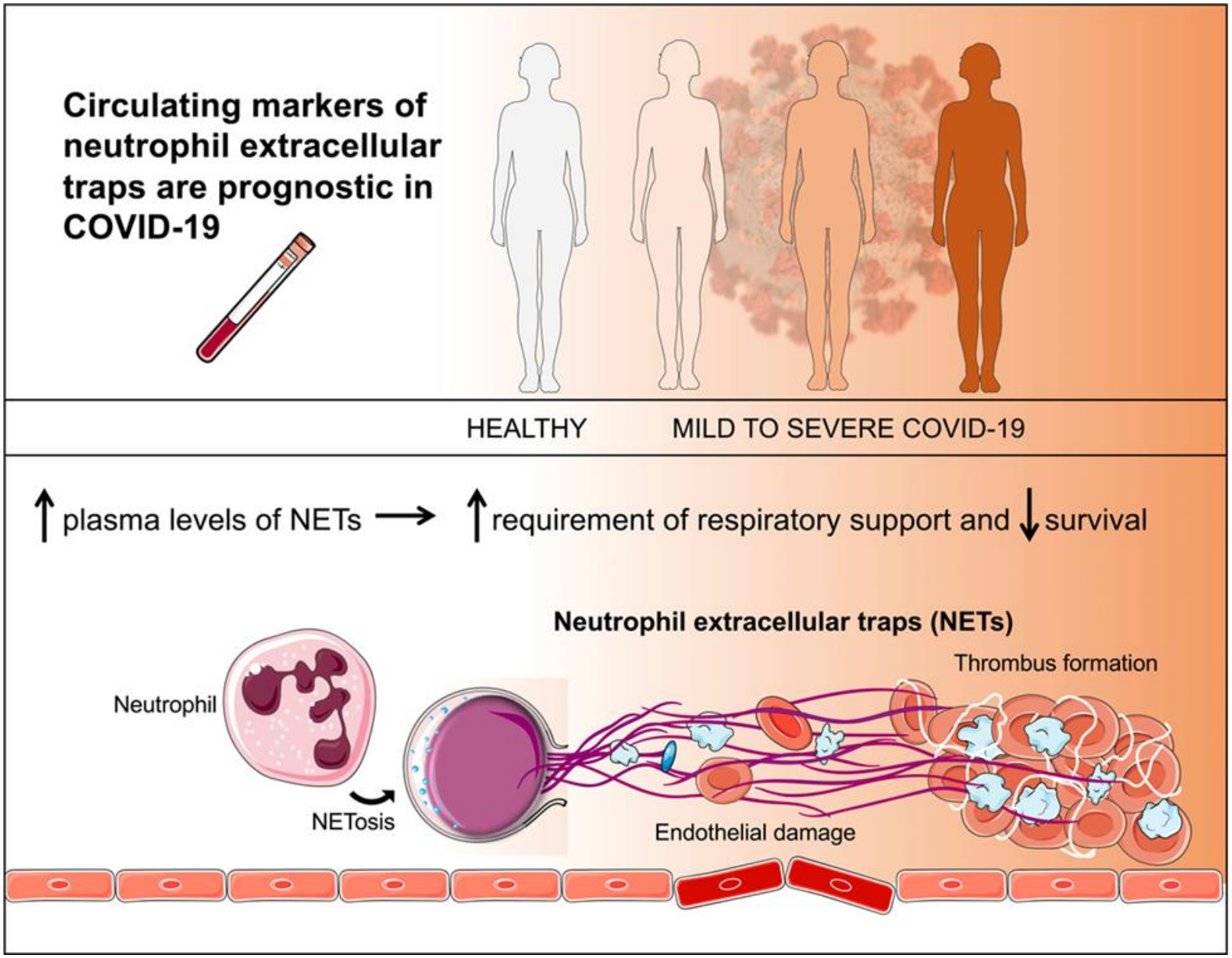
Cells **2020**, *9*, 1583; doi:10.3390/cells9071583

