Υπέρταση
Κατευθυντήριες οδηγίες στην Π.Φ.Υ.

Φραγκούλης Χρήστος

Επιμελητής Β΄, Α΄ Πανεπιστημιακή Καρδιολογική Κλινική, Ιπποκράτειο ΓΝΑ

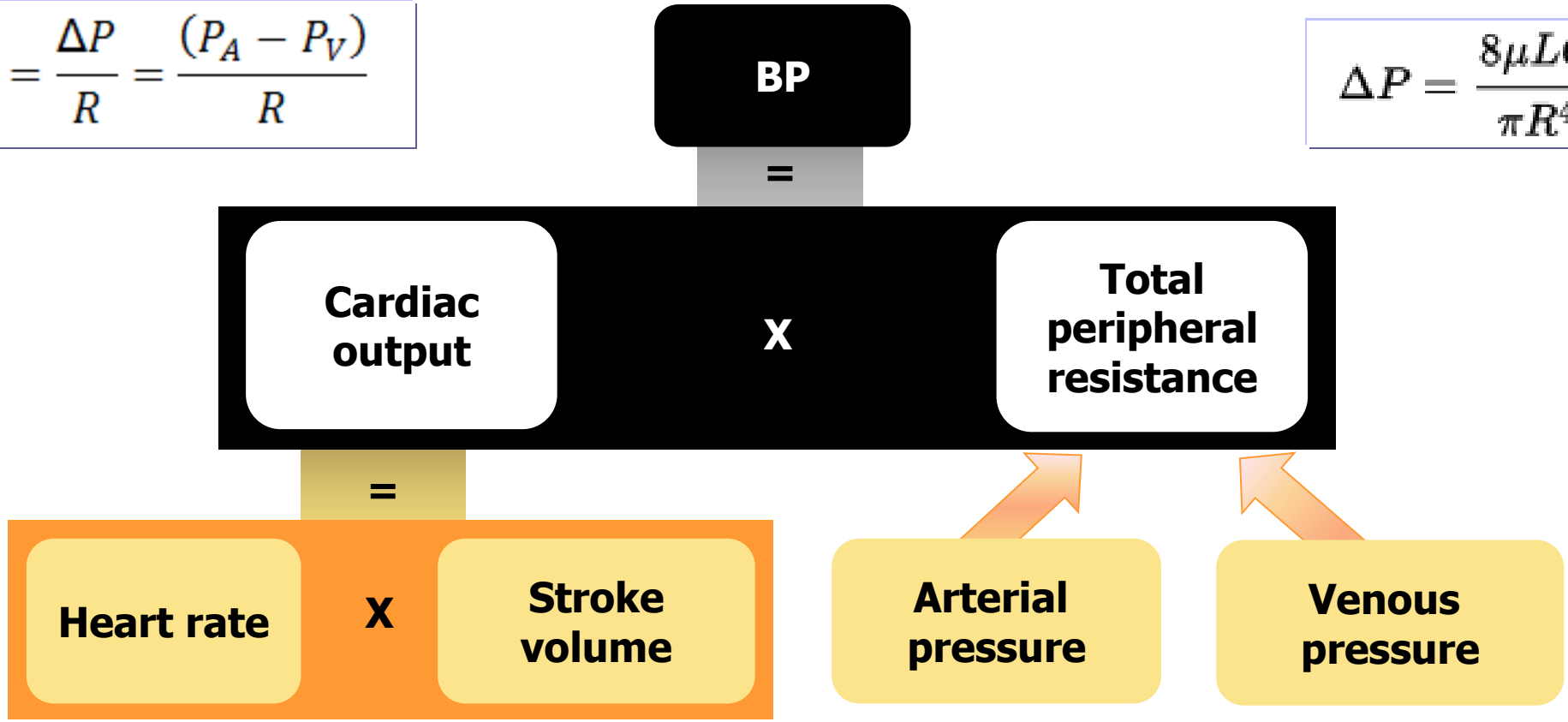
Pathophysiology of hypertension

Darcy's law (adaptation of Ohms law)

$$F = \frac{\Delta P}{R} = \frac{(P_A - P_V)}{R}$$

Pouiseuille's law

$$\Delta P = \frac{8\mu LQ}{\pi R^4},$$



Regulation of blood pressure

- BP values are maintained within the relevant range by moment-to-moment regulation of **cardiac output** and of **peripheral vascular resistance** exerted primarily at the level of the arterioles, postcapillary venules and heart.

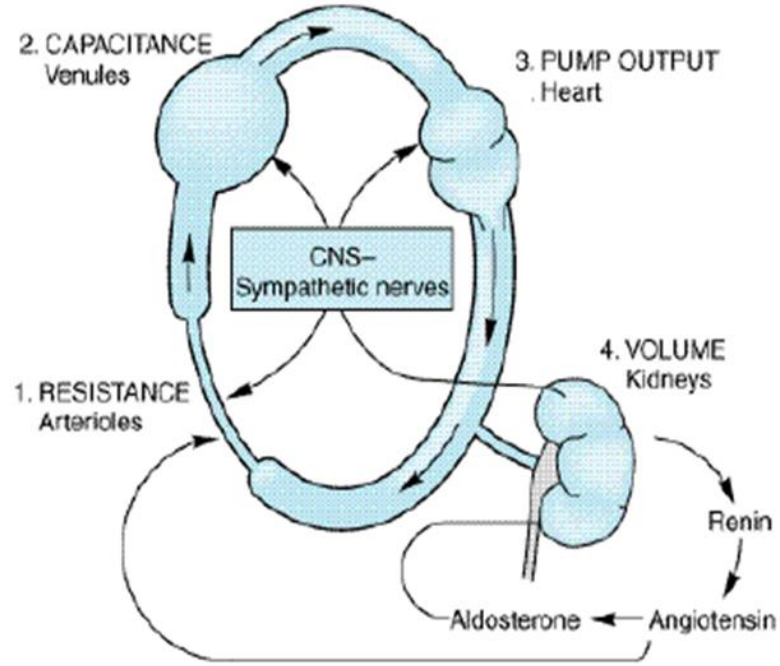
The most important dimensions of this regulation are as follows:

– The ***heart*** contributes to the maintenance of BP via cardiac output

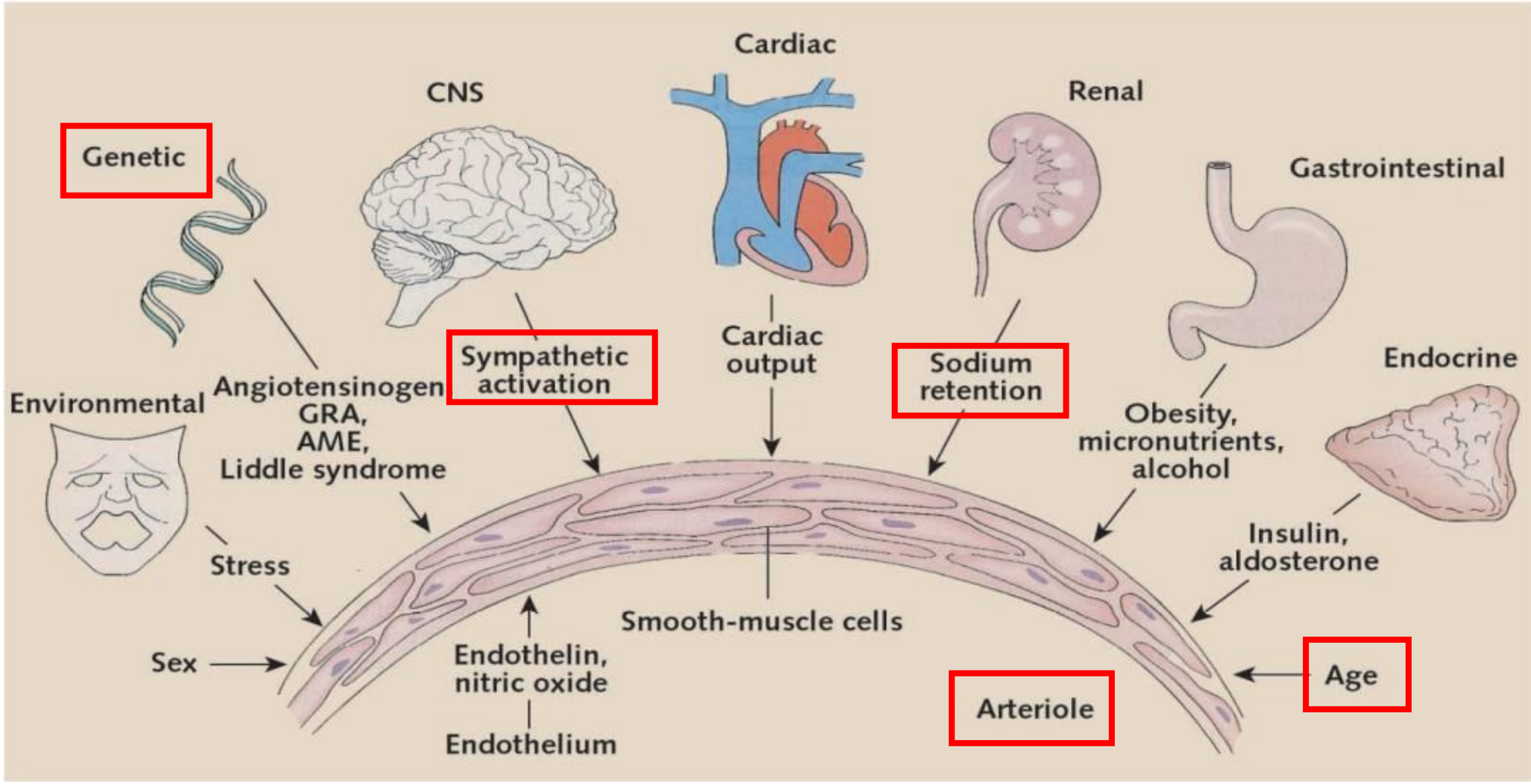
– The ***kidney*** contributes by regulating the volume of the fluid present in the vessels.

– *The* ***internal cellular lining of the walls of the blood vessels*** regulates vascular resistance via local release of hormones such as endothelin-1 and nitric oxide.

– The ***baroreceptors*** are responsible for the rapid moment-to-moment adjustments in blood pressure affected by postural changes

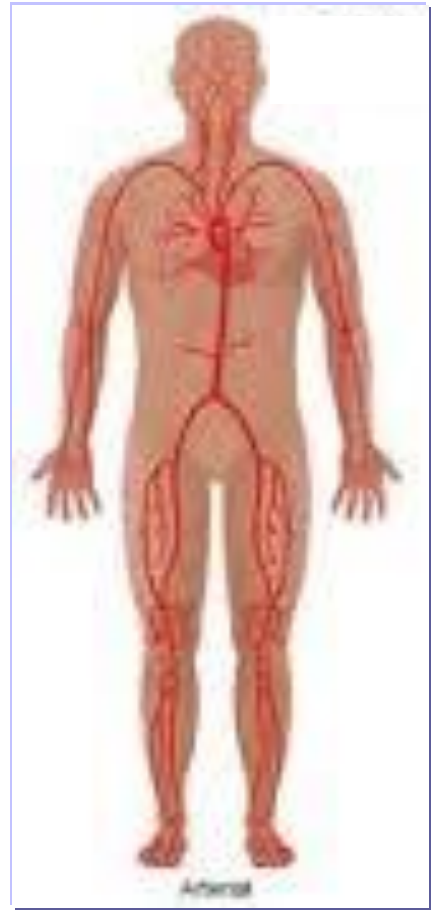


Hypertension: a multifactorial disease

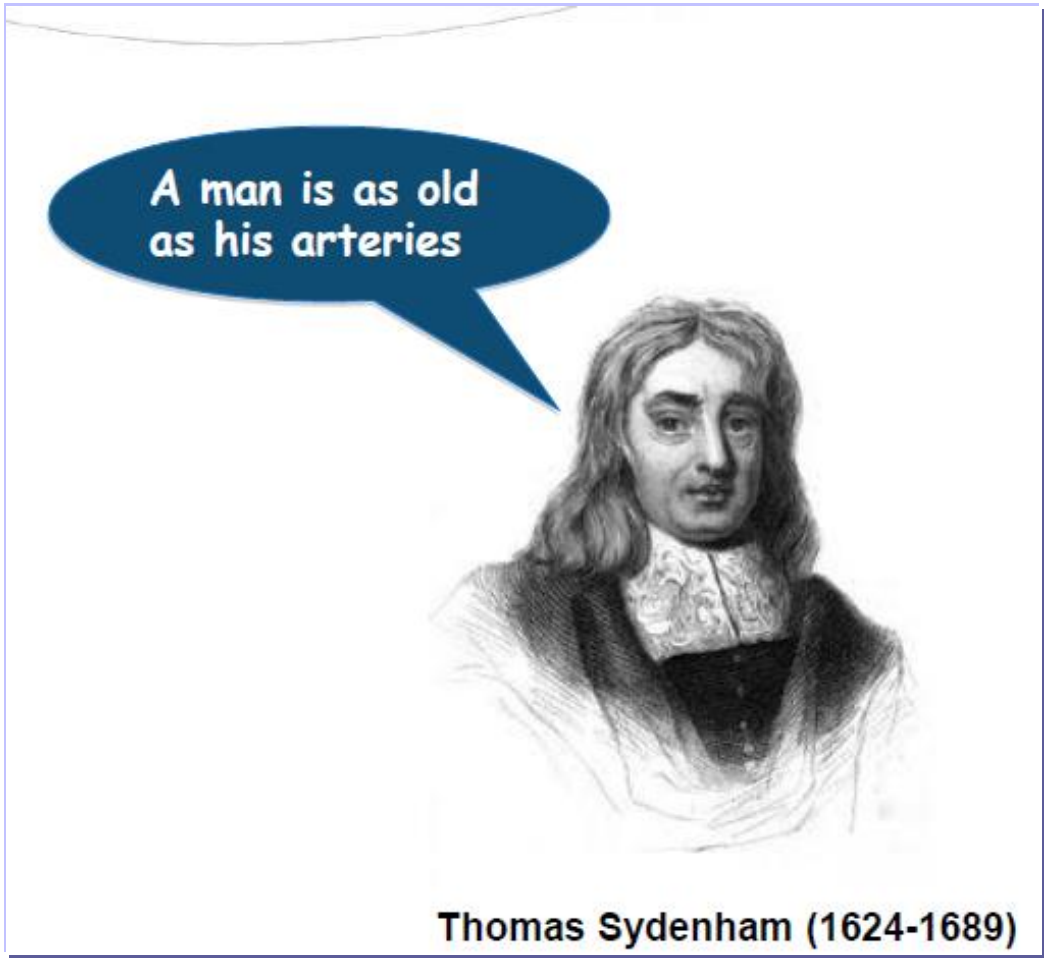


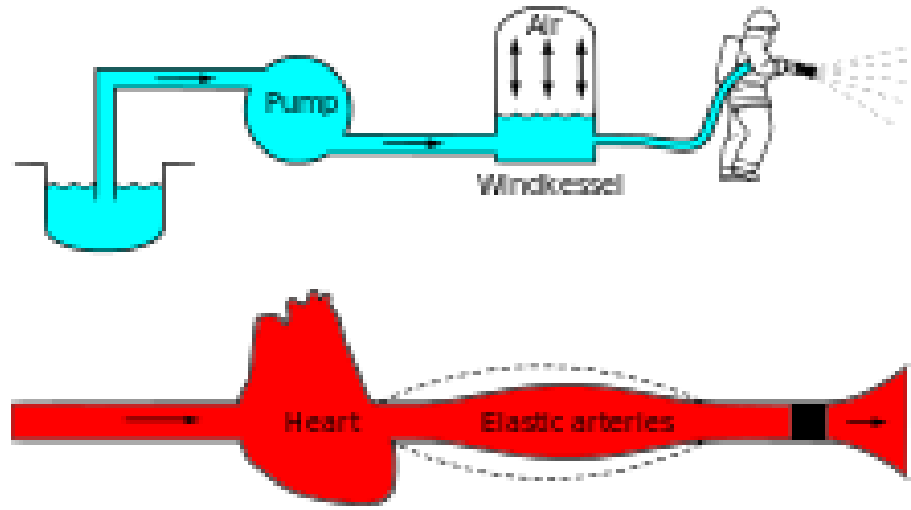
Oparil S, et al. Ann Intern Med. 2003;139:761-776

Υπέρταση και αγγεία



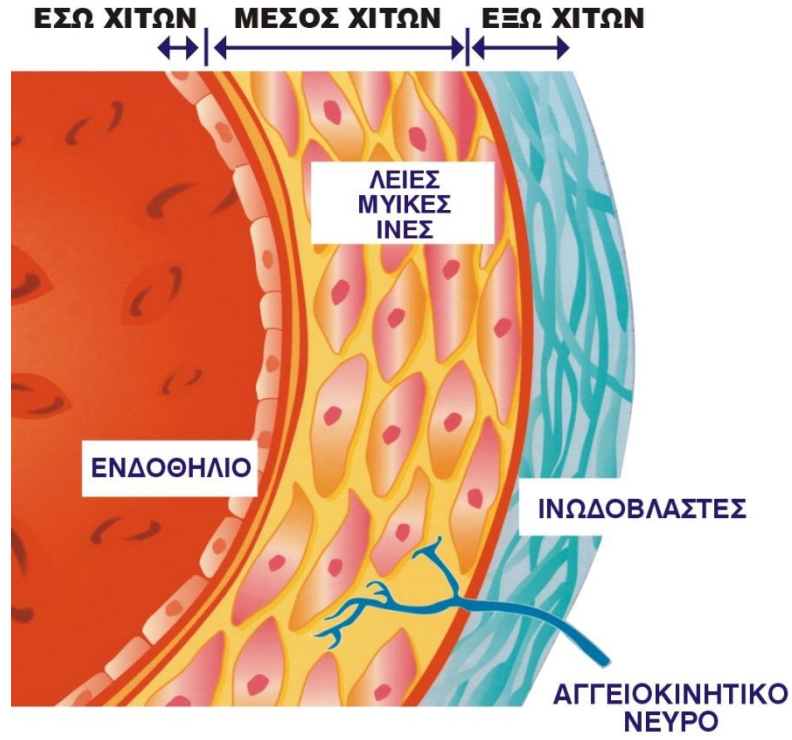
Vascular aging





Αρτηριακή υπέρταση ως αγγειακή νόσος

- Μειωμένη **διατασιμότητα** των μεγάλων αρτηριών
- Αυξημένη **ταχύτητα αγωγής** σφυγμικού κύματος
- Πρώιμη επιστροφή των **ανακλωμένων κυμάτων**
- Δυσλειτουργία του **ενδοθηλίου**
- Αυξημένες **περιφερικές αντιστάσεις**

