Cardiovascular risk and prevention

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CARDIOVASCULAR DISEASES AND RESPIRATORY SCIENCES
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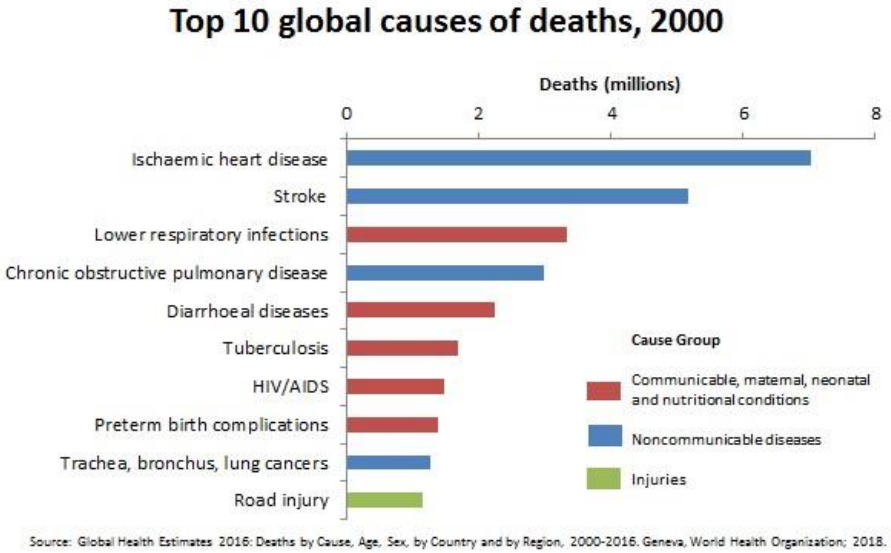
SCHOOL OF MEDICINE AND SURGERY

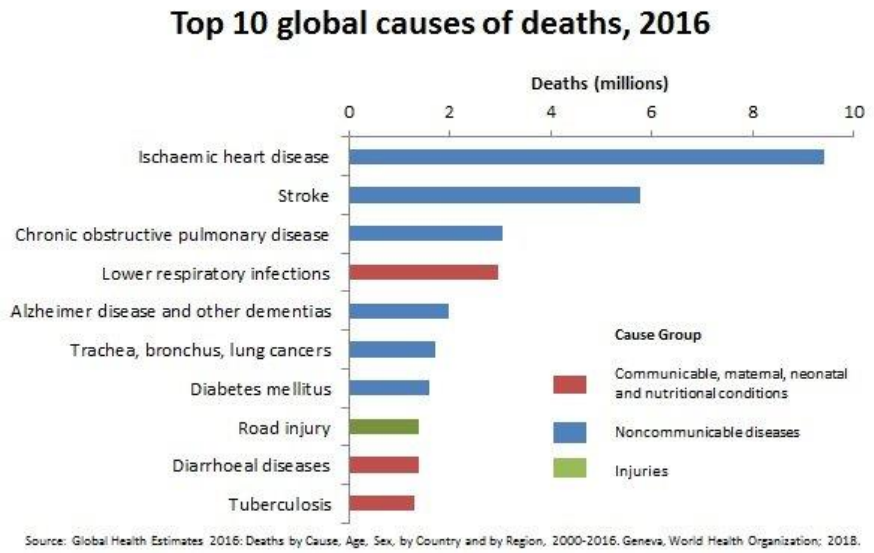
Academic year 2022/2023

Cardiovascular diseases

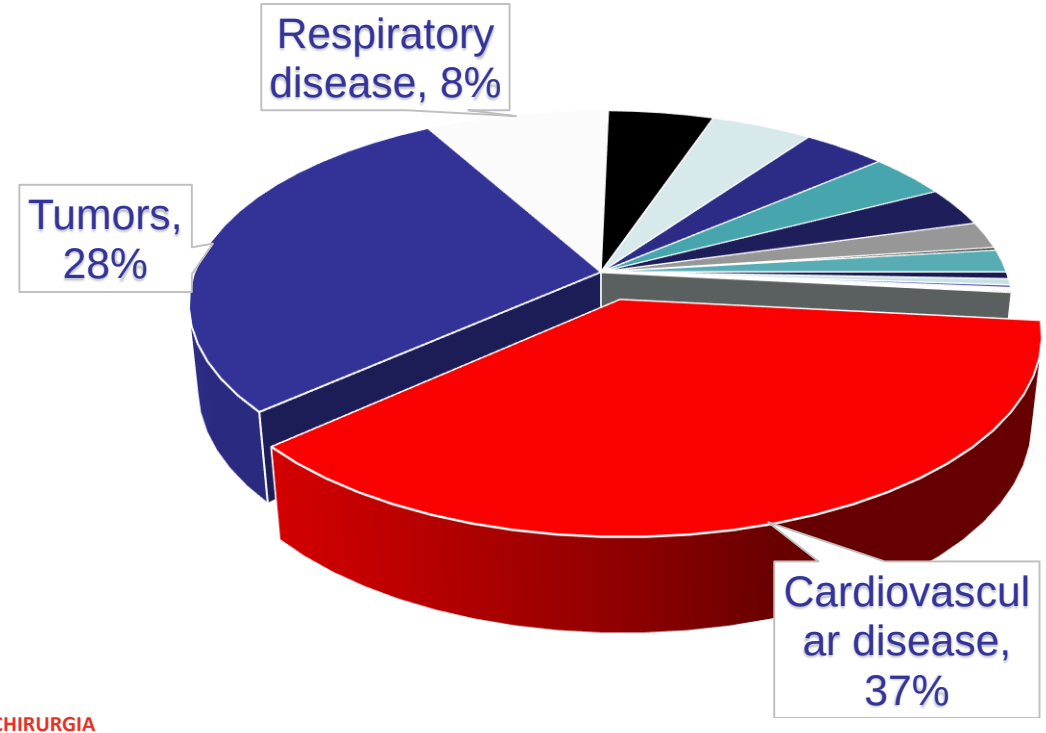
- Cardiovascular disease is the leading cause of premature death
- Stroke is the leading cause of permanent disability
- Costs for patients, healthcare systems and society are incalculable
- The majority of those at risk are not recognised or are not treated

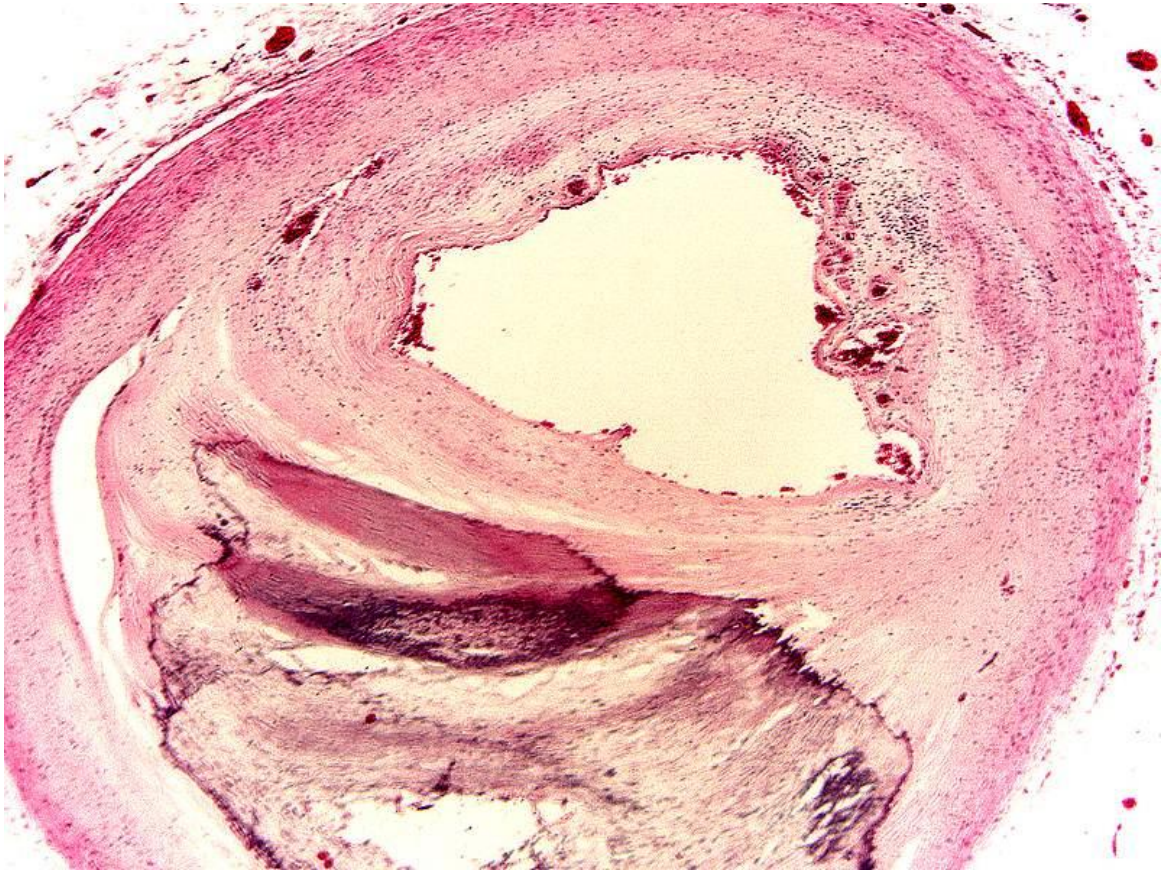
Heart disease and stroke are the leading causes of death worldwide





Causes of mortality in Italy ISTAT (2019)





Main consequences of atherosclerosis

- Myocardium
  - Angina
  - MI
- Brain
  - TIA
  - Stroke
- GI system
  - Abdominal angina
  - Mesenteric infarction
- Kidney
  - Nephrovascular hypertension
  - Chronic Kidney Disease
- Limbs
  - Trophic changes
  - Claudication
  - Cramps
  - Leriche Sindrome

Risk factors vs. risk markers

Cardiovascular risk marker:

a variable that is quantitatively **associated** with cardiovascular disease, but direct alteration of the risk marker does not necessarily alter the risk of the outcome.

Cardiovascular risk factor:

habit, behavior, circumstance or condition that **increases** a person's risk of developing cardiovascular disease

that means that there is a **causal link** between risk factor and disease and that **intervening** on this factor (if possible) will modify cardiovascular risk

Risk factors/markers – characteristics

- Independent risk prediction
- Potential for risk reclassification
- Modifiable or not
- Benefits from treatment
- Cost of potential interventions

Cardiovascular risk factors/markers

- Cigarette smoking
- Arterial hypertension
- ↑ LDL-cholesterol
- ↓ HDL-cholesterol
- Diabetes mellitus
- Advanced age
- ↑ Triglycerides
- ↑ LDL Small/dense
- Inflammation/CRP
- ↑ lipoprotein(a)
- ↑ homocistein
- Prothrombotic factors
- Obesity
- Abdominal obesity
- Sedentary lifestyle
- Family history of CVD
- Ethnic characteristics
- Psycho-social factors

Multiplicative interactions between risk factors

"Nine easily measurable risk factors "explain" over 90% of myocardial infarctions"

- Smoking
- Hypertension
- Diabetes
- Dyslipidemia
- Abdominal obesity
- Stress
- Physical inactivity
- Low intake of fruits and vegetables
- Alcohol consumption

Those with all nine factors are more than 330 times more likely to have a myocardial infarction than those with none

INTERHEART Lancet 2004

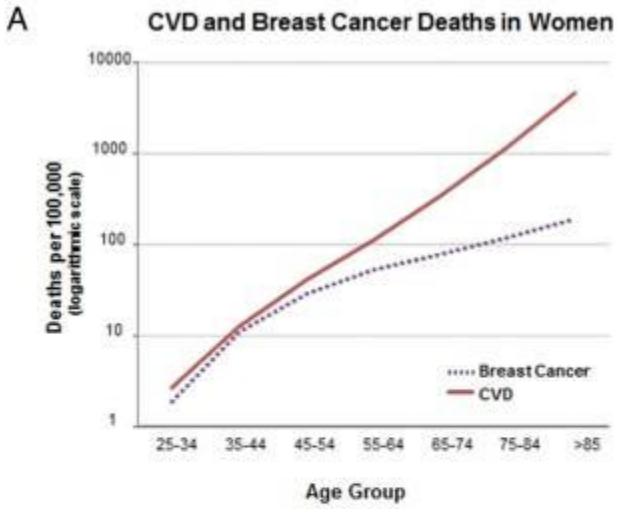
Risk factors

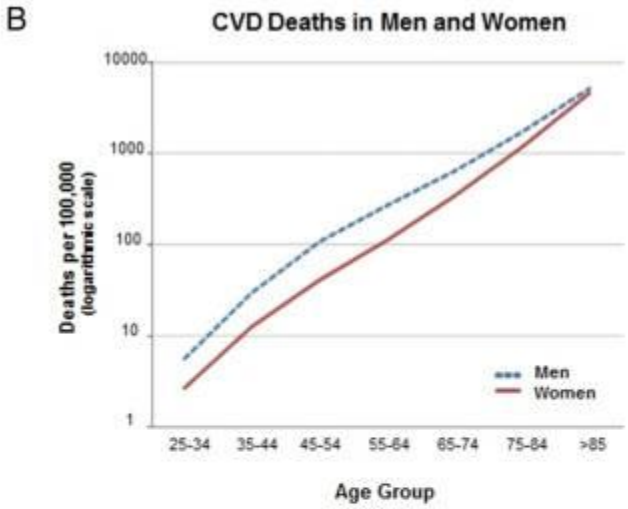
MODIFIABLE RISK FACTORS	PARTIALLY MODIFIABLE RISK FACTORS	NON-MODIFIABLE RISK FACTORS
Cigarette smoking	Arterial hypertension	Age
Alcohol abuse	Diabetes Mellitus	Sex
Diet rich in saturated fat, high calorie	Hypercholesterolemia Low HDL cholesterol	Genetic factors and family predisposition
Physical inactivity	Obesity	Personal history of cardiovascular disease

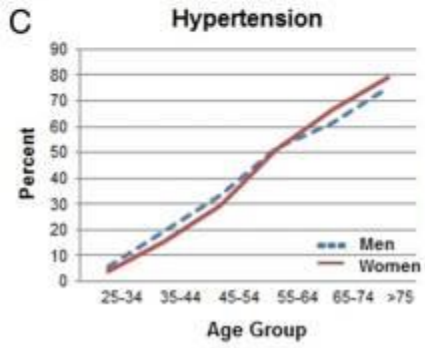
Age and sex

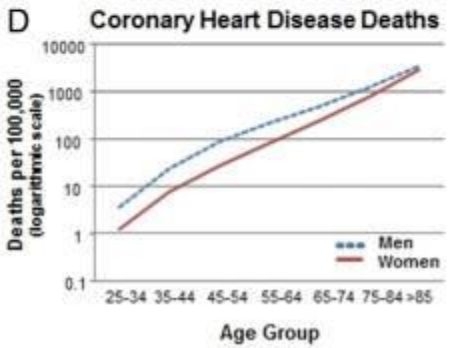
- The frequency of coronary heart disease increases progressively with age in both sexes, even in the absence of other risk factors
- The increase becomes significant after the age of 60: the average age at which the first heart attack appears is 65.8 years for men and 70.4 years for women. In men atherosclerotic coronary heart disease manifests about 10 years before women
- Cardiovascular diseases are more frequent in men than in women of childbearing age (protection exercised by estrogens). After menopause the difference cancels out
- After menopause in women, the expression of risk factors such as high blood pressure, hypercholesterolemia and hypertriglyceridemia, diabetes or impaired glucose tolerance and obesity becomes greater

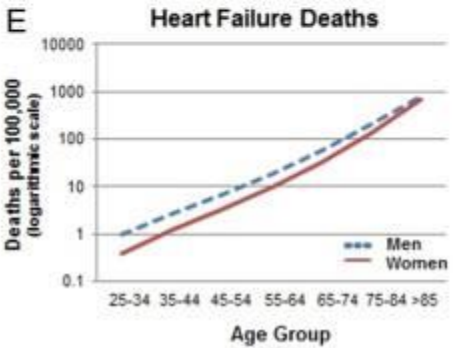
Age and sex


A
CVD and Breast Cancer Deaths in Women
Deaths per 100,000 (logarithmic scale)
10000
1000
100
10
1
Breast Cancer
CVD
25-34 35-44 45-54 55-64 65-74 75-84 >85
Age Group


B
CVD Deaths in Men and Women
Deaths per 100,000 (logarithmic scale)
10000
1000
100
10
1
Men
Women
25-34 35-44 45-54 55-64 65-74 75-84 >85
Age Group


C
Hypertension
Percent
90
80
70
60
50
40
30
20
10
0
Men
Women
25-34 35-44 45-54 55-64 65-74 >75
Age Group


D
Coronary Heart Disease Deaths
Deaths per 100,000 (logarithmic scale)
10000
1000
100
10
1
0.1
Men
Women
25-34 35-44 45-54 55-64 65-74 75-84 >85
Age Group


E
Heart Failure Deaths
Deaths per 100,000 (logarithmic scale)
10000
1000
100
10
1
0.1
Men
Women
25-34 35-44 45-54 55-64 65-74 75-84 >85
Age Group

Family predisposition

- The occurrence of episodes of premature ischemic heart disease (before the age of 55 for men and before the age of 65 for women) among relatives is associated with an incremental risk (regardless of risk factors).
- The risk is influenced by the precocity of the event, the degree of relationship (the disease in one of the parents gives a higher risk) and the number of relatives affected by coronary heart disease.

Modifiable risk factors

MODIFIABLE RISK FACTORS	PARTIALLY MODIFIABLE RISK FACTORS	NON-MODIFIABLE RISK FACTORS
Cigarette smoking	Arterial hypertension	Age
Alcohol abuse	Diabetes Mellitus	Sex
Diet rich in saturated fat, high calorie	Hypercholesterolemia Low HDL cholesterol	Genetic factors and family predisposition
Physical inactivity	Obesity Environmental pollution	Personal history of cardiovascular disease

Cigarette smoking

Heterogeneous mixture of over 4000 gaseous and corpuscular substances, originating from the process of burning tobacco leaves

The most harmful to the organism:

- **Nicotine (responsible for addiction)**
- **Carbon monoxide**
- **Irritant and oxidant substances**
- **Benzopyrene and other carcinogens.**

Cigarette smoking

- Increases blood pressure levels
- Causes damage to the integrity of the vasal endothelium, facilitating the process of atherosclerosis
- Increases plasma cholesterol levels
- The effect of smoking is synergistic with other risk factors, in particular hypercholesterolemia, hypertension and diabetes mellitus
- The higher the number of cigarettes smoked and the younger the age at which the smoking habit begins, the more serious the damage

Psychosocial factors

- Low socio-economic status, lack of social support, stress at work and in family life, depression, anxiety, hostility, and the type D personality contribute both to the risk of developing CVD and the worsening of clinical course and prognosis of CVD.
- These factors act as barriers to treatment adherence and efforts to improve lifestyle, as well as to promoting health and well-being in patients and populations. In addition, distinct psychobiological mechanisms have been identified, which are directly involved in the pathogenesis of CVD.

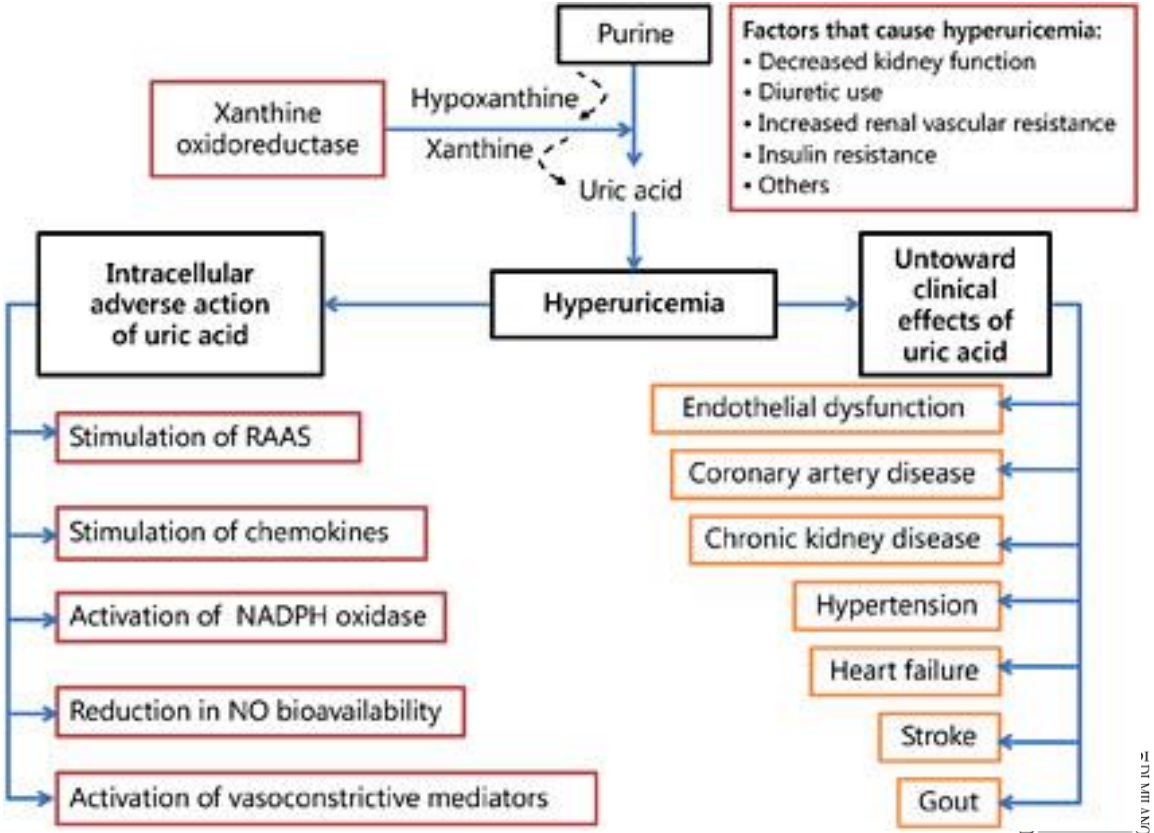
The characteristics of the type D personality are found in two broad and stable traits:
1- negative affectivity: tendency to express strong negative emotions in a stable way over time and in different situations;
2- social inhibition: tendency to inhibit the expression of negative emotions in social interactions.

These people tend to worry, take a pessimistic view of life and feel anxious and unhappy, they easily get irritated and generally feel less positive emotions, they do not share negative ones for fear of being rejected or disapproved. They also tend to have few friendships and feel uncomfortable in the presence of strangers.

- **Social isolation and low social support**
- **Stress at work and in family life**
- **Depression**
- **Anxiety**
- **Hostility and anger**
- **Type D personality («distressed»)**

Hyperuricemia

- **Commonly associated with metabolic disorders**
- **Mechanistic and epidemiological evidence of association with adverse cardiovascular outcomes**
- **No strong evidence of benefits from treatment in terms of CV risk**



Homocysteine

Homocysteine is a sulfidrilic amino acid that derives from the metabolic conversion of the essential amino acid methionine.

Action -> thrombogenic

Linked to congenital metabolism deficits (MTHFR polymorphism) and misconduct (smoking, alcohol and coffee)

Suspected role of the homocysteine on the arterial wall:

- Direct action on endothelium and vasal wall with marked atherogenic effect;
- Action on platelets, with increased adhesiveness and platelet aggregability;
- Action on coagulation factors and lipoproteins (reduction of antithrombin III activity, reduction of C protein activation, activation of factor VII, reduction of PTA activity, oxidation of LDL)

Associated with CV risk – no evidence of benefit from treatment (folic acid)

WHY CALCULATE CARDIOVASCULAR RISK?

Risk is the product of several variables distributed in the population without a clear distinction between normality and pathology (continuum)

In order to define a strategy that is consistent and proportionate to the actual risk of the individual patient, it is therefore necessary to quantify it.

Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

EAS ESC European Society of Cardiology

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
Primary Prevention	<1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high- risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary Prevention	Very-high risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

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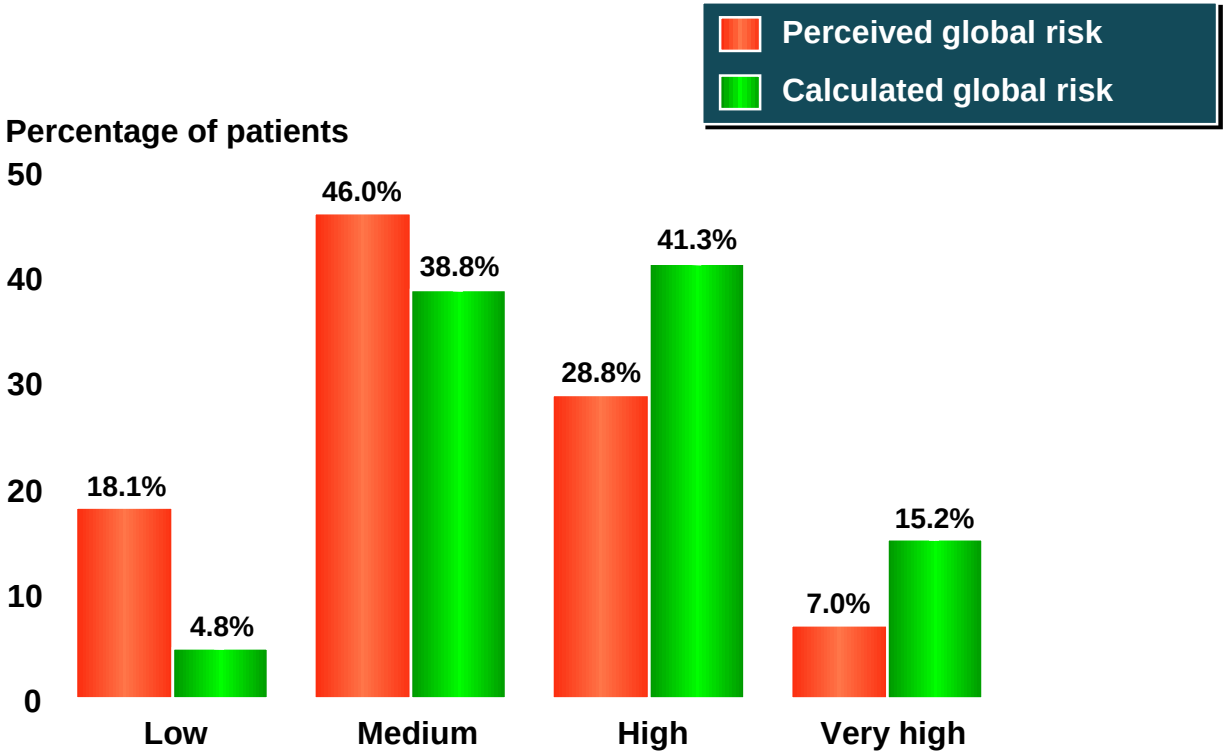
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Discrepancy between theory and practice in risk assessment



Mancia G. et al., J Hypertens 2004

Cardiovascular Risk

Absolute risk: Probability, expressed in %, of having, in the next 10 years, CV events:

- Myocardial infarction
- Sudden death
- Non-sudden cardiac death
- Coronary revascularization
- Major cerebrovascular event - hemorrhage or cerebral thrombosis (stroke, TIA)

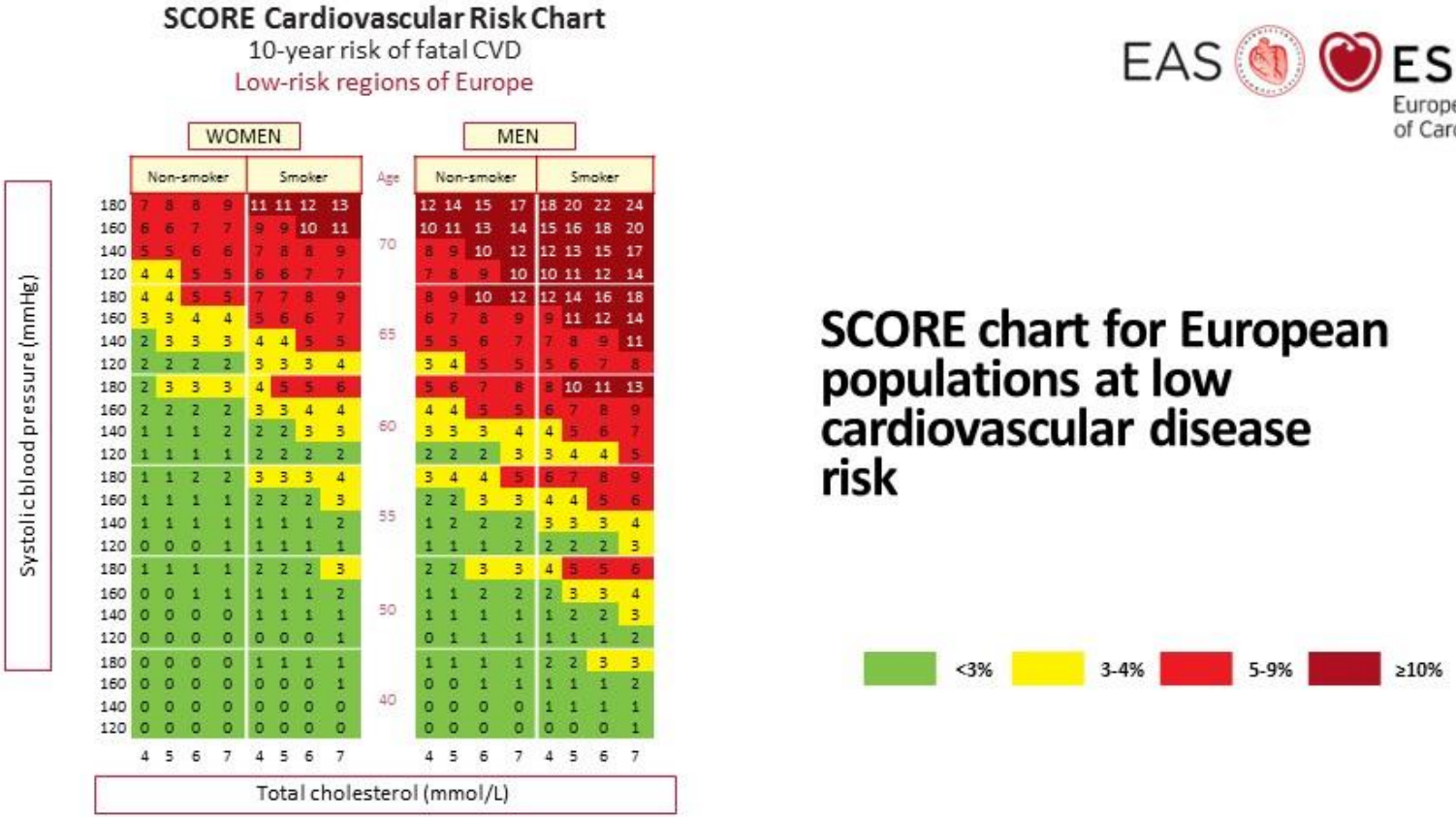
Relative Risk: the probability of an individual with specific risk factors developing an event, compared with a similar individual without those risk factors

How to estimate total cardiovascular risk?

SCORE (high-risk Systemic Coronary Risk Estimation

- 12 prospective studies from 11 European countries
- 117 098 men and 88 080 women (age 40-65)
- 10-year risk of CVD mortality (CAD, stroke, aneurysm of the abdominal aorta). Non fatal CV events (x 4 Men; x 3 Women)
- Sex, Age, total cholesterol/HDL-C ratio, SBP, smoking status
- Version for high and low risk countries

Recommendations	Class	Level
Total CV risk estimation, using a risk estimation system such as SCORE, is recommended for adults >40 years of age unless they are automatically categorised as being at *high-risk* or *very high-risk* based on documented CVD, DM (>40 years of age), kidney disease or highly elevated single risk factor.	I	C



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Risk categories

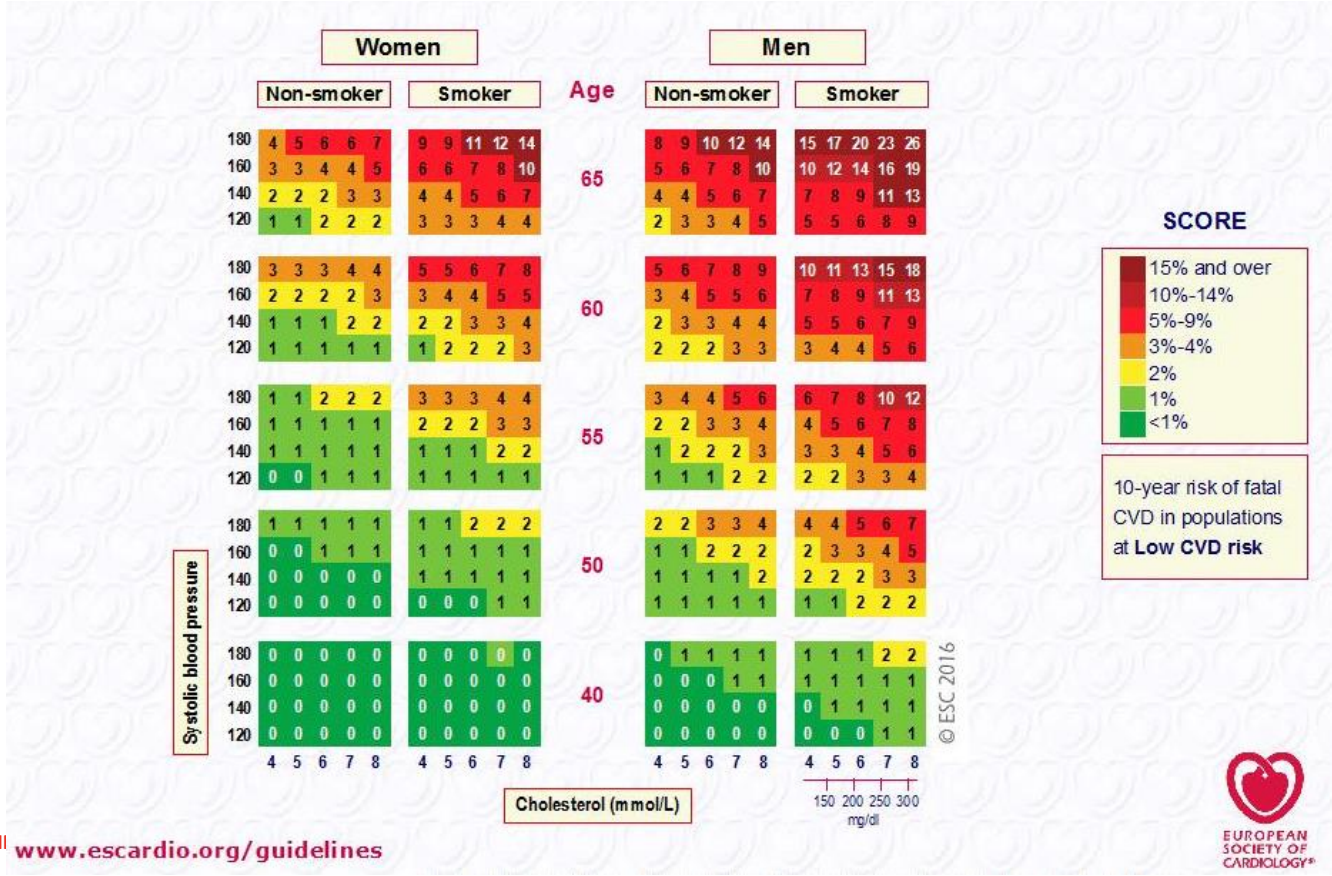
Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middleaged subjects belong to this category.
Low-risk	SCORE <1%.

Example of CV risk estimation

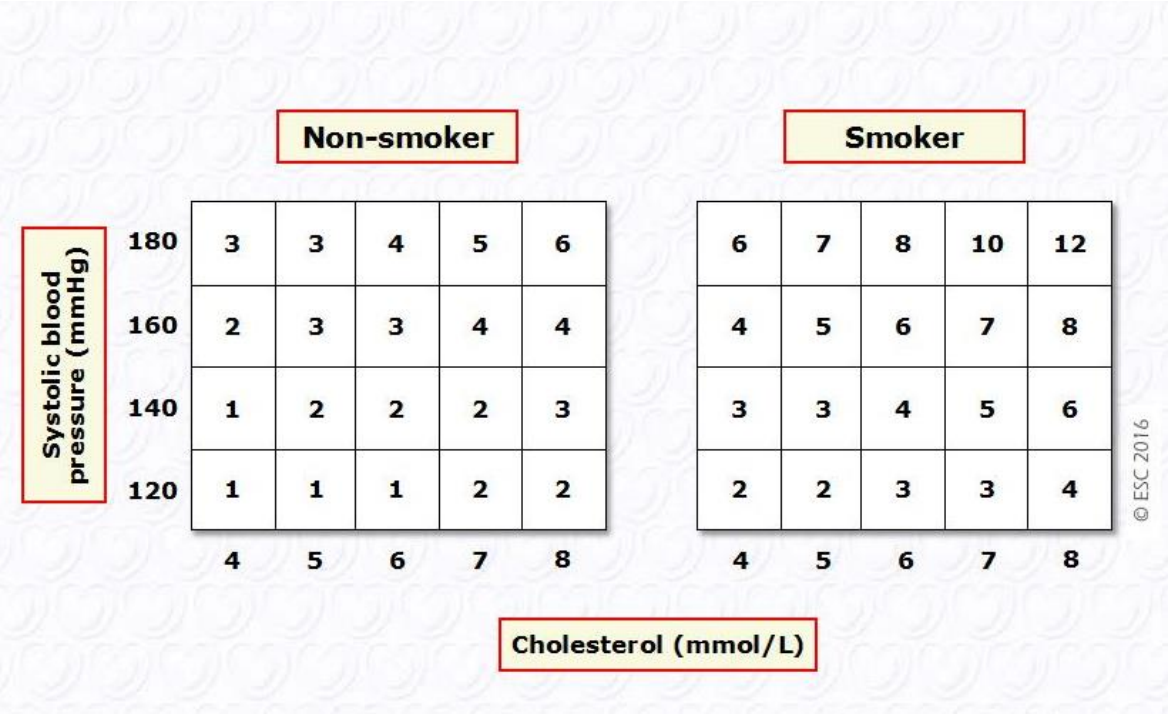
- 55 years old Italian man
- Smoker
- BP: 140/85
- Total cholesterol 230 mg/dl

Low-risk SCORE chart:

CVD mortality < 225/100000 in men, < 175/100000 in women



Relative risk SCORE chart



Clinical conditions affecting CV risk

- CKD – end stage renal disease is associated with very high CV risk
- Influenza can trigger a CV event
- Some studies have linked periodontitis to both atherosclerosis and CVD
- Patients surviving cancer after treatment with chemotherapy are at increased CV risk
- Rheumatoid arthritis (RR of 1.4 -1.5) and other autoimmune diseases
- OSAS
- Erectile disfunction

Measurment of preclinical vascular damage

- Routine screening with imaging modalities to predict future CV events is generally not reccomended in clinical practice
- Imaging methods may be considered as risk modifiers in CV risk assessment in individuals with calculated CV risk around the decisional thresholds
- Coronary artery calcium score examined through multislice CT (AGATSON score) has a very high negative predictive value.
- A recent meta analyses failed to demonstrate any added value of IMT in predicting future CVD. Many studies demonstrated the greater value of measures of atherosclerotic plaques
- Arterial stifness measured using Pulse Wave Velocity (PWV) or arterial augmentation index (AI) improves CV risk prediction for patients with calculated CV risk around the decisional thresholds.
- Ankle-brachial index (ABI) is controversial
- Echocardiography not recommended to improve CV risk prediction

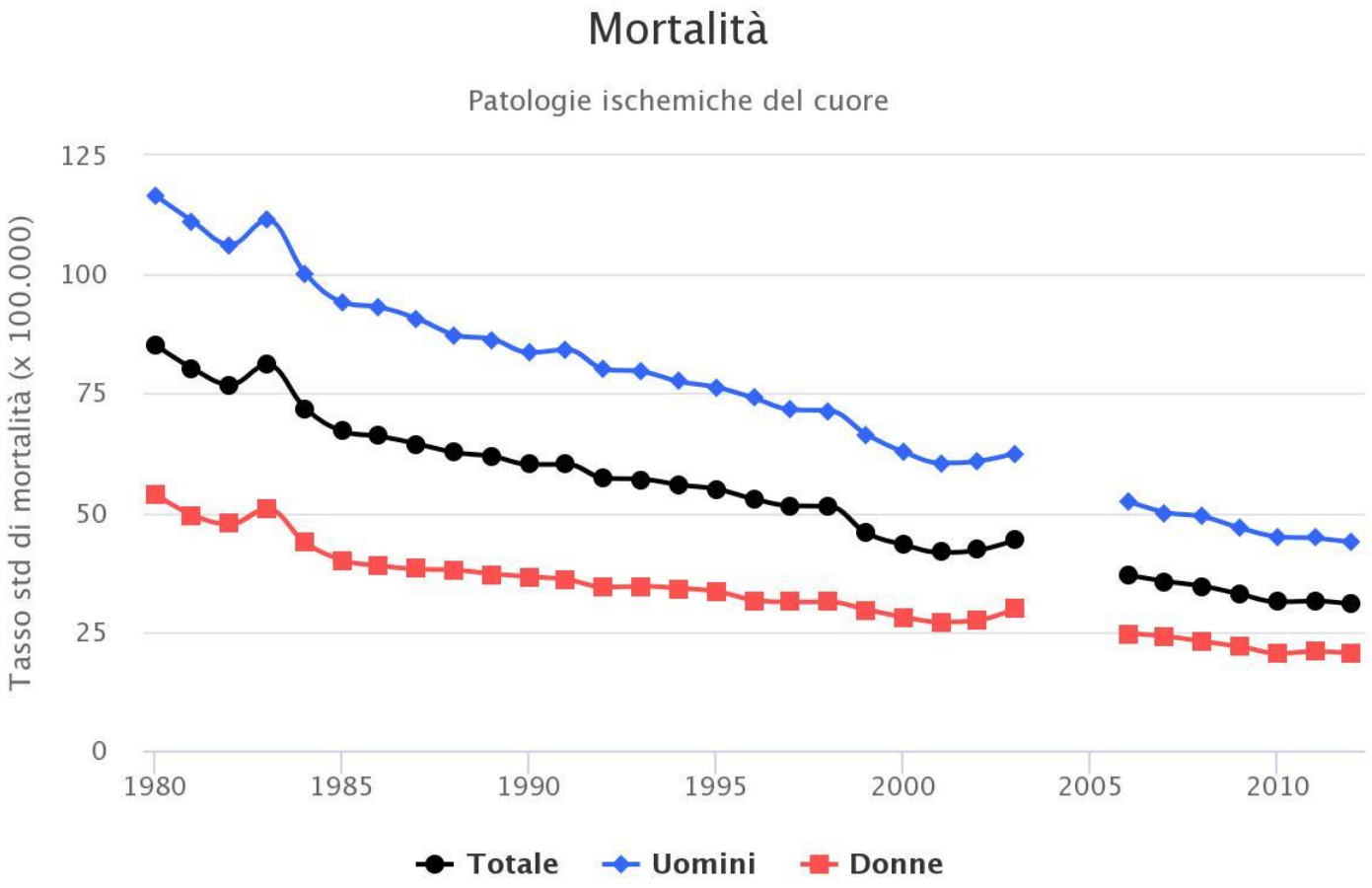
What is cardiovascular disease prevention?

- Cardiovascular disease prevention is defined as a coordinated set of actions, at the population level or targeted at an individual, that are aimed at eliminating or minimizing the impact of CVDs and their related disabilities.
  - **General population level:** promotion of healthy lifestyle
  - **Individual level:** optimisation of risk factors and tackling unhealthy lifestyle in patients at moderate to high risk of CVD or patients with estabilished CVD

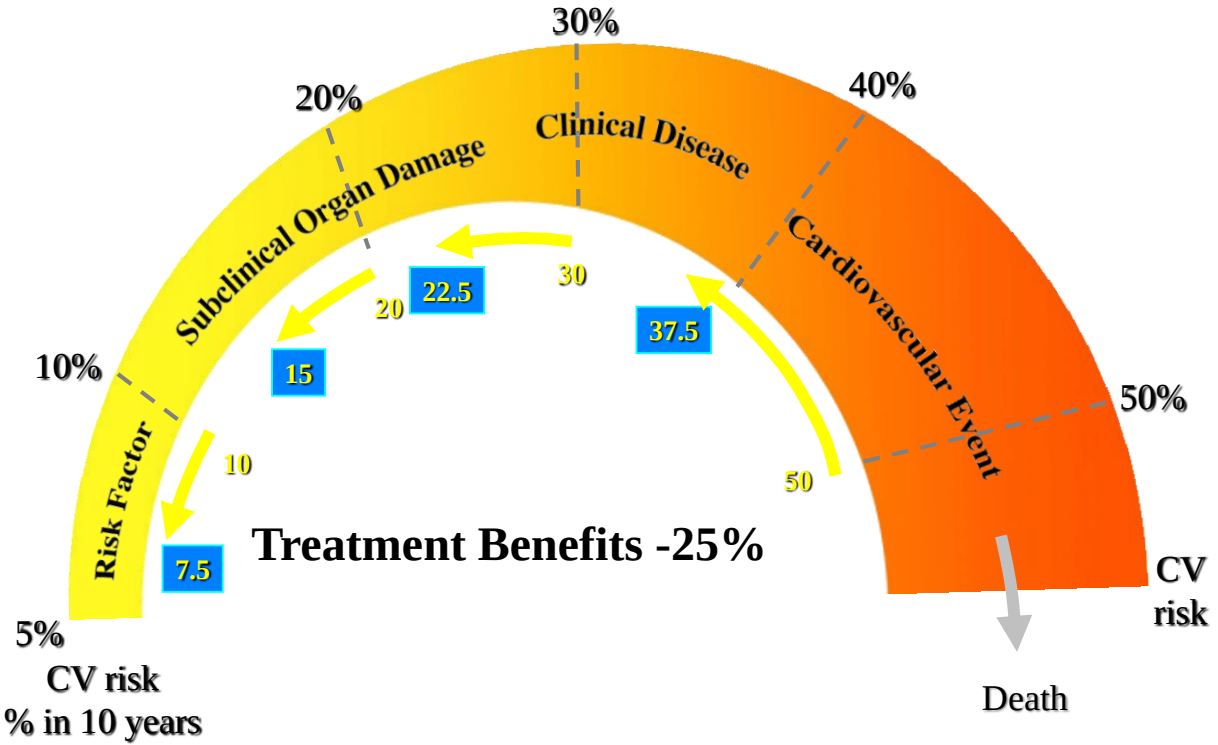
Cardiovascular prevention – basic concepts

- Primary – subjects without CVD
- 'primordial' – prevention of risk factors (e.g. weight control as prevention of diabetes and hypertension)
- Secondary – patients with CVD

Importance of cardiovascular prevention

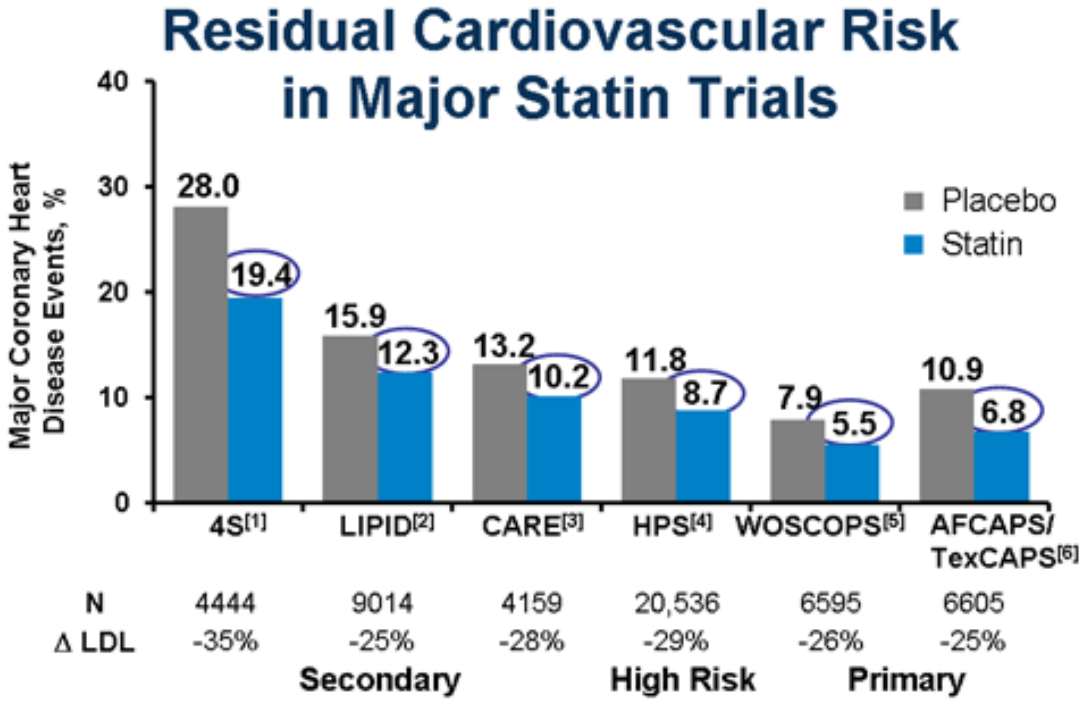


The Cardiovascular Continuum: Treatment Benefits and Residual Risk at Increasing CV Risk



Zanchetti A. Nat Rev Cardiol 2010;7:66-7

Rischio relativo, assoluto e residuo



1. 4S Group. *Lancet*. 1994;344:1383.
2. LIPID Study Group. *N Engl J Med*. 1998;339:1349.
3. Sacks FM, et al. *N Engl J Med*. 1996;335:1001.
4. HPS Collaborative Group. Lancet. 2002;360.
5. Shepherd J, et al. *N Engl J Med*. 1995;333:1301.
6. Downs JR, et al. *JAMA*. 1998;279:1615.