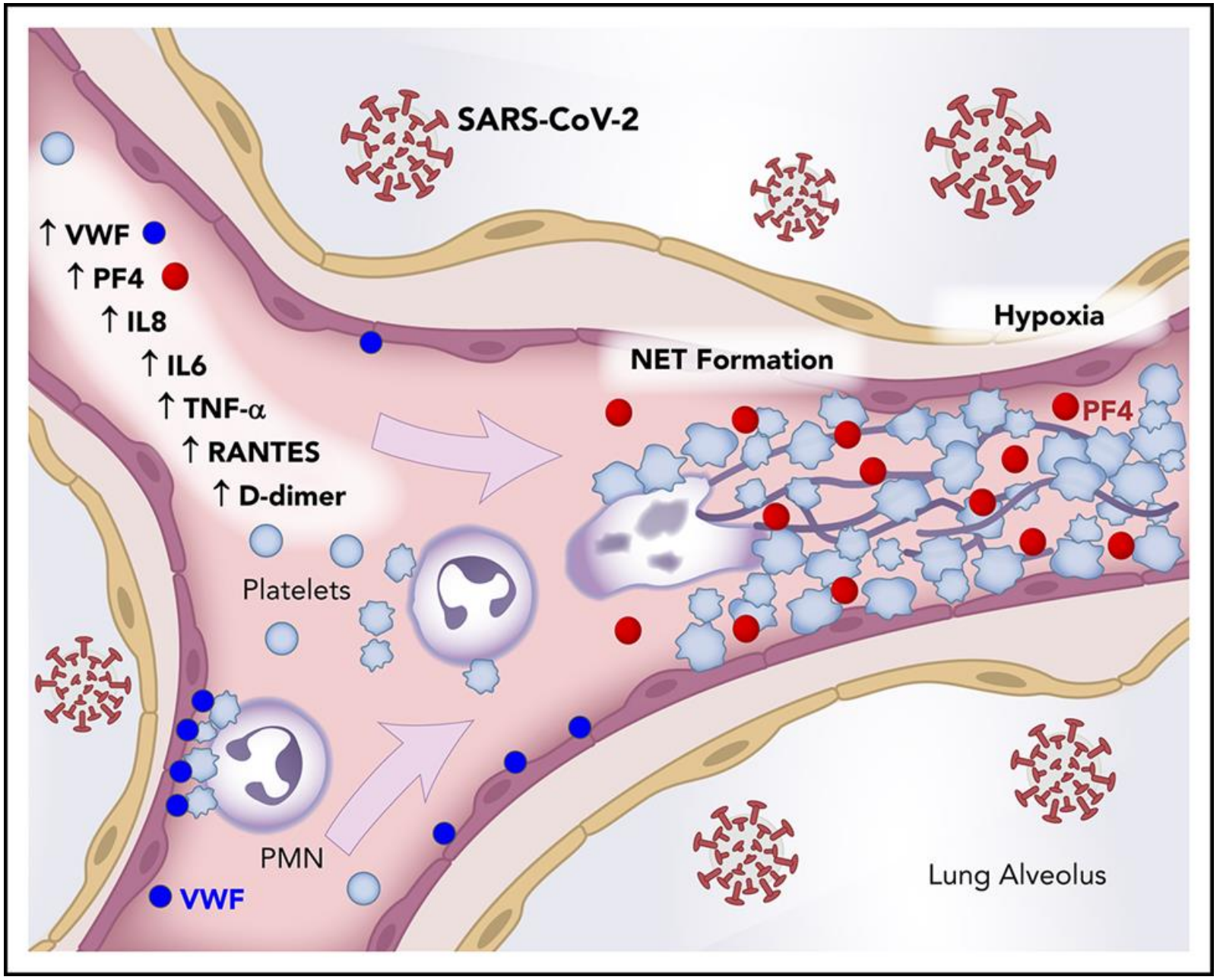
Cơ sở chọn ARBs trong điều trị THA nhiễm COVID 19