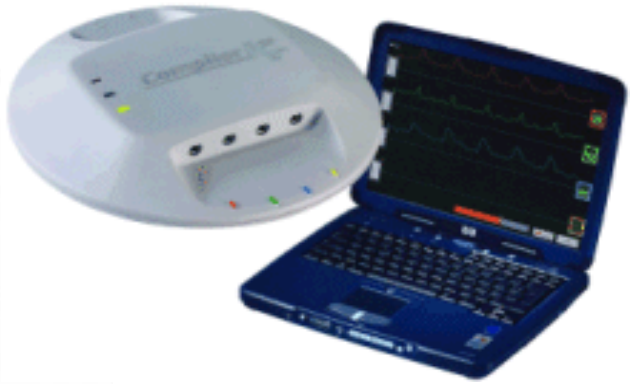


Aortic stiffness - Evaluation

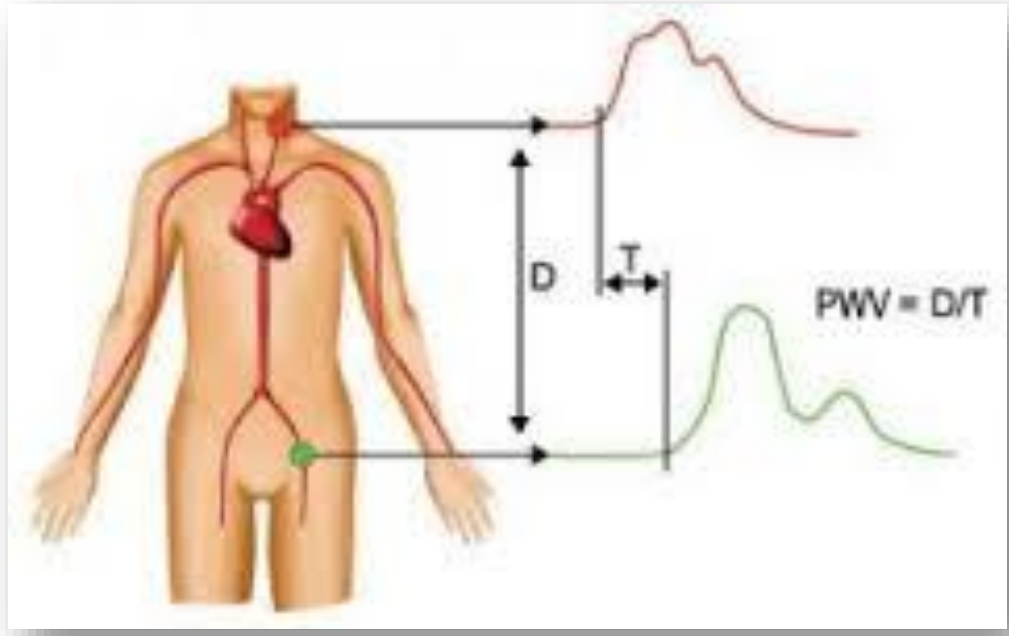
Pulse Wave Velocity

A

Tonometer



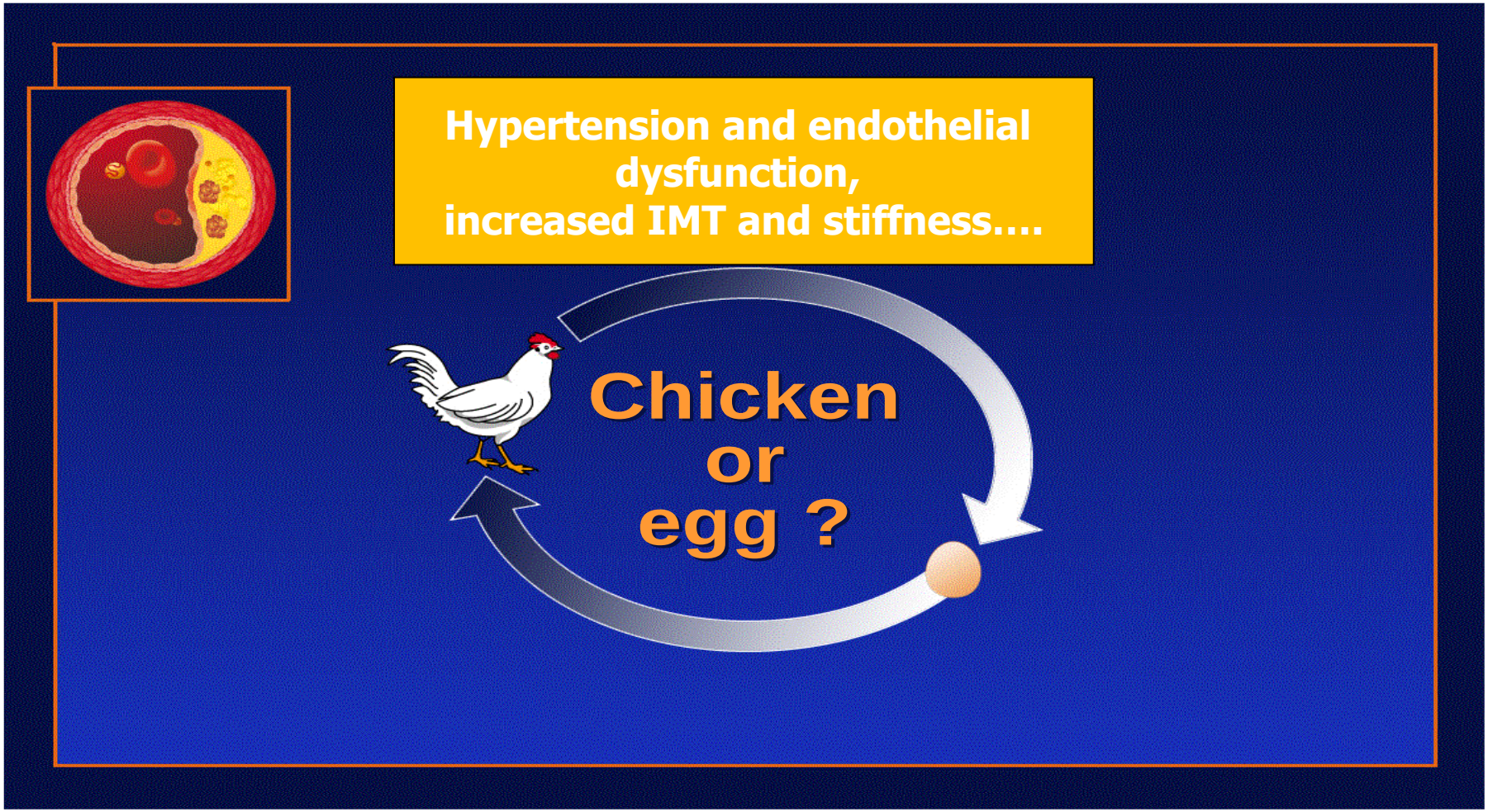
B



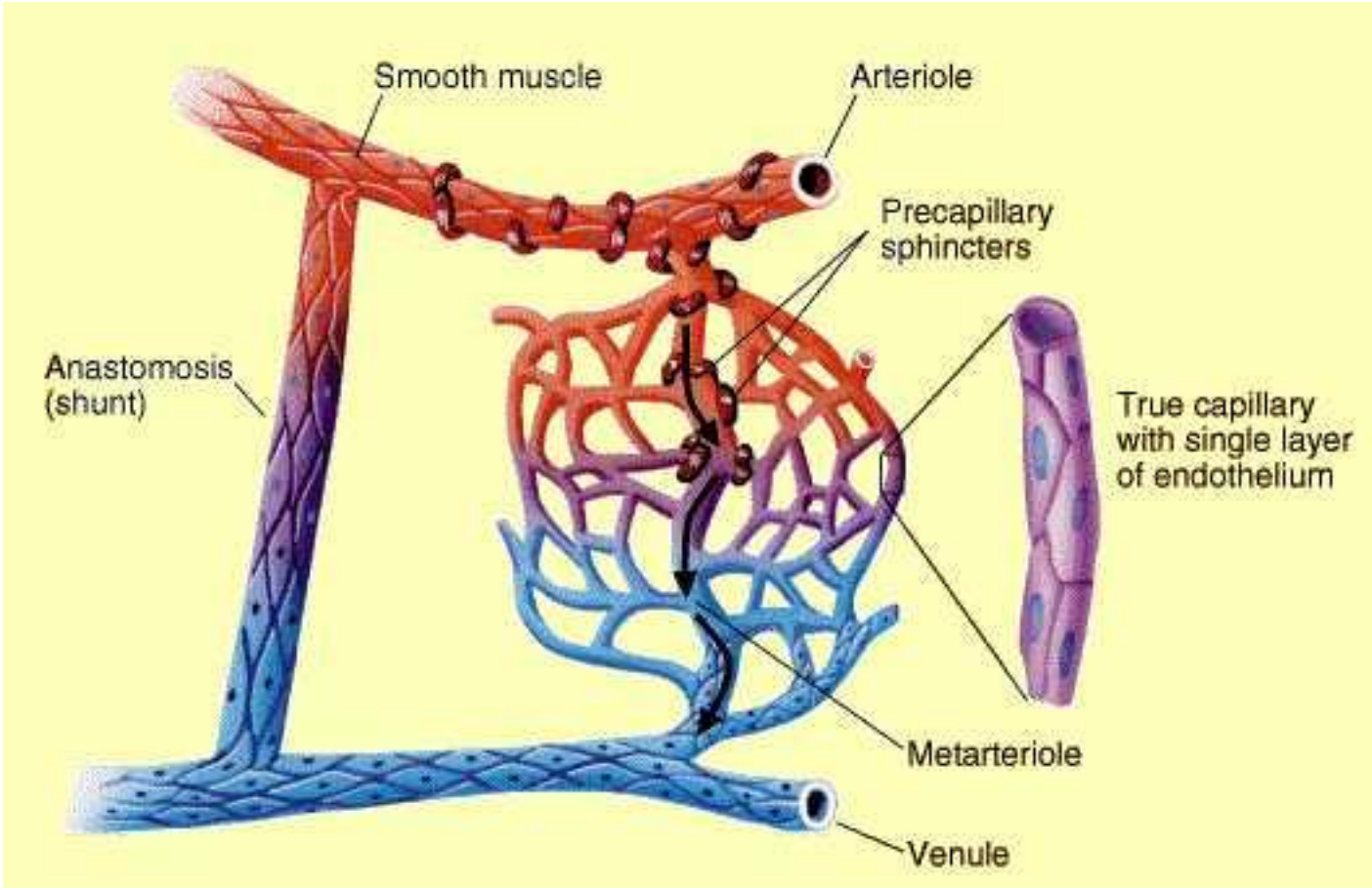
$$PWV = \frac{L\ (m)}{time\ (sec)}$$

- Easy to perform – learning curve
- Reproducible
- Not expensive ?

The data so far: The Chicken-Egg Phenomenon

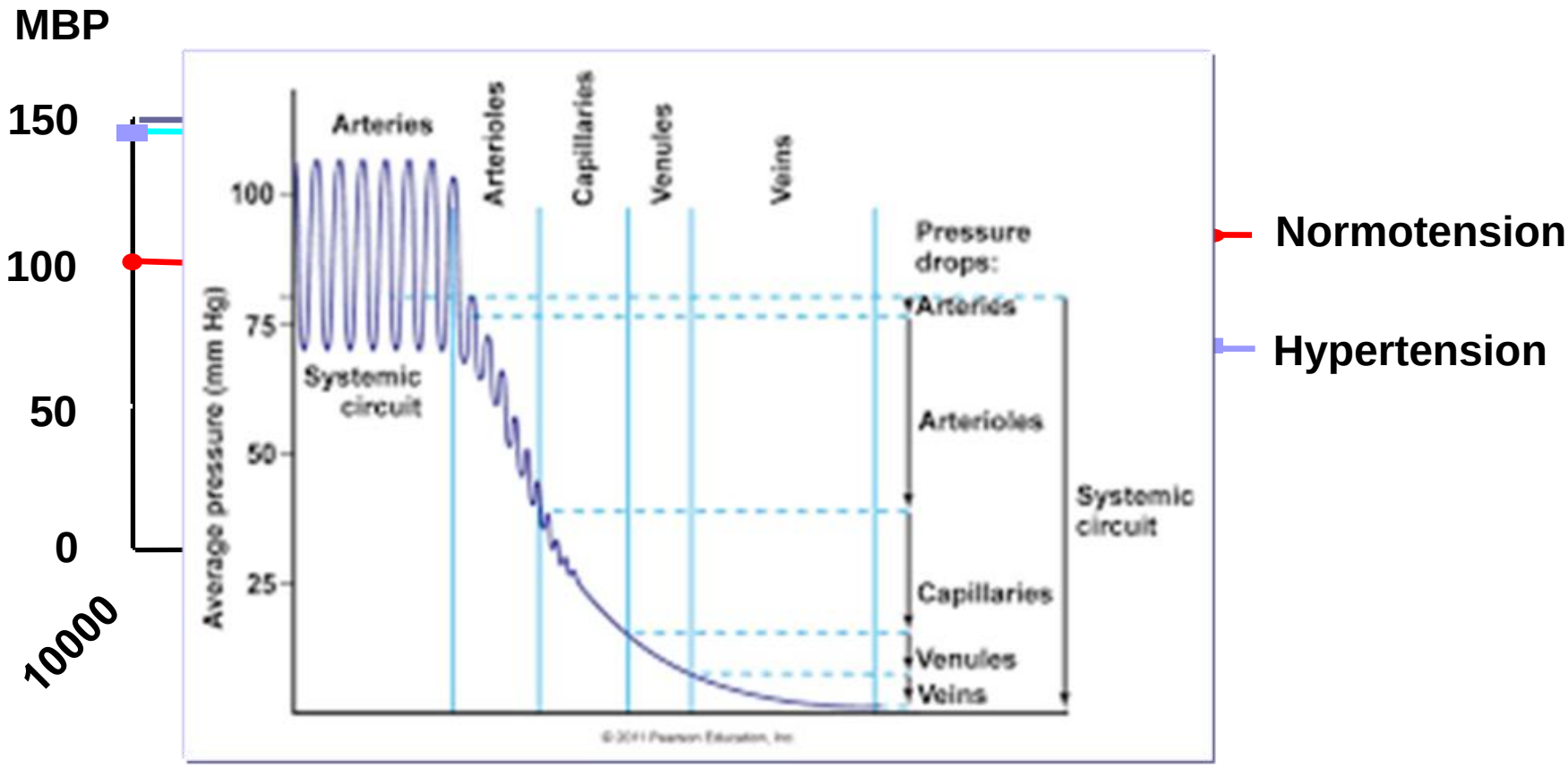


Microcirculation: structure and function



- ***Function*** **Transport and exchange of nutrients**

Microcirculation: major site of peripheral resistance



40% to 90% of the BP is located in the microcirculation

Struijker Boudier HAJ. J Hypertens.1992;10(suppl 7):S147-S156

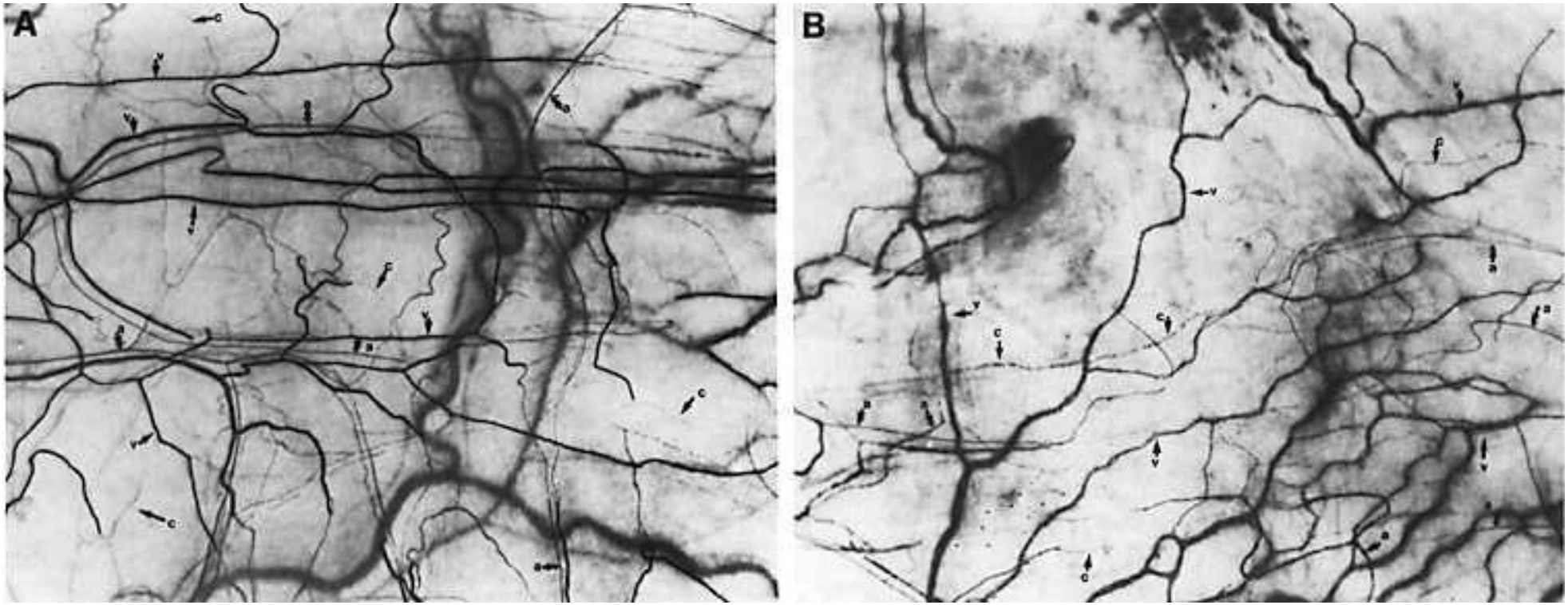
Mechanisms of increase in peripheral resistance

1. Arteriolar vasoconstriction
2. Increase in wall:lumen ratio
3. Rarefaction of microvessels

Capillary rarefaction in HT humans

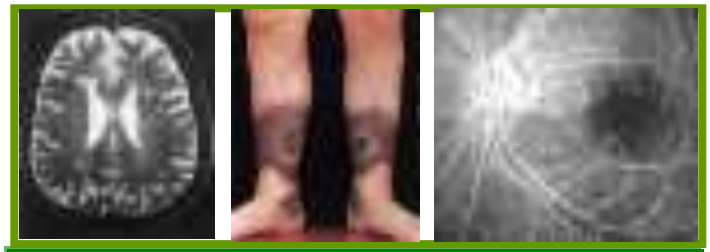
Normal

Hypertension

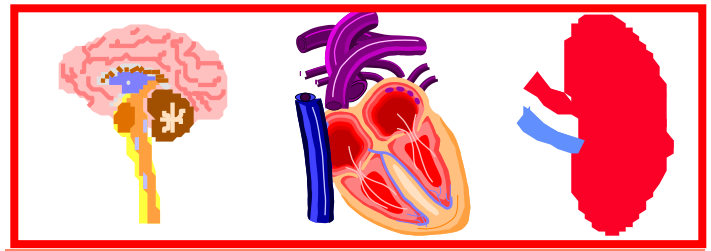


Sullivan J. Hypertension. 1993;5:844-851.

Hypertension and the microcirculation



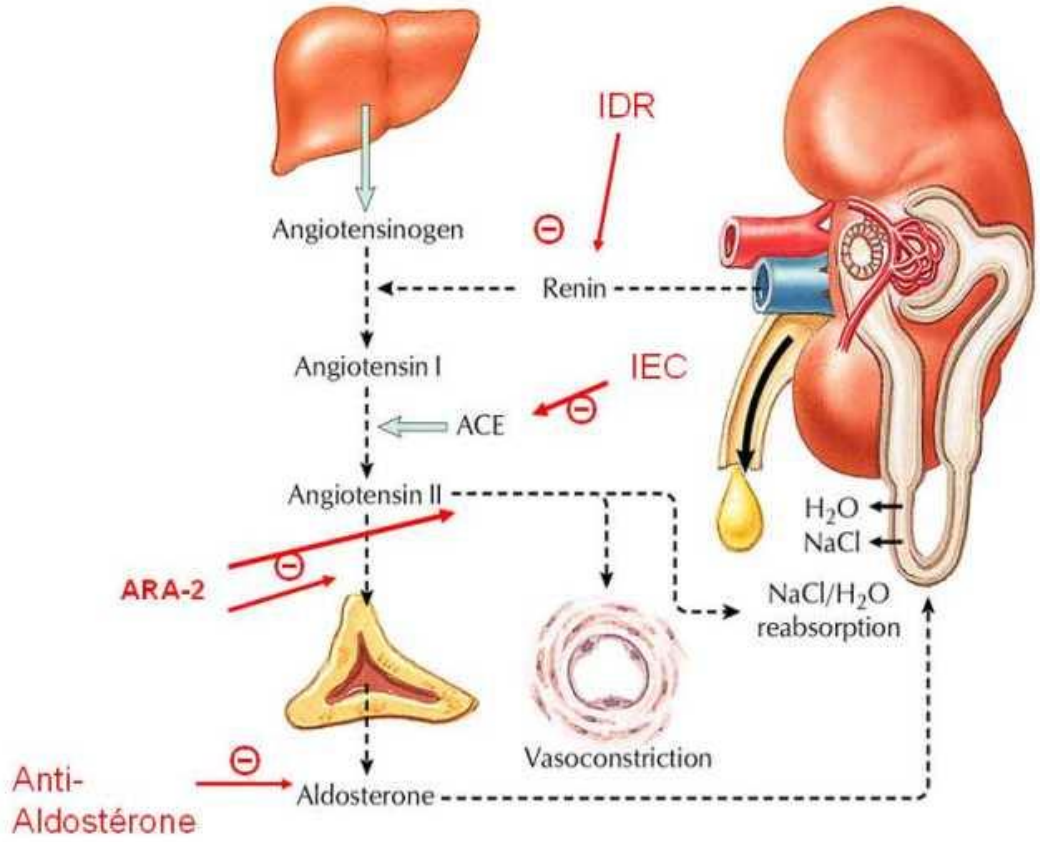
Microcirculatory disease

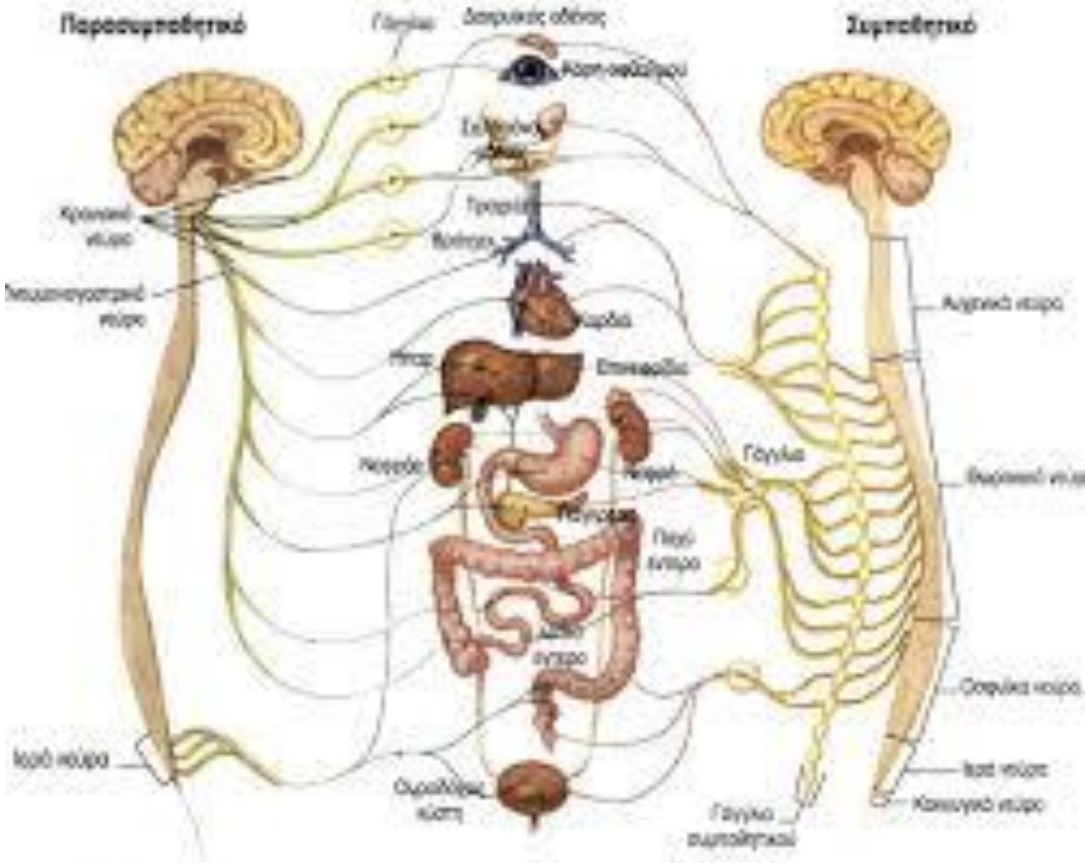


Hypertension

Increase in peripheral resistance

Υπέρταση και νευρο-ορμονικό σύστημα



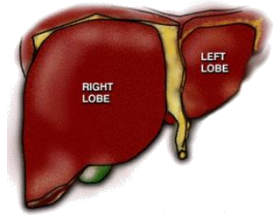


ΣΡΑΑ: το αρχαιότερο ορμονικό σύστημα

Δεν γνωρίζουμε ακόμη πολλές πτυχές του

Δεν είμαστε βέβαιοι για την ορθότητα των απόψεών μας για πολλούς από τους εμπλεκόμενους μηχανισμούς

Κλασικό Σύστημα
Ρενίνης – Αγγειοτασίνης – Αλδοστερόνης (ΣΡΑΑ)



