DIABETES AND CARDIOVASCULAR DISEASES

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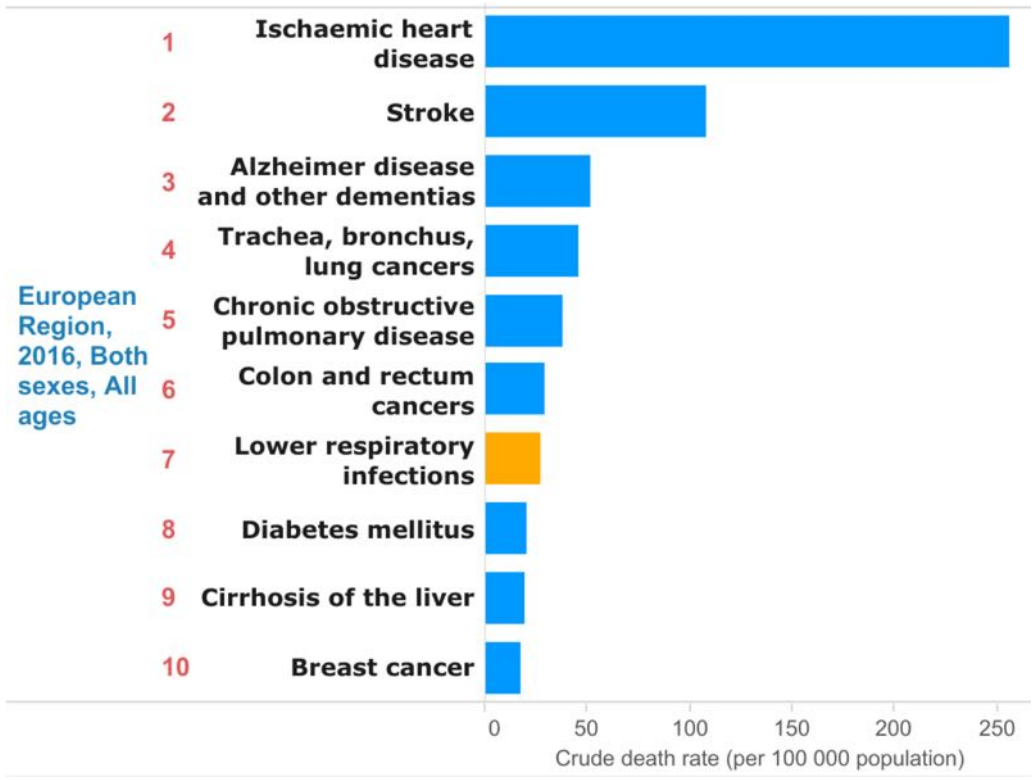
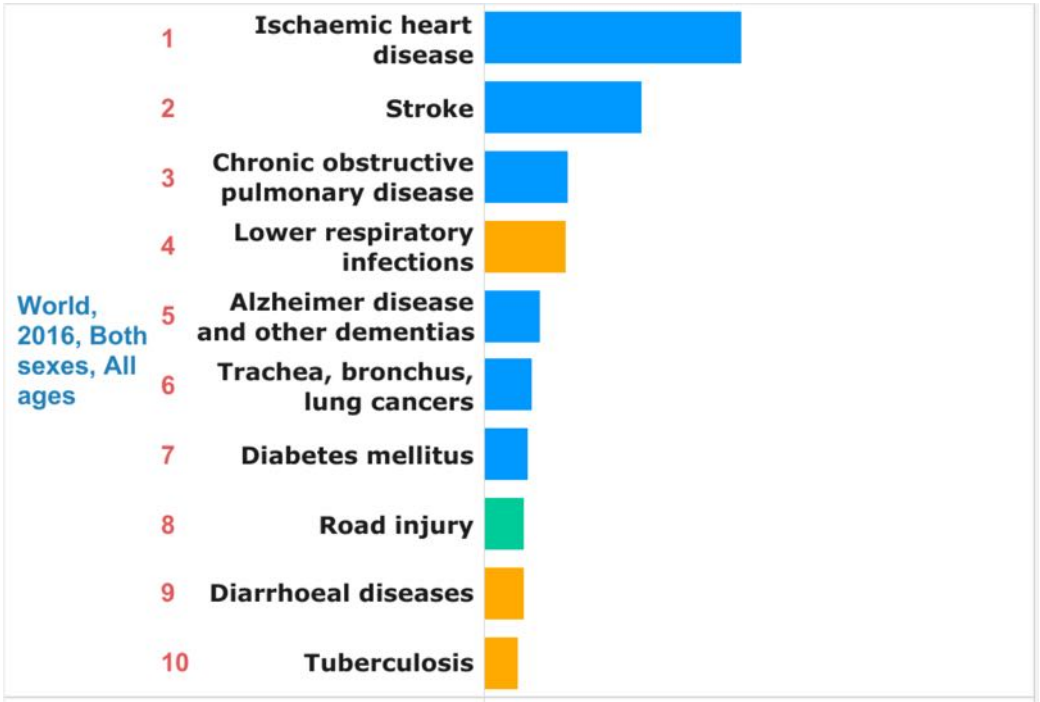
Université de Paris

Global causes of death - 2016 (WHO)

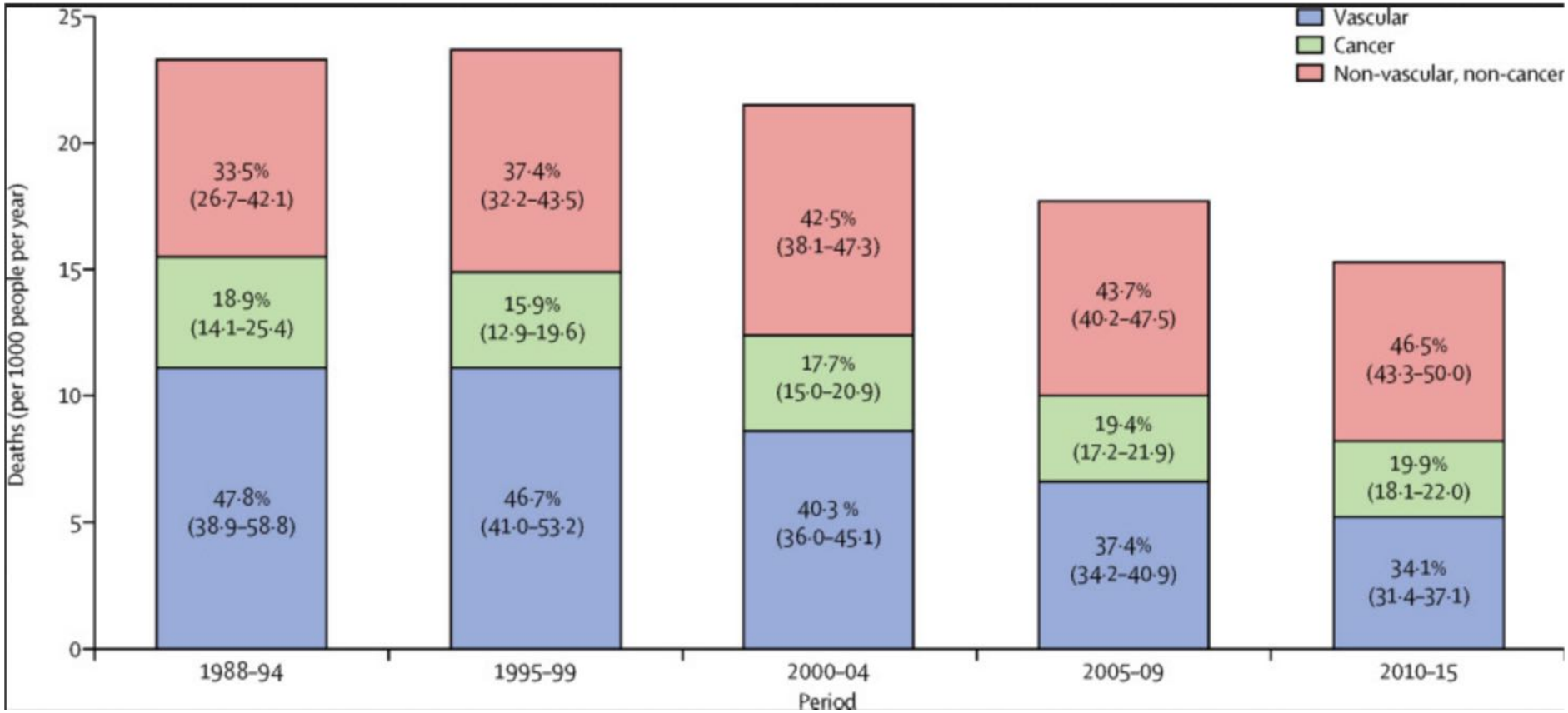




Cause group
- Communicable, maternal, perinatal and nutritional conditions
- Noncommunicable diseases
- Injuries

Causes of death in adult (USA)

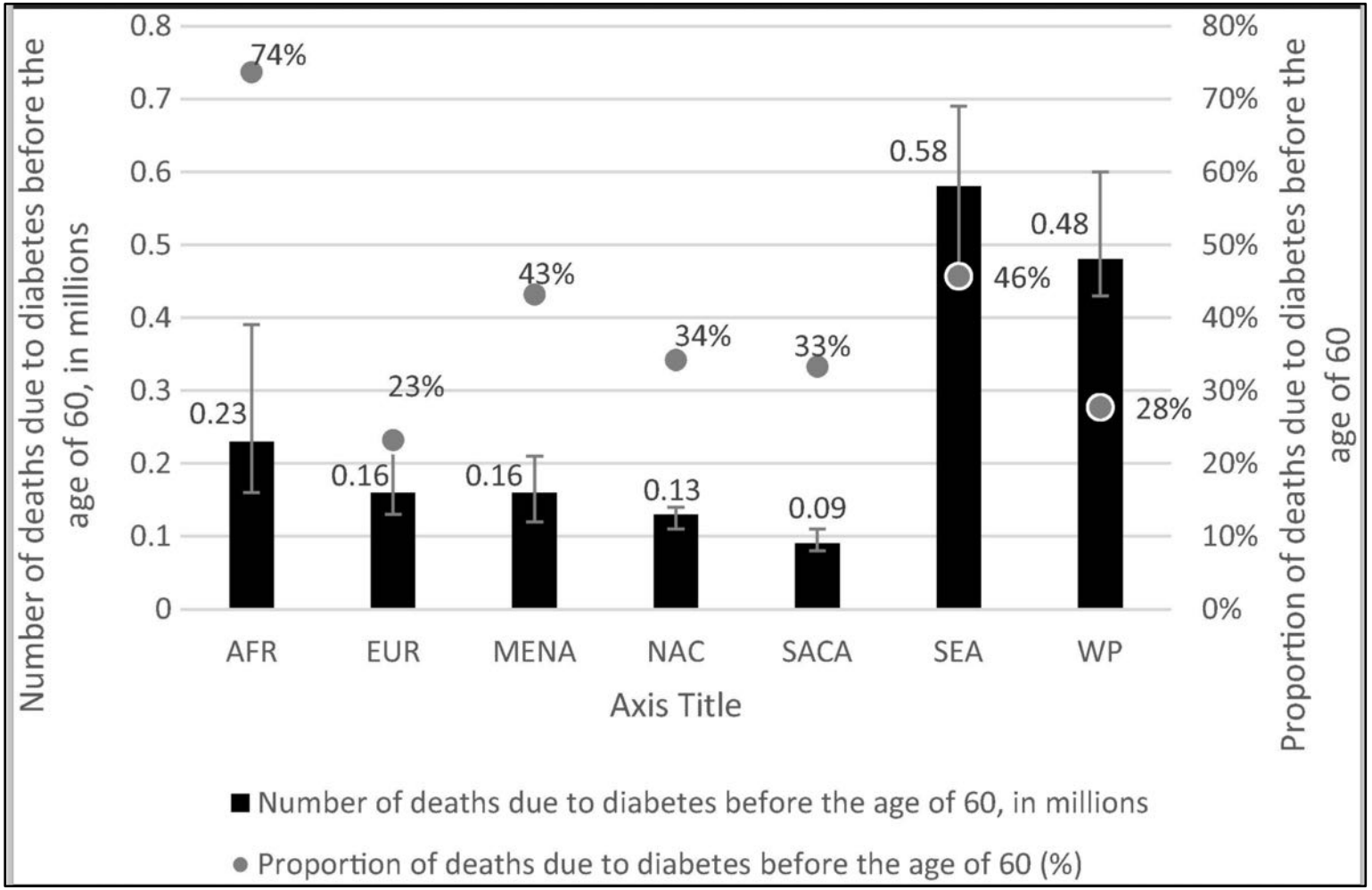
The reduction in deaths caused by vascular disease is consistent with previous reports of improved cardiovascular mortality rates, myocardial infarction, and stroke, which have been attributed to improvements in revascularisation, acute care, risk factor management, and behavioural changes;



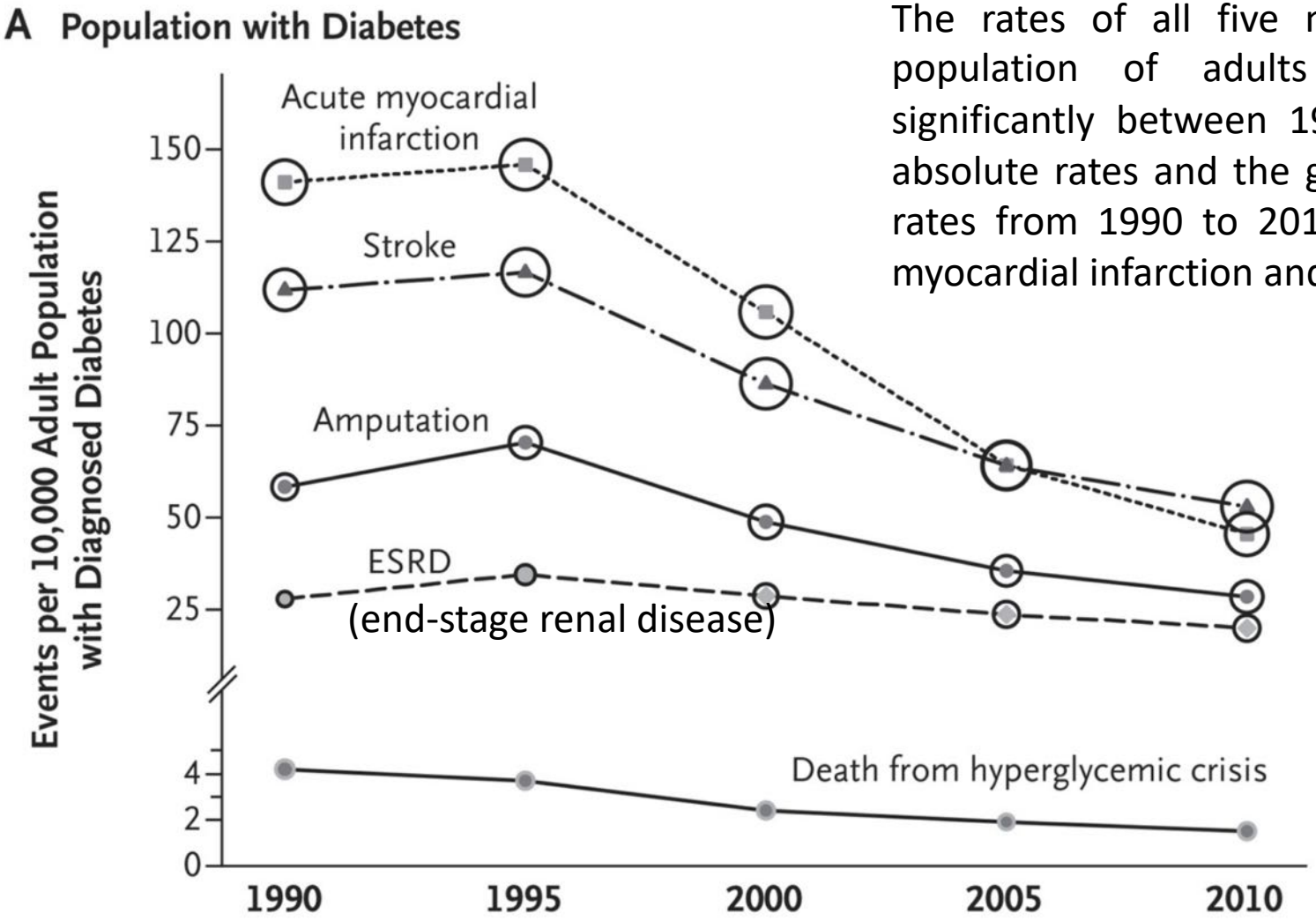
Gregg EW et al, The Lancet, 2018

The Diabetes epidemic

Diabetes accounted for 9.9% of the global all-cause mortality among people within 20-99 years (2017). Over one third of deaths attributable to diabetes occurred in people under the age of 60 years. The highest proportion of all deaths attributable to diabetes occurring before the age of 60 is in the Africa region, at 73.7%.



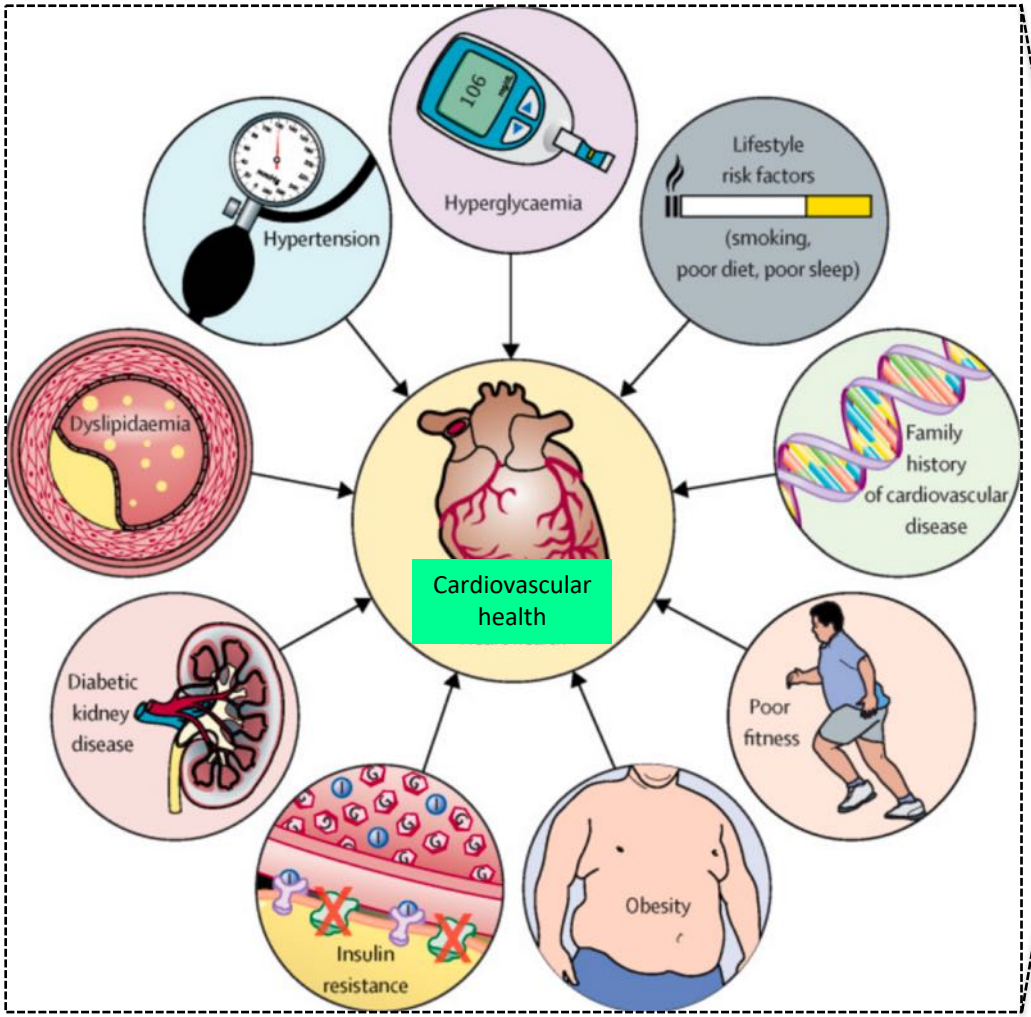
Causes of death in adult diagnosed with diabetes (USA)

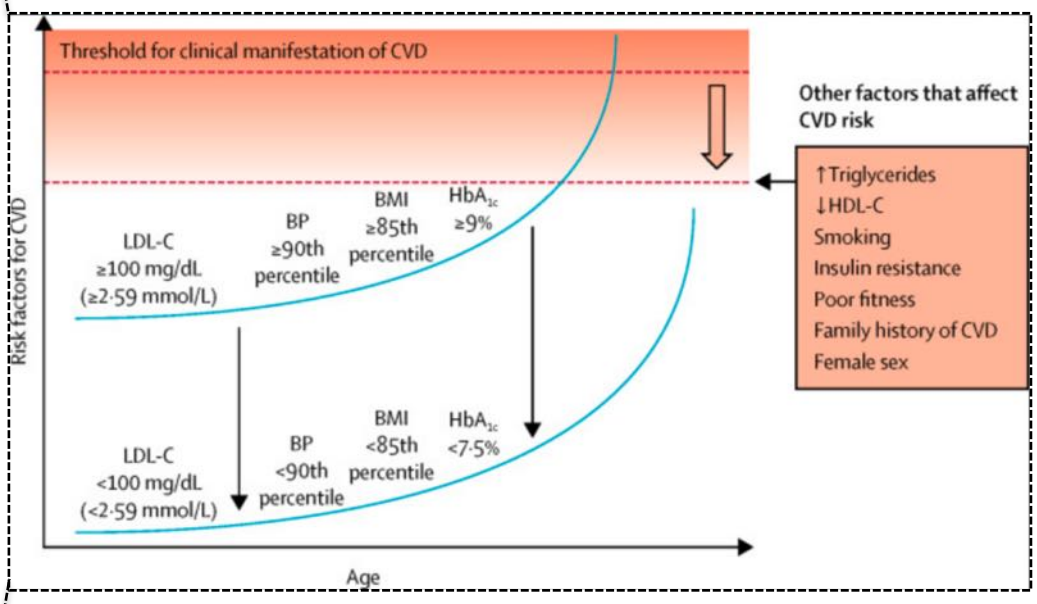


The rates of all five major complications in the population of adults with diabetes declined significantly between 1990 and 2010. The highest absolute rates and the greatest absolute declines in rates from 1990 to 2010 were observed for acute myocardial infarction and stroke.