Medscape

Prevention strategies:

	Popolazione	Alto rischio
Numero di soggetti	Alto	Basso
Costo dell'intervento	Alto	Basso
Δ rischio relativo	Frequentemente non nota	Di solito ben definita
Δ rischio assoluto	Bassa	Alta
Rischio residuo	Basso	Alto
Orizzonte temporale	Decenni	Mesi/Anni

How to reduce risk – characteristics of interventions

- Effectiveness
- Cost
- Ease of use
- Adherence and persistence
- Security

Perception of cardiovascular risk as an obstacle to successful prevention

Cardiovascular risk can be controlled by the initiative and will of the individual,
But

It has no immediate positive effect on well-being

the risk is remote, abstract and does not produce emotional response (anxiety, worry, fear)
+
Lifestyle changes require major effort
+
Drugs used in prevention may worsen quality of life

Risk factor intervention:behaviour change

- Cognitive behavioural methods are effective in supporting persons in adopting a healthy lifestyle. Individual and environmental factors impede the ability to adopt a healthy lifestyle, as does complex or confusing advice from caregivers.
- Useful tools to enhance adherence are principles of effective communication, motivational interviews, ”ten strategic step” strategy.
- Combining the knowledge and skills of caregivers (physician, nurses, psychologist, expert in nutrition, cardiac rehabilitation and sport medicine) can optimize preventive efforts

Recommendations	Class	Level
Established cognitive-behavioural strategies (e.g. motivational interviewing) to facilitate lifestyle change are recommended.	I	A
Involvement of multidisciplinary healthcare professionals (e.g. nurses, dieticians, psychologists) is recommended.	I	A
In individuals at very high CVD risk, multimodal interventions integrating medical resources with education on healthy lifestyle, physical activity, stress management and counselling on psychosocial risk factors, are recommended.	I	A

Healthy diet characteristics

- Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
- Trans unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin.
- <5 g of salt per day.
- 30–45 g of fibre per day, preferably from wholegrain products.
- ≥200 g of fruit per day (2–3 servings).
- ≥200 g of vegetables per day (2–3 servings).
- Fish 1–2 times per week, one of which to be oily fish.
- 30 grams unsalted nuts per day.
- Consumption of alcoholic beverages should be limited to 2 glasses per day (20 g/d of alcohol) for men and 1 glass per day (10 g/d of alcohol) for women.
- Sugar-sweetened soft drinks and alcoholic beverages consumption must be discouraged.

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European Heart Journal 2016;37:2315–2381-doi:10.1093/eurheartj/ehw106

Risk factor intervention: smoking cessation

- Most cost effective strategy for CVD prevention
- Brief interventions with advice to stop smoking, NRT, bupropion and varencicline are the most used strategies. New approach is e-cigarettes (needs more study on possible harmful effects)
- Smoking enhances atheroscerosis and superimposed thrombotic phenomena: it affects endothelial function, oxidative processes, platelet function, fibrinolysis, inflammation, lipid oxidation and vasomotor function → fully or partially reversible.
- Stopping smoking reduces CV deaths/MI (RR 0.57 and 0.74) compared with continued smoking.
- Professional support can increase the odds of stopping. Following the failure of these strategies, drug interventions should be offered (RR 1.60 for NRT; 1.62 for bupropion; > 2.0 for varencicline)

Risk factor intervention: smoking cessation

A–ASK:	Systematically inquire about smoking status at every opportunity.
A–ADVISE:	Unequivocally urge all smokers to quit.
A–ASSESS:	Determine the person's degree of addiction and readiness to quit.
A–ASSIST:	Agree on a smoking cessation strategy, including setting a quit date, behavioural counselling, and pharmacological support.
A–ARRANGE:	Arrange a schedule of follow-up.

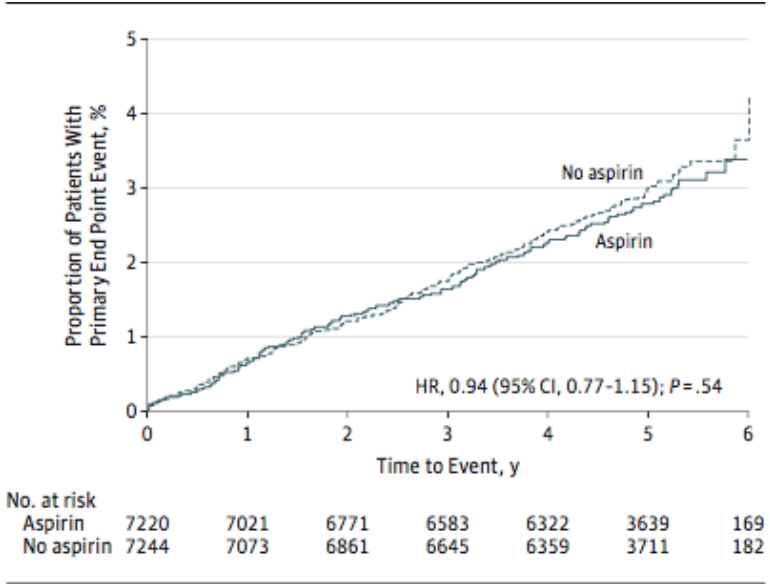
Recommendations	Class	Level
It is recommended to identify smokers and provide repeated advice on stopping with offers to help, by the use of follow up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination.	I	A
It is recommended to stop all smoking of tobacco or herbal products, as this is strongly and independently causal of CVD.	I	B
It is recommended to avoid passive smoking.	I	B

Risk factor goals and target levels

Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20–25 kg/m². Waist circumference <94 cm (men) and or <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
Lipid LDL [b] is the primary target	**Very high-risk: <1.8 mmol/L (<70 mg/dL)**, or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).[d] **High-risk: <2.6 mmol/L (<100 mg/dL)** or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL). **Low to moderate risk: <3.0 mmol/L (115 mg/dL).**
Non-HDL-C [b]	<2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL) are recommended for very high, high and low to moderate risk subjects, respectively
HDL-C	No target but >1.0 mmol/L (>40 mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.
Triglycerides	No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/L).

a. The target can be higher in frail elderly patients, or lower in most patients with DM and in some (very) high risk patients without DM who can tolerate multiple blood pressure lowering drugs
b. A view was expressed that primary care physicians might prefer a single general LDL-C goal of 2.6 mmol/L.
c. Non-HDL-C is a reasonable and practical alternative target because it does not require fasting.
d. This is the general recommendation for those at very high risk. It should be noted that the evidence for patients with chronic kidney disease is less strong

Risk factor intervention: Antiplatelet therapy



Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	III	B

Arterial hypertension

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Medicine and Surgery [H4102D]
CARDIOVASCULAR DISEASES AND RESPIRATORY SCIENCES
Cardiology 2022-4-H4102D024-H4102D084M

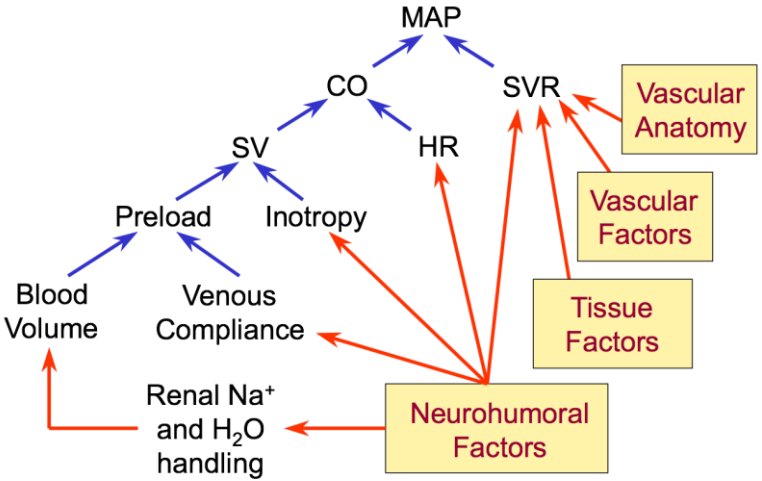
Academic year 2022/2023

pathogenesis

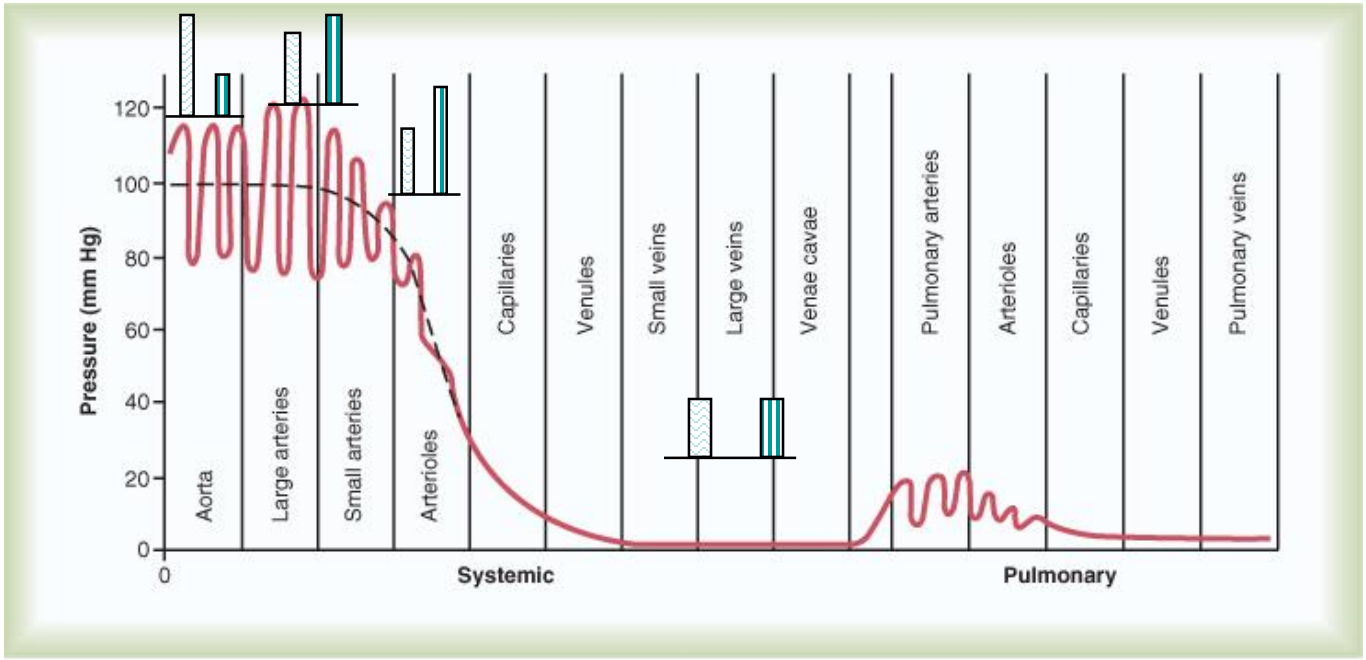
BP is the product of cardiac output and total peripheral vascular resistance.

Multiple factors are involved in short-term and long-term regulation of BP for adequate tissue perfusion; these include the following:

- Cardiac output and circulatory blood volume
- Vascular caliber, elasticity, and reactivity
- Humoral mediators
- Neural stimulation

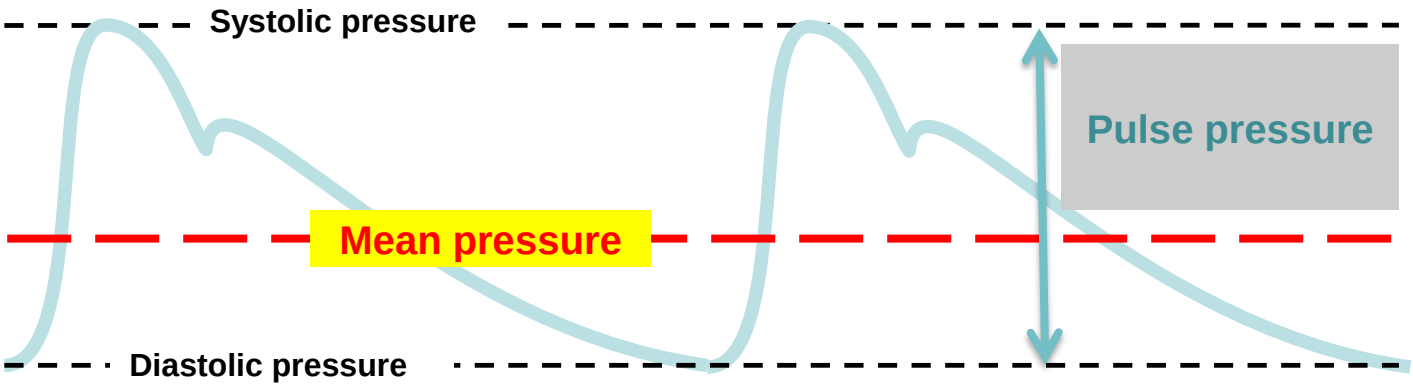


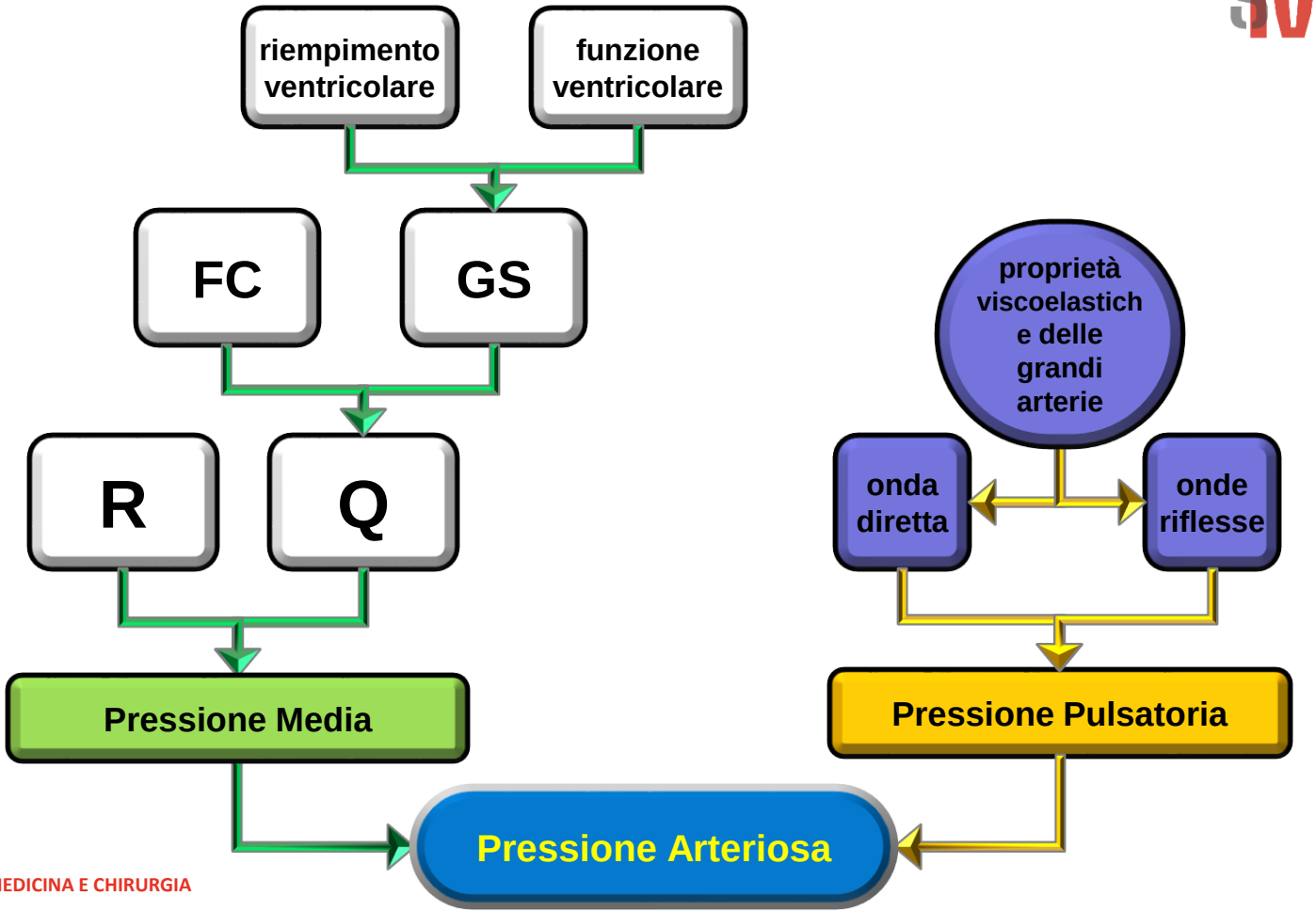
Pressure Profile of the Circulatory System



ELASTIC TISSUE

MUSCLE


Systolic pressure
Pulse pressure
Mean pressure
Diastolic pressure


riempimento ventricolare
funzione ventricolare
FC
GS
R
Q
Pressione Media
proprietà viscoelastiche delle grandi arterie
onda diretta
onde riflesse
Pressione Pulsatoria
Pressione Arteriosa

R – peripheral resistances

SCHOOL OF MEDICINE AND SURGERY

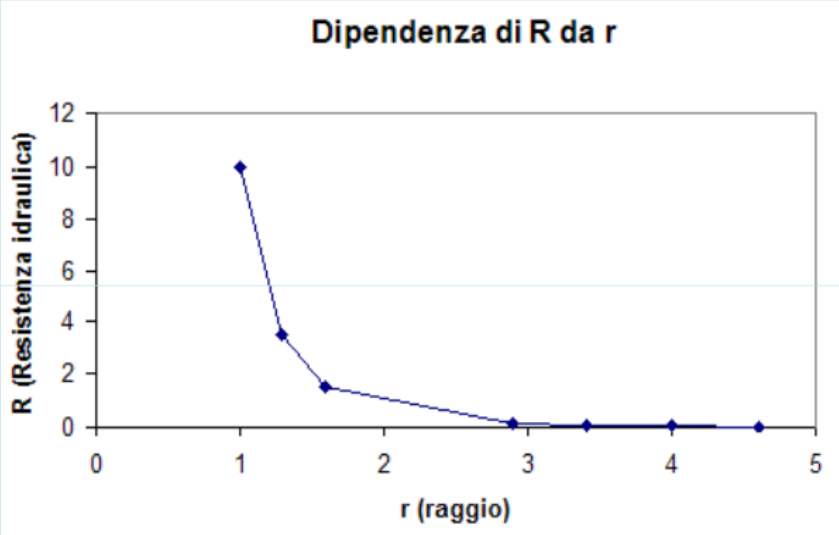
$$R = 8\eta L/\pi r^4$$

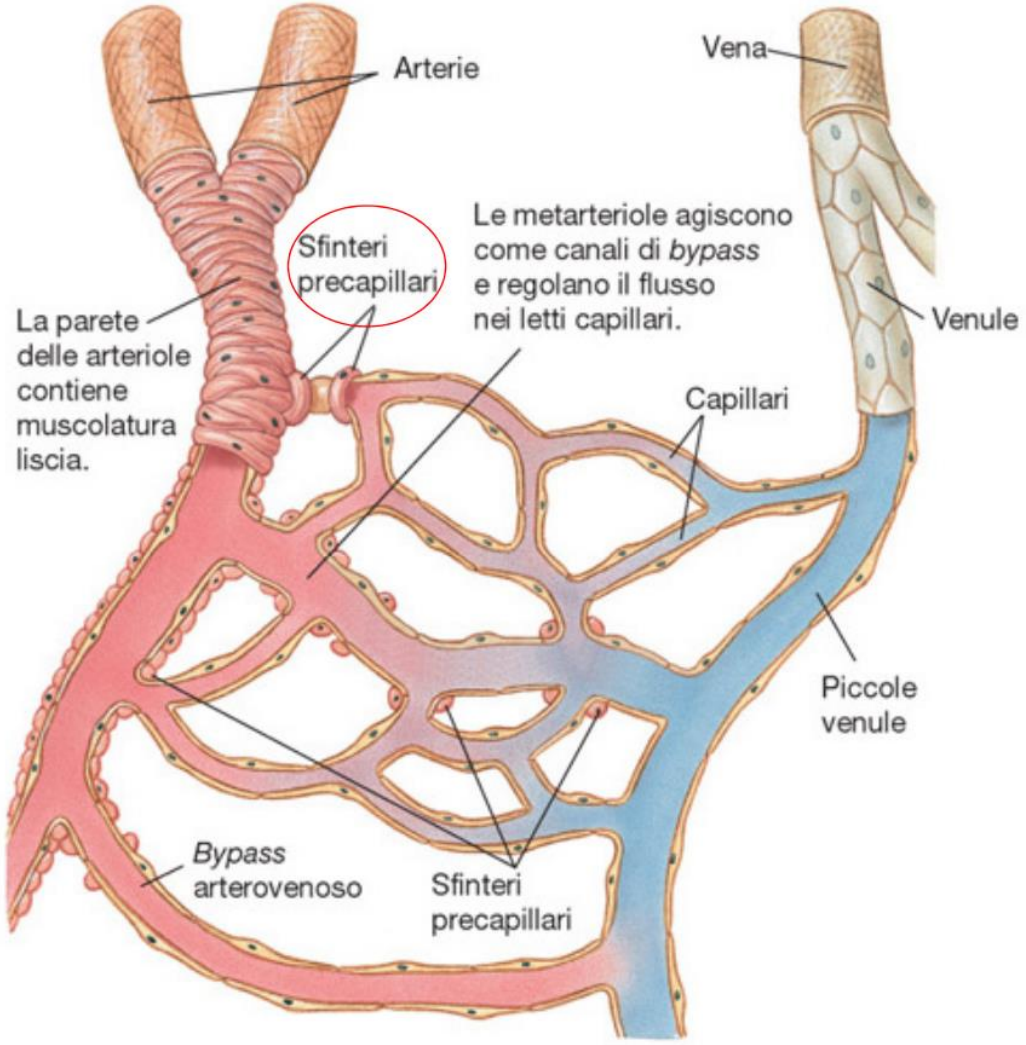
η - viscosity

L – length

r - radius

$R = 8\eta L/\pi r^4$

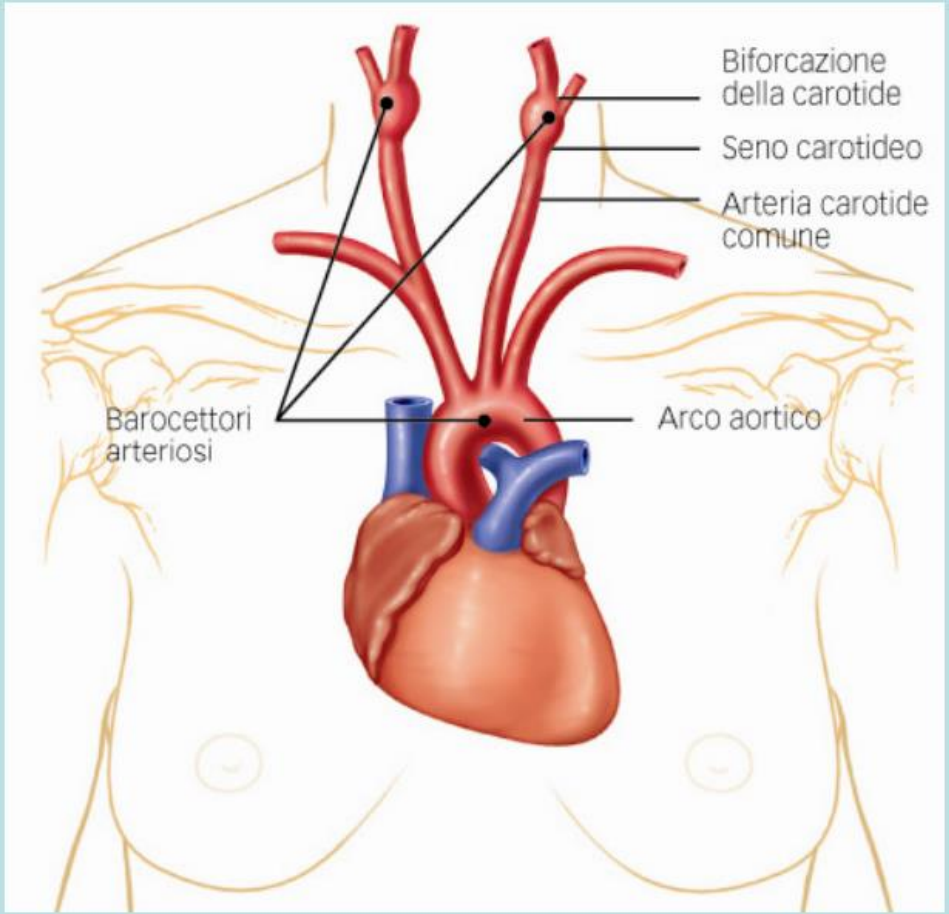



Arterie
Vena
Sfinteri precapillari
Le metarteriole agiscono come canali di *bypass* e regolano il flusso nei letti capillari.
La parete delle arteriole contiene muscolatura liscia.
Venule
Capillari
Piccole venule
Bypass arterovenoso
Sfinteri precapillari

