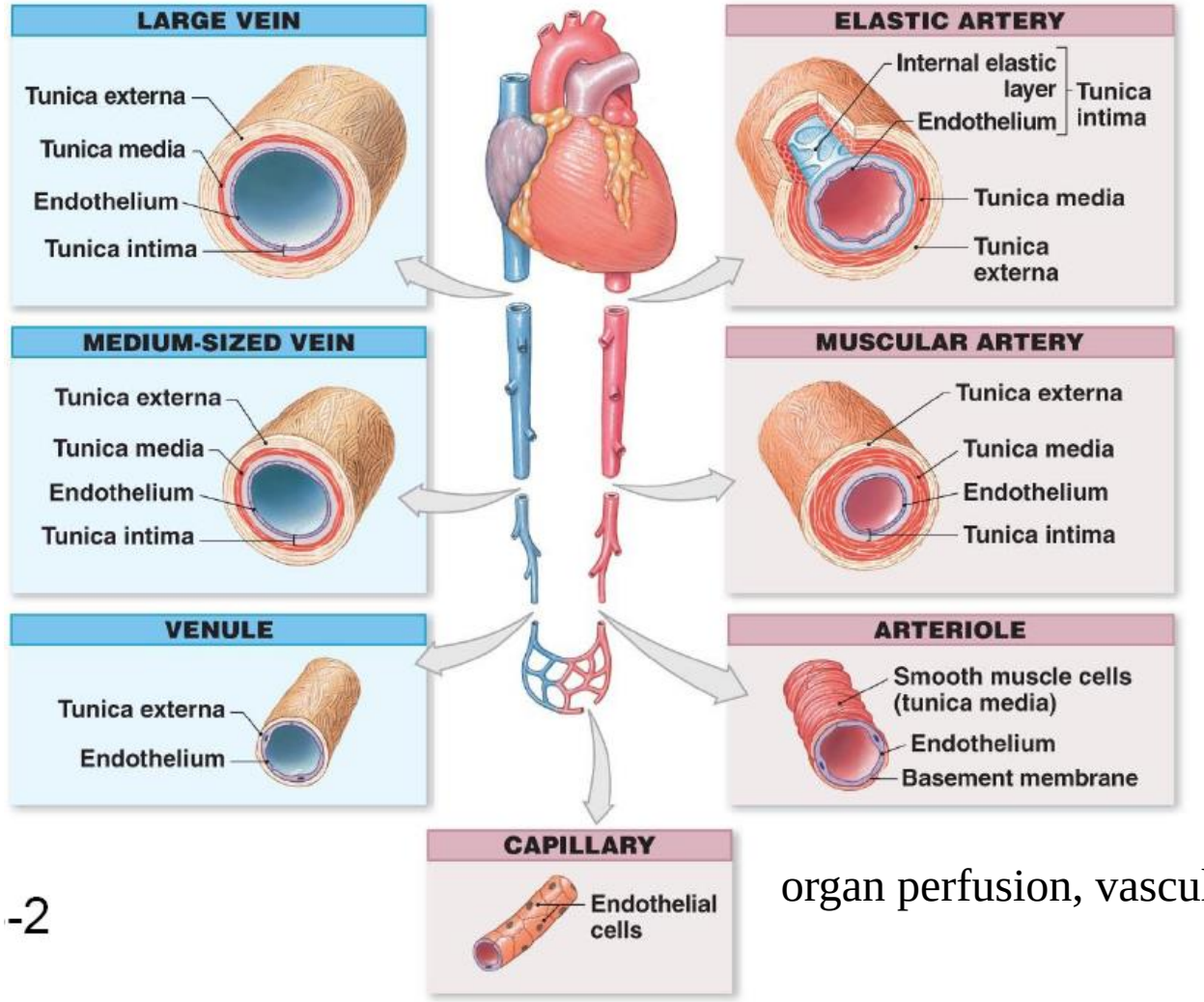
Vascular Disease; Function and Structure : Macro and Microvascular Disease

원주의대 김장영

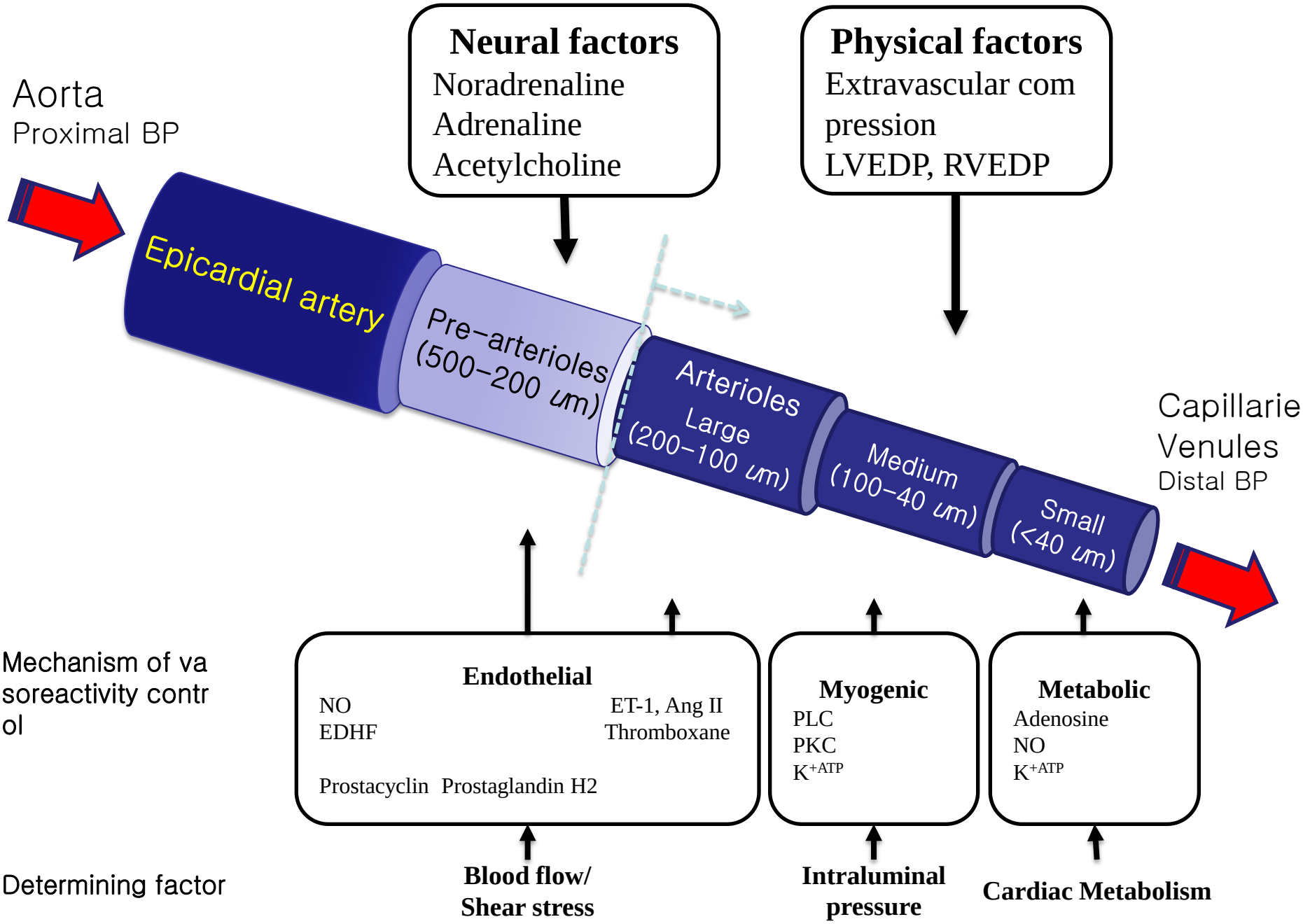
Blood Vessels : structure



-2

organ perfusion, vascular tone

Herrmann J et al. *Eur Heart J* 2012;33:2771-81



Definition (vessel size, 0.5 mm or 1mm)

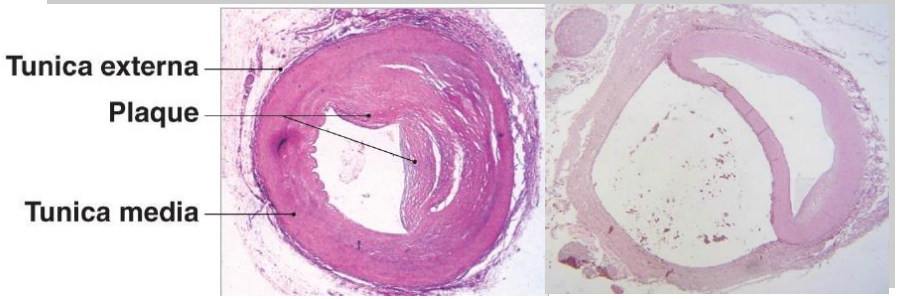
- **Macrovascular disease** is a disease of any large (*macro*) blood vessel in the body. It is a disease of the large blood vessels, including the coronary arteries, the aorta, and the sizable arteries in the brain and in the limbs.

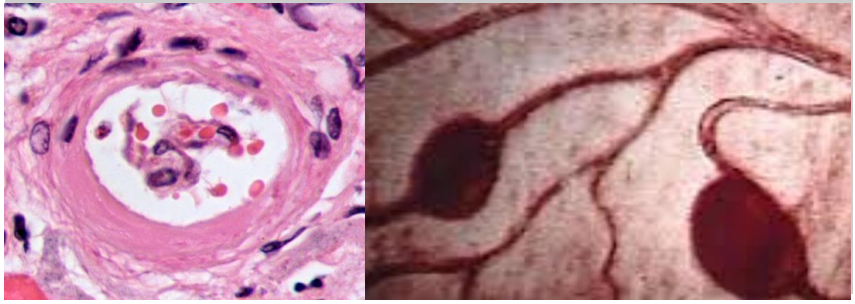
- **Microvascular disease** is an angiopathy affecting small blood vessels (the small arteries , arterioles, venules, and capillaries) in the body.

Pathology

- **Macrovessel disease**
  - Atherosclerosis (plaque)
  - Arteriosclerosis (thickening and hardening of arterial walls)
  - Aneurysms

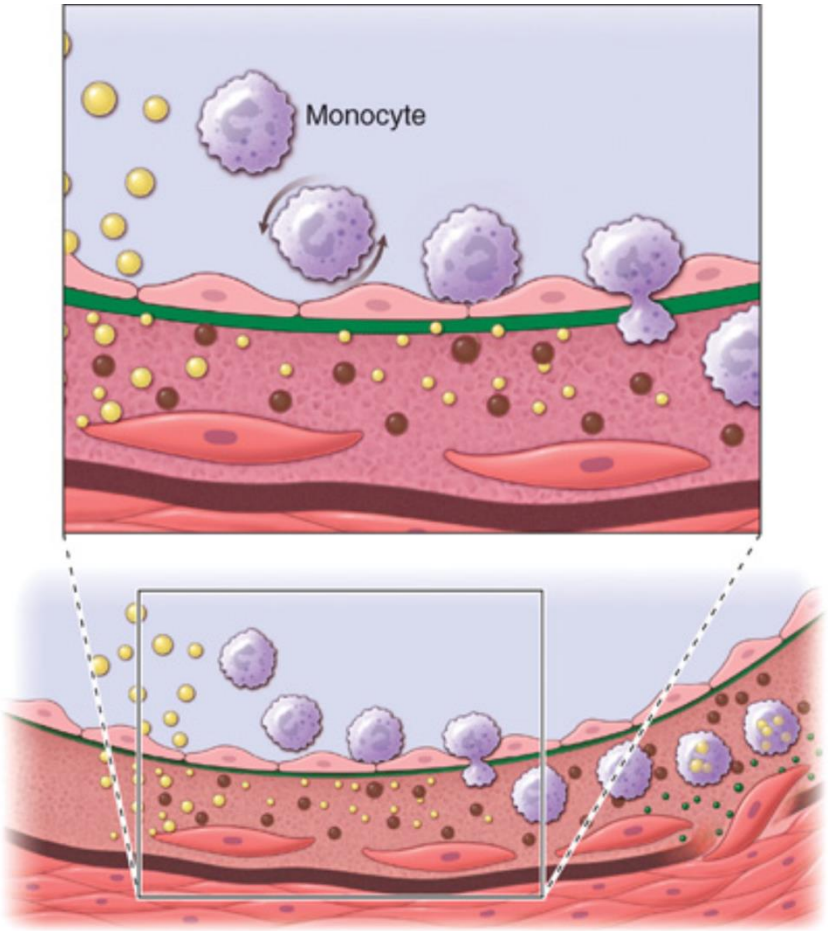
- **Microvascular disease**
  - Arteriolosclerosis
  - Aneurysms
  - Hemorrhage
  - Neovascularization
  - Obstruction