Gregg EW et al, N Engl J Med, 2014

Cardiovascular risk factors in diabetic patients





Bjornstad P et al, The Lancet Diabetes & Endocrinology, 2018

Diabetes and Cardiovascular diseases

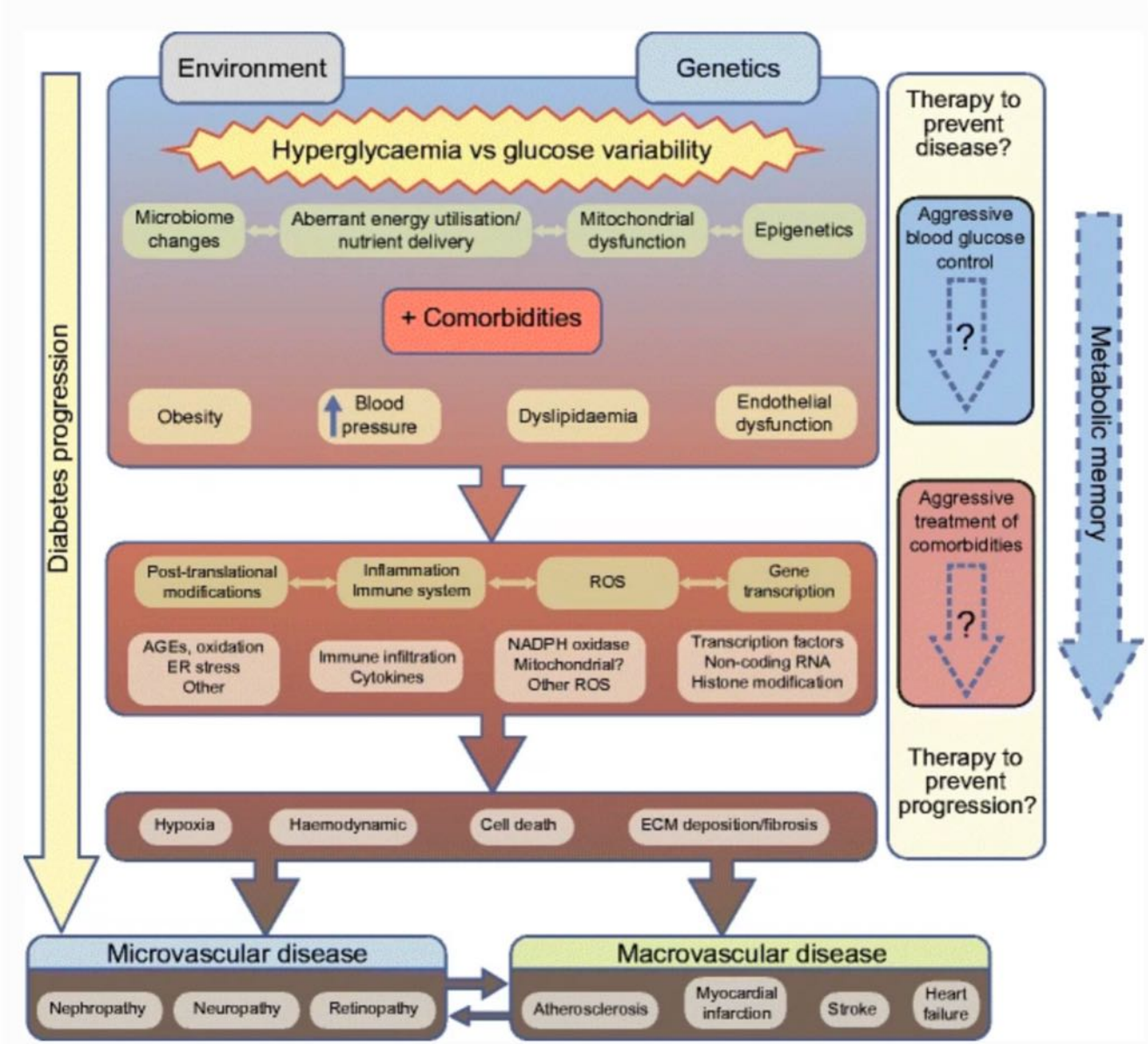
A close link exists between DM and cardiovascular disease (CVD). CVD is the most prevalent cause of mortality and morbidity in diabetic populations.

√ CVD death are higher among adults (> 18 years) with diabetes (Type 2) than those without diagnosed diabetes, largely due to an increased risk of stroke and myocardial infarction (MI).
This increased risk of CVD mortality in diabetic patients is found in both men and women.

√ CV risk factors including obesity, hypertension and dyslipidemia are common in patients with diabetes, particularly those with T2 diabetes.

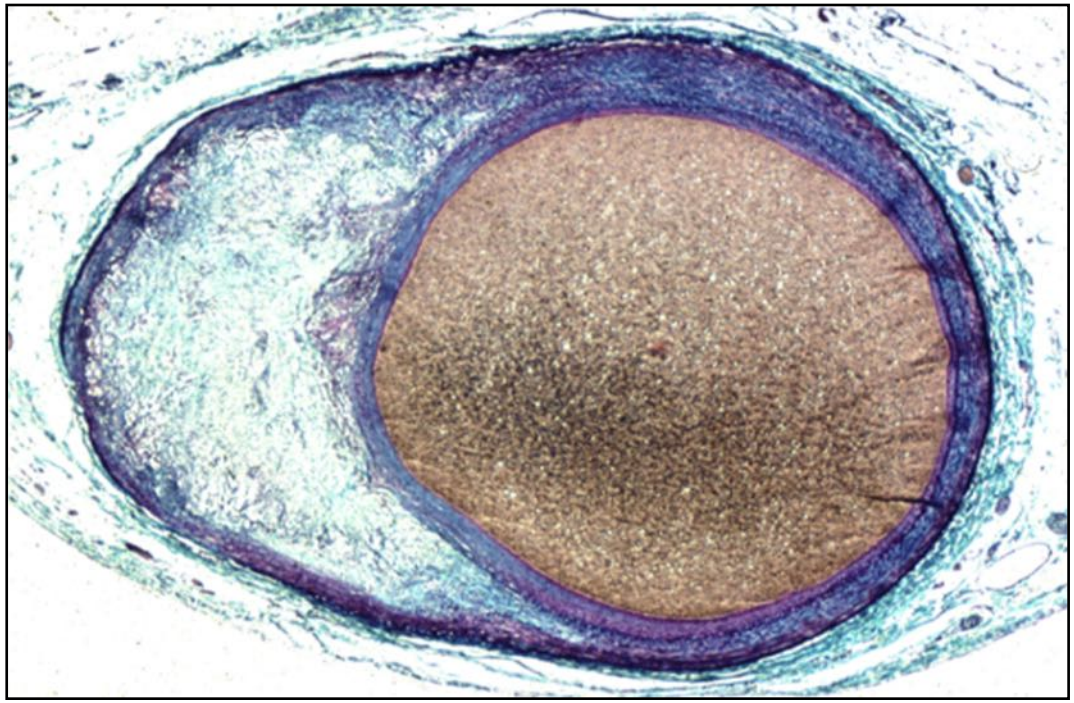
Collectively, the high rates of CV risk factors and direct biological effects of diabetes on the CV system place diabetic patients at increased risk of developing CVD, and contribute to the increased prevalence of MI, revascularization, stroke and CHF.

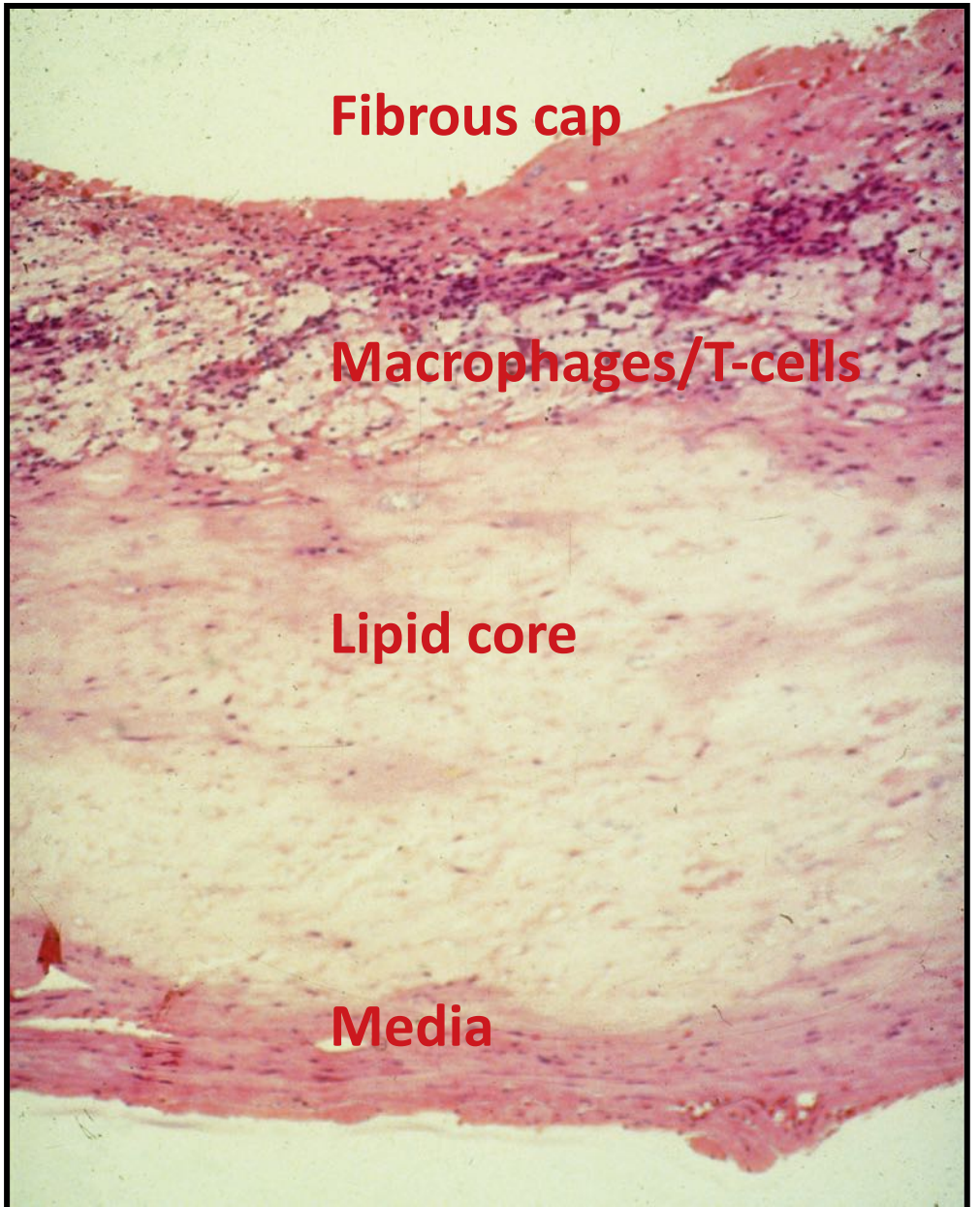
I- Diabetes and vascular complications



Forbes JM et al, Diabetologia, 2017

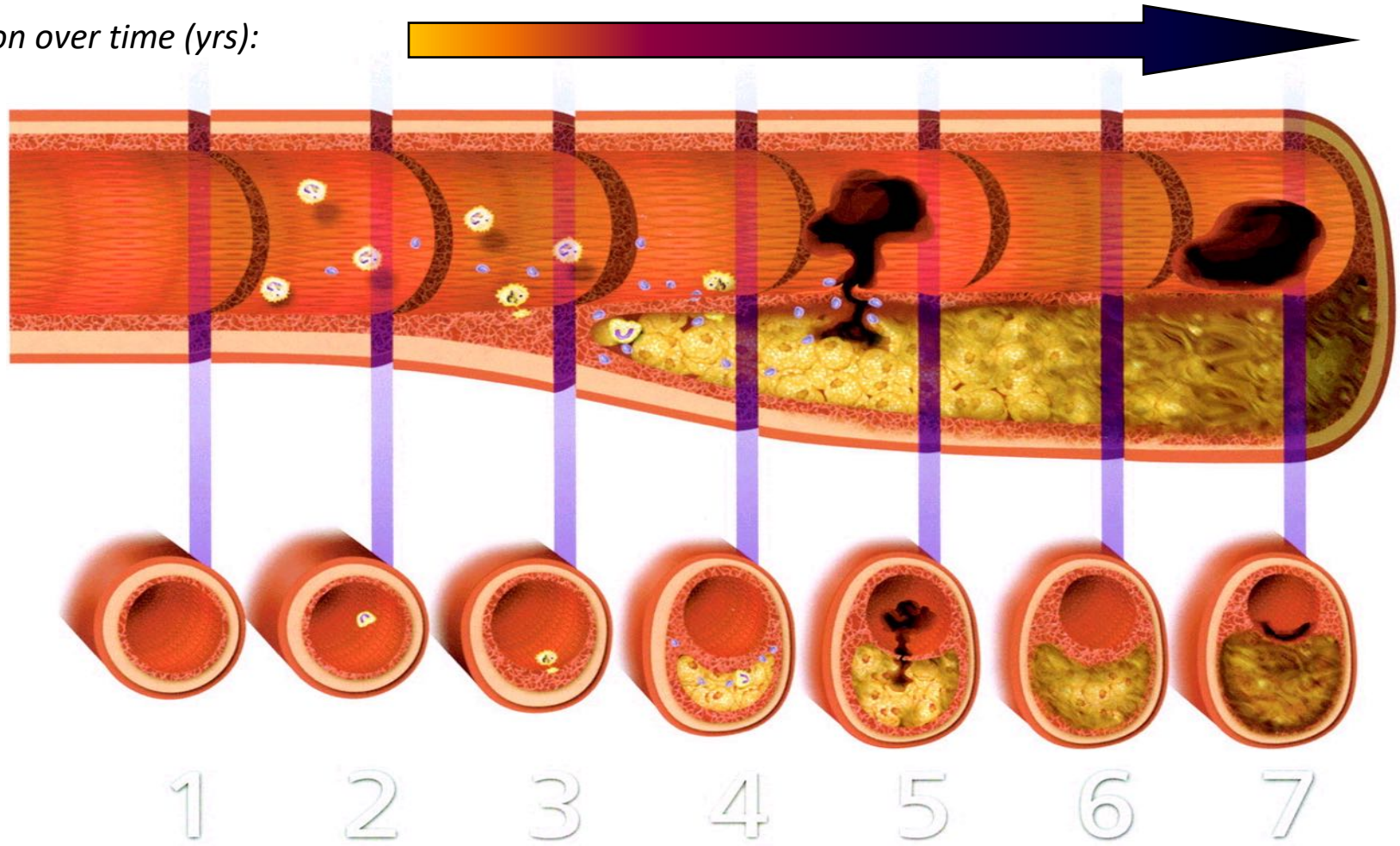
I-a Diabetes and macrocirculation: Atherosclerosis





Atherosclerotic plaque progression

Progression over time (yrs):



1 Normal Artery

2 Lesion Initiation

3 Fibro-fatty Stage

4 ***Vulnerable Plaque***

5 ***Plaque Rupture***

6 Fibrous, Calcified Plaque

7 Endothelial Erosion

Atherosclerotic plaque progression

Foam cells | Fatty streak | Extracellular fatty streak | Lipid core | Atherosclerotic plaque lipid core embedded in fibrosis | Complicated atherosclerotic plaque (plaque rupture, thrombosis, hemorrhage)

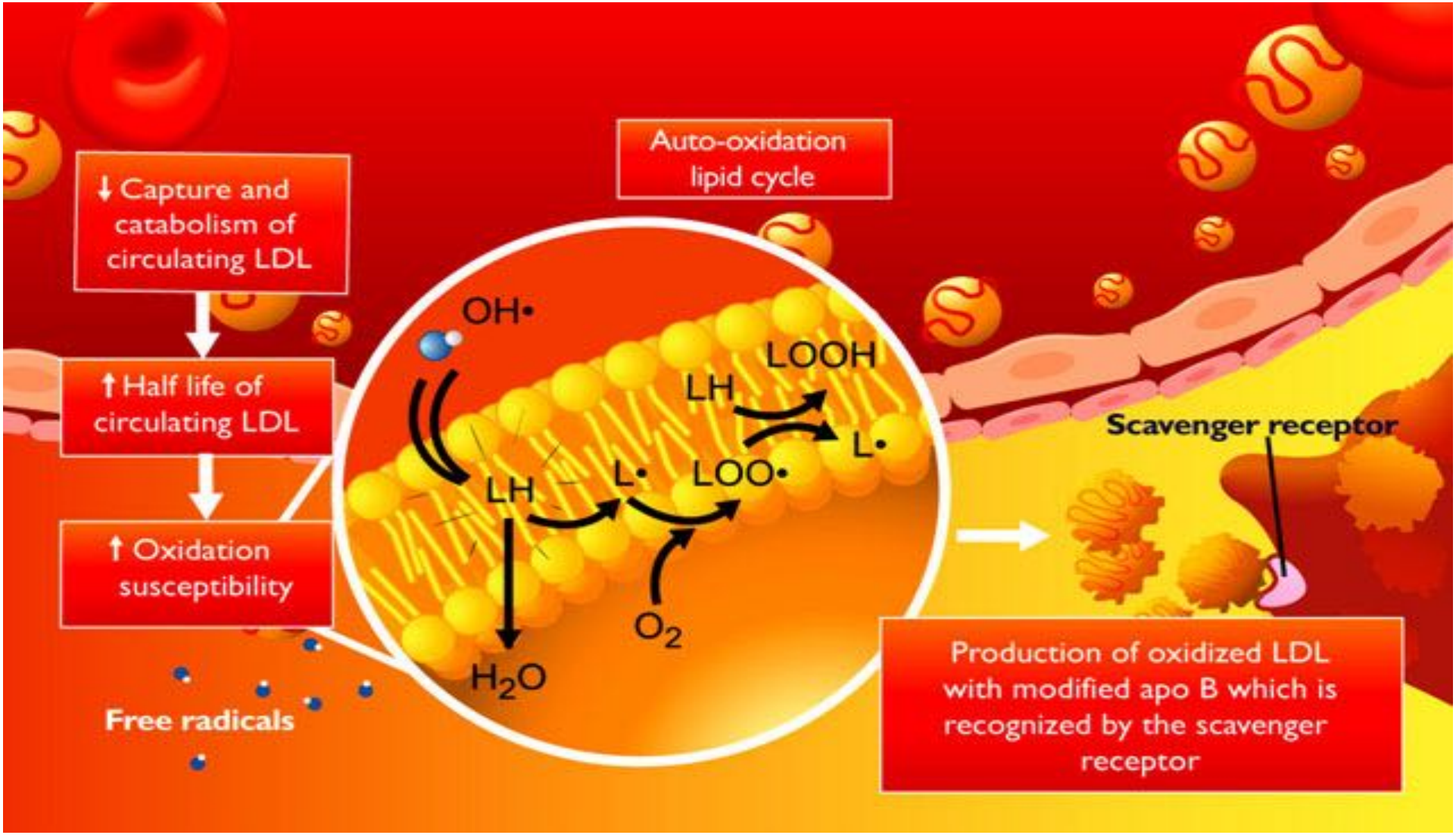
- Intra- and extracellular accumulation of lipids
- Formation of lipid core