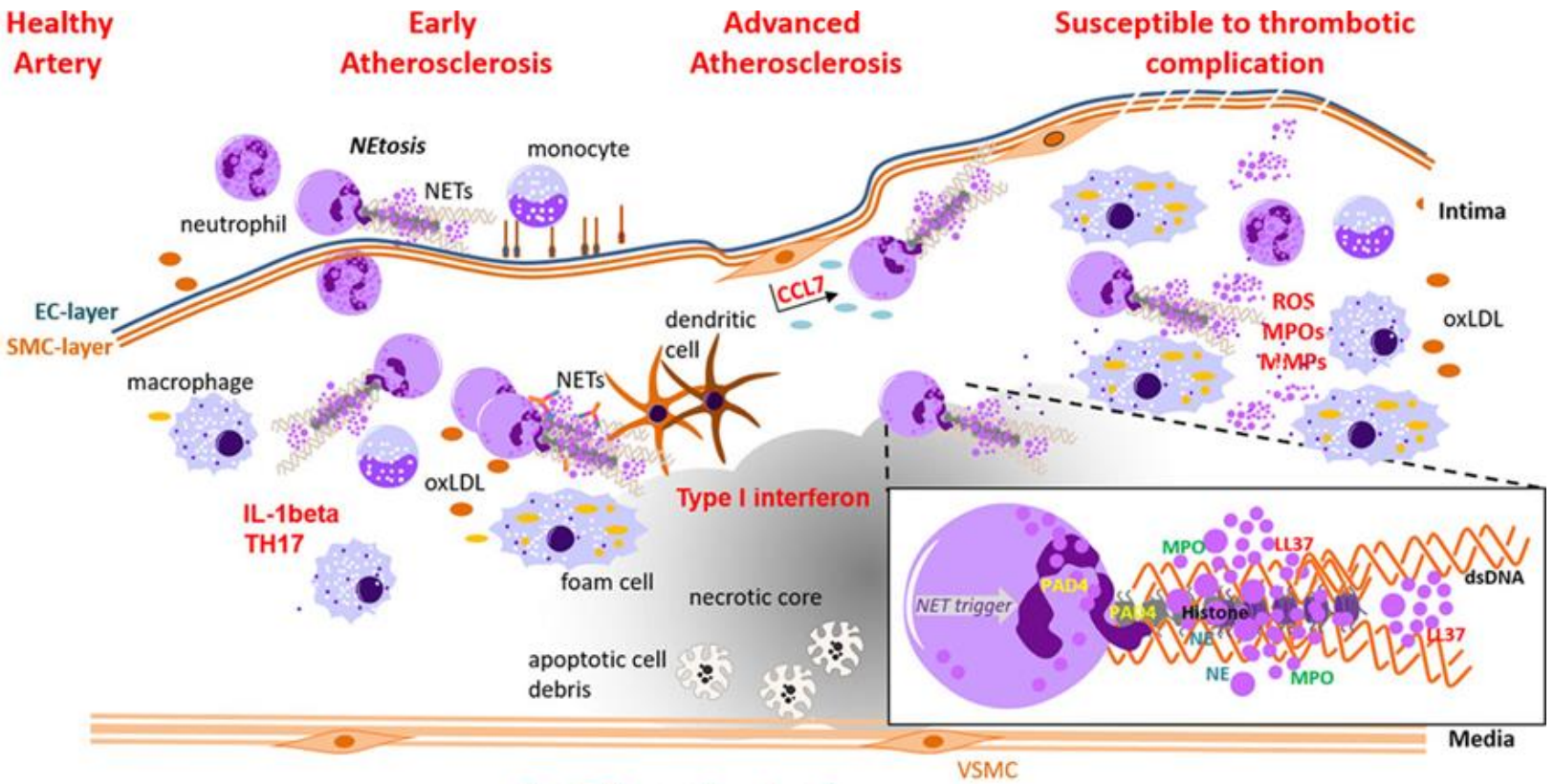




Possible increases in the expression and soluble form of ACE2 induced by RAS inhibitors would have beneficial effects of protection against lung injury and other organ damage but not infection with SARS-CoV-2


Circulating markers of neutrophil extracellular traps are prognostic in COVID-19
HEALTHY
MILD TO SEVERE COVID-19
↑ plasma levels of NETs → ↑ requirement of respiratory support and ↓ survival
Neutrophil extracellular traps (NETs)
Neutrophil
NETosis
Thrombus formation
Endothelial damage


SARS-CoV-2
↑ VWF
↑ PF4
↑ IL8
↑ IL6
↑ TNF-α
↑ RANTES
↑ D-dimer
Platelets
PMN
VWF
Hypoxia
NET Formation
PF4
Lung Alveolus

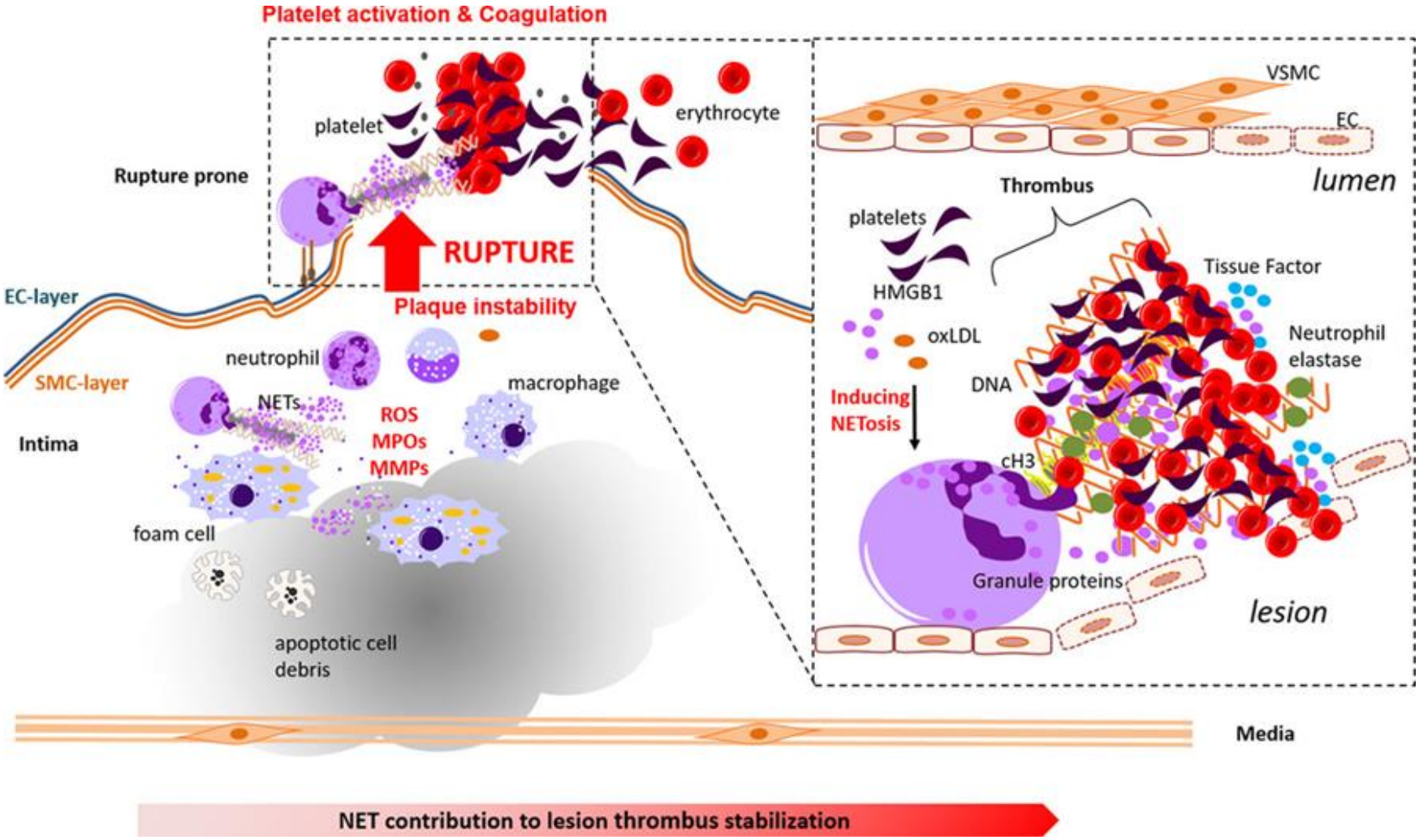


NETs mediate: *EC dysfunction* *Pro-inflammatory innate immune responses* *Thrombotic complication*