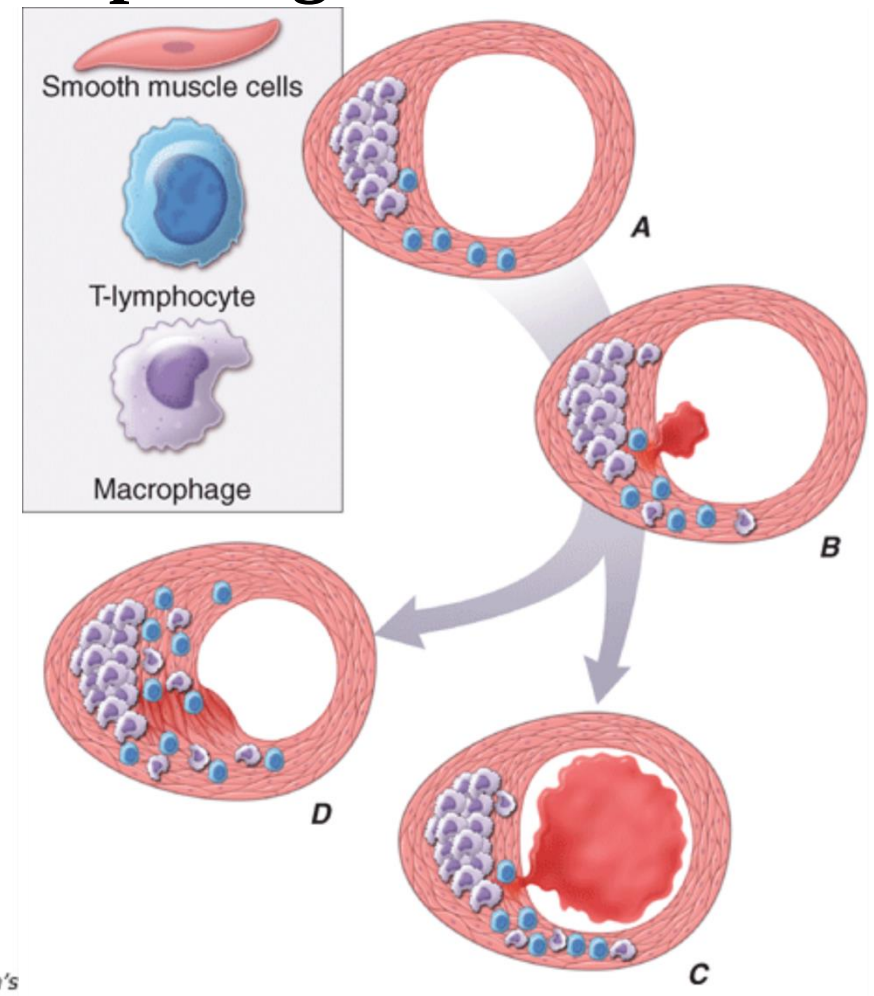




Macrovascular disease

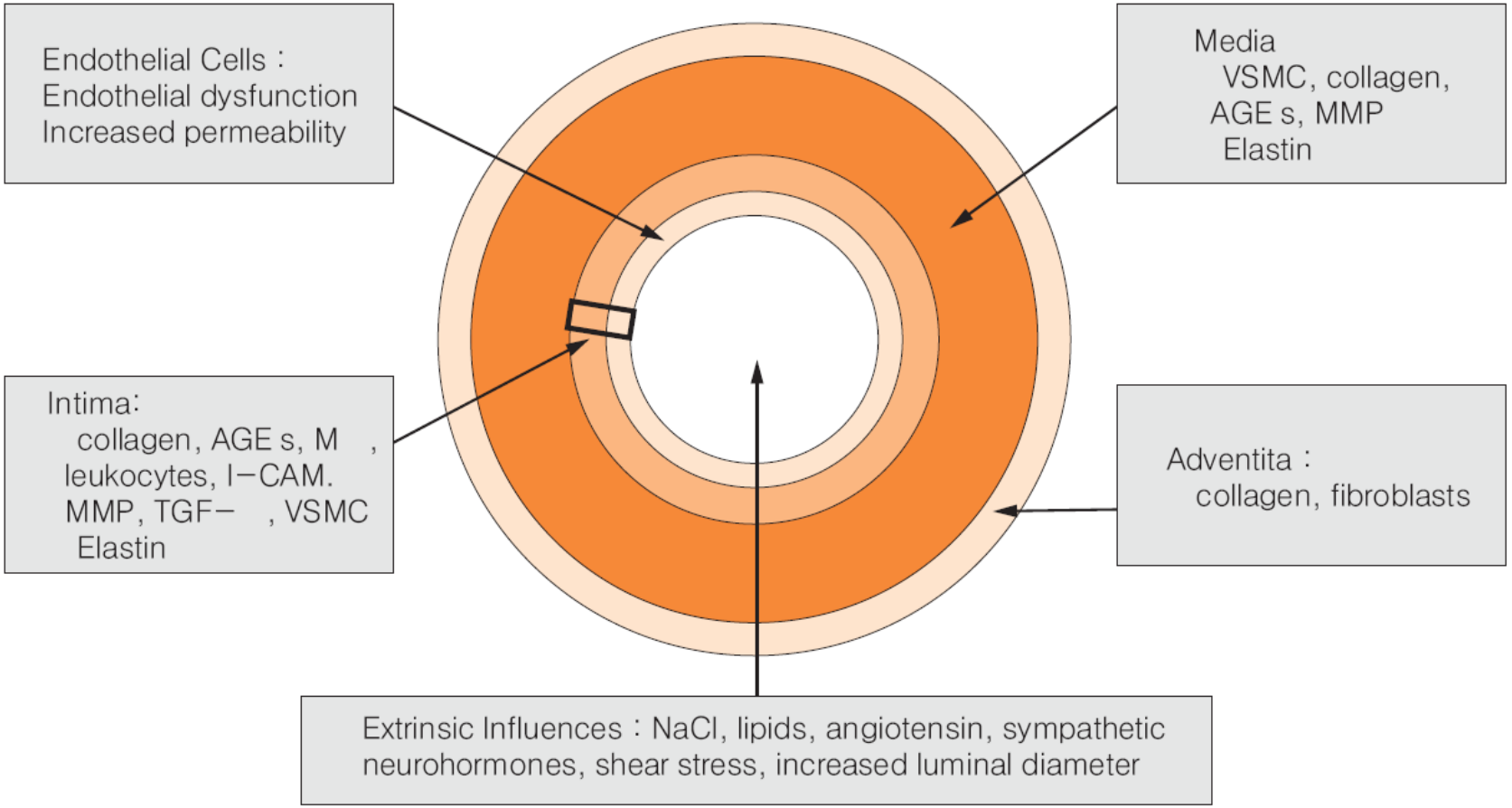
Atherosclerosis : pathogenesis





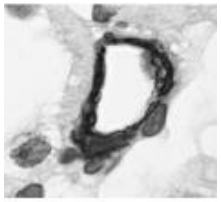
From: Chapter 241. The Pathogenesis, Prevention, and Treatment of Atherosclerosis
Harrison's Principles of Internal Medicine, 18e, 2012

Macrovascular disease
(Arteriosclerosis: pathogenesis)



Microvascular disease

Blood pressure
Obesity, genetics
Autonomic dysfunction
Insulin resistance
Estrogen deficiency
Diabetes, Uric acid



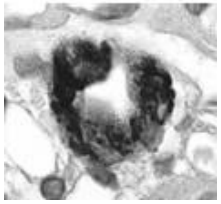
Structural changes
Inflammation
remodeling

Functional changes
Endothelial dysfunction
vasoconstriction

↑ Media/lumen ratio

Total peripheral vascular resistance ↑

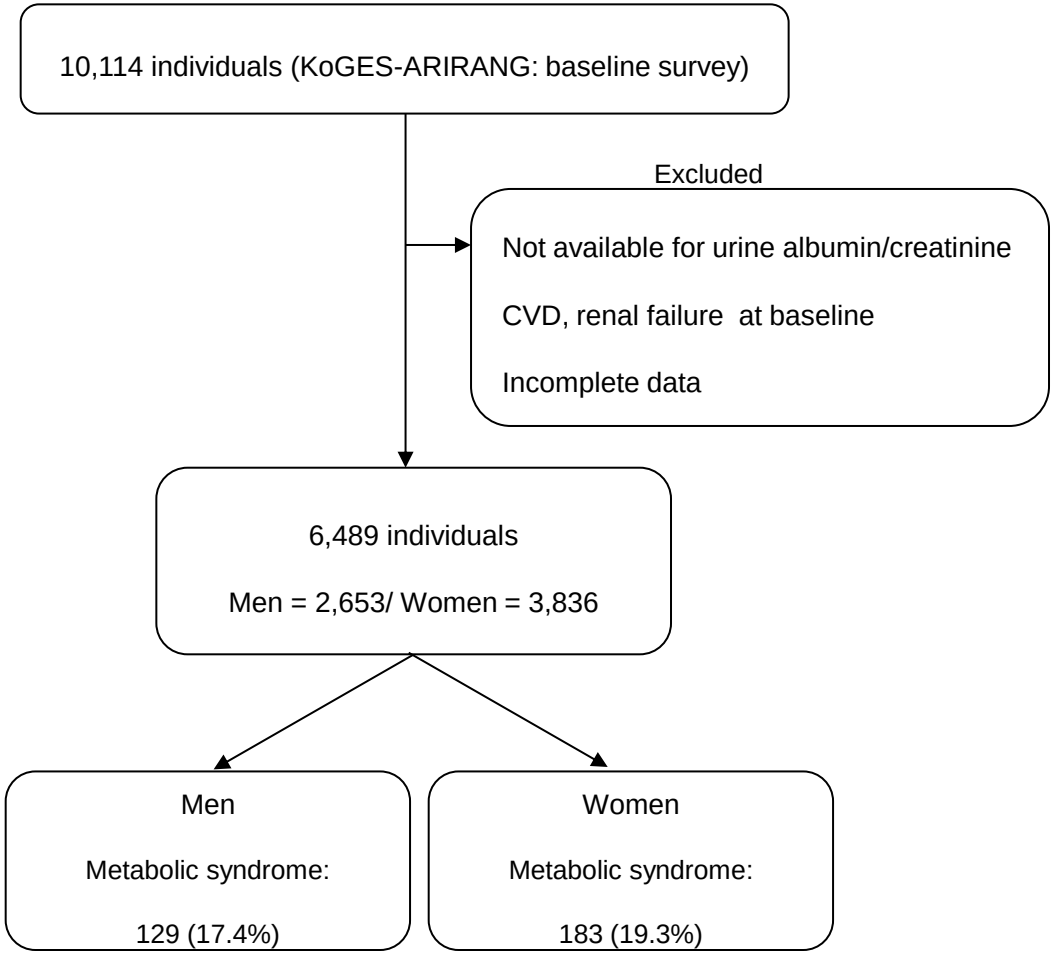
Structural and functional change of microvessel



characterized by intimal thickening, vascular smooth muscle cell proliferation, and extracellular matrix deposition, resulting in an increase in the media to lumen ratio, and later by the replacement of the vascular smooth muscle cells by areas of fibrosis and cell loss.