Development of fibrosis surrounding lipid core

- Plaque growth
- Atherothrombosis
- Plaque rupture

Asymptomatic — **Eventual clinical events**

Oxidized LDL and foam cell formation

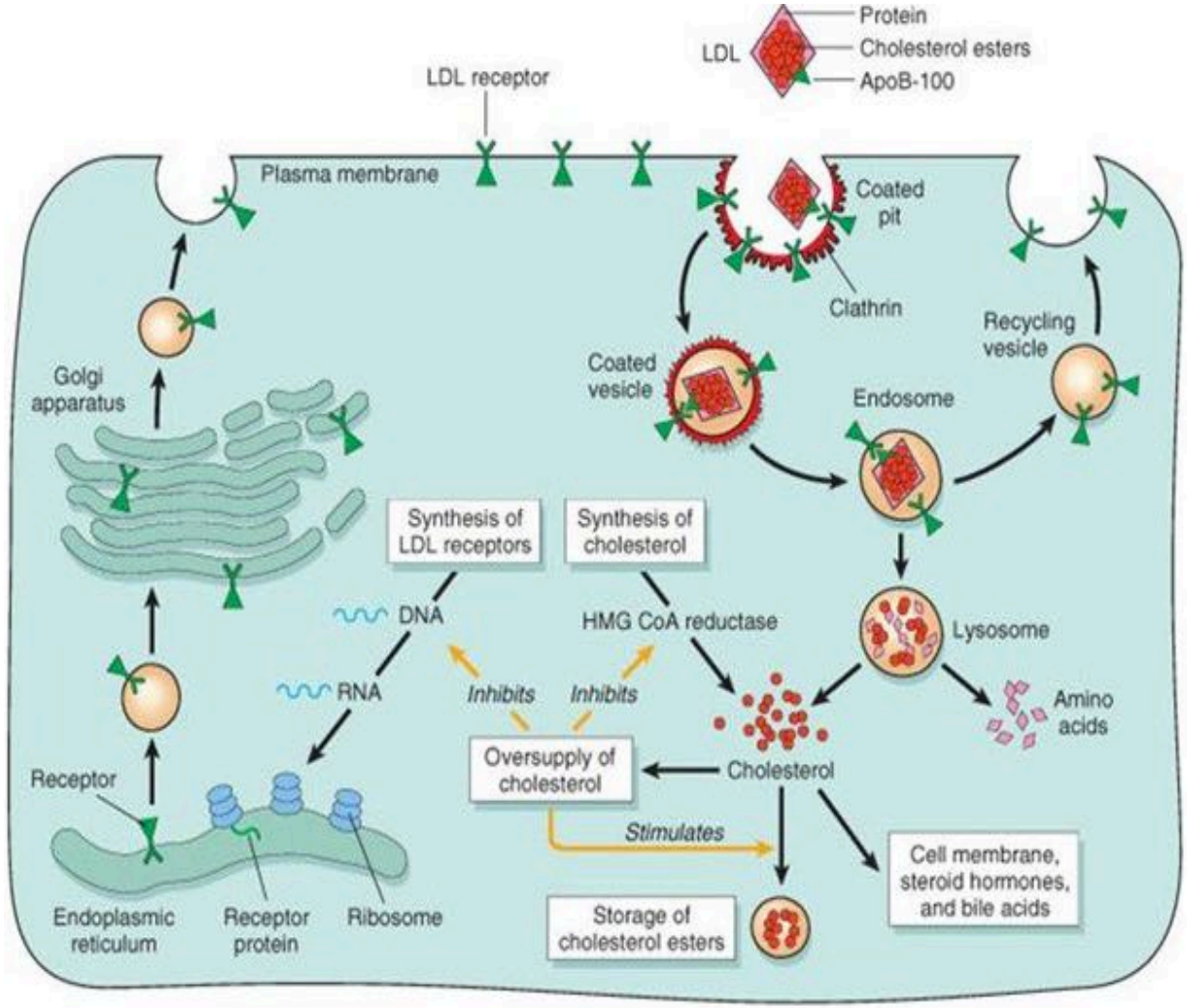


Oxidized LDL and foam cell formation

Oxidation of LDL and transformation of macrophages into foam cells

LDL / R-LDL interaction results in:
-Internalization of LDL, its degradation and its transformation into cholesterol
-Internalization of LDL-R and its recycling to the membrane

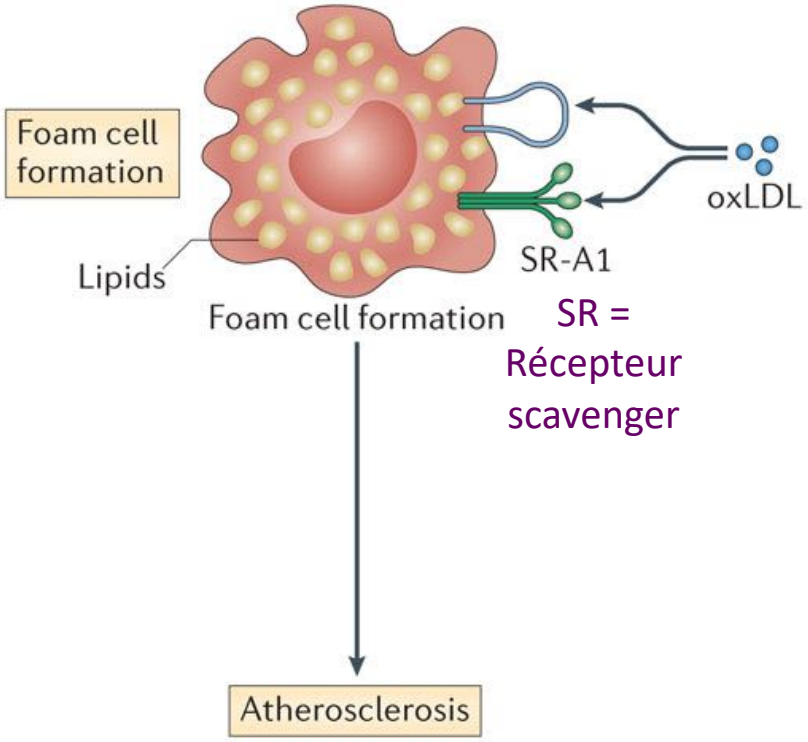
If intracellular cholesterol levels increase, intracellular LDL-R synthesis and cholesterol synthesis stop



Oxidized LDL and foam cell formation

Oxidation of LDL and transformation of macrophages into foam cells

foam cell



SR = Récepteur scavenger

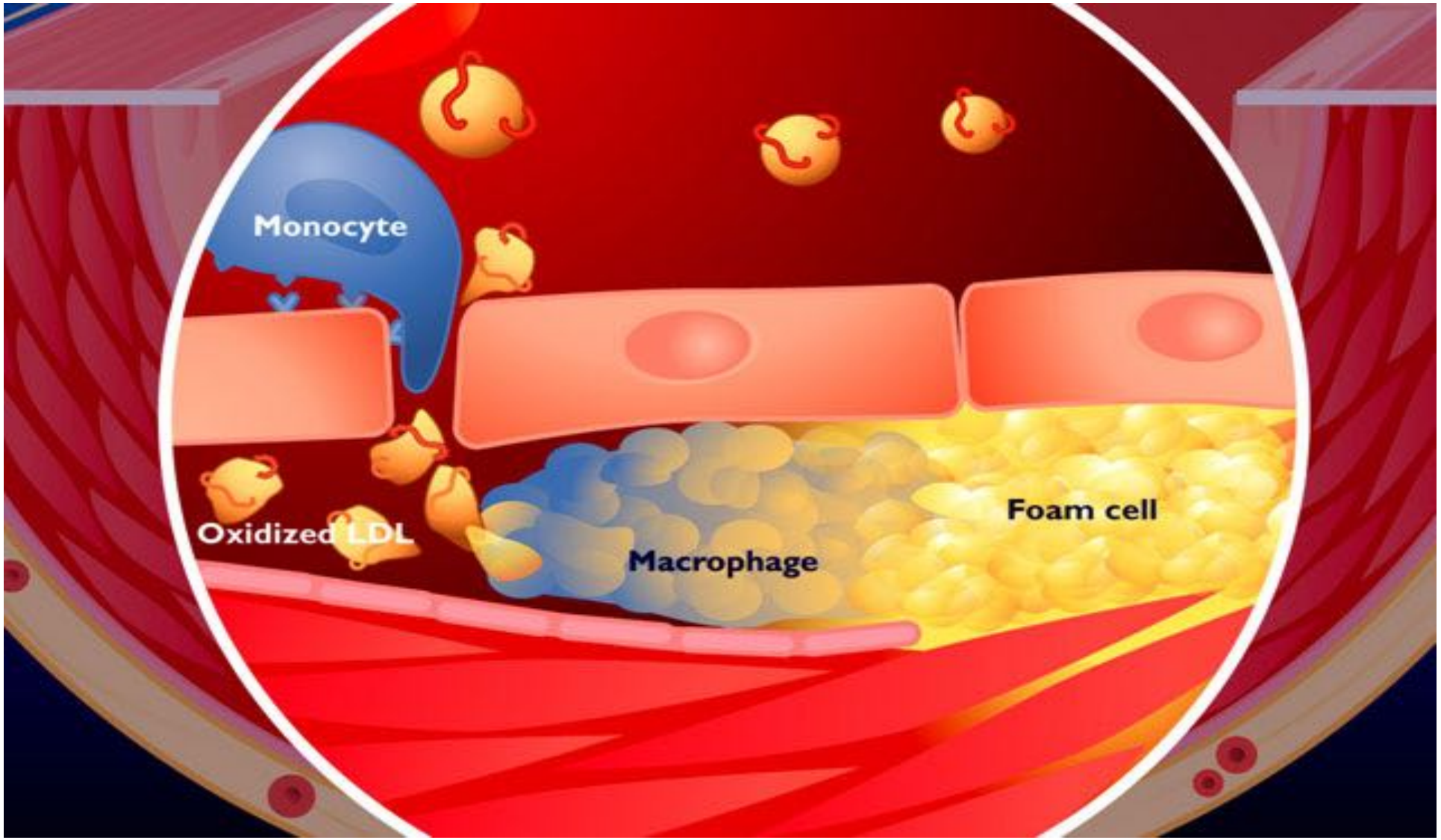
Malondialdehyde
ROS
Smoking

oxLDL are not recognized by LDL-R but by scavenger receptors .

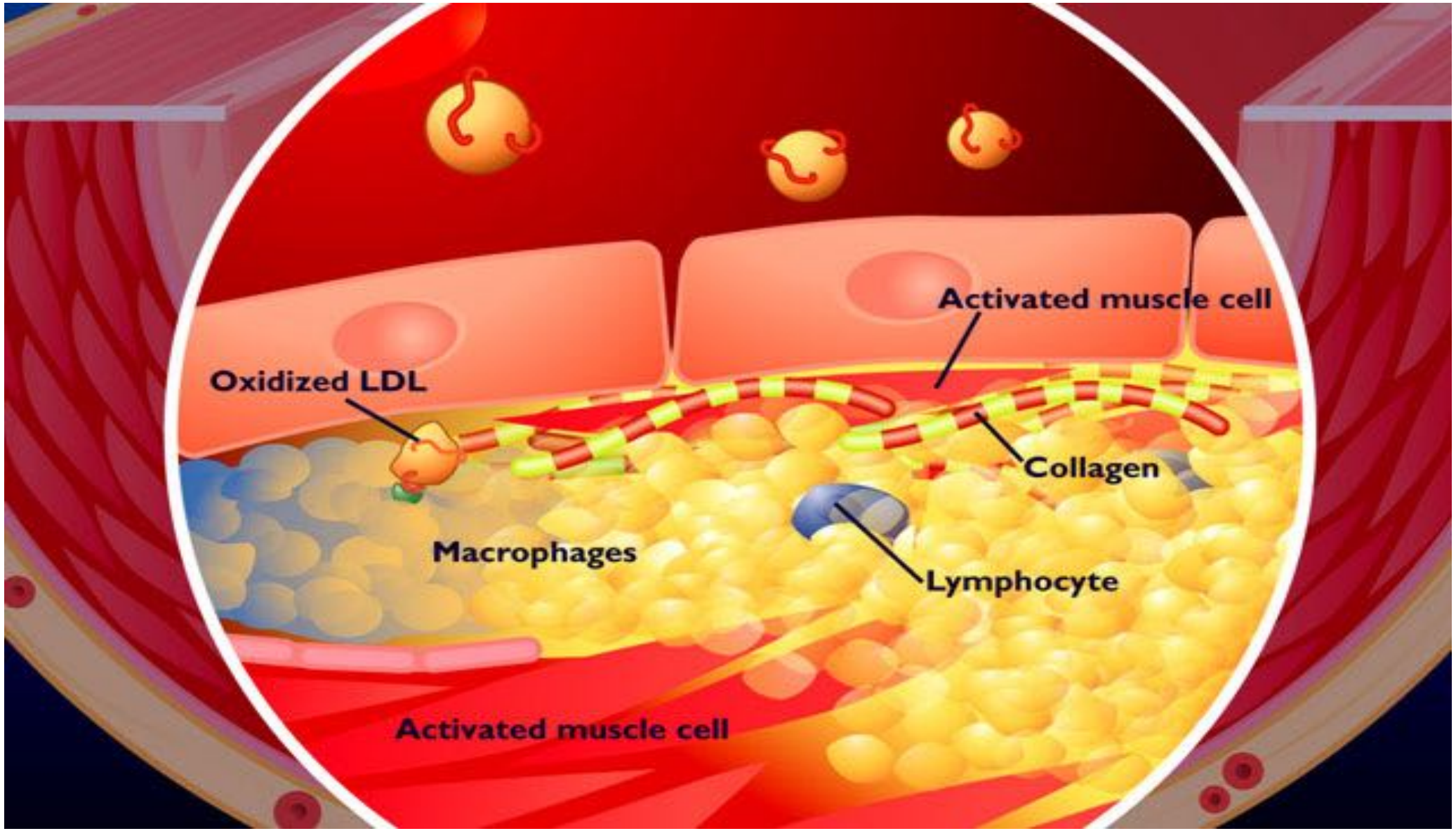
Receptor scavenger (SR-AI, SR-AII, CD36, CD68) are not under the negative control of intracellular [cholesterol]

