Arterial stiffness: clinical implications and its role in cardiovascular disease

연세대학교 심장혈관병원
심장내과
최 동 훈

Arterial stiffness

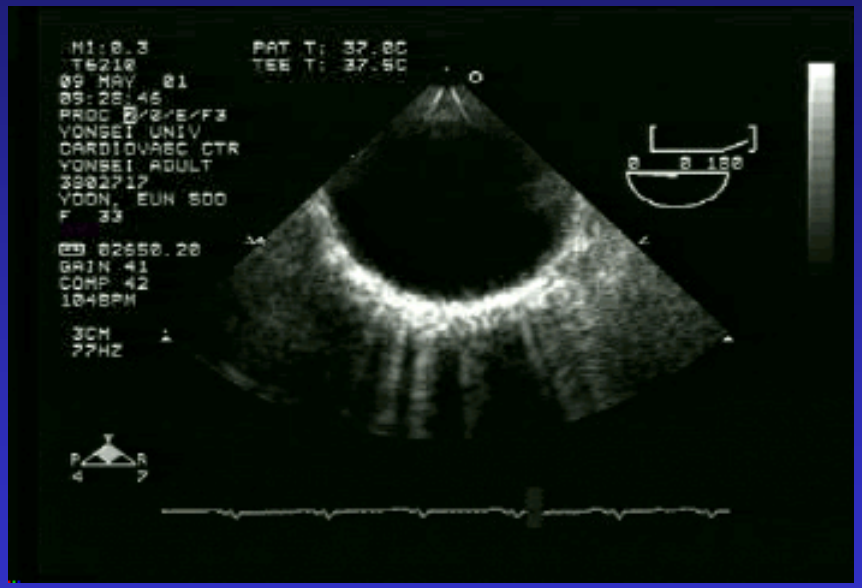
- **Definition and pathophysiology of arterial stiffness**
- Association of arterial stiffness with cardiovascular disease
- Treatment of arterial stiffness