Microvascular disease (UACR) and metabolic factors

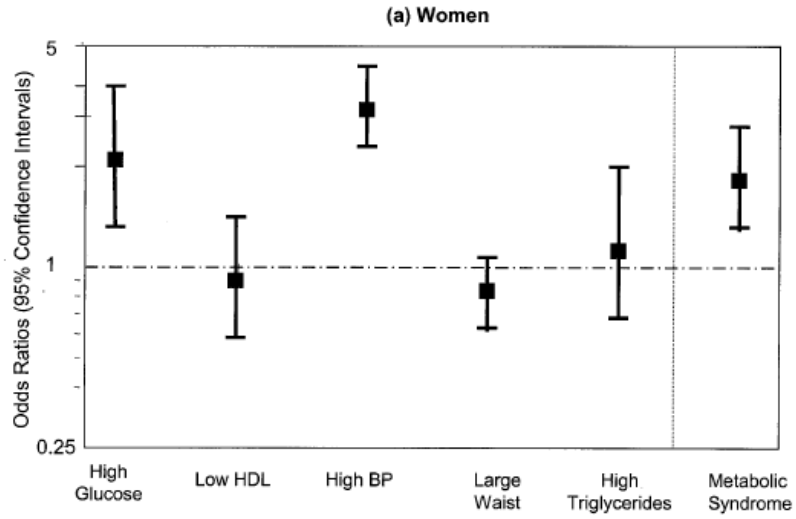
Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population (KoGES-ARIRANG)

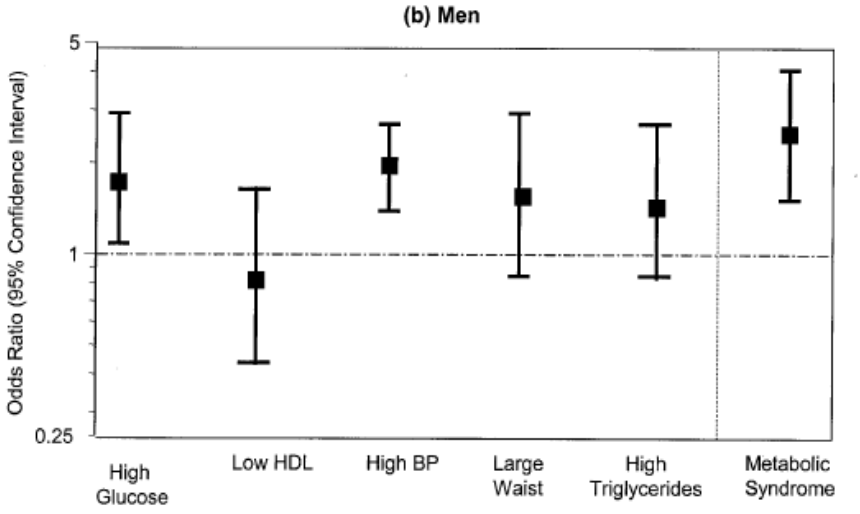


ARIRANG invited adults aged 40 to 70 years in rural areas of Wonju, Pyengchang, Keumsan, Naju, and Kangreung in Korea

	OR (95% CI)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Men (n=2653)				
UACR at baseline	<5.00	5.00-8.98	8.99-18.11	≥18.12
Metabolic syndrome	1.00	1.19 (0.91-1.56)	1.29 (0.99-1.69)	1.87 (1.43-2.45)
High WC	1.00	1.07 (0.77-1.49)	0.92 (0.66-1.29)	1.15 (0.83-1.60)
Low HDL cholesterol	1.00	1.14 (0.90-1.44)	0.99 (0.78-1.26)	0.77 (0.61-0.99)
High TG	1.00	1.39 (1.10-1.75)	1.48 (1.17-1.86)	2.05 (1.62-2.59)
High blood pressure	1.00	1.17 (0.93-1.47)	1.48 (1.17-1.88)	2.34 (1.81-3.03)
High fasting glucose	1.00	1.33 (1.01-1.76)	1.75 (1.33-2.29)	2.12 (1.61-2.79)
Women (n=3836)				
UACR at baseline	<6.52	6.52-11.29	11.30-20.25	≥20.26
Metabolic syndrome	1.00	1.41 (1.14-1.74)	1.79 (1.45-2.21)	1.90 (1.54-2.35)
High WC	1.00	1.17 (0.91-1.51)	1.14 (0.88-1.47)	1.18 (0.90-1.53)
Low HDL cholesterol	1.00	1.22 (1.01-1.47)	1.32 (1.10-1.60)	1.16 (0.96-1.41)
High TG	1.00	1.40 (1.13-1.73)	1.56 (1.27-1.92)	1.86 (1.51-2.30)
High blood pressure	1.00	1.23 (1.02-1.49)	1.60 (1.31-1.94)	2.11 (1.72-2.59)
High fasting glucose	1.00	1.07 (0.82-1.40)	1.09 (0.84-1.42)	1.57 (1.22-2.02)

UACR and Risk factors (미국영양조사)





AJH 2003; 16:952–958

Macro에 비해 microvascular disease는 미국 및 한국역학 연구를 보니 비만, 당의 증가와 인슐린 저항성, 고혈압이 중요

Disease

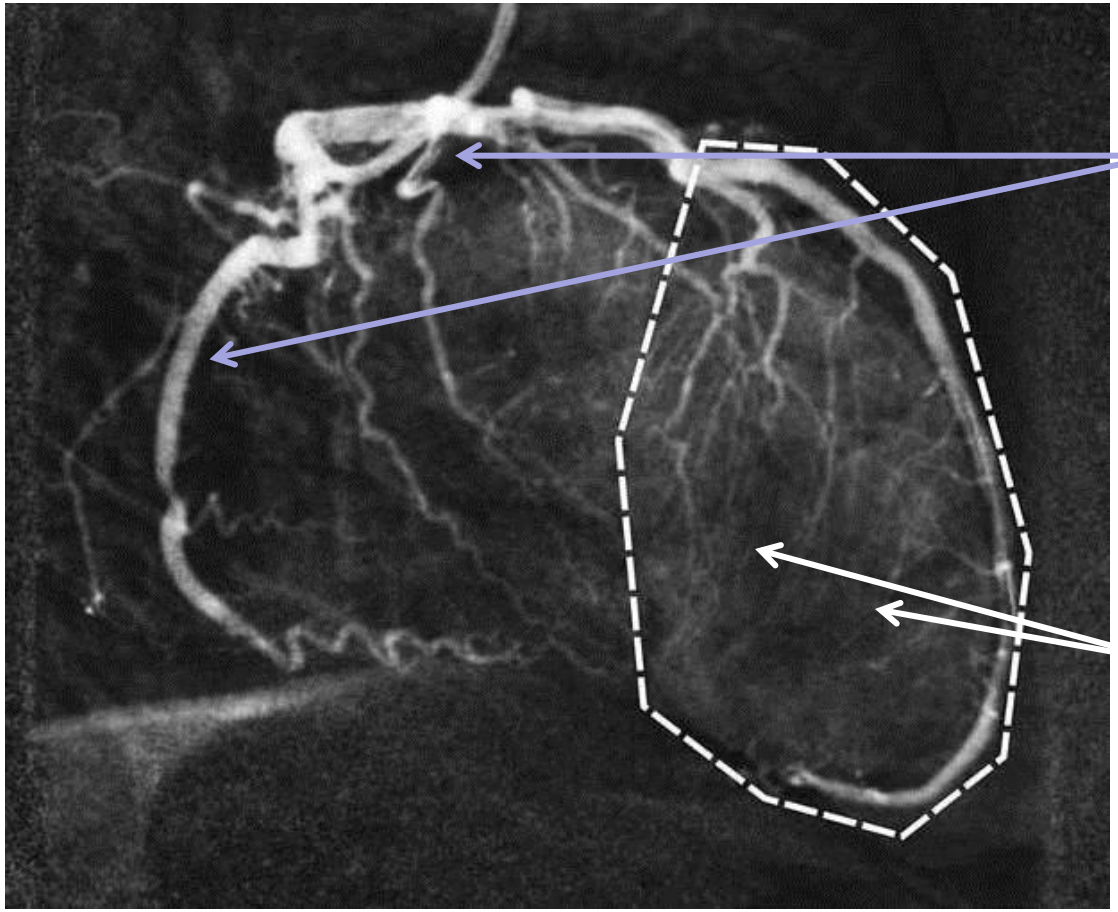
- **Macrovessel disease**
- Three common type
  - Coronary artery
  - Cerebrovascular
  - Peripheral (in the limb)

- **Microvascular disease**
  - Cardiac syndrome-X
  - Diabetes (nephropathy, neuropathy, retinopathy)
  - Hypertension-related small vessel diseases
  - Cerebral amyloid angiopathy

Coronary artery disease

Focus on microvascular disease

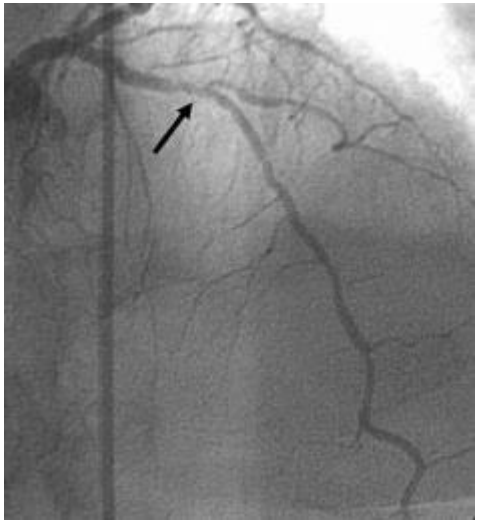
Coronary Arterial System

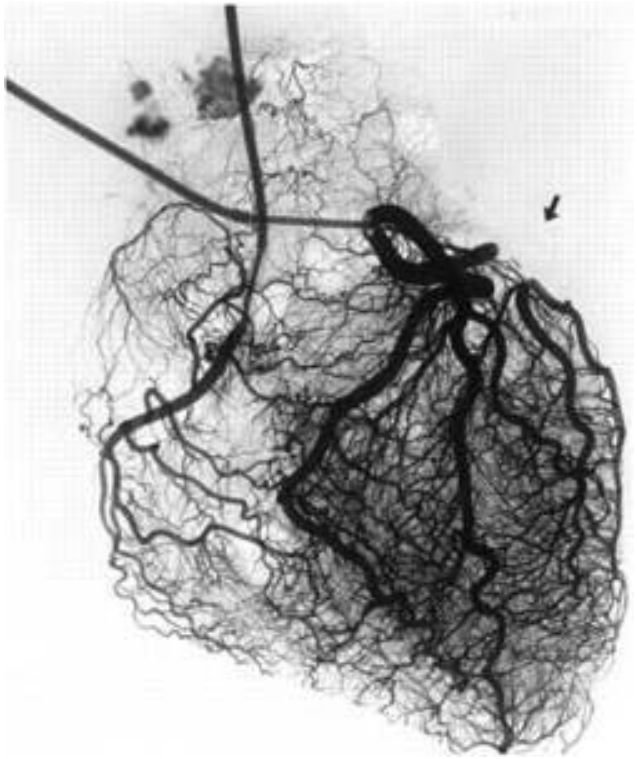


Epicardial coronary artery (>500*um*); conduit or conductance vessels

Prearteriols & Arterioles (<500*um*); resistive vessels

rich microvascular network 안 보인다





Coronary macro &microvascular disease

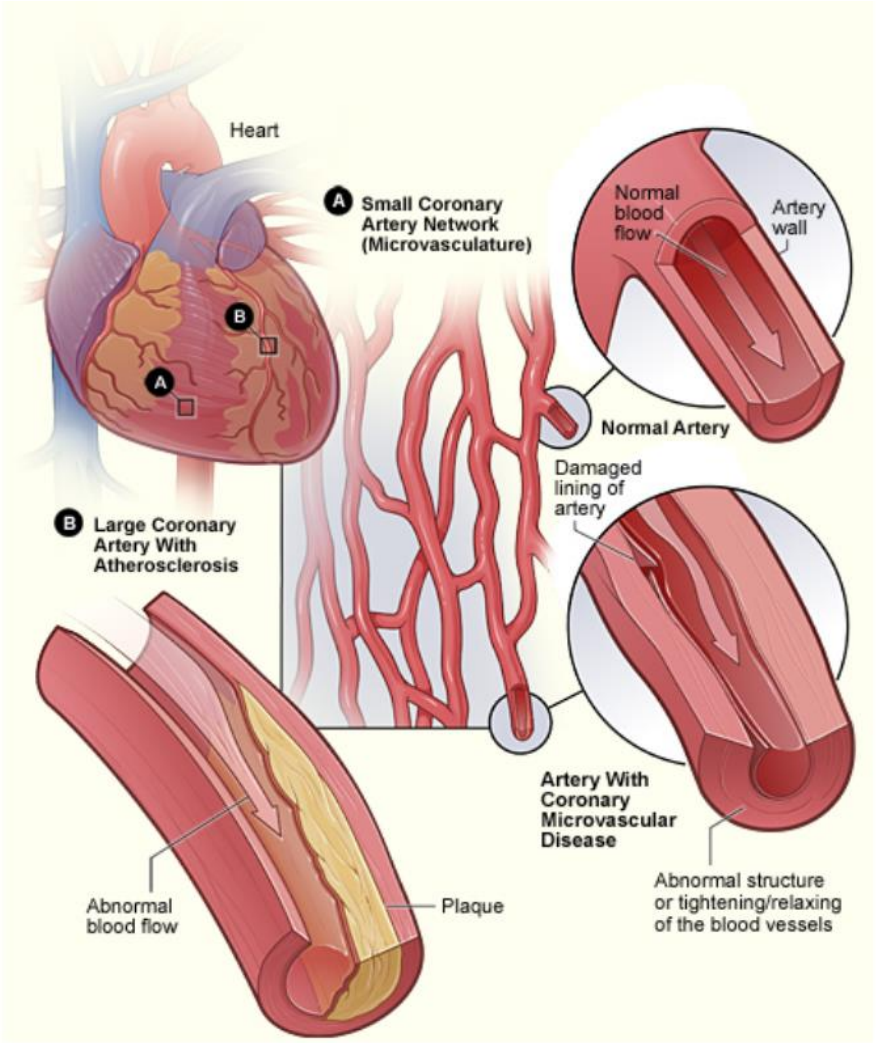


Figure A shows the small coronary artery network (microvasculature), containing a normal artery and an artery with coronary MVD. Figure B shows a large coronary artery with plaque buildup.