Very high accumulation of cholesterol in macrophages

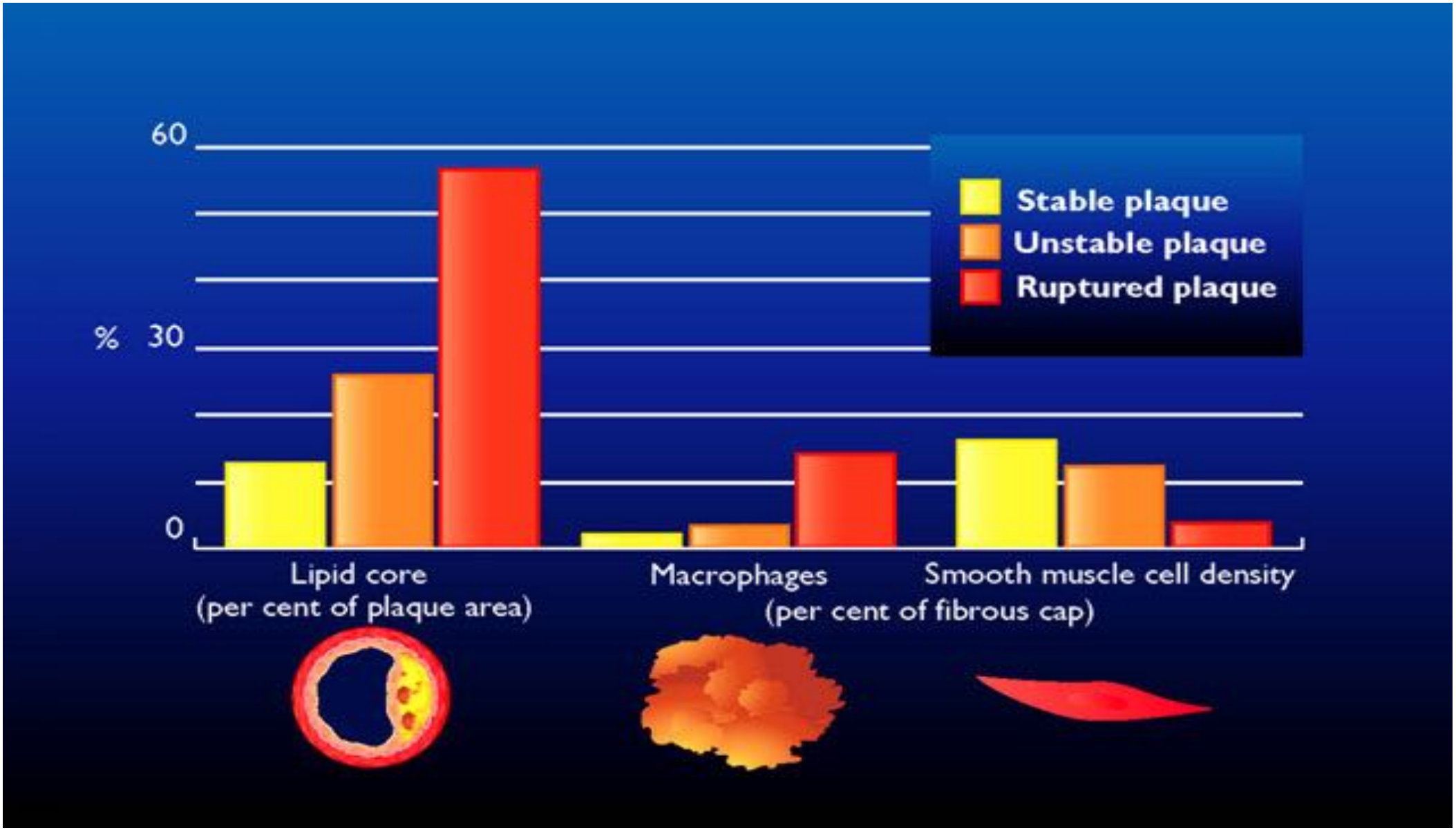
Oxidized LDL and foam cell formation



Lipid core and Fibrous cap

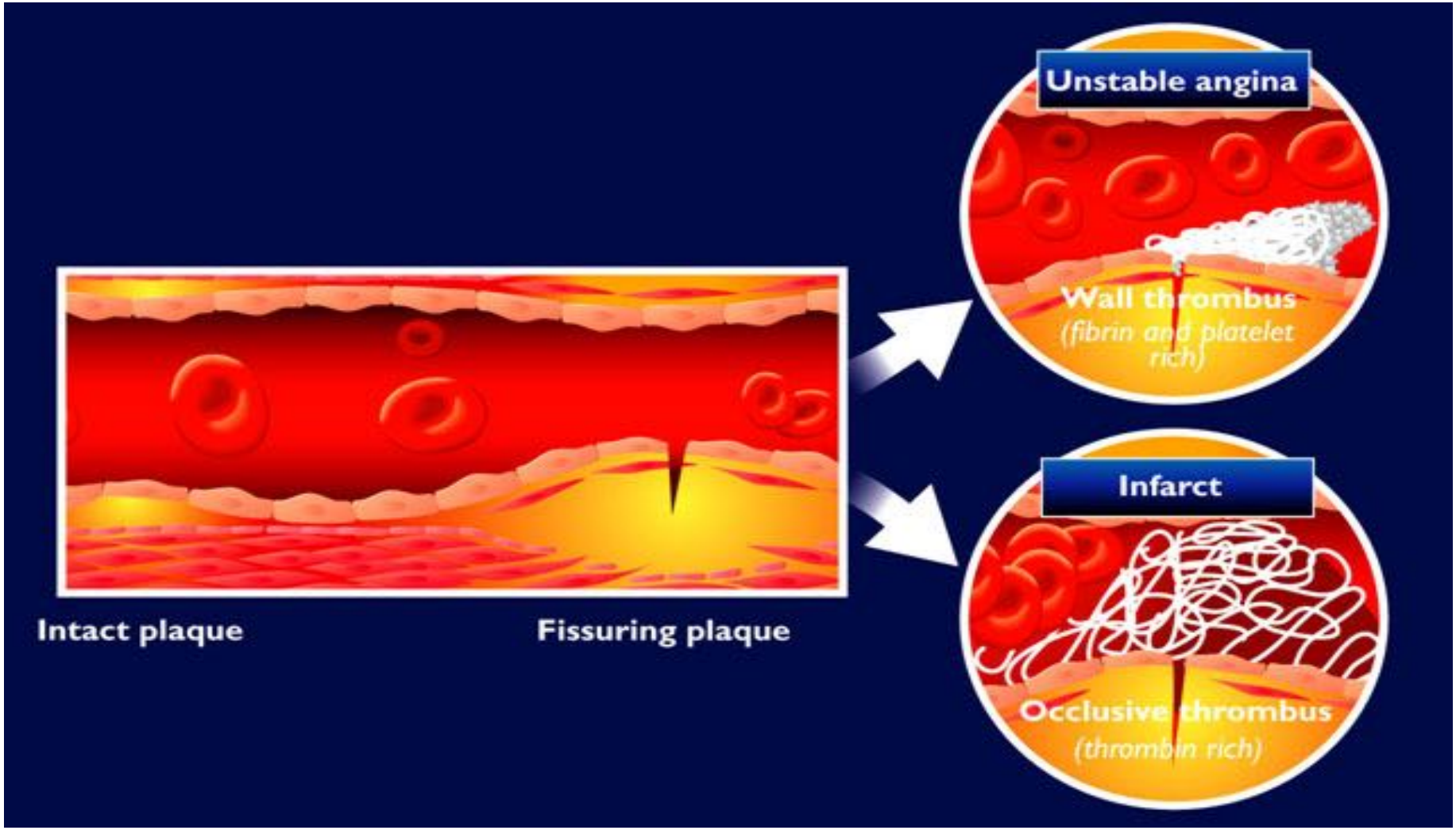


Stable and unstable atherosclerotic plaque



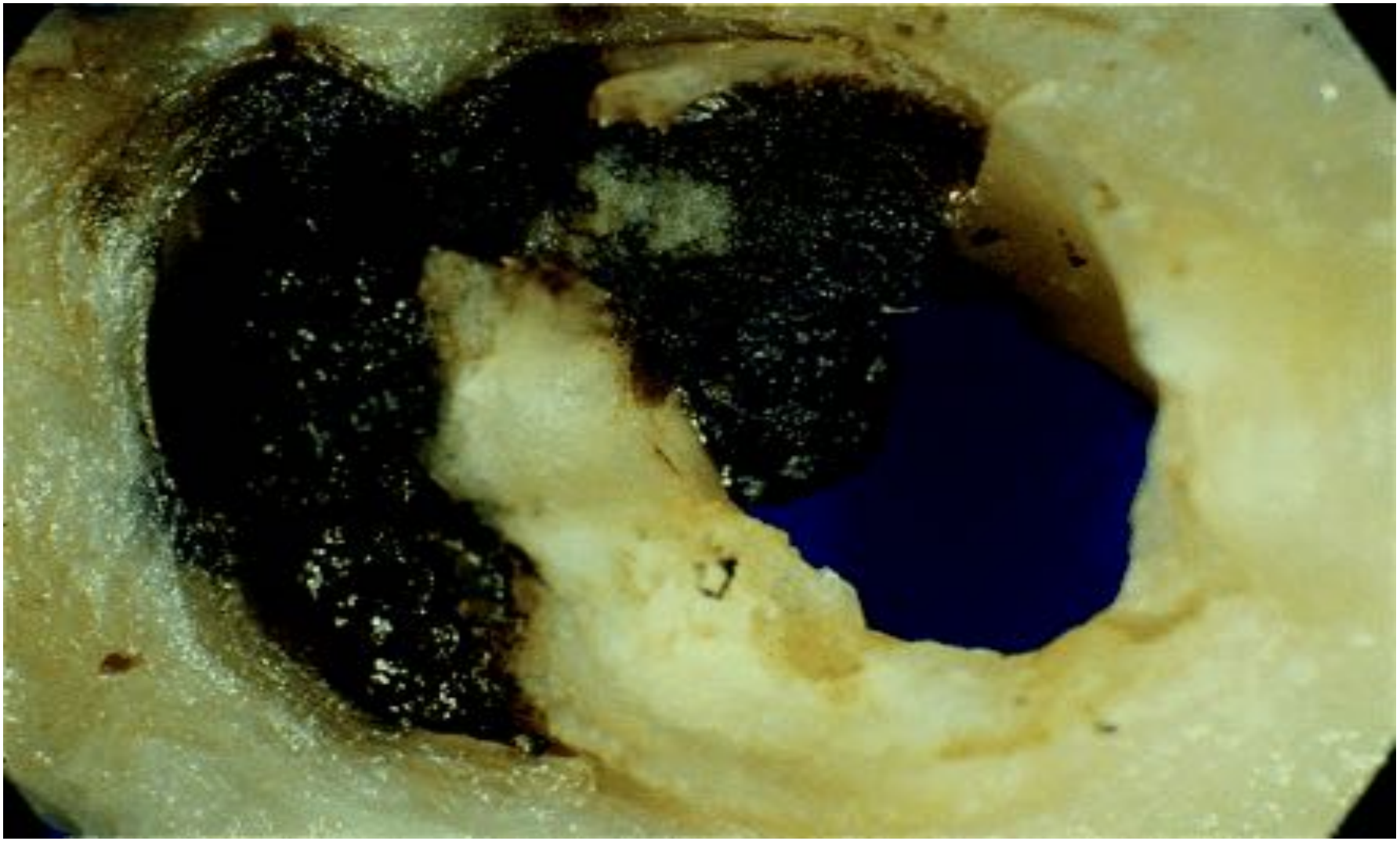
Thromboembolic complications of atherosclerotic plaque rupture

Main clinical manifestations: acute coronary syndromes (myocardial infarction, unstable angina, sudden death), stroke and acute ischemia of the lower limbs



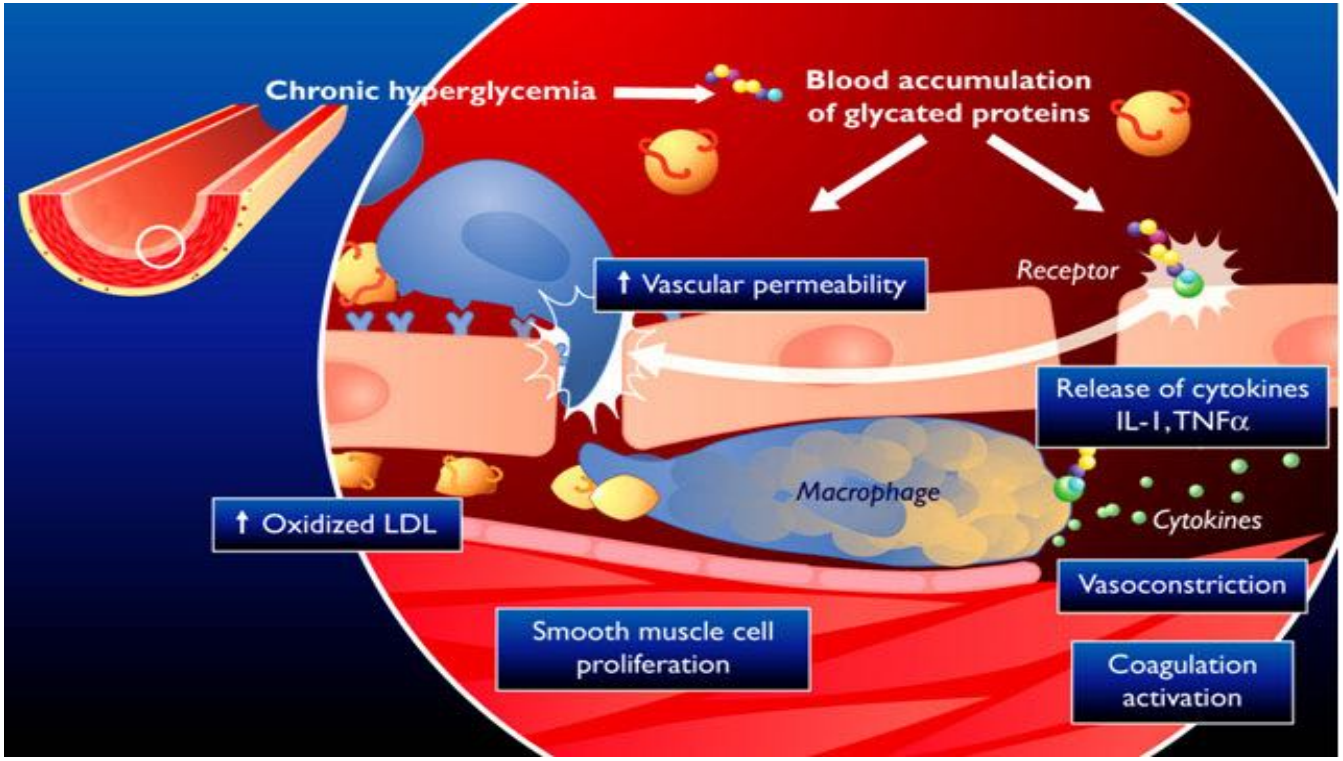
Thromboembolic complications of atherosclerotic plaque rupture

Formation of a thrombus with total or partial obstruction and appearance of clinical symptoms



Atherosclerotic plaque development

Diabetes and atherosclerosis



√ Blood flow abnormalities : eNOS dysfunction

√ Vascular permeability: VEGF

√ Capillary occlusion: Reduction in fibrinolysis

√ Inflammation

√ Reactive oxygen species overproduction

√ Advanced glycation end-products

Diabetes and atherosclerosis

Diabetes was associated with a greater atherosclerotic burden and impaired compensatory remodeling of the artery wall. Furthermore, atheroma progression, despite the high use of established medical therapies, was more rapid in patients with diabetes. This highlights the important mechanistic links that underscore the aggressive nature of atherosclerotic cardiovascular disease in patients with diabetes.

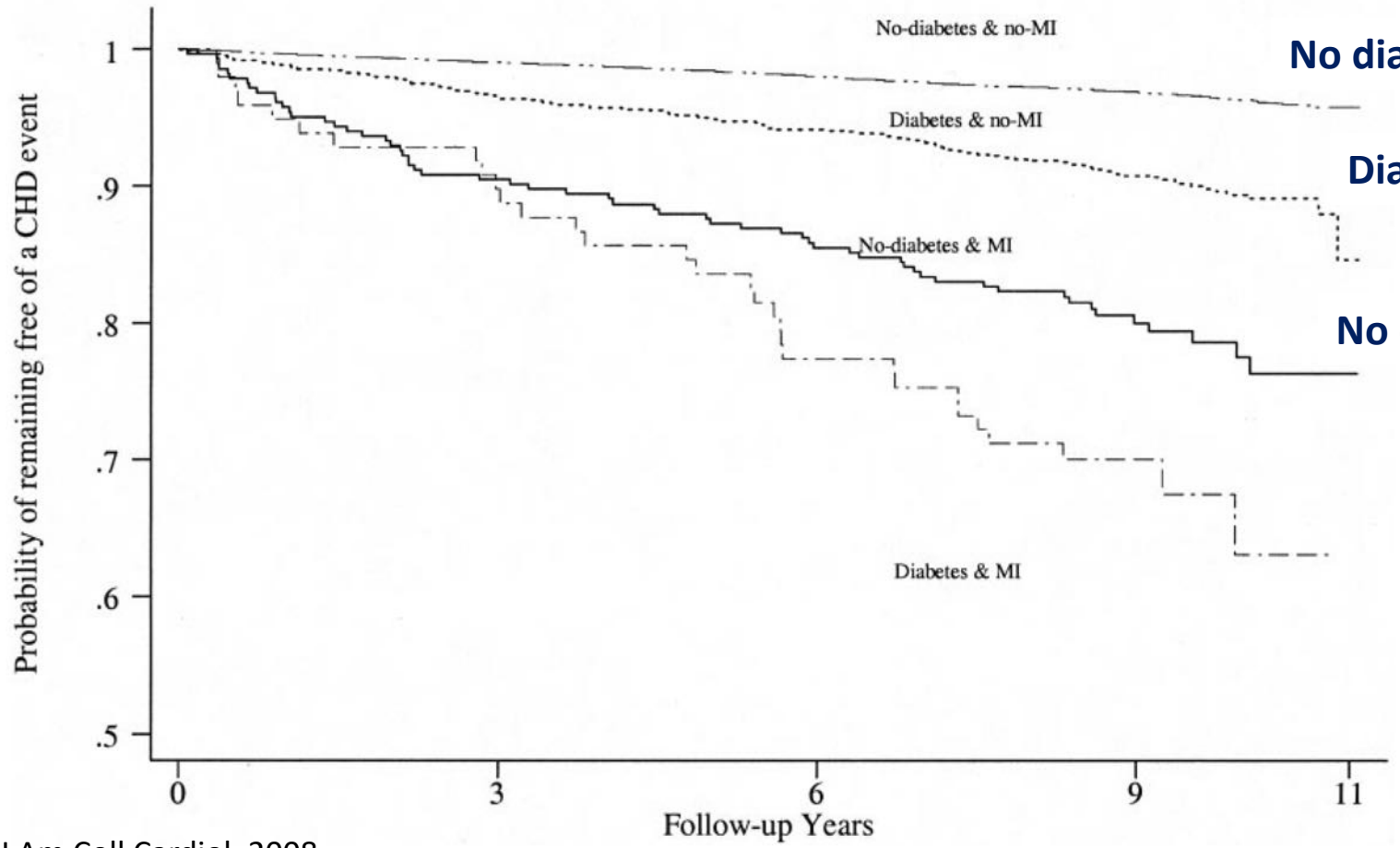
Parameter	Nondiabetic Patients (n = 1,821)	Diabetic Patients (n = 416)	p Value
Percent atheroma volume	38.1 ± 9.3	40.7 ± 9.9	<0.001
Adjusted percent atheroma volume*	37.5 ± 0.8	40.2 ± 0.9	<0.0001
Total atheroma volume (mm^3)*	192.3 ± 84.1	203.8 ± 90.4	0.03
Adjusted total atheroma volume (mm^3)	189.4 ± 7.1	199.4 ± 7.9	0.03
Atheroma volume most diseased 10-mm segment (mm^3)	62.3 ± 28.8	65.4 ± 30.6	0.06
Atheroma volume least diseased 10-mm segment (mm^3)	43.0 ± 25.9	45.4 ± 27.1	0.12
Percentage of images containing plaque	73.8 ± 27.5	76.0 ± 27.7	0.15
External elastic membrane volume (mm^3)	498.8 ± 167.2	494.9 ± 166.9	0.61
Lumen volume (mm^3)	306.5 ± 108.2	291.1 ± 104.8	0.005

Nicholls SJ et al, J Am Coll Cardiol, 2008

Diabetes and atherosclerosis

√ Diabetic patients with MI had higher risk of CHD events and mortality from CVD over 11 years compared with nondiabetic patients with MI.

√ Diabetic patients without MI had lower risk of CHD events and mortality from CVD over 11 years compared with nondiabetic patients with MI.



No diabetes & no MI

Diabetes & no MI

No diabetes & MI

Diabetes & MI

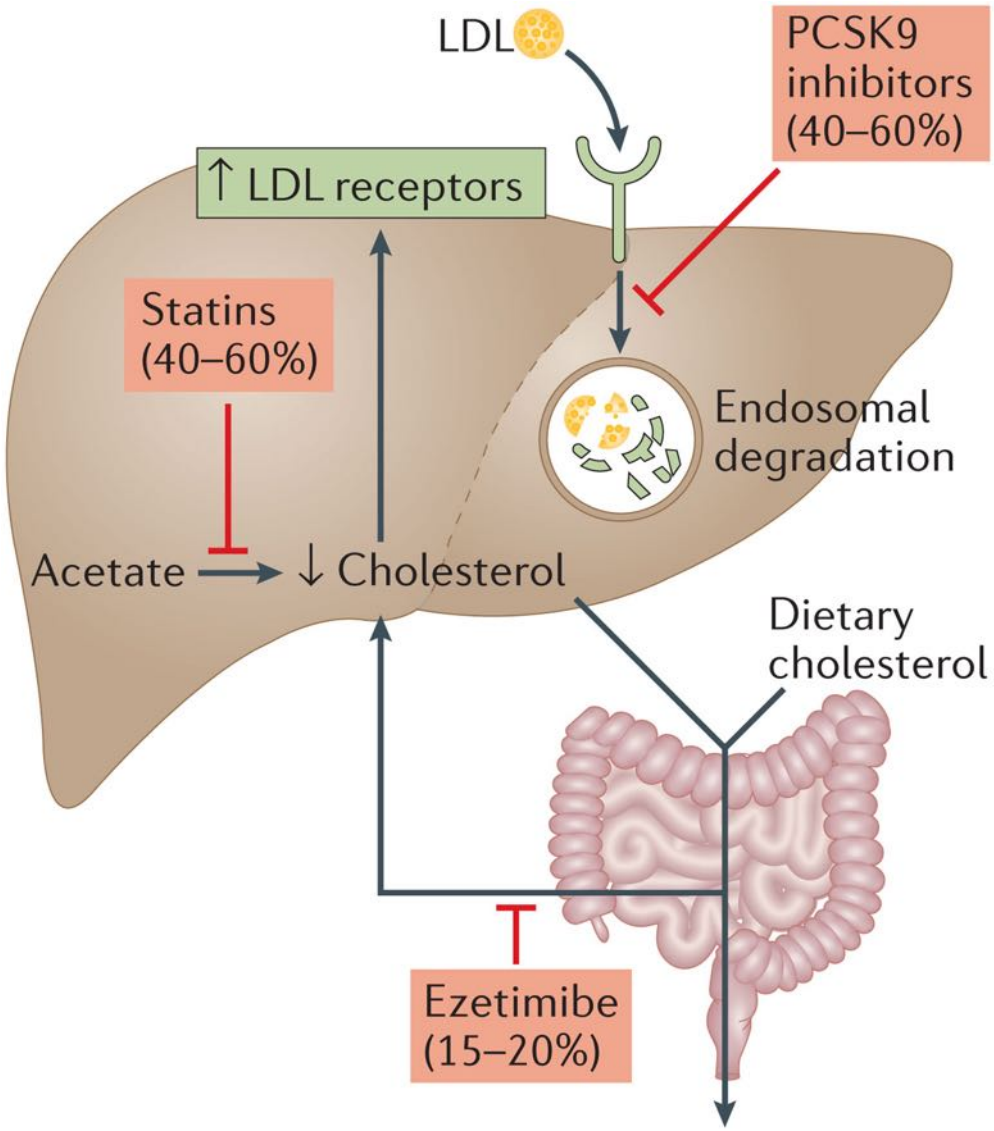
Nicholls SJ et al, J Am Coll Cardiol, 2008

Therapeutic strategies targeting atherosclerosis

Treatment strategy for dyslipidemia

Statins, ezetimibe, et PCSK9 inhibitors increase R-LDL expression and reduce intracellular LDL-cholesterol:

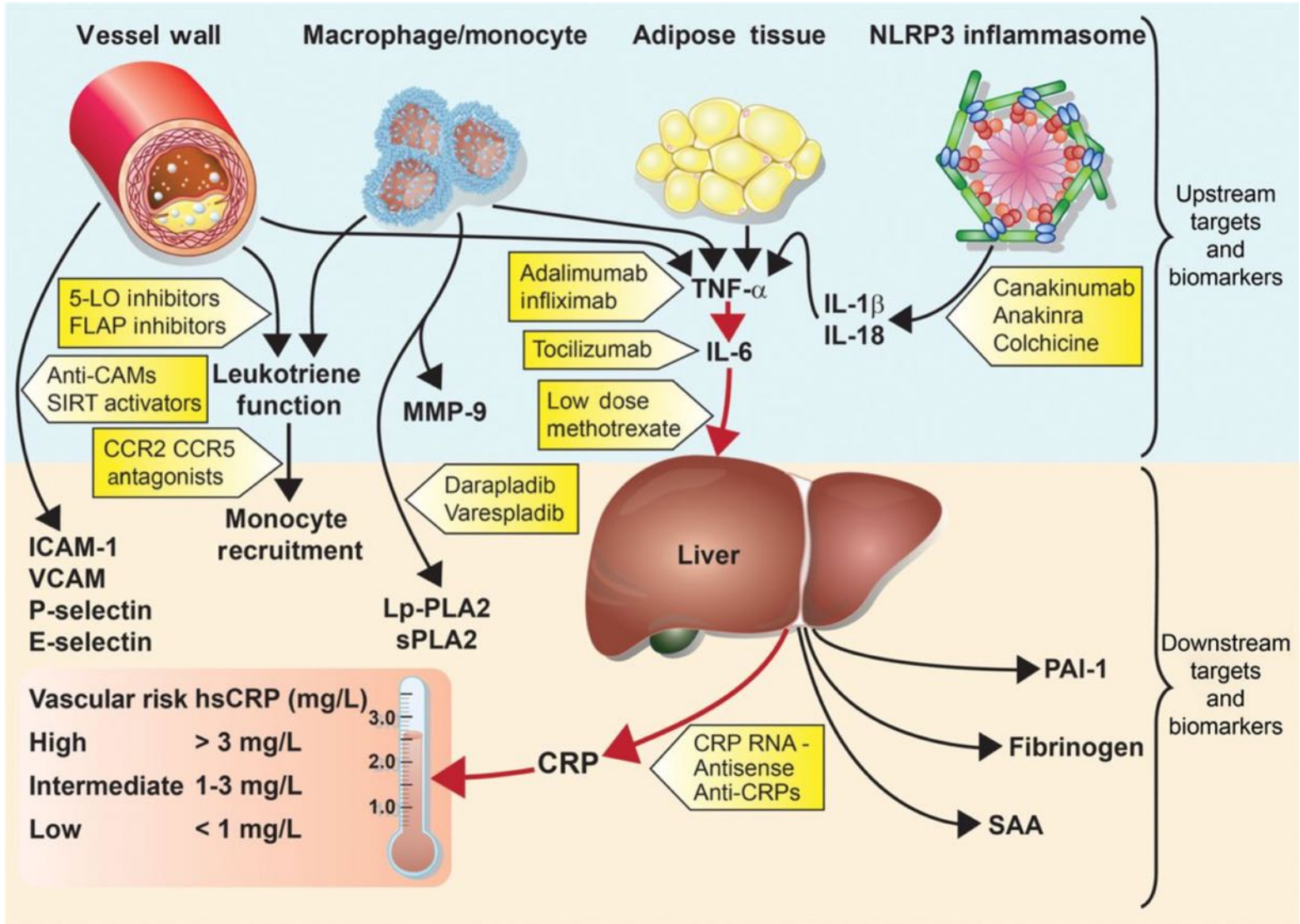
- Statins inhibit cholesterol synthesis in the liver
- Ezetimibe inhibits intestinal cholesterol uptake
- PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9) abrogate R-LDL degradation



Grundy,SM et al, Nat. Rev. Cardiol., 2016

Therapeutic strategies targeting atherosclerosis

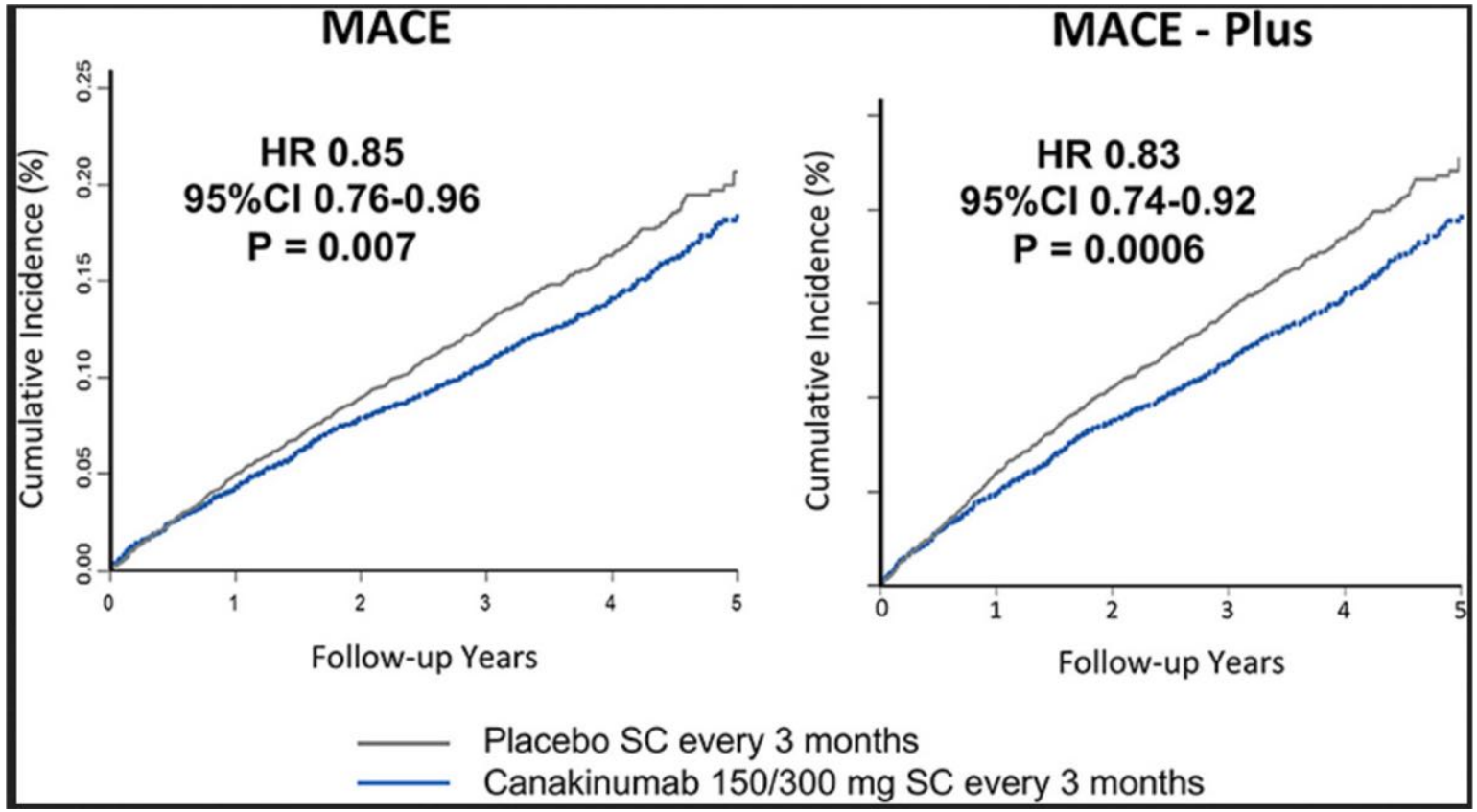
Anti-inflammatory treatment



Ridker P et al, Eur Heart J, 2014

Antiinflammatory therapy in clinical care: The CANTOS trial

CANTOS was a randomized, double-blind, placebo-controlled trial of canakinumab in 10,061 patients with a history of MI and hsCRP ≥ 2 mg/L; such patients with "residual inflammatory risk" rather than "residual cholesterol risk" are a common and very high risk group

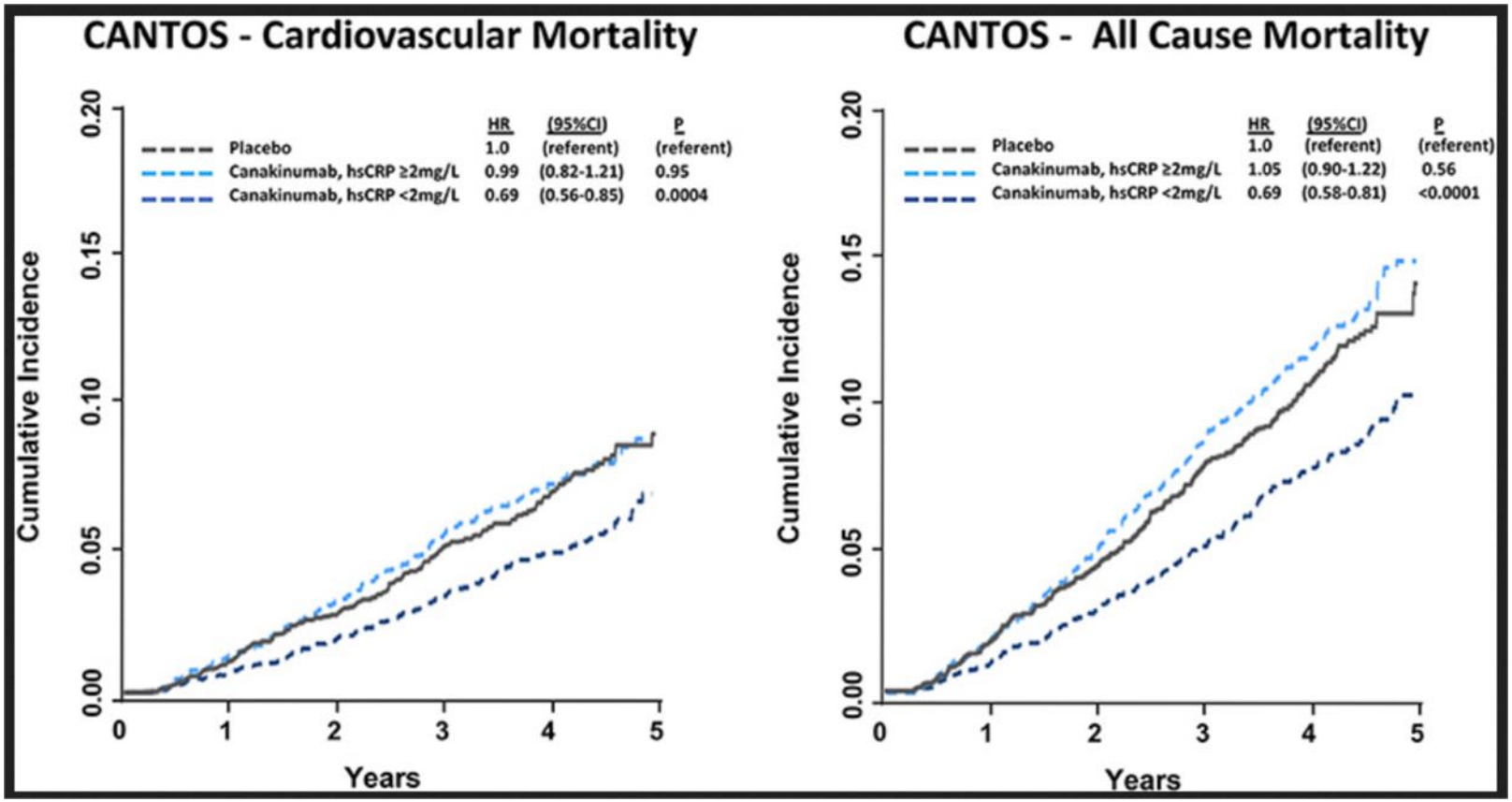


Primary endpoint of myocardial infarction, stroke, or cardiovascular death (MACE).

Secondary endpoint additional including hospitalization for unstable angina requiring urgent revascularization

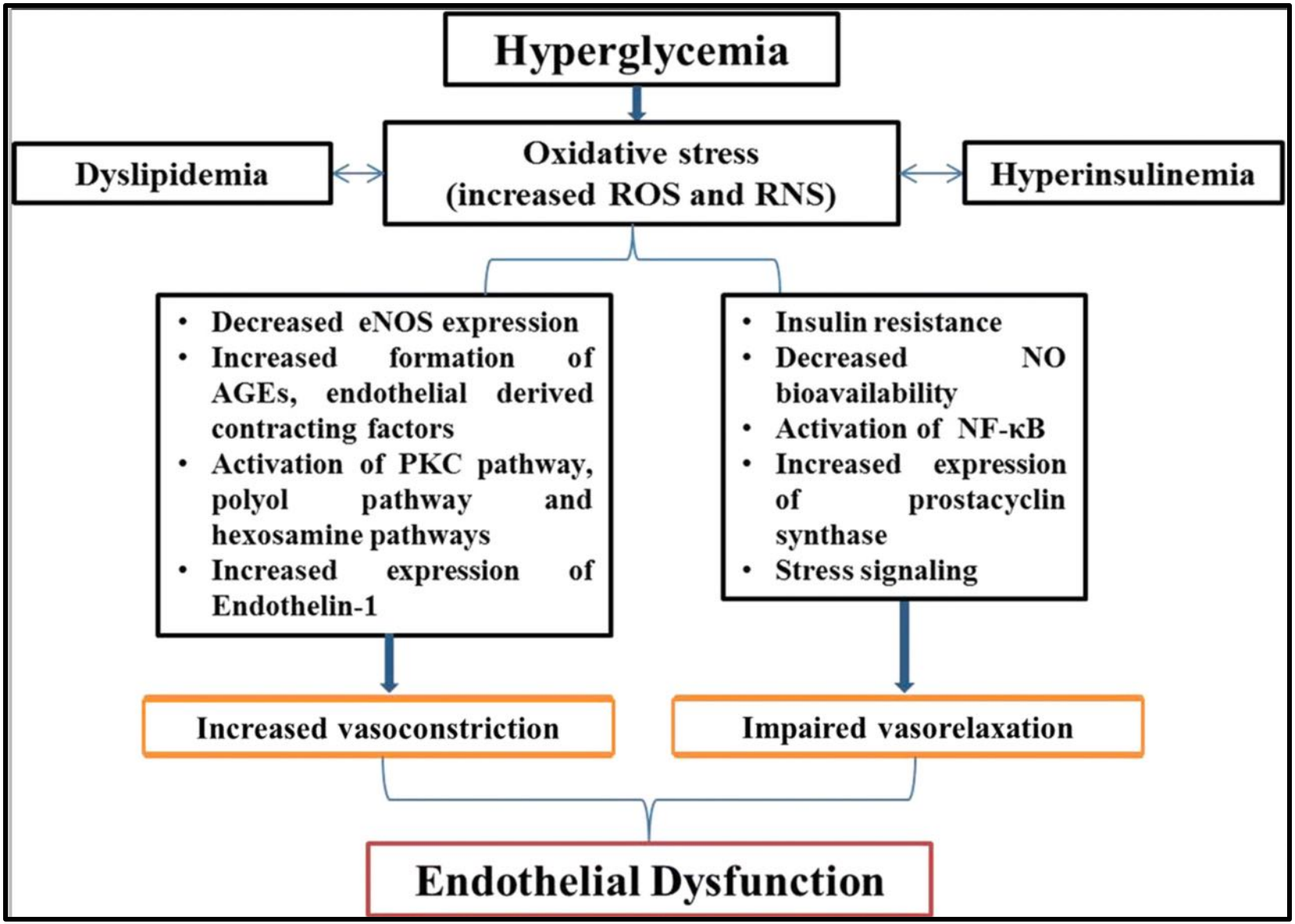
Antiinflammatory therapy in clinical care: The CANTOS trial

Cumulative incidence and hazard ratios of cardiovascular mortality and all-cause mortality among CANTOS participants allocated to either placebo or canakinumab according to whether post-randomization on-treatment hsCRP levels were above or below 2 mg/L. Hazard ratios are adjusted for age, sex, smoking status, hypertension, diabetes, body mass index, baseline concentration of hsCRP, and baseline concentration of LDL-C.



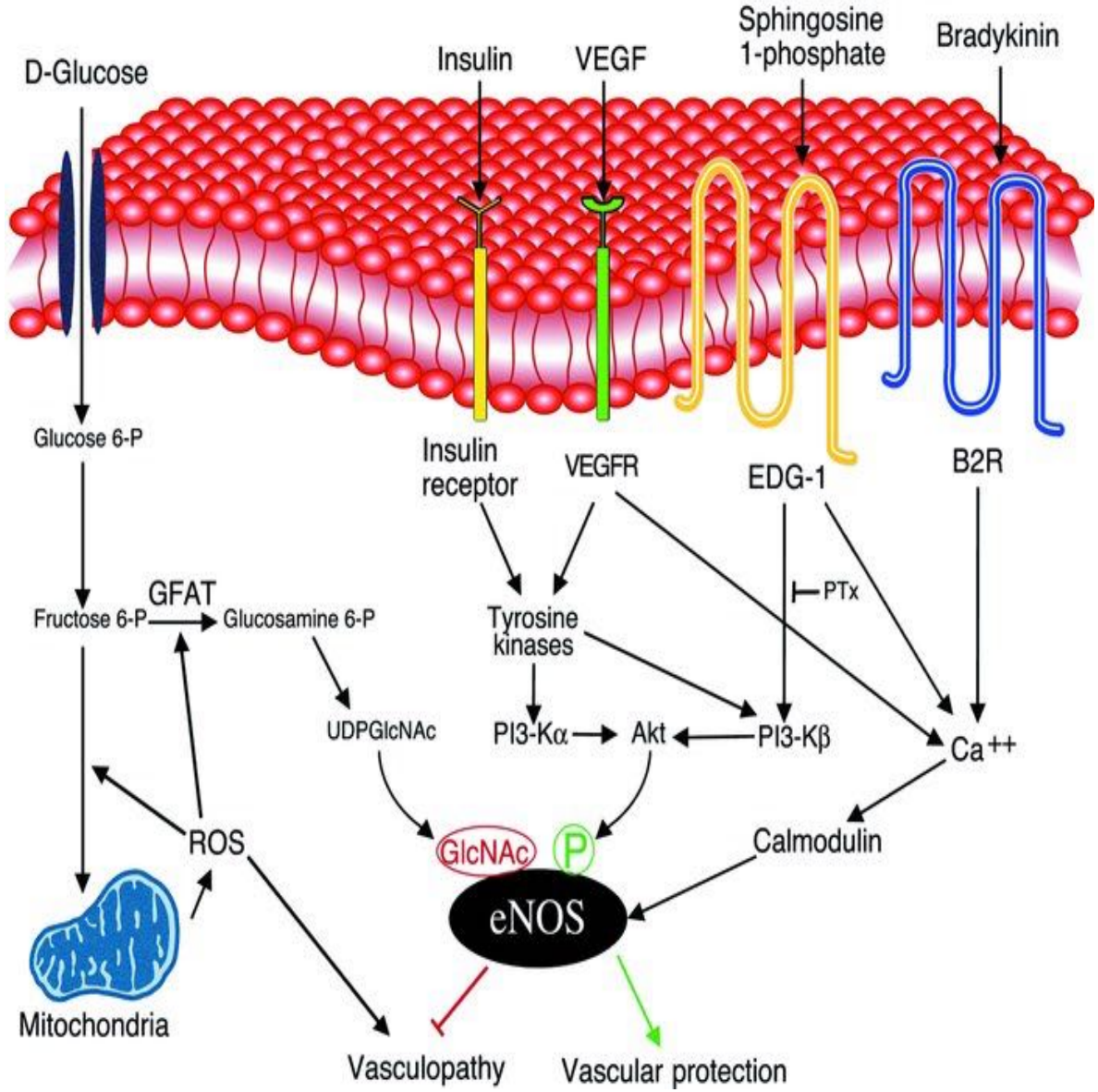
Ridker PM et al, N Engl J Med, 2017

II-b Diabetes and microcirculation



Diabetes and endothelial dysfunction: Glucotoxicity

High-glucose treatment of endothelial cells is suggested to lead to the augmentation of ROS from mitochondria, leading to the activation of the glucosamine pathway by the activation of glutamine:fructose-6-phosphate amidotransferase (GFAT, the key enzyme in this pathway), ultimately increasing eNOS O-glycosylation. Basal levels of eNOS phosphorylation (green) at serine 1179 may be reciprocally attenuated by eNOS O-glycosylation with N-acetylglucosamine (GlcNAc; red).