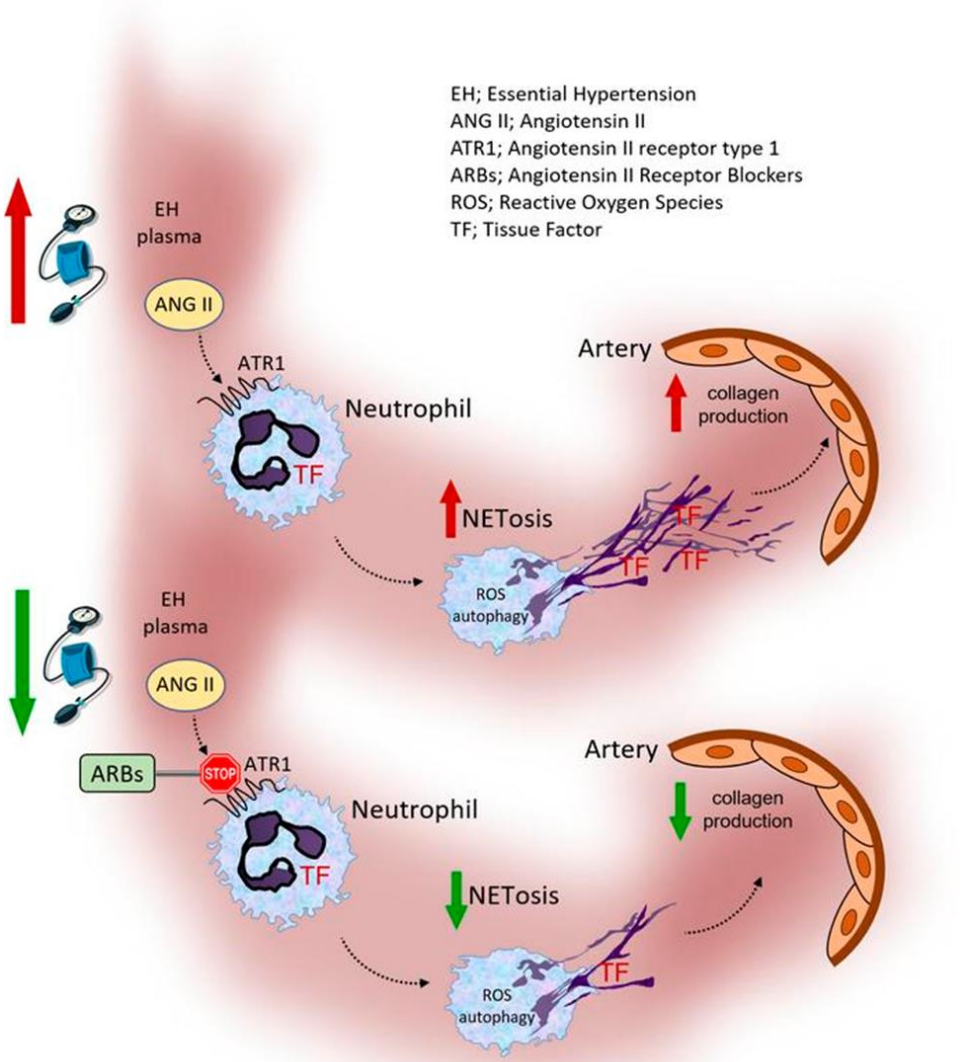
NET abundance

NET contribution to lesion size

NET contribution to thrombotic complication


Platelet activation & Coagulation
platelet
erythrocyte
Rupture prone
RUPTURE
Plaque instability
EC-layer
SMC-layer
Intima
neutrophil
macrophage
NETs
ROS
MPOs
MMPs
foam cell
apoptotic cell debris
VSMC
EC
lumen
Thrombus
platelets
HMGB1
oxLDL
Tissue Factor
Neutrophil elastase
DNA
Inducing NETosis
cH3
Granule proteins
lesion
Media
NET contribution to lesion thrombus stabilization