Cardiac syndrome-X (전형적인 증례)

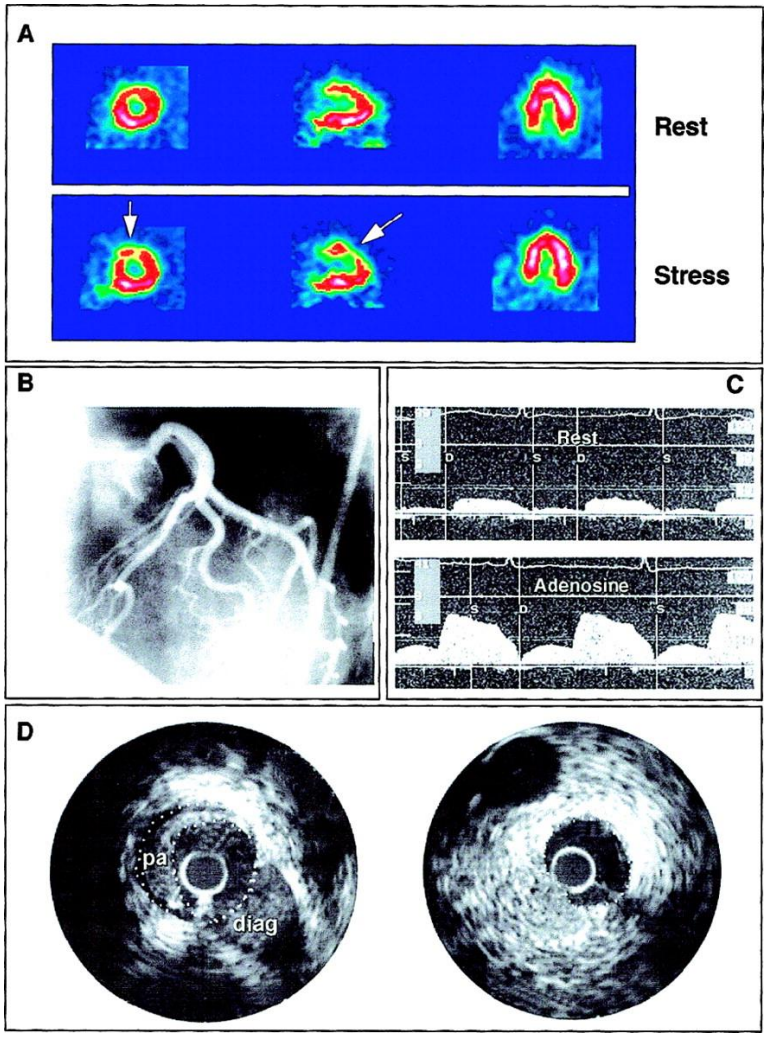
Angina

Abnormal SPECT
No obstructive CAD

Abnormal coronary reserve
And elevated LVEDP

Diffuse atherosclerosis by IVUS

Women



Galli M et al. *Circulation*. 1999;99:1774

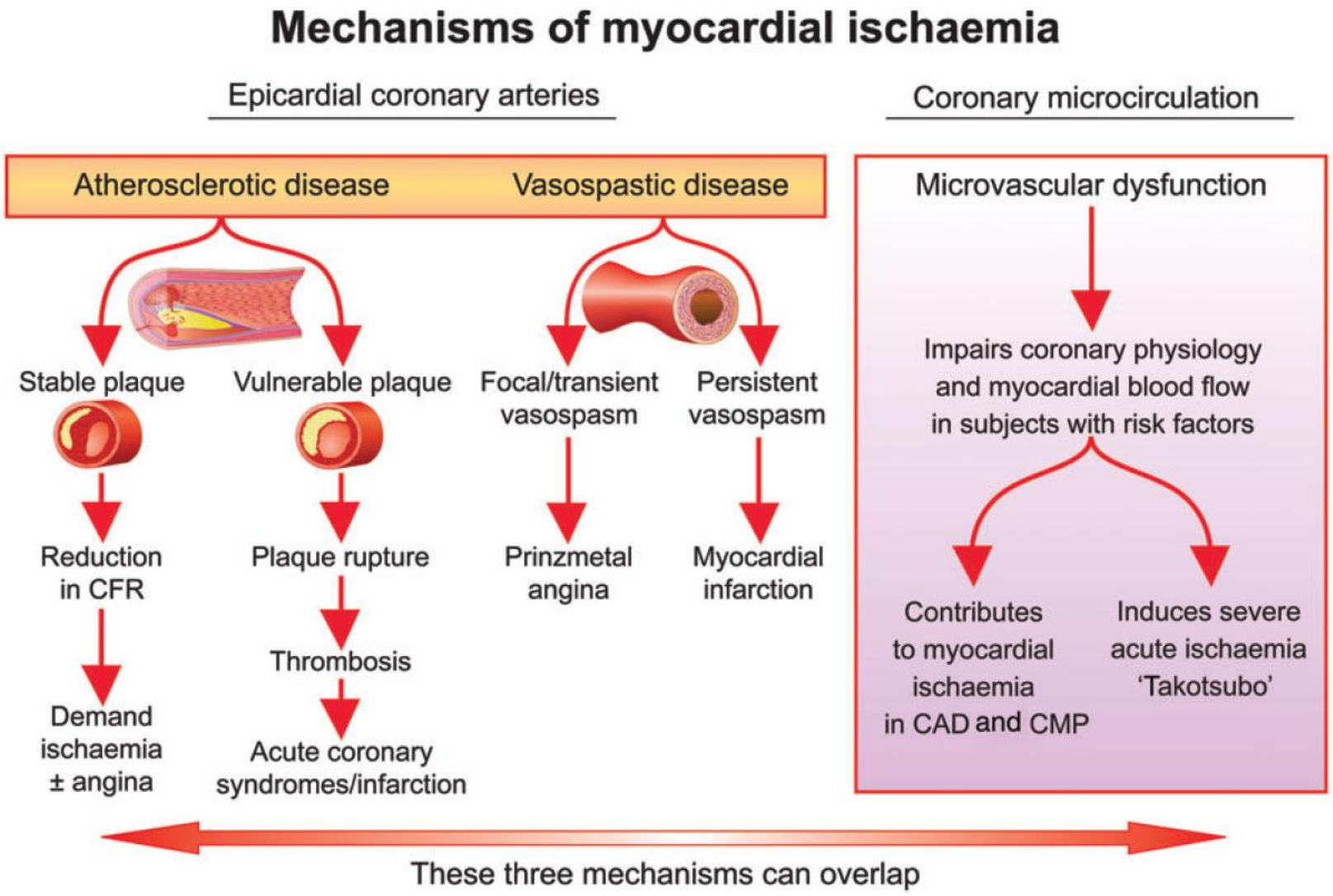
Primary Coronary Microvascular Dysfunction

Definition of Cardiac Syndrome X

- Typical stable angina, exclusively or predominantly induced by effort
- Findings compatible with myocardial ischemia/CMVD on diagnostic investigation
  - Diagnostic ST-segment depression during spontaneous or stress-induced myocardial scintigraphy or
  - Reversible prefusion defects on stress myocardial scintigraphy or,
  - Documentation of stress-related CBF abnormalities by more advanced diagnoistic techniques (eg, CMR, PET, Doppler ultrasound), or
  - Metabolic evidence of transient myocardial ischemia (cardiac PET or CMR, invasive assessment)
- Normal (or near normal; discrete very mild stenosis <20%) coronary arteries on angiography
- Absence of any other specific cardiac disease (e.g., variant angina, cardiomyopathy, valvular disease)

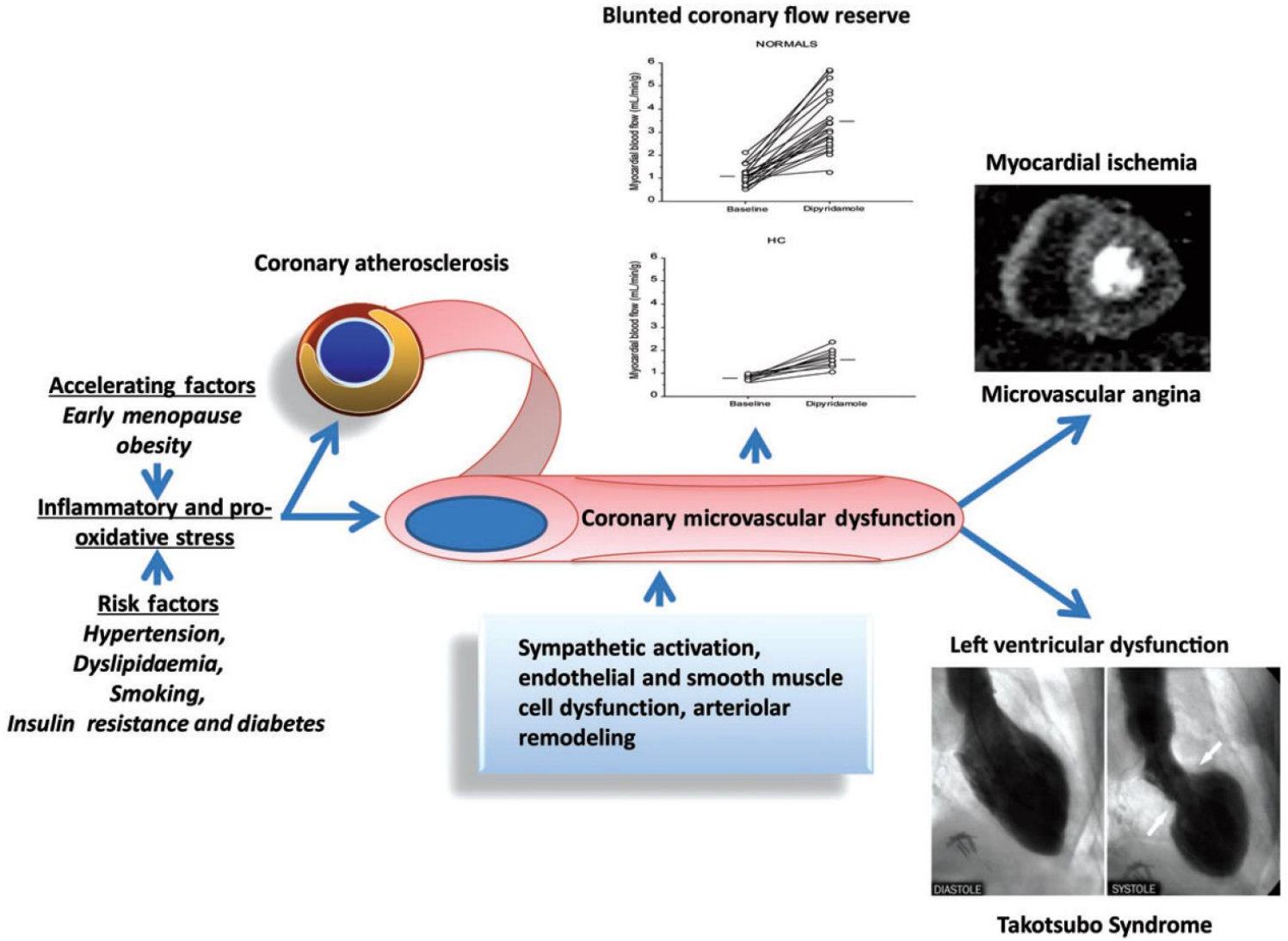
Camici PG, Crea F. *N Engl J Med* 2007;356:830-40
Herrmann J et al. *Eur Heart J* 2012;33:2771-81

Mechanisms of myocardial ischaemia



Crea F, EHJ, 2013

Scheme of the potential causes and consequences of coronary microvascular dysfunction



Crea F, EHJ, 2013

Clinical Classification of Coronary Microvascular Dysfunction (CMVD)

	Clinical setting	Main pathogenetic mechanisms
Type 1: in the absence of myocardial diseases and obstructive CAD	Risk factors Microvascular angina	Endothelial dysfunction SMC dysfunction Vascular remodelling
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy Dilated cardiomyopathy Anderson-Fabry's disease Amyloidosis Myocarditis Aortic stenosis	Vascular remodelling SMC dysfunction Extramural compression Luminal obstruction
Type 3: in obstructive CAD	Stable angina Acute coronary syndrome	Endothelial dysfunction SMC dysfunction Luminal obstruction
Type 4: iatrogenic	PCI Coronary artery grafting	Luminal obstruction Autonomic dysfunction

