

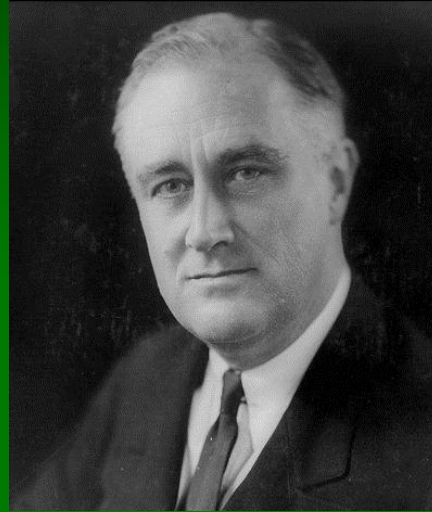
Central Aortic Pressure and Cardiovascular Outcomes in Hypertension

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Department of Cardiology

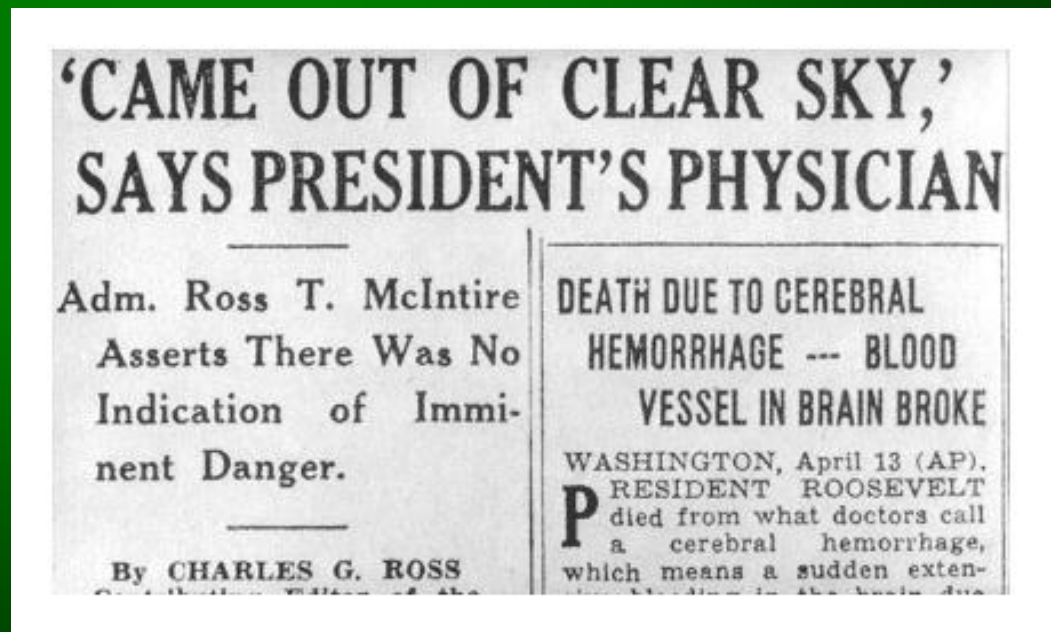


BSM Medical University, Dhaka



● Franklin D. Roosevelt, 32nd President of the US died of cerebral haemorrhage on April 12, 1945

- ✿ Admiral Ross McIntire, the president's personal physician, asserted-
 - the president had been in excellent health,
 - there was no indication of imminent danger,
 - the cerebral haemorrhage "*came out of the clear sky*"



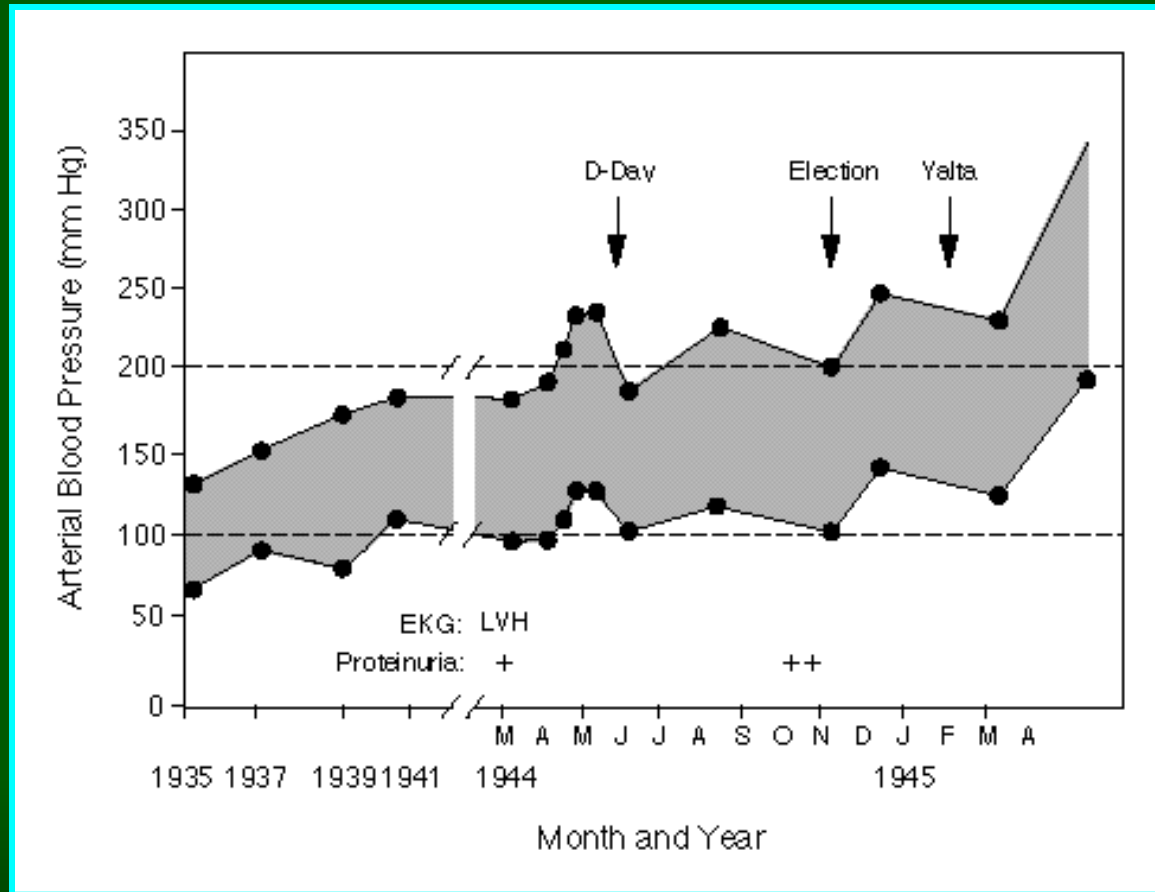
St. Louis Post-Dispatch, April 13, 1945

Steve Early, press secretary for the White House, stated officially that

“the President was given a thorough examination by seven or eight physicians, including some of the most eminent in the country, and was pronounced organically sound in every way”

Ross CG. 'Came out of clear sky,' says President's physician.
St. Louis Post-Dispatch. April 13, 1945:A2

Blood pressure records of Franklin D. Roosevelt from 1935 until his death on 12 April, 1945



Data are from the diary of Dr. Howard G. Bruenn: *Ann Intern Med* 1970;72:579-591

As late as 1945...

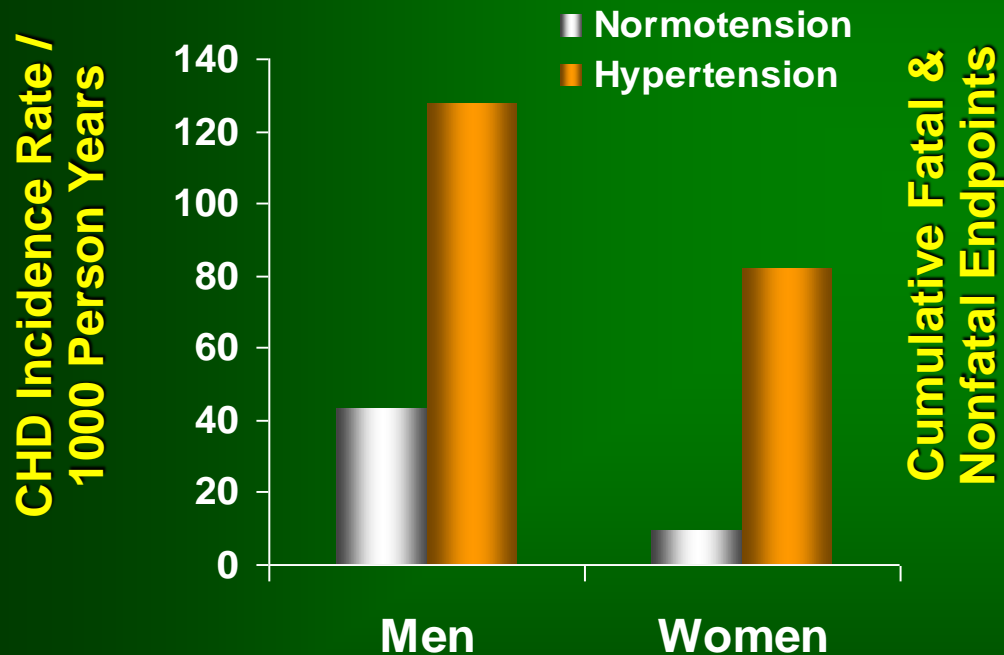
- ❖ Hypertension was not considered a disease of major clinical consequence by most physicians
- ❖ It was still viewed by the majority of physicians as “essential” to force blood through sclerotic arteries to the target organs

“... the hypertension may be an important compensatory mechanism which should be tampered, even were it certain that we control it.”

- Paul Dudley White. Heart Disease. 2nd Ed. New York, Mcmillon,1937:326

Hypertension: Historical Lessons

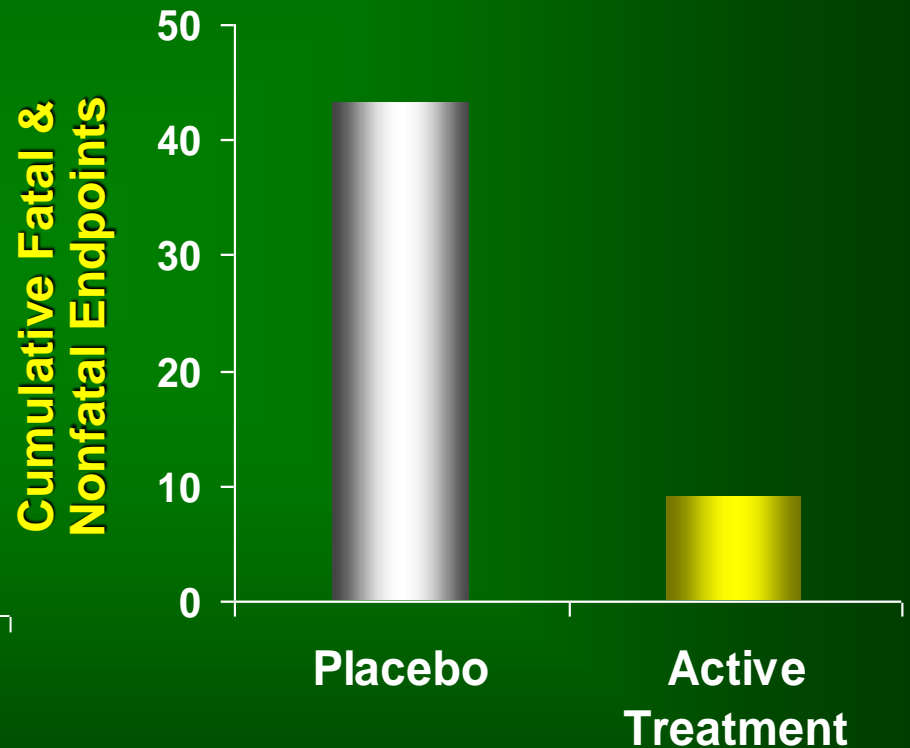
Hypertension Increases Morbidity and Mortality



THE FRAMINGHAM STUDY

Ann Intern Med. 1961;55:33-50

Treatment Decreases Morbidity and Mortality

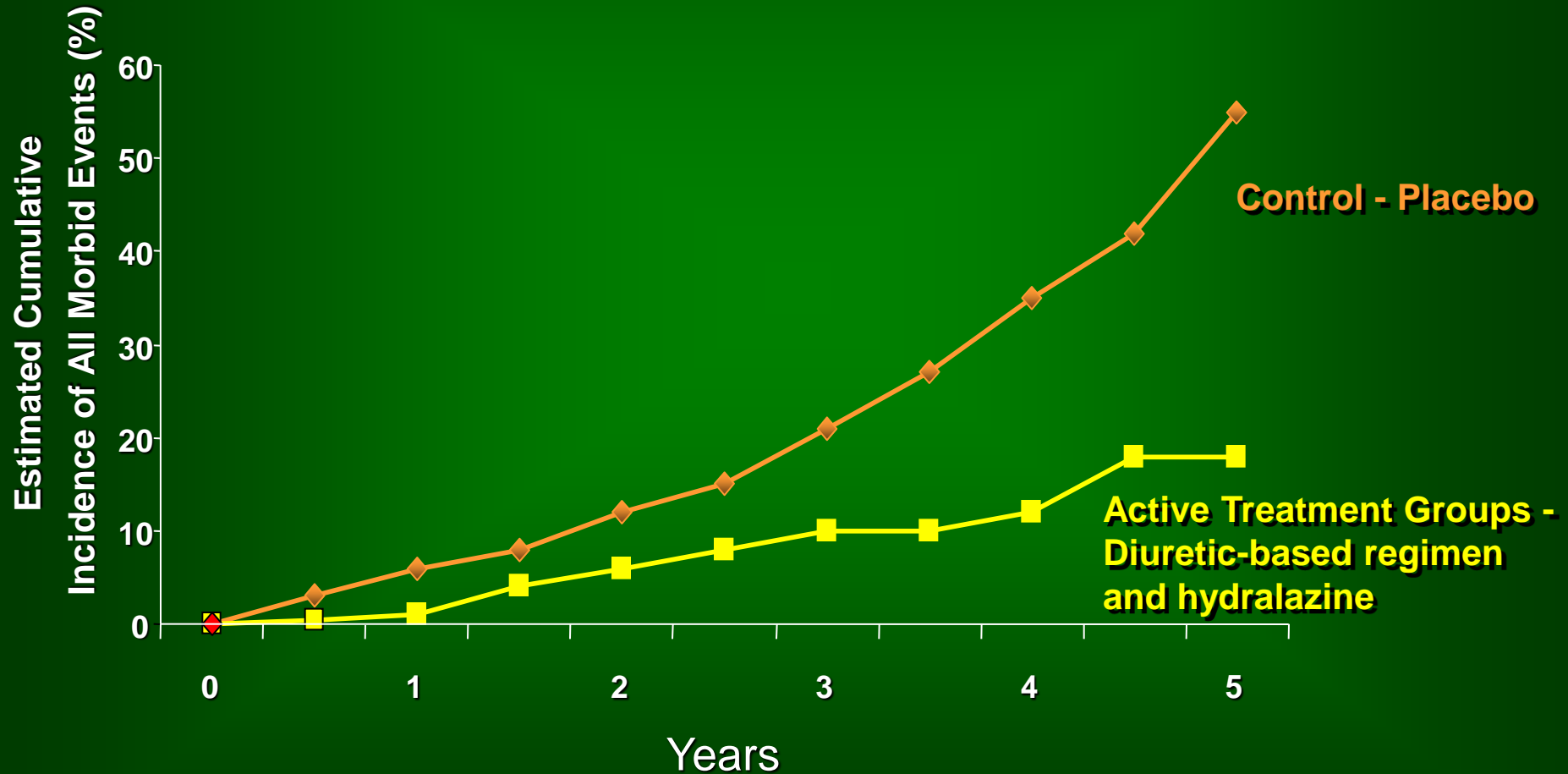


THE VET. ADM. STUDY II

JAMA. 1970;213:1143-1152

Hypertension Treatment Significantly Reduced Mortality and Morbidity

*VA Cooperative Study Group –
Estimated cumulative incidence of all morbid events over 5 years*



Evolution of Perception of Hypertension

- ❑ In the past, the severity of HTN was classified principally on the basis of DBP
- ❑ Later SBP was found to be better guide than DBP to evaluate CV and all-cause mortality ^{1,2}
- ❑ Recently pulse pressure emerged as an independent CV risk factor ^{3,4}
- ❑ Today, the hypertensive patients should be considered as having multiple risk factors

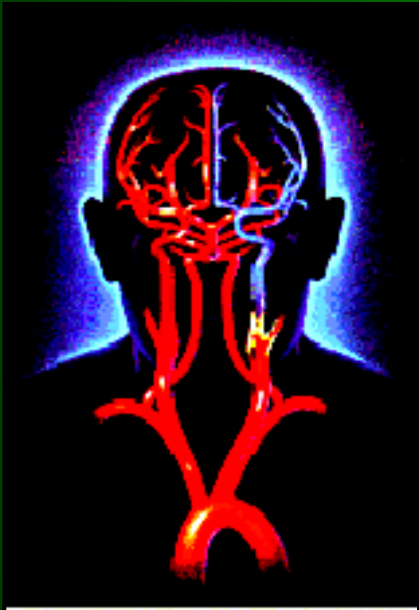
HYPERTENSION

A “Syndrome” of Metabolic Cardiovascular Abnormalities

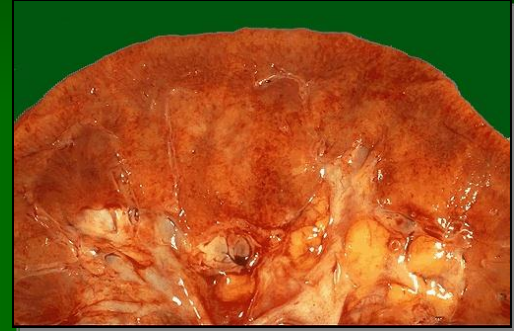
- High Blood pressure
- Glucose intolerance and insulin resistance
- Decreased renal function reserve
- Altered LV structure and function
- Altered compliance of arteries