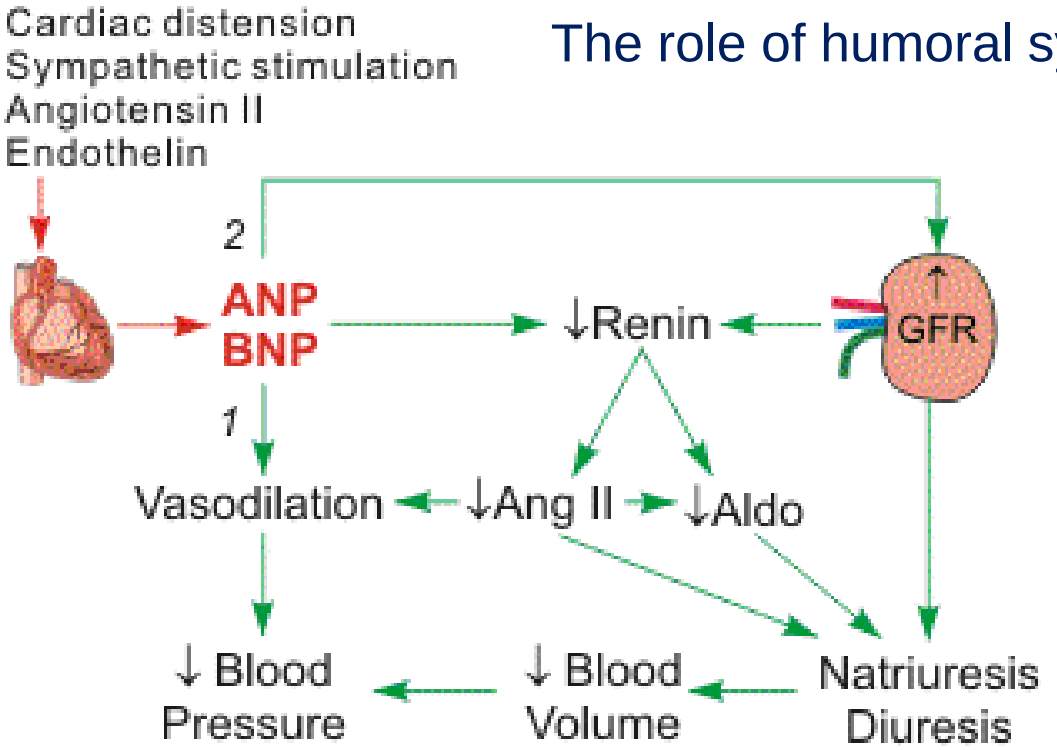
Mean BP therefore depends on:

- volemia (fluid intake, renal function, other losses)
- systolic function of the heart (β1-sympathetic activity, myocardial ischemia)
- heart rate (β1-sympathetic activity, parasympathetic activity)
- blood viscosity (heamatocrit, plasma proteins)
- peripheral resistances (α1 and β2 adrenergic activity, hormonal and local humoral factors, arteriole autoregulation)

I barocettori arteriosi

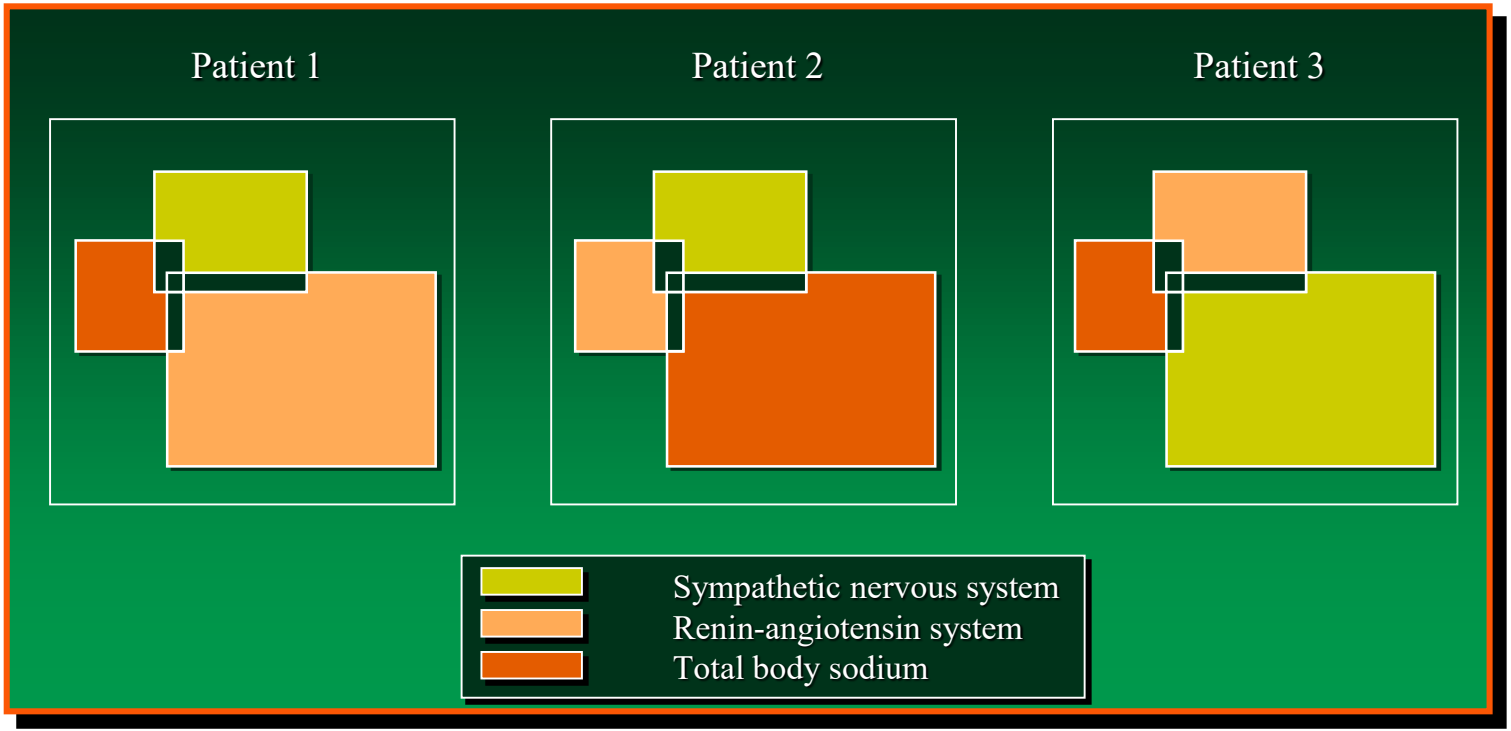


The role of humoral systems in BP regulation



Richard E. Klabunde
Cardiovascular Physiology Concepts: Atrial and Brain Natriuretic Peptides,
http://www.cvphysiology.com/Blood%20Pressure/BP017%20ANP%20new.gif

Contribution of Three BP Control Mechanisms in Hypertension Pathogenesis in Different Patients

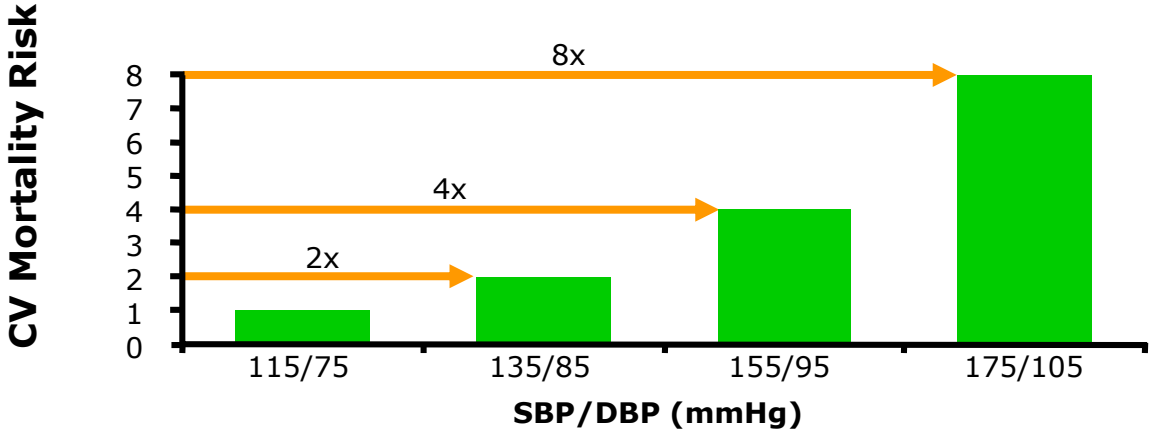


Arterial hypertension classification

Primary/essential (about 90%) – the ethiology is multifactorial and depends on the interaction of environmental and lifestyle factors (salt intake, stress, sedentary lifestyle, obesity…) and genetic influences.

Secondary (about 10%) - has known pathogenic mechanisms, develops due to an underlying pathology that, if identified in time, can often be corrected with the consequent resolution of the hypertensive state. It can be suspected in young people with severe hypertension and in patients who do not respond to therapy (false resistant hypertension)

Why focus on CV diseases and hypertension?



*Individual age 40–69 years, starting at PA 115/75 mmHg

1Volpe. Aging Clin Exp Res 2005;17 (4 Suppl.) :46-53

2Chobanian et al. JAMA 2003;289:2560-72

" High blood pressure is the most common cardiovascular disease and is one of the main risk factors for other cardiovascular and cerebrovascular diseases."

MacMahon et al. Lancet 90,335,765

Hypertension causes 7.5 million deaths per year, about 12.8% of total mortality

Prevalence of hypertension in the world

Fig. 2 | **Hypertension prevalence by world region in 2010.** Prevalence of hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication in men (part **a**) and women (part **b**). Data obtained from REF.[3].

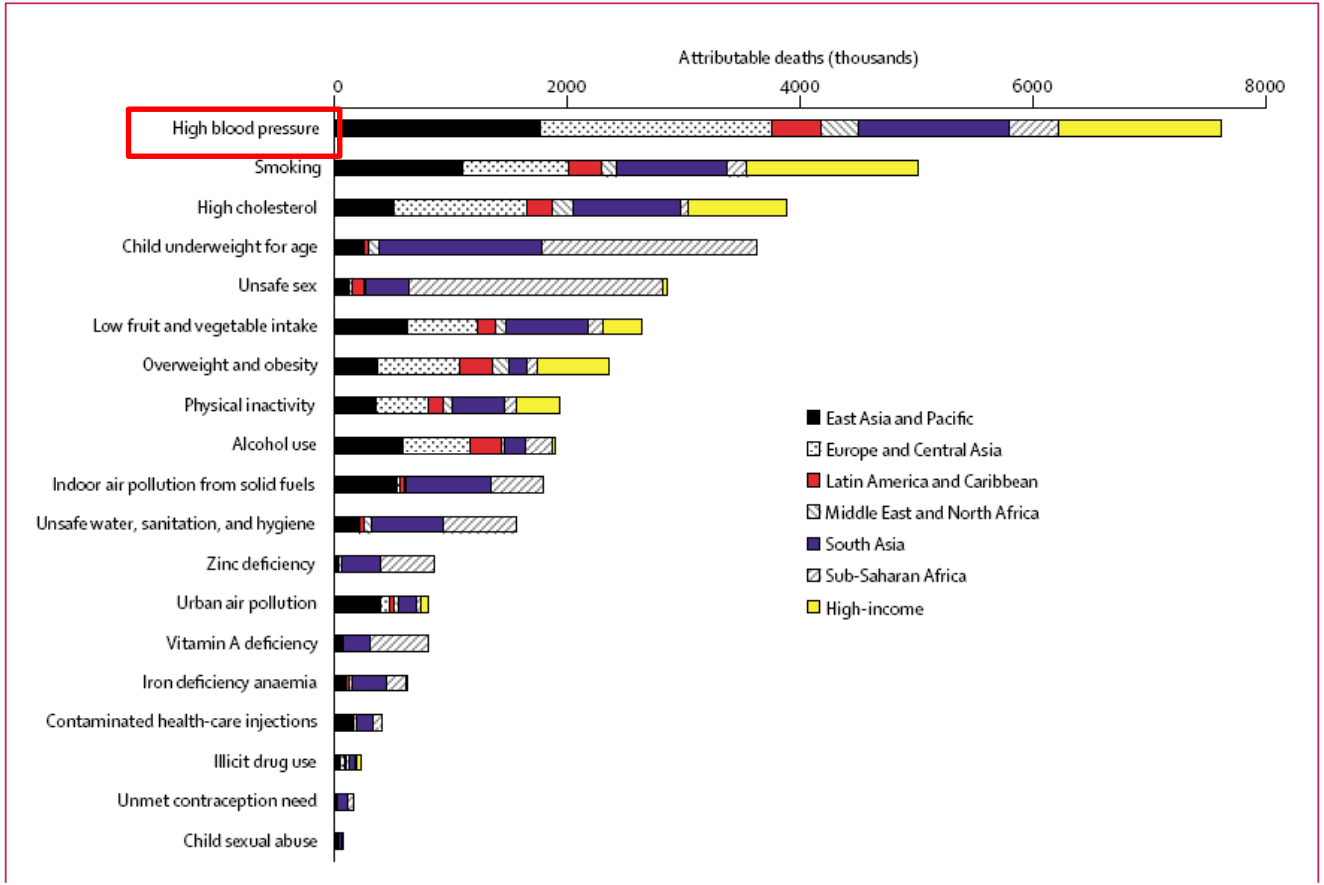
Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020

26% of the world's adult population (972 million people)

The problem of arterial hypertension

- Globally, over 1 billion people have hypertension. The worldwide prevalence of hypertension will continue to rise towards 1.5 billion by 2025[1];
- Elevated BP is the leading global contributor to premature death, accounting for almost 10 milion deaths in 2015, 4.9 milion due to ischemic heart disease and 3.5 million due to stroke.
- Hypertension is also a major risk factor for heart failure, AF, CKD, PAD and cognitive decline[2].

1. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 . to 2015: a pooled analysis of 1479 population-based measurement studies with . 19.1 million participants. Lancet 2017;
2. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on . outcome incidence in hypertension. 1. Overview, meta-analyses, and meta- . regression analyses of randomized trials. J Hypertens 2014.



MORTALITY DUE TO LEADING GLOBAL RISK FACTORS
Lopez et al. *Lancet* 2006;367:1747-1757

DIAGNOSTIC EVALUATION OF HYPERTENSIVE PATIENTS

1. Establish blood pressure levels
2. Identify causes of secondary hypertension
3. Assess global cardiovascular risk by researching the presence of other risk factors, organ damage and concomitant diseases

DIAGNOSTIC EVALUATION OF HYPERTENSIVE PATIENTS

1. Establish blood pressure levels

The first blood pressure measurement (1707-1711)

“Blood pressure continuously fluctuates to such a degree that the same two minutes of blood pressure will never be seen throughout the whole life of an animal.”

Stephen Hales (1677-1761)

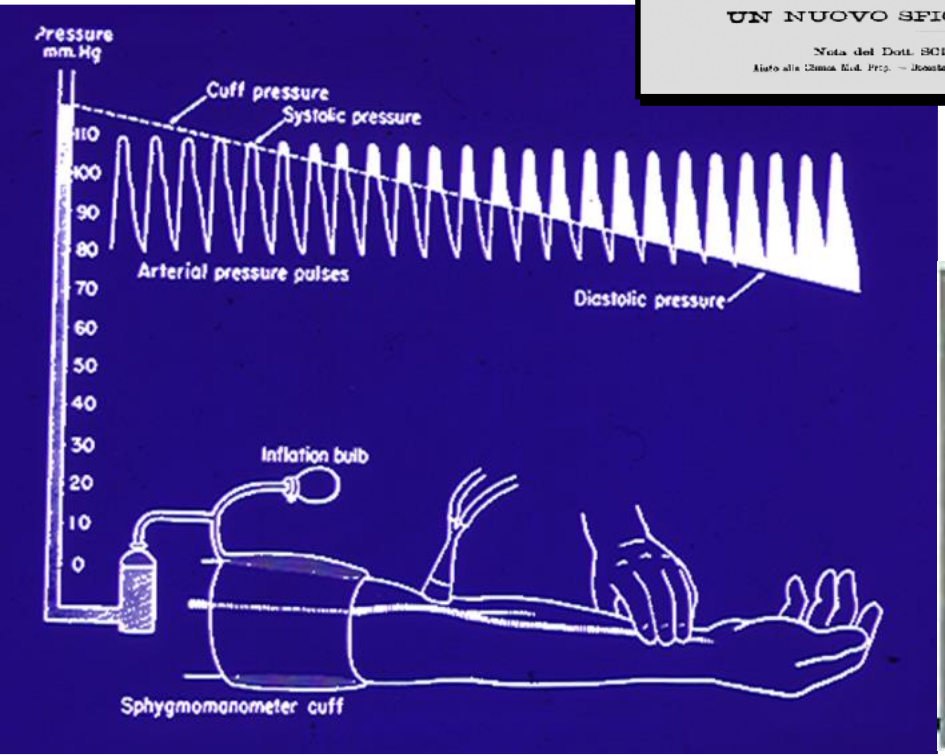
Stephen Hales

“On account of some hydraulick and hydrostatick experiments made on the blood vessels of animals”

In: Statistical Essays: Containing Hemastatick; ***London 1733****.*

F

GERY



NUM. 50 10 DICEMBRE 1886 ANNO XLVII

Gazzetta Medica di Torino

SOMMARIO

Comunicazioni originali: Scipione Riva-Rocci, Un nuovo sfigmomanometro.
Accademie e Società: Reale Accademia di medicina di Torino (Sedute 12 e 22 novembre 1886).
Note cliniche e terapeutiche: Un caso di tic facciale in un epilettico. — L'ortoterapia delle vie respiratorie. Un caso di spasmo laringeo guarito coll'elettricità. — Il kefir ai creosotati e ai carbonati di guaiacolo.
Bollettino della mortalità di Torino (3ª decade del mese di novembre).

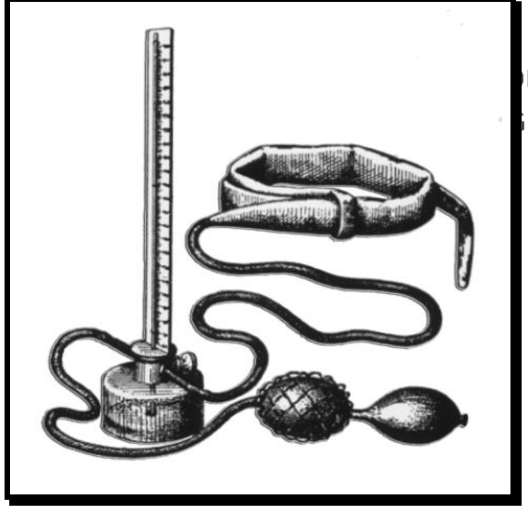
COMUNICAZIONI ORIGINALI

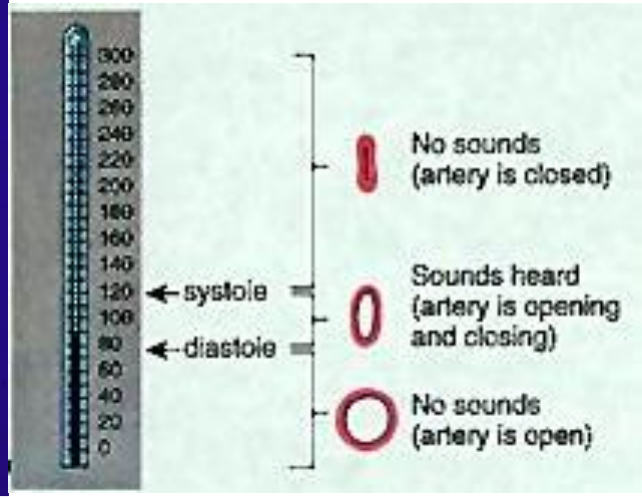
CLINICA MEDICA PROPEDEUTICA DI TORINO (PROF. C. FORLANINI)

UN NUOVO SFIGMOMANOMETRO

Nota del Dott. SCIPIONE RIVA-ROCCI

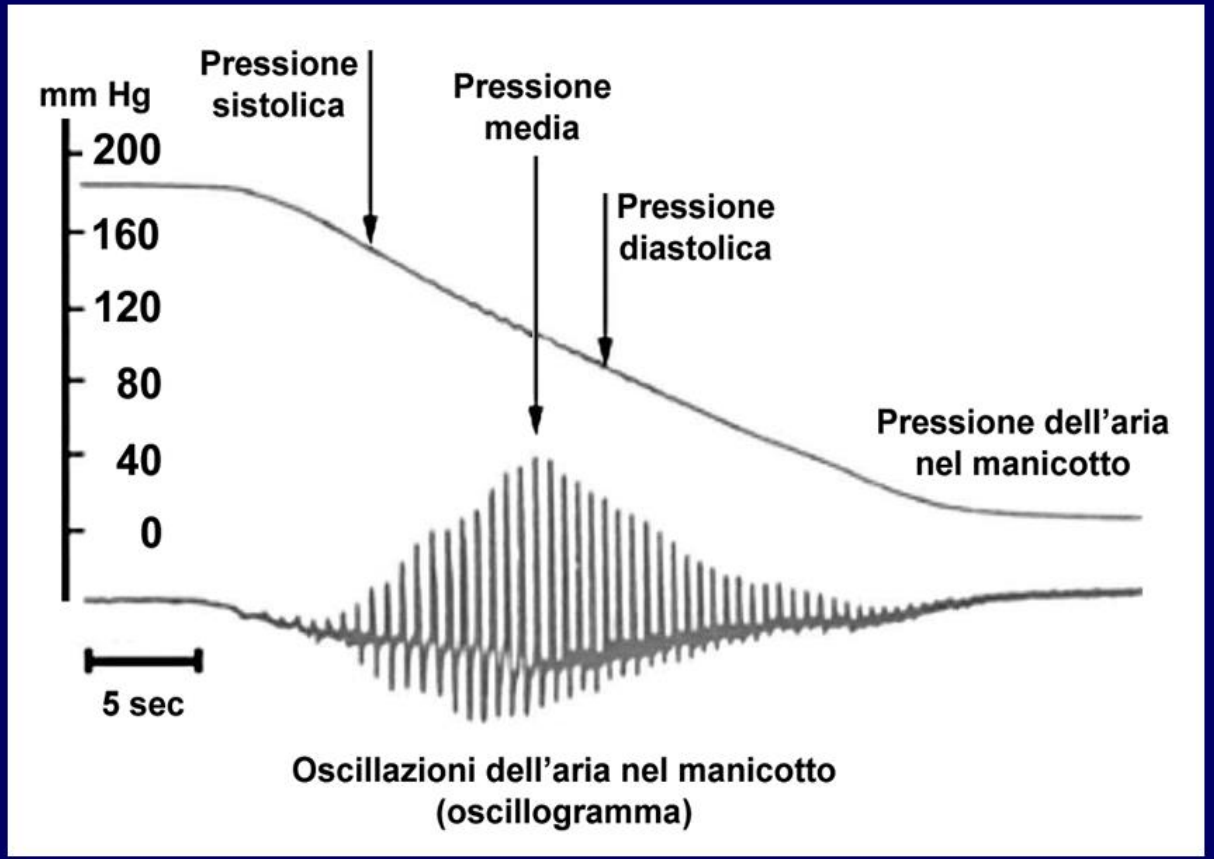
Aiuto alla Clinica Med. Prop. — Docente di Patologia Medica nella R. Univ. di Torino.





UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

OSCILLOMETRIC METHOD



Geddes L.A., 1991

Classification of office BP and definition of hypertension grade ESH/ESC GL 2018

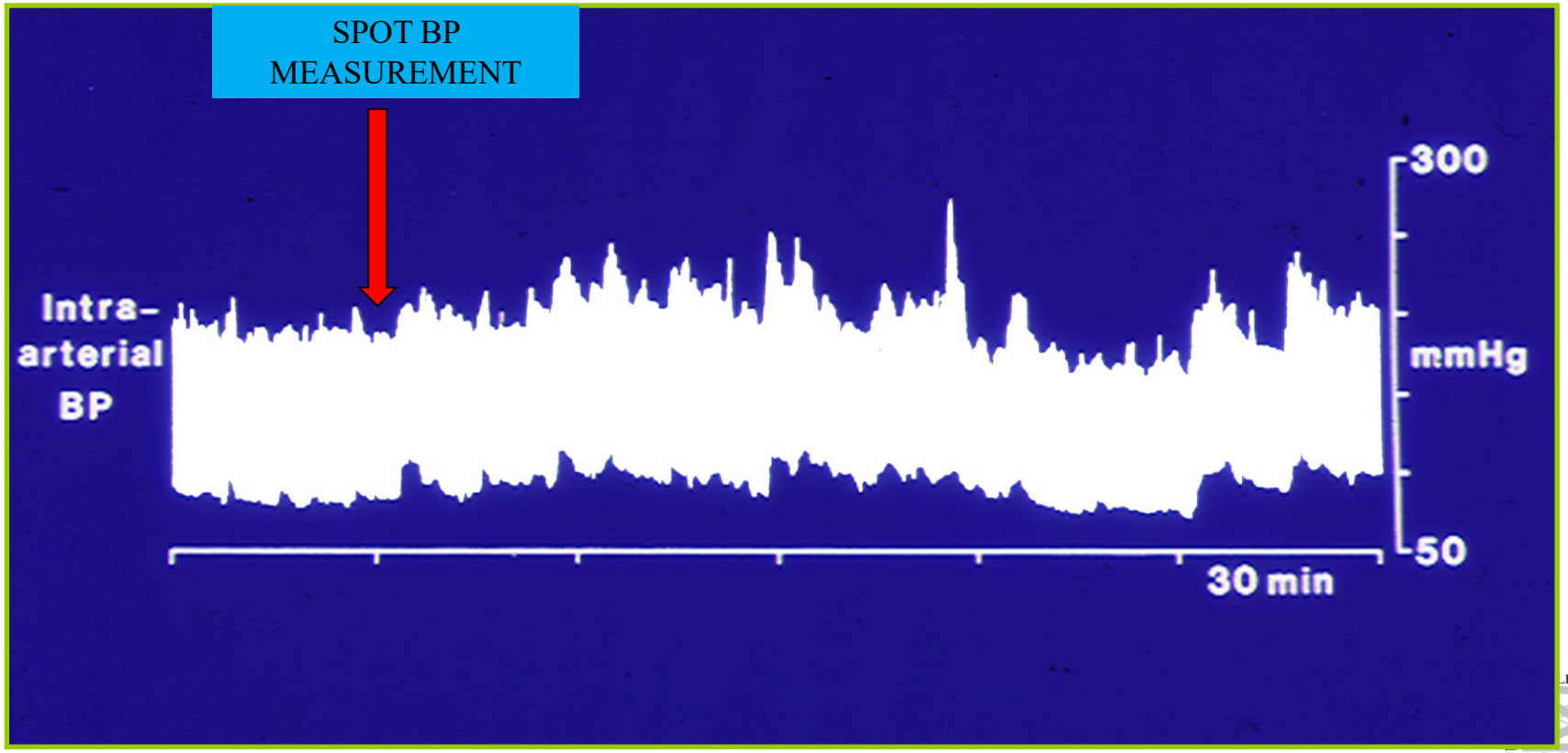
Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	and	< 80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

Categories of BP in Adults in AHA GL 2017

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

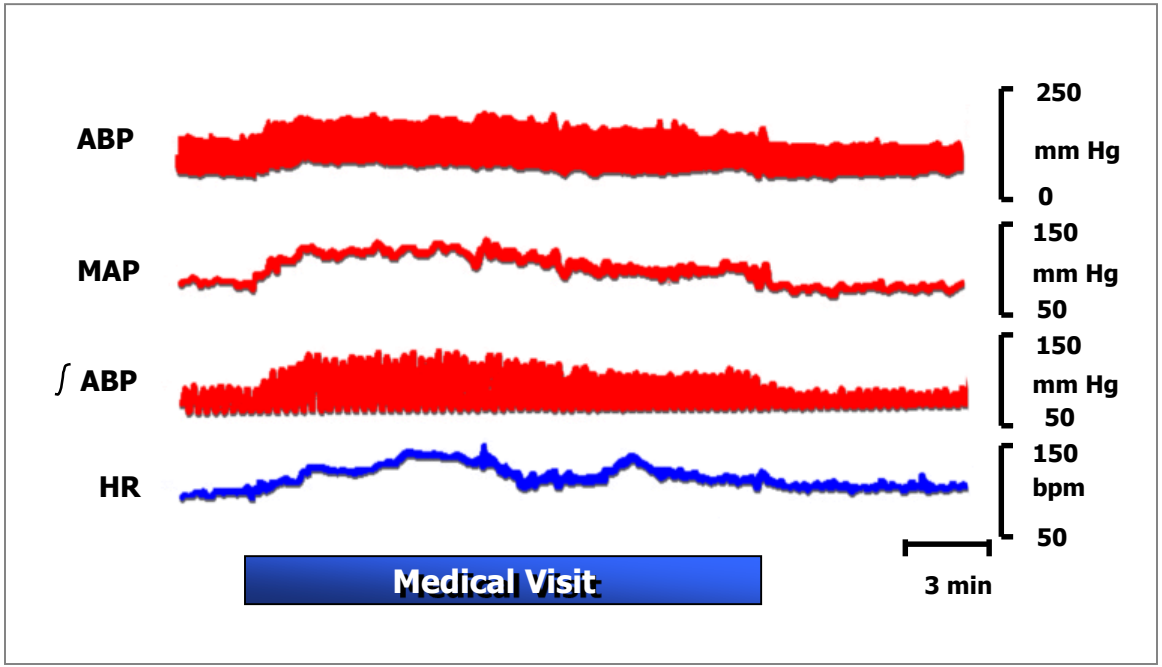
BP is a highly variable physiological parameter



Factors responsible for variability in blood pressure over the short term

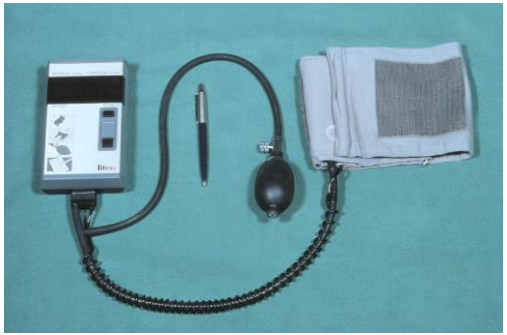
	Approximate increase in SBP (mmHg)
Psychological stress (e.g. public speaking)	20-60
Anger / conflict	20-60
Sexual intercourse	20-60
Major physical exertion (e.g. running, lifting)	20-60
Pain	20-40
Waking from sleep	20-40
Mid-morning surge	20-40
Driving	10-20
Posture (e.g. squatting etc)	10-20
Anticipation of major physical exertion	10-20
Minor physical exertion (e.g. dressing, walking)	0-20
Ambient temperature	10-20
Eating	10
Smoking	10
Telephone call	10
Distended bladder	10
Alcohol	5-10
Coffee	5-10

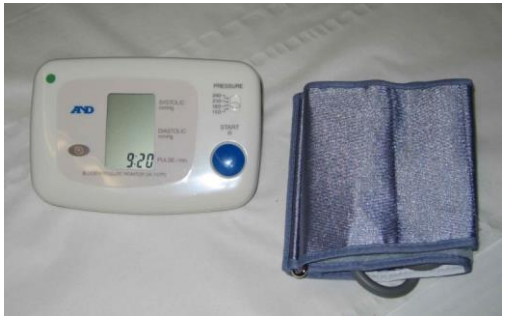
White coat effect



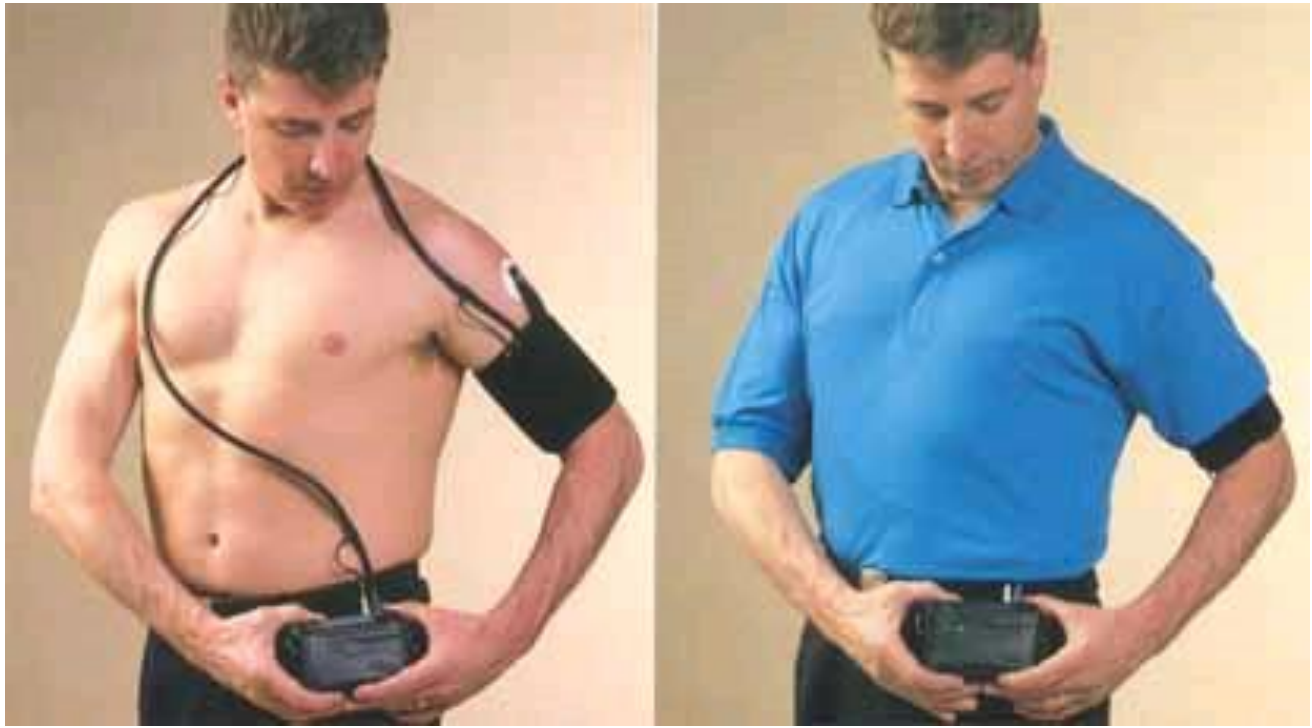
Mancia G. et al., Lancet 1983; 2: 695-698

Home Blood Pressure monitoring

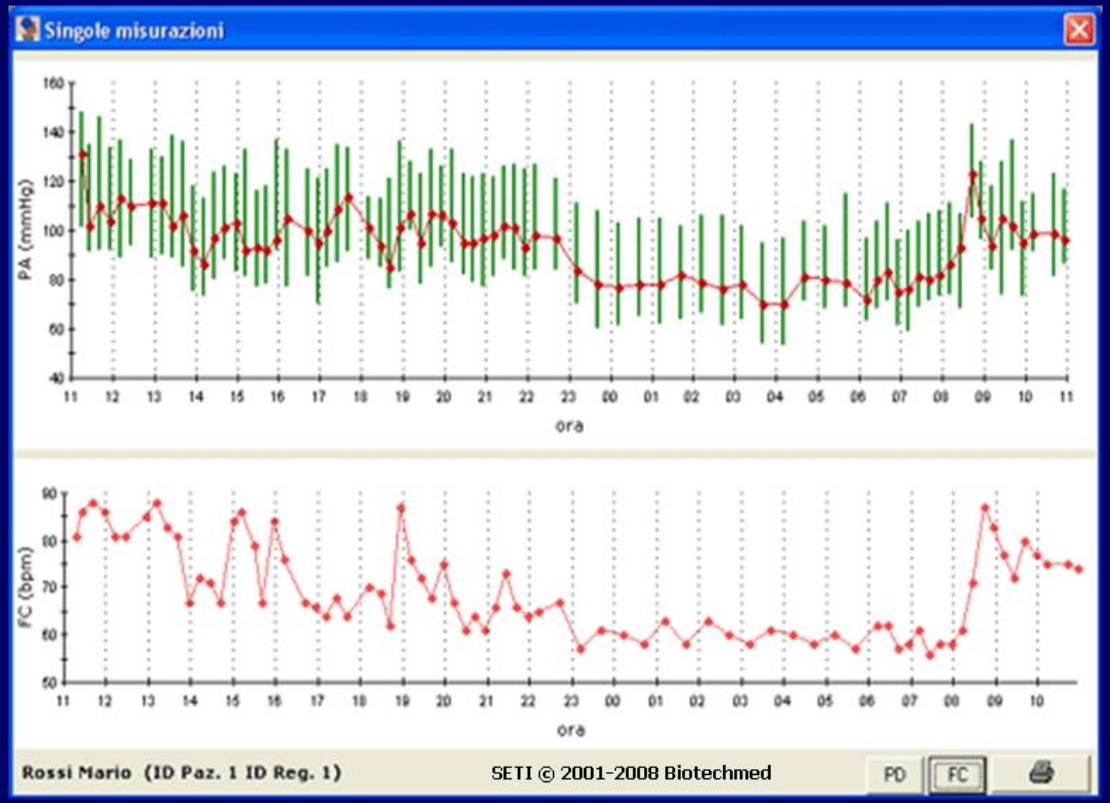




Non-invasive discontinuous ambulatory blood pressure monitoring (ABPM)



24-hour ambulatory blood pressure tracing



24-h Blood Pressure Profile in Two Patients with Hypertension (Dipper and Non-Dipper)

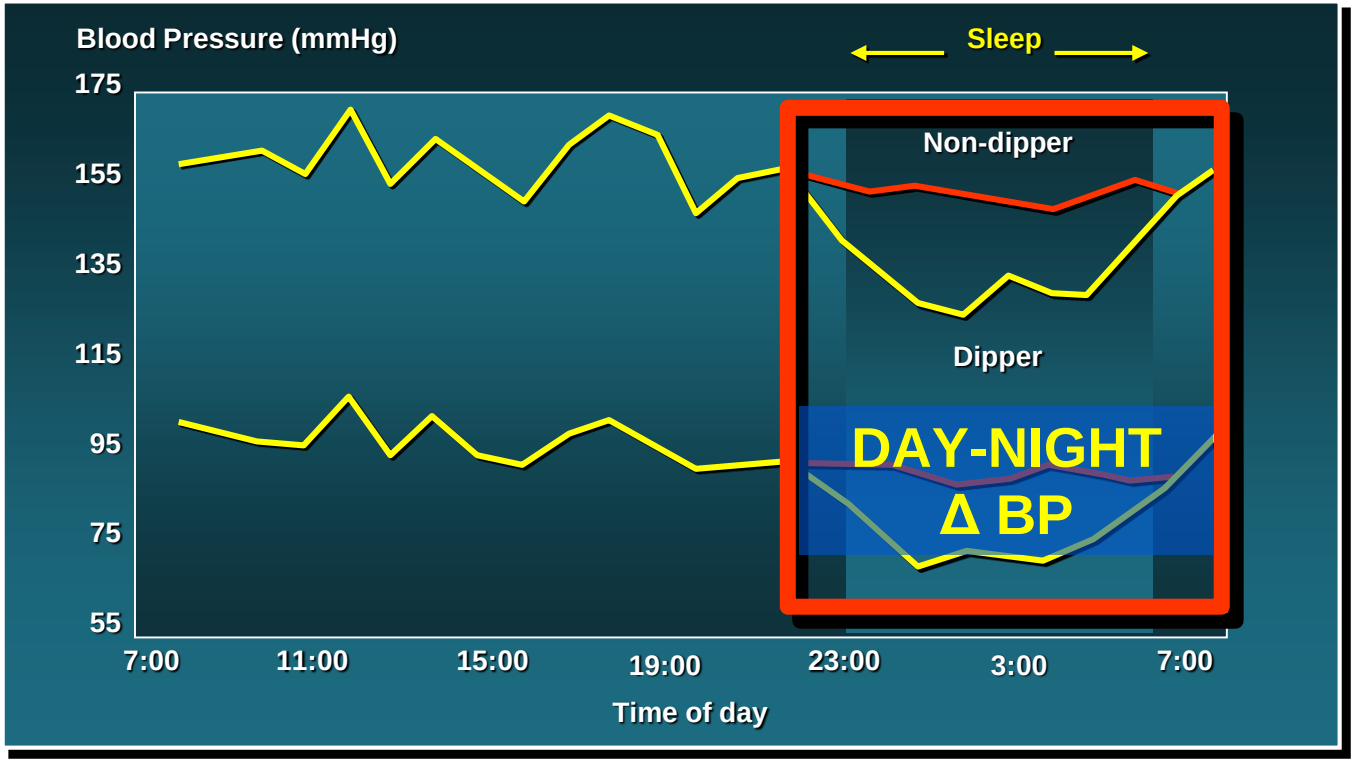
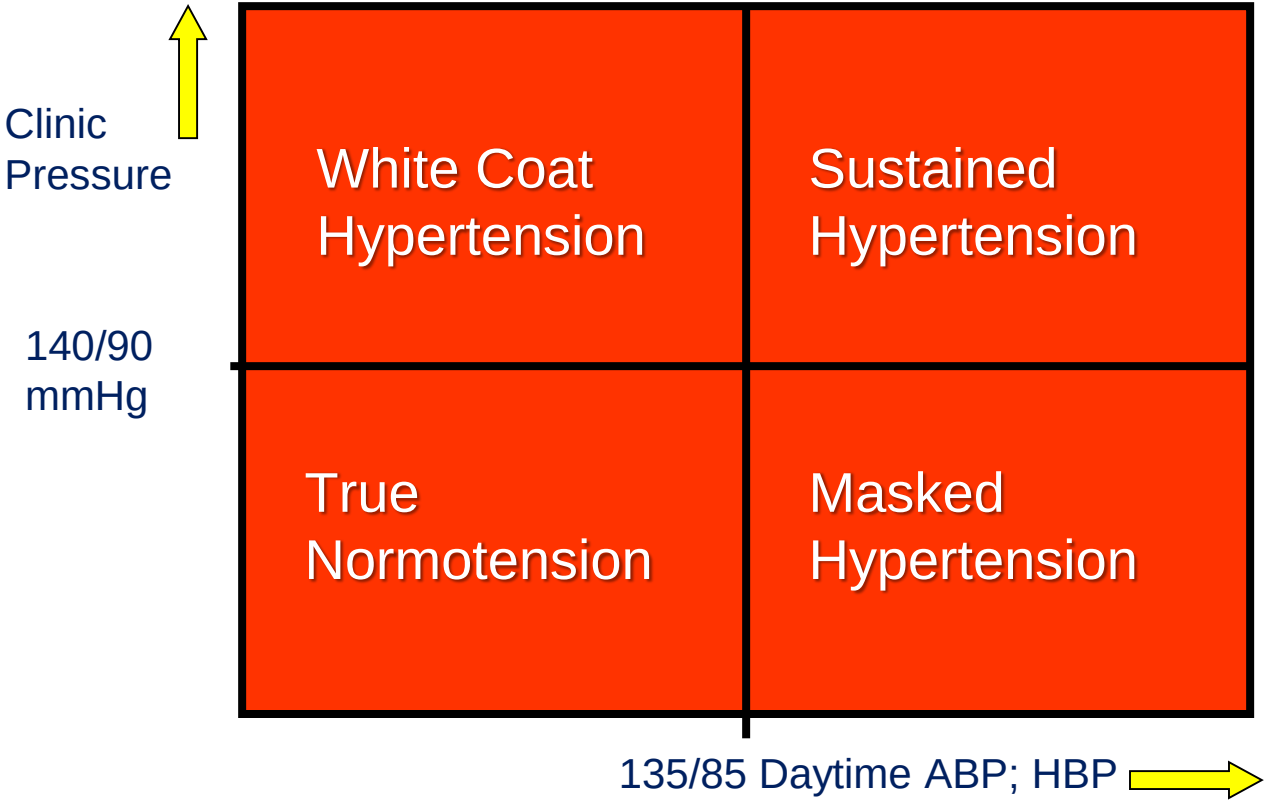
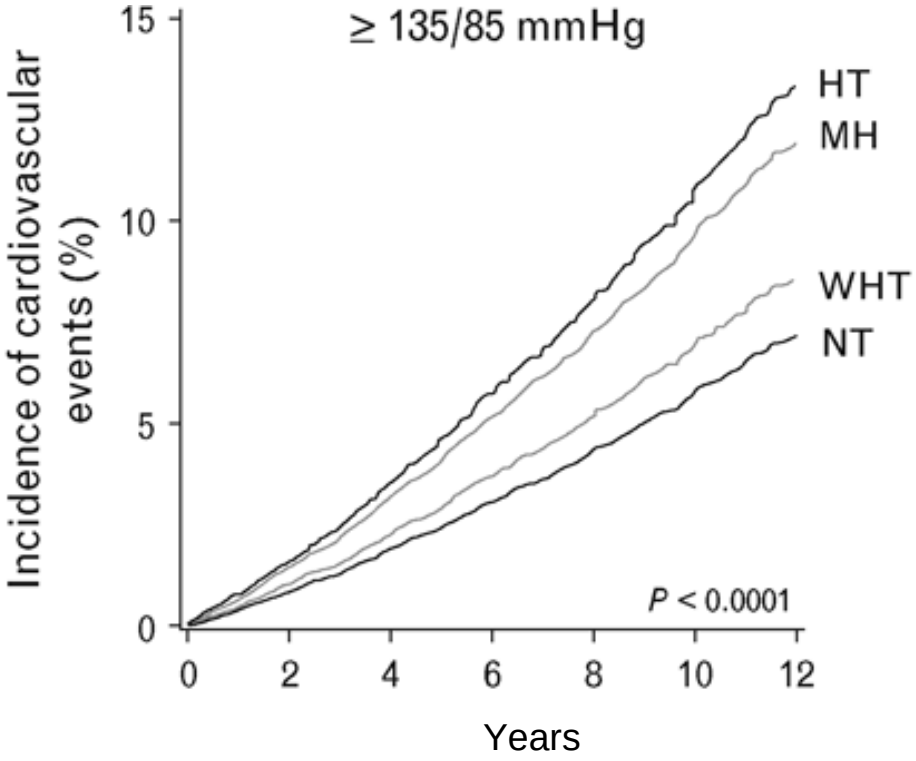


Table 9 **Definitions of hypertension according to office, ambulatory, and home blood pressure levels**

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

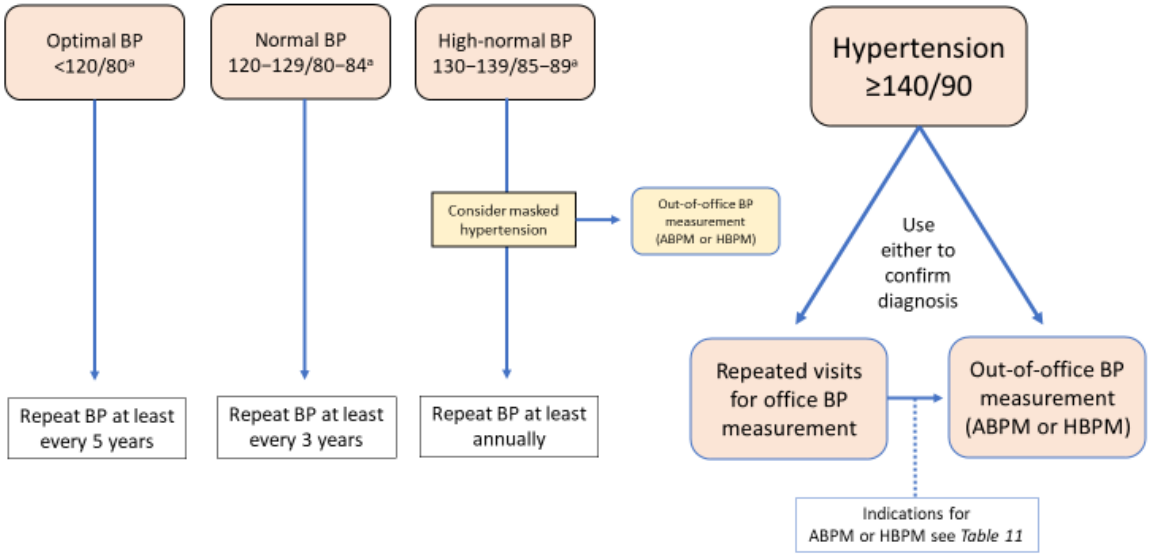

Clinic Pressure
140/90 mmHg
White Coat Hypertension
Sustained Hypertension
True Normotension
Masked Hypertension
135/85 Daytime ABP; HBP
130/80 mmHg 24h ABP

Risk of white coat and masked hypertension



Hansen TW et al. *J Hypertens.* 2007;**25**(8):1554-64.