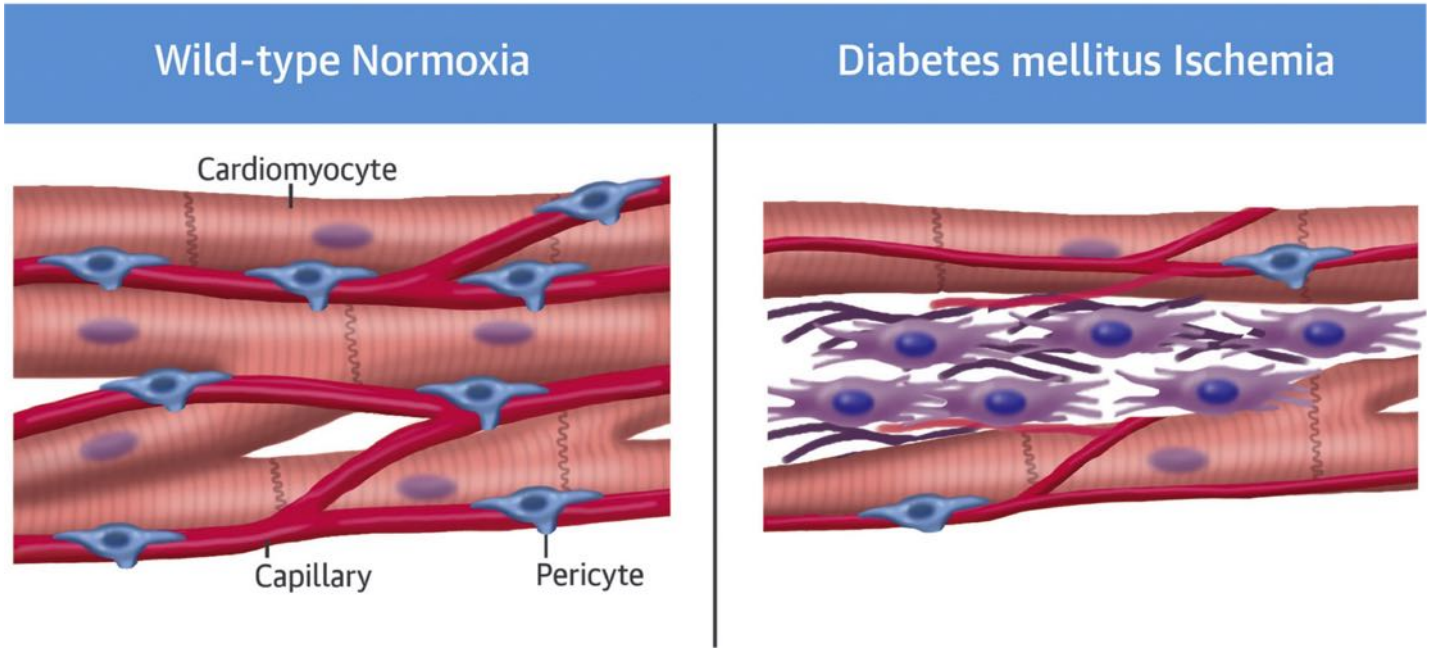
Diabetes and capillary rarefaction

√ Microvascular disorganization

√ Alteration of key pro-angiogenic pathways

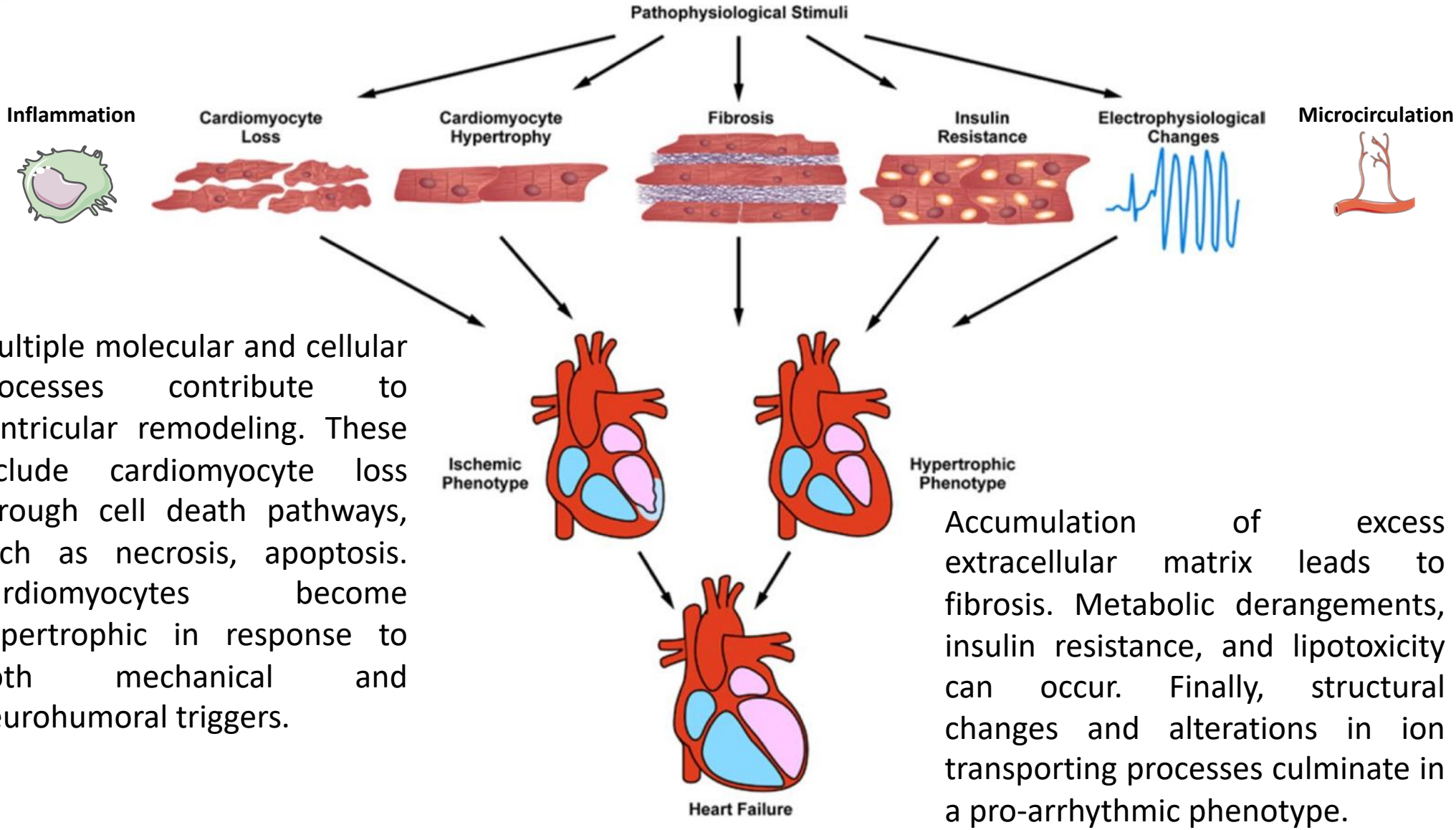
√ Increase in capillary permeability

√ Cell death



Howangyin K & Silvestre JS, Arterioscler Thromb Vasc Biol, 2014
Hinkel R et al, J Am Coll Cardiol, 2017

III- Diabetes and cardiomyopathy

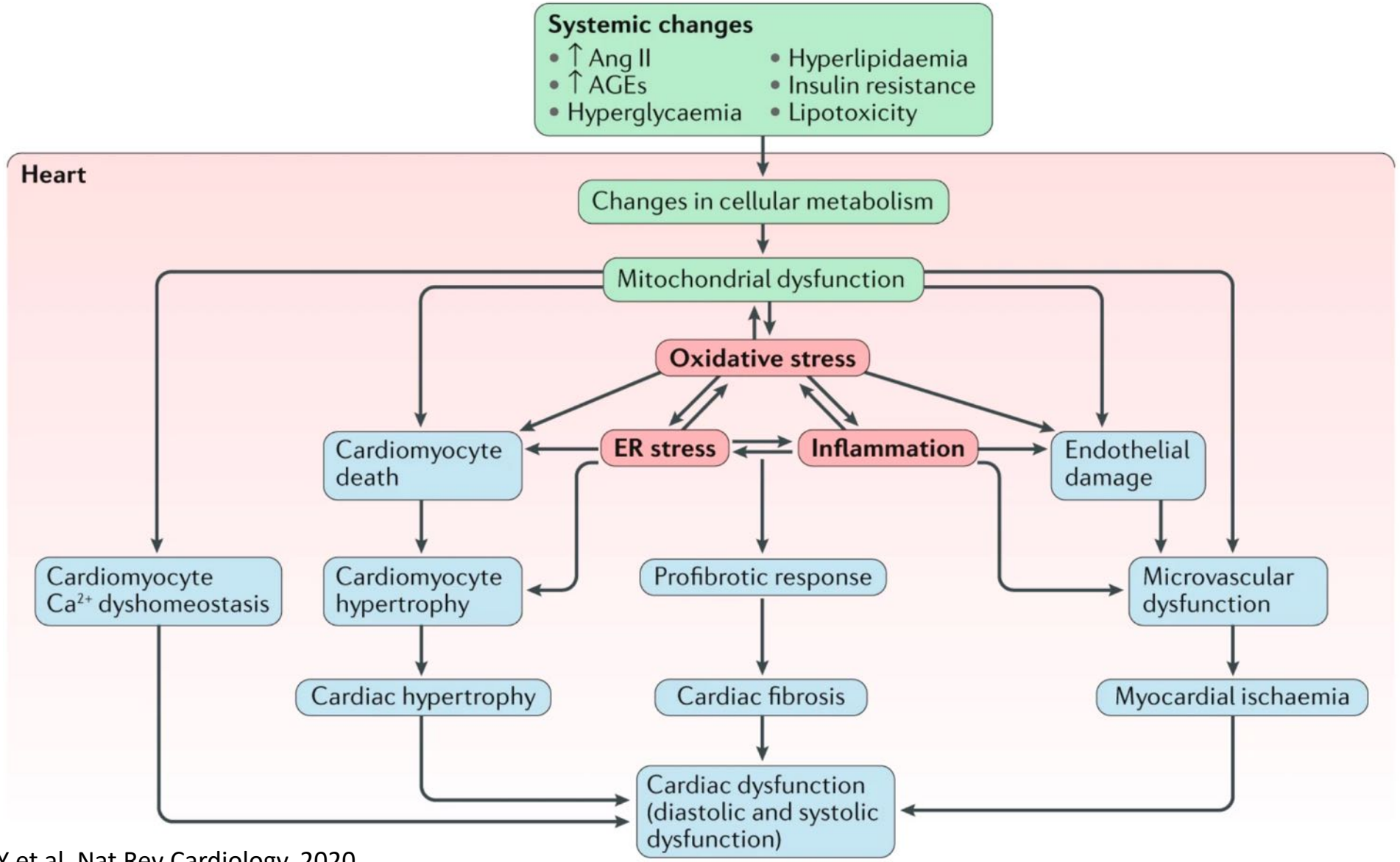


Multiple molecular and cellular processes contribute to ventricular remodeling. These include cardiomyocyte loss through cell death pathways, such as necrosis, apoptosis. Cardiomyocytes become hypertrophic in response to both mechanical and neurohumoral triggers.

Accumulation of excess extracellular matrix leads to fibrosis. Metabolic derangements, insulin resistance, and lipotoxicity can occur. Finally, structural changes and alterations in ion transporting processes culminate in a pro-arrhythmic phenotype.

Adapted from Burchfield JS et al, Circulation, 2013

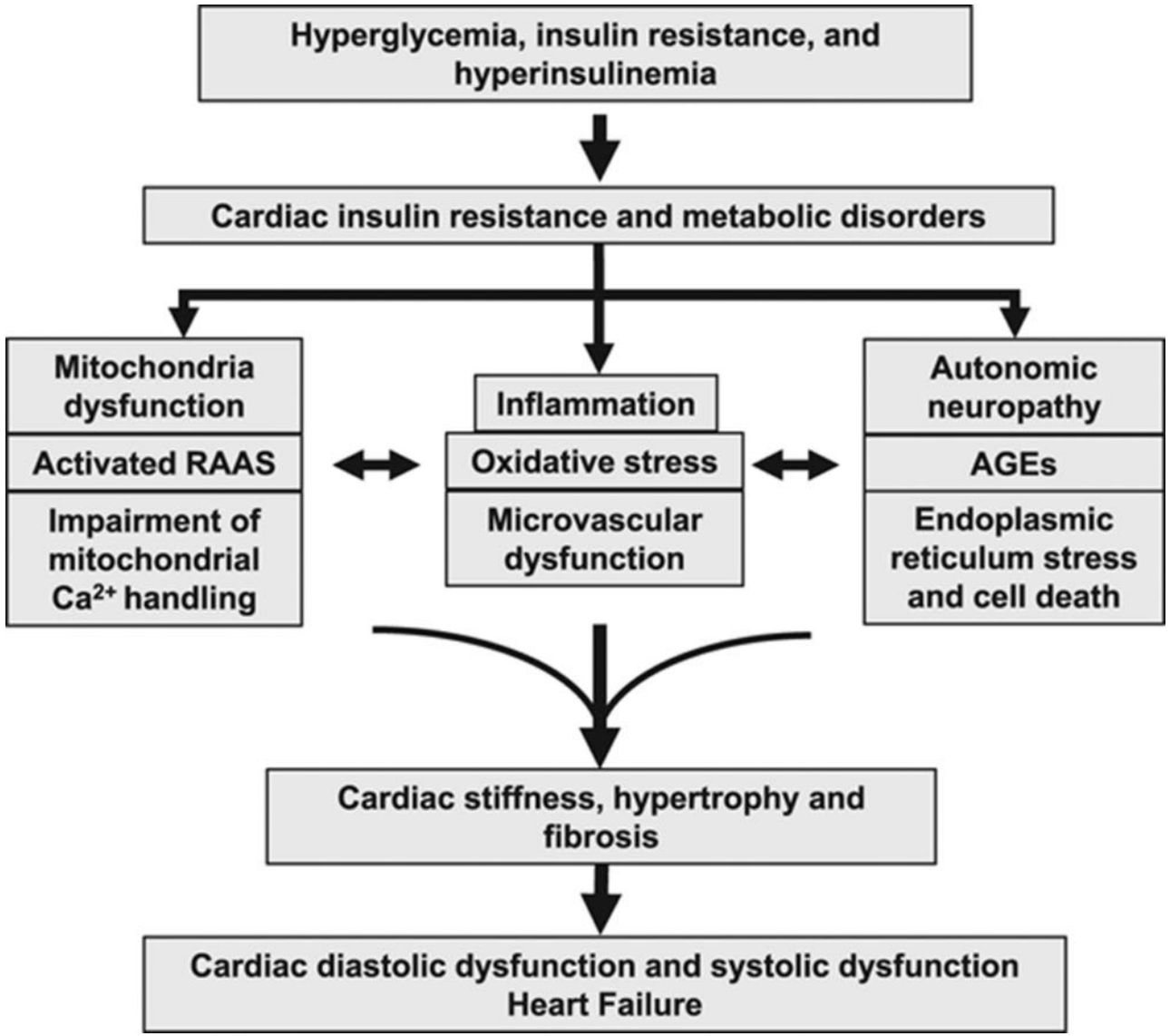
Mechanisms of diabetic cardiomyopathy



Tan Y et al, Nat Rev Cardiology, 2020

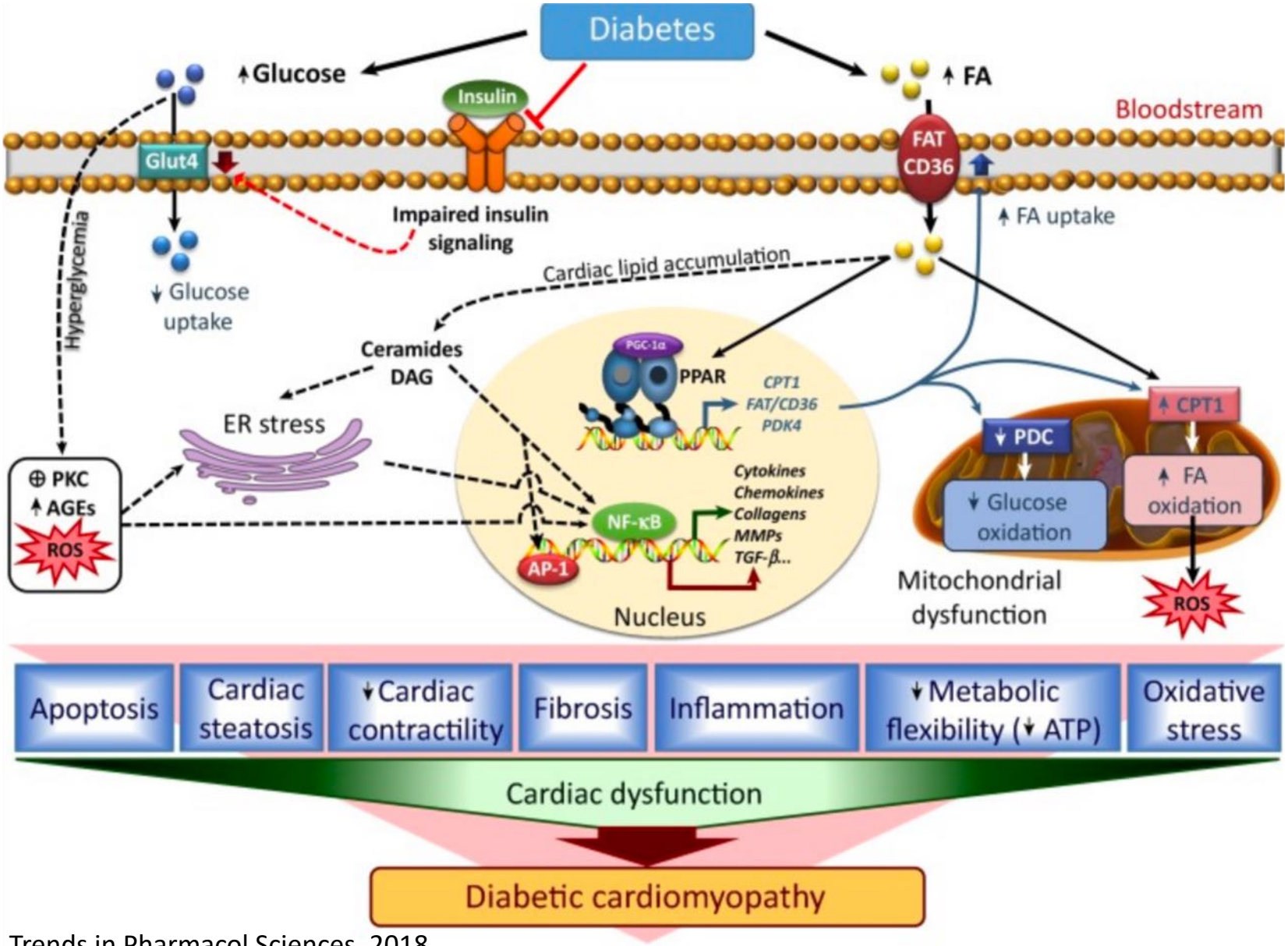
Diabetes and cardiomyopathy: Glucotoxicity

Hyperglycemia, insulin resistance, and hyperinsulinemia induce cardiac insulin resistance and metabolic disorders that increase mitochondria dysfunction, oxidative stress, advanced glycation end products (AGEs), impairment of mitochondria Ca^{2+} handling, inflammation, activation of renin–angiotensin–aldosterone system (RAAS), autonomic neuropathy, endoplasmic reticulum stress, cardiomyocyte death, as well as microvascular dysfunction. These pathophysiological abnormalities promote cardiac stiffness, hypertrophy, and fibrosis, resulting in cardiac diastolic dysfunction, systolic dysfunction, and heart failure.