Hypertensive Cardiovascular Diseases

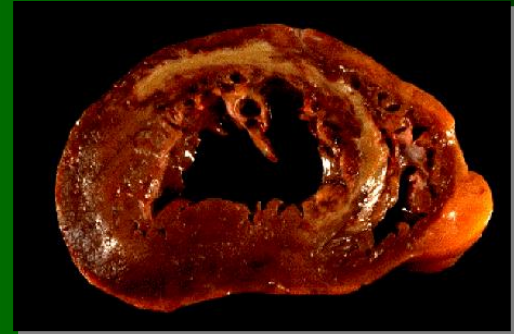
Cerebrovascular events



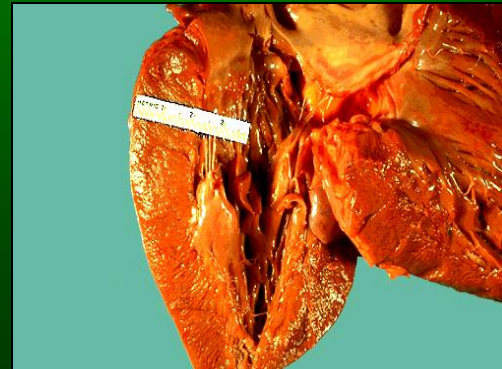
Renal disease



MI



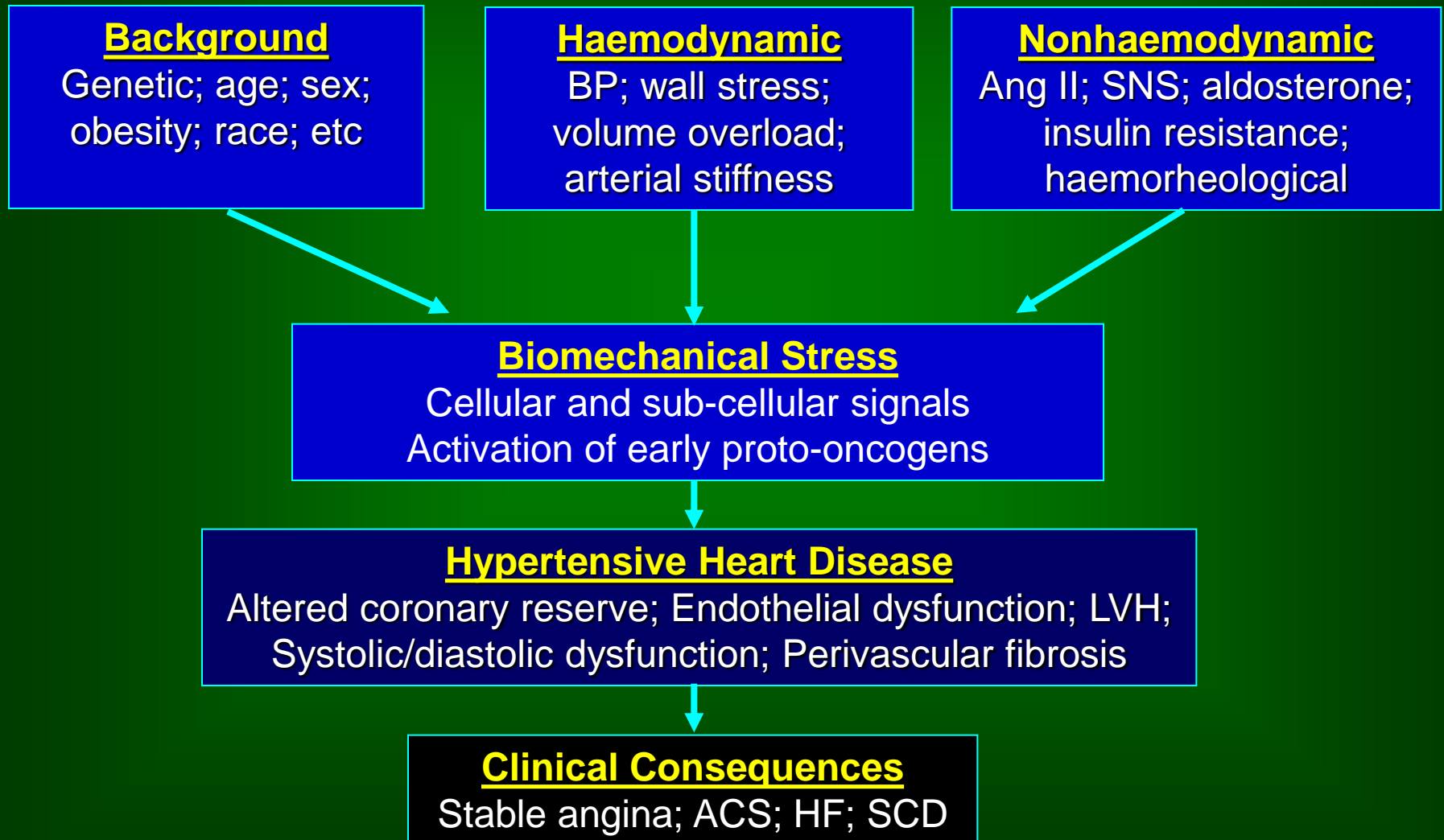
LVH



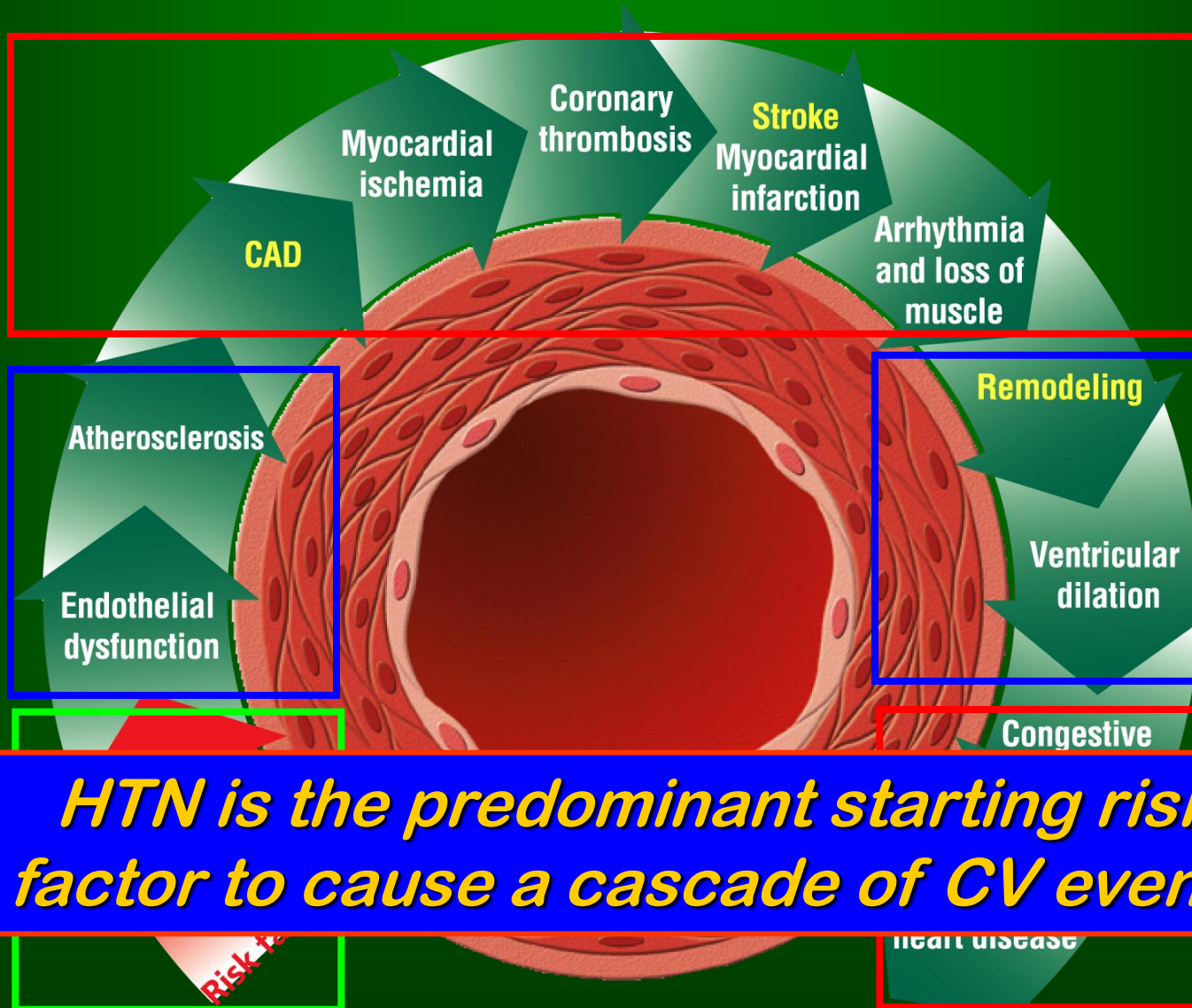
HF



Pathophysiology of Hypertensive CVD



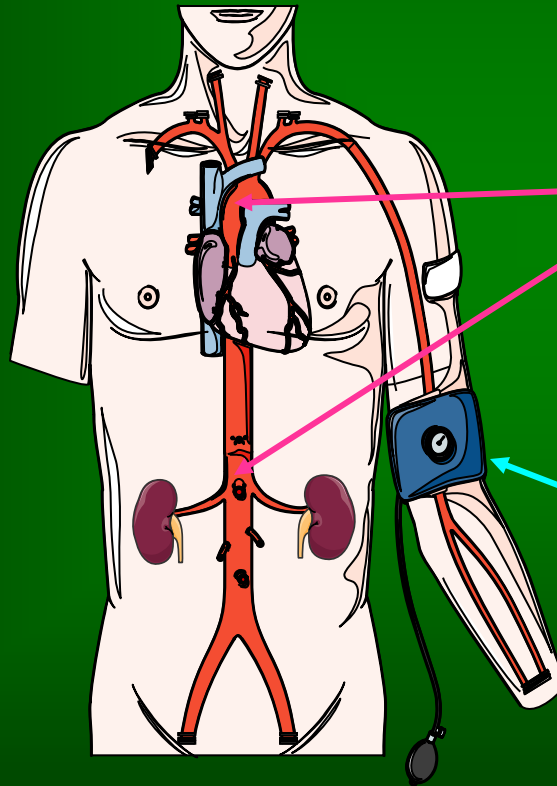
Cardiovascular disease continuum



Prevention of cardiovascular events in hypertension

- ❖ Prevention of CV events is the major goal in hypertensive patients
- ❖ Evaluation should be comprehensive and treatment has to be efficient right from the start of the CV continuum

Haemodynamic assessment in hypertensive patients



Central aortic blood pressure:-
- Blood pressure measurement at the aortic level

Brachial blood pressure

Brachial Blood Pressure

- ❖ BP is customarily measured in the upper limb by brachial cuff method
 - Systolic pressure by palpation (*Riva-Rocci, 1896*)
 - Systolic and diastolic pressure by auscultation (*Korotkov, 1905*)
- ❖ Brachial parameters (SBP, DBP, PP) are powerful predictor of cardiovascular structural damage, morbidity and mortality

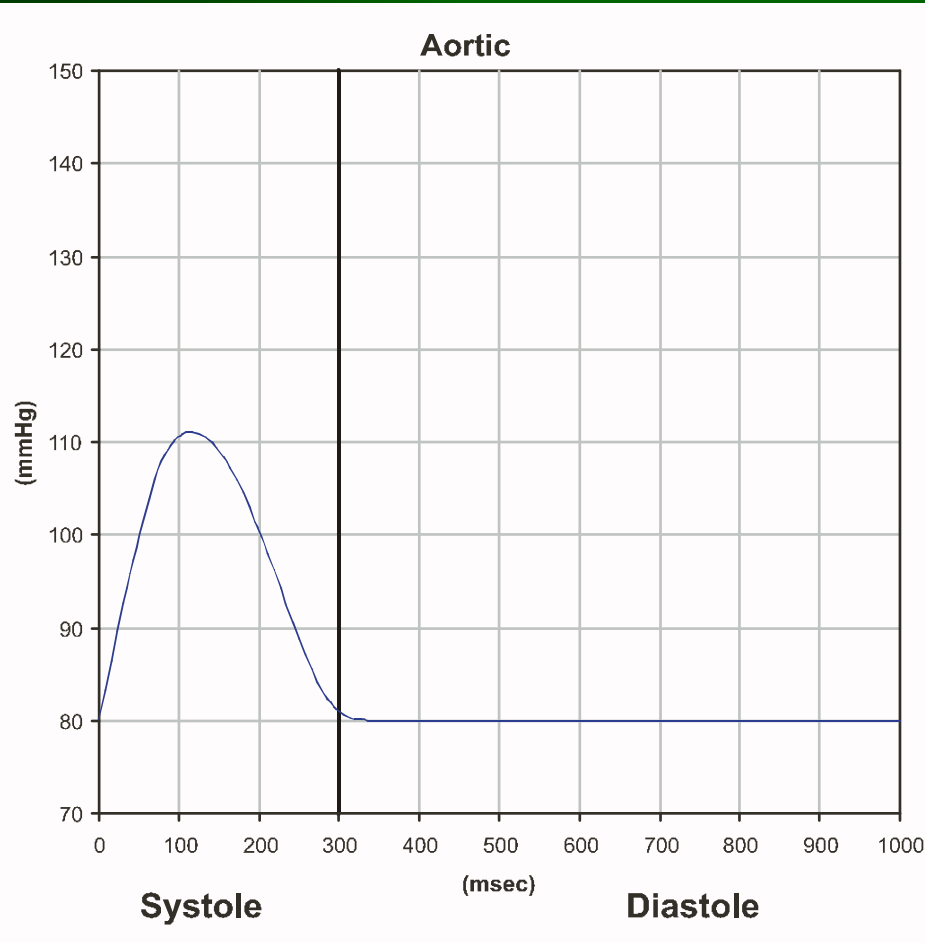
Central Aortic Pressure

- Blood pressure at the key organ level (heart, brain and kidneys)
- Central pressure is a better predictor of coronary disease than brachial pressure

Central Aortic Pressure Waveform

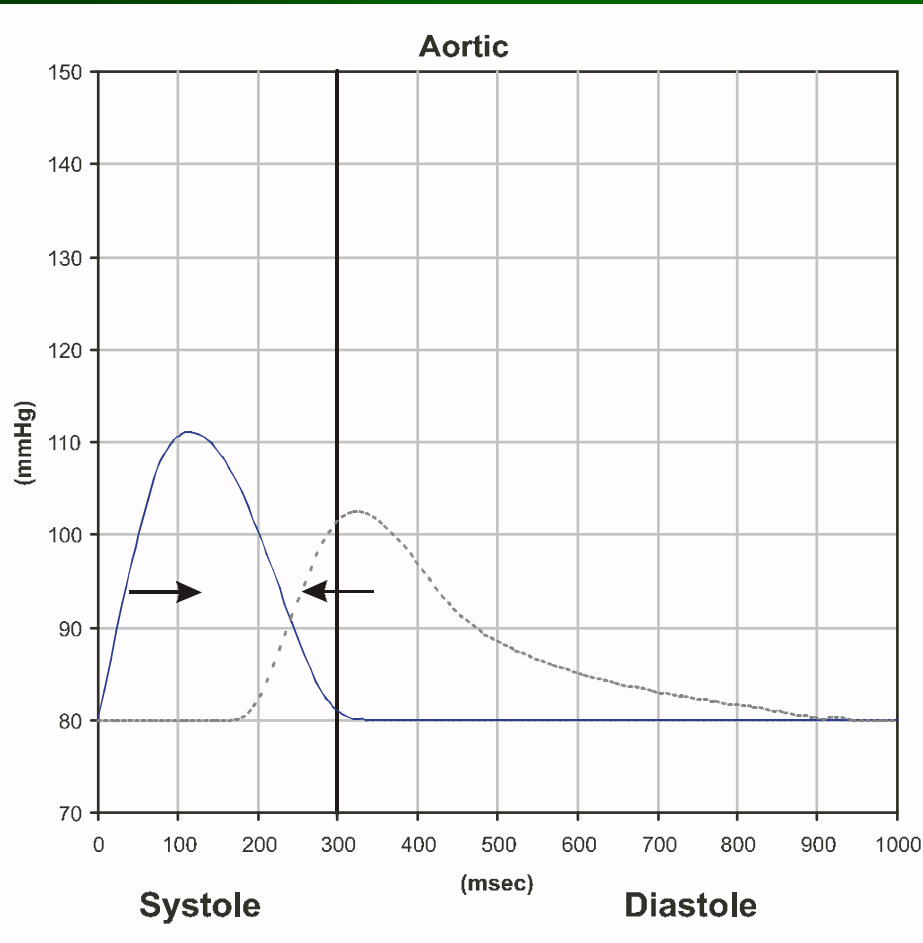
- is a composite of the forward pressure wave created by ventricular contraction and a reflected wave from peripheral arteries

Central Aortic Pressure Waveform



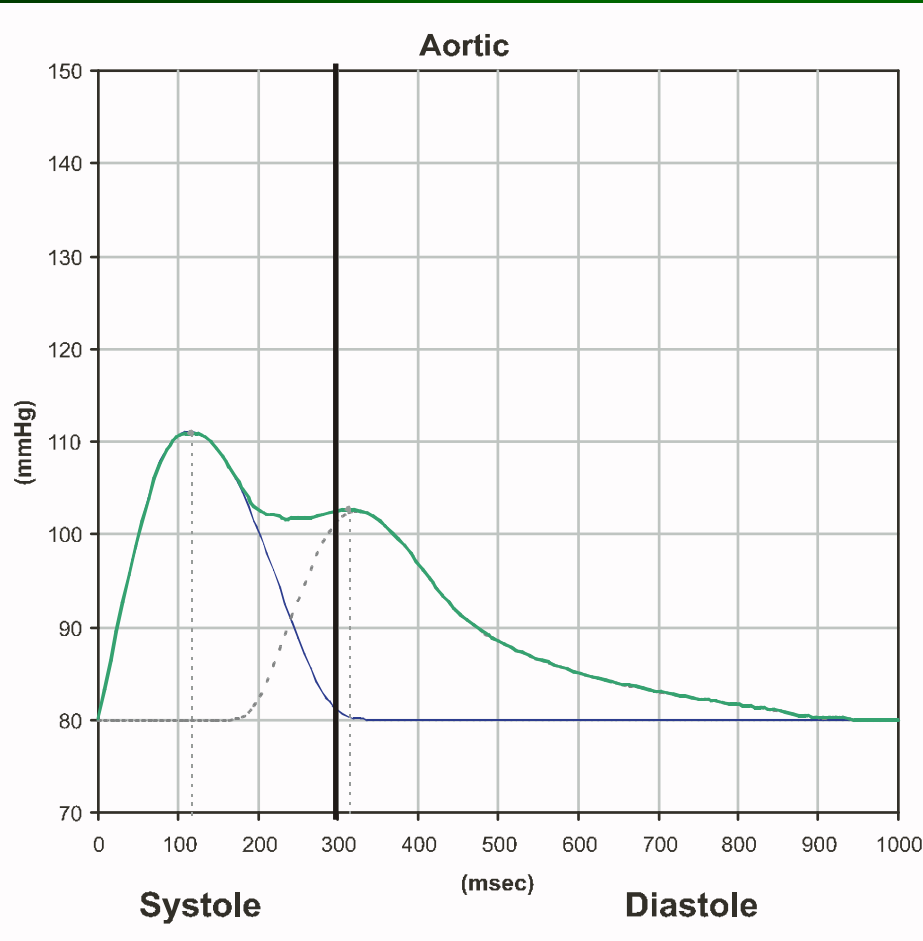
- Pressure waveform if there was no wave reflection (ie. the aorta was an open-ended tube providing a simple resistance to flow)

Central Aortic Pressure Waveform



- As the primary wave travels along the arteries it generates reflected waves from each bifurcation and from the peripheral vascular beds.
- all these small reflect-ed waves return to the heart, summing to create a reflected wave, starting even before the end of systole.