Angiotensin II thúc đẩy hình thành NETs



ARBs ức chế hình thành NETs

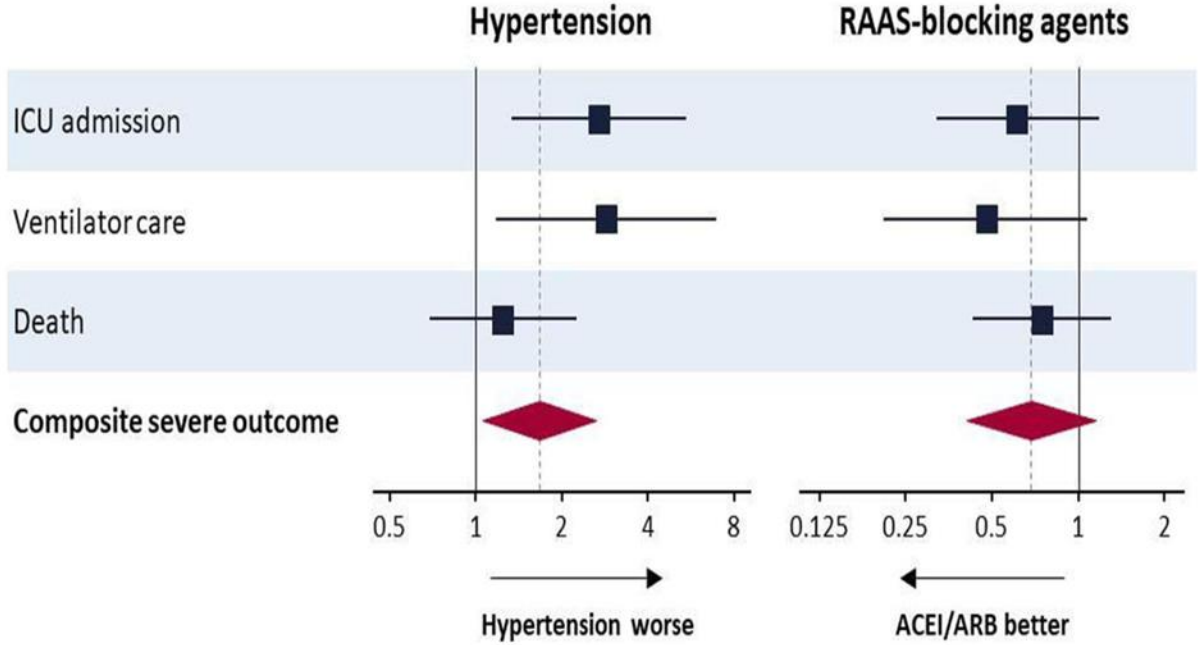


Fig. 2 Risk of adverse clinical outcomes associated with hypertension and the use of RAAS-blocking agents. RAAS, renin-angiotensin-aldosterone-system; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers

Methods: A total of 3,788 patients aged 30 years or older who were confirmed with COVID-19 with real time reverse transcription polymerase chain reaction were identified from a claims-based cohort in Korea. The primary study outcome was severe clinical events, a composite of intensive care unit admission, need for ventilator care, and death.

Conclusions: Patients with hypertension had worse COVID-19 outcomes than those without hypertension, while the use of RAAS-blocking agents was not associated with increased risk of any adverse study outcomes. The use of ACE inhibitors or ARBs did not increase the risk of adverse COVID-19 outcomes, supporting current guidance to continue these medications when indicated.

Circulation Research

ORIGINAL RESEARCH

Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19

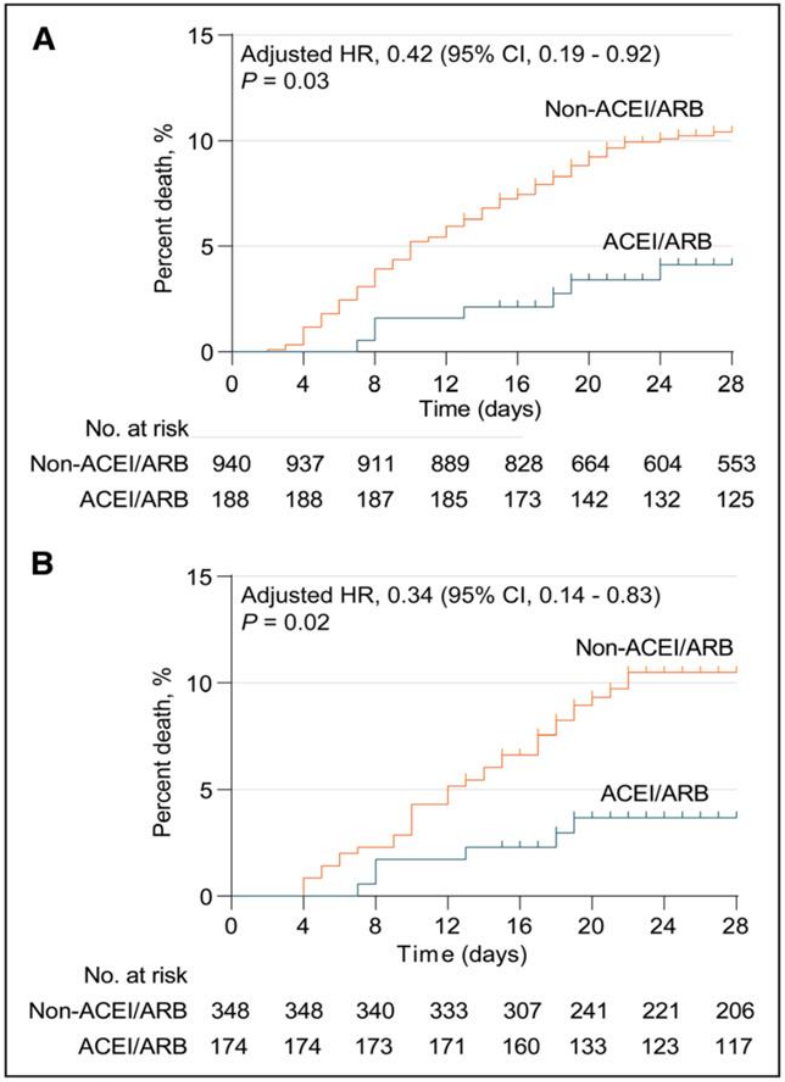
Peng Zhang,* Lihua Zhu,* Jingjing Cai,* Fang Lei,* Juan-Juan Qin,* Jing Xie, Ye-Mao Liu, Yan-Ci Zhao, Xuewei Huang, Lijin Lin, Meng Xia, Ming-Ming Chen, Xu Cheng, Xiao Zhang, Deliang Guo, Yuanyuan Peng, Yan-Xiao Ji, Jing Chen, Zhi-Gang She, Yibin Wang, Qingbo Xu, Renfu Tan, Haitao Wang, Jun Lin, Pengcheng Luo, Shouzhi Fu, Hongbin Cai, Ping Ye, Bing Xiao, Weiming Mao, Liming Liu, Youqin Yan, Mingyu Liu, Manhua Chen, Xiao-Jing Zhang, Xinghuan Wang, Rhian M. Touyz, Jiahong Xia, Bing-Hong Zhang, Xiaodong Huang, Yufeng Yuan, Rohit Loomba, Peter P. Liu, Hongliang Li

RATIONALE: Use of ACEIs (angiotensin-converting enzyme inhibitors) and ARBs (angiotensin II receptor blockers) is a major concern for clinicians treating coronavirus disease 2019 (COVID-19) in patients with hypertension.