Arteriosclerosis is

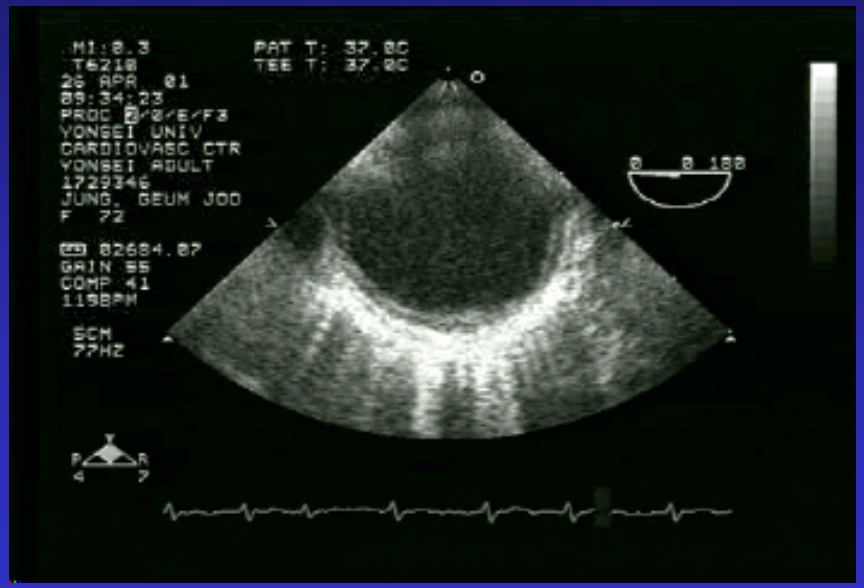
= The hardening of the arteries

Aortic stiffness

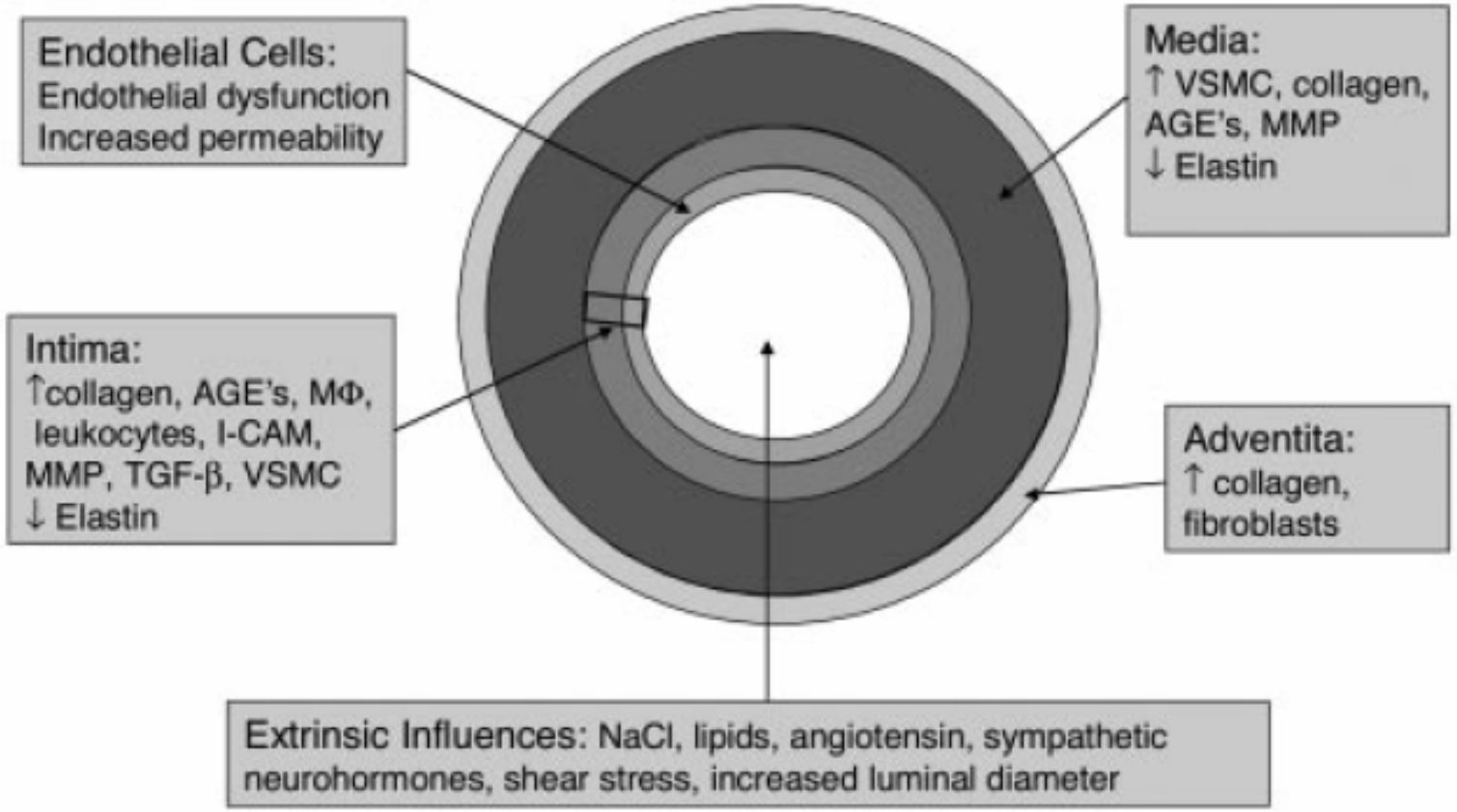
Young adults



Older adults



Pathogenesis of arterial stiffness



Zieman SJ et al. Arterioscler Thromb Vasc Biol 2005;25:932-43

Young normal aorta

Old stiff aorta

Young normal aorta

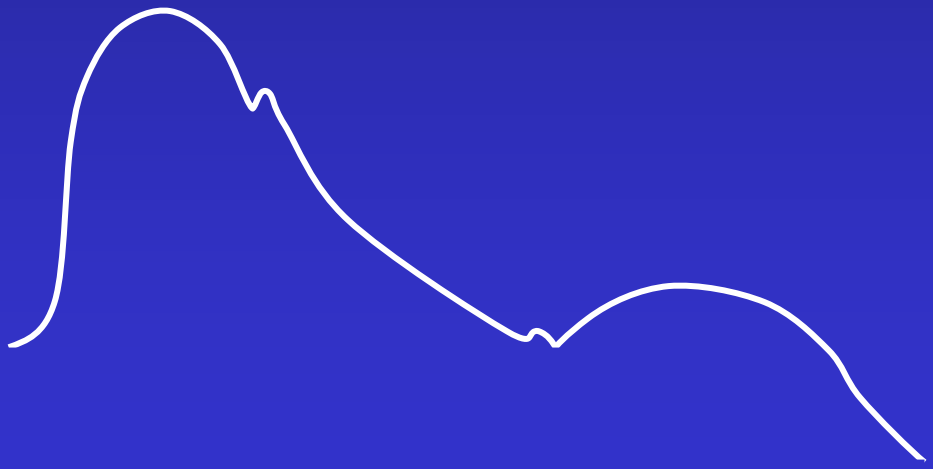
Resistance artery

Old stiff aorta

Resistance artery

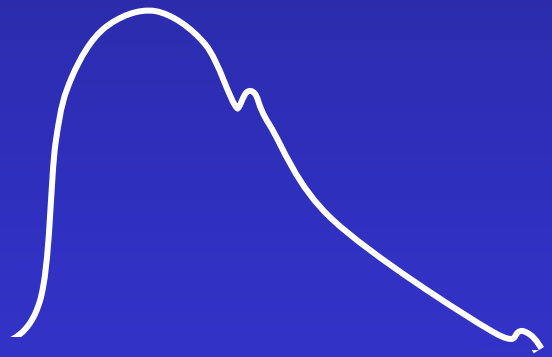
Young normal aorta

Resistance artery

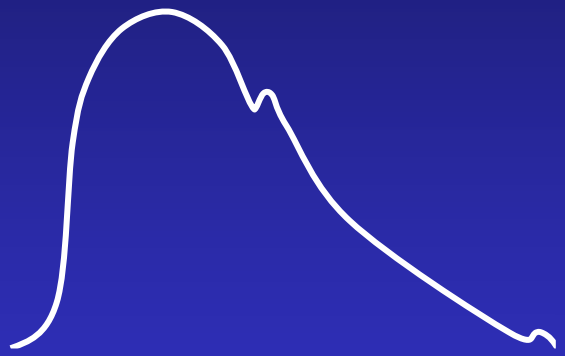


Old stiff aorta

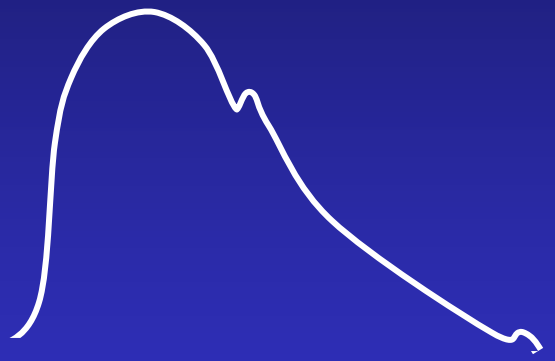
Resistance artery



Young normal aorta

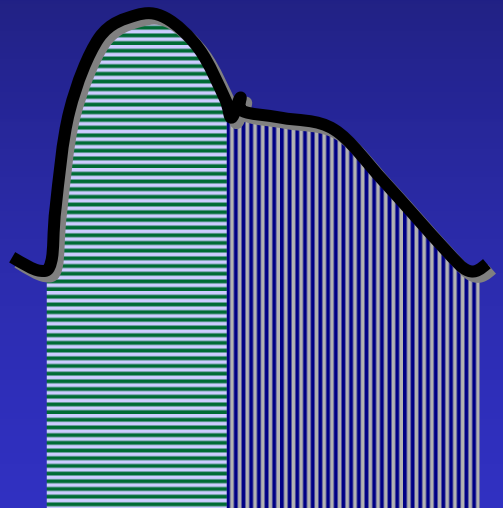