Central Aortic Pressure Waveform



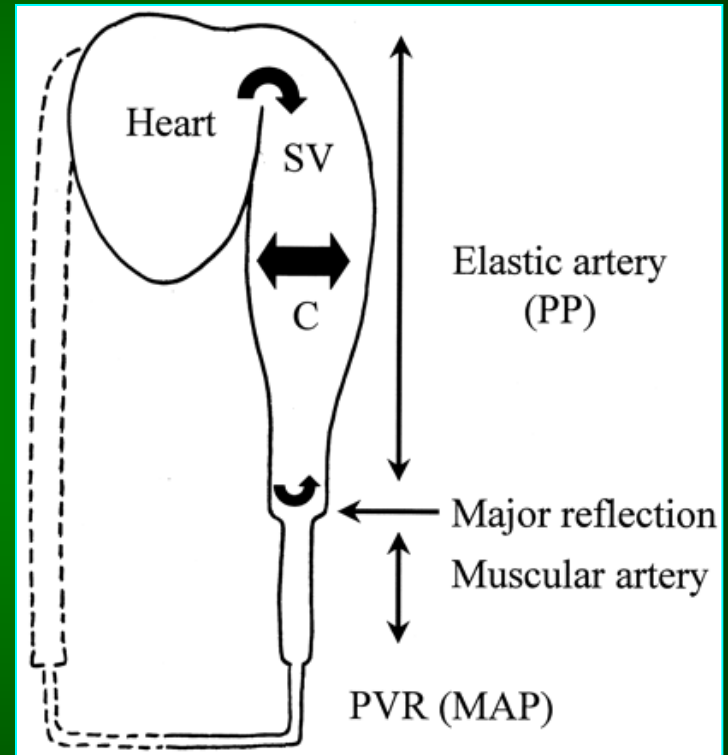
- The pressure in the aortic root is the sum of the outgoing and reflected wave (the green wave).
- note importantly how the reflected wave boosts the coronary artery perfusion pressure – the aortic root pressure – during diastole when over 95% of perfusion of the sub-endocardium takes place.

Central Aortic Pressure

Central aortic pressure parameters and LV load are determined not only by CO and PVR,

but also by

- the stiffness of conduit arteries and
- the timing and magnitude of pressure wave reflections

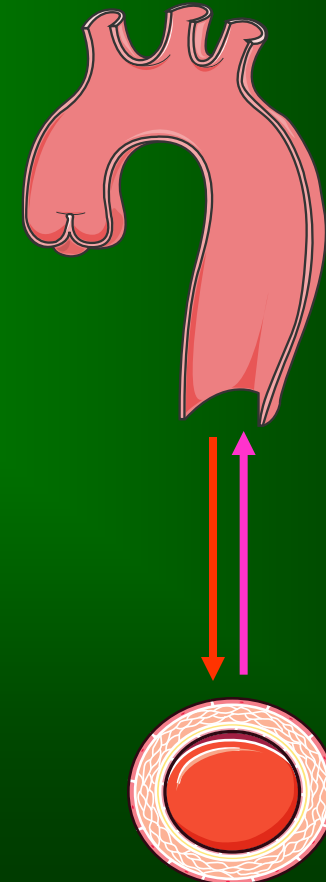
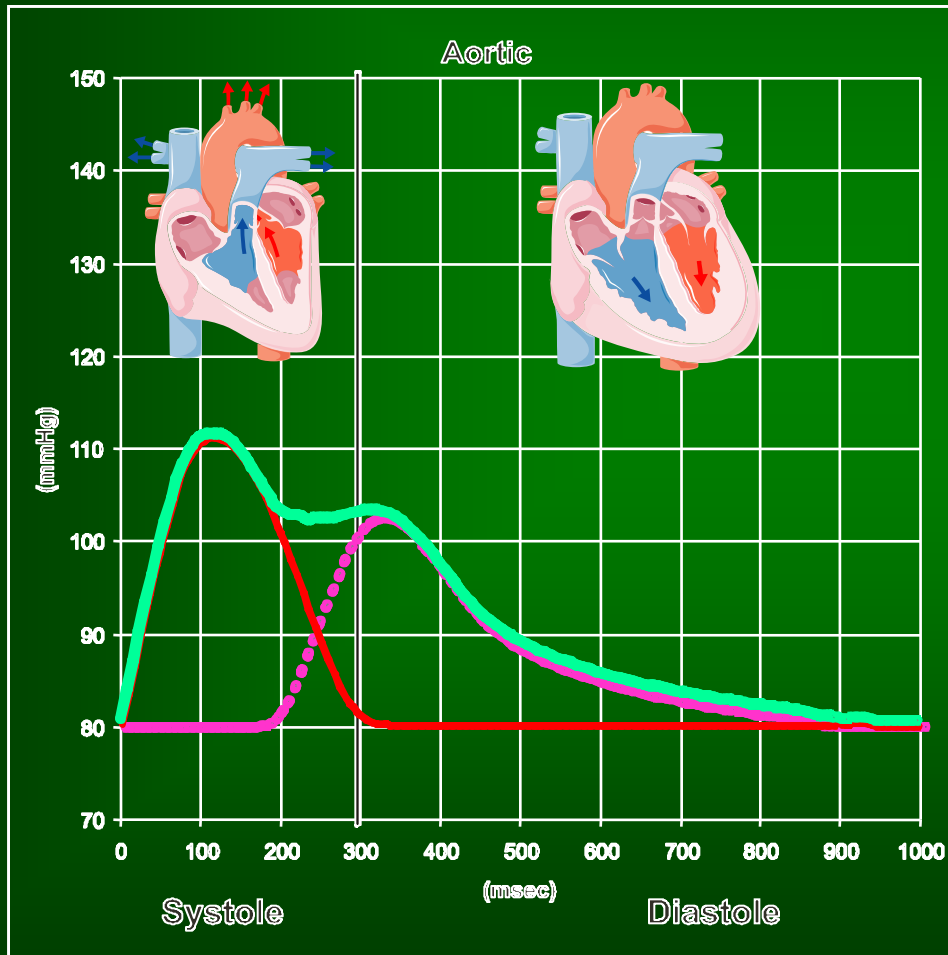


Arterial Stiffness and Central Aortic Pressure Waveform

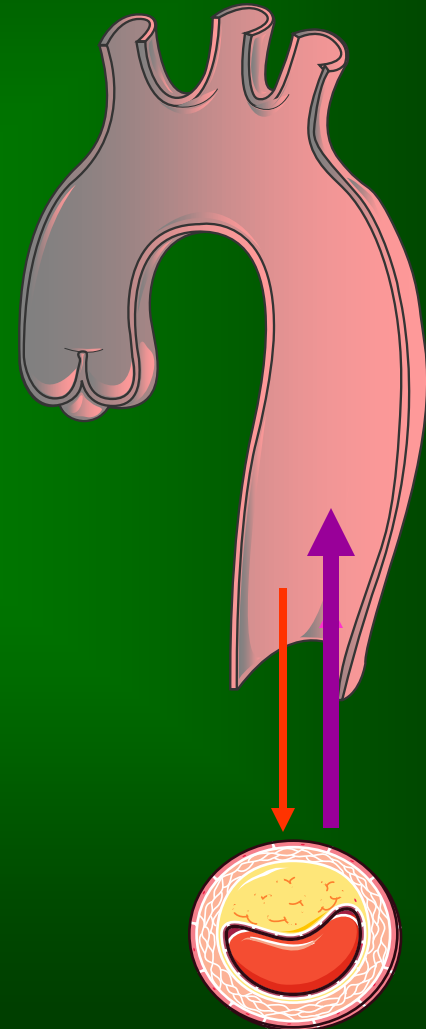
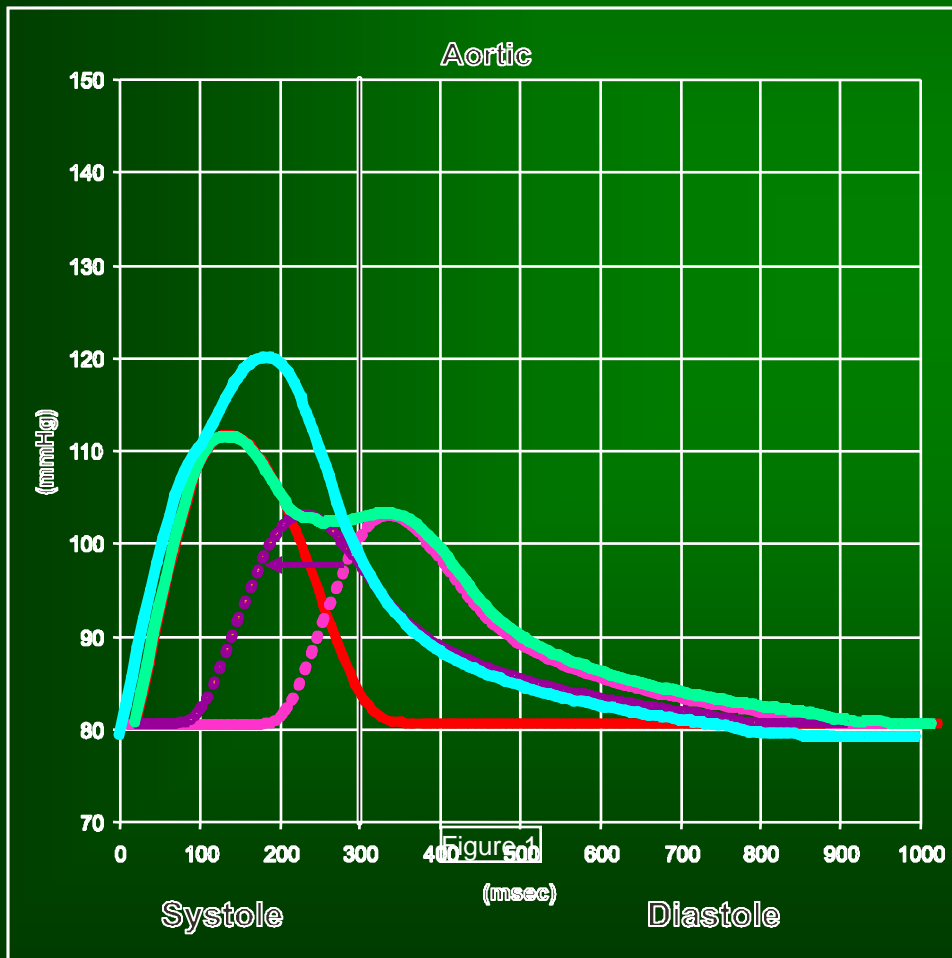
- In elastic vessels, because PWV is low, reflected wave tends to arrive back at the aortic root during diastole
- In the case of *stiff arteries* PWV increases and the reflected wave arrives back at the central arteries earlier, adding to the forward wave and augmenting the systolic pressure

Central aortic pressure waveform with compliant arteries

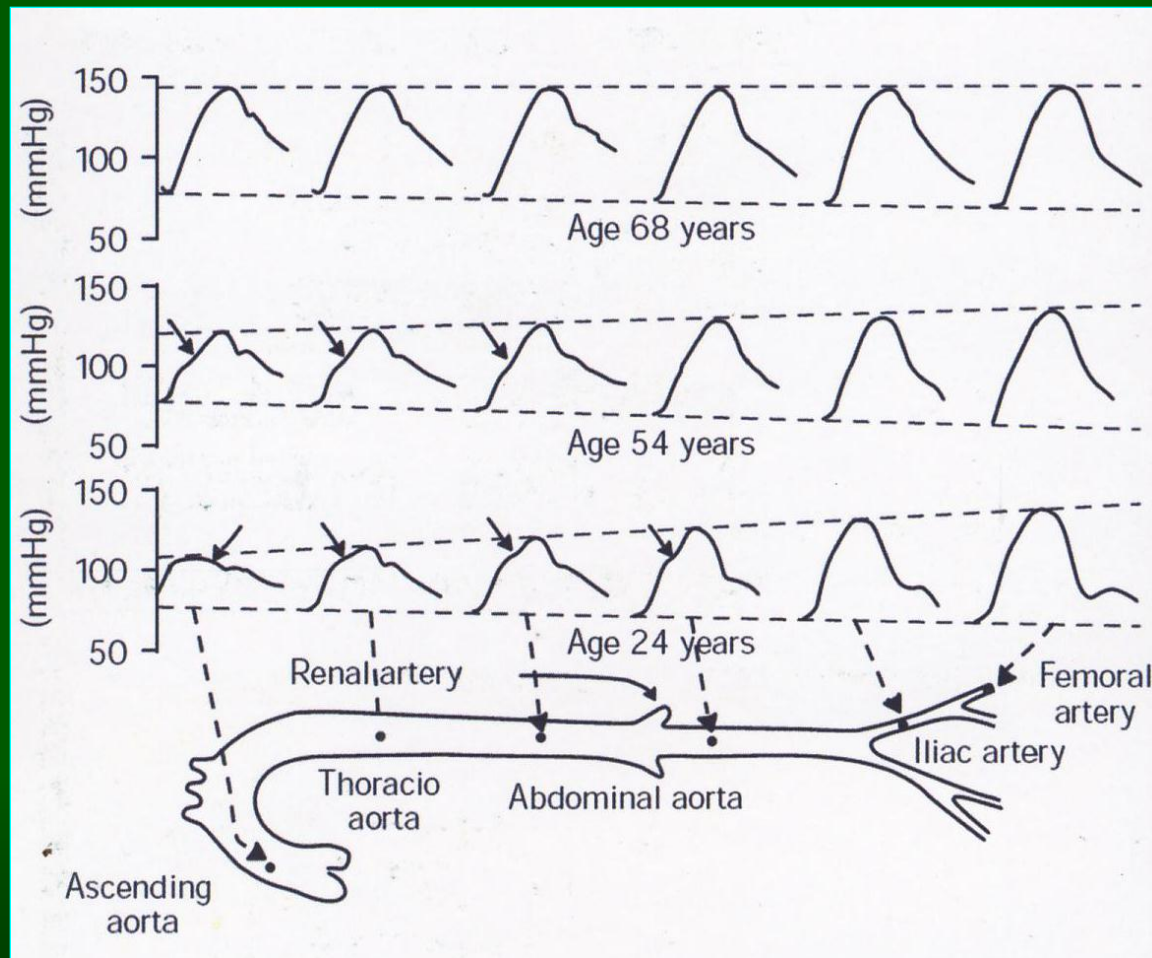
- Blood pressure in the aortic root is the sum of the outgoing and reflected wave.



Central aortic pressure waveform with stiff arteries



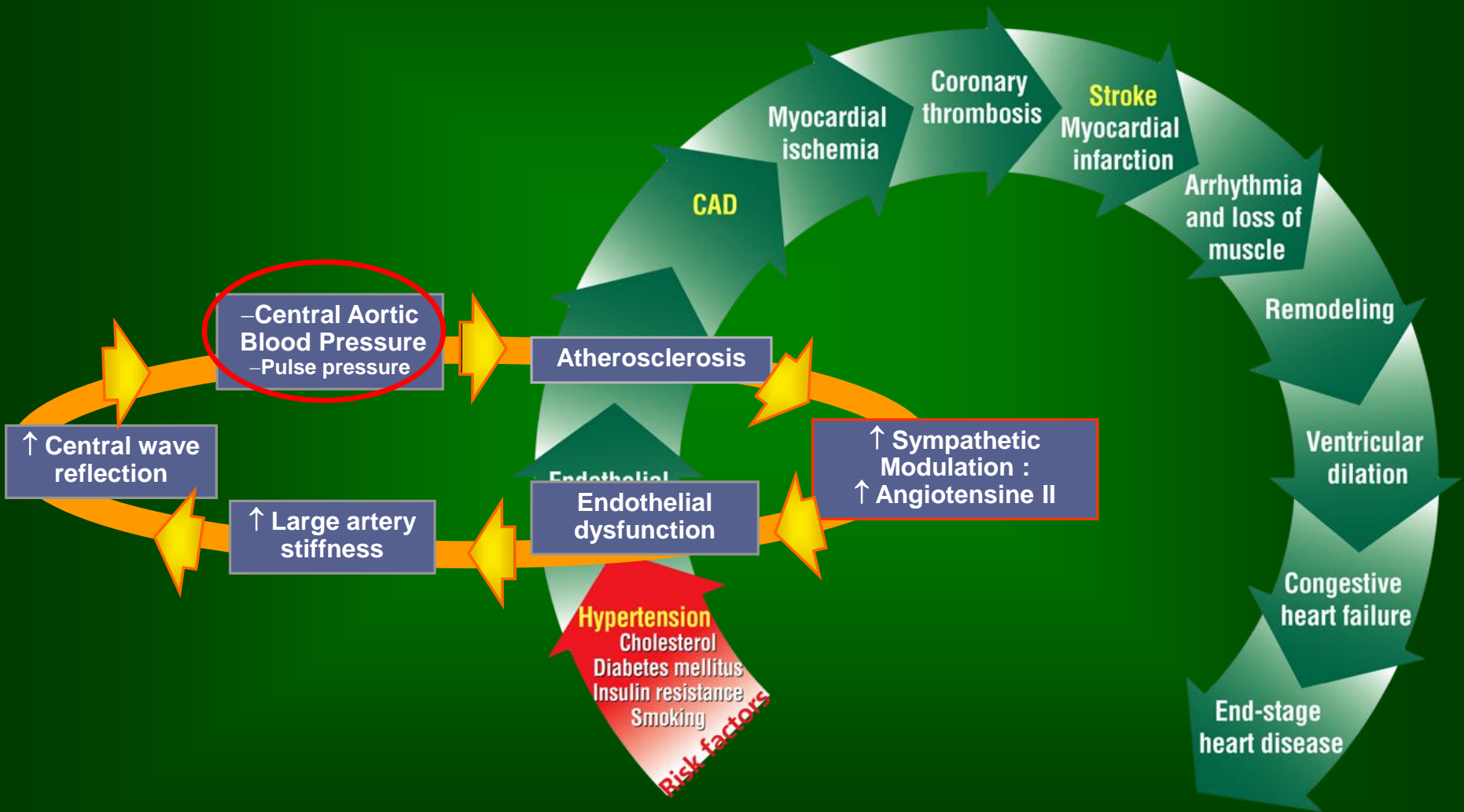
Changes of arterial waveform with age



Arterial Stiffness and Risk of Cardiovascular Events

Arterial stiffness is generally accepted as a predictive factor for cardiovascular morbidity and mortality