Αγγειοτασινογόνο

καθεψίνη χυμάση tpA

Αγγειοτασσίνη I

Αλδοστερόνη

Αγγειοτασσίνη II

ρενίνη

↓ Renal Arterial Pressure

↓ [Na^+] in Renal Tubular Fluid

↑ Renal Sympathetic Nerve Activity

ΜΕΑ

Βραδυκινίνη

Αδρανή προϊόντα

AT1 Υποδοχείς

Σπειραματοσκλήρυνση

Κατακράτηση νατρίου

Αγγειοσύσπαση

Υπερπλασία ΛΜΚ

AT2 Υποδοχείς

Αγγειοδιαστολή

Αντι-υπερπλαστικές ιδιότητες

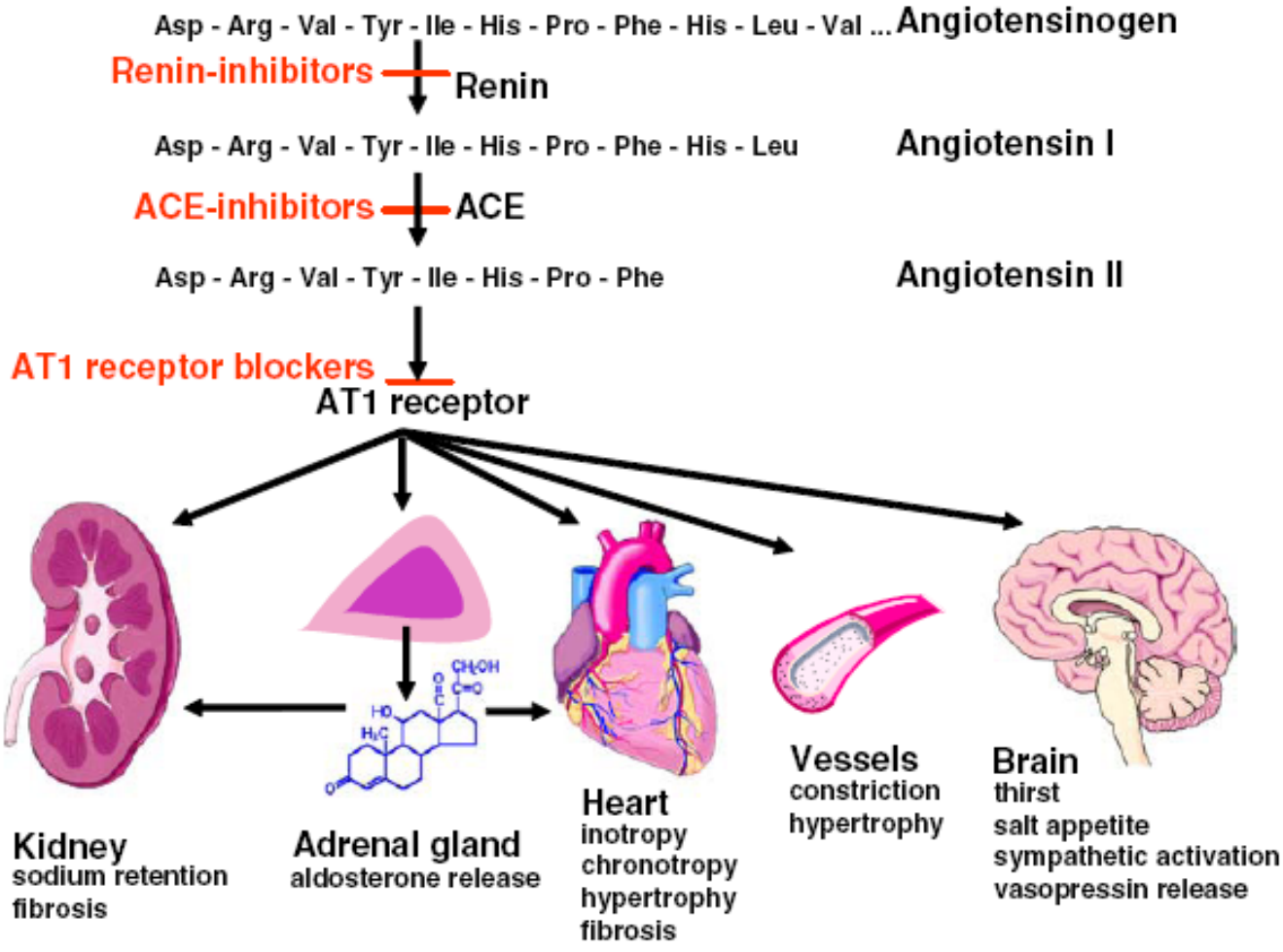
HYPERTENSION

↑BP

↑ Ang II
↓NO
Subclinical inflammatory reaction

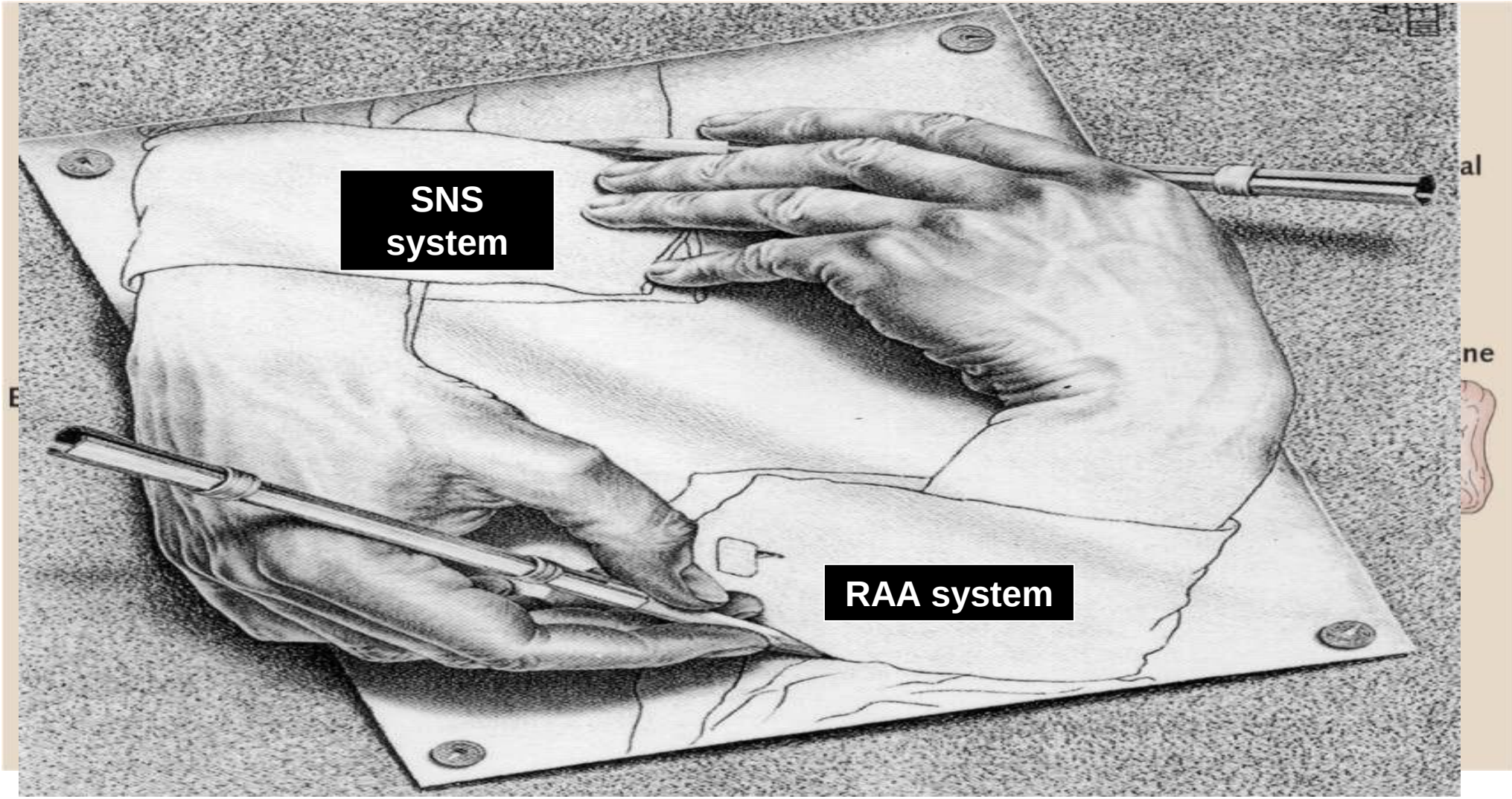
TARGET ORGAN DAMAGE

Θεραπευτική παρέμβαση στον άξονα ρενίνης – αγγειοτασίνης - αλδοστερόνης



J Mol Med 2008;86:615-621

Hypertension: a multifactorial disease

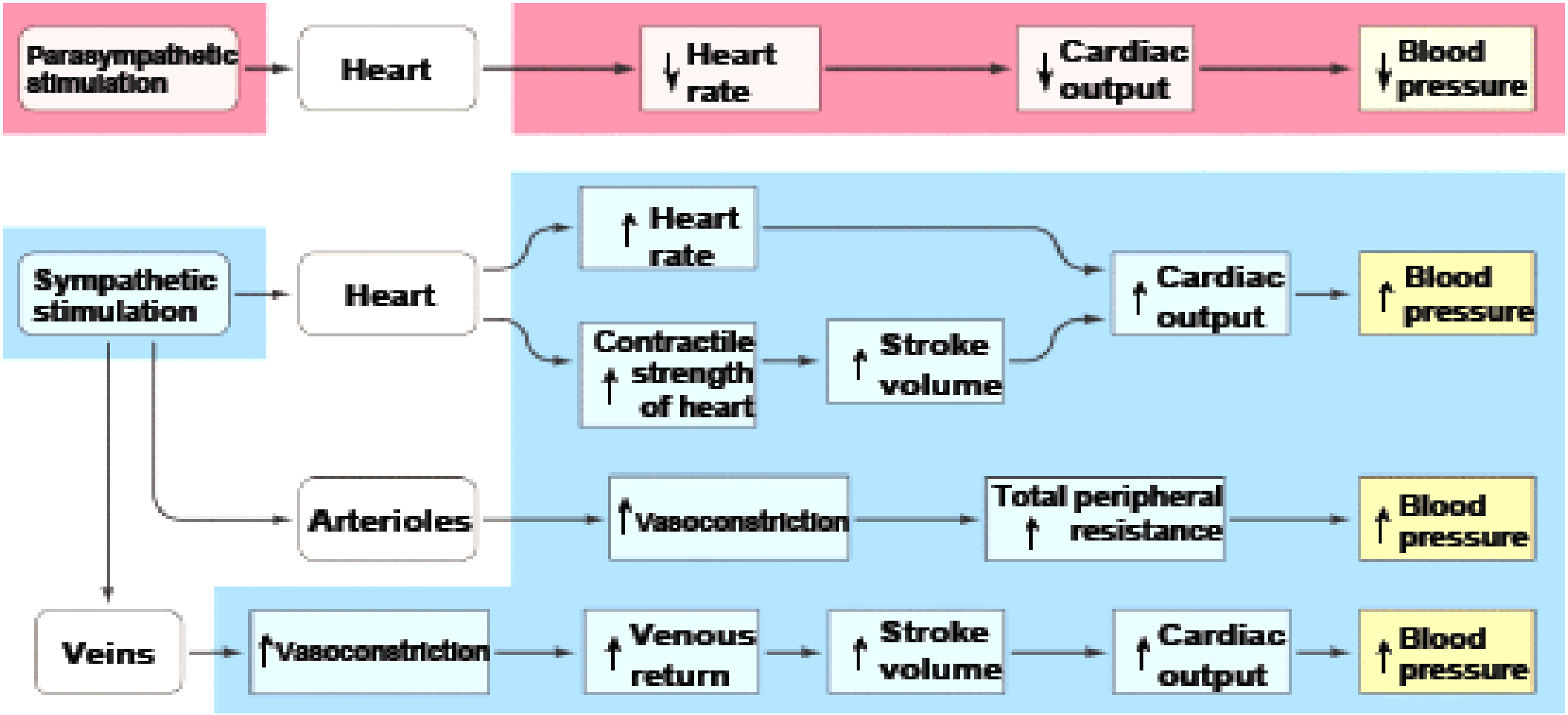


Oparil S, et al. Ann Intern Med. 2003;139:761-776

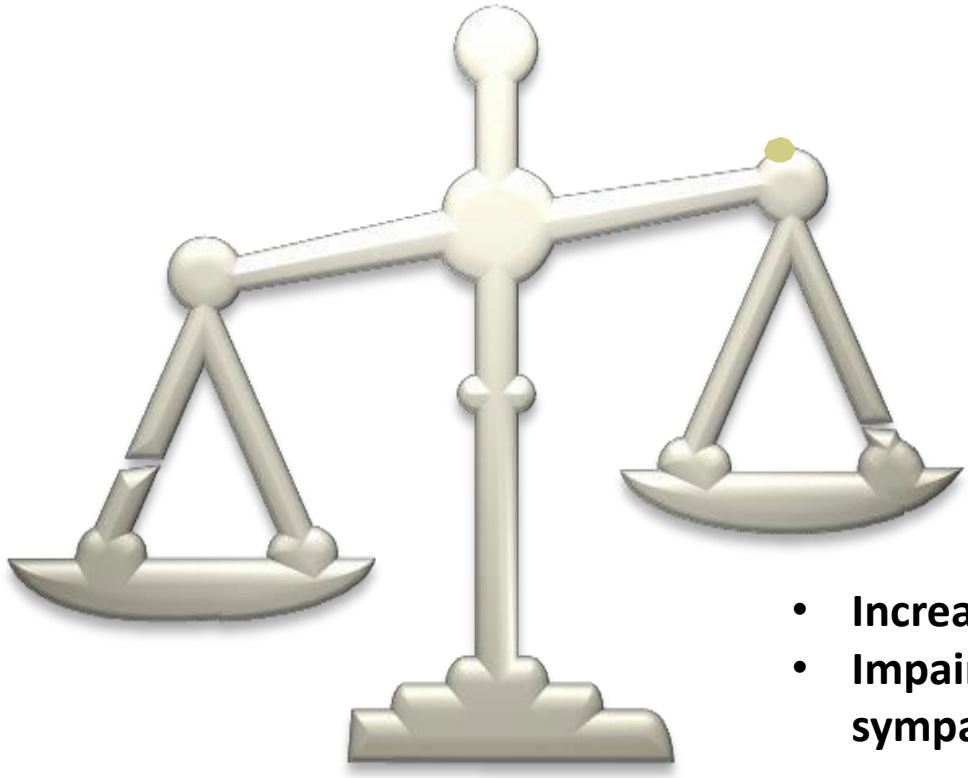
ΣΝΣ και ΑΥ: Ιστορική αναδρομή

- 1664: Willis: **Πρώτη ανατομική περιγραφή του ΣΝΣ**
- 1727: Pourfois du Petit: Αγγειοδιαστολή των αρτηριολίων μετά από διατομή των αυχενικών συμπαθητικών νεύρων
- 1840: Stelling: **Αγγειοκινητικές ίνες στα συμπαθητικά νεύρα**
- 1848: Ludwig: Αγγειοκινητικό κέντρο
- *1946: Von Euler: Η νορεπινεφρίνη ως νευροδιαβιβαστής του ΣΝΣ*
- *1951: Hoobler: **Χειρουργική συμπαθεκτομή για κακοήθη υπέρταση***
- *1959: Γαγγλιοπληγικά ως αποτελεσματικά αντιυπερτασικά*
- *1960s: **β-αναστολείς***
- *1968: Hagbarth and Vallbo: Μικρονευρογραφία, περιοχική norepinephrine spillover*
- *2009: Ardian group: **Διαδερμική δια καθετήρος κατάλυση της συμπαθητικής νεύρωσης του νεφρού σε ασθενείς με ανθεκτική υπέρταση***

Regulation of blood pressure



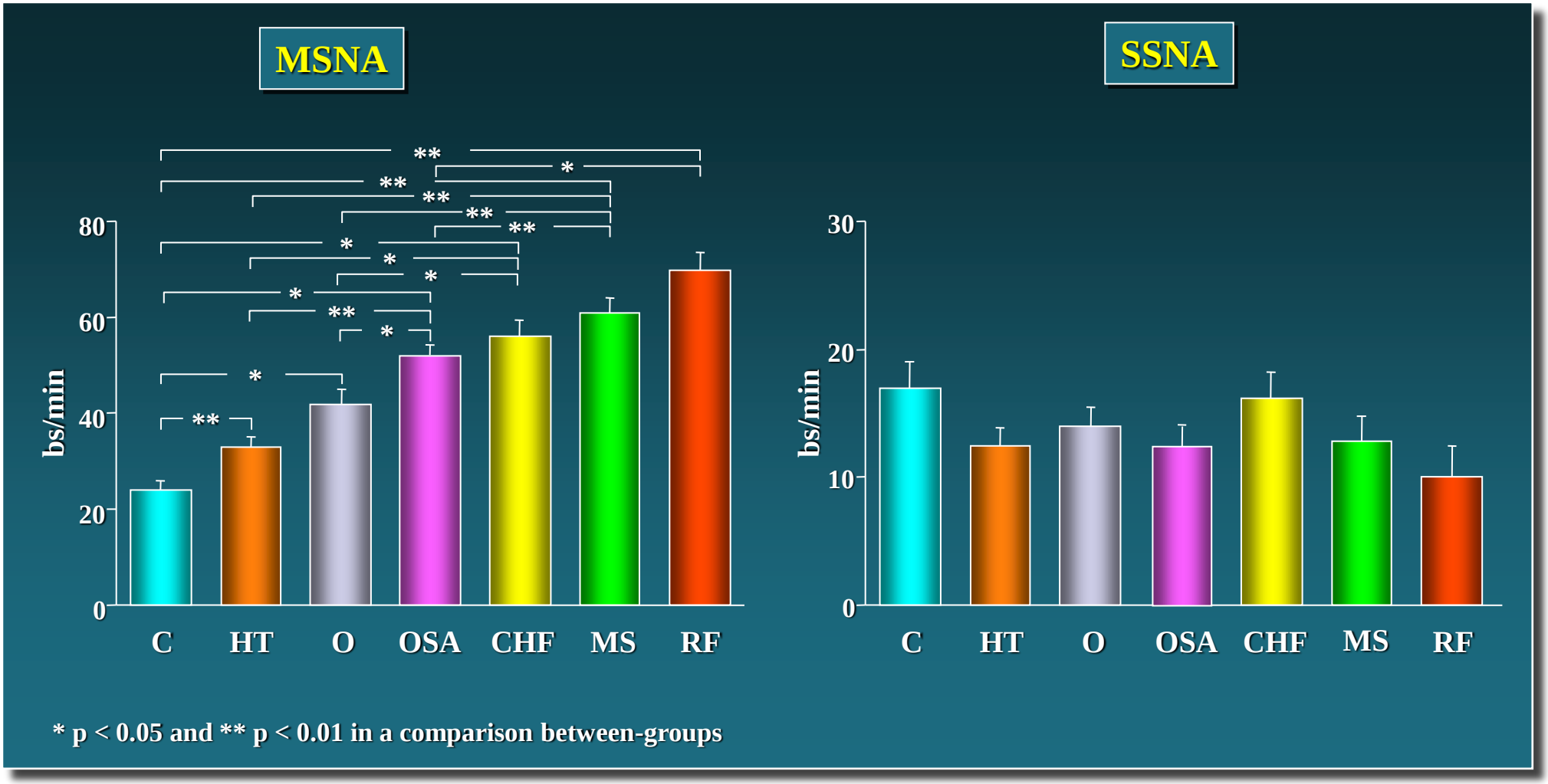
CV disease: Autonomic imbalance



Decreased parasympathetic tone

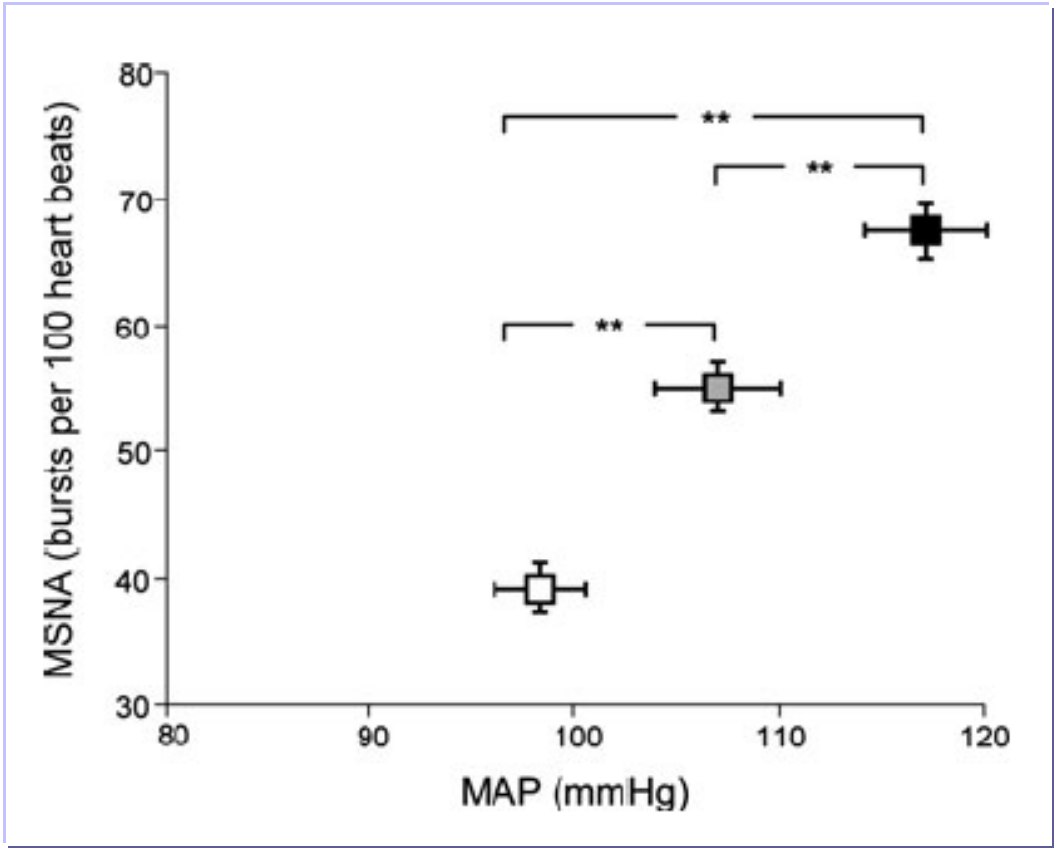
- Increased sympathetic tone
- Impaired baroreflex control of sympathetic activity

MSNA and SSNA in healthy controls (C) and in patients with Hypertension (HT), Obesity (O), Obstructive sleep apnea (OSA) , Congestive Hear Failure (CHF), Metabolic syndrome (MS) or renal failure (RF)



Mancia and Grassi, Circ Res 2014; 114: 1804-1814

Η αδρενεργική δραστηριότητα είναι ευθέως ανάλογη της σοβαρότητας της ΑΥ



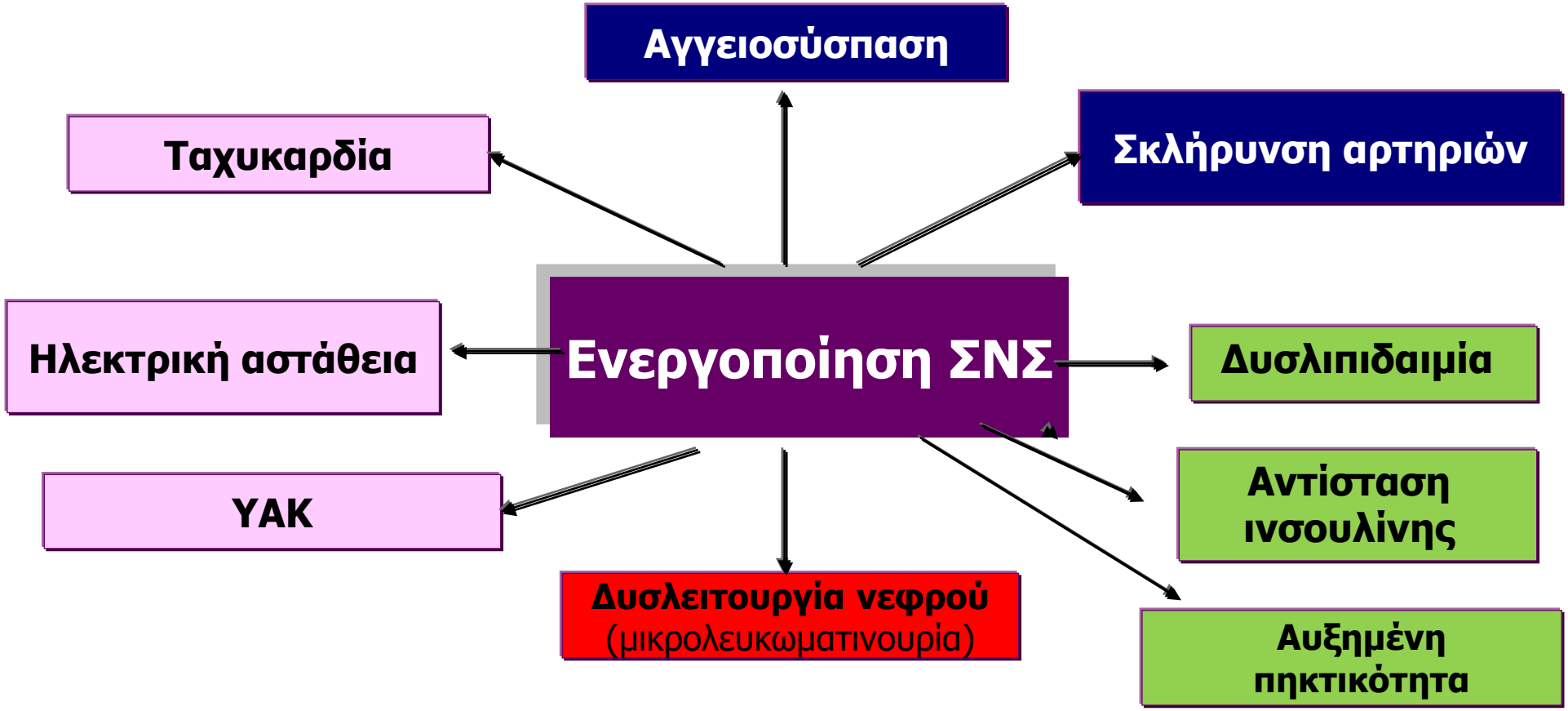
Severe hyprertensives

Mild to moderate hypertensives

Normotensives

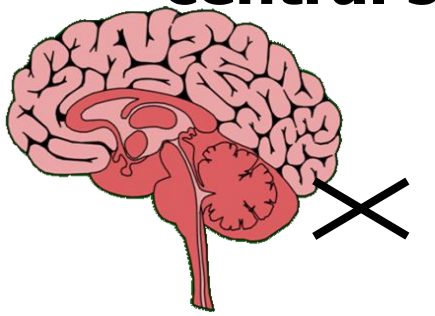
Grassi G, Exp Physiol 2009

Ανεπιθύμητες επιδράσεις της ενεργοποίησης του ΣΝΣ



G.Grassi et al, Exp Physiol 2009;95:581

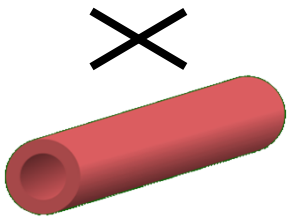
Current therapeutic strategies for reducing excessive central sympathetic nerve activity in hypertension