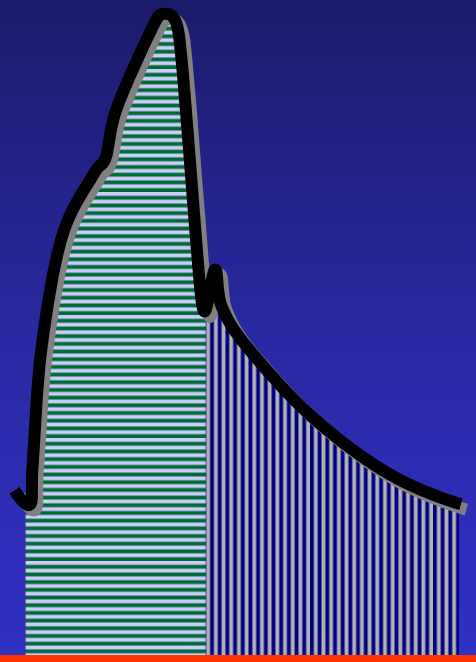
Old stiff aorta



Pressure during systole is a major determinant of myocardial O2 requirement

Pressure during diastole is a major determinant of CBF





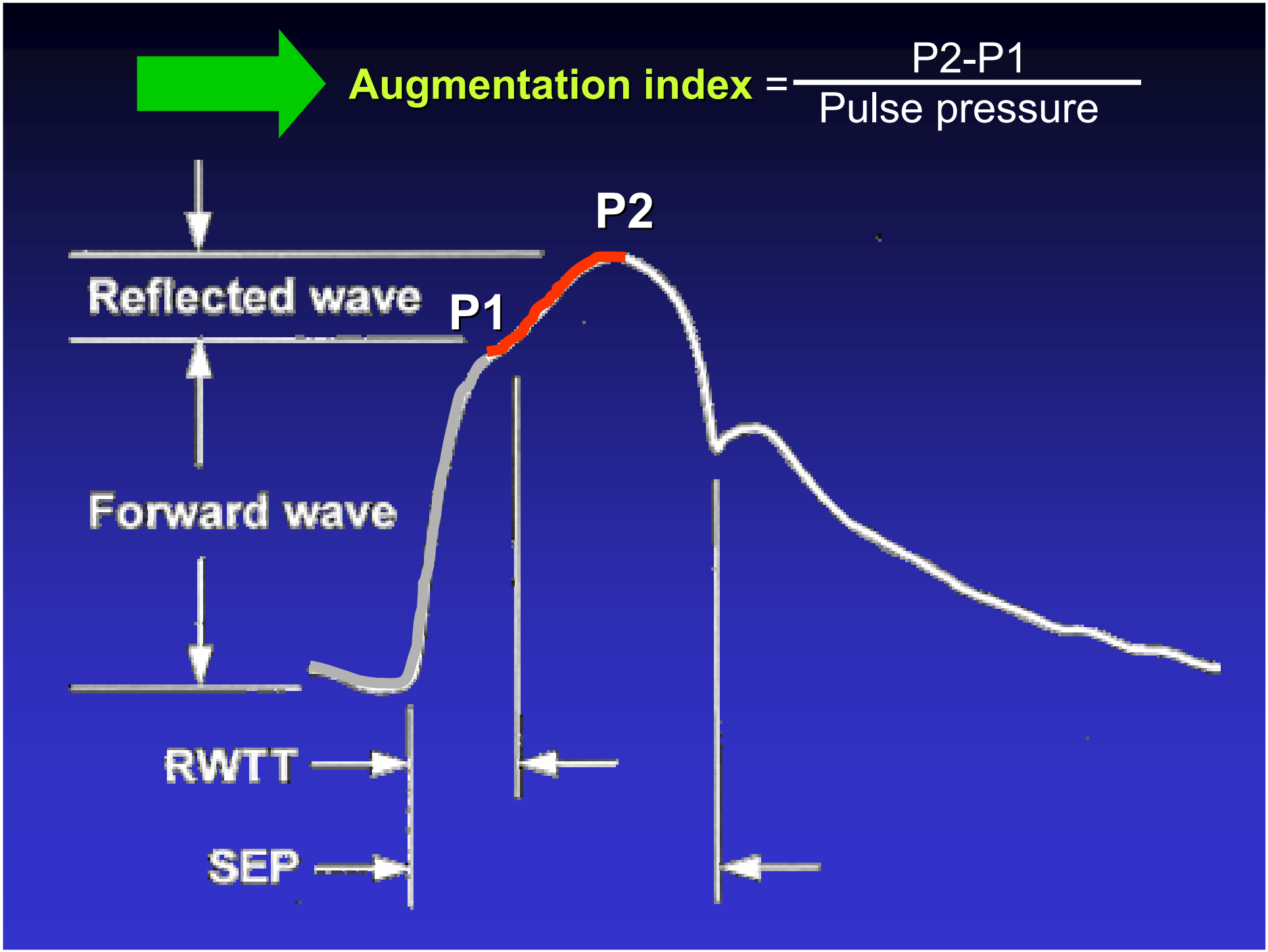
Efficient arterial system

Inefficient arterial system

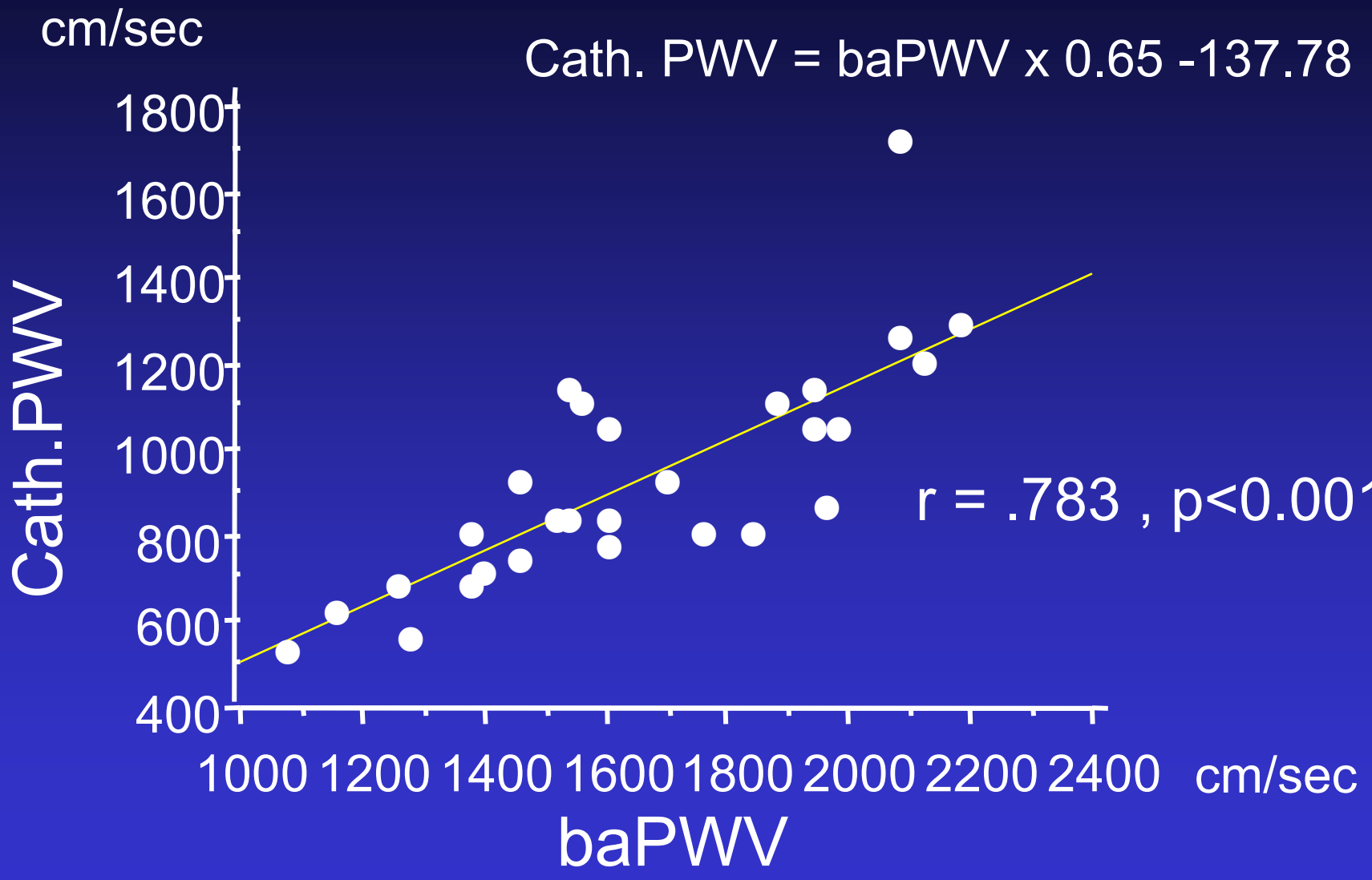
Index of arterial stiffness

- Compliance
  = $\Delta D / \Delta P$ (cm/mmHg)
  Absolute diamenter (or area) change for a pressure increment
- Distensibility
  = $\Delta D / \Delta P \cdot D_{baseline}$ ($mmHg^{-1}$)
  Relative diameter (or area) change for a pressure increment
- Young's Elastic Modulus
  = $\Delta P \cdot D / \Delta D X h$(mmHg/cm)
- Beta index(Stiffness index)
  = Ln(Ps/Pd)/ [(Ds-Dd)/Dd]
- Pulse wave velocity(cfPWV, baPWV)
  = Distance / ΔTime delay (cm/sec)
  Speed of travel of the pulse along an arterial segment

Local Stiffness


Augmentation index = P2-P1 / Pulse pressure
P2
Reflected wave
P1
Forward wave
RWTT
SEP

Relationship of aortic PWV（catheter method）and baPWV



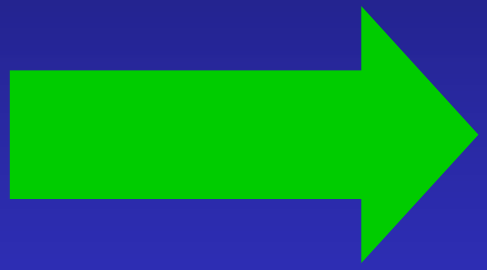
Yamashina A, Hypertension Res, 2002;25:359

Arterial stiffness

- Definition and pathophysiology of arterial stiffness
- **Association of arterial stiffness with cardiovascular disease**
- Treatment of arterial stiffness

Recent change in paradigm

Arterial stiffness and systolic hypertension is a normal aging process. You don't need to treat it