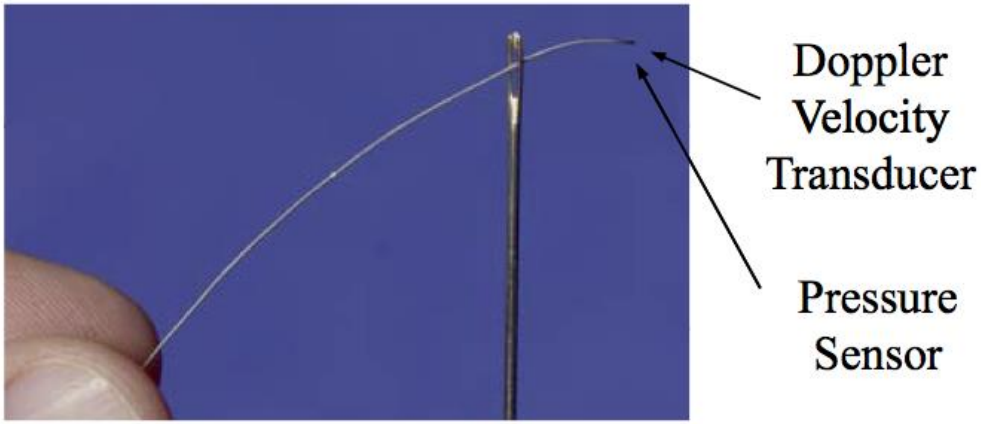
Camici PG, Crea F. *N Engl J Med* 2007;356:830-40
Herrmann J et al. *Eur Heart J* 2012;33:2771-81

Modalities to Assess Coronary Microvascular Function

Method	Tracer	Primary parameter	Secondary parameter	Microvascular distinction	Endothelial assessment	Pros	Cons
PET	Radioisotopes	MBF (0.6-1.3 mL/min/g)	MBF reserve (>2-2.5)	No	No	Validated and reproducibility	Limited availability, radioactivity
SPECT	Radioisotopes	Perfusion (no defect)	(perfusion reserve)	No	No	Availability, low cost	MBF only with dynamic upgrade, radioactivity
MDCT	Iodine contrast	MBF (0.6-1.3 mL/min/g)	MBF reserve (>2-2.5)	No	No	Availability	Investigational, image quality, radiation
MRI	Gadolinium	MBF (0.7-1.1 mL/min/g)	MBF reserve (>2-2.5)	No	No		Investigational, technical limitation
MCE	Echo contrast	Perfusion, MBF option (0.5-2.9 mL/min/g)	MBF reserve (>2-2.5)	No	No	One-stop test, no radiation, or radioactivity	Volumetric modeling, image quality
Doppler Echo	Echo contrast	Flow velocity (24-36 cm/s)	Flow reserve (>2-2.5)	No	No		No MBF option, position and image dependent
TFC	Iodine contrast	Contrast flow velocity (18-24)	TFC reserve (>2-2.5)	Assumed if no epicardial dx	No	Ease of use, low cost	No CBF option, subjectivity
MBG	Iodine contrast	Contrast staining (Grade 3)	None	Assumed if no epicardial dx	No	Ease of use, low cost	No CBF option, subjectivity
ICD	None	Flow velocity (10-20 cm/s)	CFR	Assumed if no epicardial dx	Yes	Direct measurement	No CBF option, subjectivity
ICD + QCA/IVUS	Iodine contrast	CBF (44-59 mL/min)	CBF reserve (>2-2.5)	Yes	Yes	Complete assessment	Costs, invasiveness
TPS	Saline	IMR (15-22 U)	None	Yes	Yes	Complete assessment	Costs, invasiveness

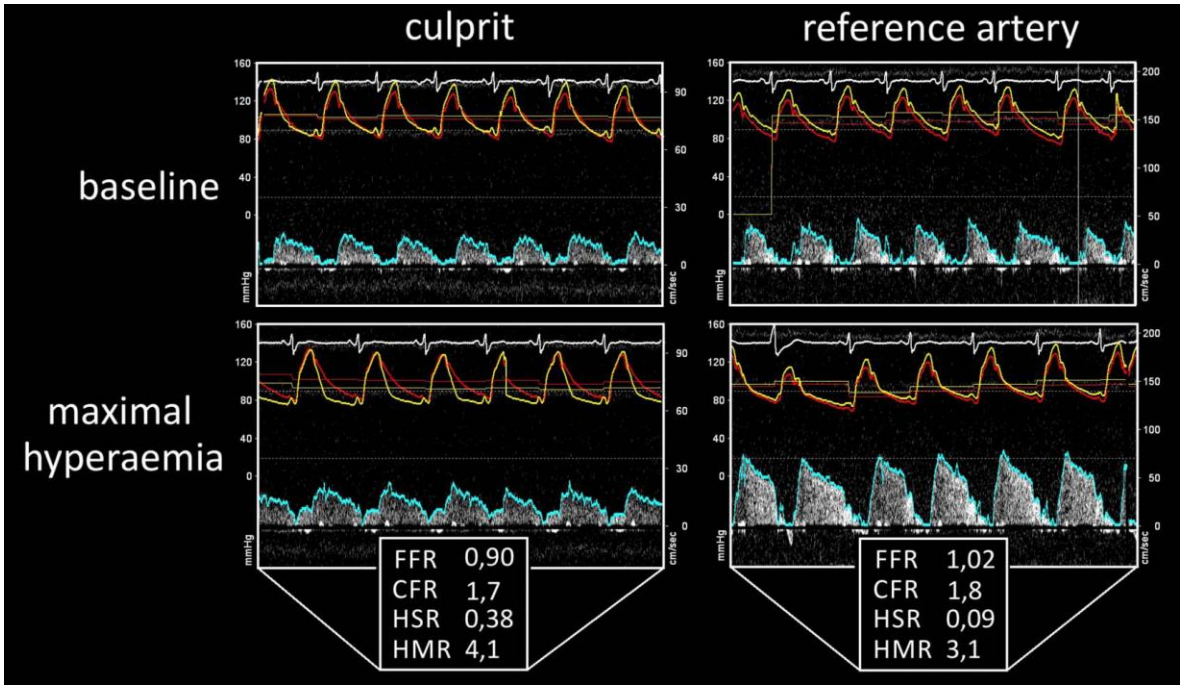
Herrmann J et al. *Eur Heart J* 2012;33:2771-81

ComboMap *Pressure and Flow* System, Volcano Therapeutics

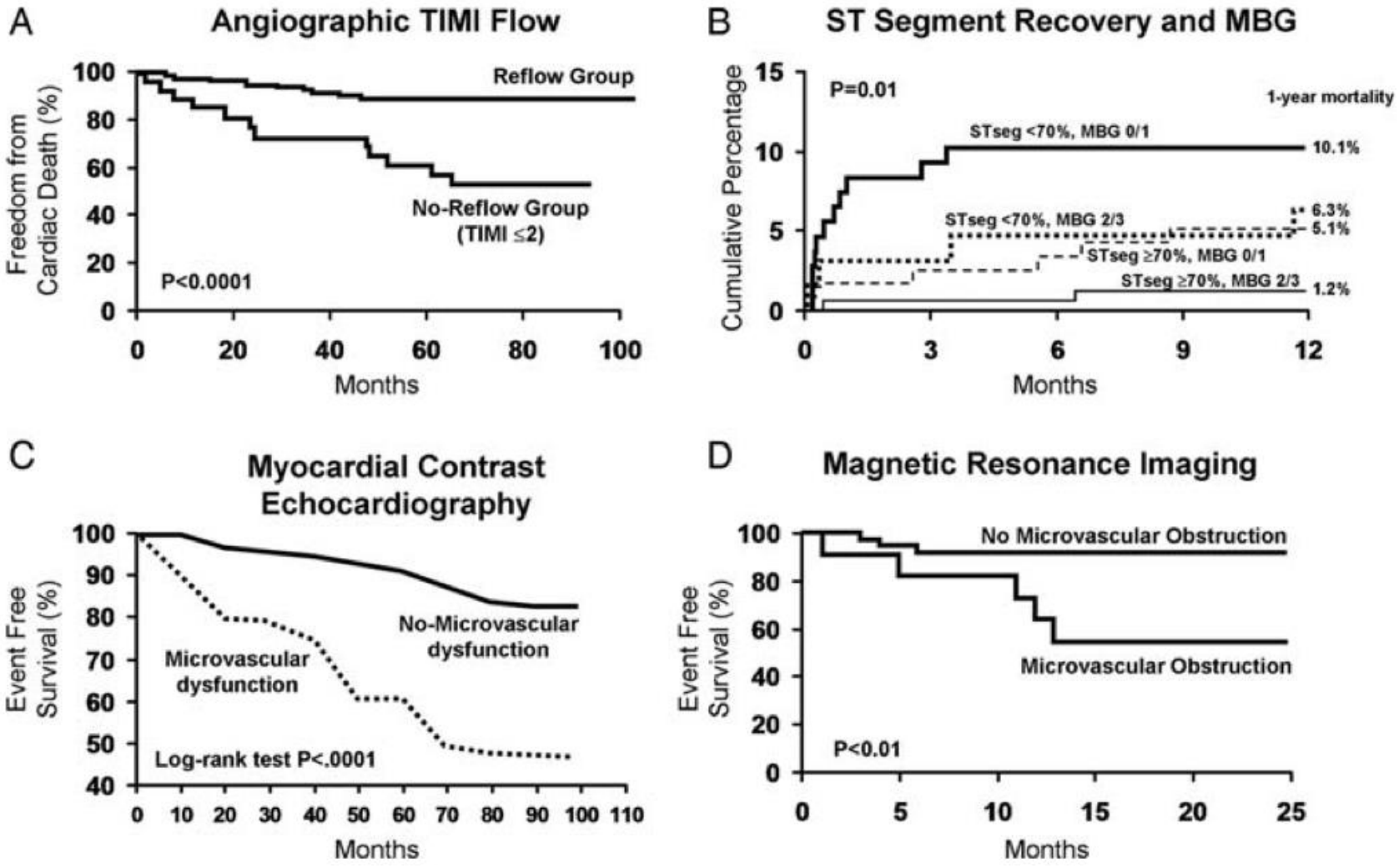


- hMR (hyperemic Microvascular Resistance)

  = mean Pd/hAPV (mmHg·cm^{-1}·s)

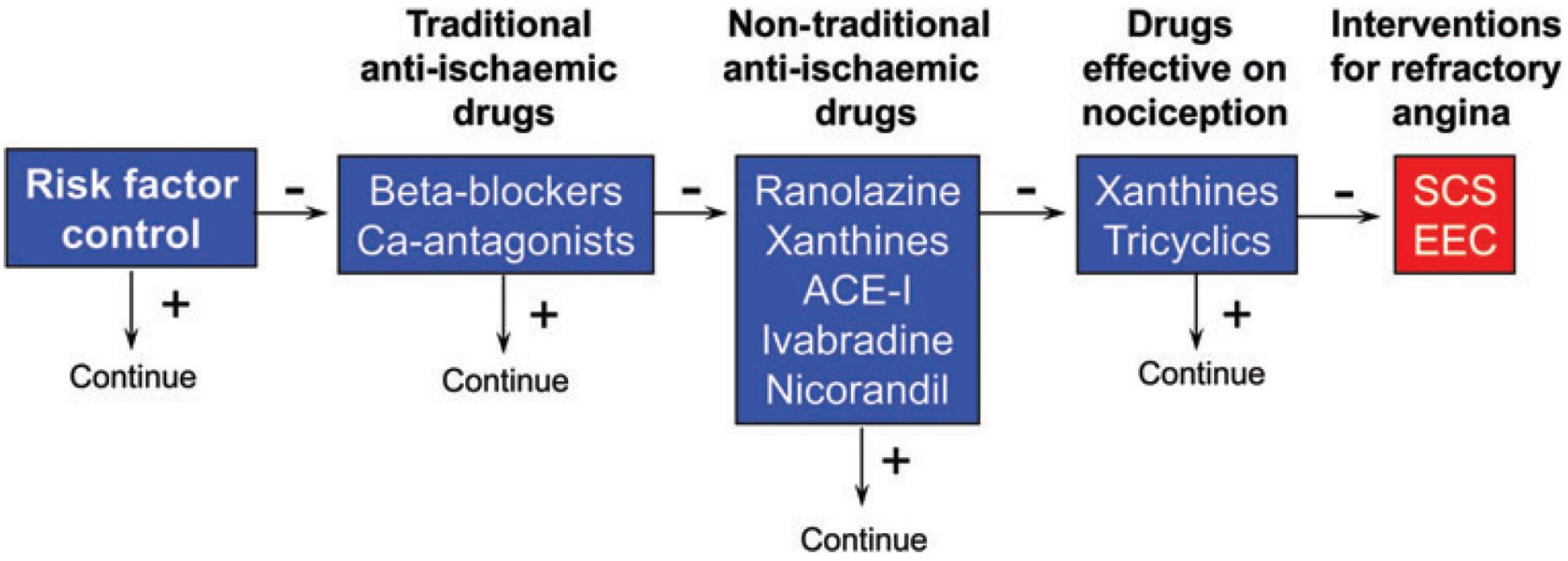


Prognostic Indicator Function of the Coronary Microcirculation



Herrmann J et al. *Eur Heart J* 2012;33:2771-81

Treatment algorithm for patients with microvascular angina



SCS, spinal cord stimulation; EEC, enhanced external counterpulsation.