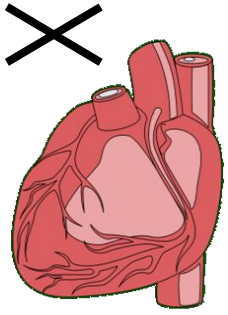


Centrally acting drugs
Imidazoline agonists

α_1-blockers

ß-blockers





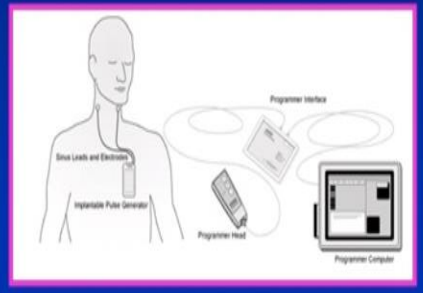
HEART

PERIPHERAL RESISTANCE

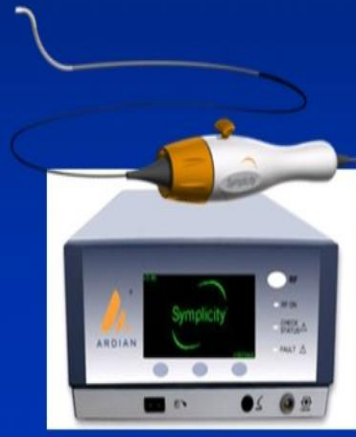
Changes in life style
Weight loss
Aerobic exercise training

Device-Based Approaches to Hypertension Management

Baroreflex Sensitisation

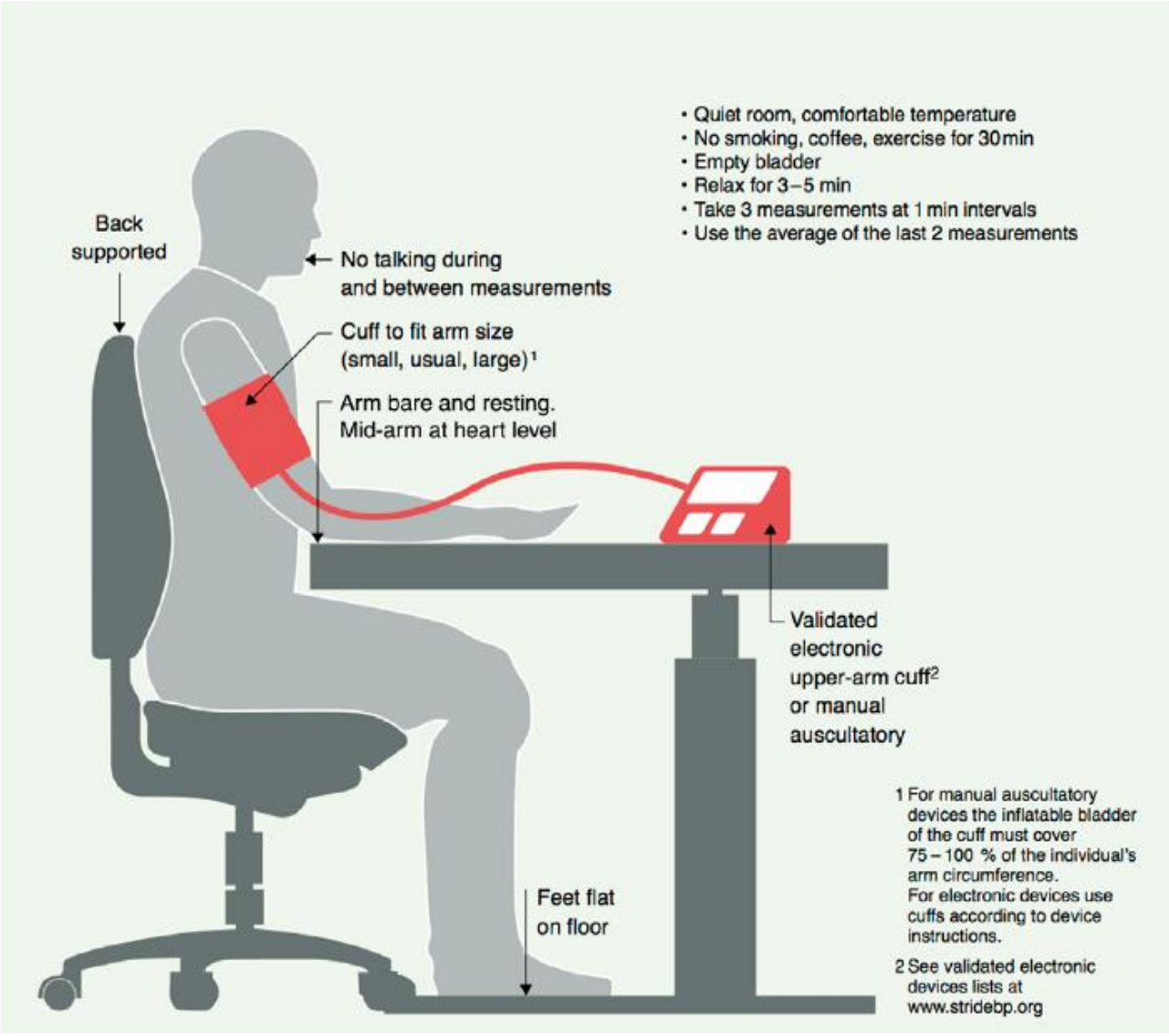


Renal Sympathetic Denervation



Διάγνωση

Measurement of BP



ISH 2020

4.1 Conventional office blood pressure measurement

1 Auscultatory or oscillometric semiautomatic or automatic sphygmomanometers are the preferred method for measuring BP in the doctor's office. These devices should be validated according to standardized conditions and protocols.[44] BP should 2 initially be measured in both upper arms, using an appropriate cuff size for the arm circumference. A consistent and significant SBP difference between arms (i.e. >15 mmHg) is associated with an increased CV risk,[45] most likely due to atheromatous vascular disease. Where there is a difference in BP between arms, ideally established by simultaneous measurement, the arm with the higher BP values should be used for all subsequent measurements.

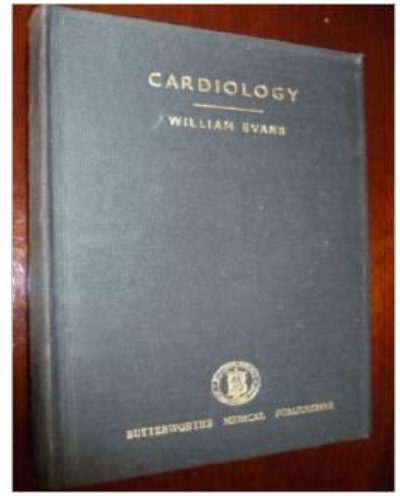
3 In older people, people with diabetes, or people with other causes of orthostatic hypotension, BP should also be measured 1 min and 3 min after standing. Orthostatic hypotension is defined as a reduction in SBP of ≥20 mmHg or in DBP of ≥10 mmHg within 3 min of standing, and is associated with an increased risk of mortality and CV events.[46] Heart rate should also be recorded at the time of BP measurements because resting heart rate is an independent predictor of CV morbid or fatal events,[47] although heart rate is not included in any CV risk algorithm. *Table 8* summarizes the recommended procedure for routine office BP measurement. It is emphasized that office BP is often performed improperly, with inadequate attention to the standardized conditions recommended for a valid measurement of office BP. Improper measurement of office BP can lead to inaccurate classification, overestimation of a patient's true BP, and unnecessary

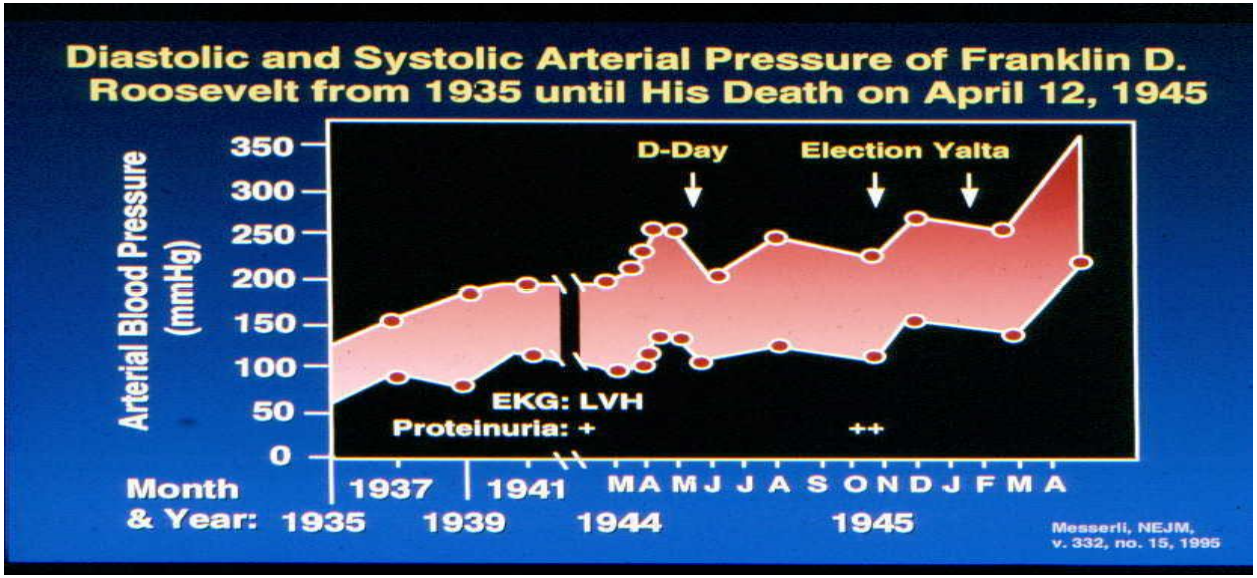
ESH 2018

HTN Management: Historical perspectives

- *In a patient with mild benign hypertension—[defined as a] blood pressure <200/<100 mm Hg, there is no indication for use of hypotensive drugs. Continued observation is desirable and conservative treatment consisting of reassurance, mild sedatives, and weight reduction is indicated.*

  Friedberg C. Diseases of the Heart 1949.





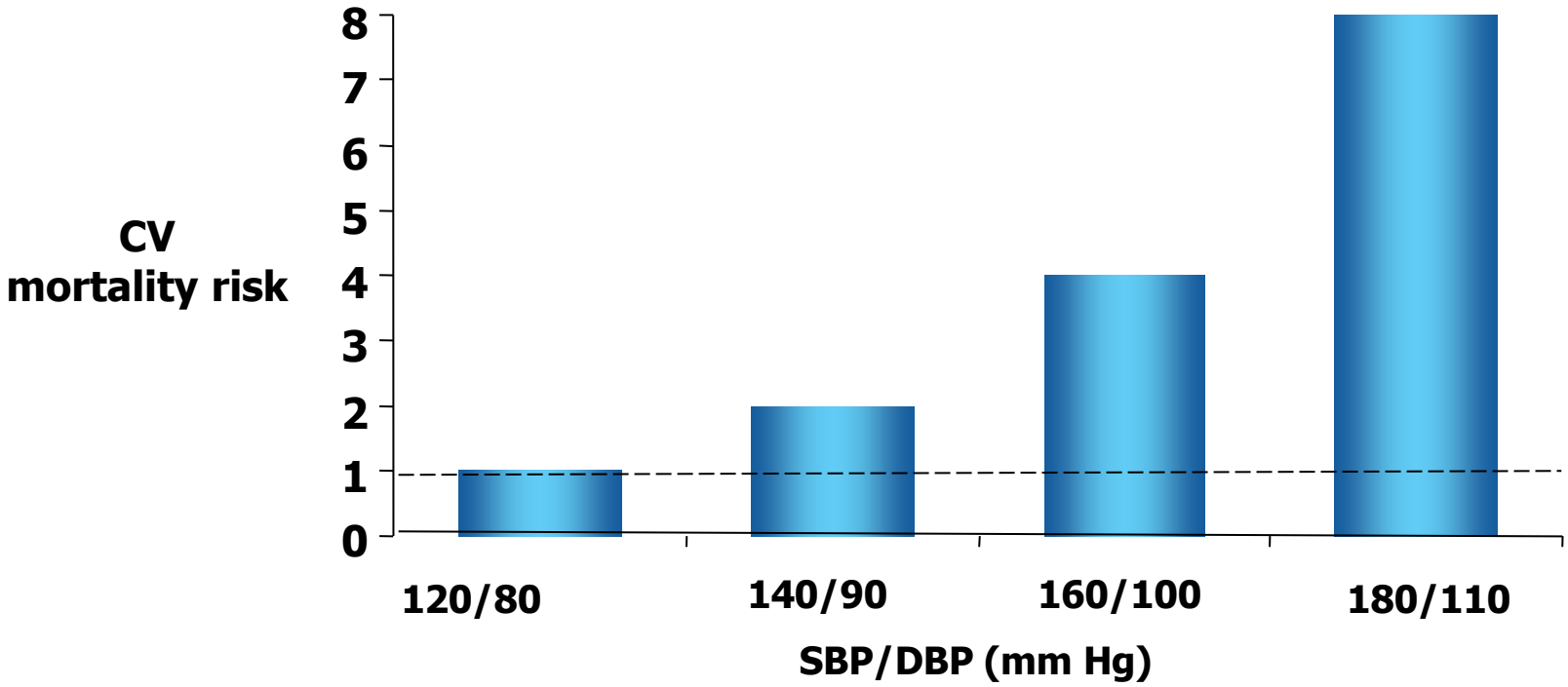
ESH

2013 ESH/ESC Hypertension Guidelines

SBP<140mmHg (Class I)

CV Mortality Risk

Doubles with each 20/10 mm Hg BP increment



Individuals aged 40-70 years, starting at BP 120/80 mm Hg

Lewington S, et al. Lancet 2002; 60: 1903-1913

Table 3 Classification of office blood pressure[a] and definitions of hypertension grade[b]

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

4.9 Confirming the diagnosis of hypertension

BP can be highly variable, thus the diagnosis of hypertension should not be based on a single set of BP readings at a single office visit, unless the BP is substantially increased (e.g. grade 3 hypertension) and there is clear evidence of HMOD (e.g. hypertensive retinopathy with exudates and haemorrhages, or LVH, or vascular or renal damage). For all others (i.e. almost all patients), repeat BP measurements at repeat office visits have been a long-standing strategy to confirm a persistent elevation in BP, as well as for the classification of the hypertension status in clinical practice and RCTs. The number of visits and the time interval between visits varies according to the severity of the hypertension, and is inversely related to the severity of hypertension.

Table 6. Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

10-year CV risk categories (SCORE system)

Very high risk	**People with any of the following:** **Documented CVD, either clinical or unequivocal on imaging.** • **Clinical CVD** includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm and PAD. • **Unequivocal documented CVD on imaging** includes significant plaque (i.e. ≥ 50% stenosis) on angiography or ultrasound. It does not include increase in carotid intima-media thickness. • **Diabetes mellitus with target organ damage**, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia • **Severe CKD** (eGFR < 30 mL/min/1.73 m^2) • **A calculated 10-year SCORE of ≥ 10%**
High risk	**People with any of the following:** • **Marked elevation of a single risk factor**, particularly cholesterol > 8 mmol/L (> 310 mg/dL) e.g. familial hypercholesterolaemia, grade 3 hypertension (BP ≥ 180/110 mmHg) • **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, that may be moderate risk) • **Hypertensive LVH** • **Moderate CKD (eGFR 30–59 mL/min/1.73 m^2)** • **A calculated 10-year SCORE of 5–10%**
Moderate risk	**People with:** • **A calculated 10-year SCORE of 1% to < 5%** • **Grade 2 hypertension** • **Many middle-aged people** belong to this category
Low risk	**People with:** • **A calculated 10-year SCORE of < 1%**

Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

Correction factors for the SCORE CV risk estimates in first-generation immigrants to Europe

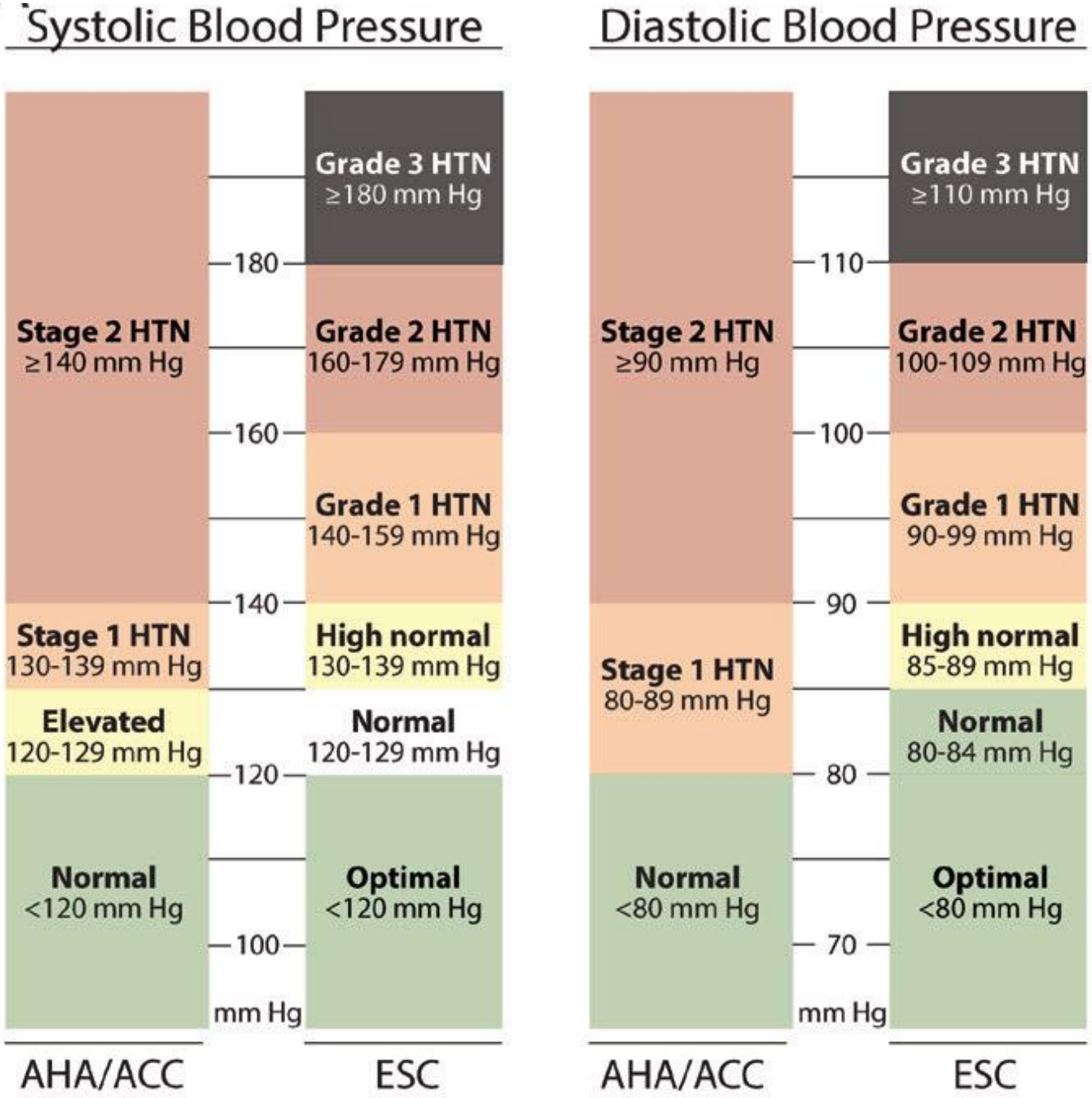
Region of origin	Multiplication factor
Southern Asia	1.4
Sub-Saharan Africa	1.3
Caribbean	1.3
Western Asia	1.2
Northern Africa	0.9
Eastern Asia	0.7
South America	0.7

Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

Classification of hypertension stages according to BP levels, presence of CV risk factors, HMOD, or comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥ 3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

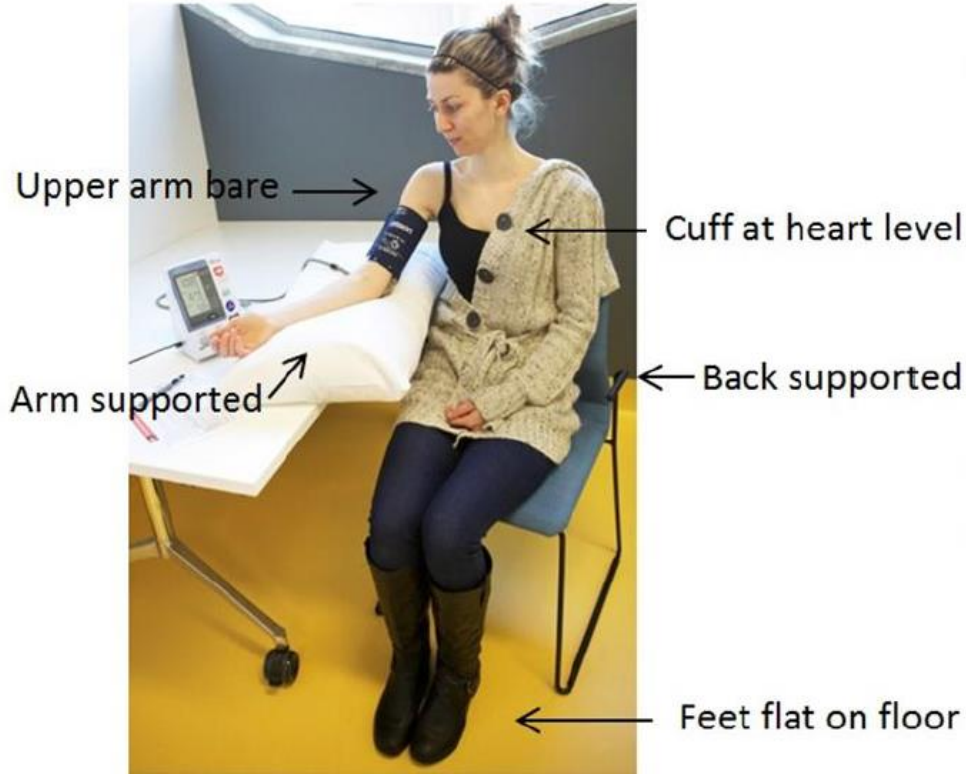
Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104


Systolic Blood Pressure
Diastolic Blood Pressure
Grade 3 HTN
≥180 mm Hg
Grade 2 HTN
160-179 mm Hg
Grade 1 HTN
140-159 mm Hg
High normal
130-139 mm Hg
Normal
120-129 mm Hg
Optimal
<120 mm Hg
Stage 2 HTN
≥140 mm Hg
Stage 1 HTN
130-139 mm Hg
Elevated
120-129 mm Hg
Normal
<120 mm Hg
180
160
140
120
100
mm Hg
AHA/ACC
ESC
Grade 3 HTN
≥110 mm Hg
Grade 2 HTN
100-109 mm Hg
Grade 1 HTN
90-99 mm Hg
High normal
85-89 mm Hg
Normal
80-84 mm Hg
Optimal
<80 mm Hg
Stage 2 HTN
≥90 mm Hg
Stage 1 HTN
80-89 mm Hg
Normal
<80 mm Hg
110
100
90
80
70
mm Hg
AHA/ACC
ESC

Unattended office blood pressure measurement

- ✓ '**White-coat effect**' can be substantially reduced or eliminated.
- ✓ Improve the **reproducibility** of BP measurement.
- ✓ BP values are **lower** than those obtained by conventional OBP measurement and are similar to, or even less than, those provided by daytime ABPM or HBPM.
- ✓ Office SBP readings may be at least 5–15 mmHg higher.