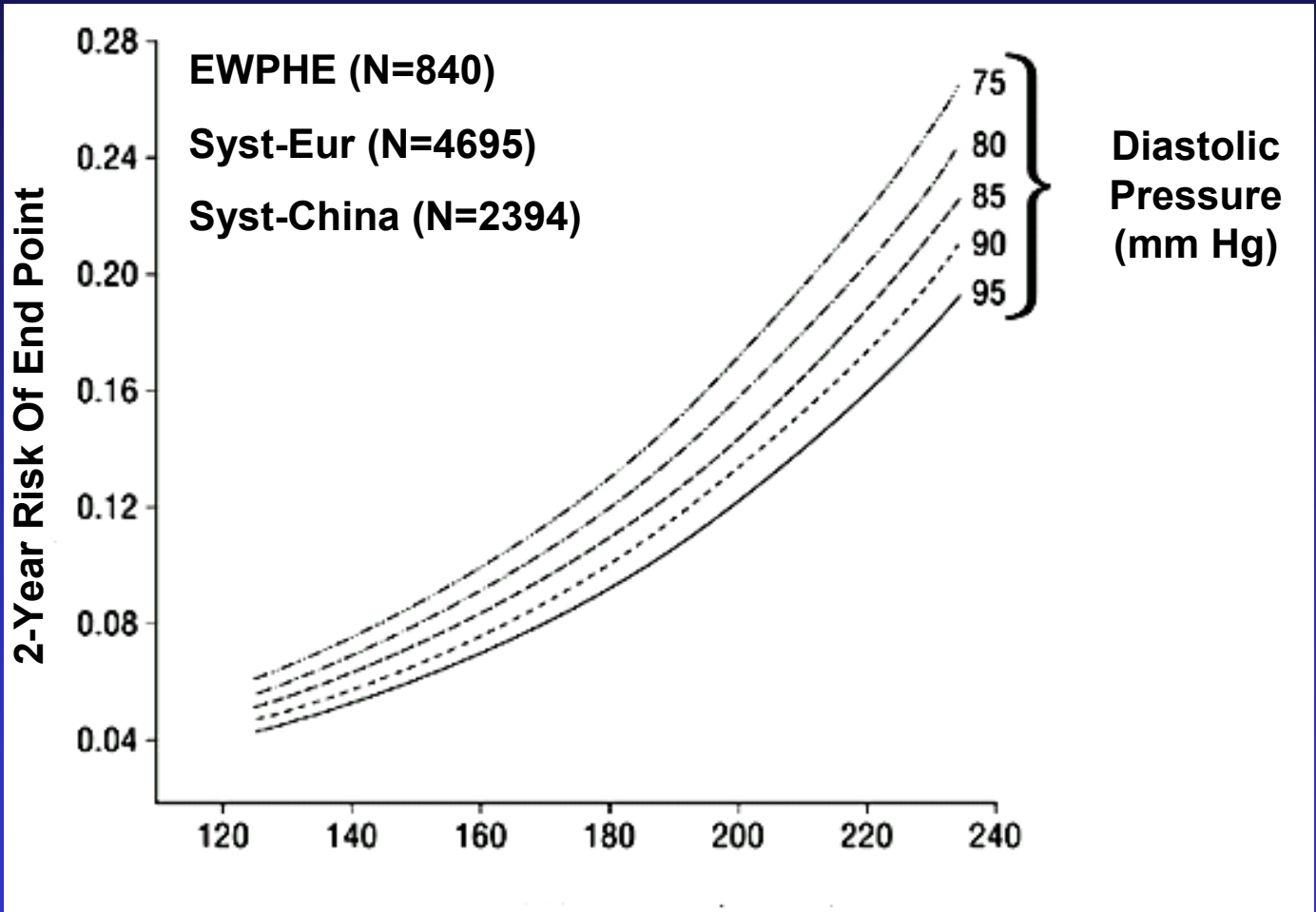


Arterial stiffness in an independent risk factor For adverse cardiovascular prognosis

Arterial Stiffness

- SBP as a more informative CV risk factor in patients older than 50 years
- PP is an independent marker of CV risk
- In subjects > 50 years of age, arterial stiffness becomes the main determinant of increased SBP and PP

Pulse Pressure Predicts Risk Best In Older Hypertensives
A Meta-Analysis



Blacher et al. Arch Intern Med. 2000;160

Anglo-Scandinavian ascot Cardiac Outcomes Trial

CAFÉ

Differential Impact of Blood Pressure-Lowering Drugs on Central Arterial Pressure Influences Clinical Outcomes - Principal Results of the Conduit Artery Function Evaluation (CAFÉ) Study in ASCOT