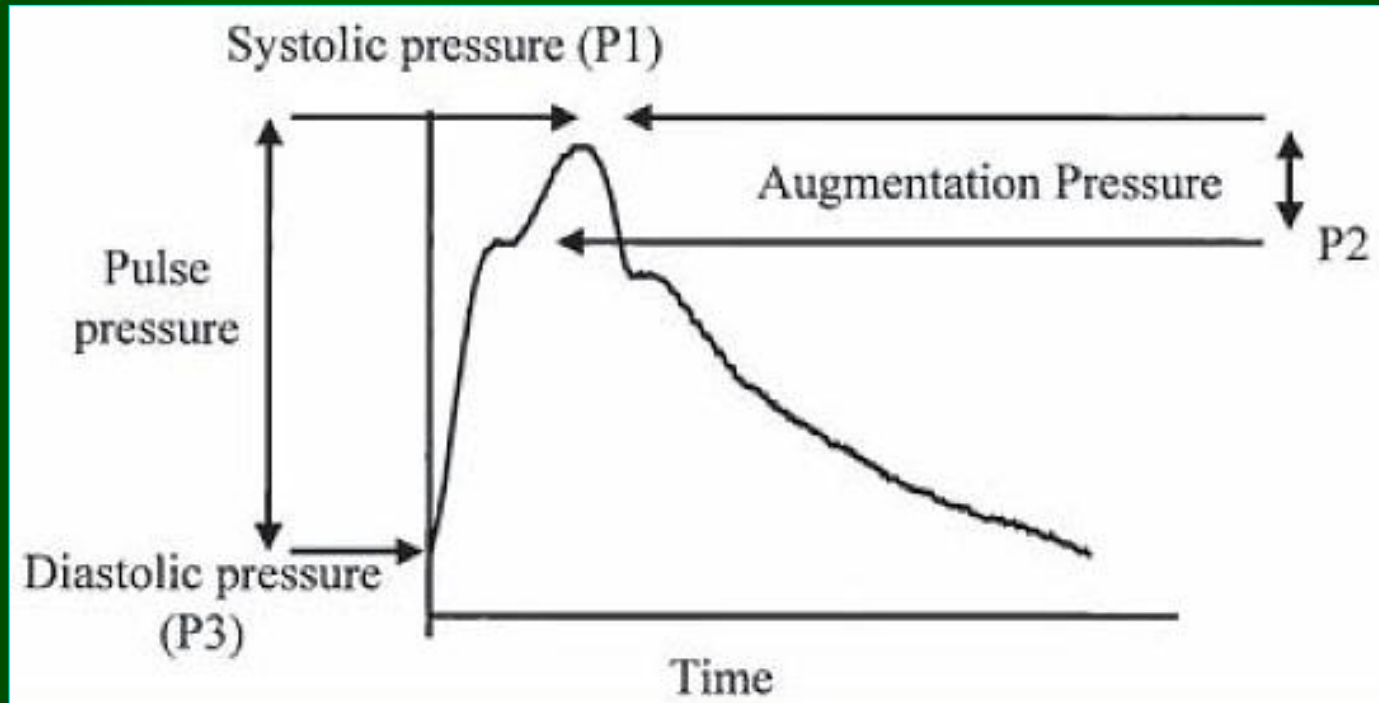
Atherosclerosis, arterial stiffness and central aortic pressure



Assessment of Arterial Stiffness

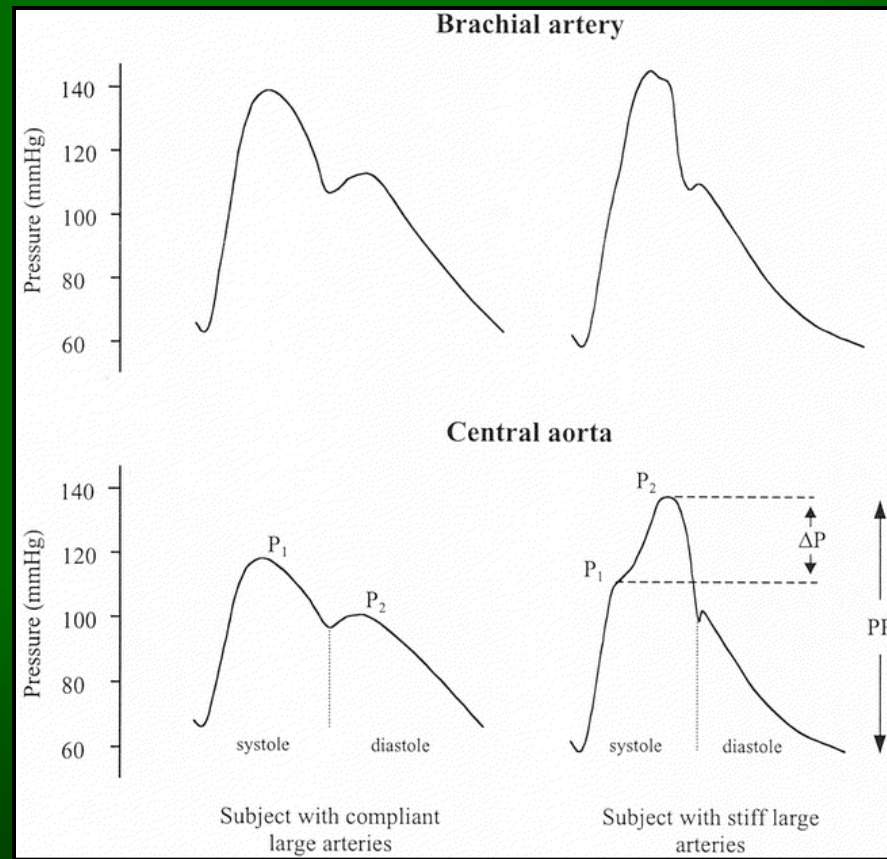
- ❖ Pulse pressure
- ❖ Pulse wave velocity (PWV)
- ❖ Central pulse wave analysis:
 - central pulse pressure
 - central systolic pressure
 - augmentation index

Central pulse waveform analysis

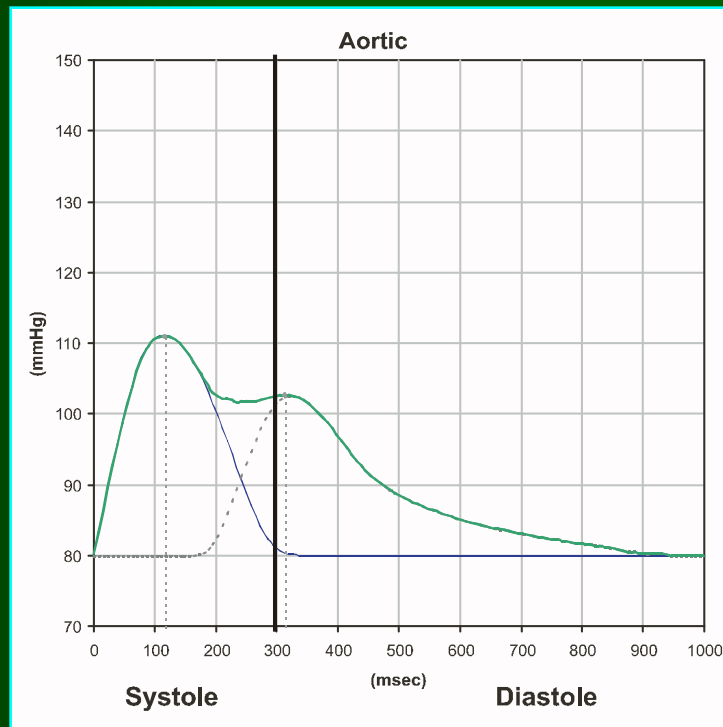


Augmentation index: $100 \times (P1 - P3) / (P2 - P3)$

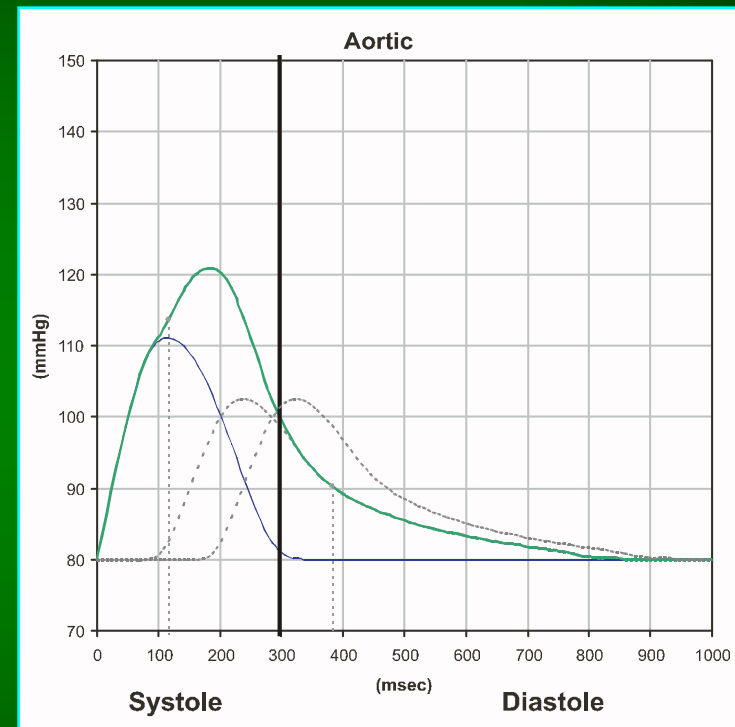
Pulse pressure amplification in brachial artery and central aorta in subjects with compliant and stiff large arteries



Clinical implications of central aortic pressure in patients with stiff arteries



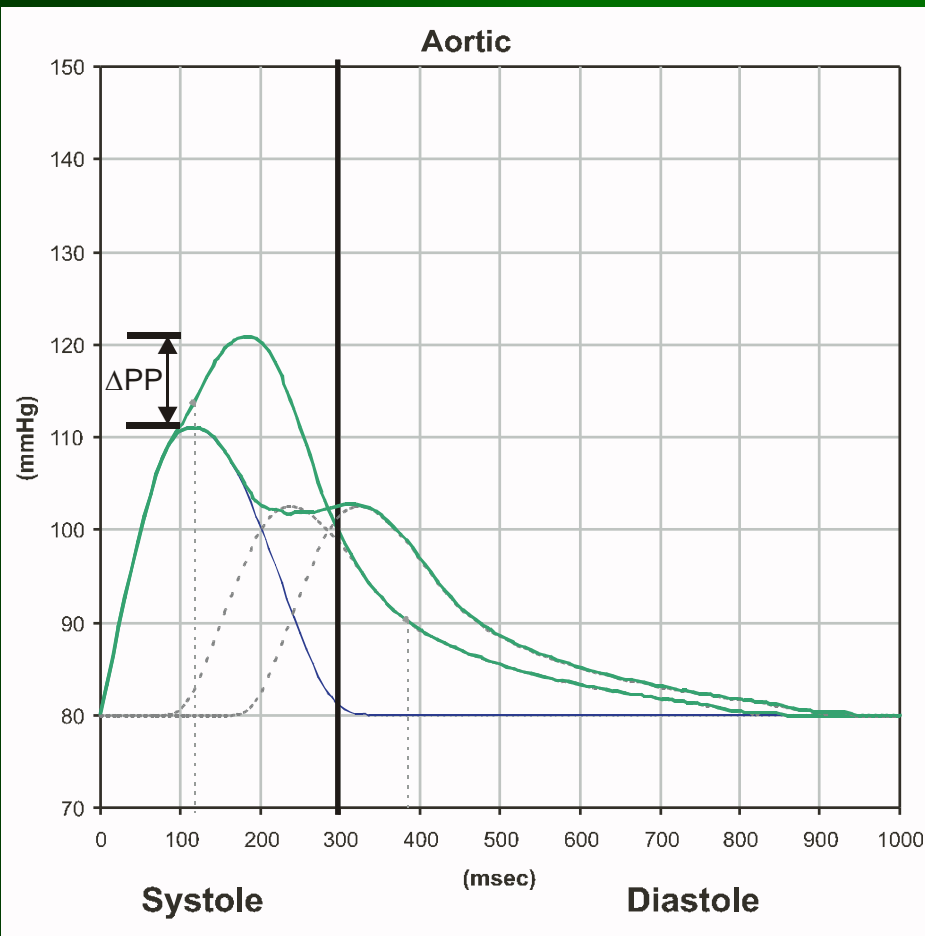
Compliant arteries



Stiff arteries

- patients with arterial stiffness has a very different aortic pressure waveform.
- This has three important clinical implications.

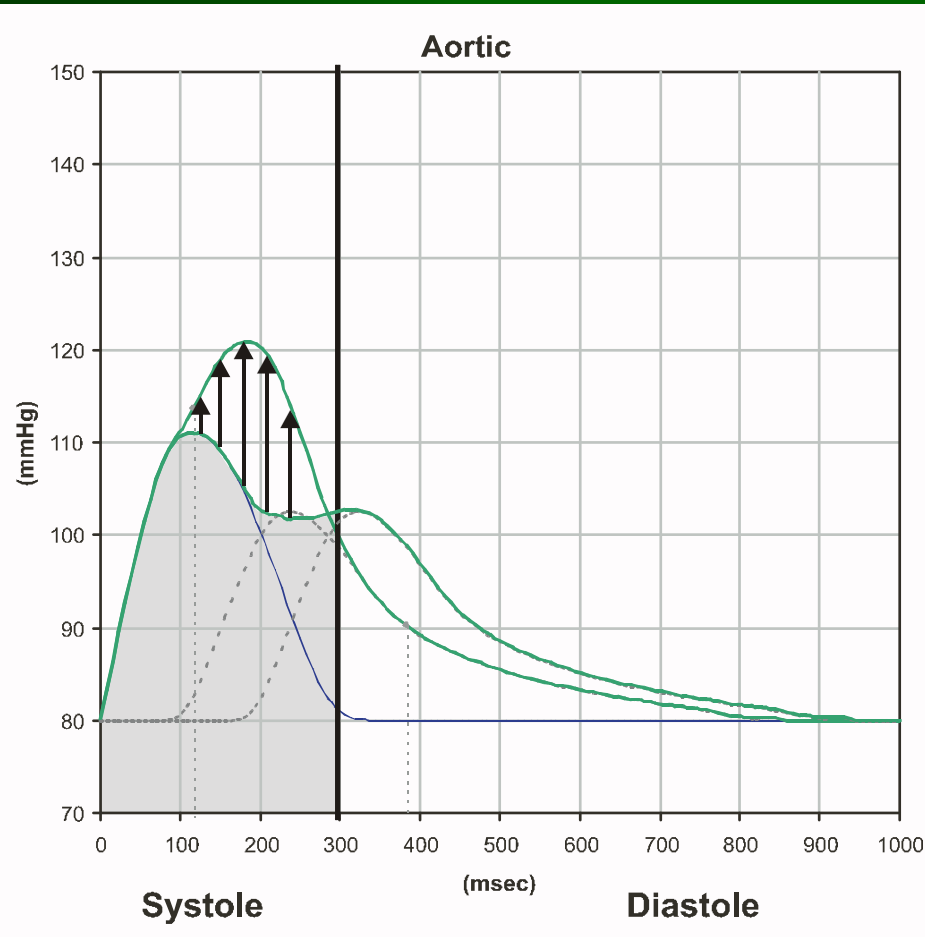
Central aortic pressure in patients with stiff arteries



3 important clinical implications:

- First, the central systolic pressure and central pulse pressure is increased.
 - an increase in the central pulse pressure that drives cerebral blood flow increases stroke risk.
- * *This change in central systolic pressure can occur without any changes occurring in peripheral cuff systolic pressure.*

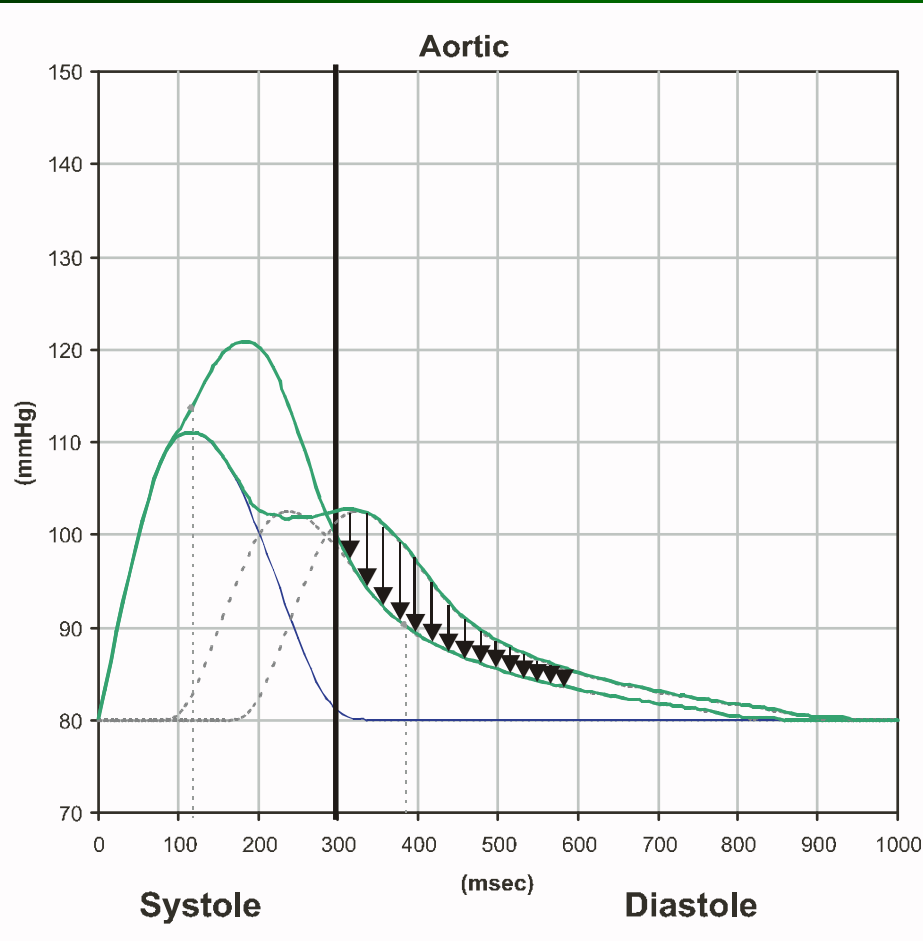
Central aortic pressure in patients with stiff arteries



3 important clinical implications:

- Second, there is an increase in left ventricular load (LV load).
- increase in LV load accelerates increase in LV mass and increases risk of LV hypertrophy

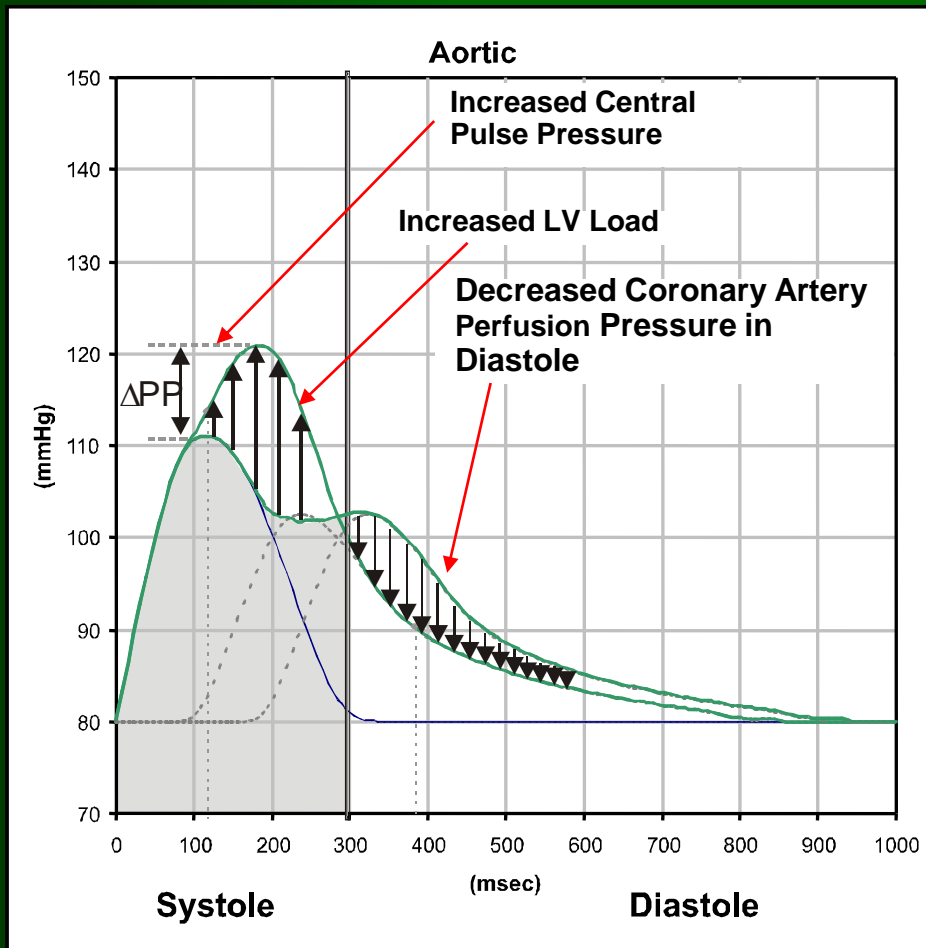
Central aortic pressure in patients with stiff arteries



3 important clinical implications:

- Third, the pressure that is perfusing the coronary arteries during diastole is reduced, increasing the risk of myocardial ischemia.