- ❖ Controversy about its quantitative **relationship** to conventional OBP measurement (which has been the basis for all previous epidemiological and clinical trial data).
- ❖ Limited evidence on the **prognostic value**.
- ❖ **Feasibility** in routine clinical practice has been questioned.



Out of office BP measurement

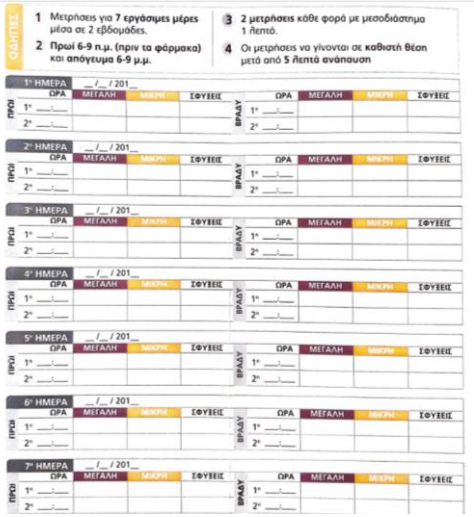


Table 9 Definitions of hypertension according to office, ambulatory, and home blood pressure levels

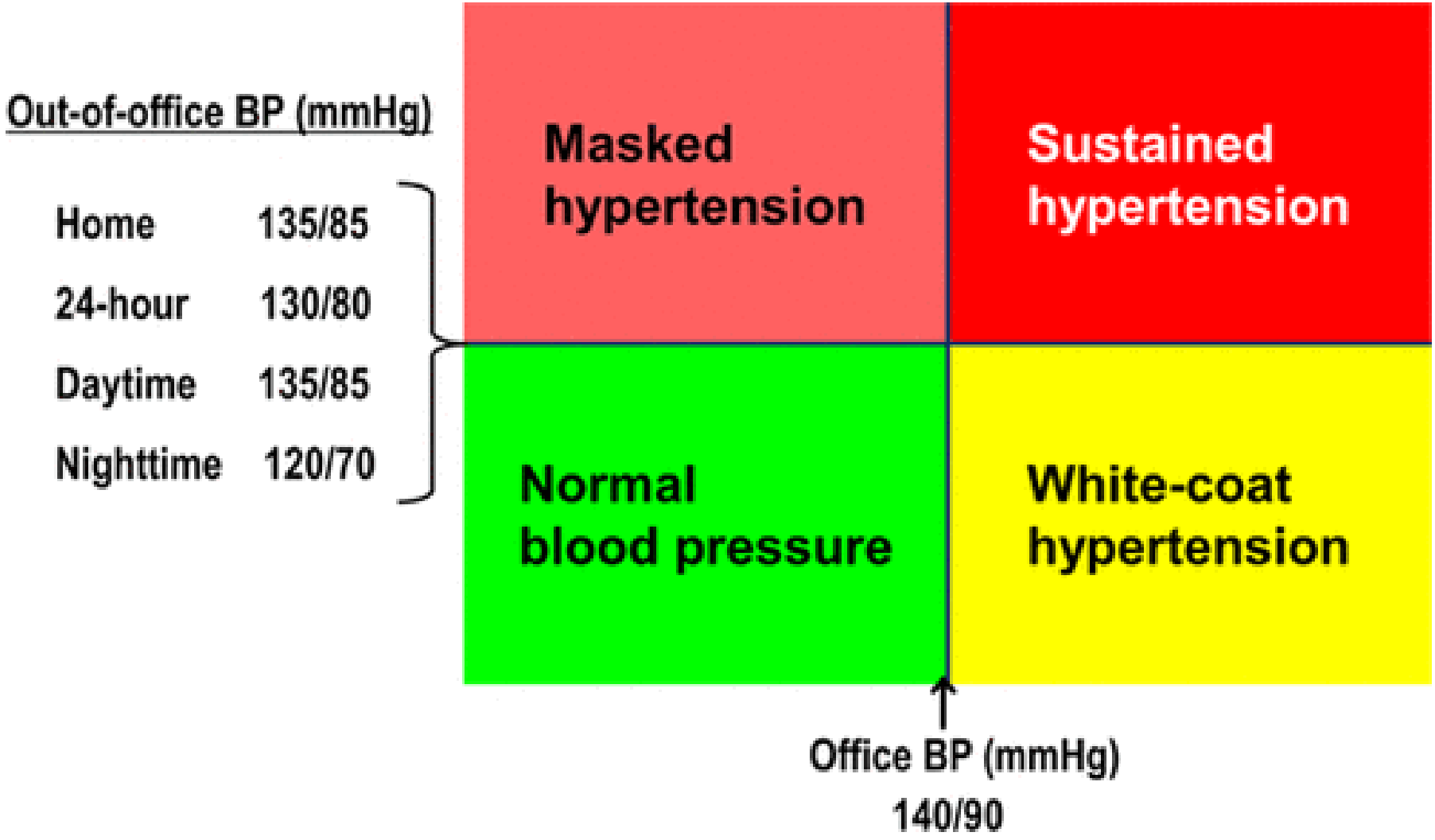
Category	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

CENTRAL ILLUSTRATION: Clinic, Home, and Ambulatory Blood Press Measurements

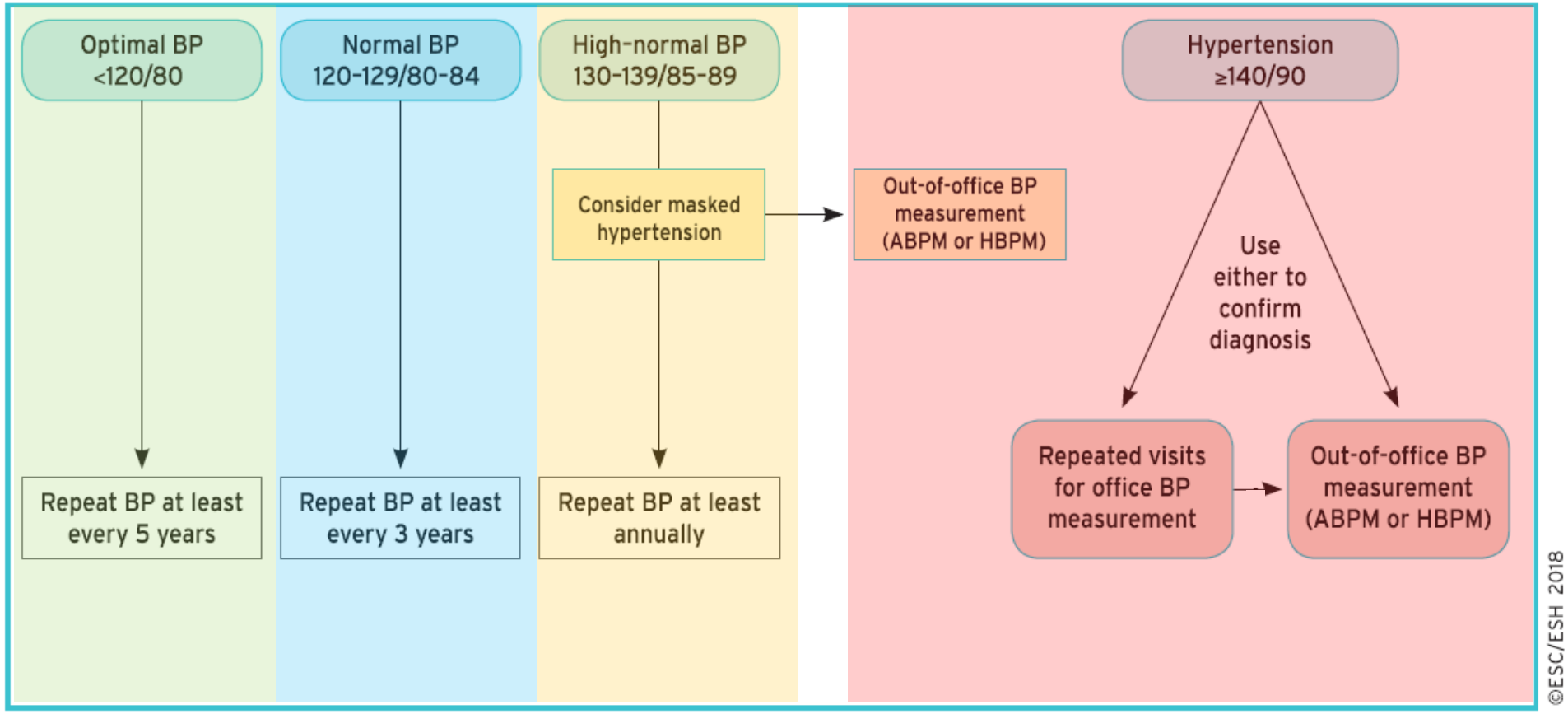
Clinic Measurements	Home BP Monitoring	Ambulatory BP Monitoring
Description		
• BP measured in a medical setting • Patient should be seated, resting quietly with their back supported and feet flat on the floor	• BP measured while seated at home, resting quietly with back supported and feet flat on the floor • BP readings obtained in the morning and evening	• BP measured during routine activities • 48 to 72 readings obtained over 24 hours
Strengths		
• Associated with cardiovascular outcomes • Only method that has been used to guide treatment in large outcome trials	• Strong association with cardiovascular outcomes • Detects white coat and masked hypertension	• Strong association with cardiovascular outcomes • Detects white coat and masked hypertension • BP measured at work and at night (i.e., during sleep)
Weaknesses		
• Less precise as only 1 or 2 BP measurements typically obtained • Many factors affect the accuracy of readings • Requires training and frequent re-training of staff	• Patients may not correctly measure and report their BP • Requires patient training and re-training • Many home devices are not validated	• Not tolerated by some patients • Equipment is not widely available • Requires two clinic visits: to set up and return the device

Muntner, P. et al. J Am Coll Cardiol. 2019;73(3):317-35.

Classification of hypertension subtypes



Screening and diagnosis of hypertension



Clinical evaluation

A. Medical history

1. Risk factors
2. History and symptoms of HMOD, CVD, stroke, and renal disease
3. History of possible secondary hypertension
4. Antihypertensive Drug Treatment

B. Physical examination and clinical investigations

1. Body habitus
2. Signs of HMOD
3. Secondary hypertension

C. Assessment of hypertension mediated organ damage

1. 12-lead ECG
2. Labs (ACR, Creatinine, eGFR)
3. Fundoscopy (Grade II or III and all diabetes)
4. More specific (EchoCardio, Carotid U/S, Abdominal U/S and Doppler, PWV, ABI, Brain imaging)

Table 14 Routine workup for evaluation of hypertensive patients

Routine laboratory tests
Haemoglobin and/or haematocrit
Fasting blood glucose and glycated HbA_{1c}
Blood lipids: total cholesterol, LDL cholesterol, HDL cholesterol
Blood triglycerides
Blood potassium and sodium
Blood uric acid
Blood creatinine and eGFR
Blood liver function tests
Urine analysis: microscopic examination; urinary protein by dipstick test or, ideally, albumin:creatinine ratio
12-lead ECG

eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; HbA_{1c} = haemoglobin A1c.

Secondary hypertension

The prevalence of secondary hypertension is reported to be 5–15%

Cause	Prevalence in hypertensive patients	Suggestive symptoms and signs	Screening Investigations
Obstructive sleep apnoea	5–10%	Snoring; obesity (can be present in non-obese); morning headache; daytime somnolence	Epworth score and ambulatory polygraphy
Renal parenchymal disease	2–10%	Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD	Plasma creatinine and electrolytes, eGFR; urine dipstick for blood and protein, urinary albumin:creatinine ratio; renal ultrasound
Renovascular disease			
Atherosclerotic renovascular disease	1–10%	Older; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit	Duplex renal artery Doppler or CT angiography or MR angiography
Fibromuscular dysplasia		Younger; more common in women; abdominal bruit	

Endocrine causes			
Primary Aldosteronism	5 - 15%	Mostly asymptomatic; muscle weakness (rare)	Plasma aldosterone and renin, and aldosterone:renin ratio; hypokalaemia (in a minority): note hypokalaemia can depress aldosterone levels
Phaeochromocytoma	<1%	Episodic symptoms (the 5 'Ps'): paroxysmal hypertension, pounding headache, perspiration, palpitations, and pallor; labile BP; BP surges precipitated by drugs (e.g. beta-blockers, metoclopramide, sympathomimetics, opioids, and tricyclic antidepressants)	Plasma or 24 h urinary fractionated metanephrines
Cushing's syndrome	<1%	Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use	24 h urinary-free cortisol
Thyroid disease (hyper- or hypothyroidism)	1 - 2%	Signs and symptom of hyper- or hypothyroidism	Thyroid function tests
Hyperparathyroidism	<1%	Hypercalcaemia, hypophosphataemia	Parathyroid hormone, Ca^{2+}
Other causes			
Coarctation of the aorta	<1%	Usually detected in children or adolescence; different BP (≥20/10 mmHg) between upper–lower extremities and/or between right–left arm and delayed radial-femoral femoral pulsation; low ABI interscapular ejection murmur; rib notching on chest X-ray	Echocardiogram

ΘΕΡΑΠΕΙΑ ΑΥ

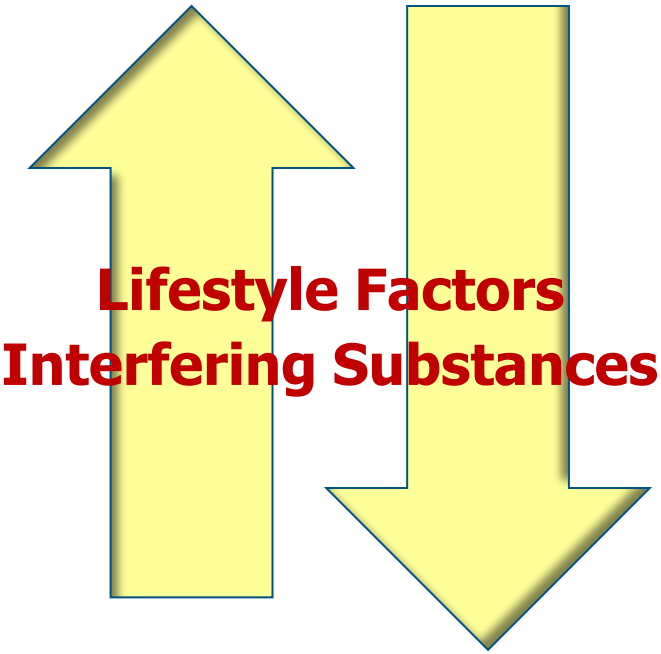
Treatment of Hypertension

Identify & reverse contributing factors

Always if BP≥130/85mmHg

Increase

- Physical activity
- Fiber intake
- K^+



Decrease

- Salt intake
- Alcohol use
- Obesity/OSAS
- Use of:
  - NSAIDs, stimulants, sympathomimetics, oral contraceptives, licorice, ephedra

NSAID=nonsteroidal anti-inflamatory drug.

C. Tsioufis

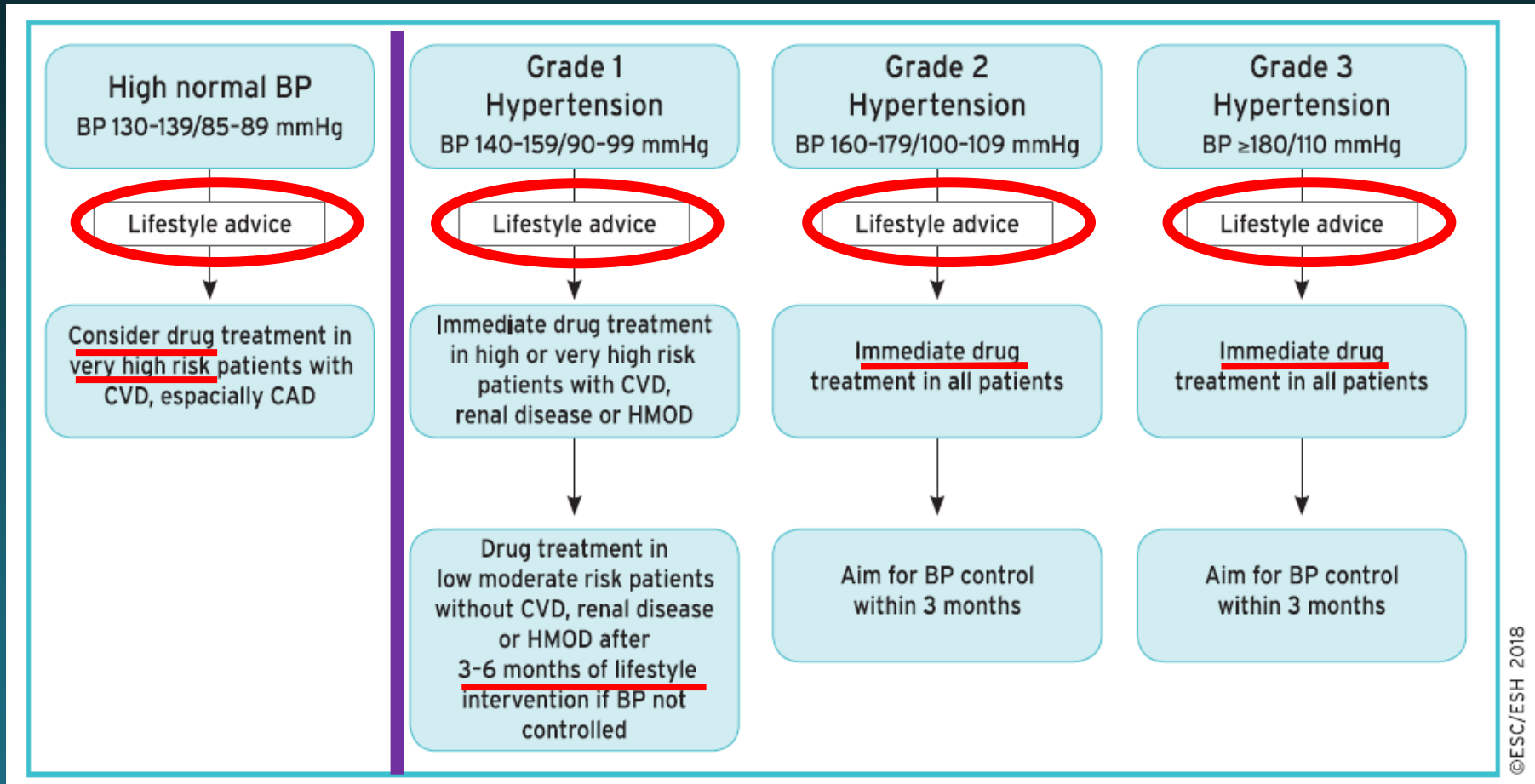
Calhoun DA et al. Circulation. 2008;117:e510-e526.

- **Appropriate treatment of hypertension**
  - **When to start, what BP to target**

Definitions of hypertension by office and out-of-office blood pressure levels (mmHg)

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake)	≥135	and/or	≥85
Nighttime (or asleep)	≥120	and/or	≥70
24-h	≥130	and/or	≥80
Home BP	≥135	and/or	≥85

Initiation of lifestyle changes and antihypertensive drug treatment



BP targets in 2020

- 2013 ESH/ESC GDLs: OBP<140/90 mmHg for all

- 2014 JNC 8:
- If age<60 yrs: OBP<140/90 mmHg
- If age≥60 yrs: OBP<150/90 mmHg

- 2015 SPRINT: OBP<120mmHg for selected individuals increased CV risk with BP >130 mmHg and >50 yrs old
- 2016 Meta-analysis: OBP<130 mmHg

- 2017 ACC/AHA GDLs: OBP<130/80 mmHg for all

- 2018 ESH/ESC GDLs: OBP<140/80 mmHg for all, <130 mmHg in pts<65 yrs old, <u>if tolerated</u>

Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 - 65 years	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65 - 79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

How to achieve the BP targets – Antihypertensive drugs

Treatment strategies and choice of drugs

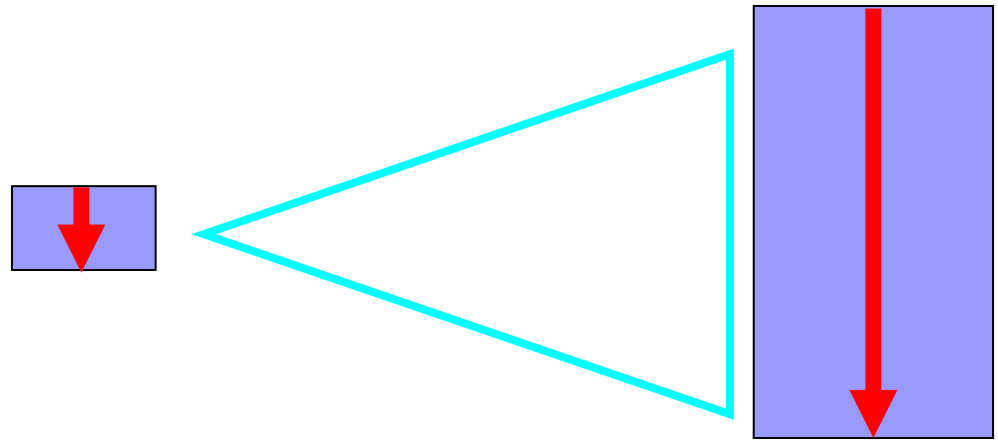
1st principle

- **The main benefit from antihypertensive therapy comes from BP reduction per se**

BP Reductions as Little as 2 mm Hg Reduce the Risk of CV Events by Up to 10%

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years

2 mm Hg decrease in mean SBP



7% reduction in risk of ischemic heart disease mortality

10% reduction in risk of stroke mortality

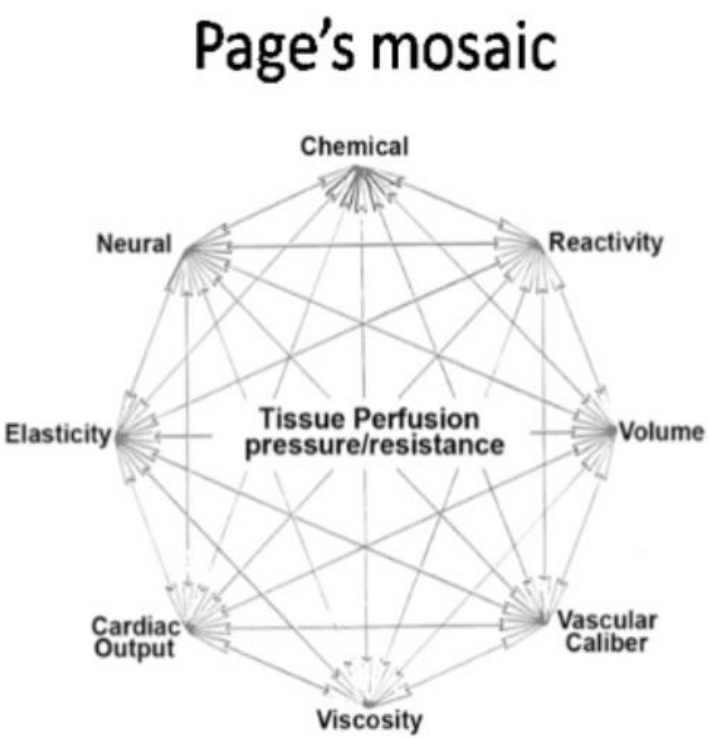
Lewington S et al. Lancet 2002;360:1903-1913.