Screening and diagnosis of hypertension



DIAGNOSTIC EVALUATION OF HYPERTENSIVE PATIENTS

2 Identify causes of secondary hypertension

Patient characteristics that should raise the suspicion of secondary hypertension

Characteristic
Younger patients (< 40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood
Acute worsening hypertension in patients with previously documented chronically stable normotension
Resistant hypertension
Severe (grade 3) hypertension or a hypertension emergency
Presence of extensive HMOD
Clinical or biochemical features suggestive of endocrine causes of hypertension or CKD
Clinical features suggestive of obstructive sleep apnoea
Symptoms suggestive of phaeochromocytoma or family history of phaeochromocytoma

When to suspect a secondary cause of arterial hypertension?

SCHOOL OF MEDICINE AND SURGERY

Family history of juvenile hypertension or secondary form of hypertension

Family history of cerebrovascular event at a young age (<40 years)

Early onset hypertension and/or early stroke

2° - 3° grade hypertension or resistant hypertension (PA>140/90 mmHg with 3 full dose drugs, one of which is a diuretic)

Adrenal incidentaloma

Hypokalemia (spontaneous or caused by diuretics), also normal-low K+ levels on ACE-I, ARB or with CKD

Common causes of secondary hypertension - 1

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 + 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 Fibromuscular dysplasia	1–10%	Older; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit Younger; more common in women; abdominal bruit	Duplex renal artery Doppler or CT angiography or MR angiography
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

Common causes of secondary hypertension - 2

Cause	Prevalence in hypertensive patients	Suggestive symptoms and signs	Screening Investigations
Phaeochromocytoma	< 1%	Episodic symptoms – the 5 'Ps': paroxysmal hypertension, pounding headache, perspiration, palpitations, 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, hypophosphatemia	Parathyroid hormone, Ca^{2+}
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

Medications and other substances that may increase BP

Medication/substance	
Oral contraceptive pill	Especially oestrogen containing – cause hypertension in ~5% of women, usually mild but can be severe
Diet pills	For example, phenylpropanolamine and sibutramine
Nasal decongestants	For example, phenylephrine hydrochloride and naphazoline hydrochloride
Stimulant drugs	Amphetamine, cocaine, and ecstasy – these substances usually cause acute rather than chronic hypertension
Liquorice	Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism
Immunosuppressive medications	For example, cyclosporin A (tacrolimus has less effect on BP and rapamycin has almost no effect on BP), and steroids (e.g. corticosteroids, hydrocortisone)
Antiangiogenic cancer therapies	Antiangiogenic drugs, such as VEGF inhibitors (e.g. bevacizumab), tyrosine kinase inhibitors (e.g. sunitinib), and sorafenib, have been reported to increase BP
Other drugs and substances that may raise BP	Anabolic steroids, erythropoietin, non-steroidal anti-inflammatory drugs, herbal remedies (e.g. ephedra, ma huang)

Other causes

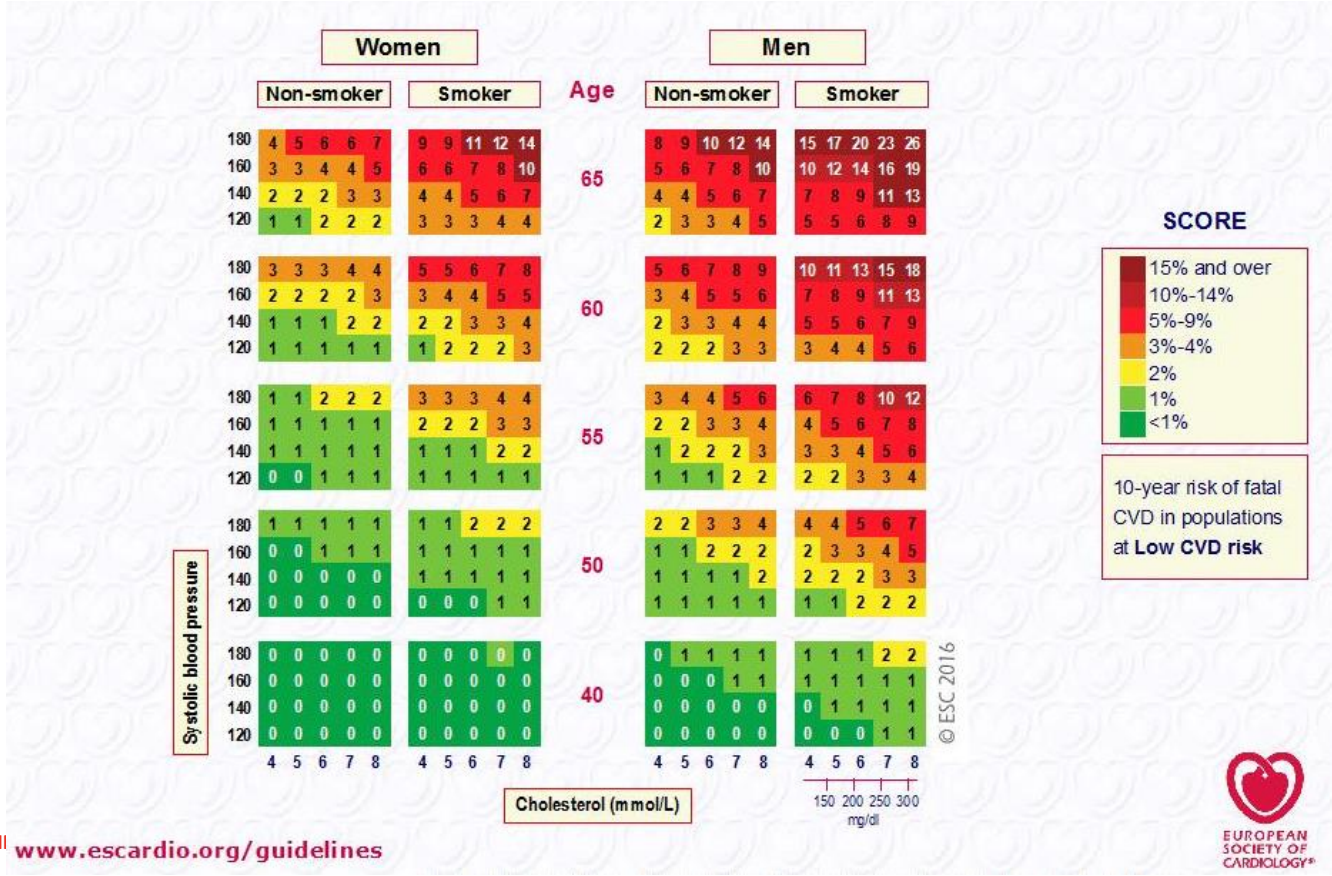
- ✓ Intracranic mass and other causes of intracranic hypertension
- ✓ Lead toxicity
- ✓ Acute stress (pain!)
- ✓ Eclampsia e pre-eclampsia
- ✓ Polycythemia

DIAGNOSTIC EVALUATION OF HYPERTENSIVE PATIENTS

3 Assess global cardiovascular risk by researching the presence of other risk factors, organ damage and concomitant diseases

Low-risk SCORE chart:

CVD mortality < 225/100000 in men, < 175/100000 in women



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 – high risk	High risk
	≥ 3 risk factors	Low –moderate risk	Moderate – high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate – high risk	High risk	High risk	High – very high risk
Stage 3 (symptomatic disease)	Symptomatic CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

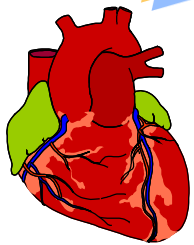
Factors influencing CV risk in patients with hypertension

Demographic characteristics and laboratory parameters
Sex (men > women)
Age
Smoking – current or past history
Total cholesterol and HDL-C
Uric acid
Diabetes
Overweight or obesity
Family history of premature CVD (men aged < 55 years and women aged < 65 years)
Family or parental history of early onset hypertension
Early onset menopause
Sedentary lifestyle
Psychosocial and socioeconomic factors
Heart rate (resting values > 80 beats per min)

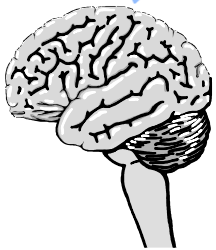
Asymptomatic HMOD
Arterial stiffening: Pulse pressure (in older people) ≥ 60 mmHg Carotid–femoral PWV > 10 m/s
ECG LVH
Echocardiographic LVH
Microalbuminuria or elevated albumin–creatinine ratio
Moderate CKD with eGFR > 30–59 mL/min/1.73 m^2 (BSA) or severe CKD eGFR < 30 mL/min/1.73 m^2
Ankle–brachial index < 0.9
Advanced retinopathy: haemorrhages or exudates, papilloedema
Established CV or renal disease
Cerebrovascular disease: ischaemic stroke, cerebral haemorrhage, TIA
CAD: myocardial infarction, angina, myocardial revascularization
Presence of atheromatous plaque on imaging
Heart failure, including HFpEF
Peripheral artery disease
Atrial fibrillation

Hypertension:
Action on target organs

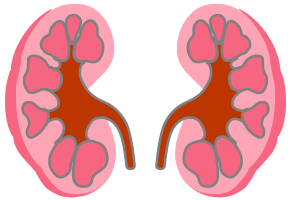
Hypertension



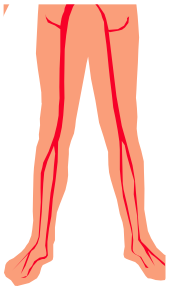
Angina pectoris
Unstable angina
Myocardial infarction
Sudden death
Congestive heart failure



TIA
Ischemic stroke
Hemorrhagic stroke



Renovascular
pathology
Renal failure



Claudication
Aneurysm
Limb Ischemia

Routine diagnostic tests - Laboratory

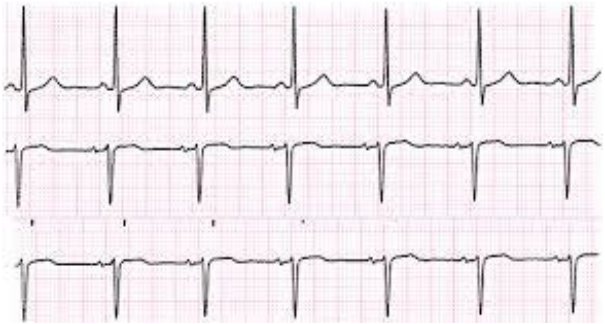
- Fasting blood sugar
- Total cholesterolemia
- Cholesterol - LDL
- Cholesterol – HDL
- Fasting triglyceridemia
- Potassium
- Uricemia
- Plasma creatininemia
- Creatinine clearance (Cockroft formula – Gault) or estimated glomerular filtration rate (MDRD or CKD-EPI formula)
- Hemoglobin and hematocrit
- Urinalysis (complemented by a stick test for microalbuminuria and a urinary sediment analysis)
- Glucose tolerance test if fasting blood glucose is > 5.6 mmol/L (102 mg/dL)

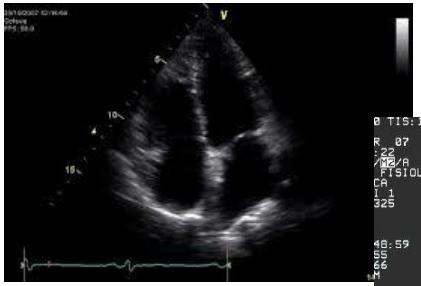
Diagnostic tests

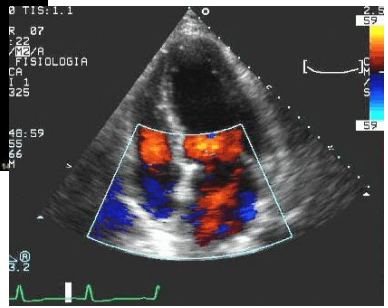
- Electrocardiogram
- Echocardiogram
- Carotid ultrasonographic evaluation
- Quantitative measurement of albuminuria in the presence of a positive stick
- Lower limbs / upper limbs pressure index
- Examination of the ocular fundus
- Blood pressure measurement at home and 24-hour monitoring
- Pulse wave velocity measurement

Indicators of cardiac subclinical organ damage

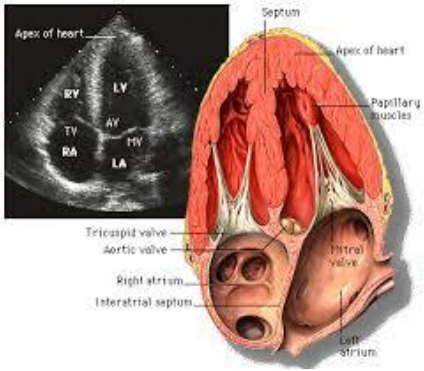
Electrocardiography:
Left Ventricular hypertrophy, ischemia, arrhythmias, "strain"
Echocardiography:
Left Ventricular Hypertrophy, Contractile Function, Left Ventricle Geometry, Diastole (Distensibility)





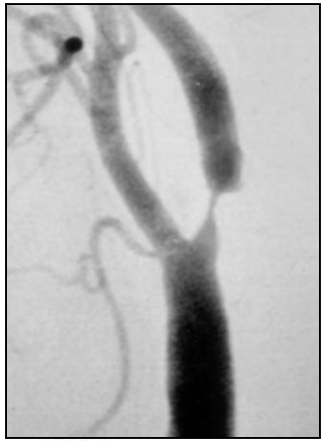


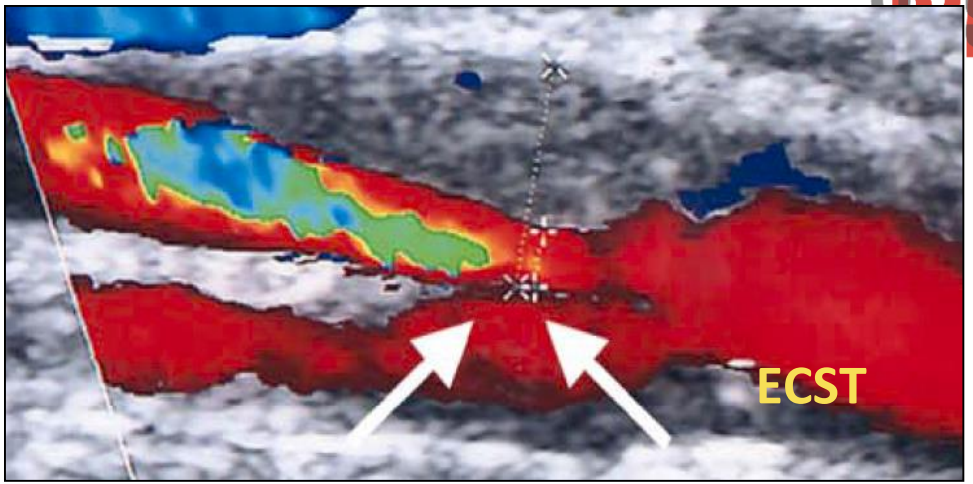
Left Ventricular Hypertrophy

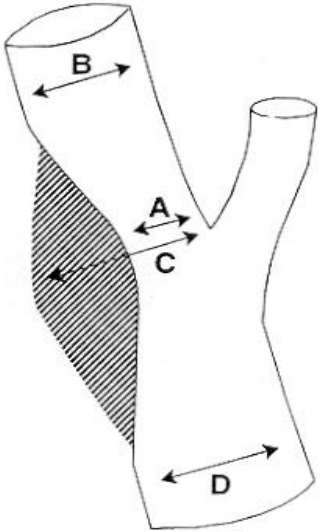


Risk of : **cardiovascular events**
cardiovascular and all-cause mortality
is 2-8 times higher

in individuals with left ventricular mass (MVS) above normal compared to subjects with normal MVS



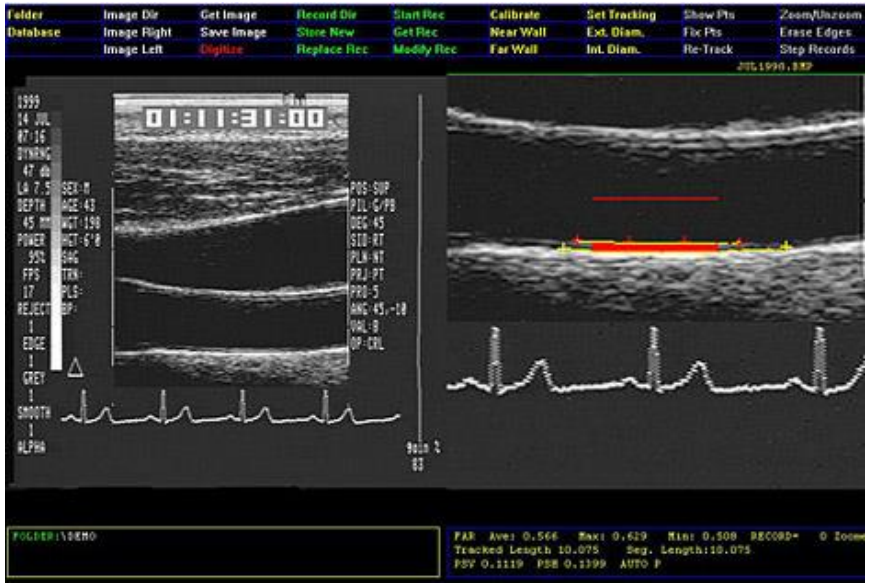




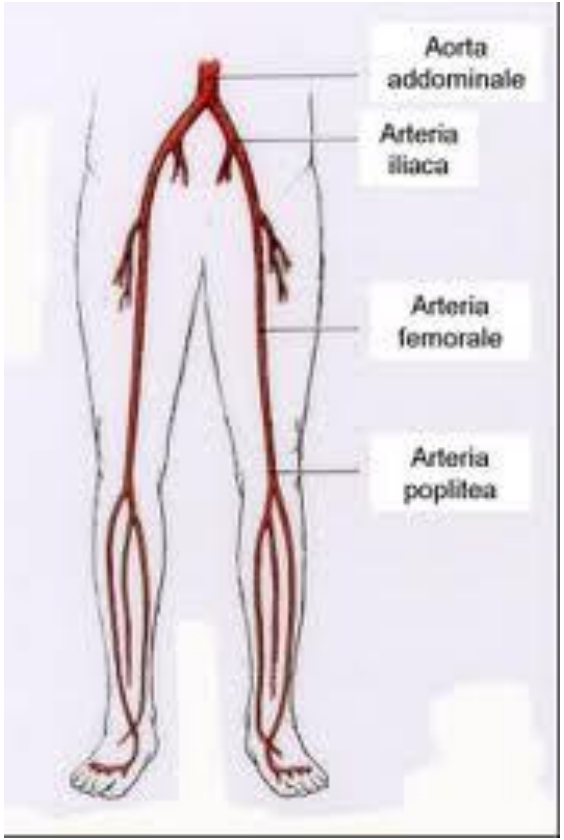
ECST $\frac{C - A}{} \times 100\%$

NASCET $\frac{B - A}{B} \times 100\%$

Rothwell 1994, Stroke 25:2435-39


Folder
Database
Image Dir
Image Right
Image Left
Get Image
Save Image
Digitize
Record Dir
Store New
Replace Rec
Start Rec
Get Rec
Modify Rec
Calibrate
Near Wall
Far Wall
Set Tracking
Ext. Diam.
Int. Diam.
Show Pts
Fix Pts
Re-Track
Zoom/Unzoom
Erase Edges
Step Records
01:11:31:00
FOLDER:\DEMO
Tracked Length 10.075
Seg. Length:10.075

Identification of subclinical atherosclerosis



Doppler US of lower limbs

ABI

Indicators of subclinical organ damage at the renal level

SCHOOL OF MEDICINE AND SURGERY

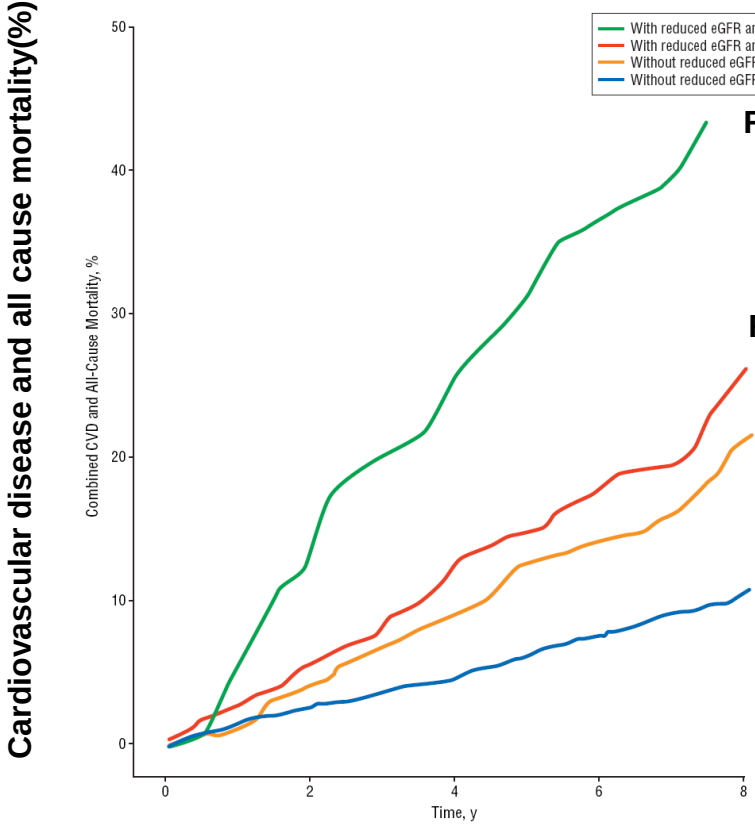
✓ ESTIMATED GLOMERULAR FILTRATE (eGFR),

(CALCULATED ON THE BASIS OF CREATININE)

✓ MICROALBUMINURIA O PROTEINURIA

Cross-Classification of Microalbuminuria and Reduced Glomerular Filtration Rate

Associations Between Cardiovascular Disease Risk Factors and Clinical Outcomes



Reduced eGFR and MA +

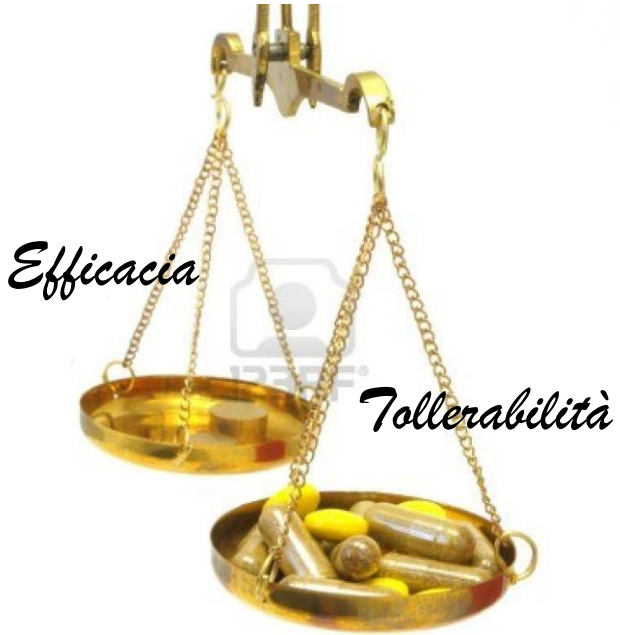
Reduced eGFR and MA -

Normal eGFR and MA +

Normal eGFR and MA -

Framingham Heart Study, Arch Intern Med. 2007

HYPERTENSION TREATMENT



Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension*

	Nonpharmacological Intervention	Dose	Approximate Impact on SBP	
			Hypertension	Normotension
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	-5 mm Hg	-2/3 mm Hg
Healthy diet	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	-11 mm Hg	-3 mm Hg
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.	-5/6 mm Hg	-2/3 mm Hg
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	-4/5 mm Hg	-2 mm Hg

*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension. DASH indicates Dietary Approaches to Stop Hypertension; and SBP, systolic blood pressure.