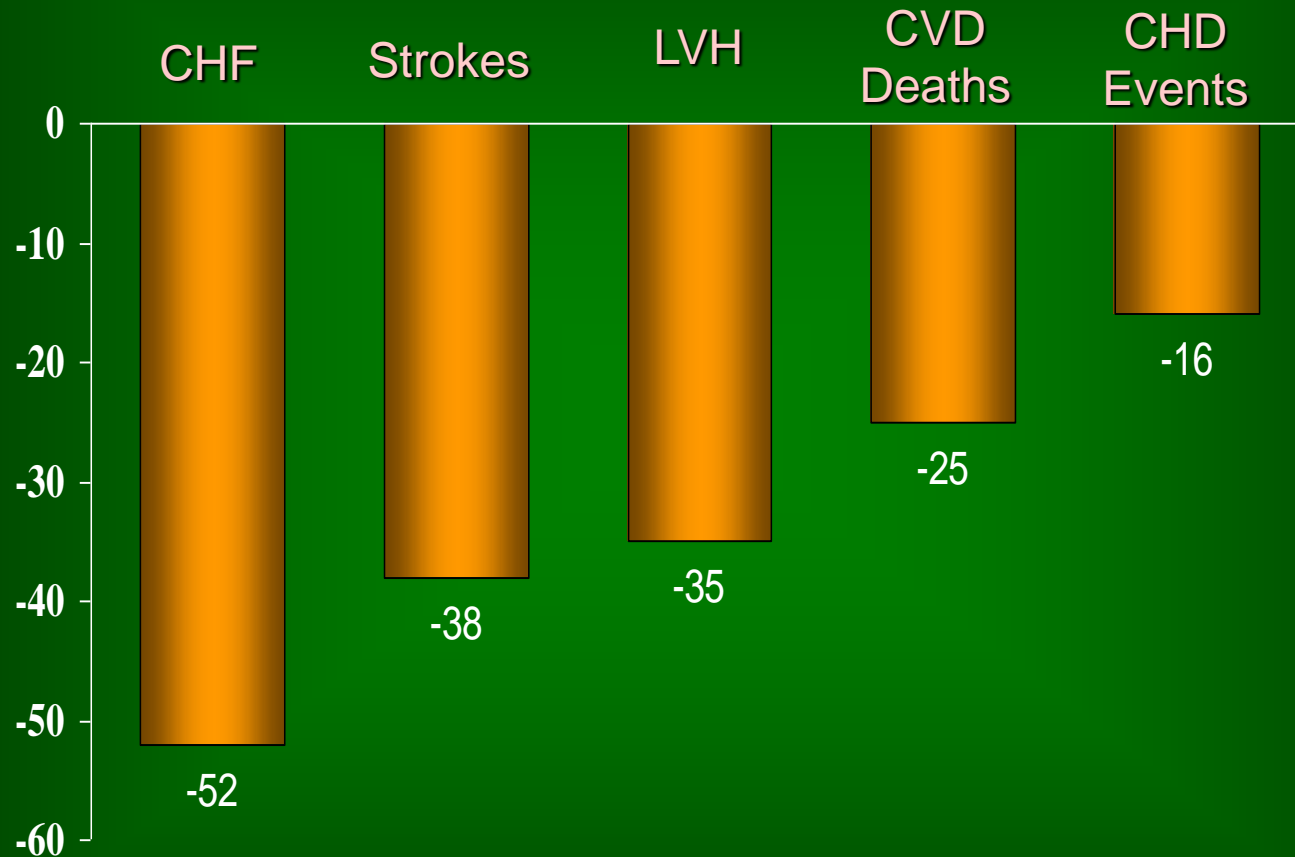
Increased arterial stiffness independently increases the risk of all three major CV outcomes



- This earlier return to the heart of the reflected pressure wave (due to stiffening of the arteries) changes the aortic root pressure waveform, ... with 3 key clinical implications
- Central pulse pressure increases ... increasing risk of stroke and renal failure
- LV Load increases.... increasing LV mass, and accelerating progress towards LV hypertrophy and heart failure
- Coronary artery perfusion pressure in diastole reduces.... increasing risk of myocardial ischemia

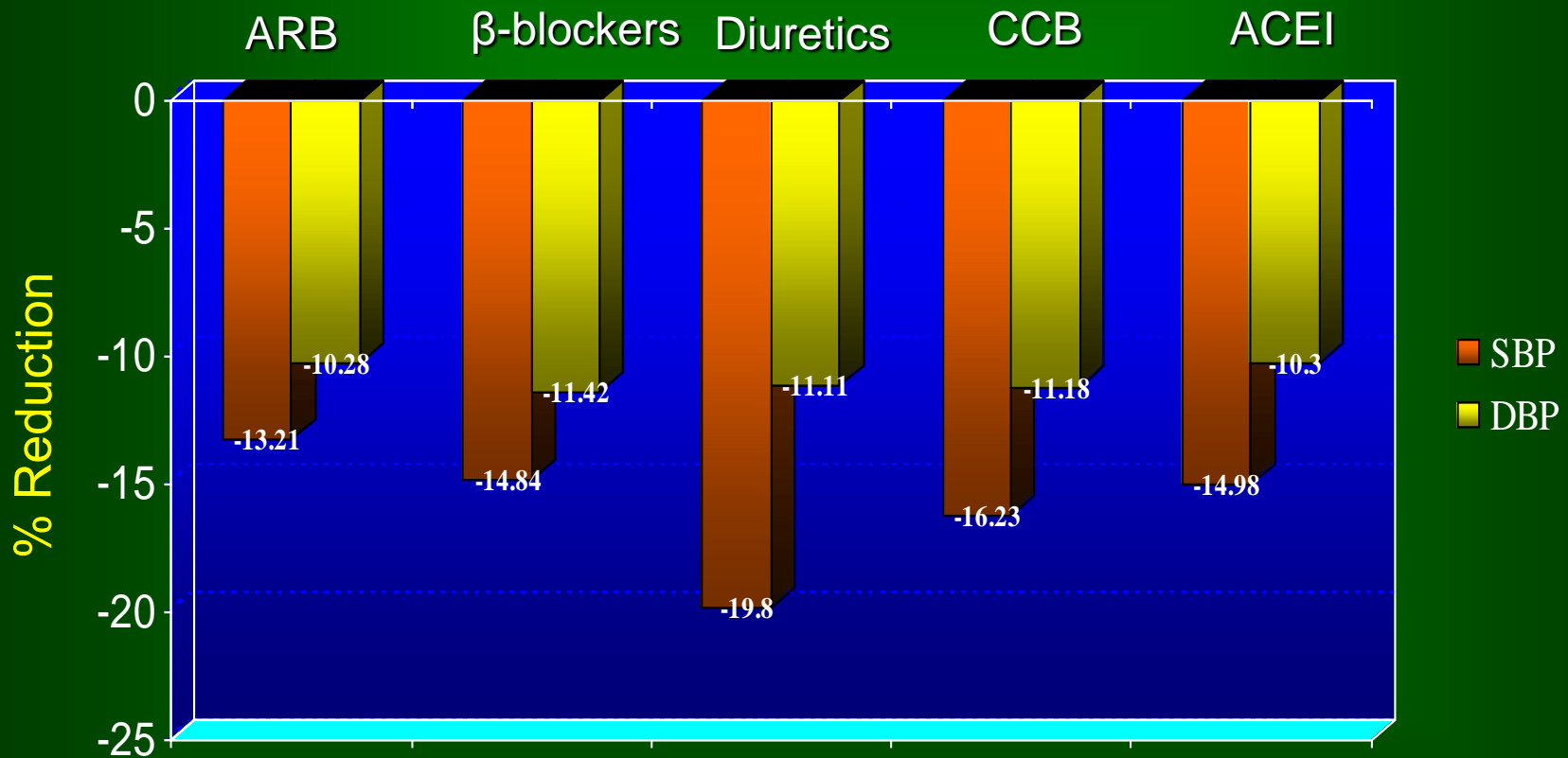
Impact of antihypertensive
drug treatment on
cardiovascular outcome

Effects of Antihypertensive Drug Treatment on CV Mortality and Morbidity



Combined result from 17 randomised, placebo-controlled treatment trials; decreased in events-treated compared to control

BP Reduction by Drug Classes



The Anglo-Scandinavian Cardiac Outcomes Trial



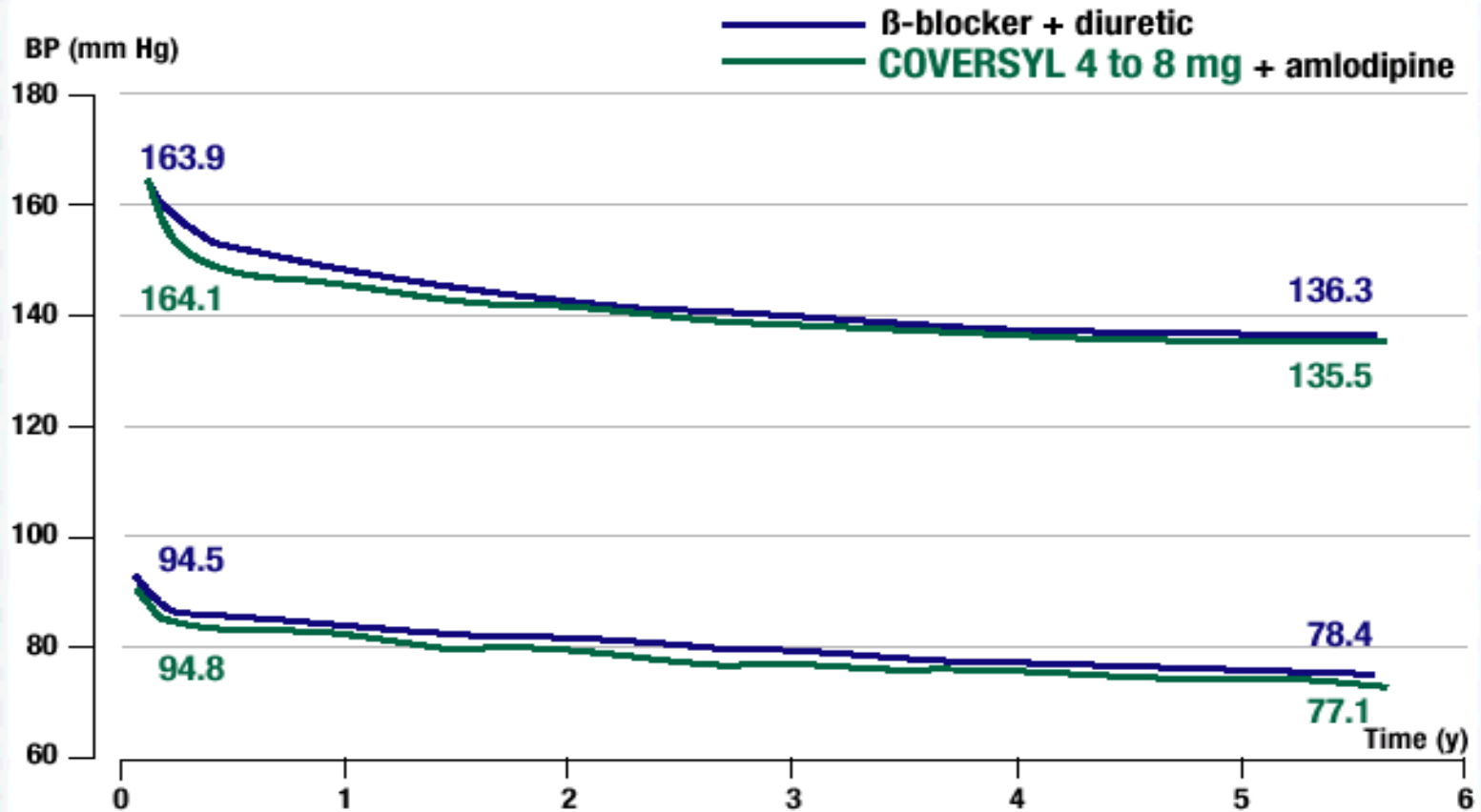
Randomised controlled trial of prevention of CHD and other vascular events by blood pressure lowering and by cholesterol lowering

ASCOT: *Primary Objectives*

- ❑ To assess non fatal MI and fatal CHD of the standard anti-hypertensive regimen (β -blocker +/- diuretic) with a more contemporary regimen (Ca channel blocker +/- ACE inhibitor)
- ❑ To compare the effect on non fatal MI and fatal CHD of a statin vs. placebo among patients with a total cholesterol ≤ 6.5 mmol/l

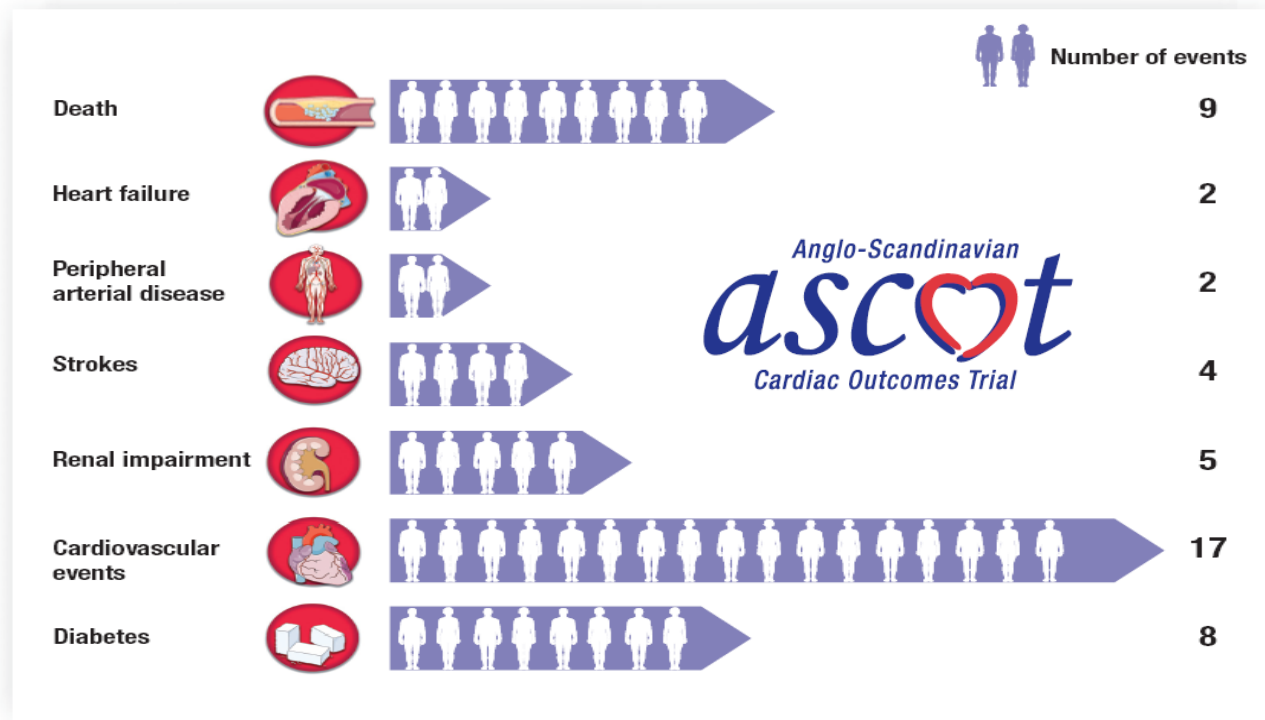
ASCOT:BPLA

Same degree of BP reduction with
Perindopril/Amlodipine and Atenolol/Thiazide



Is it sufficient to control brachial BP to prevent cardiovascular outcome?