OBJECTIVE: To determine the association between in-hospital use of ACEI/ARB and all-cause mortality in patients with hypertension and hospitalized due to COVID-19.

METHODS AND RESULTS: This retrospective, multi-center study included 1128 adult patients with hypertension diagnosed with COVID-19, including 188 taking ACEI/ARB (ACEI/ARB group; median age 64 [interquartile range, 55–68] years; 53.2% men) and 940 without using ACEI/ARB (non-ACEI/ARB group; median age 64 [interquartile range 57–69]; 53.5% men), who were admitted to 9 hospitals in Hubei Province, China from December 31, 2019 to February 20, 2020. In mixed-effect Cox model treating site as a random effect, after adjusting for age, gender, comorbidities, and in-hospital medications, the detected risk for all-cause mortality was lower in the ACEI/ARB group versus the non-ACEI/ARB group (adjusted hazard ratio, 0.42 [95% CI, 0.19–0.92]; *P*=0.03). In a propensity score-matched analysis followed by adjusting imbalanced variables in mixed-effect Cox model, the results consistently demonstrated lower risk of COVID-19 mortality in patients who received ACEI/ARB versus those who did not receive ACEI/ARB (adjusted hazard ratio, 0.37 [95% CI, 0.15–0.89]; *P*=0.03). Further subgroup propensity score-matched analysis indicated that, compared with use of other antihypertensive drugs, ACEI/ARB was also associated with decreased mortality (adjusted hazard ratio, 0.30 [95% CI, 0.12–0.70]; *P*=0.01) in patients with COVID-19 and coexisting hypertension.

CONCLUSIONS: Among hospitalized patients with COVID-19 and coexisting hypertension, inpatient use of ACEI/ARB was associated with lower risk of all-cause mortality compared with ACEI/ARB nonusers. While study interpretation needs to consider the potential for residual confounders, it is unlikely that in-hospital use of ACEI/ARB was associated with an increased mortality risk.



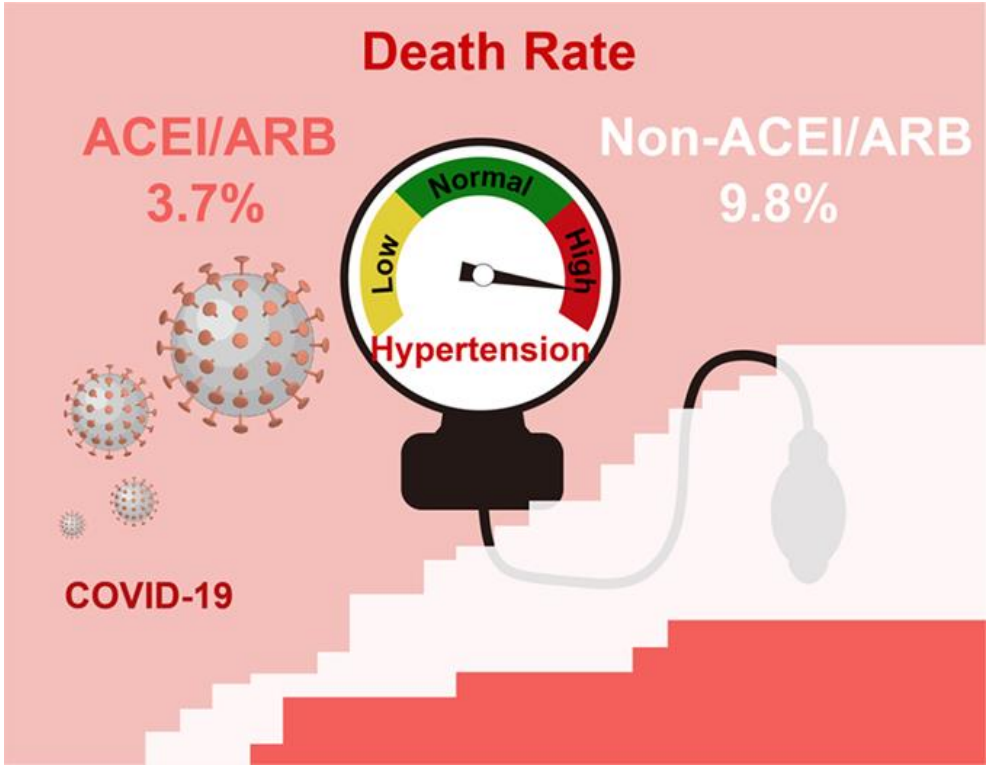


Figure 2. Kaplan-Meier curves for cumulative probability of Coronavirus disease 2019 (COVID-19) mortality during 28-day follow-up duration in ACEI (angiotensin-converting enzyme inhibitor)/ARB (angiotensin II receptor blocker) or non-ACEI/ARB cohort among 1128 patients with hypertension.