Diabetes

Focus on microvascular disease

Diabetes: complications

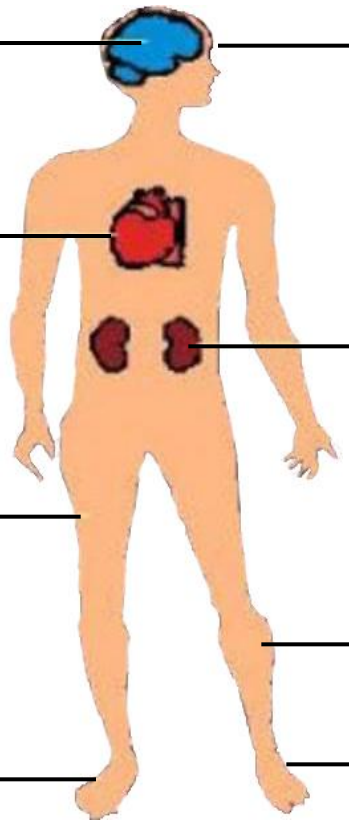
Macrovascular

Stroke

Heart disease and hyptertension

Peripheral vascular disease

Foot problems



Microvascular

Diabetic eye disease (retinopathy and cataracts)

Renal disease

Neuropathy

Foot problems

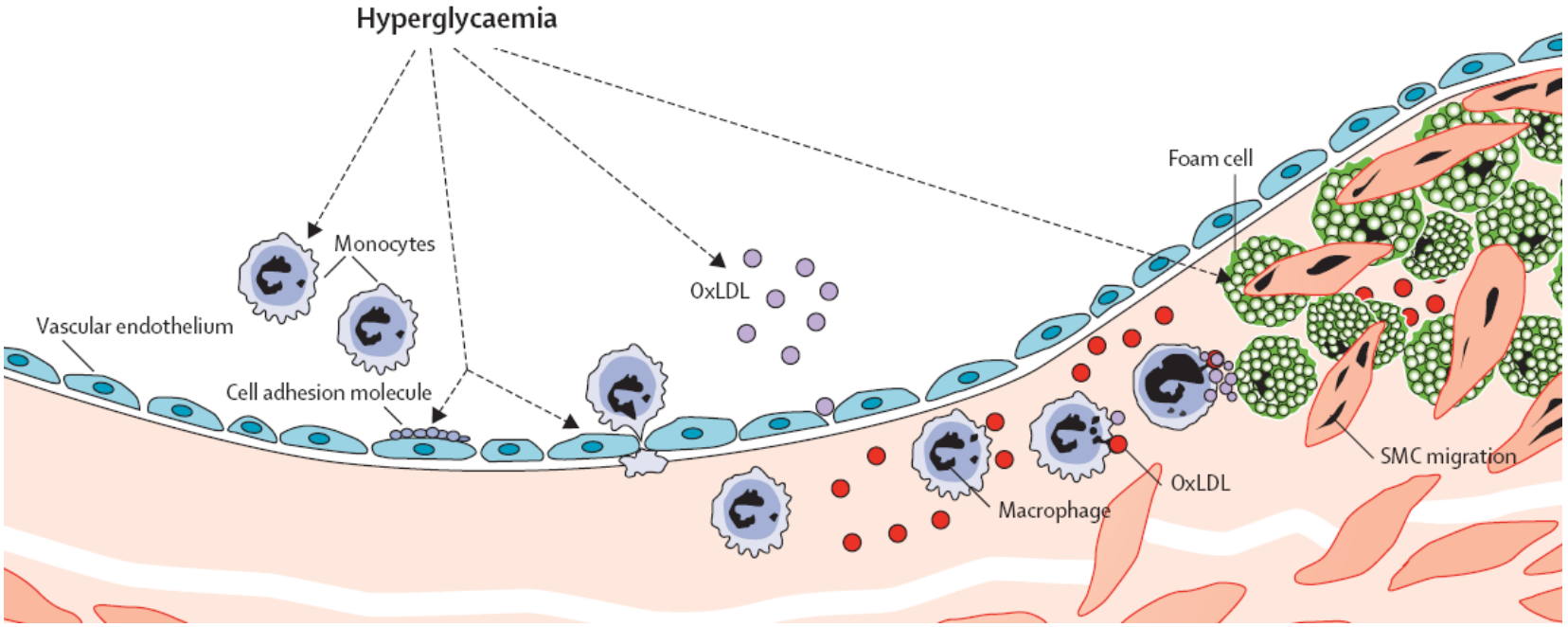
Type 1 diabetes, hyperglycaemia, and the heart

Ravi Retnakaran, Bernard Zinman

Lancet 2008; 371: 1790–99

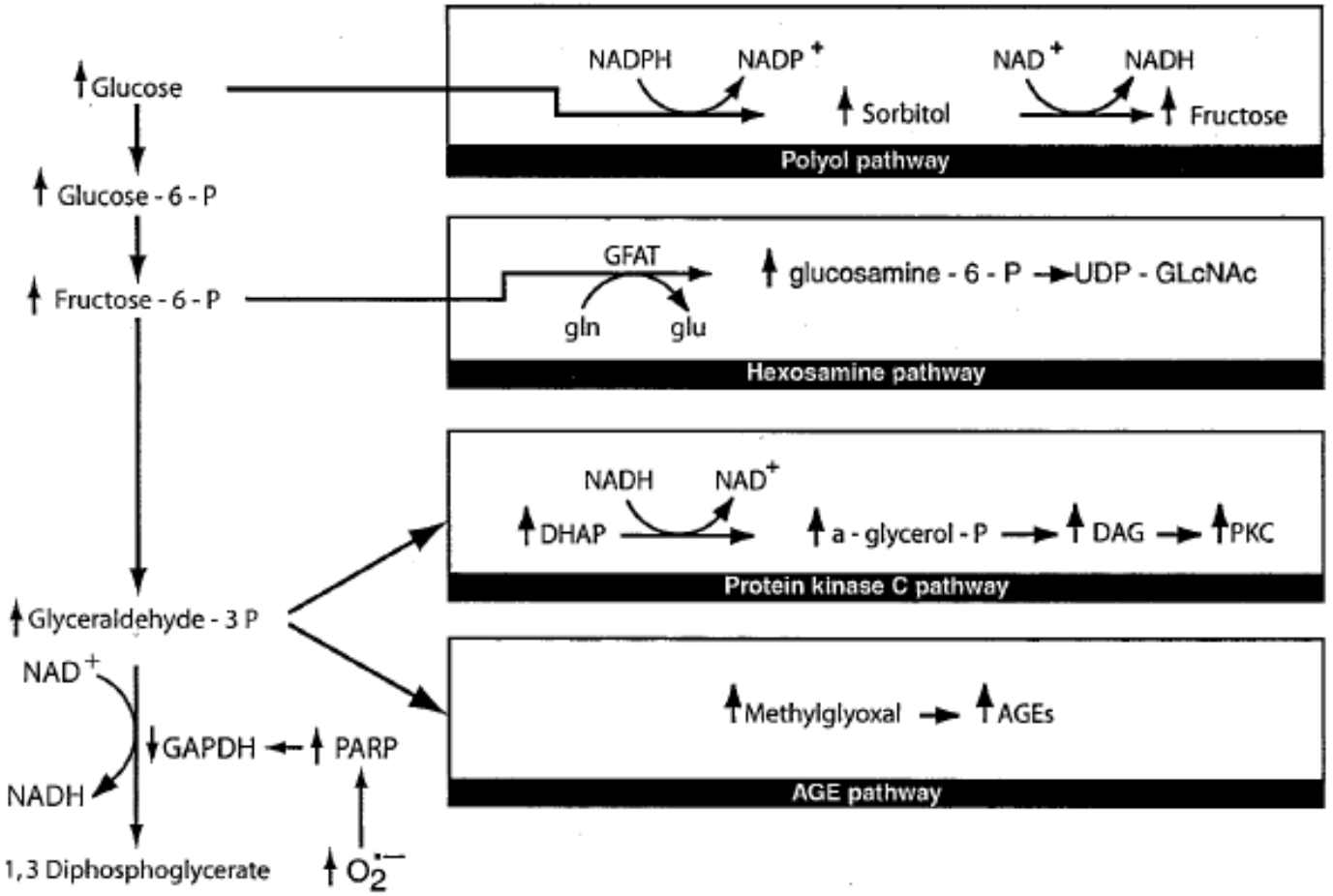
Type 1 diabetes is associated with a substantially increased risk of cardiovascular disease tha

Hyperglycemia is toxic at several steps in the atherosclerosis process



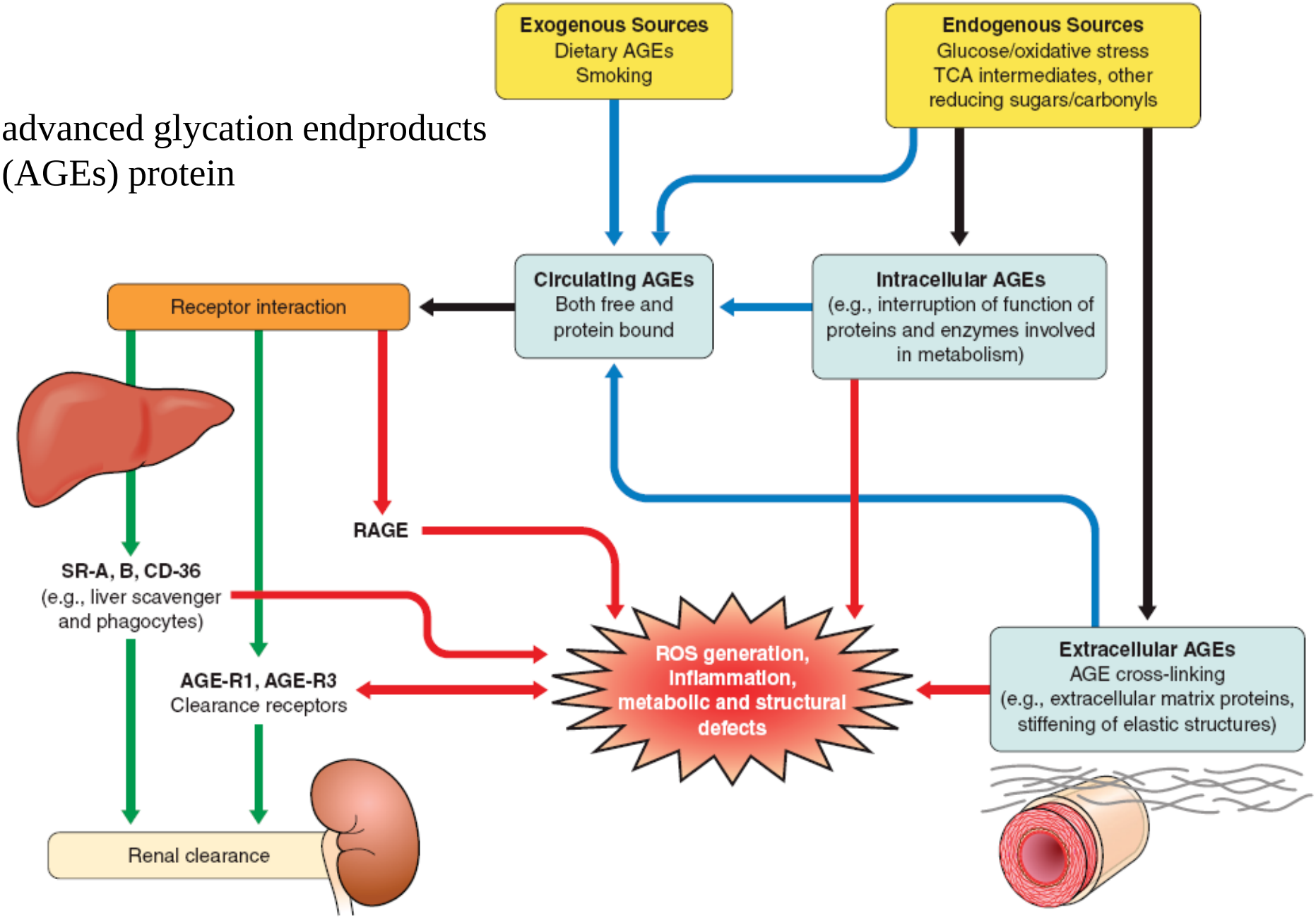
Retnakaran R, Zinman B. Lancet 2008;371:1790-99.