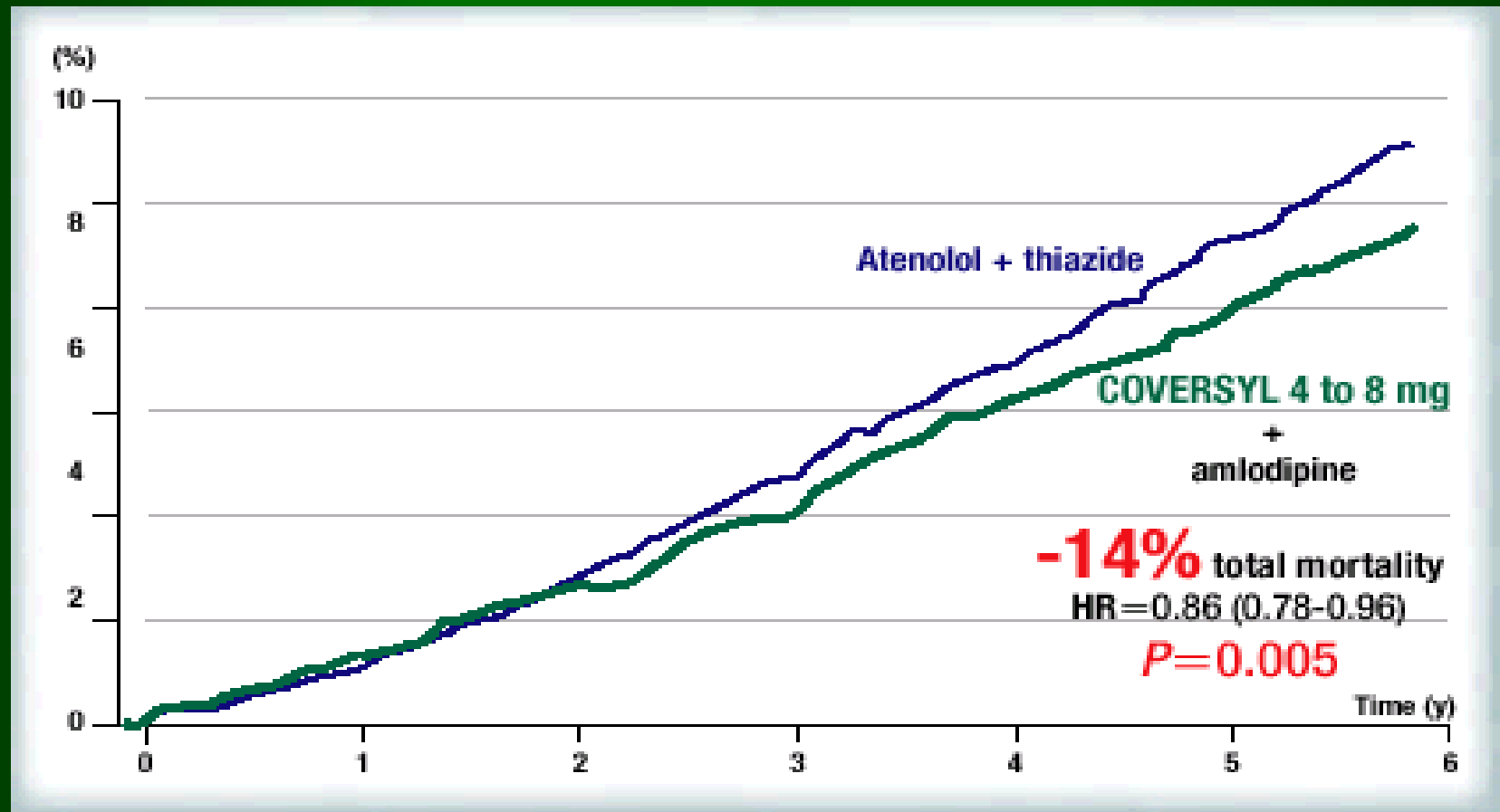
Follow up of 100 hypertensives treated with β -blocker + diuretic for 4/6 years⁵



= 47 events/100 treated patients!

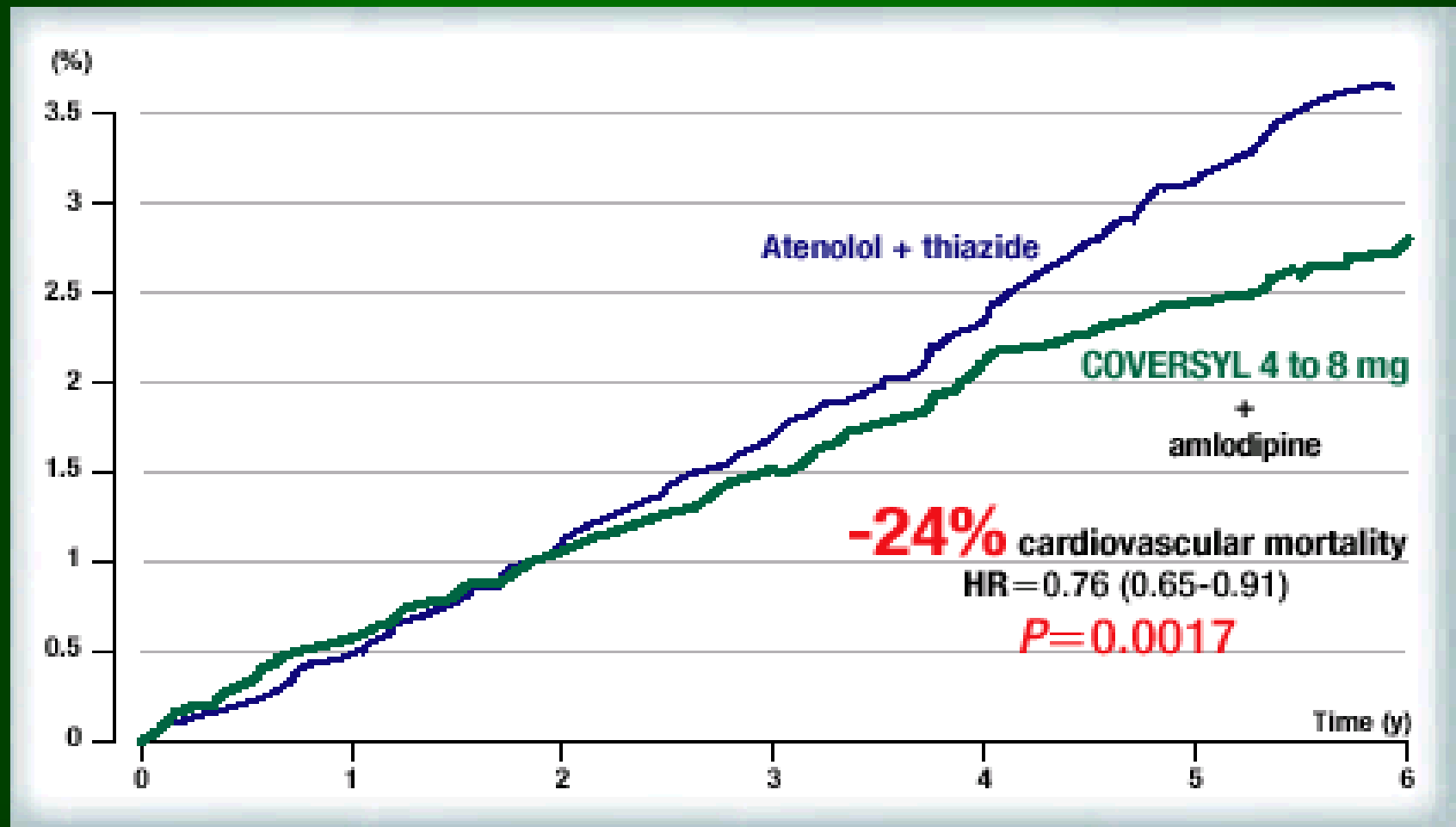
ASCOT: BPLA

All-cause Mortality: -14% reduction



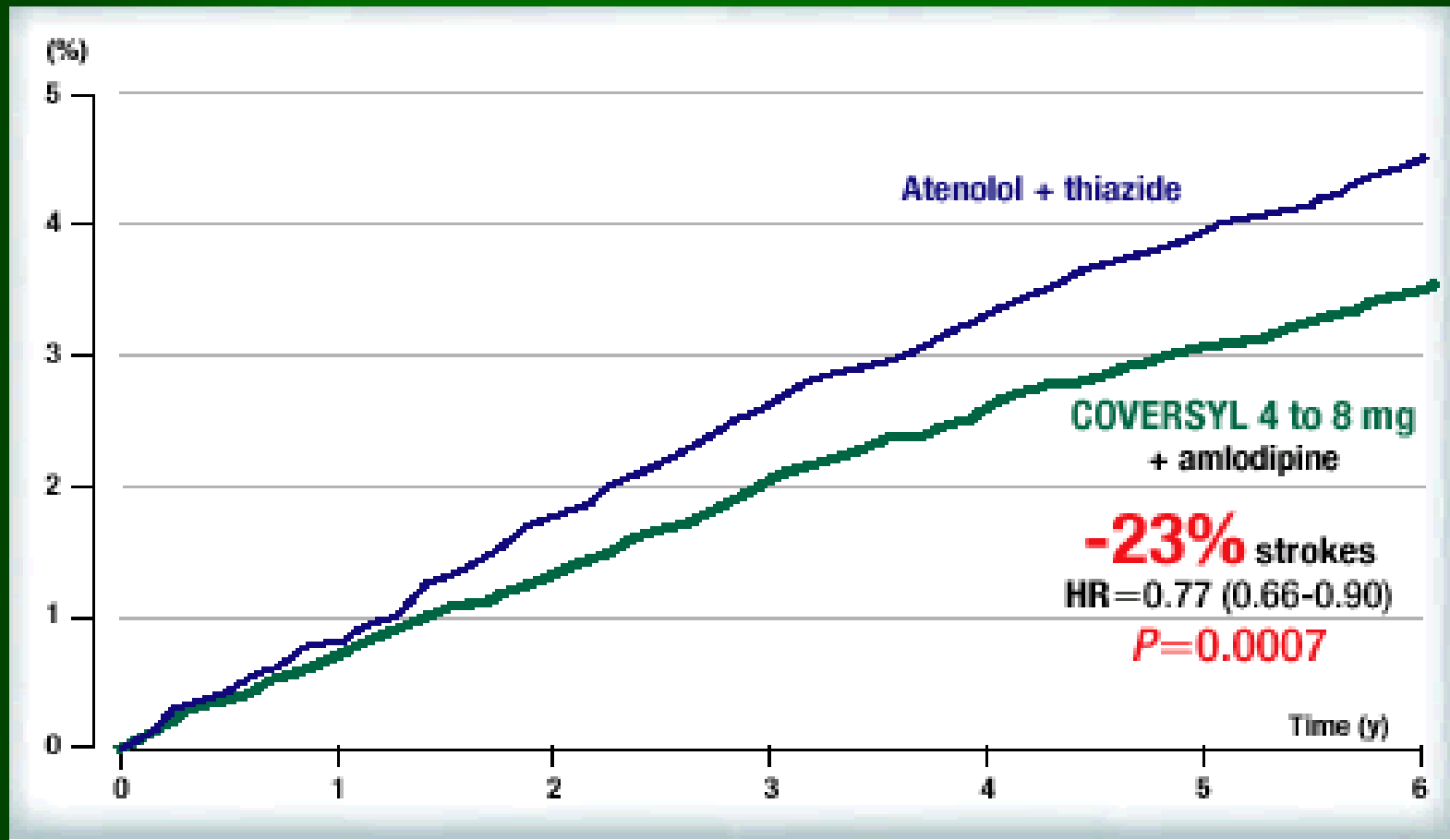
ASCOT: BPLA

Cardiovascular Mortality: -24% reduction



ASCOT: BPLA

Fatal and Nonfatal Strokes: -23% reduction



ASCOT showed long-term superiority of Amlodipin/Perindopril regimen compared to Atenolol/Thiazide regimen with respect to CV events with similar BP control

What is the missing link ?

- ❖ Different effects of drug classes on central aortic pressure parameters may be a potential mechanism to explain the different clinical outcomes between two treatment arms in ASCOT Trial

The CAFÉ Study

Circulation American Heart Association
JOURNAL OF THE AMERICAN HEART ASSOCIATION Learn and Live.

Letter by Cameron et al Regarding Article, "Differential Impact of Blood Pressure-Lowering Drugs on Central Aortic Pressure and Clinical Outcomes: Principal Results of the Conduit Artery Function Evaluation (CAFÉ) Study"
James D. Cameron, Ian T. Meeklethor and Sarah A. Hope
Circulation 2006;114:538

DOI: 10.1161/CIRCULATIONAHA.106.628842
7234
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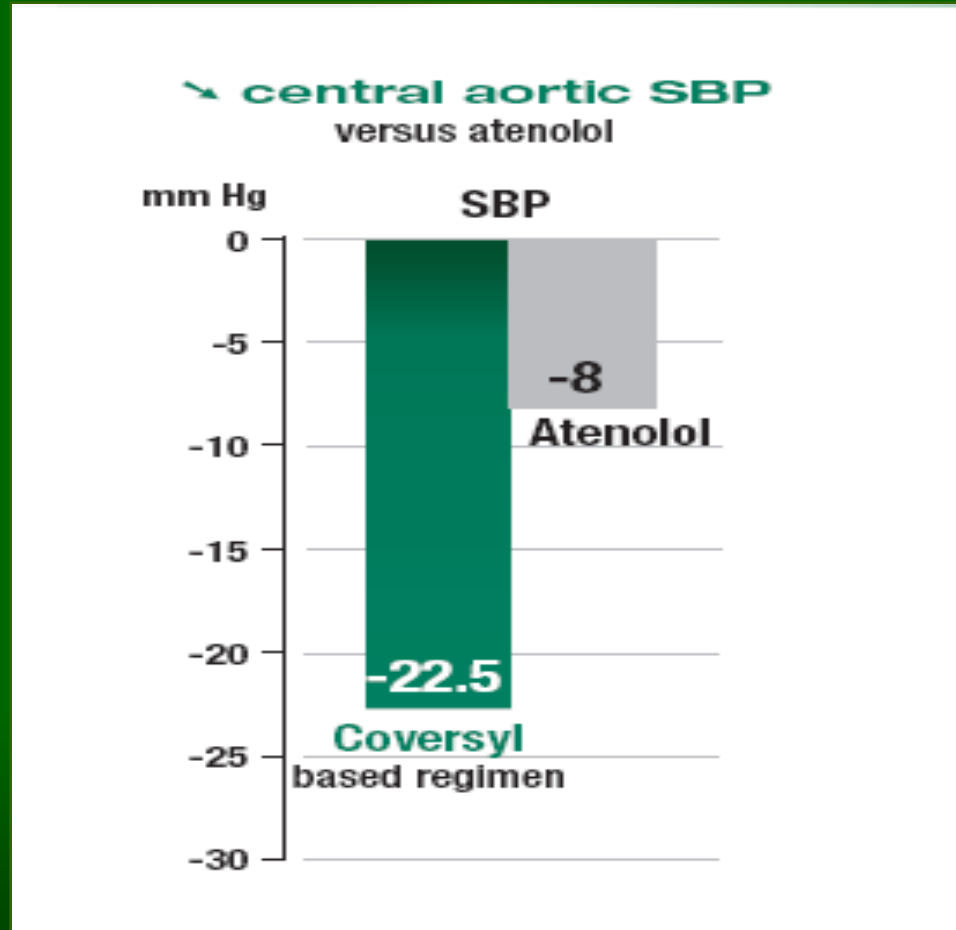
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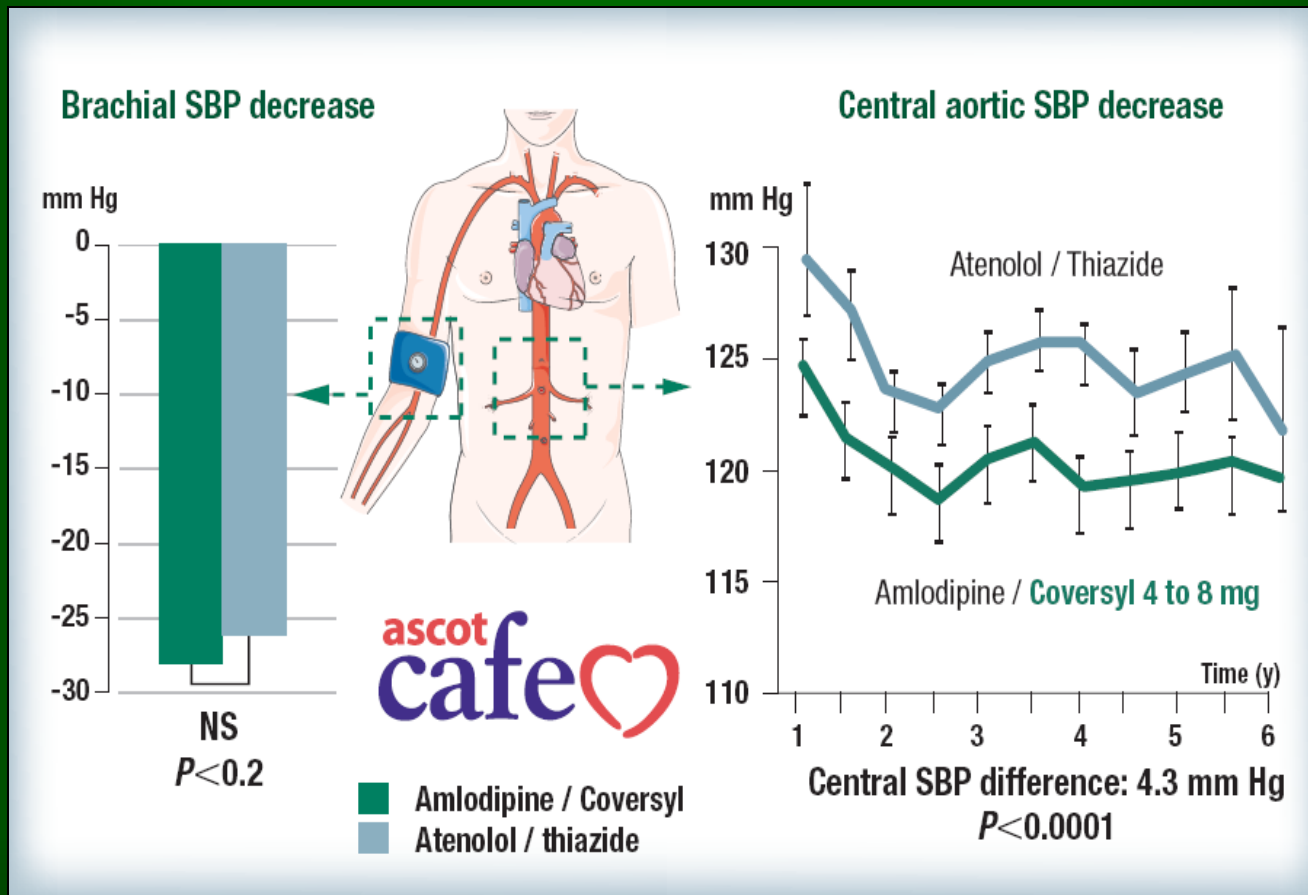
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❖ The Conduit Artery Function Evaluation (CAFÉ) study, a substudy of ASCOT examined the impact of two different BP lowering-regimens on central aortic pressures and haemodynamics.