Treatment strategies and choice of drugs

2st principle

Recommendations	Class	Level
Among all antihypertensive drugs ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like such as chlortalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.	I	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart-rate control.	I	A

Drug selection - Mosaic theory



Page IH. The mosaic theory. In: Page IH, ed. Hypertension Mechanisms. New York, NY: Grune & Stratton: 1987:910-916 (chapter 160)

Which element of the mosaic is most relevant?

Selection of antihypertensive drugs

3st principle

- Individualized treatment

  - Based on the plasma renin levels?
  - Based on the haemodynamic profile - HOTMAN?
  - Based on salt sensitivity?
  - Based on patient's characteristics (age, BMI, gender)?

Selection of antihypertensive drugs

4st principle

Based on the presence of

- **Subclinical TOD (ie RAS blockers for LVH, microalbuminuria),**
- **Clinical status (ie beta blockers post MI),**
- **and/or metabolic profile (RAS blockers for MS)**

Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

Contraindications for major antihypertensive drugs

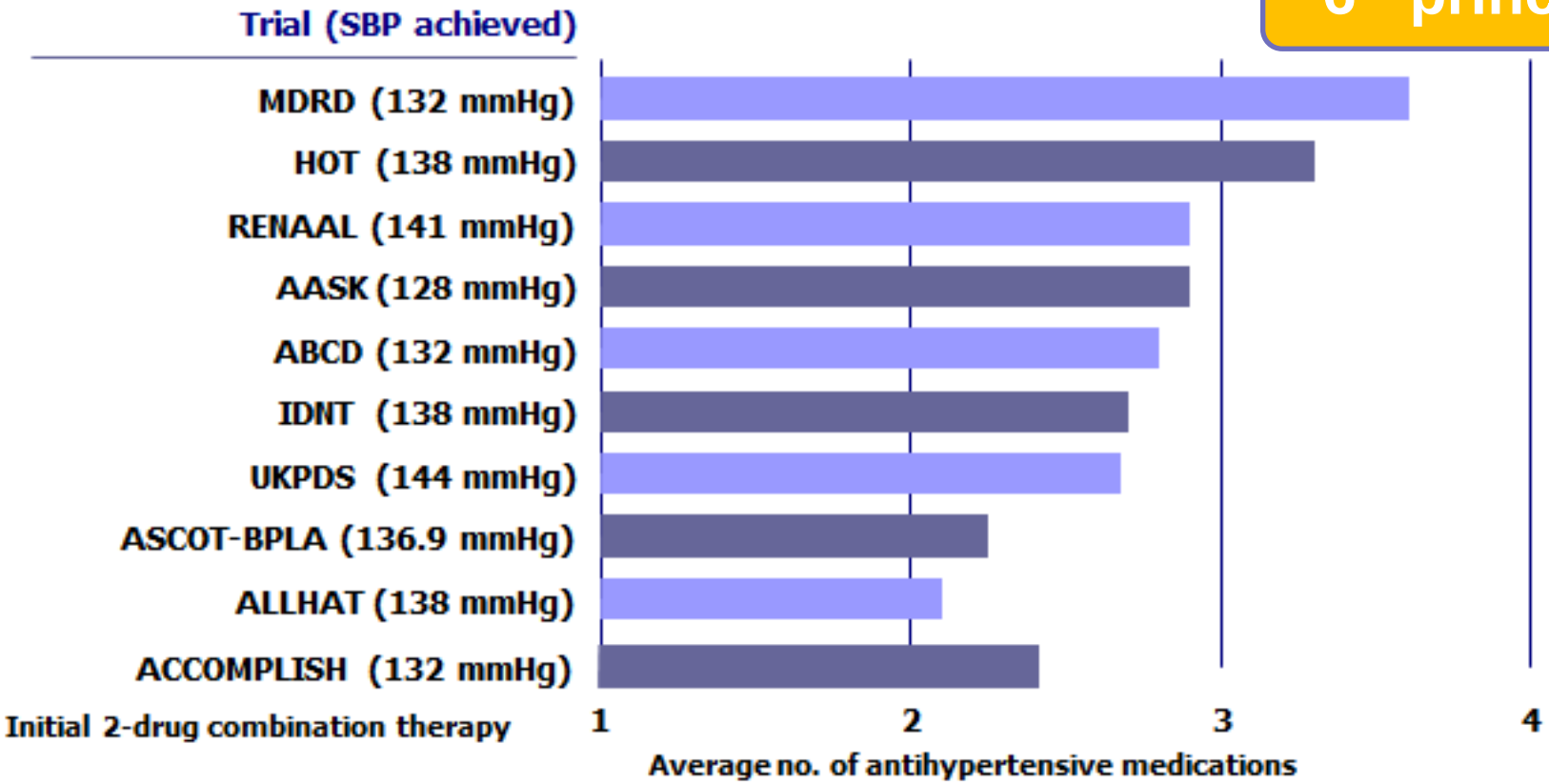
5st principle

	Contraindications	*Conditions that require careful use*
Ca channel blockers	Bradycardia (non-dihydropyridines)	Heart failure
ARB	Pregnancy Hyperkalemia	Renal artery stenosis[a]
ACE inhibitors	Pregnancy Angioneurotic edema Hyperkalemia	Renal artery stenosis[a]
Diuretics (thiazide)	Hypokalemia	Gout Pregnancy Impaired glucose tolerance
β-Blockers	Asthma Marked bradycardia	Impaired glucose tolerance Obstructive pulmonary disease Peripheral artery disease

Hypertension Research (2014) 37, 291–300

Multiple Antihypertensive Agents are Needed to Reach BP Goal

6st principle



Bakris et al. Am J Med 2004;116(5A):30S–8
Dahlöf et al. Lancet 2005;366:895–906
Jamerson et al. Blood Press 2007;16:80-6
Jamerson et al. N Engl J Med 2008;359:2417-28

Ο θεραπευτικός αλγόριθμος

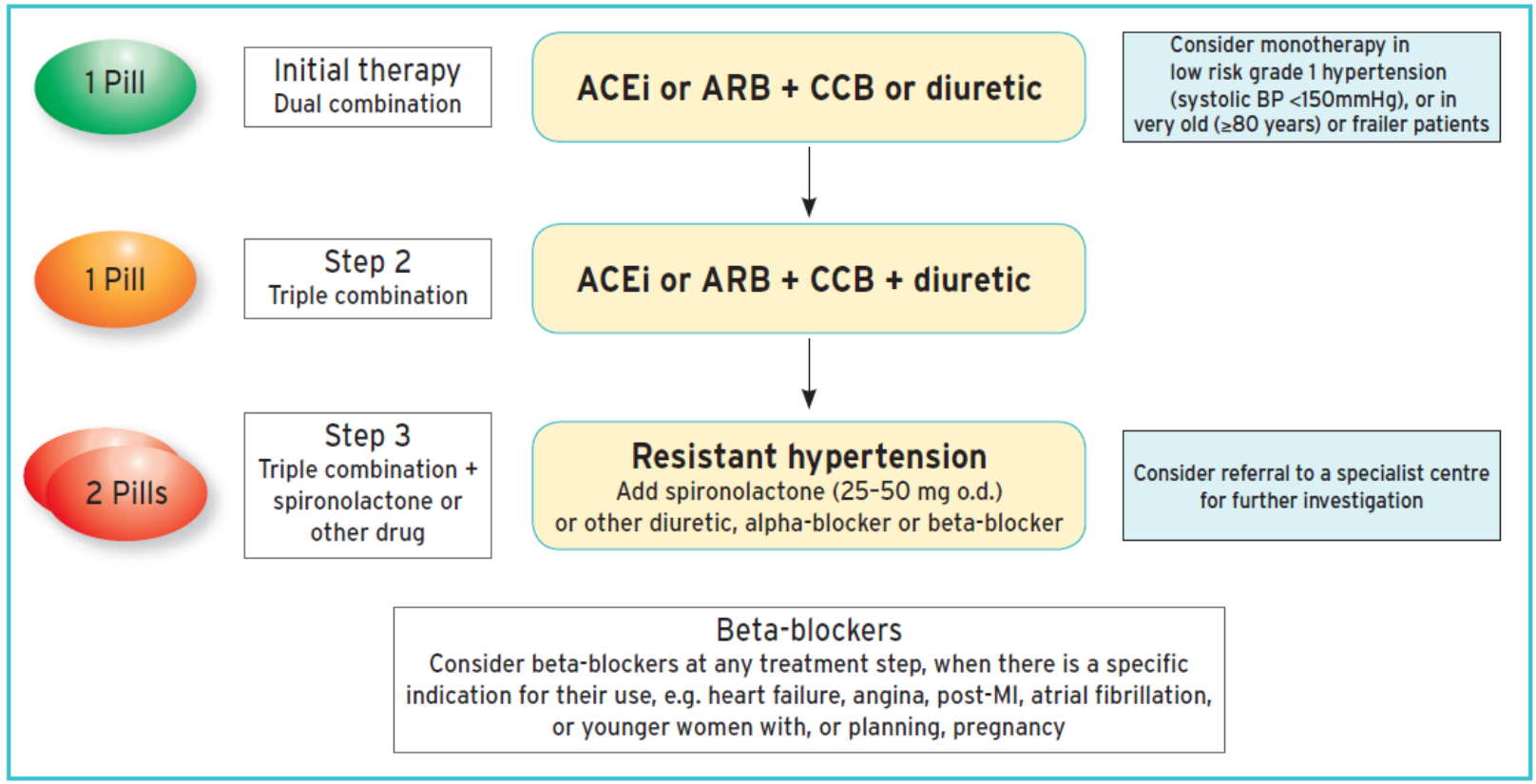


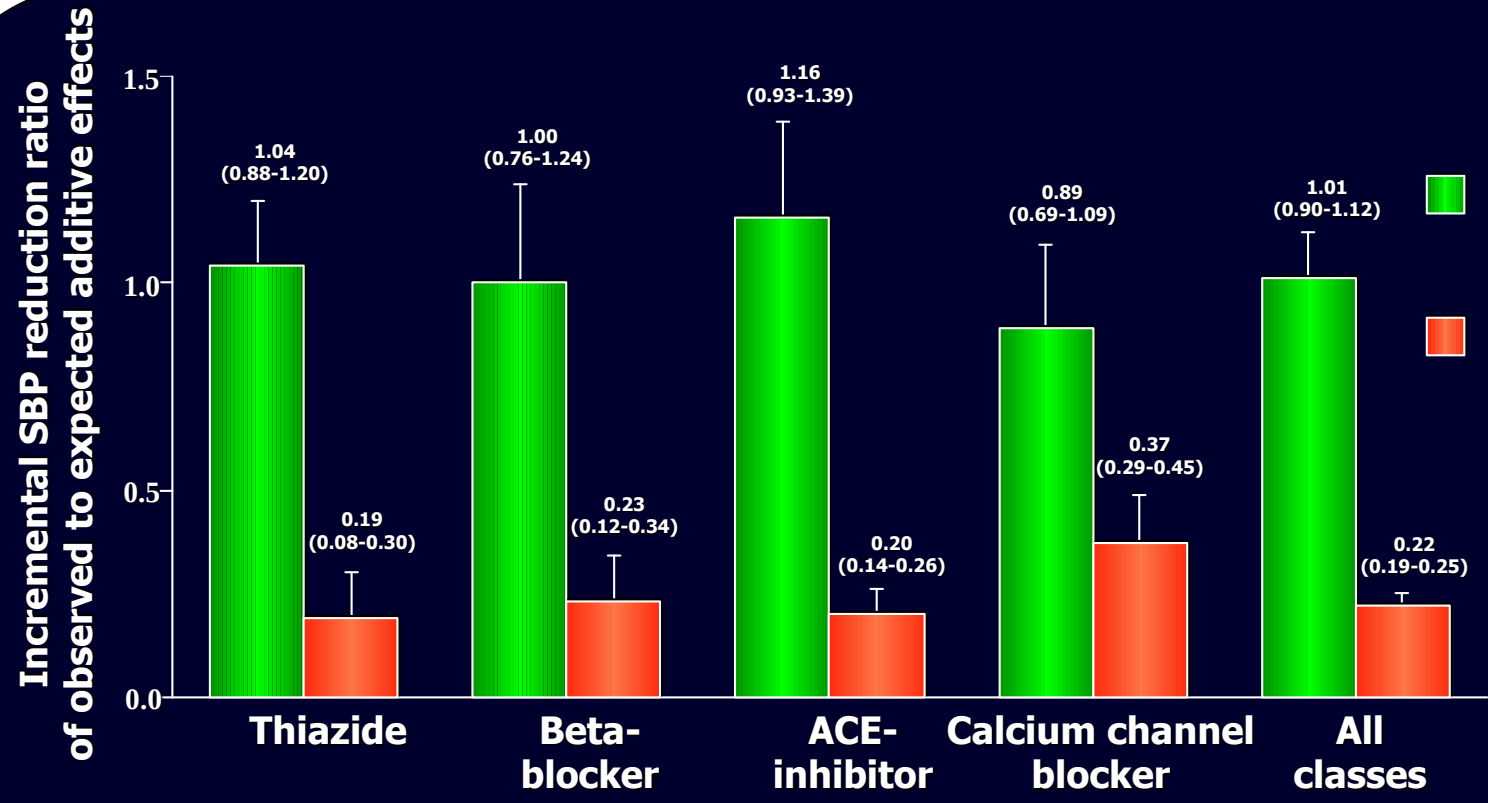
Figure 4 Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.

ESH Guidelines 2018

Advantages of combinations

- Efficacy
- Safety/Tolerability
- Compliance (Fixed formulations)

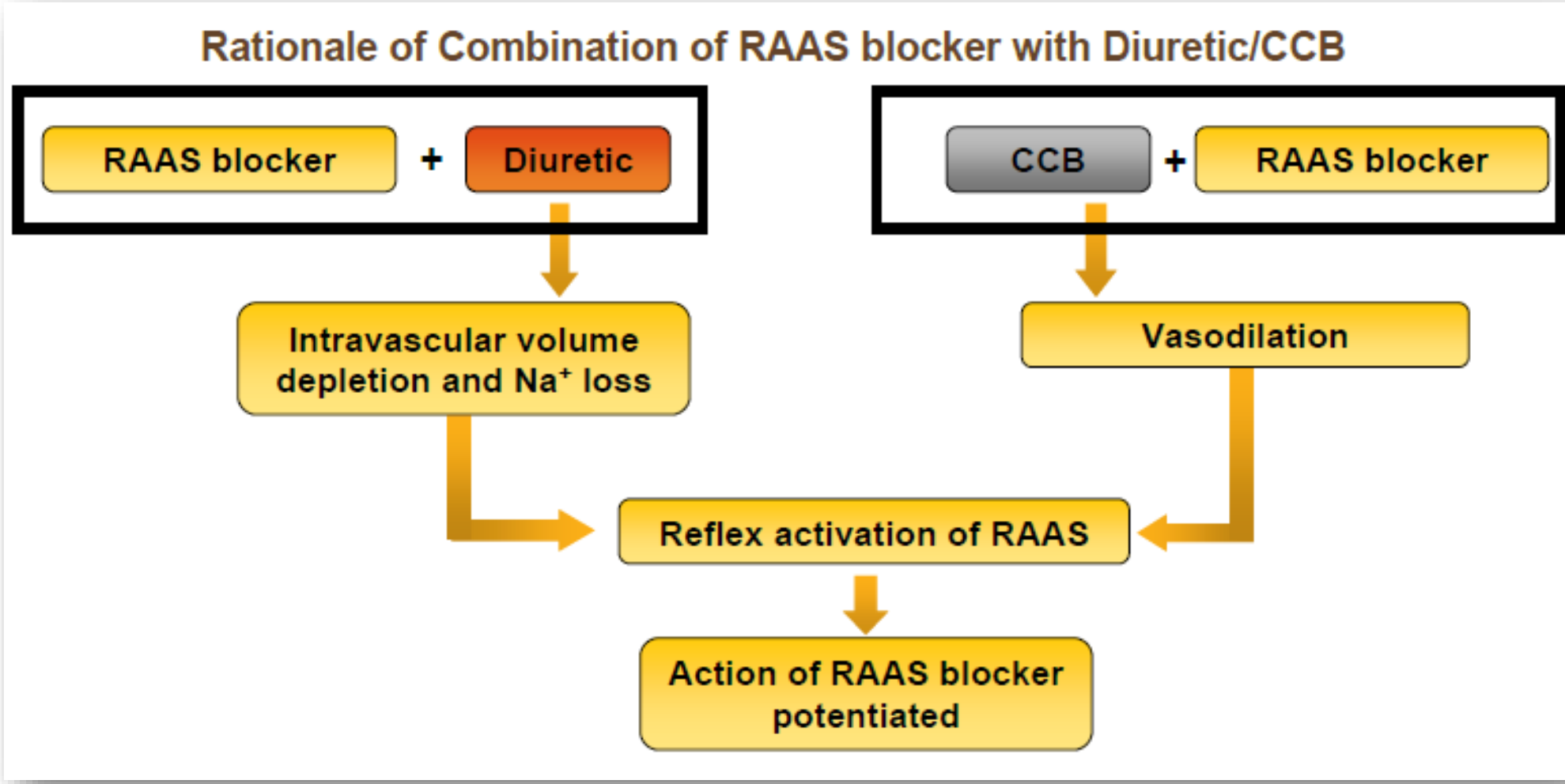
Ratio of observed to expected incremental BP-lowering effects* of adding a drug or doubling the dose according to the class of drug (n = 11000, 42 studies)



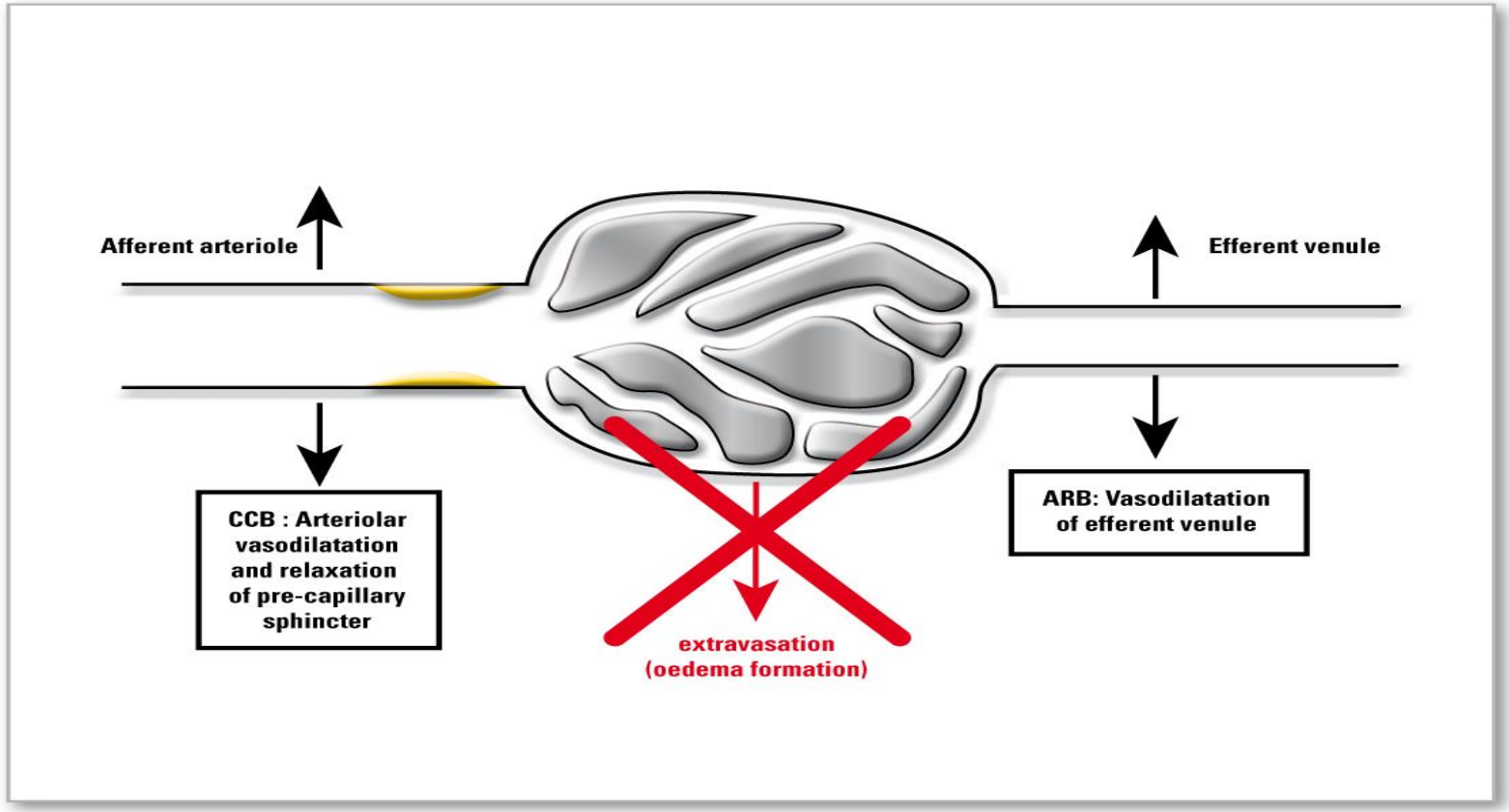
* The expected incremental effect is the incremental blood pressure reduction of the added (or doubled drug), assuming an additive effect and allowing for the smaller reduction from 1 drug (or dose of 1 drug) given the lower pretreatment blood pressure because of the other

Wald DS et al., Am J Med 2009; 122: 290

Rationale of Common Combinations



The CCB-ARB combination targets two key pathways:
synergy for decreasing oedema



Fogari R et al. J Hum Hypertens. 2007;21:220-4.