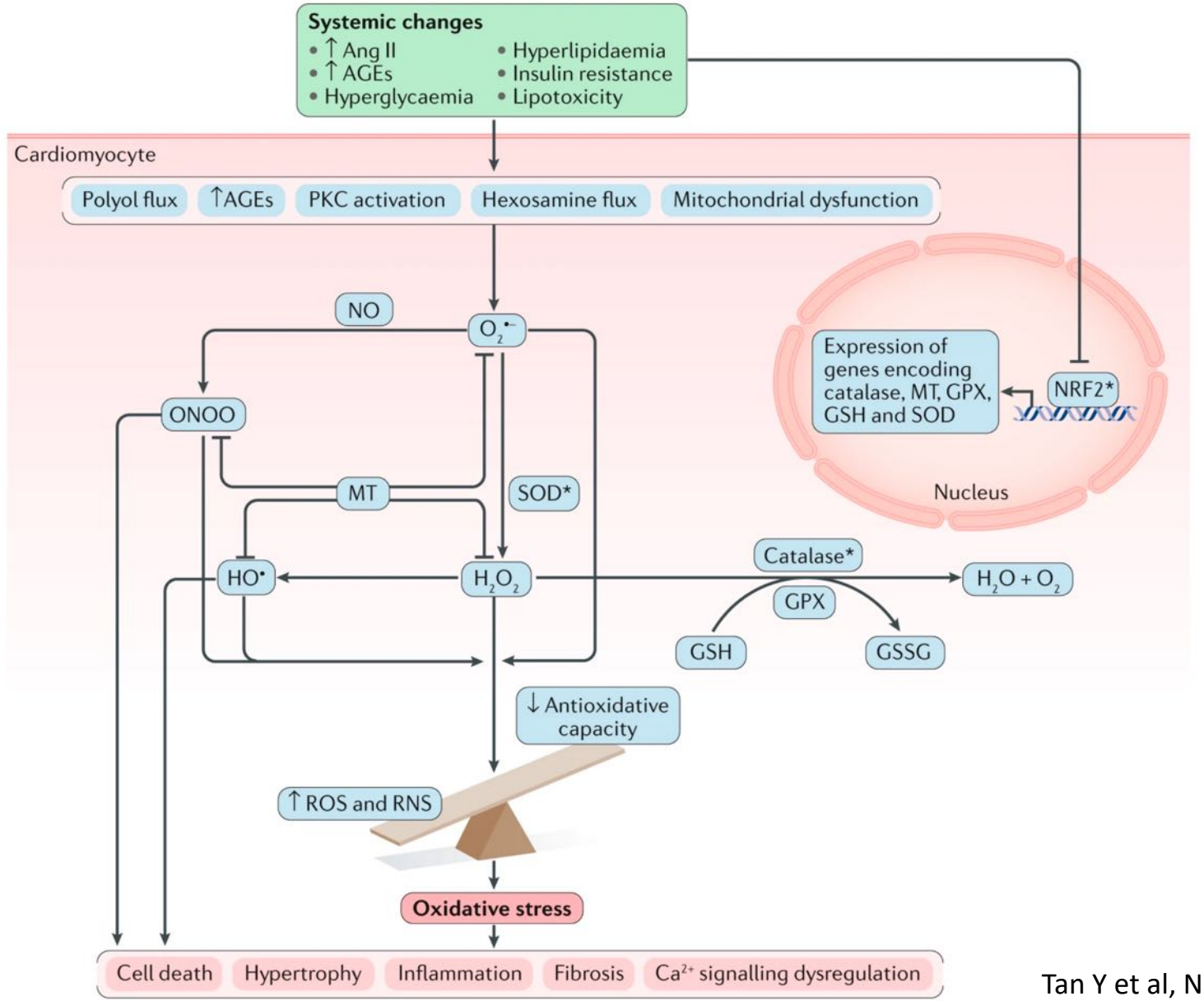
Jia G et al, Circ Res, 2018

Diabetes and cardiomyopathy: lipotoxicity



Palomer X et al, Trends in Pharmacol Sciences, 2018

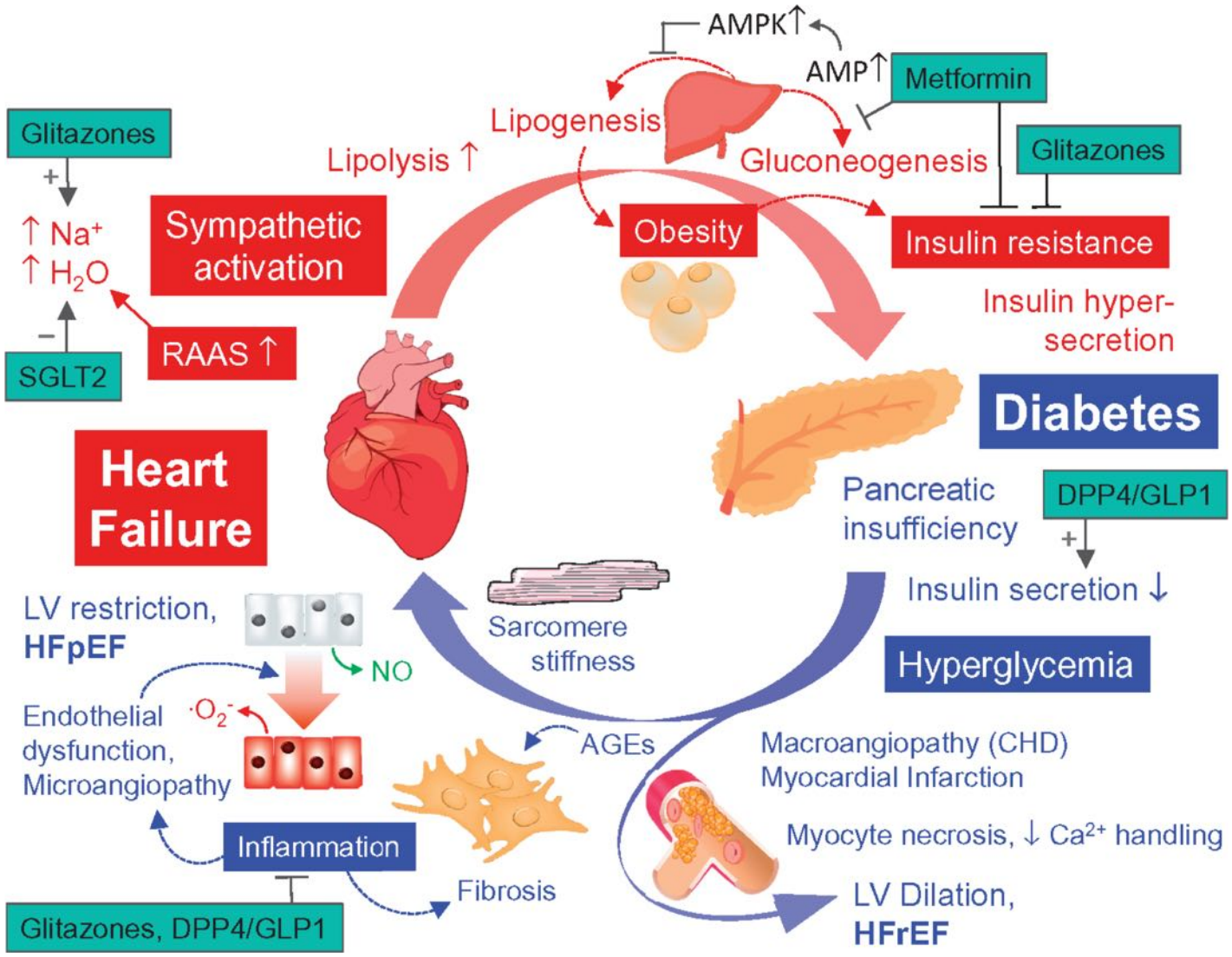
Diabetes and cardiomyopathy: Oxidative stress



Tan Y et al, Nat Rev Cardiology, 2020

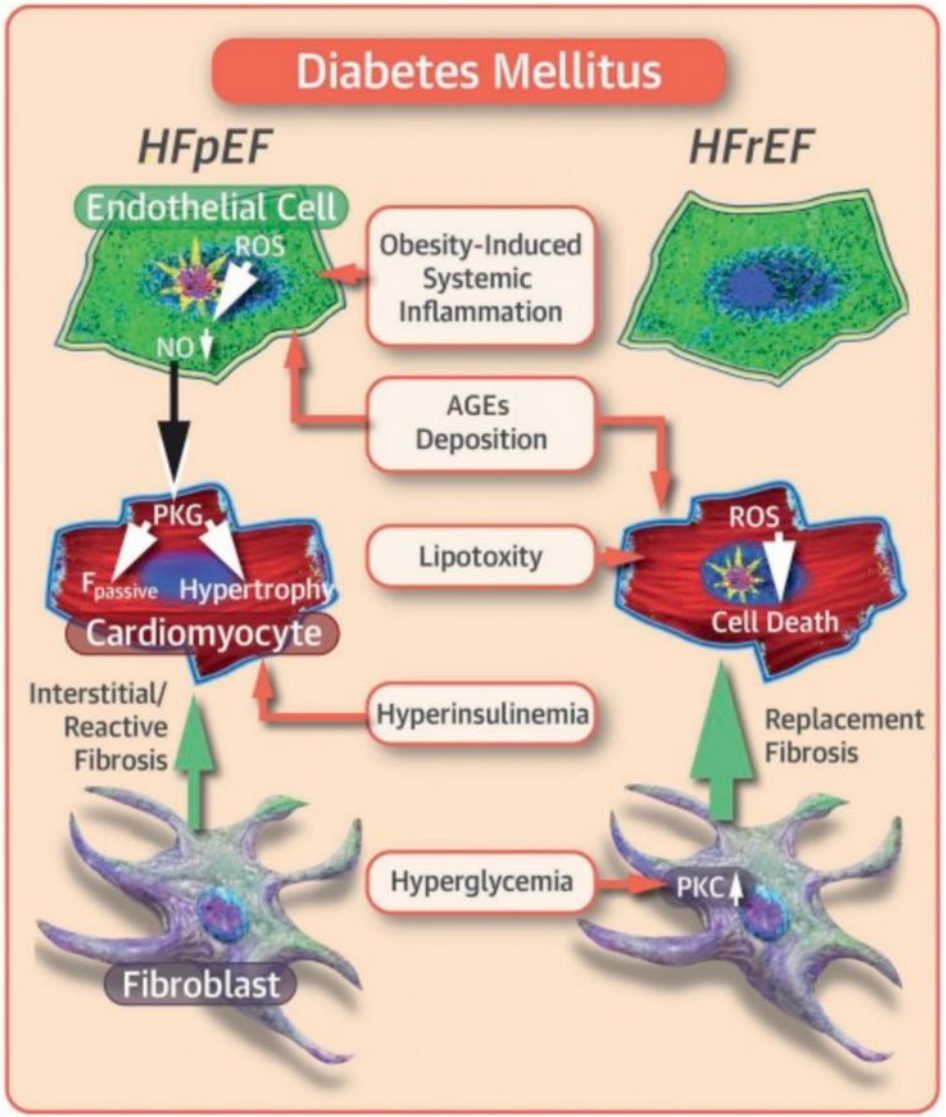
Systemic interdependance of heart failure and diabetes

In diabetes, hyperglycaemia induces macro- and microvascular dysfunction, and myocardial ischaemia and/or infarction bias towards systolic dysfunction (heart failure with reduced ejection fraction), while in the absence of ischaemia, diastolic dysfunction (heart failure with preserved ejection fraction) prevails through a combination of sarcomere stiffness and fibrosis



Maack C et al, Eur Heart J, 2018

Diabetes exerts distinct effects on myocardial remodeling in HFpEF and HFrEF



Diabetes leads to worse clinical outcomes in HFpEF than in HFrEF

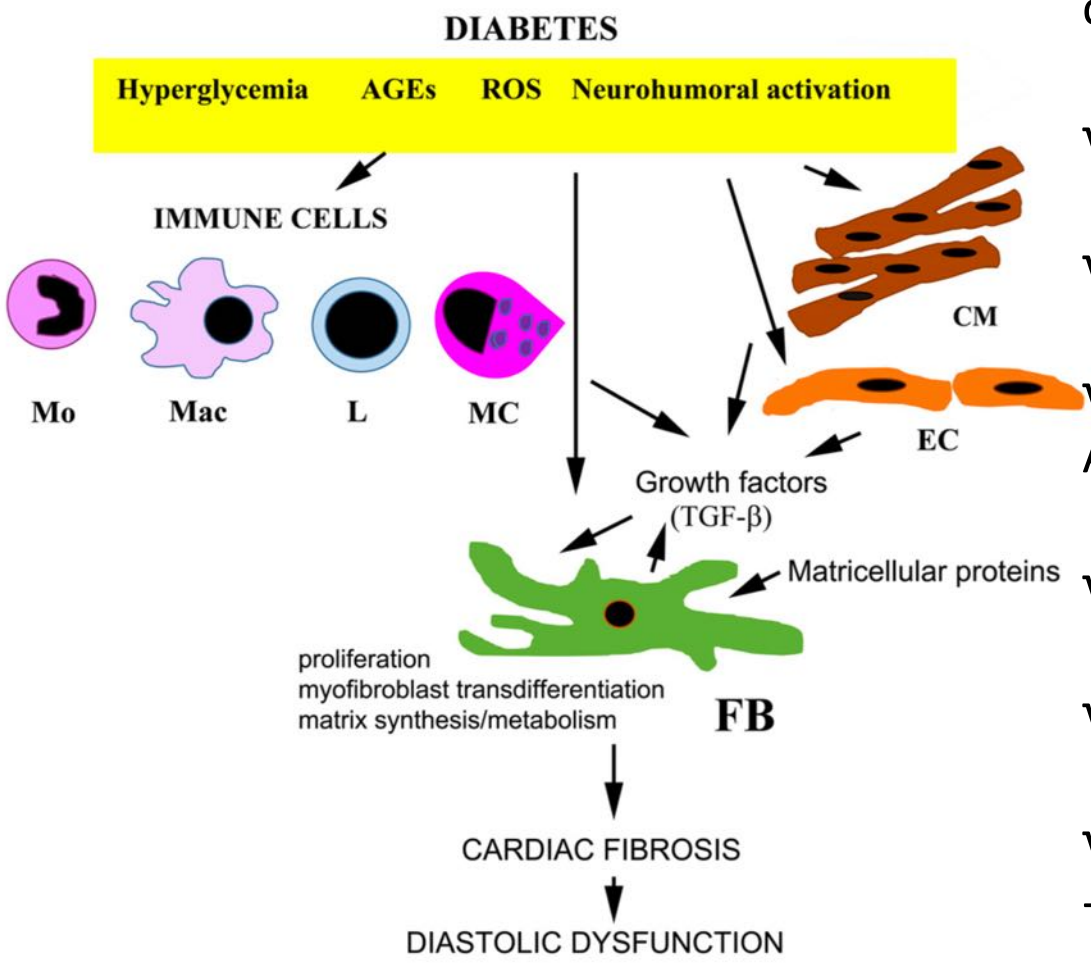
Myocardial remodeling is driven by microvascular endothelial inflammation in HFpEF and by cardiomyocyte cell death in HFrEF.

In HFpEF, DM mainly increases cardiomyocyte hypertrophy and stiffness, probably because of hyperinsulinemia and microvascular endothelial inflammation.

In HFrEF, DM augments replacement fibrosis because of cardiomyocyte cell death induced by lipotoxicity or advanced glycation end products.

Paulus WJ et al, JACC Heart failure, 2018

IV- Diabetes and the extracellular matrix compartment



Russo I et al, J Mol Cell Cardiol, 2016

√ Pro-inflammatory cytokines and chemokines: TNFα, IL1β, CCl2

√ Endothelin-1

√ Oxidative stress

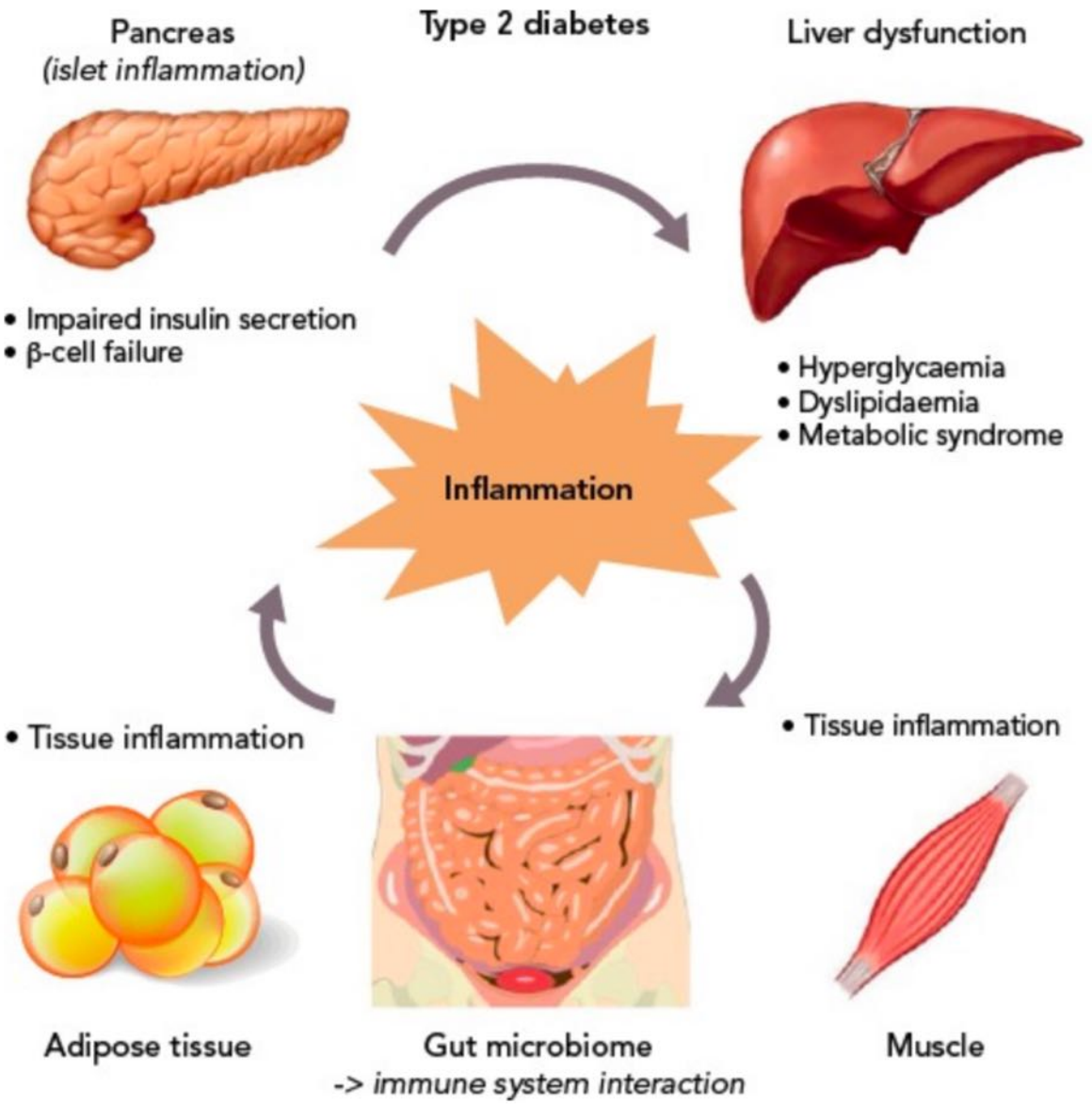
√AGE/RAGE: MEC degradation, ROS, TGFβ, AT1 activation, Inflammation

√Adipokine

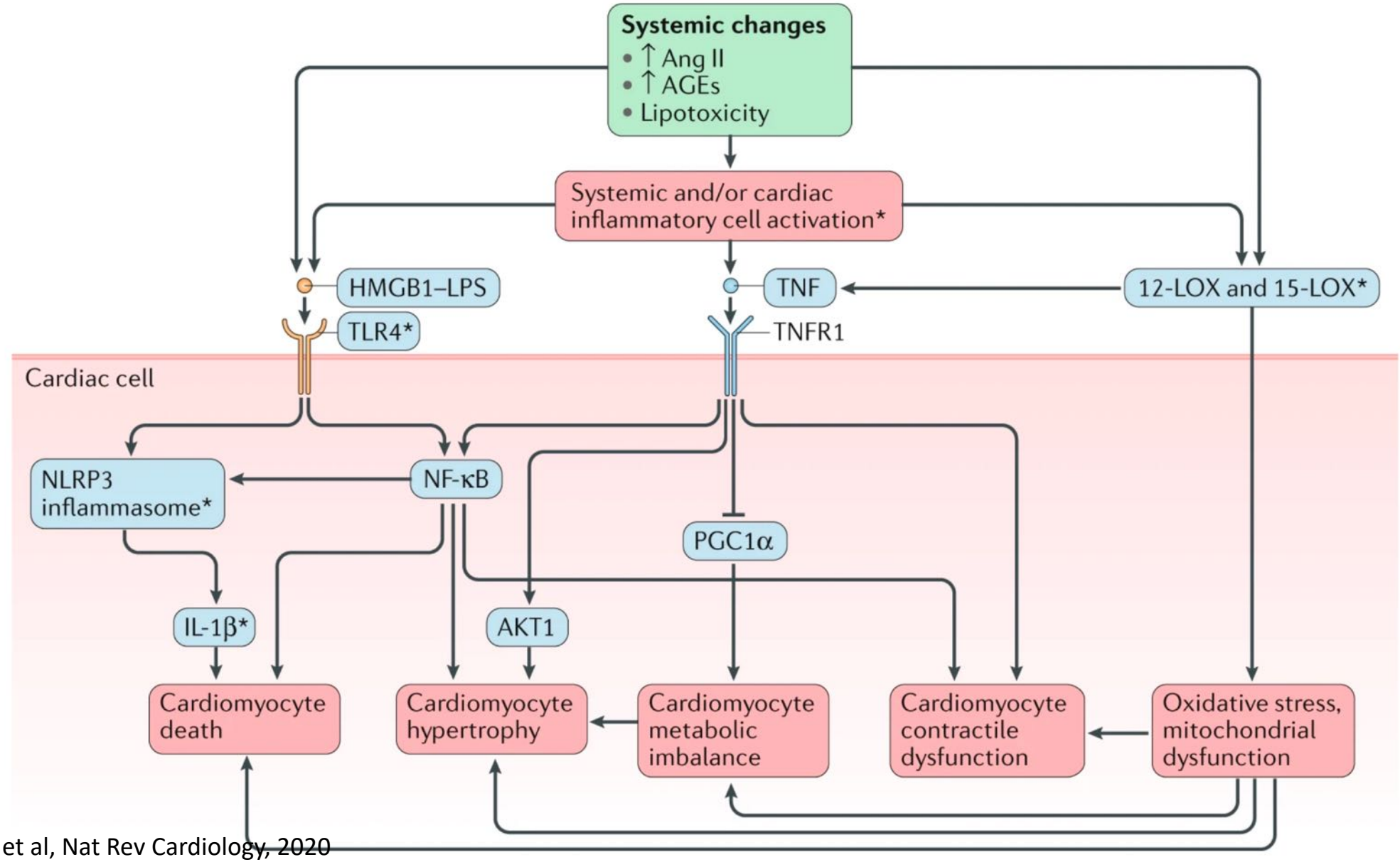
√Matricellular proteins: TSP1/Ang2

√MicroRNAs:
+ miR125b, miR199a
-miR150, miR29b, miR30a
miR133 overexpression attenuated the fibrotic response