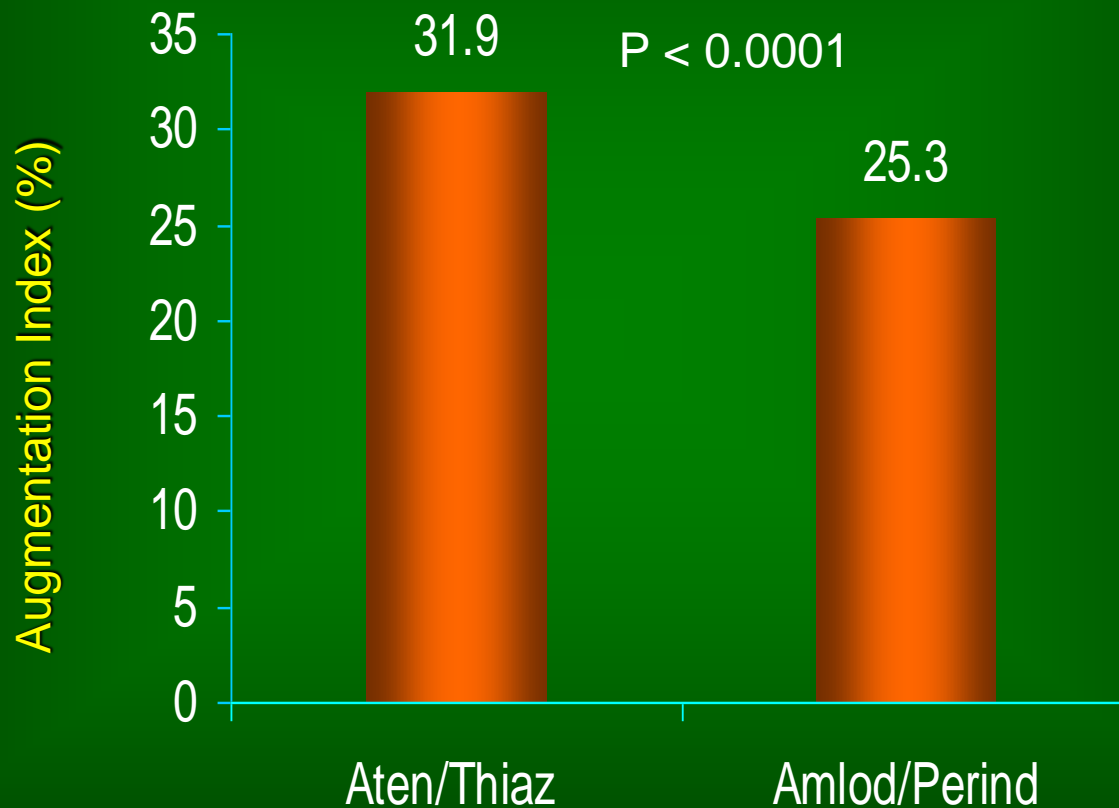
Effects of Perindopril based regimen and Atenolol based regimen on central aortic SBP



Difference in brachial SBP and central aortic BP in CAFÉ study



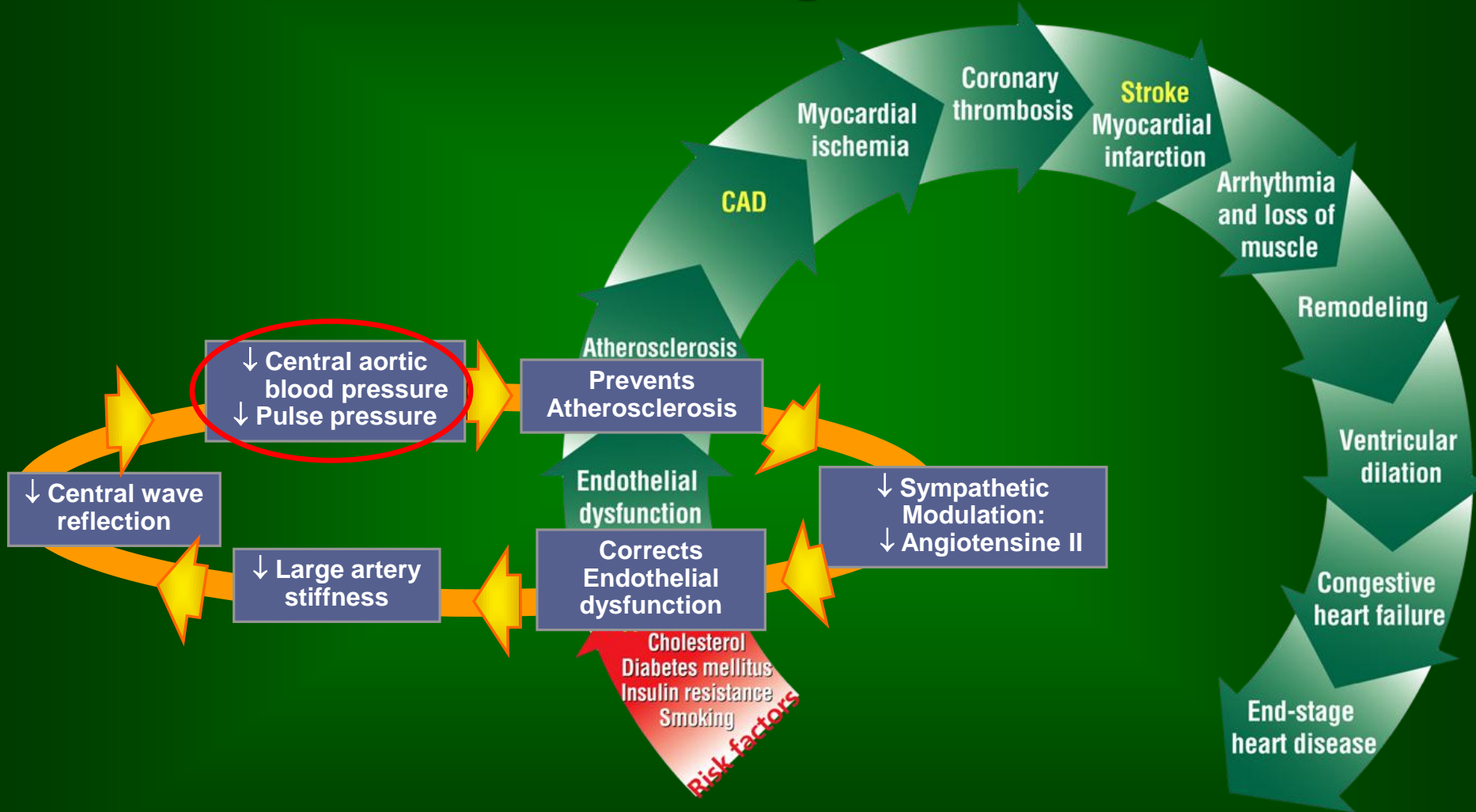
Lower Augmentation Index with Amlodipine/Perindopril regimen



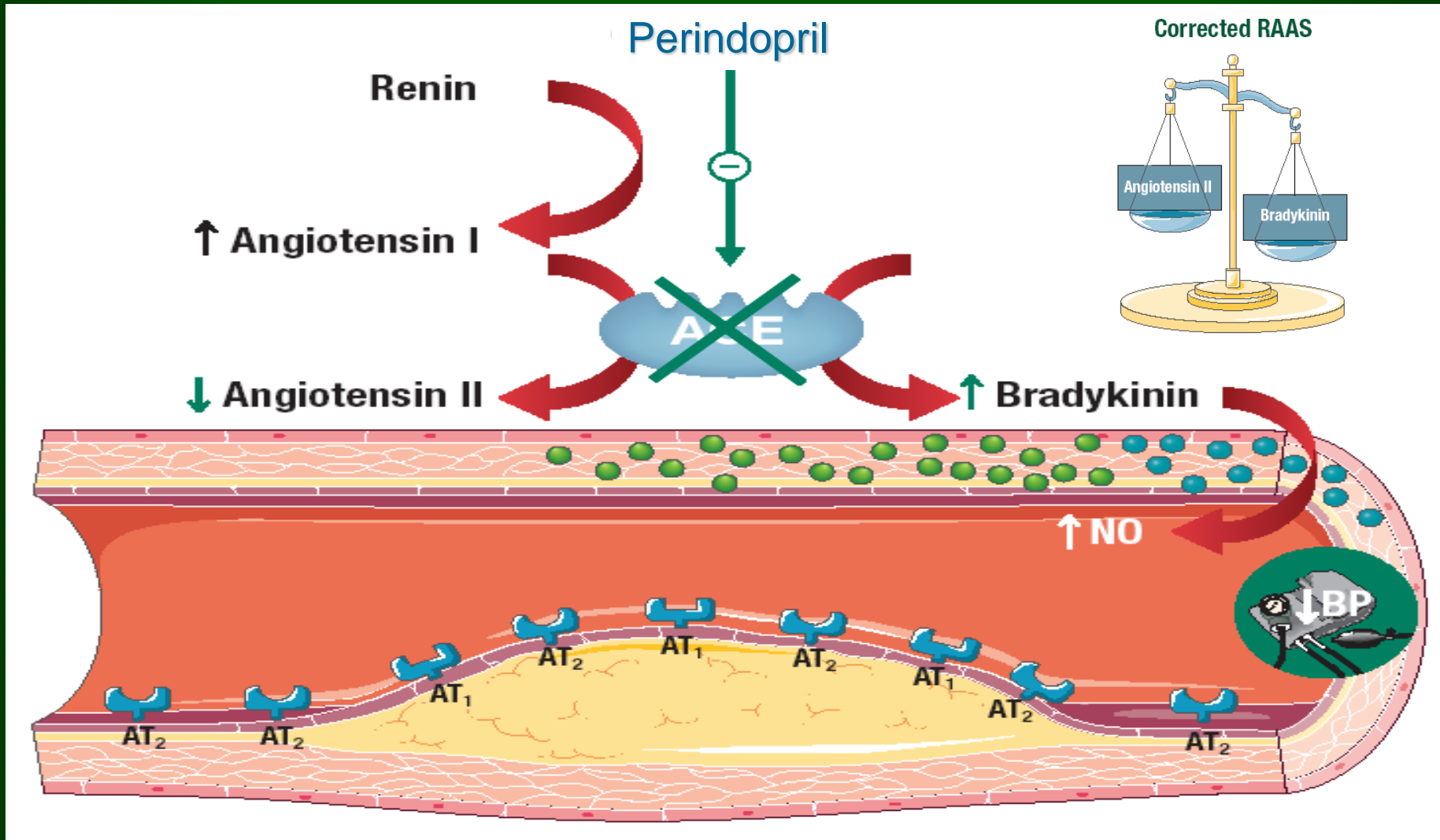
CAFÉ: Summary

- Amlodipine ± Perindopril showed substantial and consistent difference in central aortic BP and haemodynamics compared to Atenolol/Thiazide, despite similar brachial SBP changes
- Differential effects on Central aortic SBP and central aortic PP may explain the differences in clinical outcomes observed in ASCOT-BPLA
- Central aortic PP may be a determinant of CV outcome

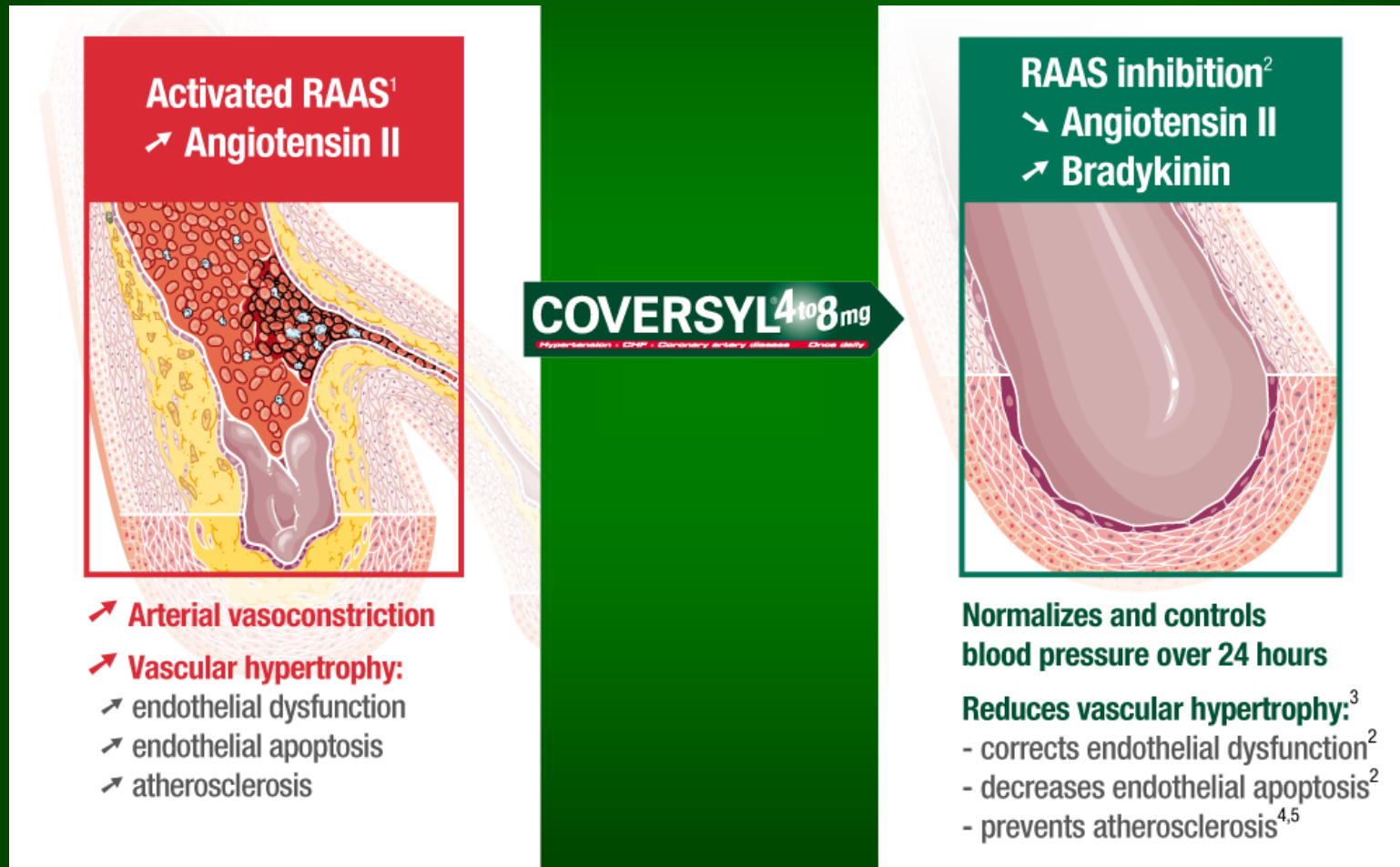
How Perindopril decreases central aortic pressure?



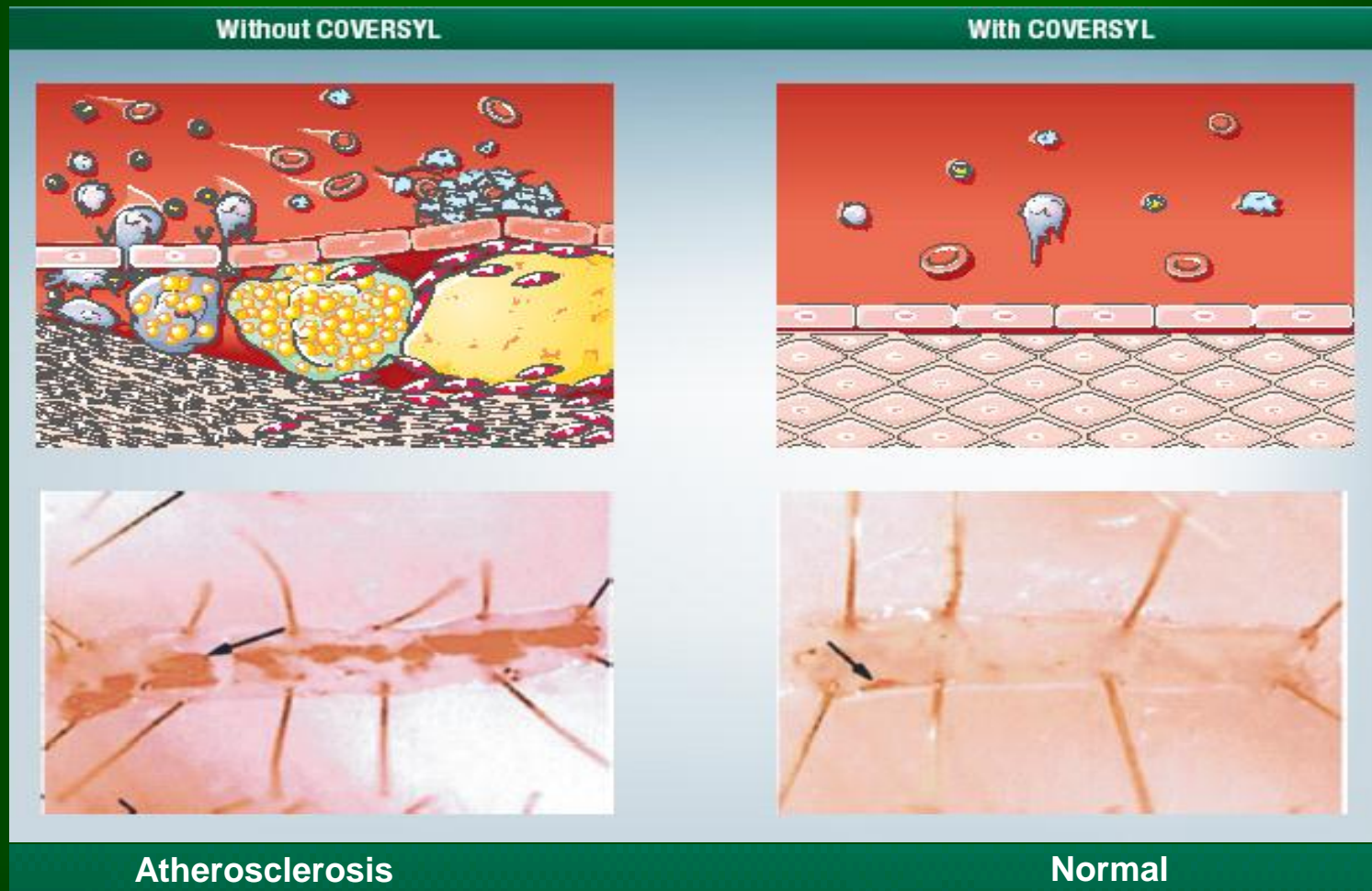
Perindopril decreases angiotensin II and increases bradykinin and NO



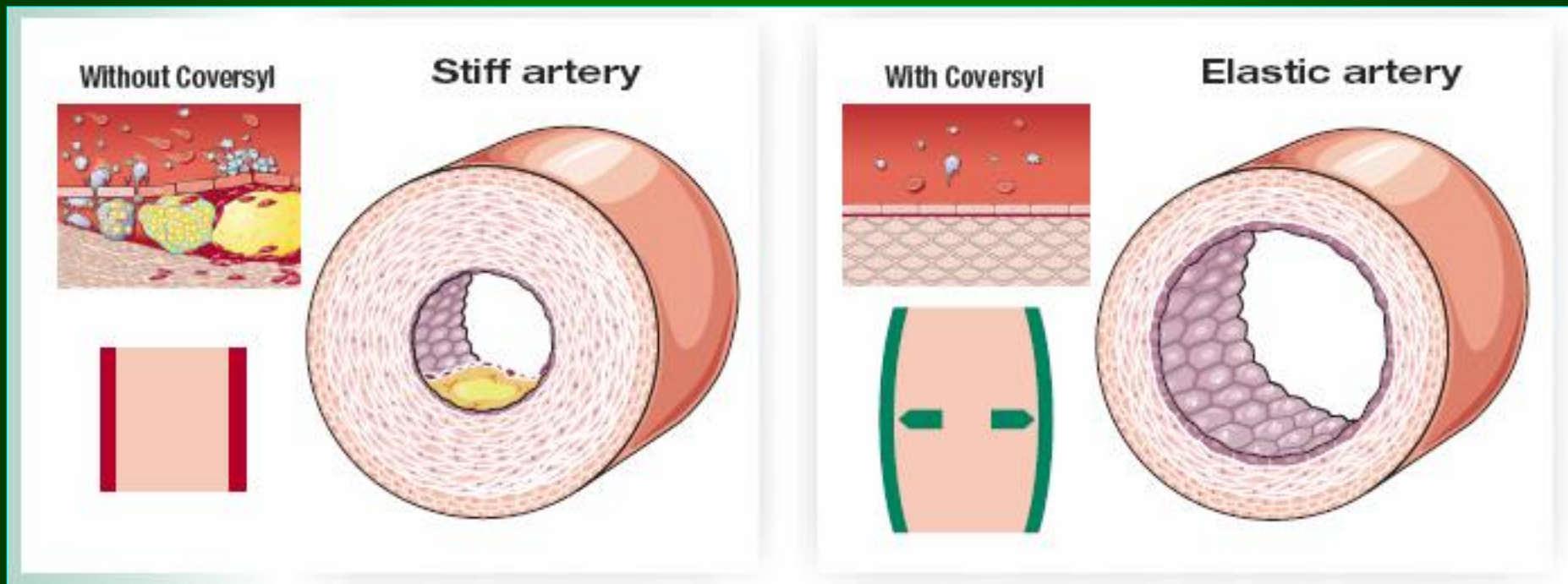
Perindopril corrects endothelial dysfunction