Resources: Your Guide to Lowering Your Blood Pressure With DASH—How Do I Make the DASH? Available at: https://www.nhlbi.nih.gov/health/resources/heart/hbp-dash-how-to.

Top 10 Dash Diet Tips. Available at: http://dashdiet.org/dash_diet_tips.asp

Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension* (cont.)

	Nonpharmacological Intervention	Dose	Approximate Impact on SBP	
			Hypertension	Normotension
Physical activity	Aerobic	● 90–150 min/wk ● 65%–75% heart rate reserve	-5/8 mm Hg	-2/4 mm Hg
	Dynamic resistance	● 90–150 min/wk ● 50%–80% 1 rep maximum ● 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg	-2 mm Hg
	Isometric resistance	● 4 × 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk ● 8–10 wk	-5 mm Hg	-4 mm Hg
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol† to: ● Men: ≤2 drinks daily ● Women: ≤1 drink daily	-4 mm Hg	-3 mm

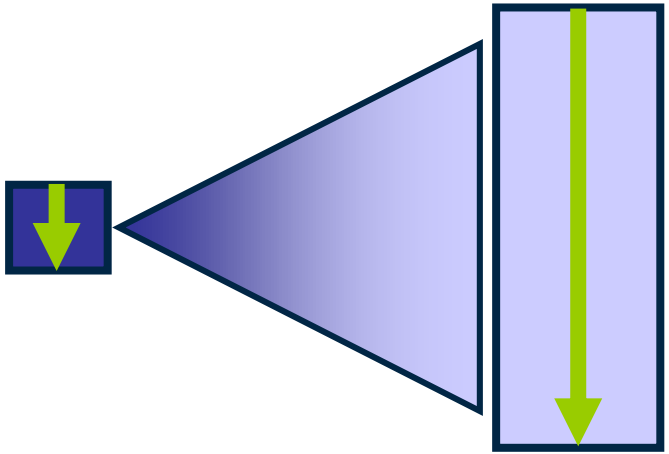
*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.
†In the United States, one “standard” drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

Lowering BP reduces cardiovascular risk

Small SBP reductions yield significant benefit

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

2 mmHg decrease in mean SBP



7% reduction in risk of ischaemic heart disease mortality

10% reduction in risk of stroke mortality

Adapted from Lewington et al. *Lancet.* 2002

Lifestyle changes

Aims:

- Lower blood pressure values,
- Control other CV risk factors,
- Reduce the number of drugs and the dose of antihypertensive therapy
- Lifestyle changes are also advisable for individuals with high-normal blood pressure and additional risk factors in order to reduce the risk of developing frank hypertension.

Non-pharmacological treatment

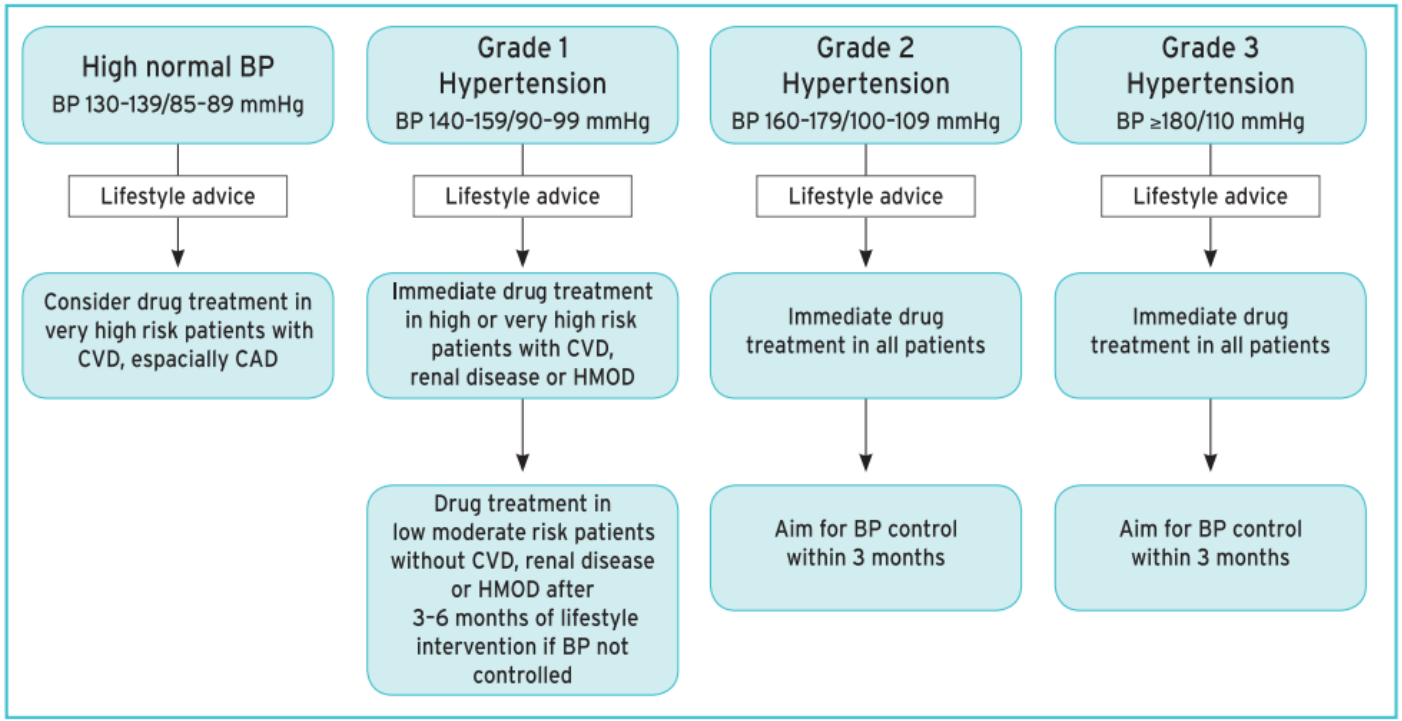
Lifestyle modifications that have been shown to reduce blood pressure or cardiovascular risk, and should therefore be considered include:

- ❑ **abolition of smoking;**
- ❑ **weight loss;**
- ❑ **reduction of excessive consumption of alcoholic beverages;**
- ❑ **exercise;**
- ❑ **low sodium diet;**
- ❑ **increase in the dietary intake of fruits and vegetables and reduction in the intake of total and saturated fats.**

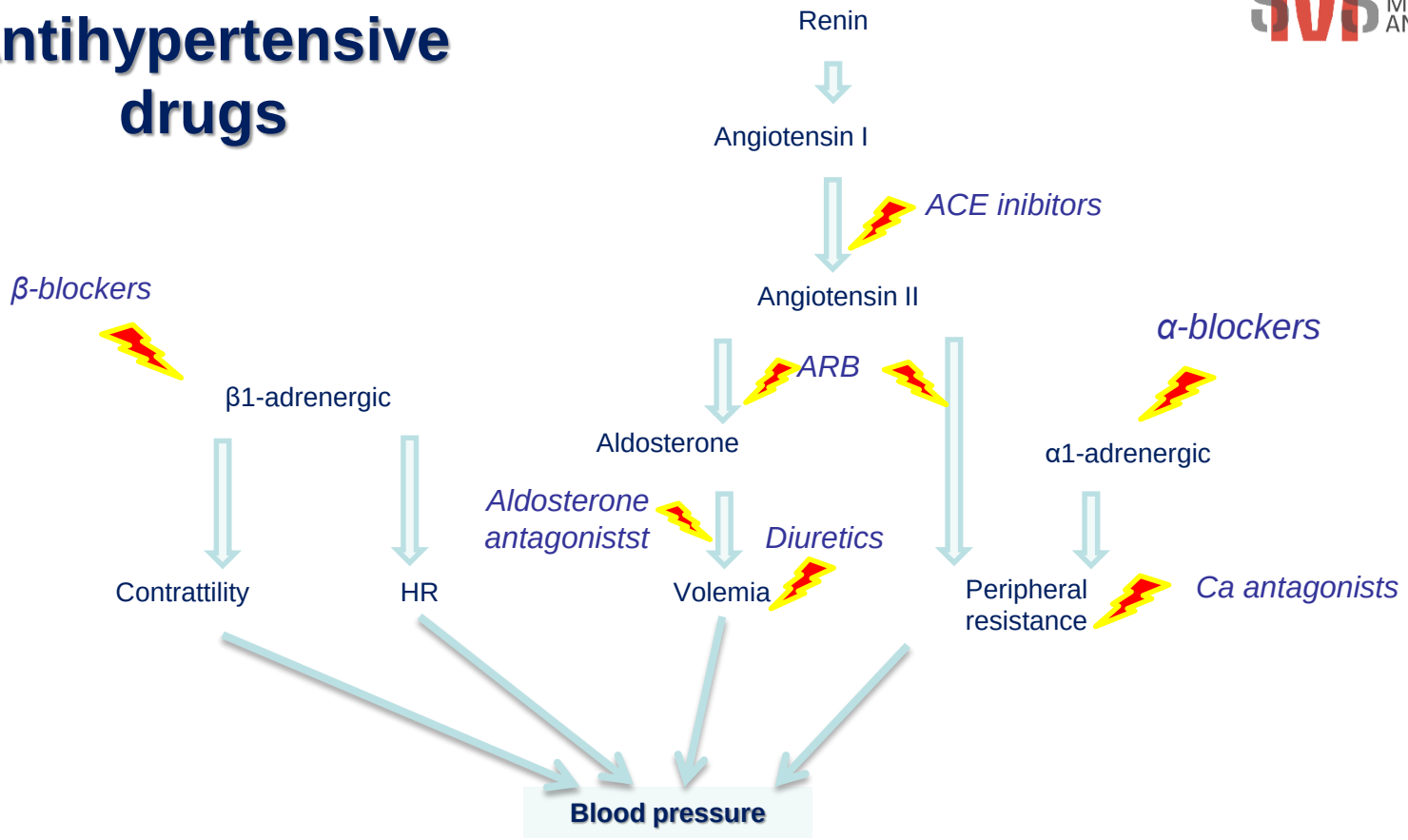
Specific objectives

- Limit salt consumption to <5 g per day
- Limit alcohol consumption to <14 units per week (men) and <8 units (women), avoiding compulsive consumption (binge drinking)
- Increase the consumption of vegetables fresh fruits, nuts, unsaturated fatty acids; reduce red meat; prefer low-fat dairy products
- avoid obesity (BMI >30 kg/m2 or waist circumference >102 cm in men and >88 cm in women), trying to achieve optimal values of BMI (about 20–25 kg/m2) and waist circumference (<94 cm in men and <80 cm in women)
- perform regular aerobic physical activity (e.g. at least 30 min of moderate exercise 5–7 days a week)
- cease smoking

2018 ESC/ESH Guidelines
When to start antihypertensive treatment



Antihypertensive drugs



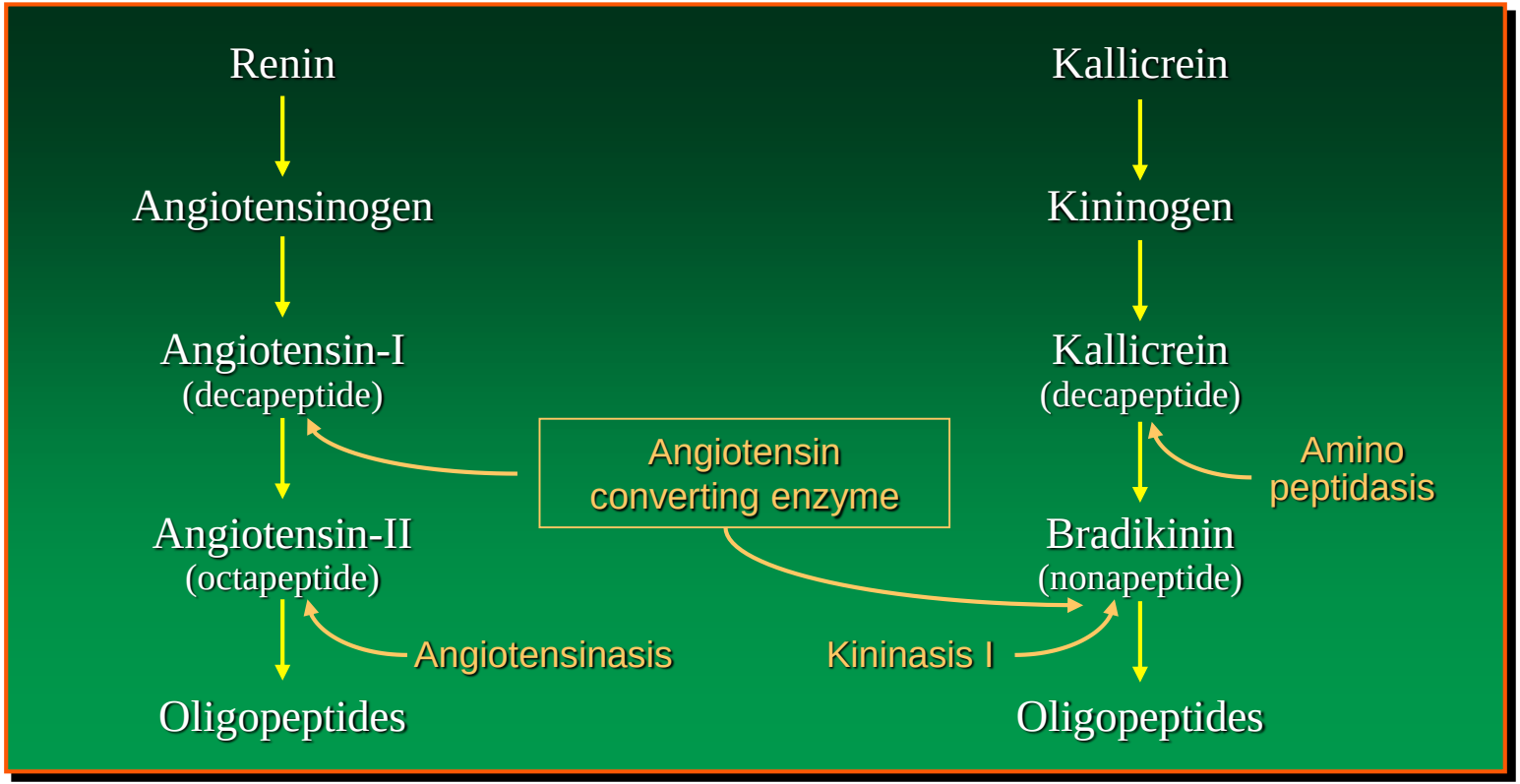
Main antihypertensive drugs classes

- Diuretics
- Beta blockers
- Calcium channel blockers
- ACE inhibitors
- Angiotensin II receptor antagonists
- Alpha1 blockers
- Central adrenergic receptor blockers

ACEI/ARBs: Hemodynamic Effects

	Acute	Chronic
Cardiac output	=	=
Heart rate	=	=
PVR	↓	↓
BP	↓	↓

Renin and Bradikinin



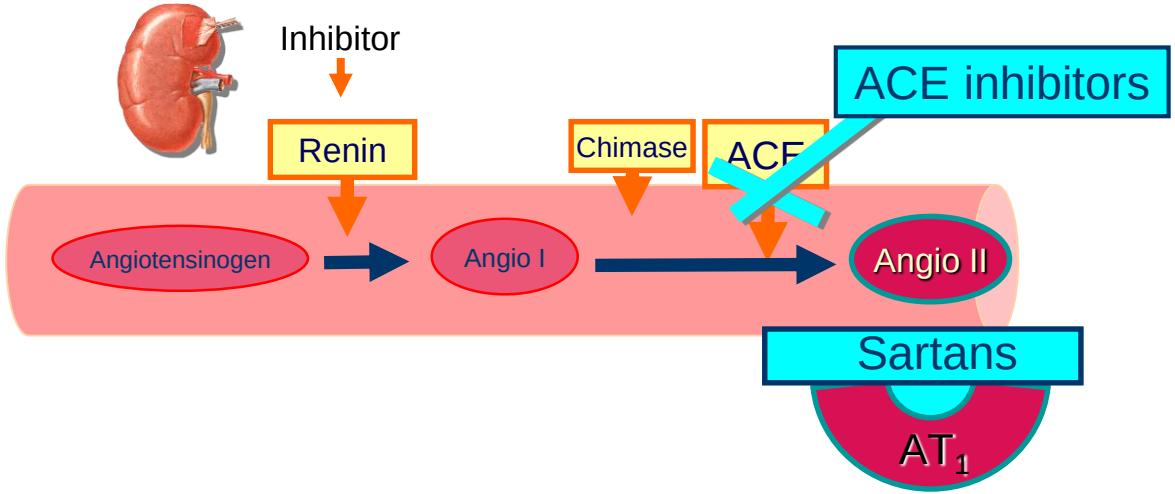
Cough and ACE inhibitors

- Features: Insisting, non-productive, persistent
- Onset: 2-4 weeks (from a few hours after the first administration to a few months)
- Prevalence: From 0.2 to 33%
- Female: unrelated age, severity hypertension or heart failure, dose
- Pathogenesis: Lung accumulation of bradykinins, prostaglandins, substance P; stimulation J receptors
- Treatment: Regression with suspension

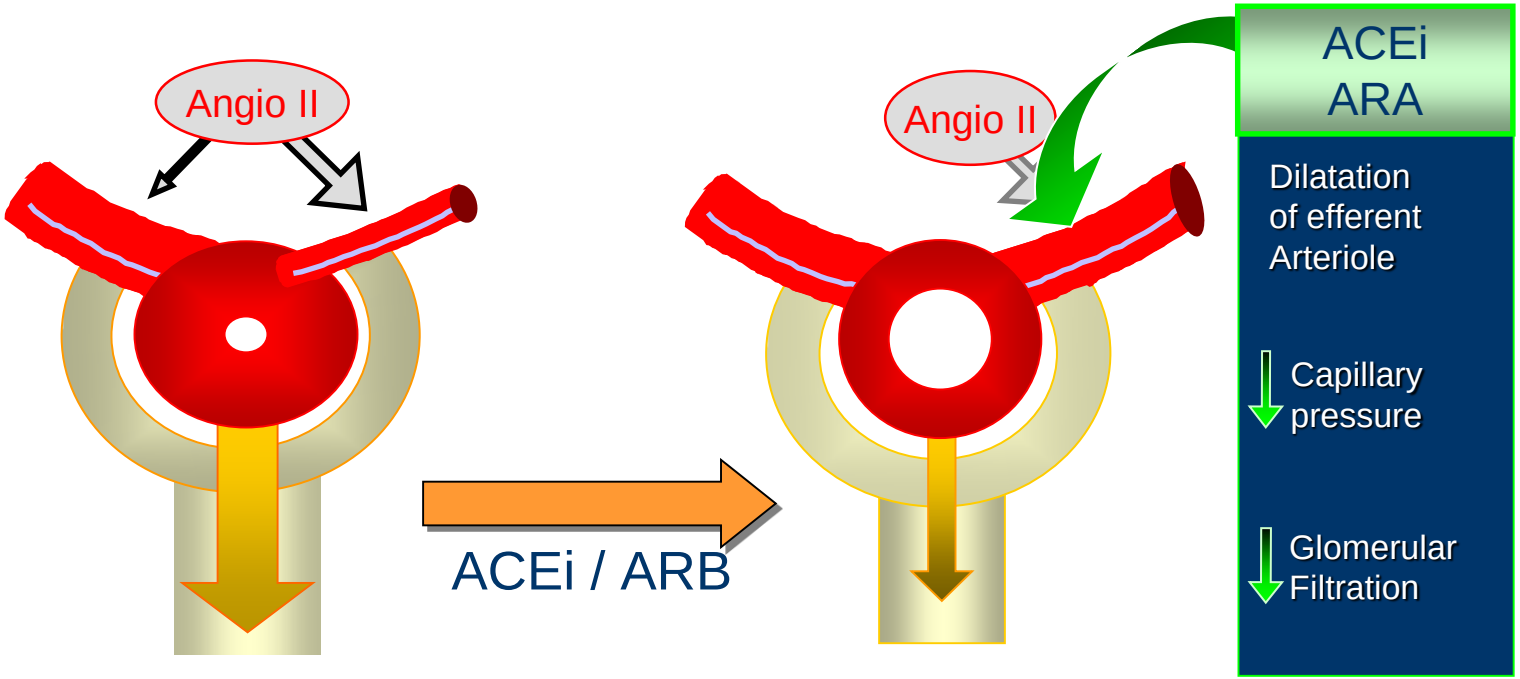
ACEIs and ARBs

- Less effective in some patient groups (elderly, blacks)
- Favourable metabolic effects
- Side effects:
  - Dry cough (only ACEI) – most common
  - Angioedema (only ACEI)
  - Hyperkalemia
- Best tolerated antihypertensives
- Controindicated in pregnancy and bilateral renal stenosis
- Require monitoring of kalemia