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RAMIC: Design of a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of ramipril in patients with COVID-19

Author links open overlay panelVeeralAjmera[ab]Wesley K.Thompson[c]Davey M.Smith[d]AtulMalhotra[e]Ravindra L.Mehta[f]VaishalTolia[g]JeffreyYin[h]KrishnaSriram[i]Paul A.Insel[ij]SummerCollier[a]LisaRichards[b]RohitLoomba[ab]

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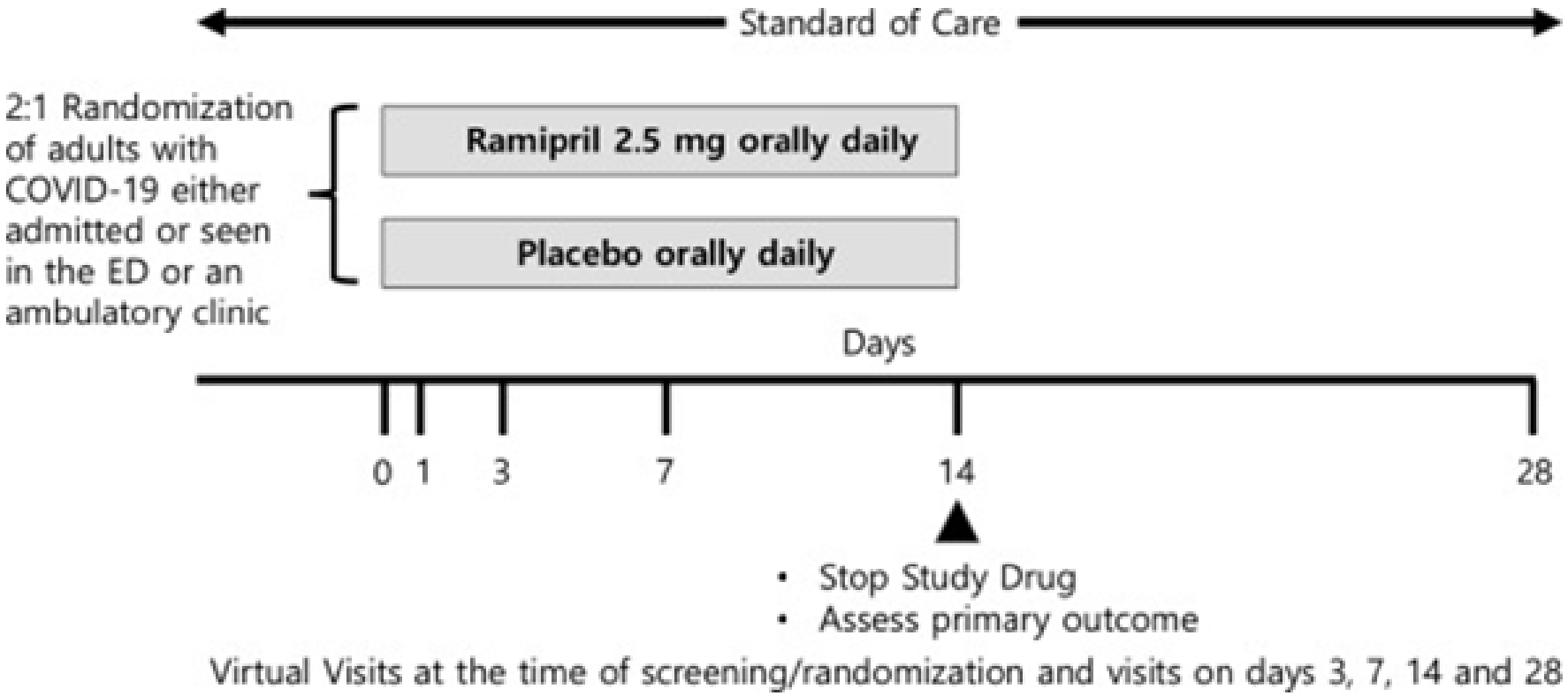