Metabolic Pathways Leading to Microvascular Complications

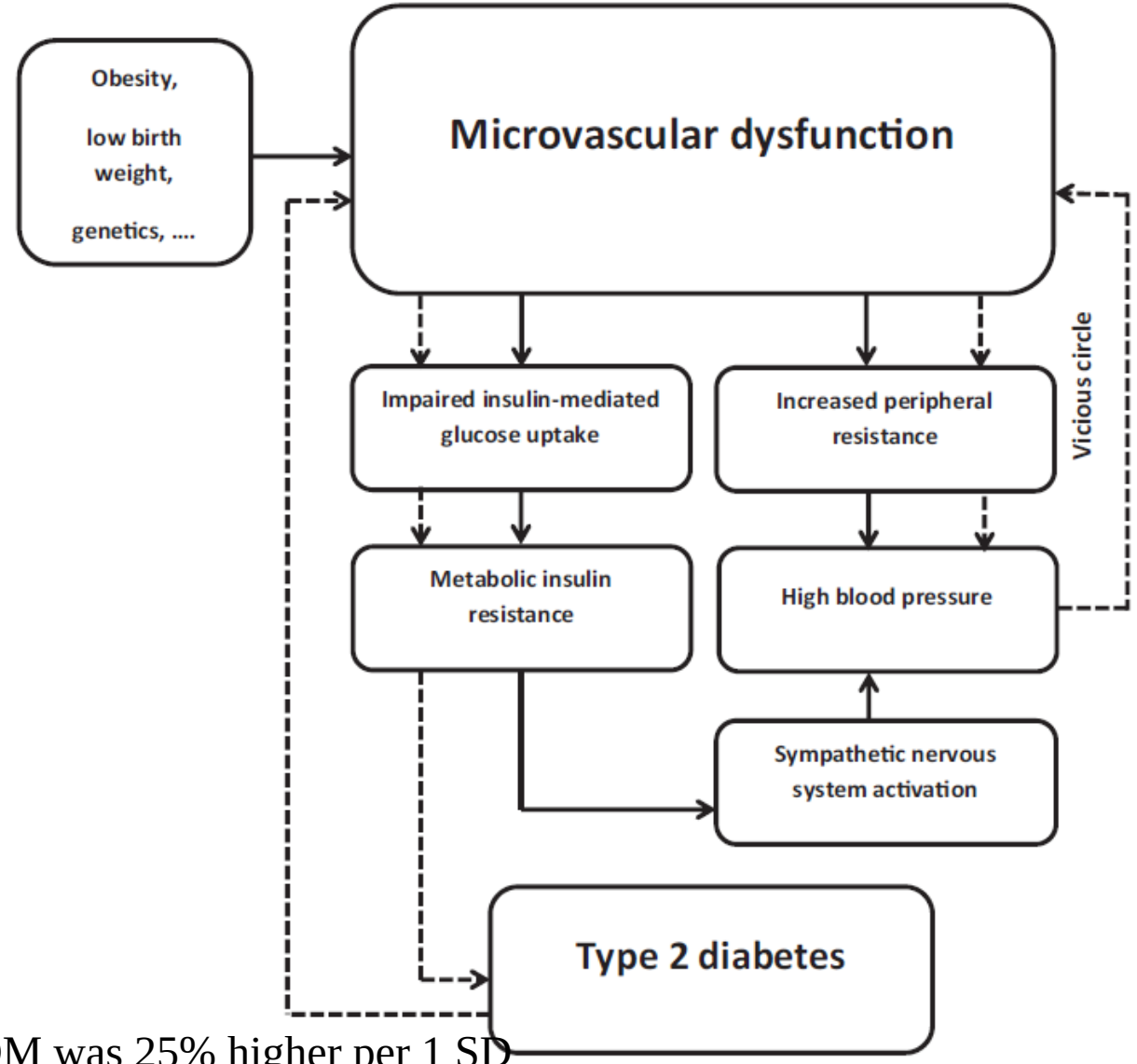


Brownlee M. Diabetes 54:1615, 2005

advanced glycation endproducts (AGEs) protein



contribution of microvascular dysfunction to insulin resistance, type 2 diabetes and hypertension



incident T2DM was 25% higher per 1 SD greater microvascular dysfunction

Intersection of Microangiopathy and Macroangiopathy in Accelerated Atherosclerosis

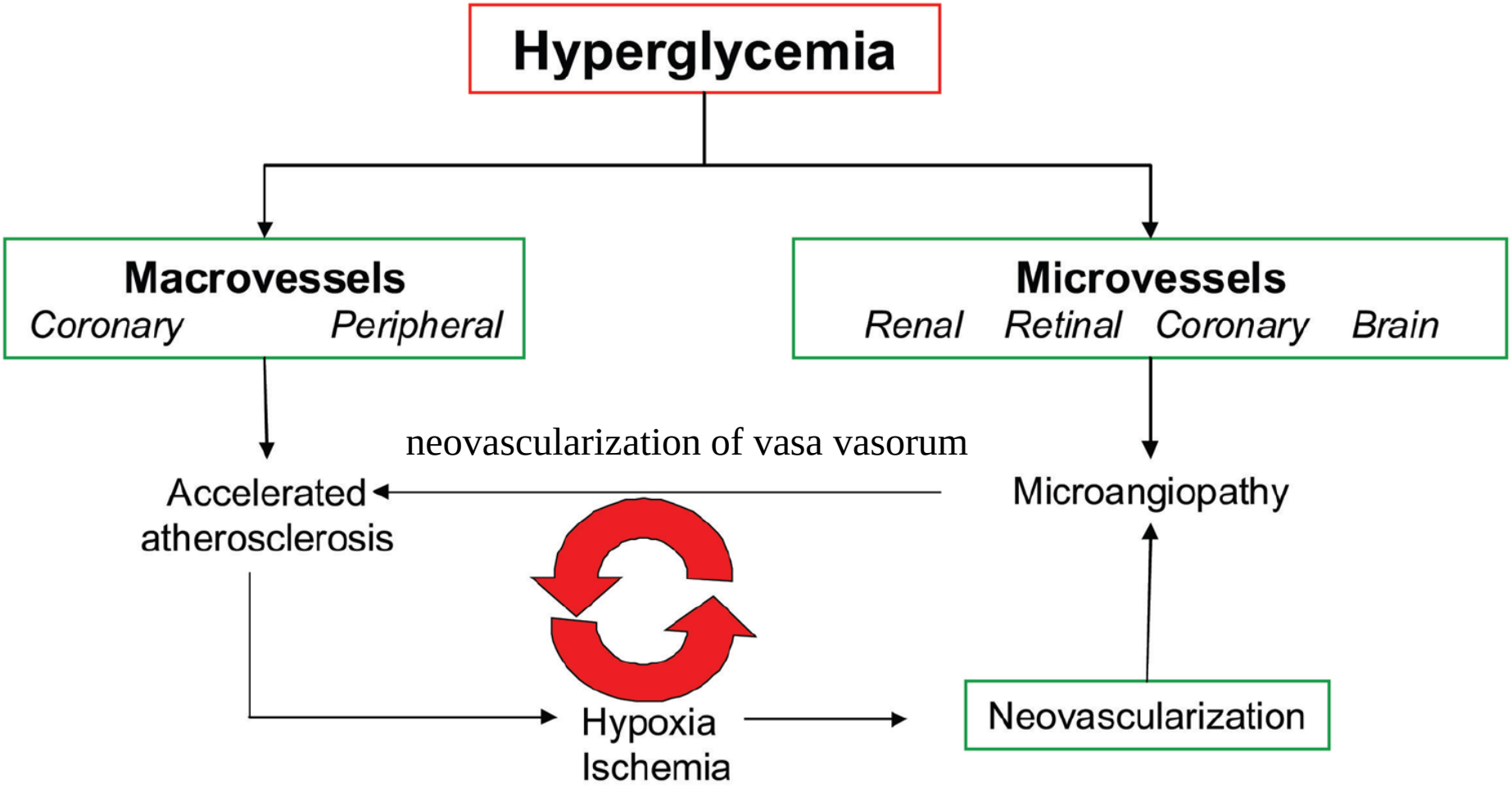
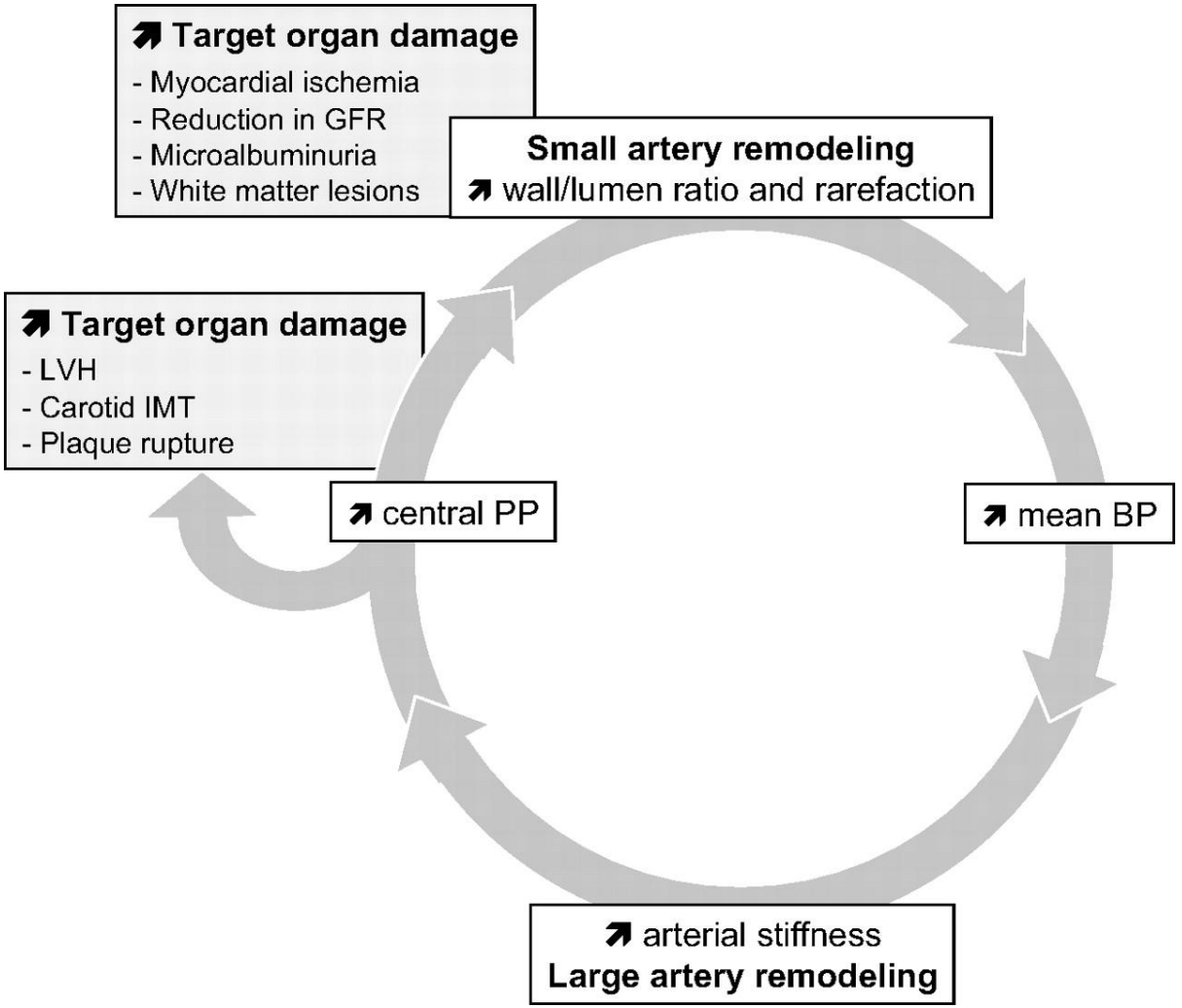
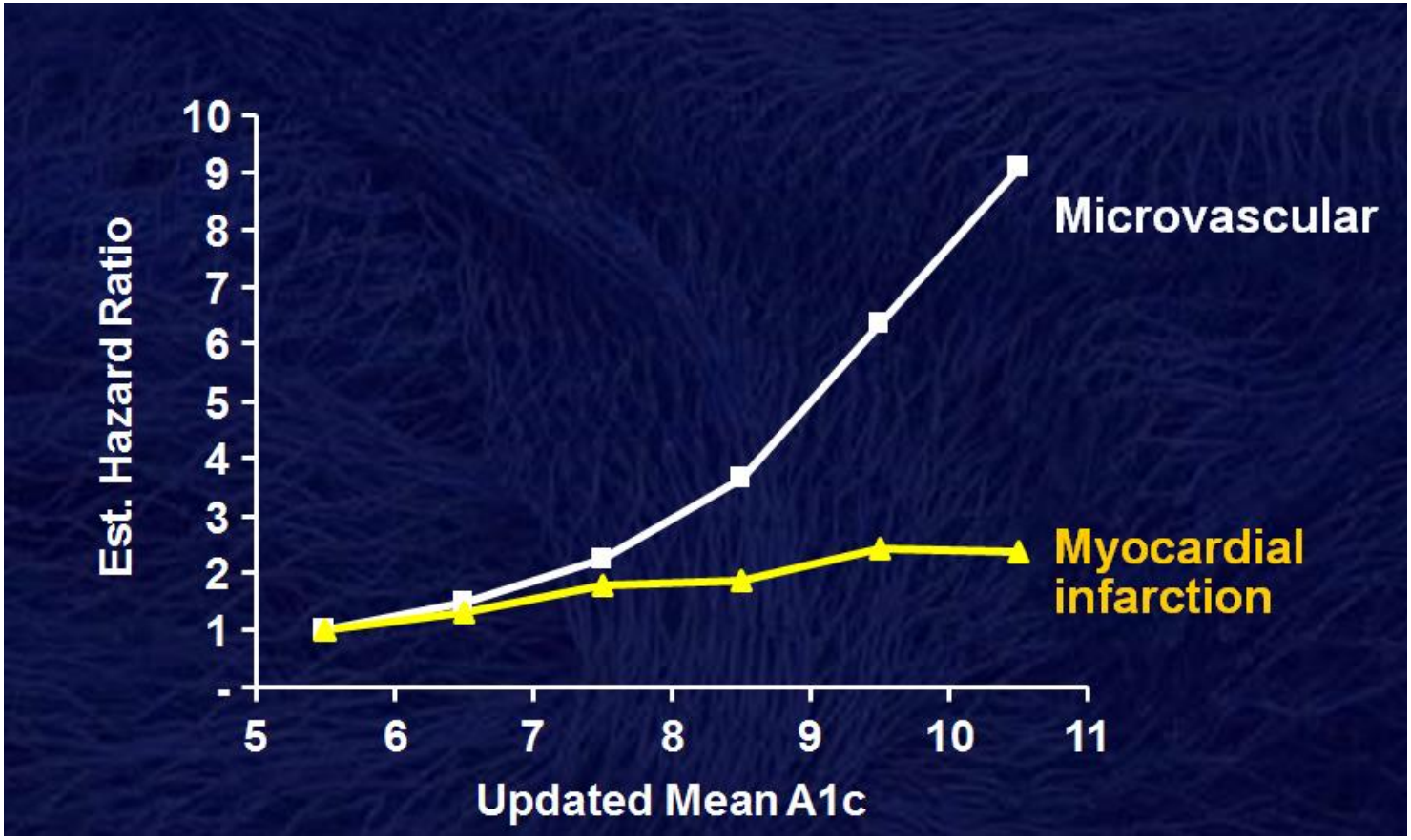