Pharmacological Blockade of the Renin-Angiotensin-Aldosterone System



Effects of RAA System Blockade on Glomerular Hemodynamics



Calcium channel blockers: Hemodynamic Effects

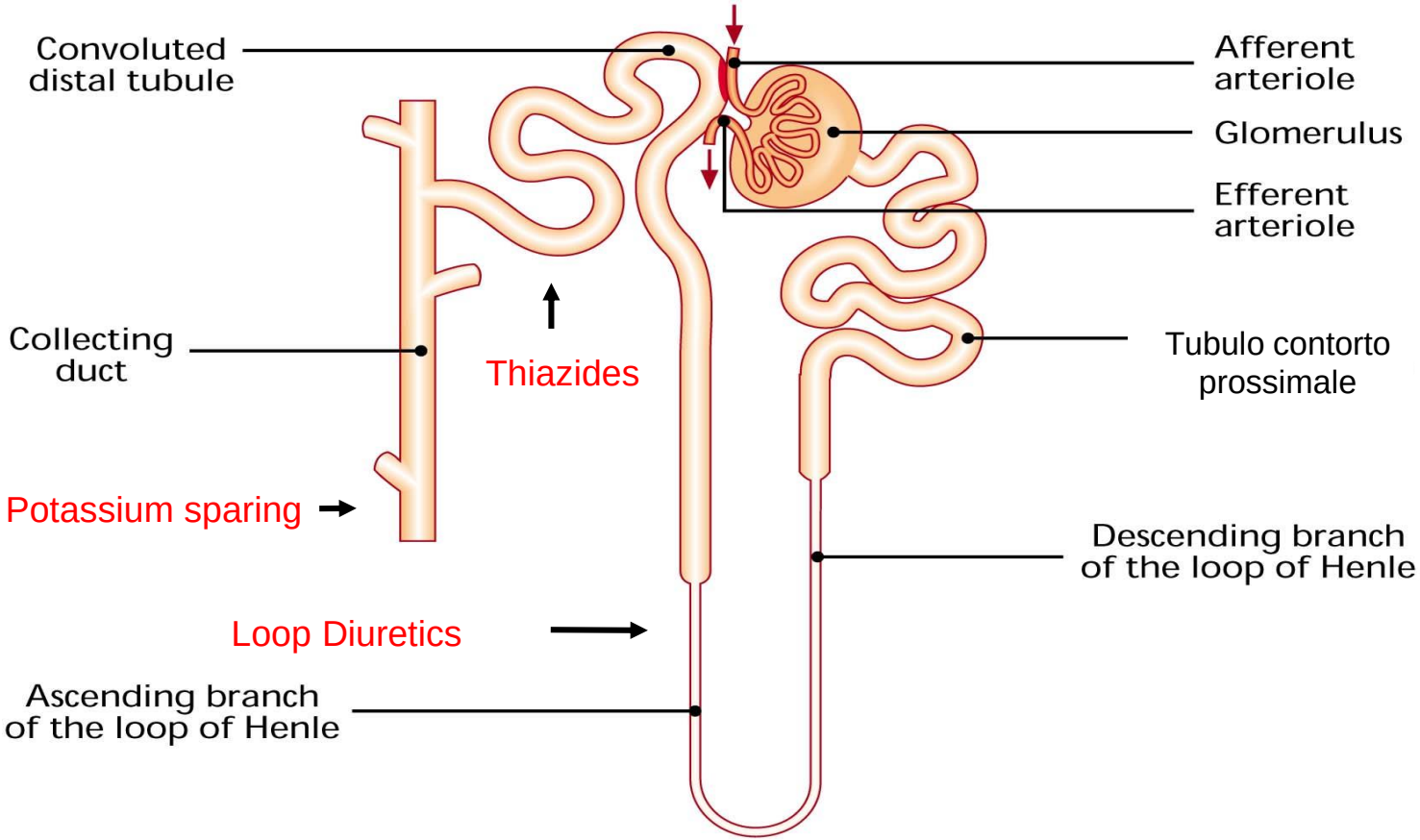
	Acute	Chronic
Cardiac output	=↑	=
Heart rate	=↑	=
PVR	↓	↓
BP	↓	↓

Calcium antagonists

- Effective in most patients
- Short acting compounds may cause hypotension (avoid)
- Neutral metabolic effects
- Common side effects:
  - Ankle edema (less if with ACEI/ARB) – most common
  - Flushing
  - Constipation
  - Gum hypertrophy
- Dihydropiridines (amlodipine, nifedipine, lercanidipine, nimodipine, lacidipine) are mainly used (mainly cause vasodilation)
- Non-dihydropiridines (verapamil, diltiazem) – cardiodepressive effects (bradycardia, reduced contractility) – less commonly used in HT

Available antihypertensive drugs

- Diuretics
- Beta blockers
- Calcium channel blockers
- ACE inhibitors
- Angiotensin II receptor antagonists
- Alpha1 blockers
- Central adrenergic receptor blockers


Convoluted distal tubule
Afferent arteriole
Glomerulus
Efferent arteriole
Collecting duct
Thiazides
Tubulo contorto prossimale
Potassium sparing
Descending branch of the loop of Henle
Loop Diuretics
Ascending branch of the loop of Henle

Diuretics

- Effective in most patients
- Significant side effects:
  - Thiazides – hyperglycemia, diabetes
  - Hypokalemia (thiazides, loop D)
  - Hyperkalemia (potassium sparing D)
  - Gynecomastia (spironolactone)
- Short acting drugs not suitable for long term Tx (furosemide!)
- Thiazides less effective with low eGFR (<30)

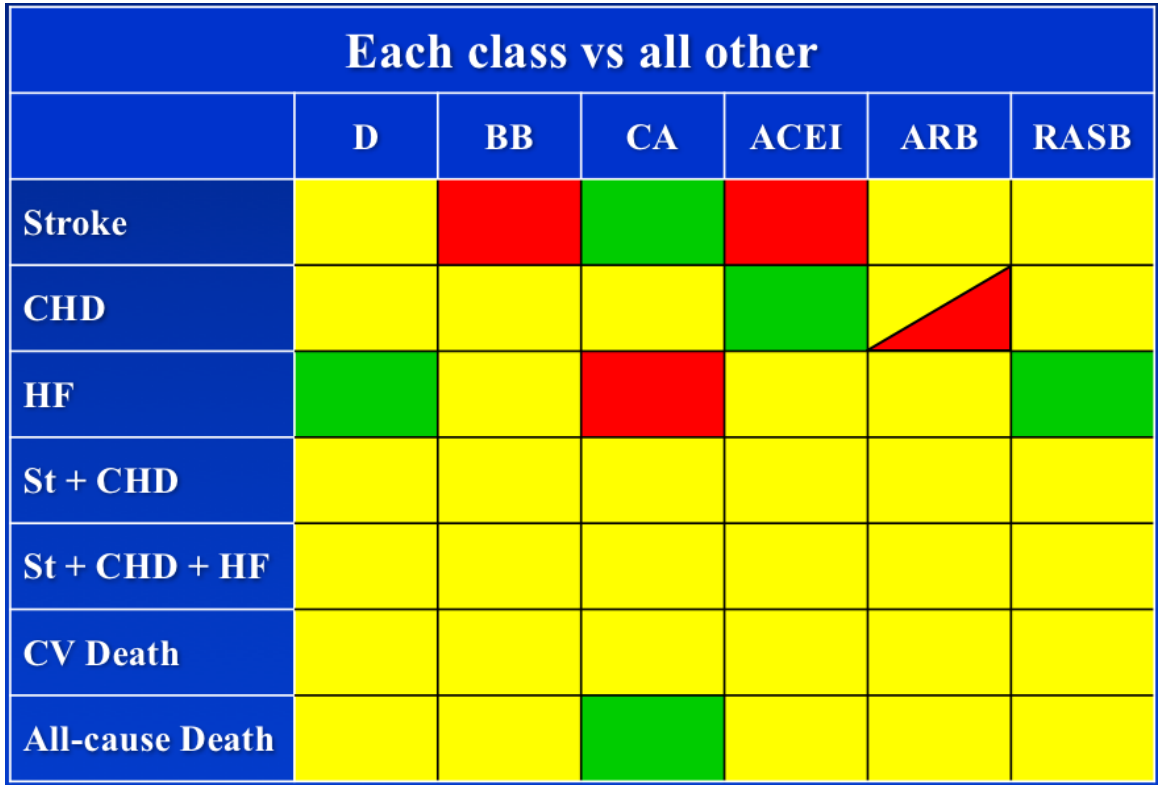
Beta-blockers

- Less effective in some patients (e.g. blacks)
- Significant side effects:
  - May favour hyperglycemia, diabetes (esp. with thiazides)
  - Bradycardia
  - Bronchospasm
  - Erectile dysfunction
  - Sleep disturbances
- Newer drugs with vasodilating properties prefrrable (nebivolol, carvedilol)

Alpha-blockers

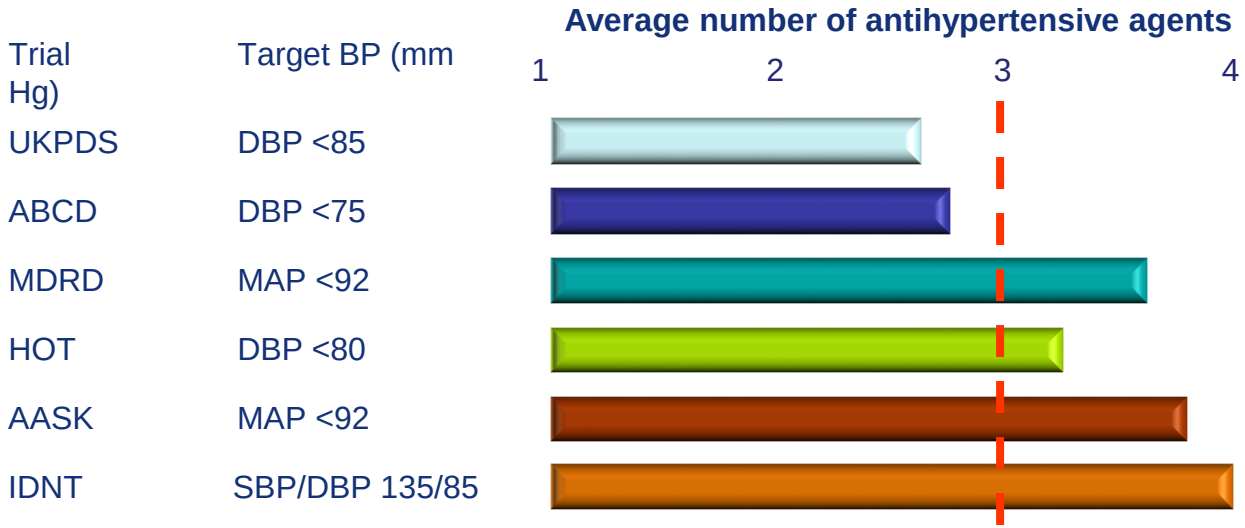
- Not first line drugs
- Orthostatic hypotension (elderly!)
- Favourable metabolic profile
- Useful in prostatic hypertrophy

Summary results of the direct comparisons of each class vs all other classes of BP-lowering drugs on seven major outcomes



Thomopoulos, Parati, Zanchetti, J Hypertens 2015; 33: 1321-1341

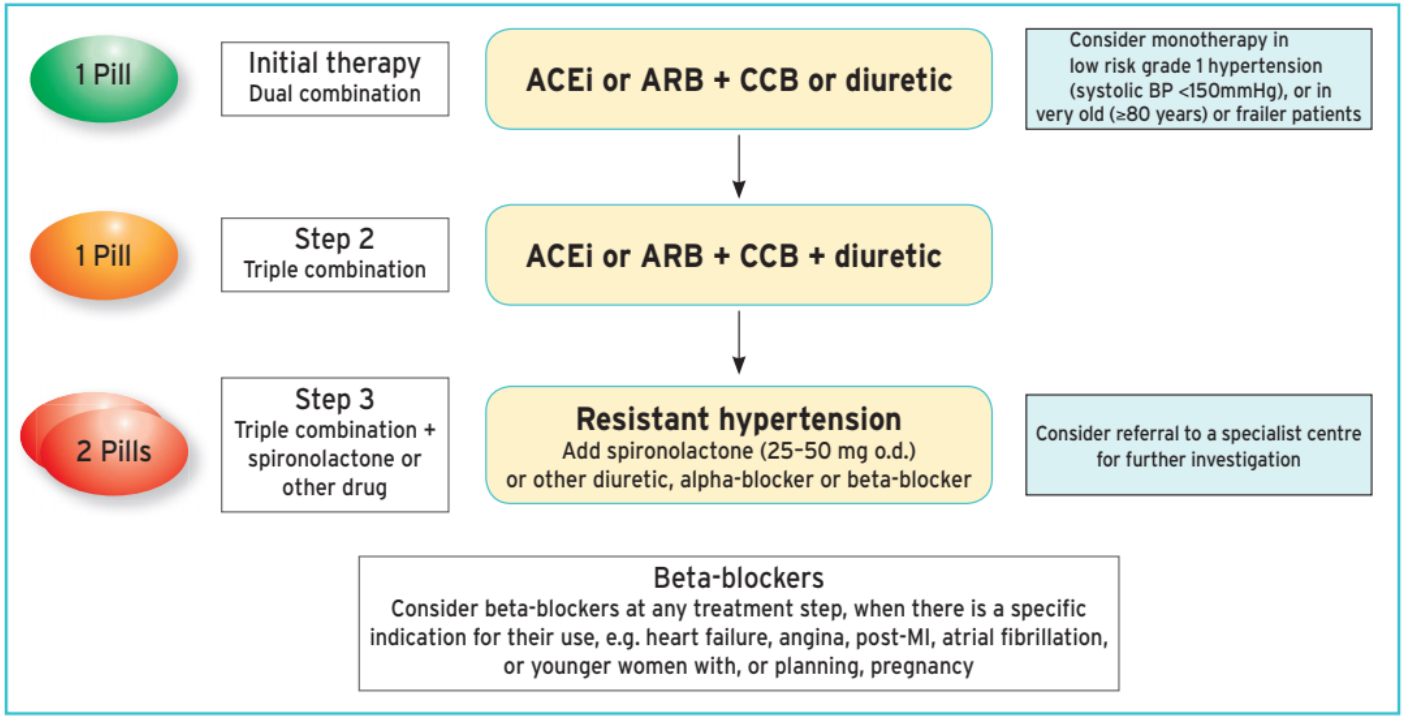
Multiple antihypertensive agents are needed to achieve target BP



DBP, diastolic BP; SBP, systolic BP; MAP, mean arterial pressure; UKPDS, United Kingdom Prospective Diabetes Study; ABCD, Appropriate Blood Pressure Control in Diabetes; MDRD, Modification of Diet in Renal Disease; HOT, Hypertension Optimal Treatment; AASK, African American Study of Kidney Disease; IDNT, Irbesartan Diabetic Nephropathy Trial

Bakris GL et al. Am J Kidney Dis 2000 ;36: 646-661

2018 ESC/ESH Guidelines
Antihypertensive therapy algorithm



Initation of BP lowering treatment

Older patients

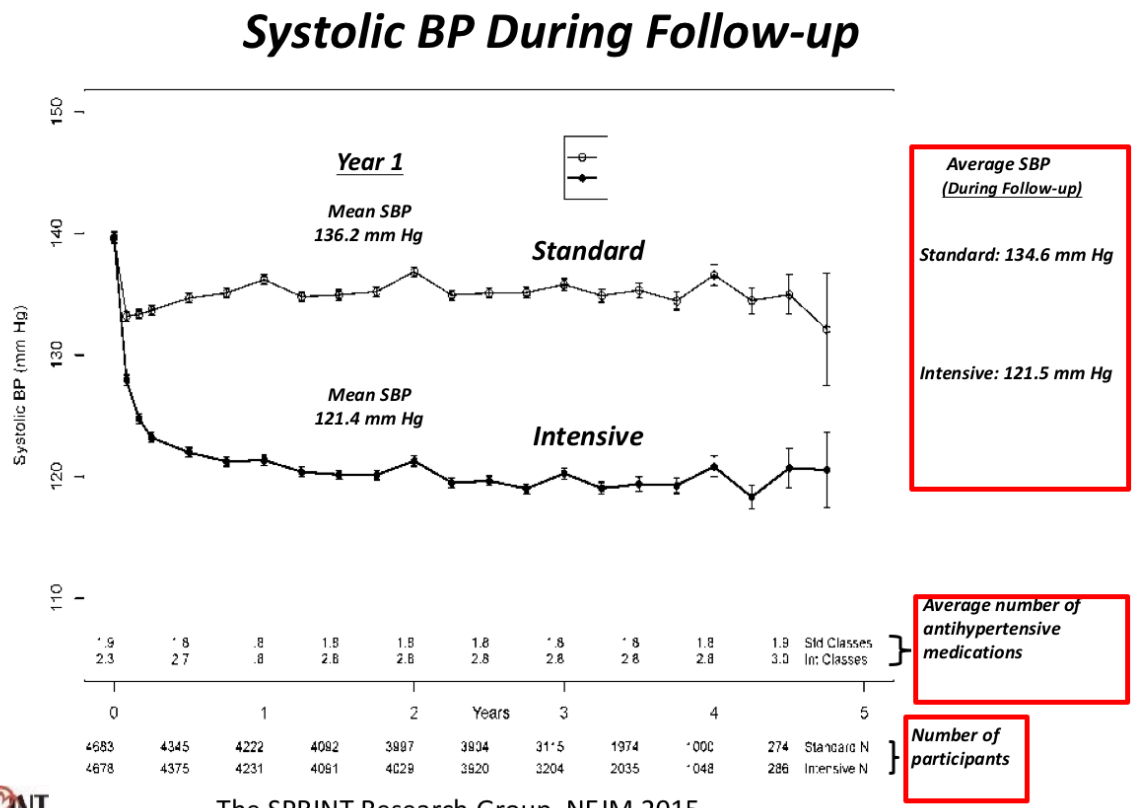
In **fit older** patients with hypertension (even if age > 80 years), BP lowering drugs treatment and lifestyle intervention are recommended when SBP is **≥160 mmHg.**	IA
BP-lowering drug treatment and lifestyle intervention are recommended in the **fit older patients (> 65 years** but not over 80 years) when SBP is the **grade 1 range** (140-159 mmHg), provided that treatment is well tollerated.	IA
Antihypertensive treatment may also be considered in frail older patients if tolerated	IIb B
Withdrawal of BP lowering drug treatment on the basis of age, even when patients attain age of ≥ 80 years, is not recommended, provided that treatment is well tollerated	III A

Summary of office BP thresholds for treatment

SCHOOL OF MEDICINE AND SURGERY

Age group	Office SBP treatment threshold (mmHg)					Diastolic treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18–65 years	≥ 140	≥ 140	≥ 140	≥ 140	≥ 140	≥ 90
65–79 years	≥ 140	≥ 140	≥ 140	≥ 140	≥ 140	≥ 90
≥ 80 years	≥ 160	≥ 160	≥ 160	≥ 160	≥ 160	≥ 90
Diastolic treatment threshold (mmHg)	≥ 90	≥ 90	≥ 90	≥ 90	≥ 90	

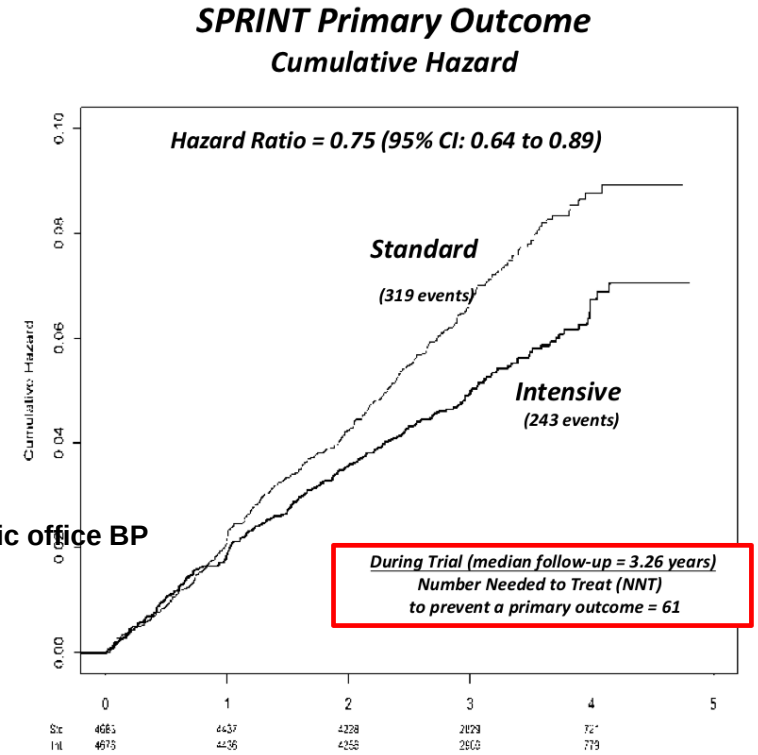
Office BP treatment targets in hypertensive patients



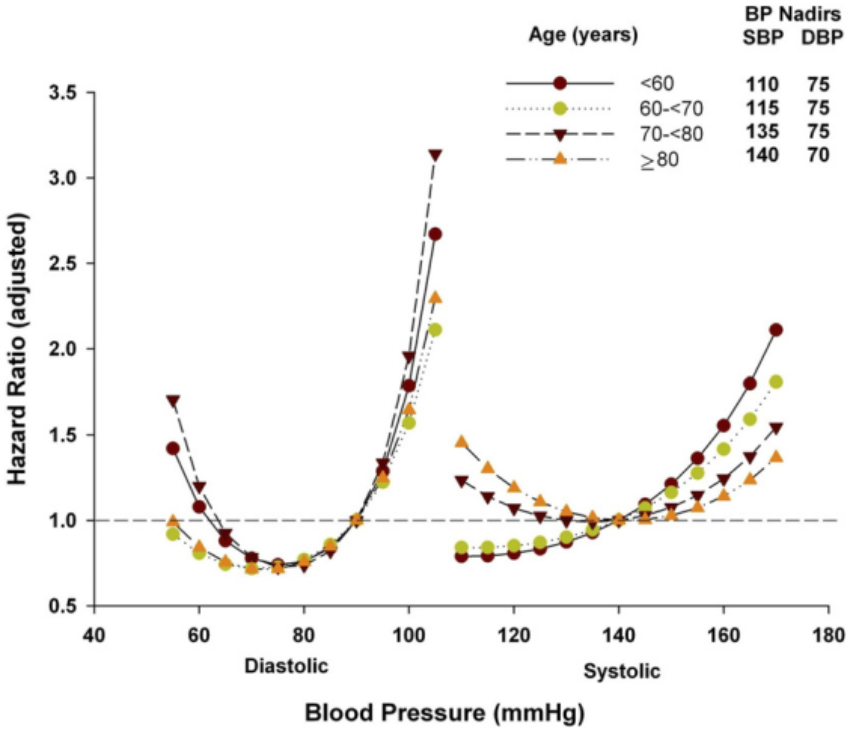
The SPRINT Research Group. NEJM 2015

Office BP treatment targets in hypertensive patients

Unattended automatic office BP measurement



Risk of Adverse Outcomes by Age and Blood Pressure



Am J Med. 2010;123:719 –26

Office BP treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Diastolic treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/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	< 80 to 70
65–79 years	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	< 80 to 70
≥ 80 years	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	< 80 to 70
Diastolic treatment target range(mmHg)	< 80 to 70	< 80 to 70	< 80 to 70	< 80 to 70	< 80 to 70	

Resistant Hypertension

Definition

Resistant hypertension is defined as a systolic and/or diastolic pressure > 140/90 mmHg, despite adequate lifestyle correction and drug therapy with at least three drugs at full or maximum tolerated dosage, of which at least one diuretic.

Diagnosis should be confirmed with MAP 24 h or home monitoring

Guidelines for Management of Hypertension
ESC-ESH 2018

Resistant hypertension

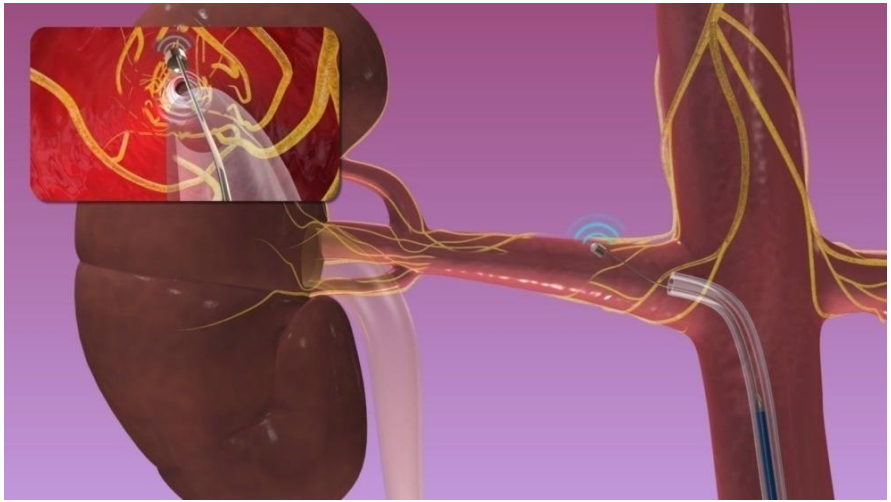
2013	2018
Mineralocorticoid receptor anta alph cons exis (Cla	Recommended treatment of resistant v- er se loop lol of doxazosin. (Classe IB)

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

Catheter-Based Treatment for Achieving Renal Sympathetic Denervation

Symplicity® Catheter System™
Ardian, Inc., Palo Alto, CA, USA



increased reabsorption of Na+
increased renin secretion
reduction of renal flow

radiofrequency ablation of renal afferences and efferences of the sympathetic nervous system, resulting in isolation of the renal parenchymal and iuxtaglomerular structures from abnormal stimulation by adrenergic efferences.

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

This calls for earlier intervention in the natural history of hypertension, before organ damage develops or

The earlier the better

insufficiently treated

The earlier the better

Thomopoulos, Parati, Zanchetti, J.Hypertens 2014

“ At the beginning, a disease is easy to cure, but difficult to diagnose; as time passes, not having been treated or recognized at the outset, it becomes easy to diagnose, but difficult to cure”

Niccolò Machiavelli, *Il Principe*, 1513