Perindopril inhibits the development of atherosclerosis



Perindopril prevents arterial stiffness independent of BP reduction



ESH/ESC-2007 guidelines emphasize the importance of central aortic blood pressure

3.1.7 Central blood pressure

Due to the variable superimposition of incoming and reflected pressure waves along the arterial tree, aortic systolic and pulse pressure (i.e. the pressure exerted at the level of the heart, brain and kidney) may be different from the conventionally measured brachial pressure [162]. Furthermore, the claim has long been made that peripheral

and central systolic and pulse pressure are affected by antihypertensive treatment. Invasive measurement of central aortic blood pressure is confined to research and a method has been described

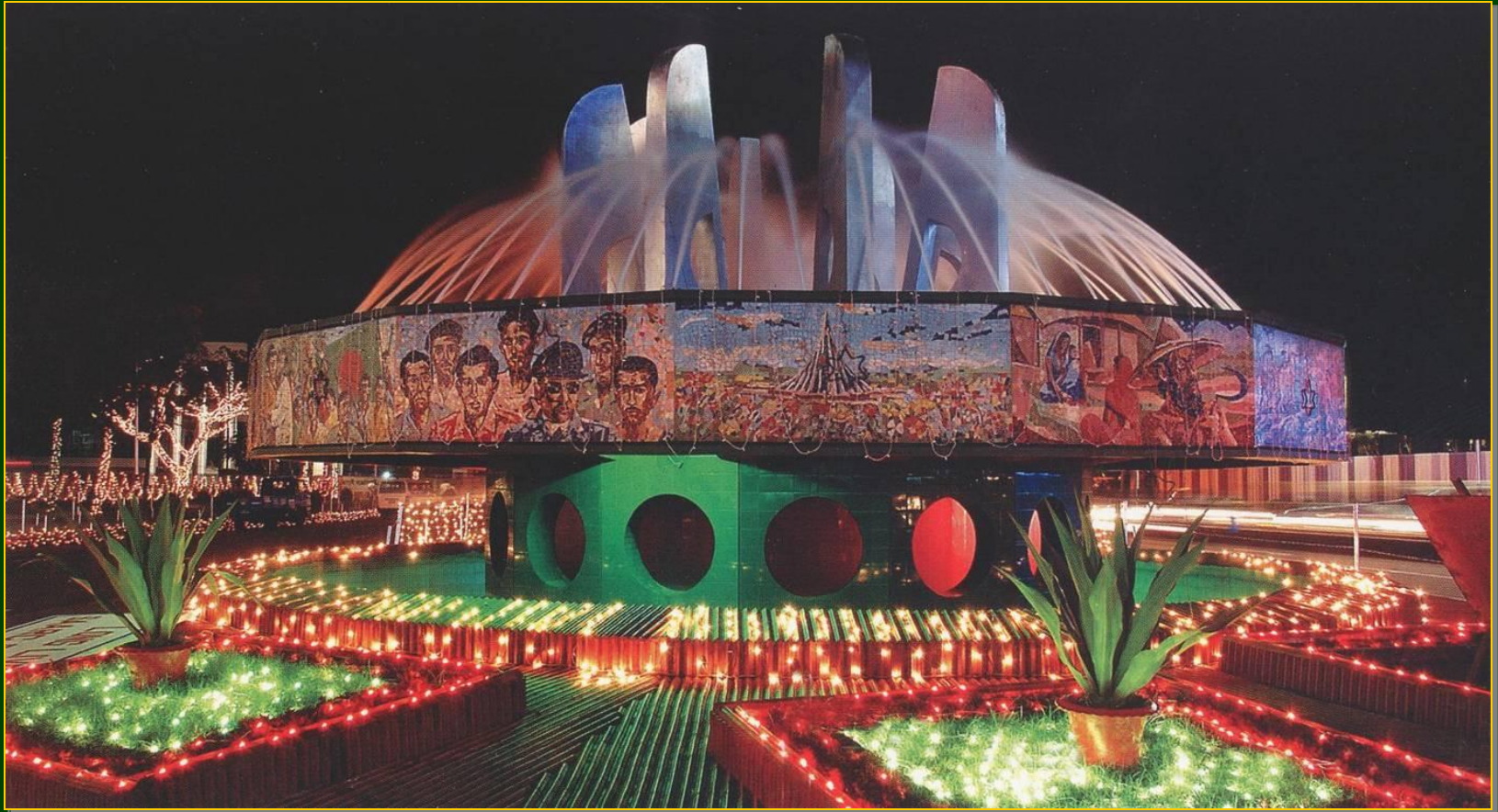
for the non-invasive measurement of aortic blood pressure by calculating the “augmentation index” from the pulse wave pressure contour recorded from a peripheral artery [164,165]. Use of this method has confirmed that the effects of antihypertensive drugs on central systolic and pulse pressure do not invariably reflect those seen at the brachial artery level [166,167]. Furthermore, the results obtained in a large substudy performed within a randomized trial have shown that central pulse pressure as assessed from the “augmentation index” is significantly related to cardiovascular events [166]. However, the prognostic role of central

Summary (1)

- ❖ Brachial blood pressure parameters (SBP, DBP, PP) are powerful predictor of CV structural damage, morbidity and mortality
- ❖ Arterial stiffness and raised PP are independent risk factors for CV disease
- ❖ It is conceivable that the measurement of arterial stiffness and estimation of central pressures could become an important part of the assessment of hypertensive patients

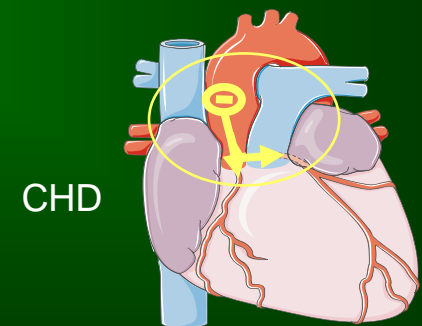
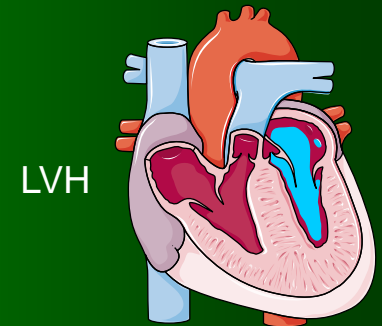
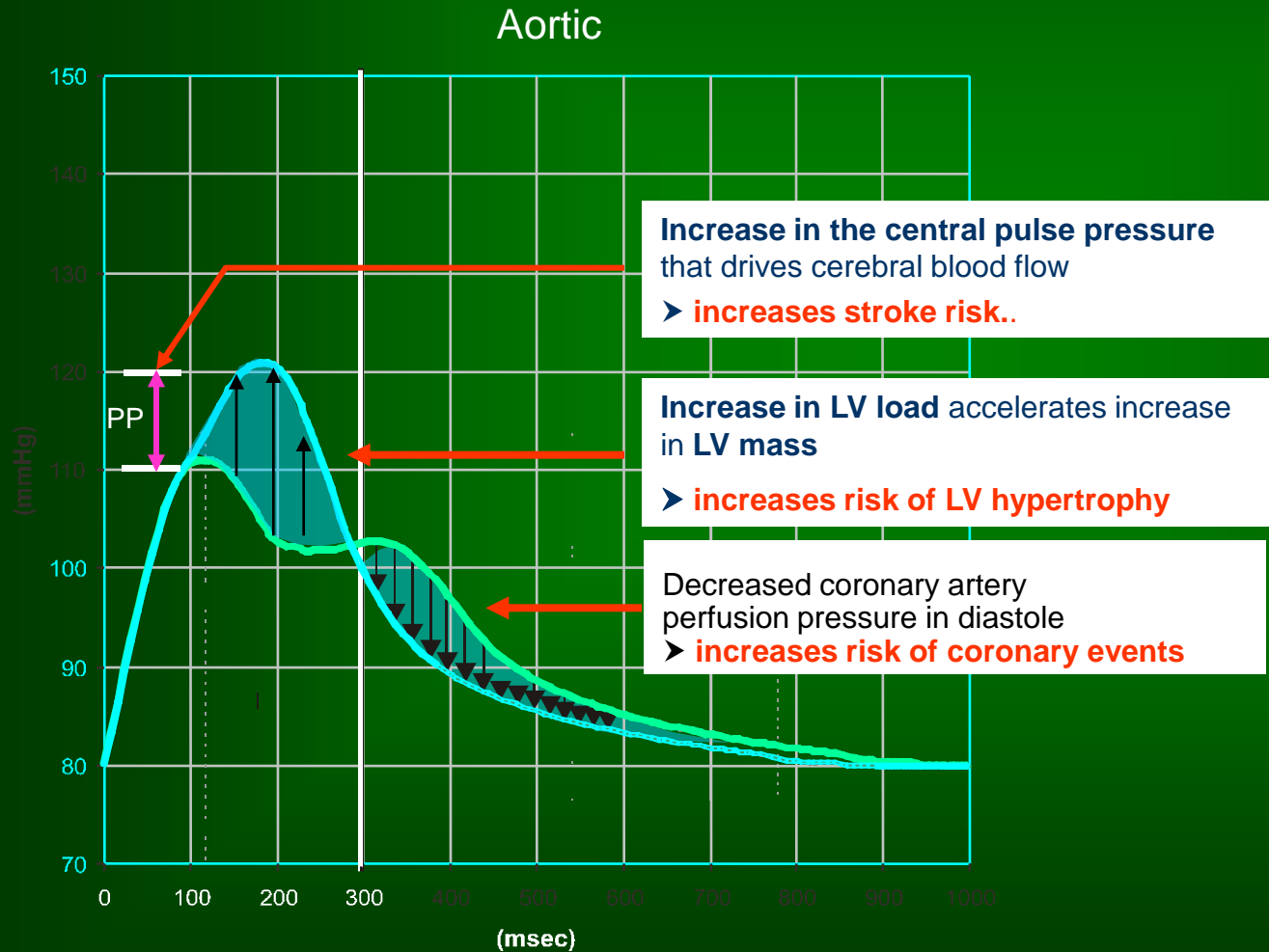
Summary (2)

- ❖ Thus far, pharmacotherapy has focused on BP-lowering properties of antihypertensive drugs
- ❖ Reduction of arterial stiffness, and thereby reducing central systolic and pulse pressure is an additional target



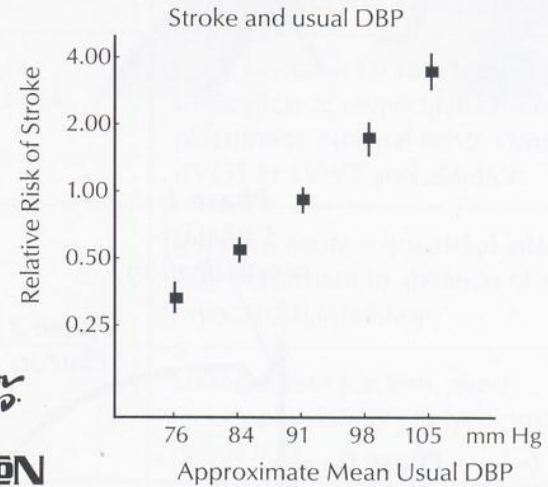
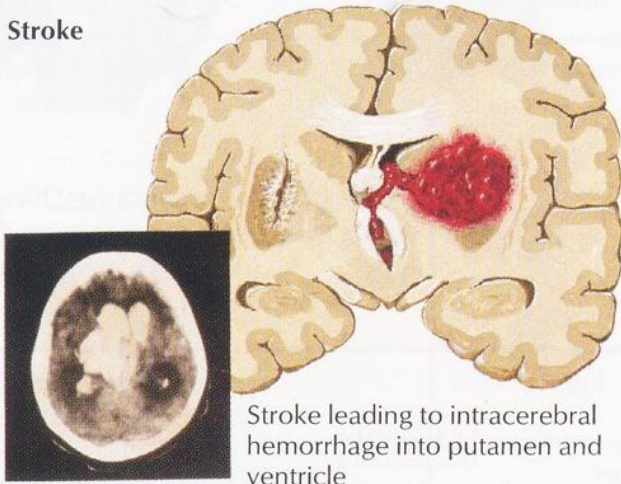
Thank you

Increased arterial stiffness independently increases the risk of all three major CV outcomes



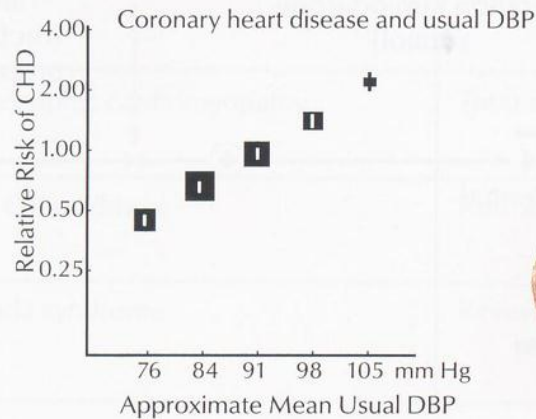
Relative Risk of Stroke and CHD According to Diastolic Blood Pressure

Stroke

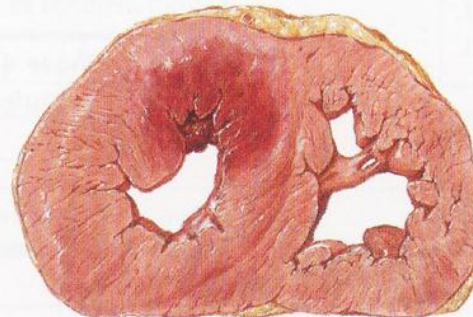


F. Netter M.D.
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Coronary Heart Disease

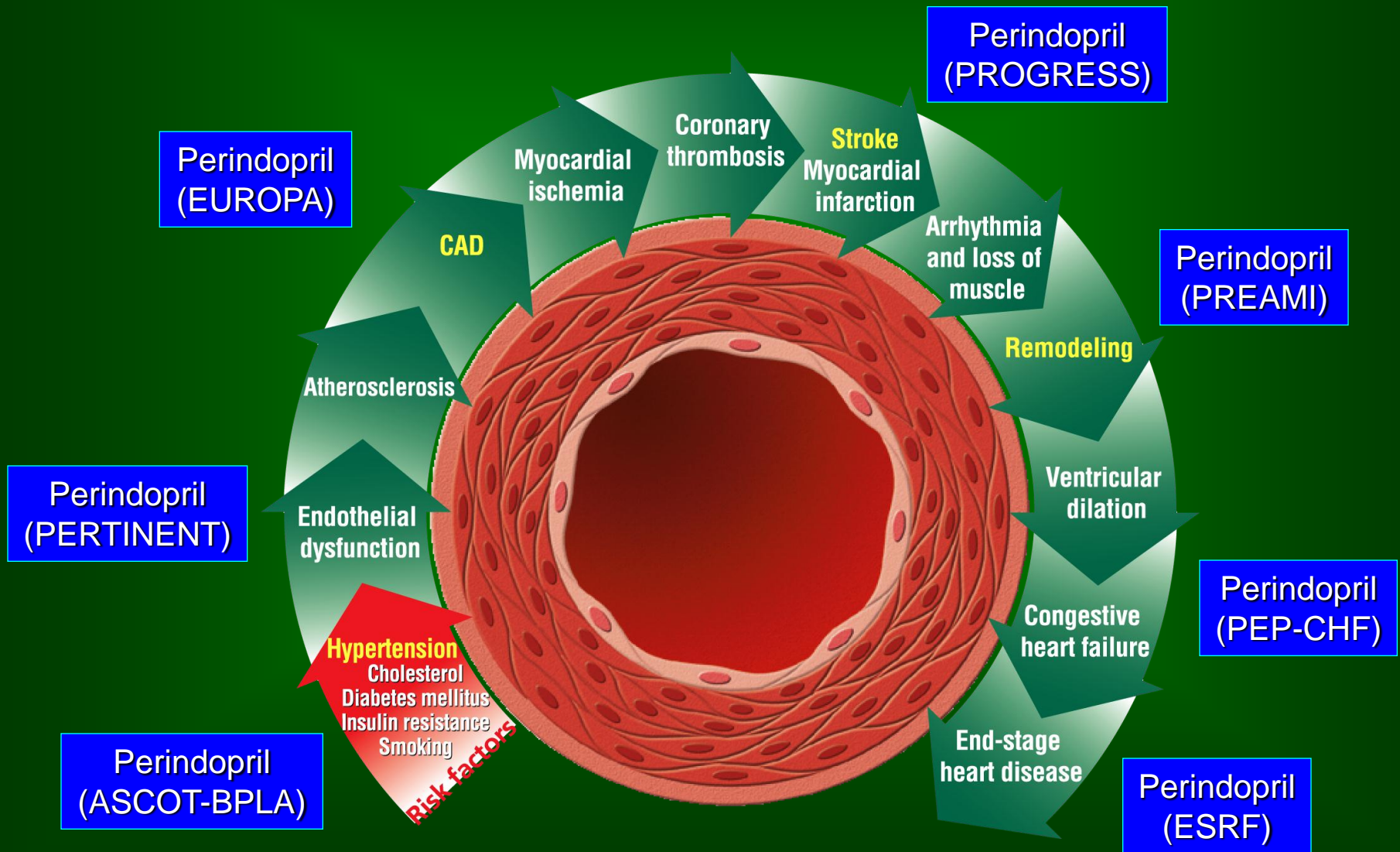


Cardiac hypertrophy and anteroseptal infarct with coronary heart disease



Angina

Perindopril along the CVD continuum



Overwhelming evidence

Perindopril provides **100% positive** result in **5 landmark trials** comprising **50,000** patients