Objects of CAFÉ study

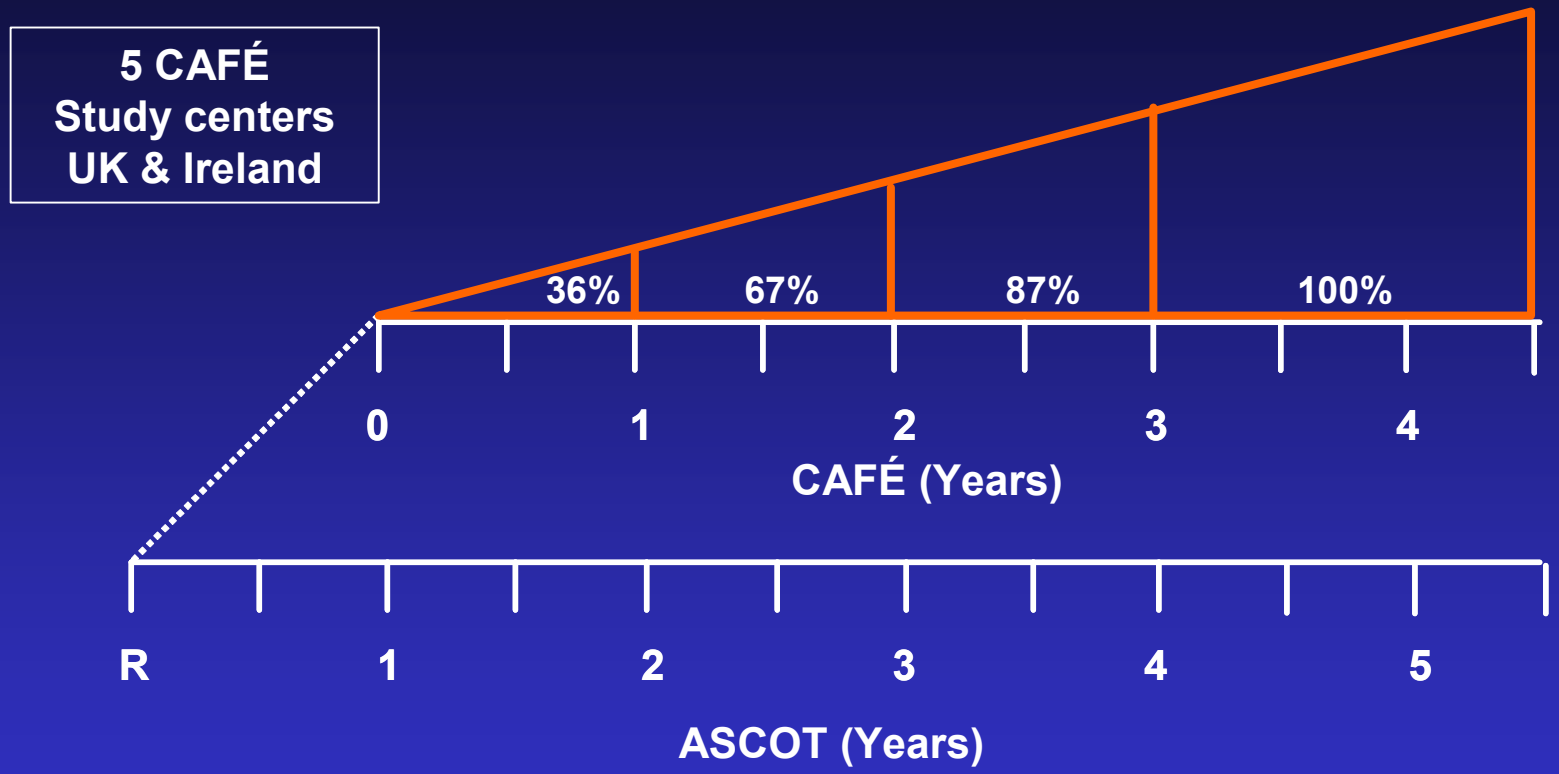
- **Primary Objective**

- Whether different blood pressure-lowering regimens in ASCOT(atenolol+ thiazide versus amlodipine+ perindopril) make differential effects on central aortic pressures and hemodynamics

- **Secondary Objective**

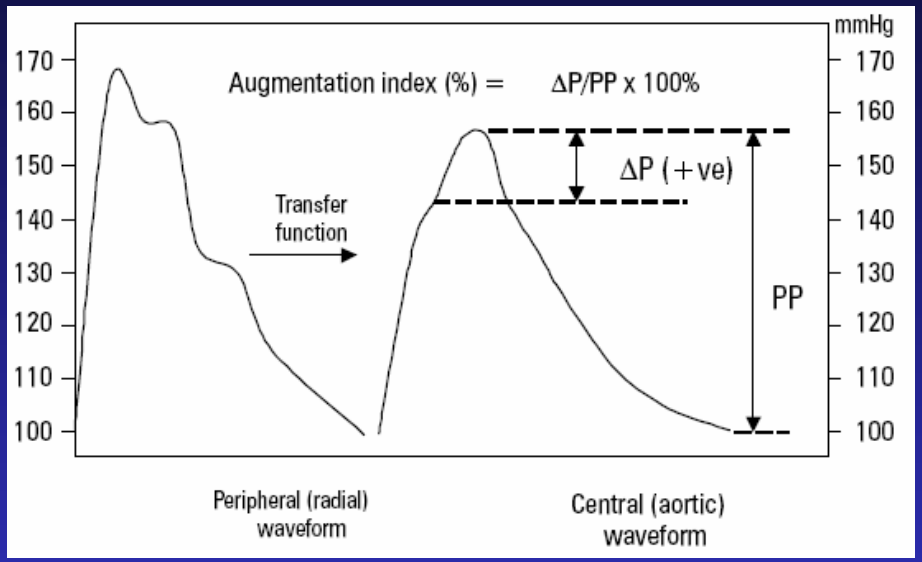
- Whether central aortic pressures are an important determinant of clinical outcomes in ASCOT

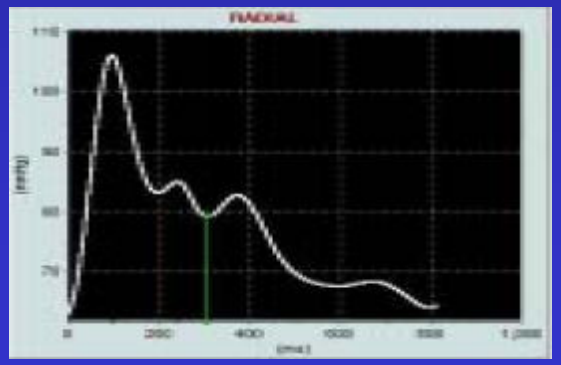
CAFÉ Study Design



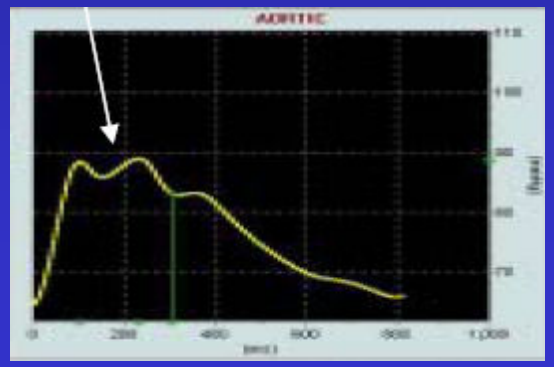
- >70% of ASCOT patients at 5 study centers recruited
- 80% of patients had > 1 tonometry measurement
- Average 3.4 tonometry measurements/patients
- Average follow up after first tonometry measurement was 3 years