Figure 1. Large/small artery cross-talk: a vicious circle of aggravation between microcirculation and macrocirculation in hypertensives.



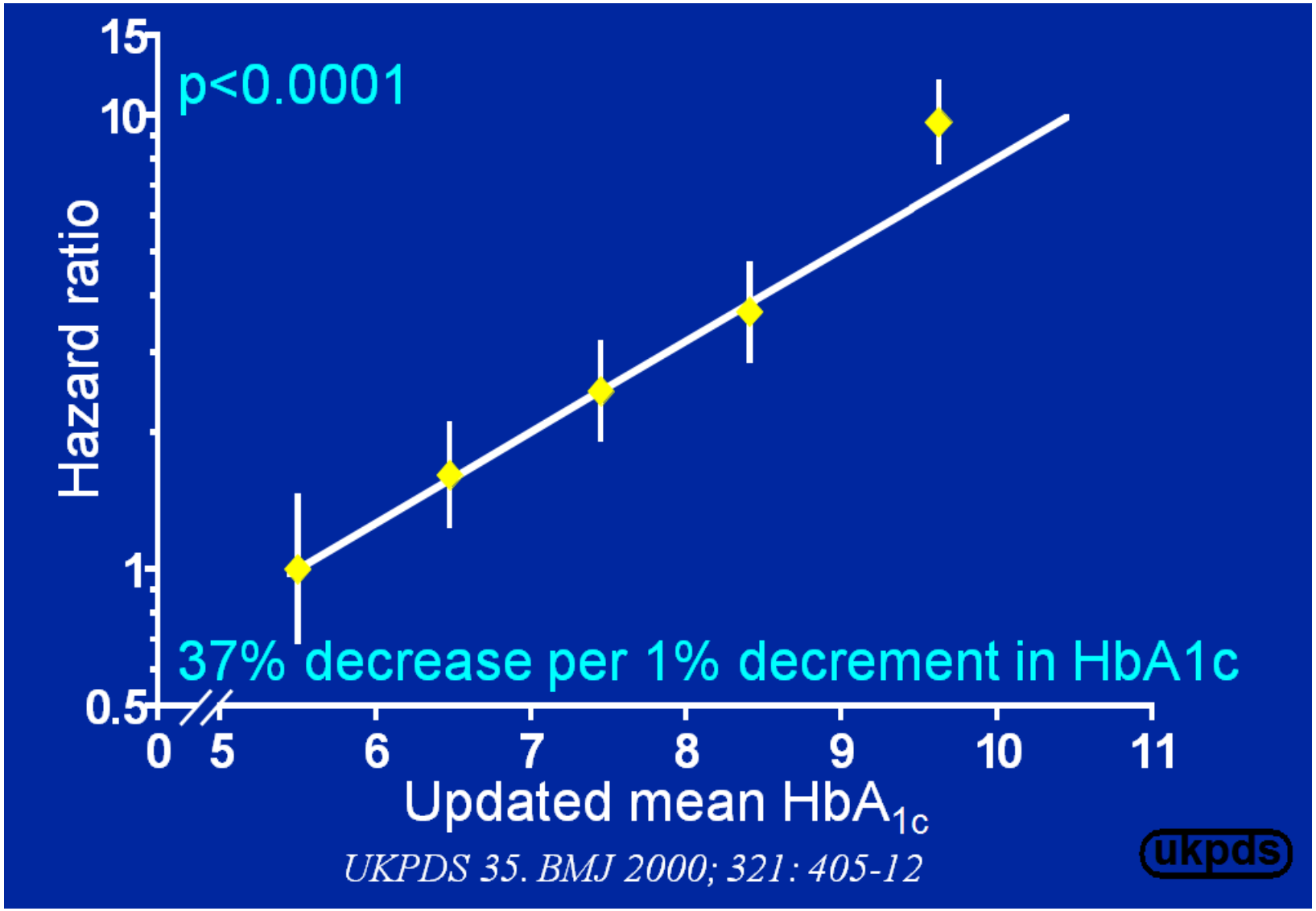
Laurent S et al. *Hypertension*. 2009;54:388-392

UKPDS: A1c as Predictor of Micro- and Macrovascular Disease



Stratton IM et al. *BMJ*. 2000; 321:405-412.

Microvascular Endpoints

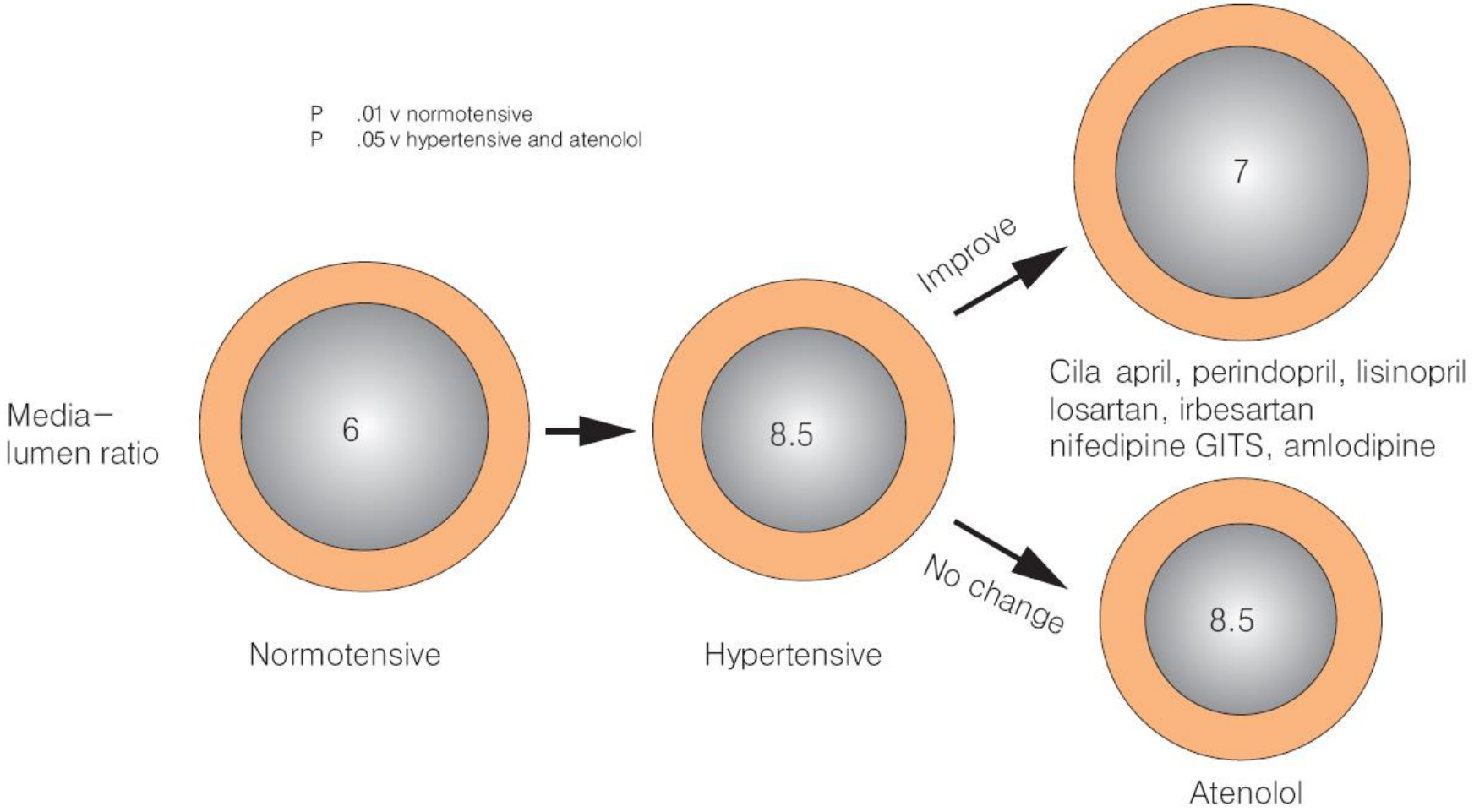


Glucose Control and microvascular complication

The intensive glucose control policy maintained a lower over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

12%	for any diabetes related endpoint	p=0.029
25%	for microvascular endpoints	p=0.0099
21%	for retinopathy at twelve years	p=0.015
33%	for albuminuria at twelve years	p=0.000054

소혈관 재형성에 고혈압 약제

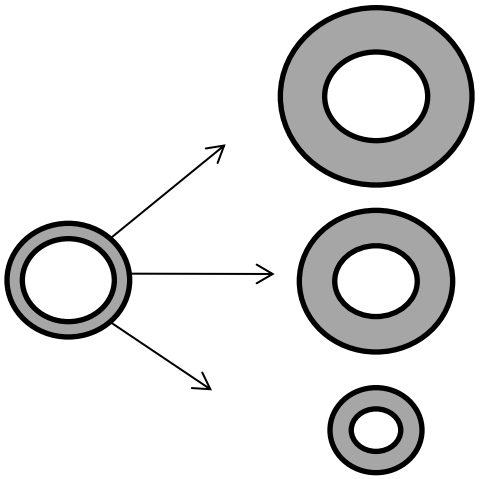


What we can see is only 5% of the total artery tree.

Courtesy of Dr. Gibson

감사합니다

Normal **hypertensive**



Hypertrophic
Outward remodeling
(no change in passive lumen diameter)

Hypertrophic
inward remodeling
(reduced passive lumen diameter)

Eutrophic
inward remodeling
(reduced passive lumen diameter)

Vessel type
Conduit arteries

Resistance vessels
(small arteries, arterioles)