V- Diabetes and the inflammatory compartment

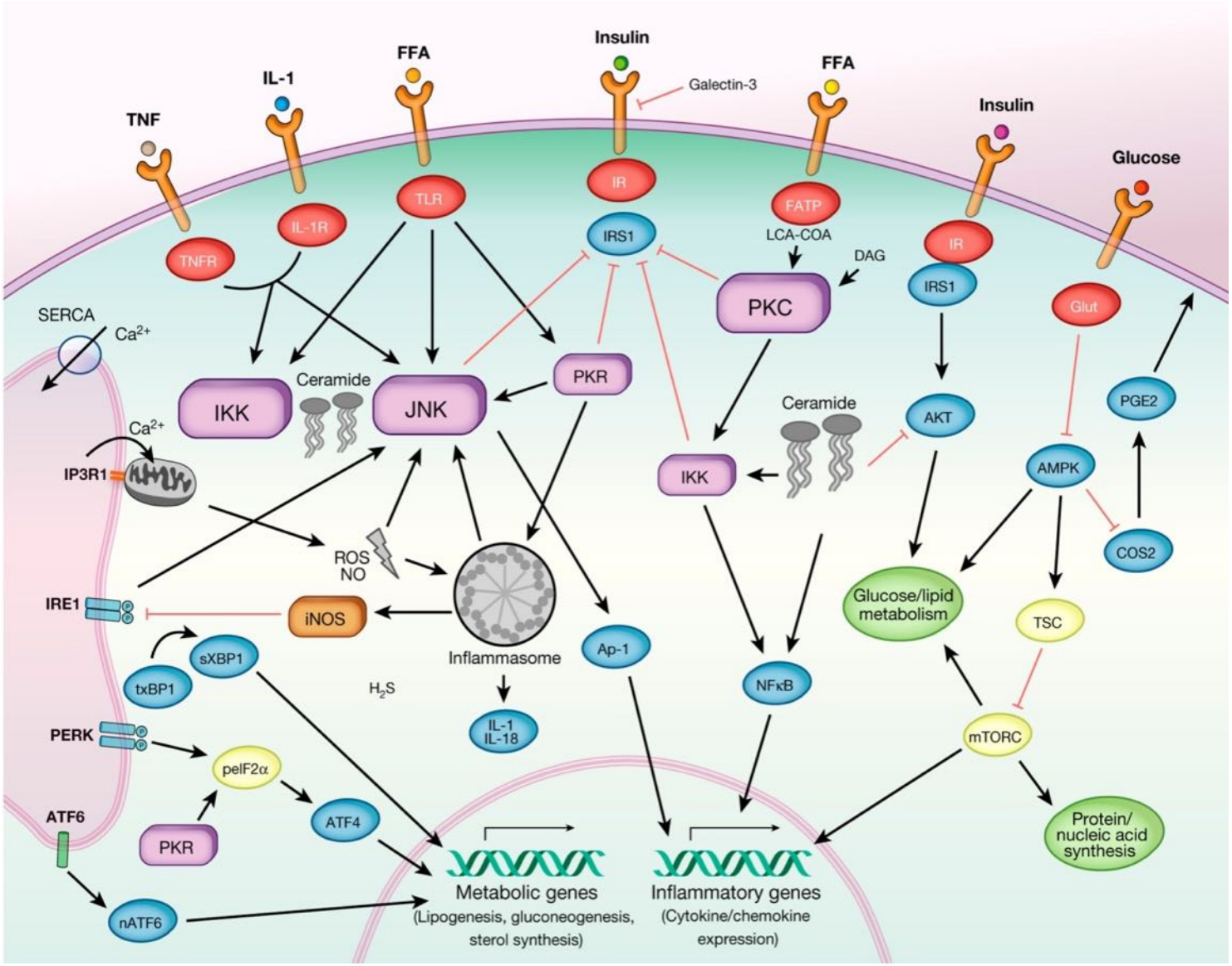


Pro-inflammatory pathways that regulate the development of diabetic cardiomyopathy



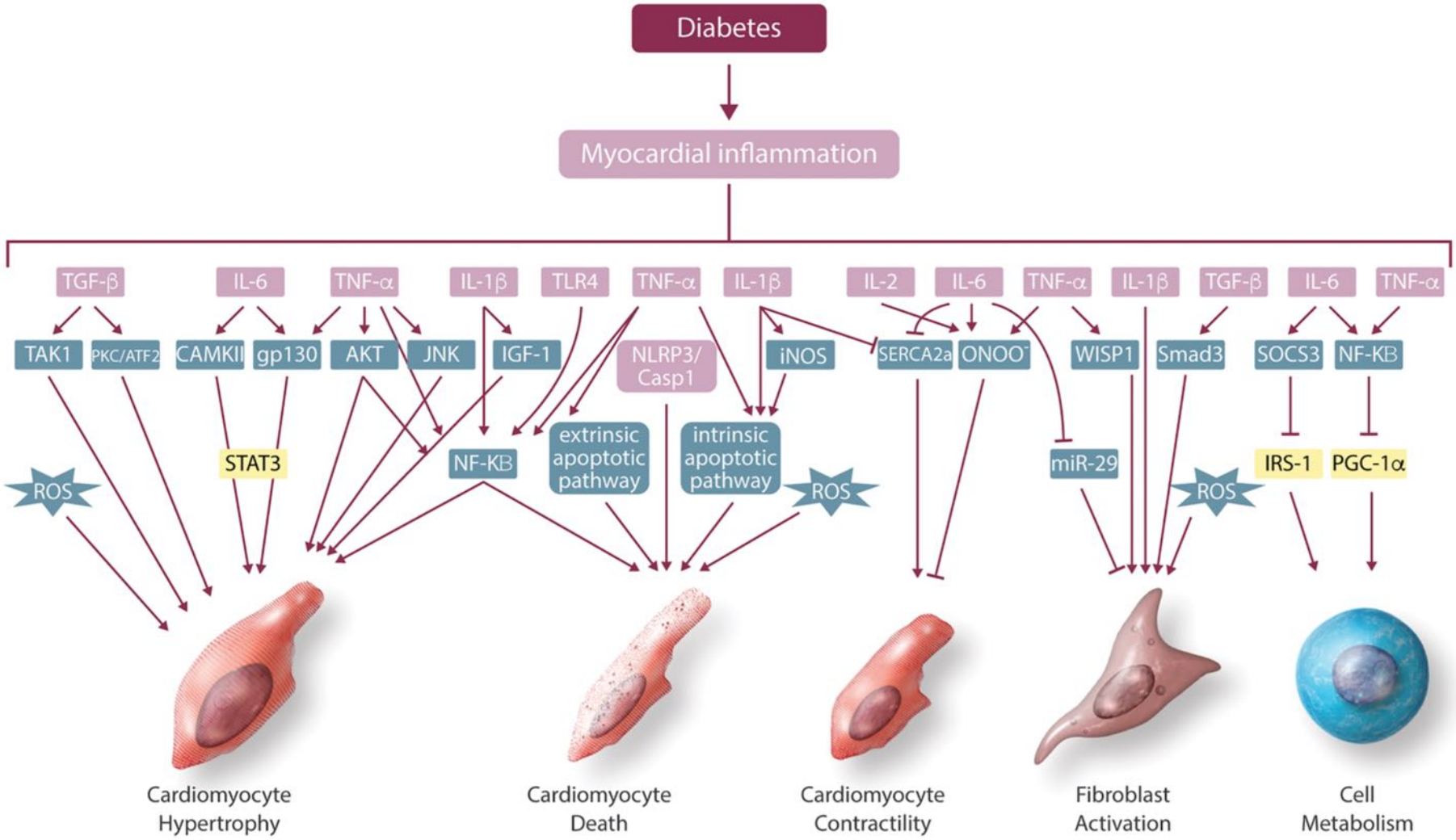
Tan Y et al, Nat Rev Cardiology, 2020

Diabetes and immuno-metabolism



Hotamisligil SG et al. Nature, 2017

Diabetes and immuno-metabolism



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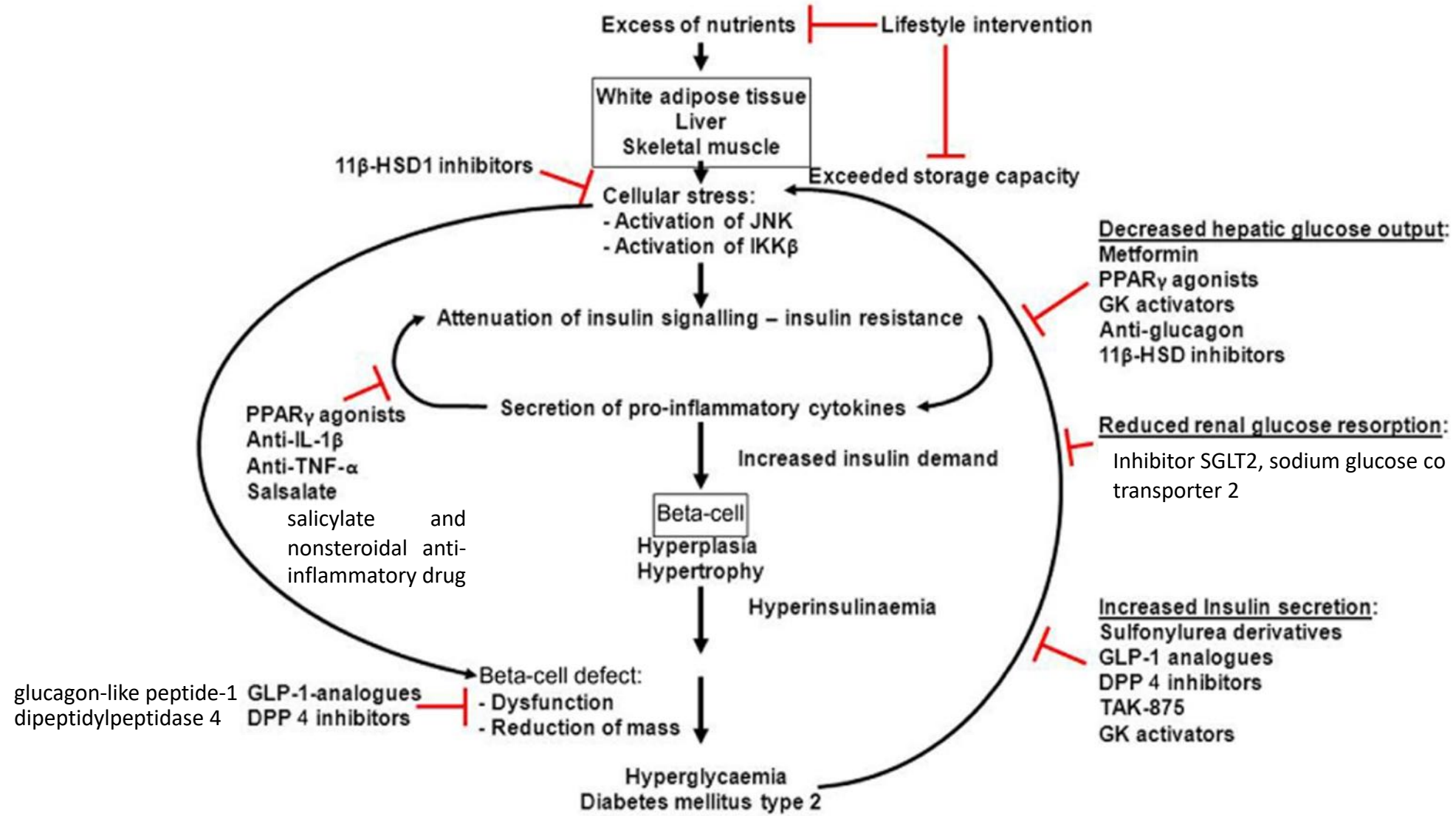
VI- Treatment of type 2 diabetes



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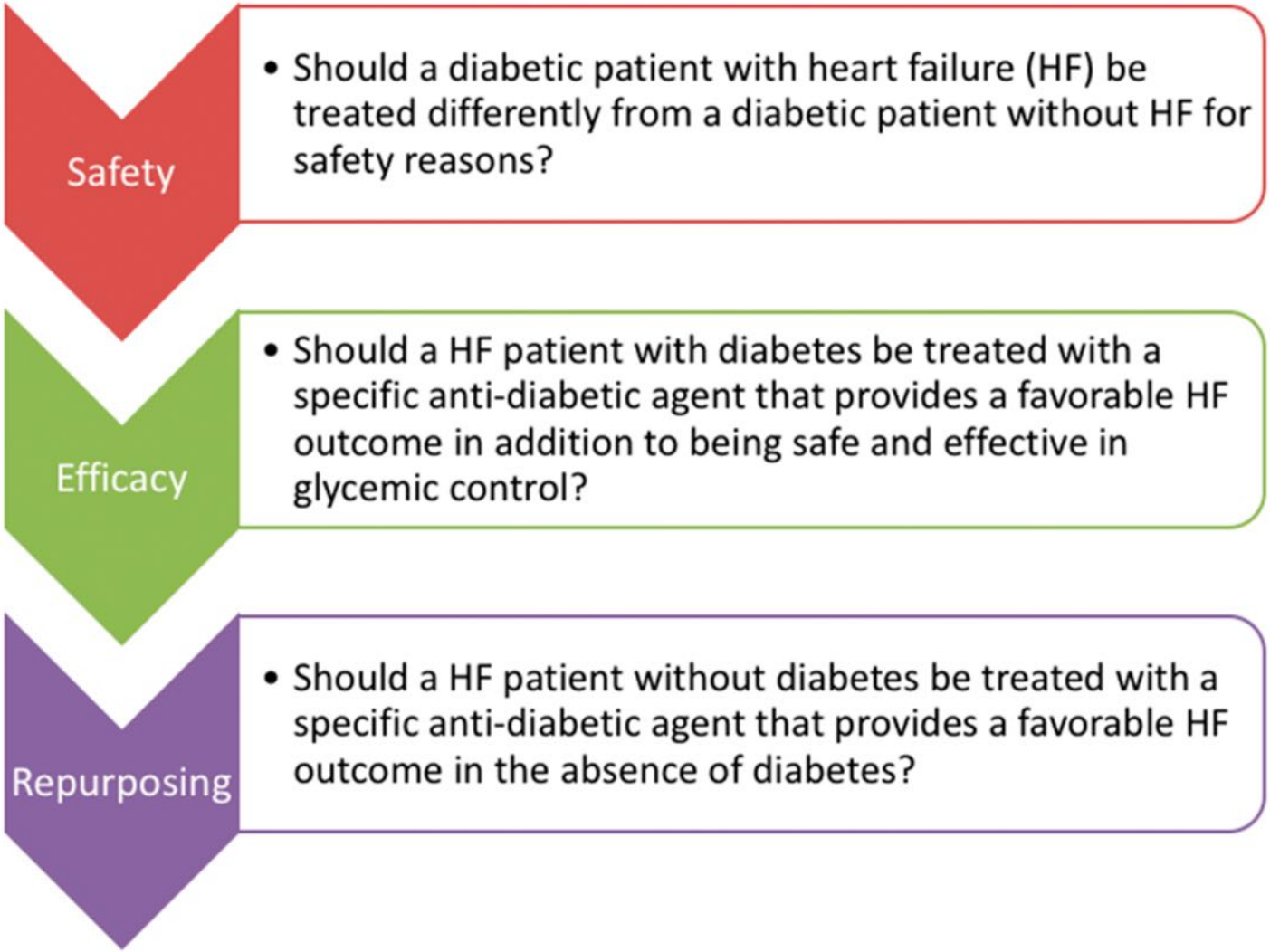
Treatment of diabetic patient with heart failure

Basic concepts concerning the use of anti-diabetic drugs in patients with heart failure.

An important and yet under-investigated issue is the differential efficacy of anti-diabetic drugs in men and women. In two meta-analyses, diabetes was associated with a less favourable CV risk profile and a higher risk of death from CAD in females compared with males



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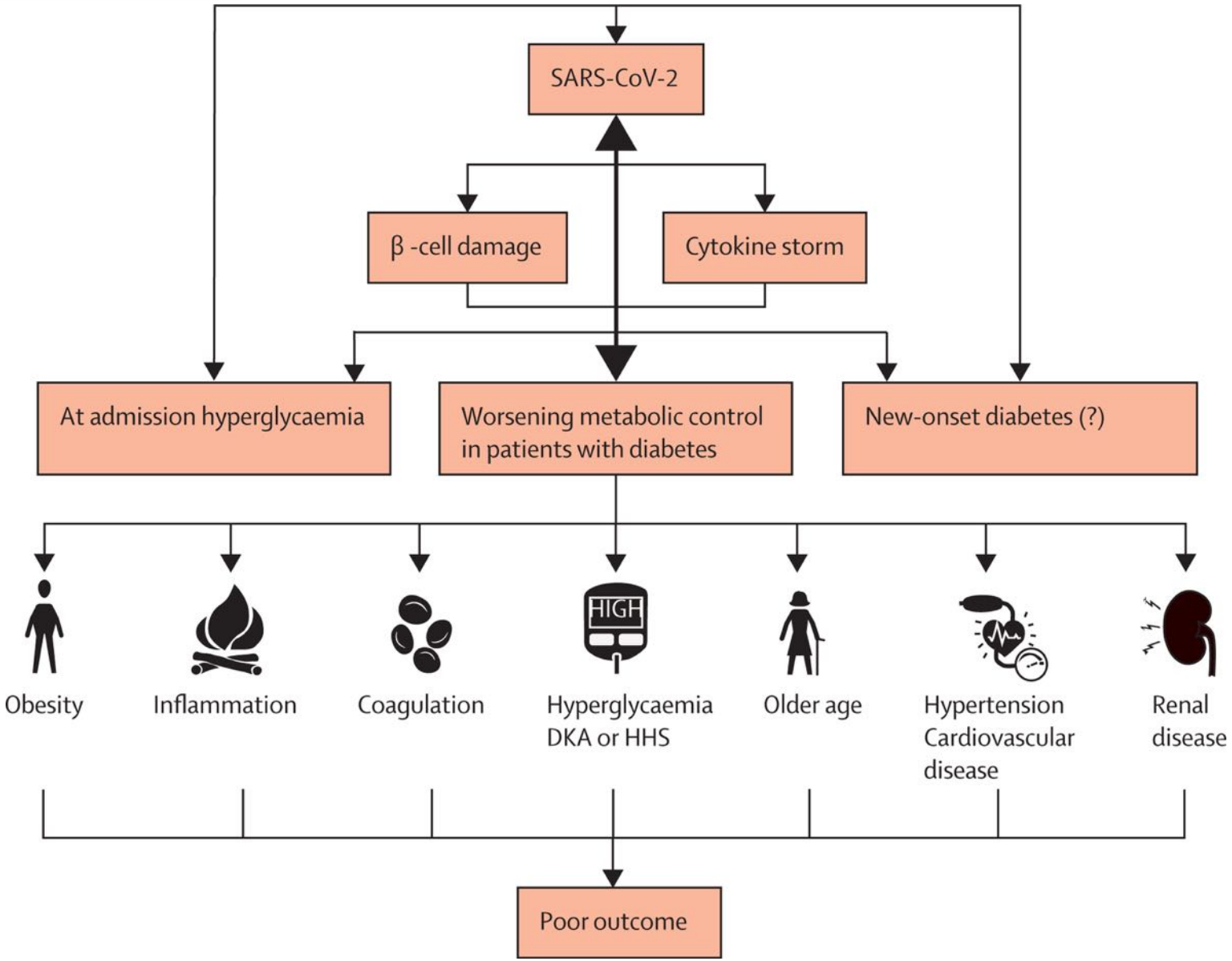
COVID-19 in people with diabetes: understanding the reasons for worse outcomes



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