Pulse Wave Analysis: Augmentation index





Pressure transfer function
(Degree of amplification)



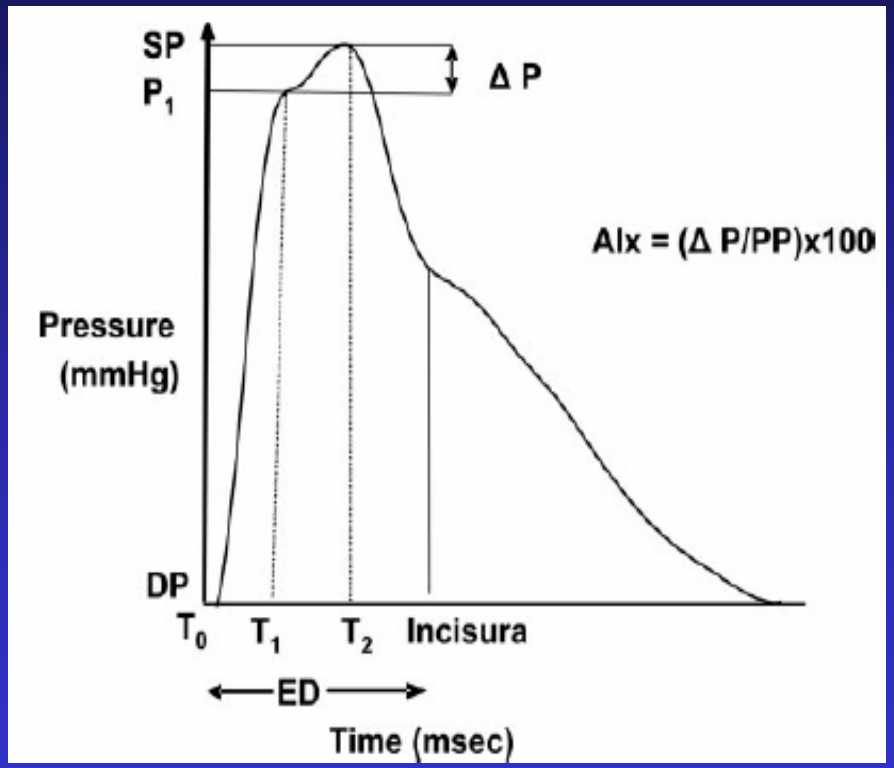
Radial a.

Aorta

Radial artery pulse wave analysis

- Radial artery pulse wave
  - Radial artery applanation tonometry
    - Millar Tonometer
  - Pulse wave analysis

  ⇒Derived Central aortic pressure
    - SphygmoCor



Mean Proportion of Time(%) on BP Lowering Medication by Treatment Group*

	Year 1	All Study
Randomized to Amlodipine		
Amlodipine	90.0	80.7
Perindopril	56.0	66.7
Amlodipine + Perindopril	47.8	55.5
Randomized to Atenolol		
Atenolol	88.1	73.5
Bendroflumethiazide	69.8	74.2
Atenolol + Bendroflumethiazide	60.2	59.6

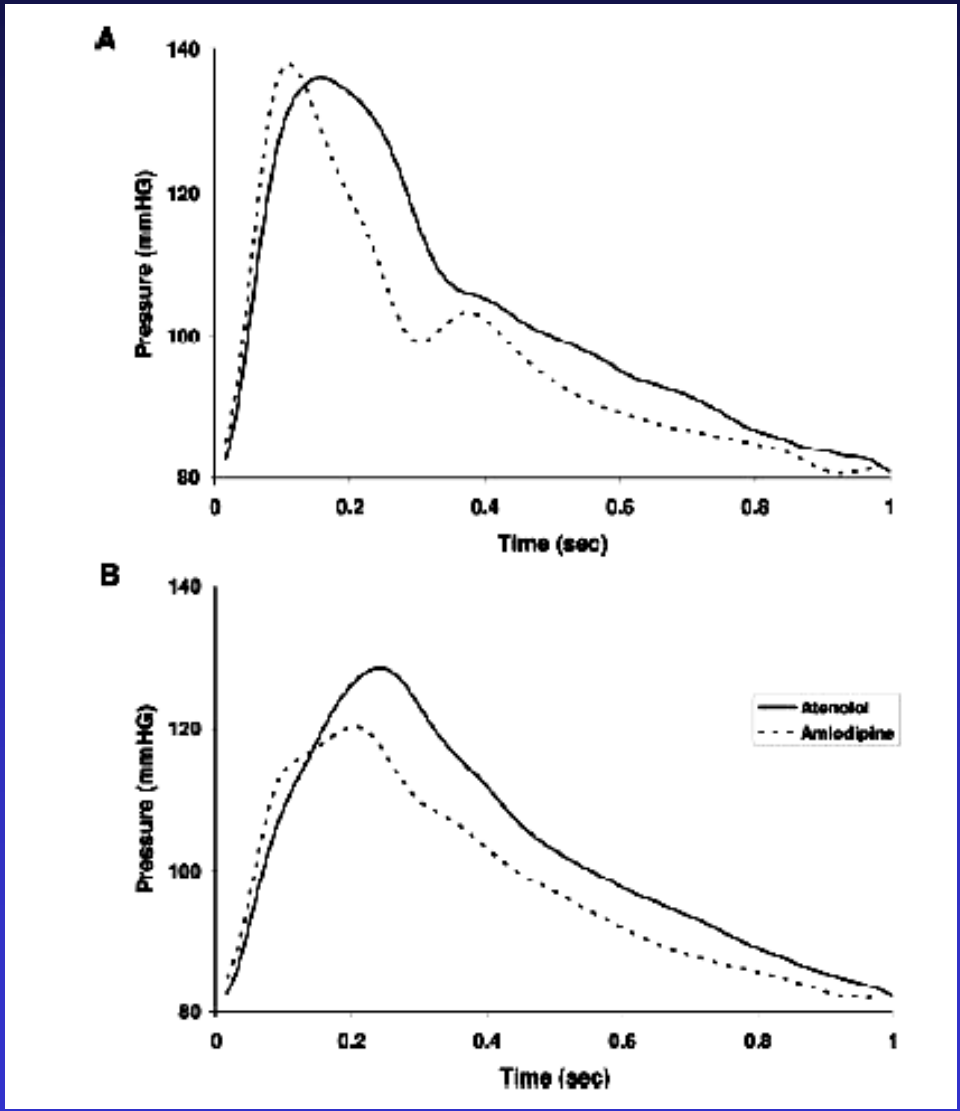
**from time of randomization into ASCOT*