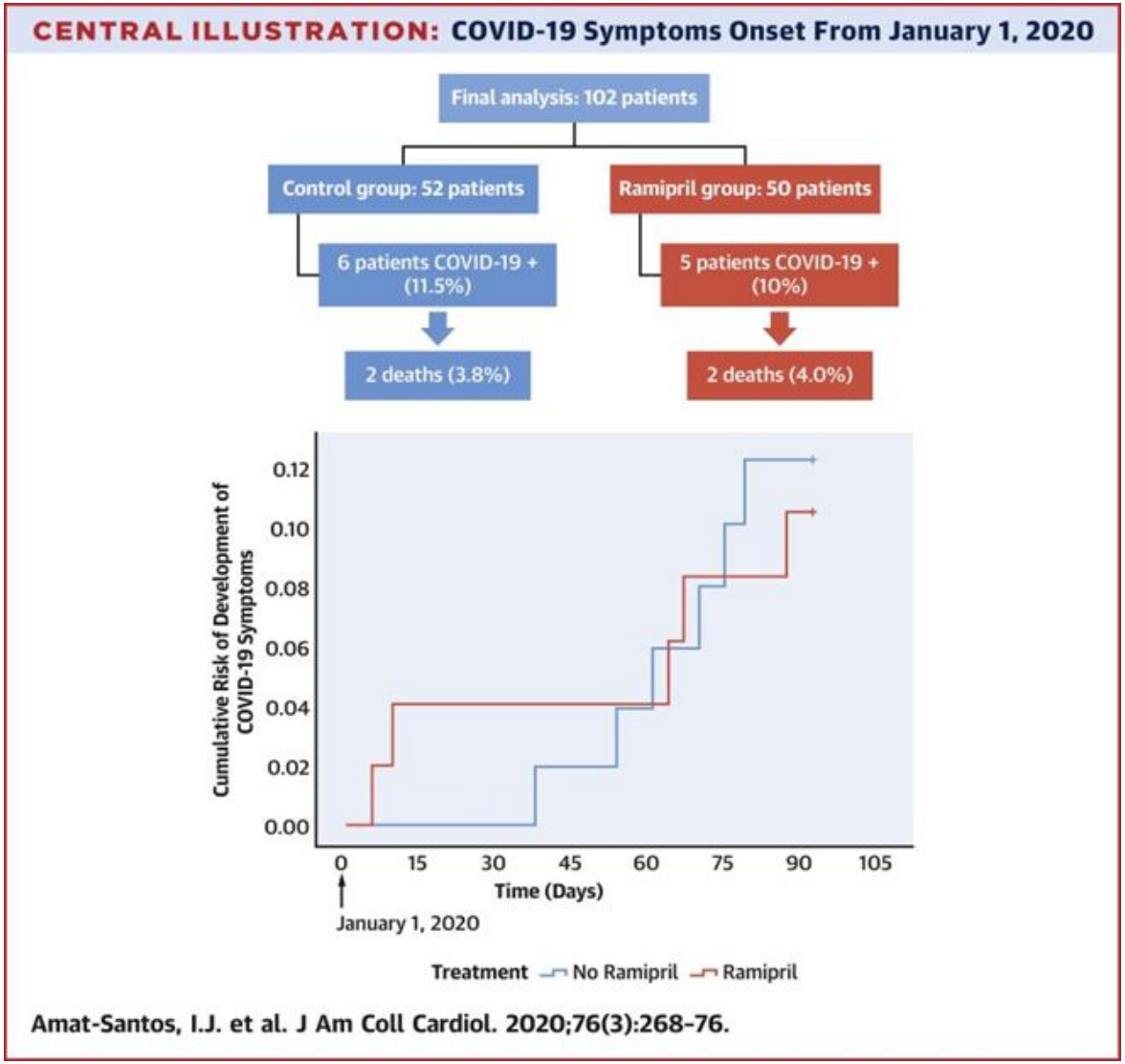

Conclusions

RAMIC is designed to assess the efficacy of treatment with ramipril for 14 days to decrease ICU admission, mechanical ventilator use and mortality in patients with COVID-19 and leverages virtual study visits and endpoint adjudication to mitigate risk of infection and to preserve PPE (ClinicalTrials.gov, NCT04366050).

World Health Organization

4.2 COVID-19 and hypertension

sometimes unclear, however, whether this risk was independent of other risk factors *(92)*. Initial reports have identified higher rates of HTN among severely ill, hospitalized COVID-19 patients, with overall HTN rates of 50–56% *(93, 94)*. It had been unclear if this relationship was causal or confounded by age and other comorbidities associated with HTN, including obesity, diabetes and chronic kidney disease. Concerns regarding use of angiotensin-converting enzyme inhibitors (ACEis) in these patients were raised due to identification of angiotensin-converting enzyme 2 (ACE2), the monocarboxypeptidase that inactivates angiotensin II and thereby counters the activation of the classic renin–angiotensin–aldosterone system (RAAS), as the functional receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *(95, 96)*. The WHO conducted a rapid review of evidence related to the use ACEis or ARBs in COVID patients which identified 11 observational studies. No studies were found that were designed to directly assess whether ACEis or ARBs increase the risk of acquiring COVID-19. After adjustment for confounders, history of ACEi or ARB use was not found to be associated with increased severity of COVID-19 illness. There were no studies that addressed the potential benefits and harms of

World Health Organization

initiating ACEis or ARBs as treatment for patients with COVID-19 *(97)*. Accordingly, discontinuation of ACEis or ARBs may yield worse outcomes than continuation of their use in patients with a diagnosis of COVID-19. In contrast to the uncertainty about the potential benefit of initiating RAAS blocker use in patients with COVID-19, there is a clear potential for harm in withdrawing these agents in high-risk COVID-19 patients with established myocardial injury, HTN or heart failure *(96)*. Most of the world's professional societies either recommend or strongly encourage continuing ACEis/ARBs in COVID-19-infected patients *(98)*. Further research that will address key unanswered questions about the role of the RAAS in the pathogenesis and possible treatment of COVID-19 and other coronavirus-based diseases is urgently needed. Prospective studies – in particular, ongoing randomized, placebo-controlled trials such as the Ramipril for the Treatment of COVID-19 (RAMIC) trial (ClinicalTrials.gov number, NCT04366050)

KẾT LUẬN

- THA và ĐTĐ luôn song hành trên bệnh nhân ĐTĐ gây biến chứng tim mạch nghiêm trọng
- Bên cạnh thay đổi lối sống và chế độ tiết thực cần sử dụng thuốc hạ huyết áp
- Vai trò ACEis và ARBs luôn được khuyến cáo ưu tiên (ADA 2021) lý do ngoài tác dụng hạ huyết áp còn có vai trò bảo vệ và hạn chế biến chứng tim mạch
- Trong Đại Dịch COVID-19 nhóm thuốc ACEis và ARBs vẫn được WHO 2021 khuyến cáo sử dụng

Chân thành cám ơn sự theo dõi của quý đồng nghiệp