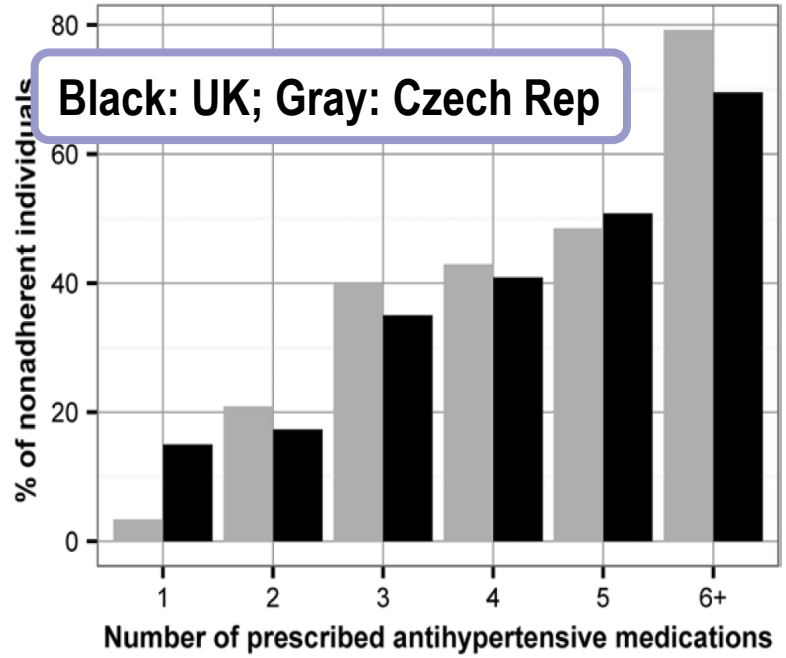
Gustafsson D. J Cardiovasc Pharmacol. 1987;10 Suppl 1:S121-31.

Predictors of Non-adherence to Antihypertensive Medications

Clinical Predictors of Nonadherence to Antihypertensive Treatment

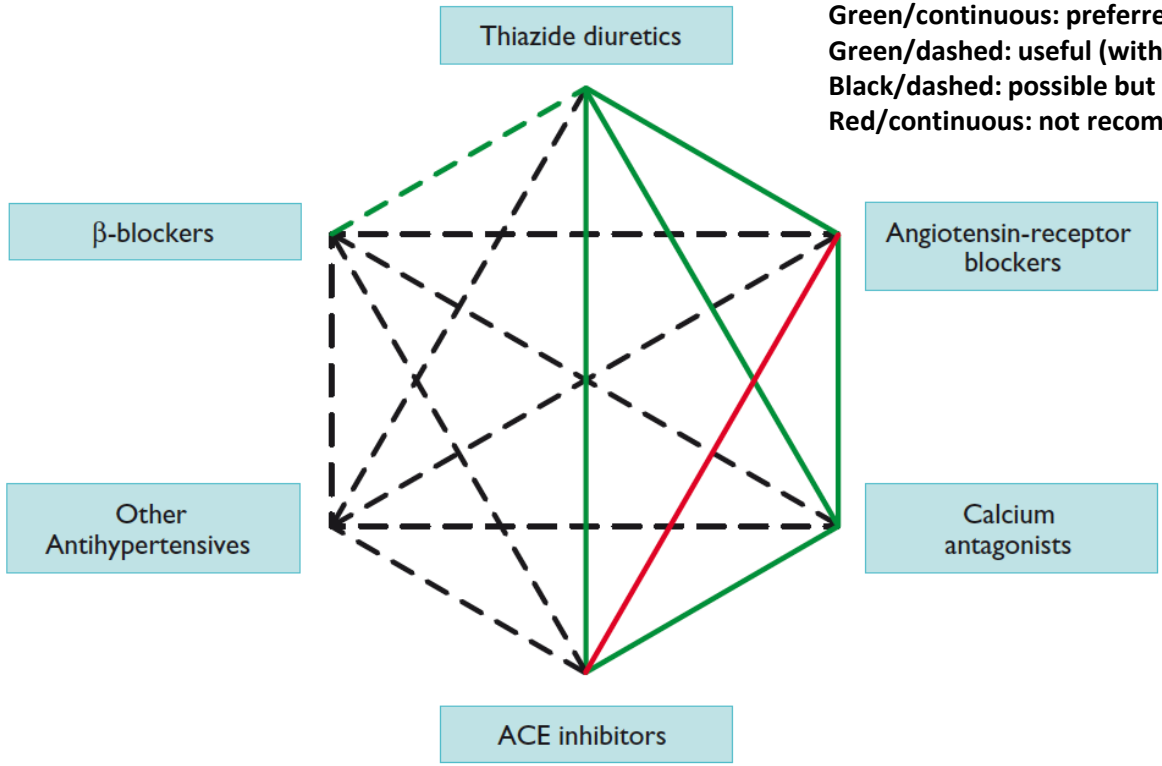
Phenotype	United Kingdom		Czech Republic	
	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	0.67 (0.59–0.77)	<0.001	0.69 (0.59–0.80)	<0.001
Women	1.65 (1.16–2.33)	0.005	1.55 (1.09–2.20)	0.014
No. of med.	1.85 (1.58–2.16)	<0.001	1.77 (1.47–2.12)	<0.001
Prescribed diuretics	1.65 (1.01–2.70)	0.047	1.18 (0.76–1.83)	0.457

Nonadherence increases with increasing drug prescriptions



Gupta P, et al. Hypertension. 2017;69:1113-1120

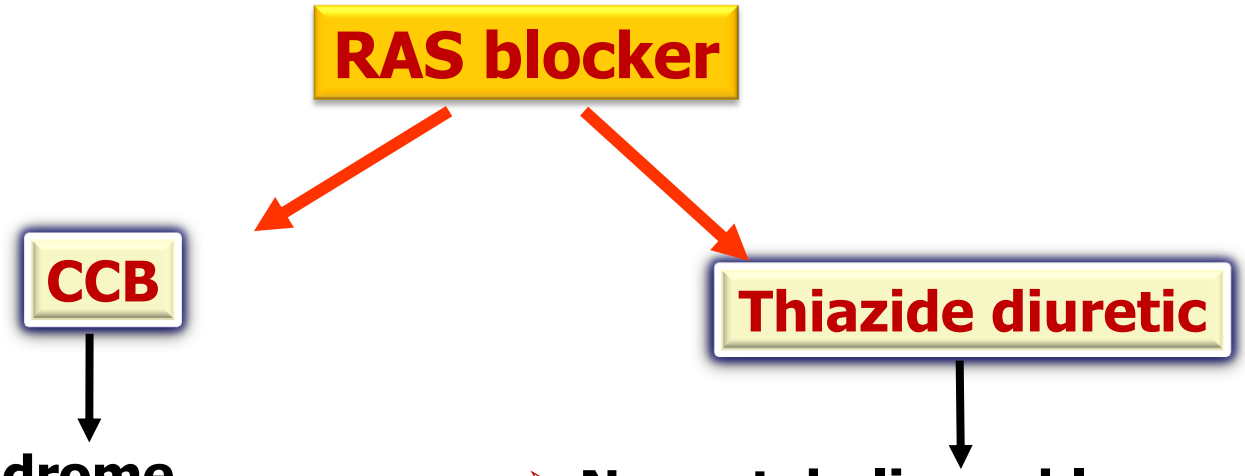
Possible combinations of antihypertensive drug classes



Green/continuous: preferred
Green/dashed: useful (with some limitations)
Black/dashed: possible but less well tested
Red/continuous: not recommended

Only dihydropyridines to be combined with β-blockers (except for verapamil or diltiazem for rate control in AF)
Thiazides + β-blockers increase risk of new onset DM
ACEI + ARB combination discouraged (IIIA)

Selecting Patients Suitable for RAS Blockade with CCB or Diuretic



- Metabolic syndrome
- Impaired fasting glucose
- Family history of diabetes
- Lipid profile alterations
- Need to avoid hypokalemia

- No metabolic problems
- Low risk of developing diabetes
- Hypervolemia (elderly, HF)

Three Drug Combinations

- In no less than 15-20% of HTs BP control cannot be achieved by a two drug combination
- When three drugs are required, the most rational combination appears to be

  a RAS blocker,

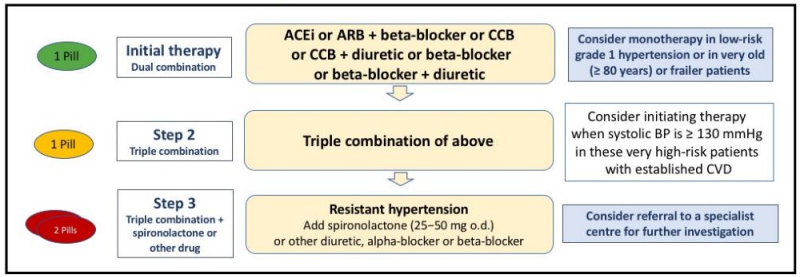
  a calcium antagonist and

  a diuretic at effective doses

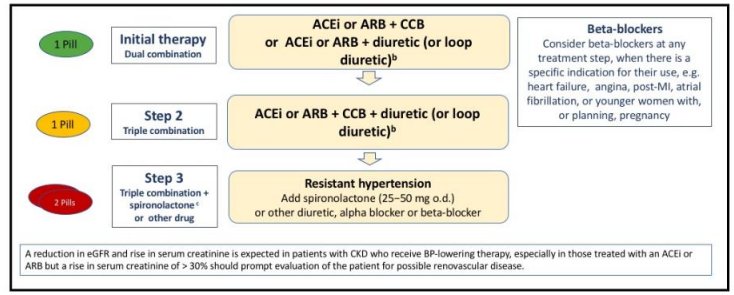
ESH/ESC 2013 Hypertension Guidelines

Drug-treatment strategies

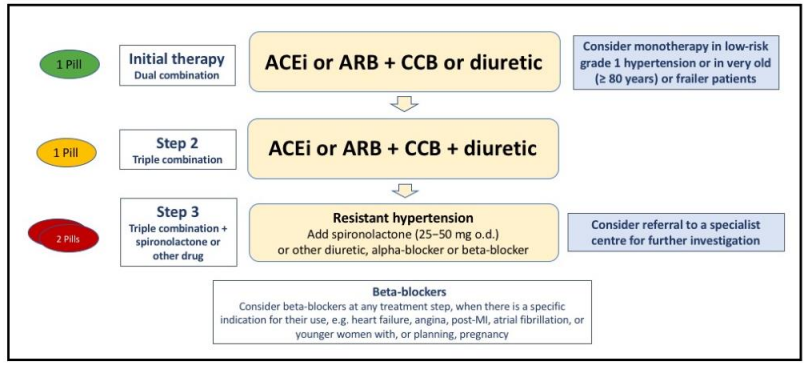
Hypertension and CAD



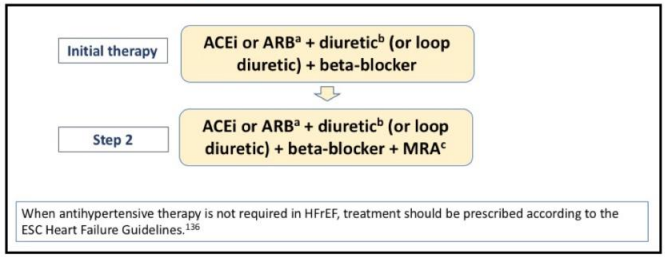
Hypertension and CKD



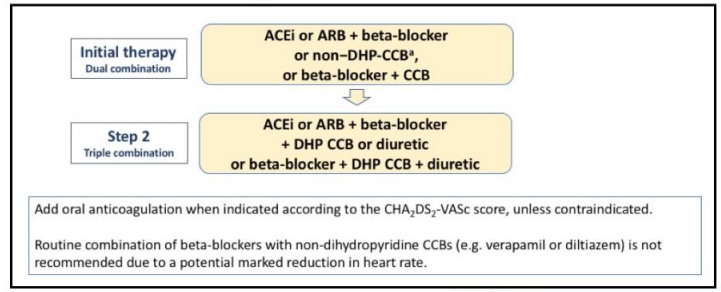
Core drug-treatment strategy for uncomplicated hypertension



Hypertension and HRrEF



Hypertension and AF



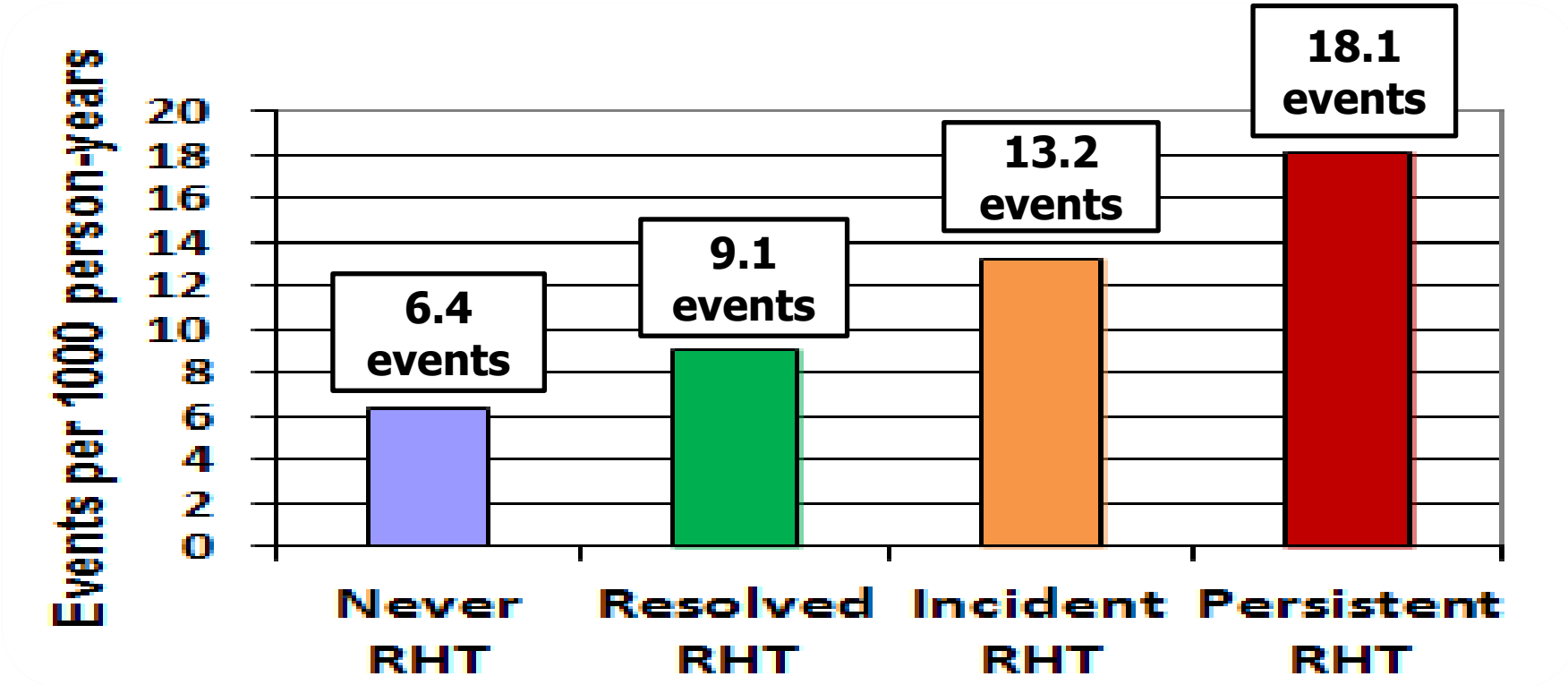
ESC European Society of Cardiology

Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

European Society of Hypertension

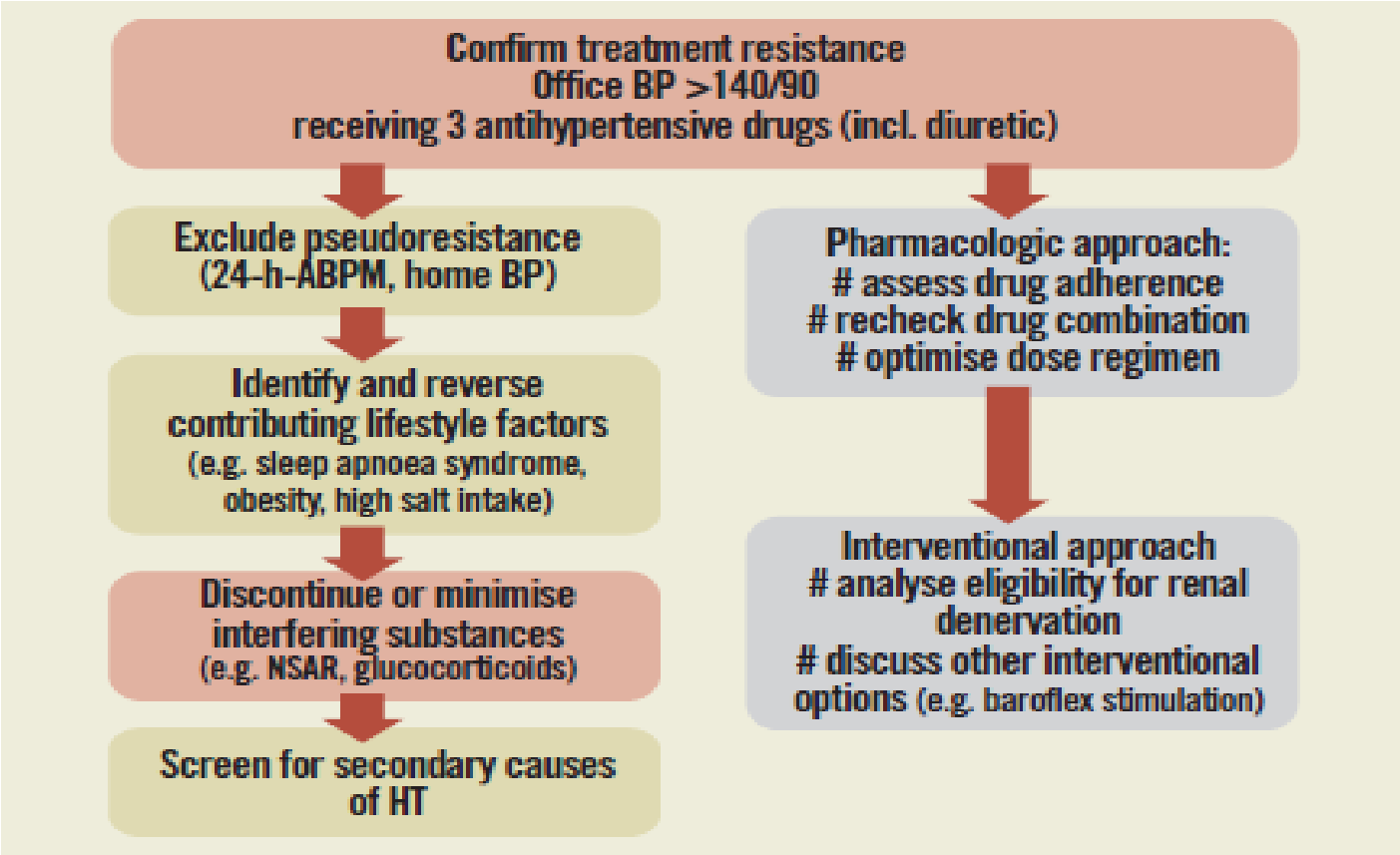
Patterns of RHT and CV events

1911 treated hypertensive patients for a mean period of 3.9 years follow up



Tsioufis C, et al. J Hypertens. 2013, November

Diagnostic algorithm for uncontrolled HTN

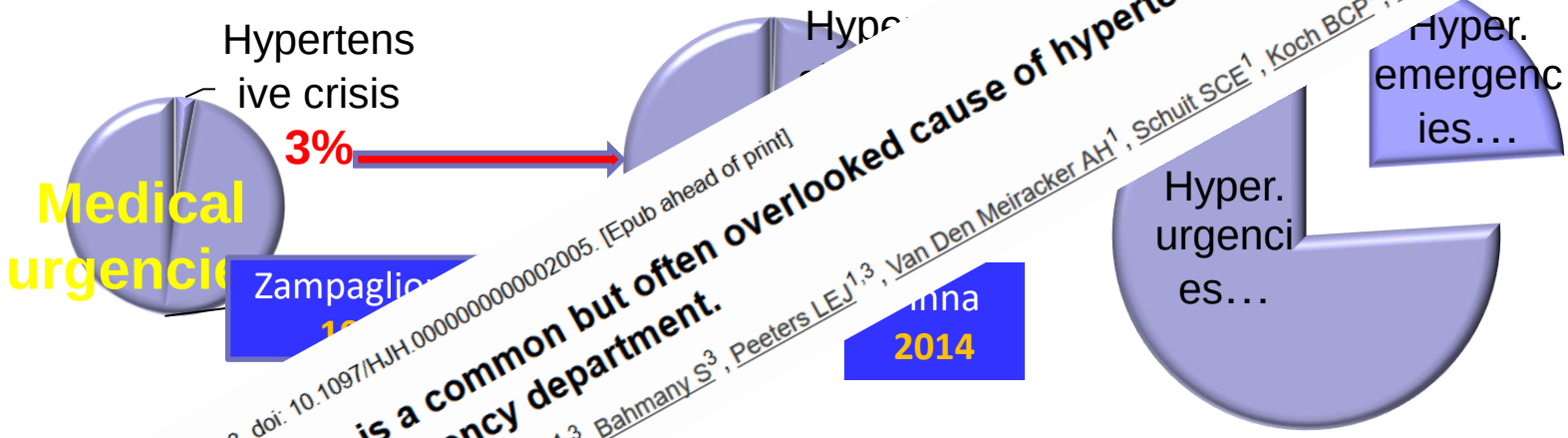


Updated ESH position paper on interventional therapy of resistant hypertension

Roland E. Schmieder[1]*, MD; Josep Redon[2], MD; Guido Grassi[3,4], MD; Sverre E. Kjeldsen[5], MD; Giuseppe Mancia[6], MD; Krzysztof Narkiewicz[7], MD; Gianfranco Parati[8], MD; Luis Ruilope[9], MD; Philippe van de Borne[10], MD; Costas Tsioufis[11], MD

SIZE OF THE PROBLEM-EPIDEMIOLOGY

- 456,259 hospitalizations hypertensive emergency occurred from 2000 to 200
- In 2025, more than 47 million patients will develop a hypertensive emer
- 1-2% of hypertensive patients will have an episode of hypertensive



J Hypertens. 2018 Nov 23. doi: 10.1097/HJH.0000000000002005. [Epub ahead of print]

Drug nonadherence is a common but often overlooked cause of hypertensive urgency and emergency at the emergency department.

Overgaauw N[1,2], Alsma J[1,2], Brink A[1], Hameli E[1,3], Bahmany S[3], Peeters LEJ[1,3], Van Den Meiracker AH[1], Schuit SCE[1], Koch BCP[3], Versmissen J[1].

- ertensive urgencies
- ypertensive emergencies

ertensive or Coronary heart disease

- Large number of antihypertensive drugs
- **Non-adherence**

Deshmukh A, et al. Am J Cardiol. 2011 Nov 1;108(9):1277-82
Zampaglione B, et al. Hypertension 1996; 27:144–147
Pinna G, et al. PLoS One. 2014 Apr 2;9(4):e93542
Lane DA, et al. Am J Hypertens 2009; 22:1199–1204
Saguner AM, et al. Am J Hypertens 2010; 23:775–780

Diagnostic work-up for patients with a suspected hypertension emergency

Common tests for all potential causes
Fundoscopy is a critical part of the diagnostic work-up
12-lead ECG
Haemoglobin, platelet count, fibrinogen
Creatinine, eGFR, electrolytes, LDH, haptoglobin
Urine albumin:creatinine ratio, urine microscopy for red cells, leucocytes, and casts
Pregnancy test in women of child-bearing age
Specific tests by indication
Troponin, CK-MB (in suspected cardiac involvement, e.g. acute chest pain or acute heart failure) and NT-proBNP
Chest X-ray (fluid overload)
Echocardiography (aortic dissection, heart failure, or ischaemia)
CT angiography of thorax and/or abdomen in suspected acute aortic disease (e.g. aortic dissection)
CT or MRI brain (nervous system involvement)
Renal ultrasound (renal impairment or suspected renal artery stenosis)
Urine drug screen (suspected methamphetamine or cocaine use)

Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

Hypertensive emergencies requiring immediate BP lowering with i.v. drug therapy

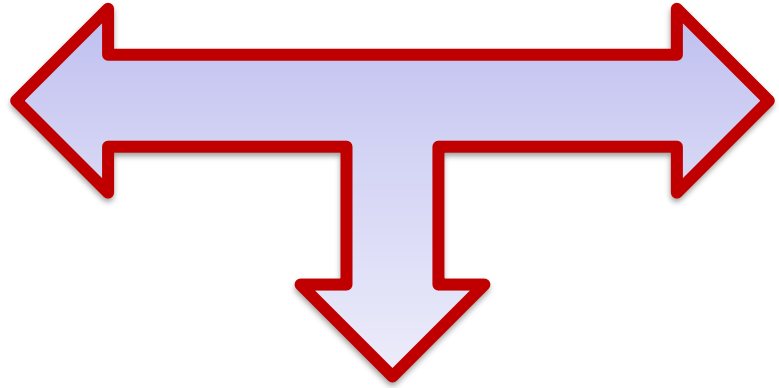
Clinical presentation	Time line and target for BP reduction	First-line treatment	Alternative
Malignant hypertension with or without acute renal failure	Several hours Reduce MAP by 20–25%	Labetalol Nicardipine	Nitroprusside Urapidil
Hypertensive encephalopathy	Immediately reduce MAP by 20–25%	Labetalol Nicardipine	Nitroprusside
Acute coronary event	Immediate reduce SBP to < 140 mmHg	Nitroglycerine Labetalol	Urapidil
Acute cardiogenic pulmonary oedema	Immediately reduce SBP to < 140 mmHg	Nitroprusside or nitroglycerine (with loop diuretic)	Urapidil (with loop diuretic)
Acute aortic dissection	Immediately reduce SBP to < 120 mmHg and heart rate to < 60 bpm	Esmolol AND nitroprusside or nitroglycerine or nicardipine	Labetalol OR metoprolol
Eclampsia and severe pre-eclampsia/HELLP	Immediately reduce SBP to < 160 mmHg and DBP to < 105 mmHg	Labetalol or nicardipine and magnesium sulphate	Consider delivery

Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

Επεμβάσεις για την υπέρταση

Δευτεροπαθής υπέρταση

- ***Stent στην εστενωμένη νεφρική αρτηρία***
- ***Stent στη στένωση του ισθμού της αορτής***
- ***Χειρουργική αφαίρεση αδενώματος από τα επινεφρίδια***



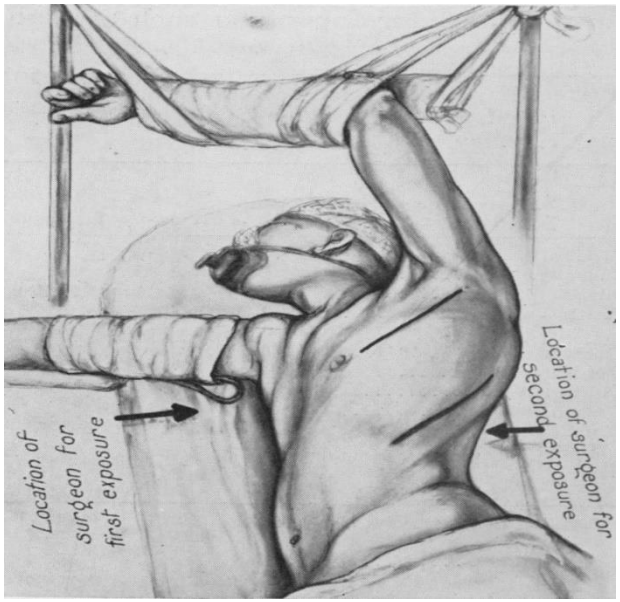
Ιδιοπαθής υπέρταση
Ανθεκτική υπέρταση

Συμπληρωματικές επεμβάσεις

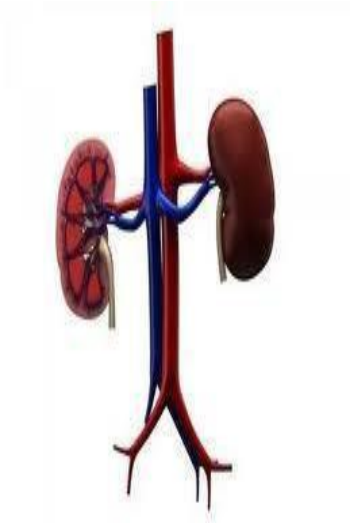
Βαριατρική χειρουργική
CPAP

Εξελίξεις στην επεμβατική θεραπεία της υπέρτασης

30's-50's Surgical sympathectomy



2009-Renal Denervation



Carotid Baroreceptor Stimulation

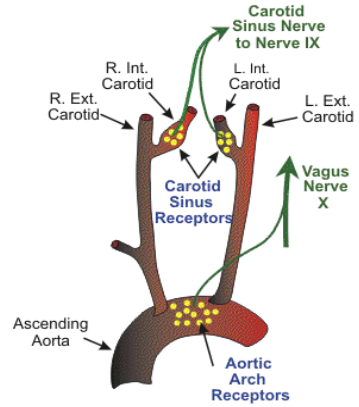
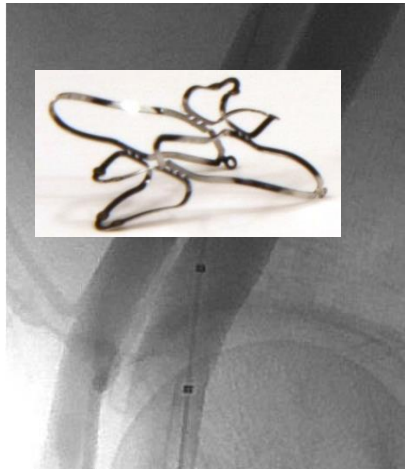
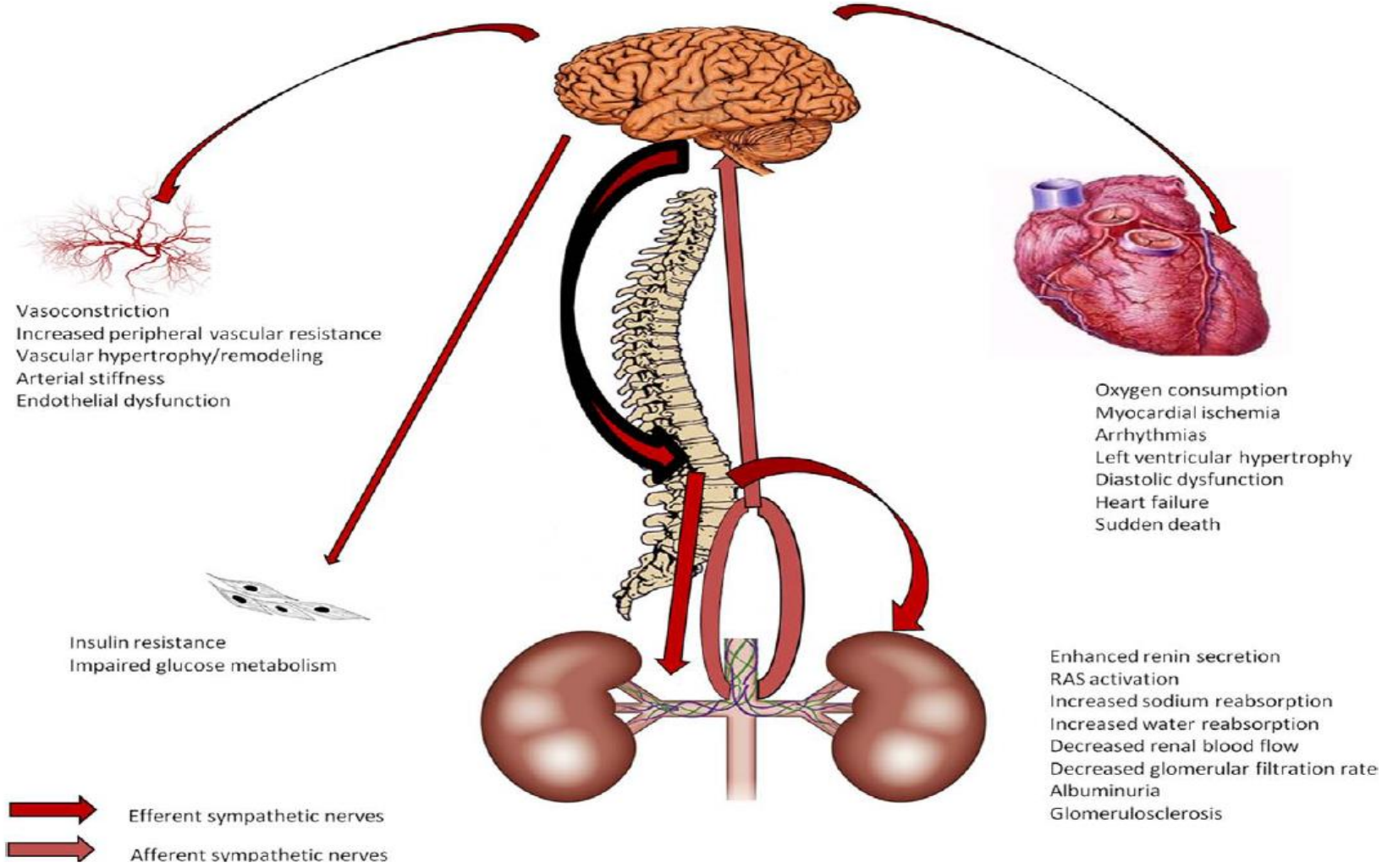


Figure 1. Location and innervation of arterial baroreceptors.

Iliac A-V anastomosis

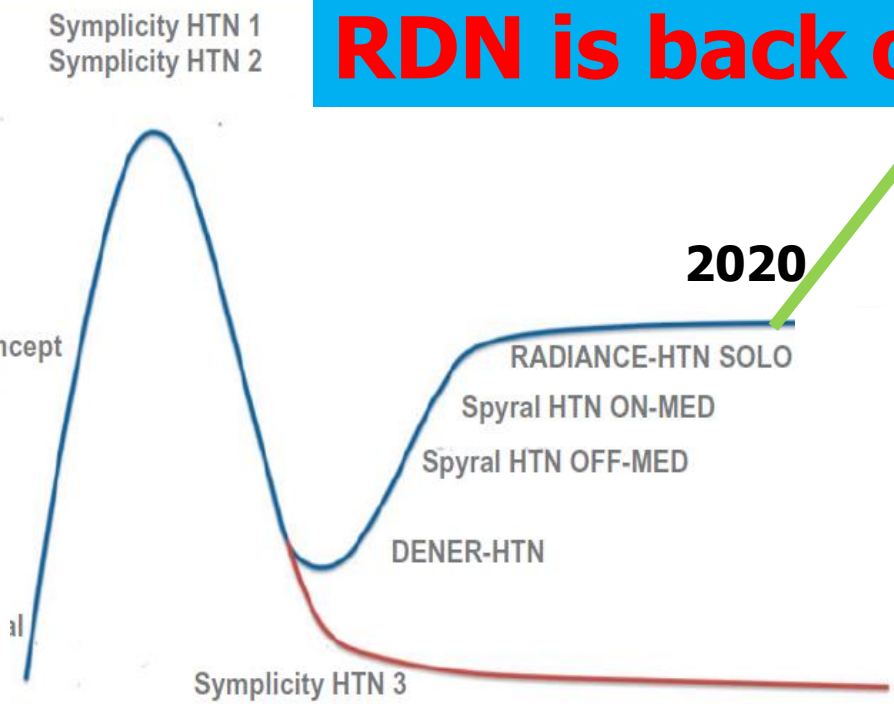


How does RDN work?



Papademetriou V, Tsioufis C, Doumas M. Circulation 2014

RDN is back on track



Mahfoud F, et al. Eur Heart J. 2018 Dec 14;39(47):4144-4149

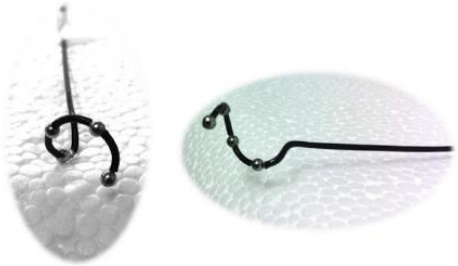


Fig. 1. The NephroBlate™ device with its helical probe.

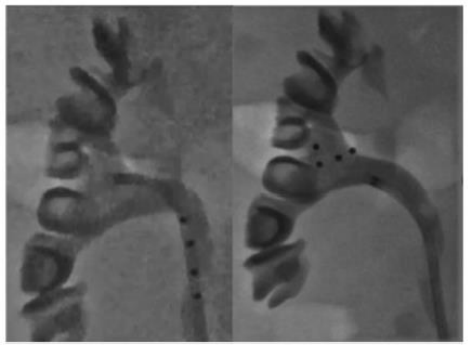
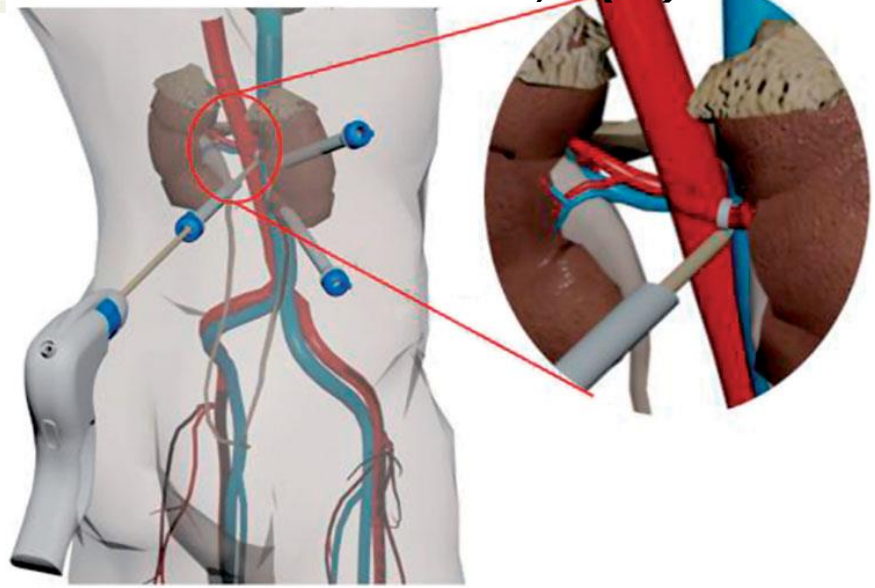


Fig. 2. Cinematography of the NephroBlate™ device in the swine renal pelvis.

Patel NJ, et al. Cardiovasc Revasc Med. 2018 Oct 11



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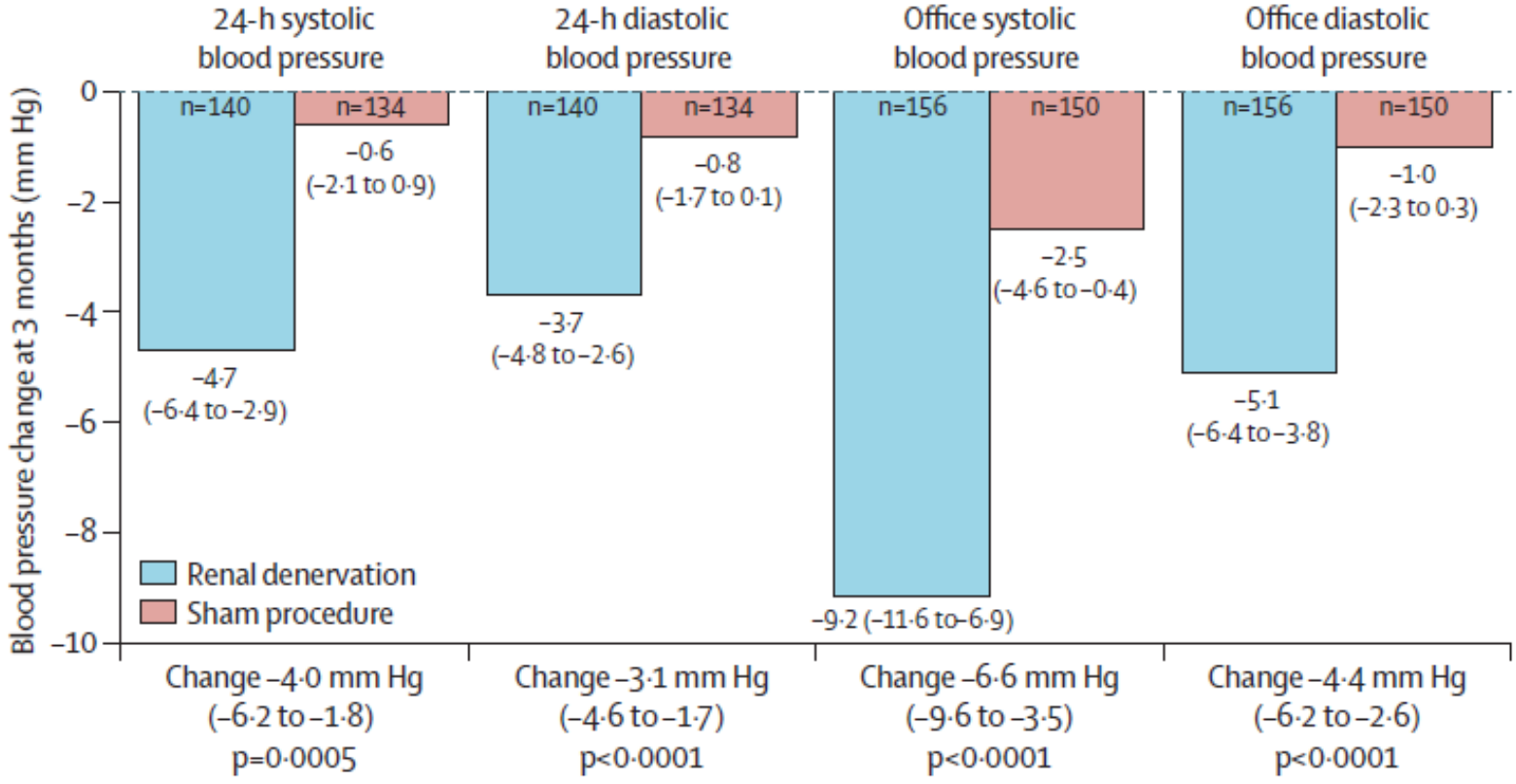
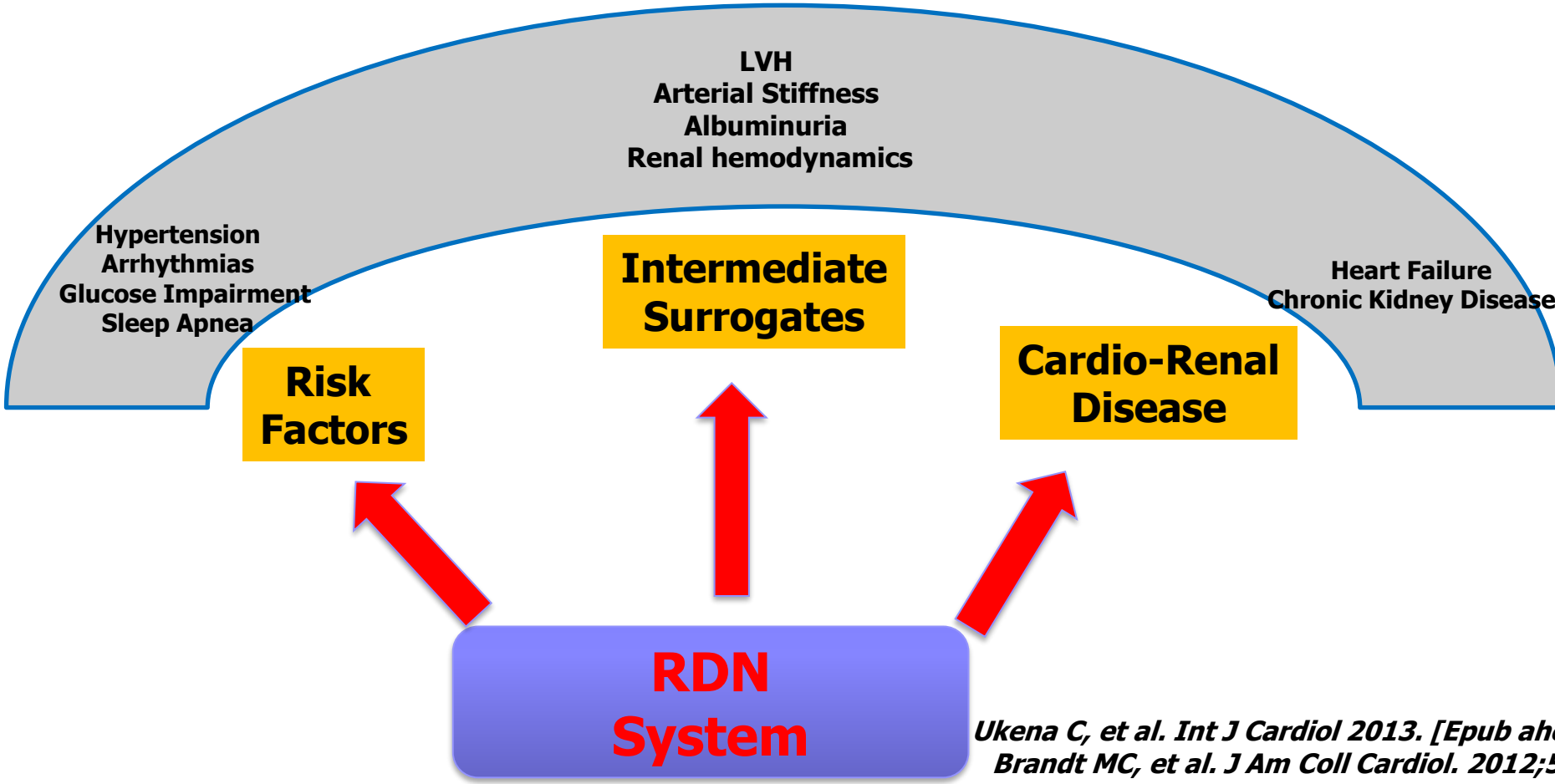
Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial

*Michael Böhm, Kazuomi Kario, David E Kandzari, Felix Mahfoud, Michael A Weber, Roland E Schmieder, Konstantinos Tsioufis, Stuart Pocock, Dimitris Konstantinidis, James W Choi, Cara East, David P Lee, Adrian Ma, Sebastian Ewen, Debbie L Cohen, Robert Wilensky, Chandan M Devireddy, Janice Lea, Axel Schmid, Joachim Weil, Tolga Agdirlioglu, Denise Reedus, Brian K Jefferson, David Reyes, Richard D'Souza, Andrew S P Sharp, Faisal Sharif, Martin Fahy, Vanessa DeBruin, Sidney A Cohen, Sandeep Brar, Raymond R Townsend, on behalf of the SPYRAL HTN-OFF MED Pivotal Investigators**



Lancet. 2020 Mar 27;S0140-6736(20)30554-7

The burden of RDN potential effects ….beyond BP lowering



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Mahfoud F, et al. Eur Heart J 2014
Tsioufis C, et al, JHH 2014

THANK YOU!