- **Monotherapy : Atenolol; 3.5% Amlodipine; 7%**
- **Average number of BP lowering drugs/patients: 2.2**

Hemodynamic Data

Parameter	Atenolol	Amlodipine	Difference (Atenolol-Amlodipine)	Statistics t-test(P)
Brachial SBP	133	133.2	0.7	0.2
(mm Hg)	(133, 134.7)	(132.5, 133.8)	(-0.4, 1.7)	
Brachial DBP	78.6	76.9	1.6	<.0001
(mm Hg)	(78.1, 79.1)	(76.4, 77.4)	(0.9, 2.4)	
Brachial PP	55.3	56.2	-0.9	.06
(mm Hg)	(54.6, 56)	(55.6, 56.9)	(-1.9, 0)	
Heart rate	58.6	69.3	-10.7	<.0001
(BPM)	(58, 59.2)	(68.6, 69.9)	(-11.5, -9.8)	

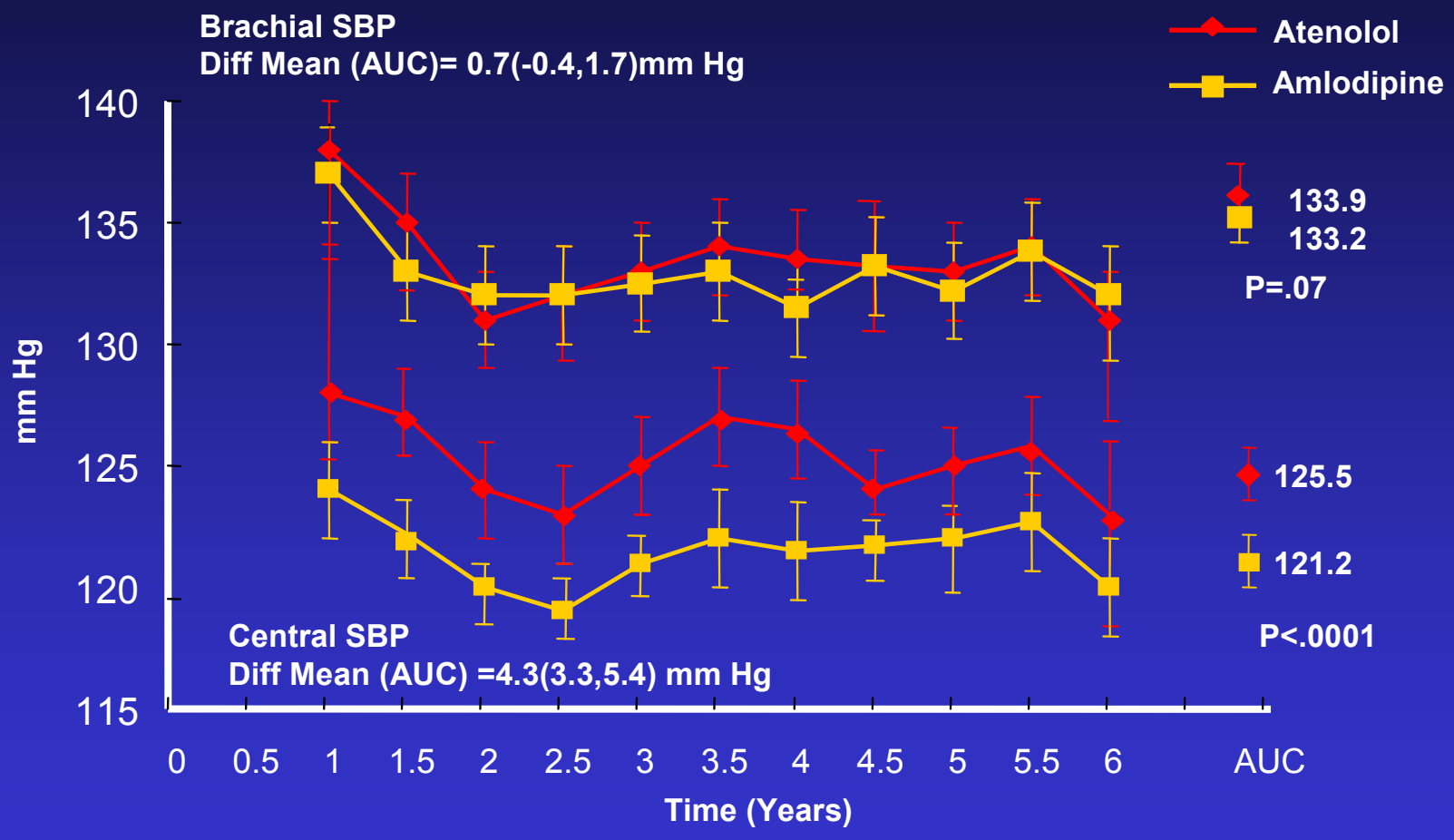
Hemodynamic Data - Example



- Atenolol Group
  - Broader peripheral waveform
  - More prominent late systolic peak in central aortic waveform

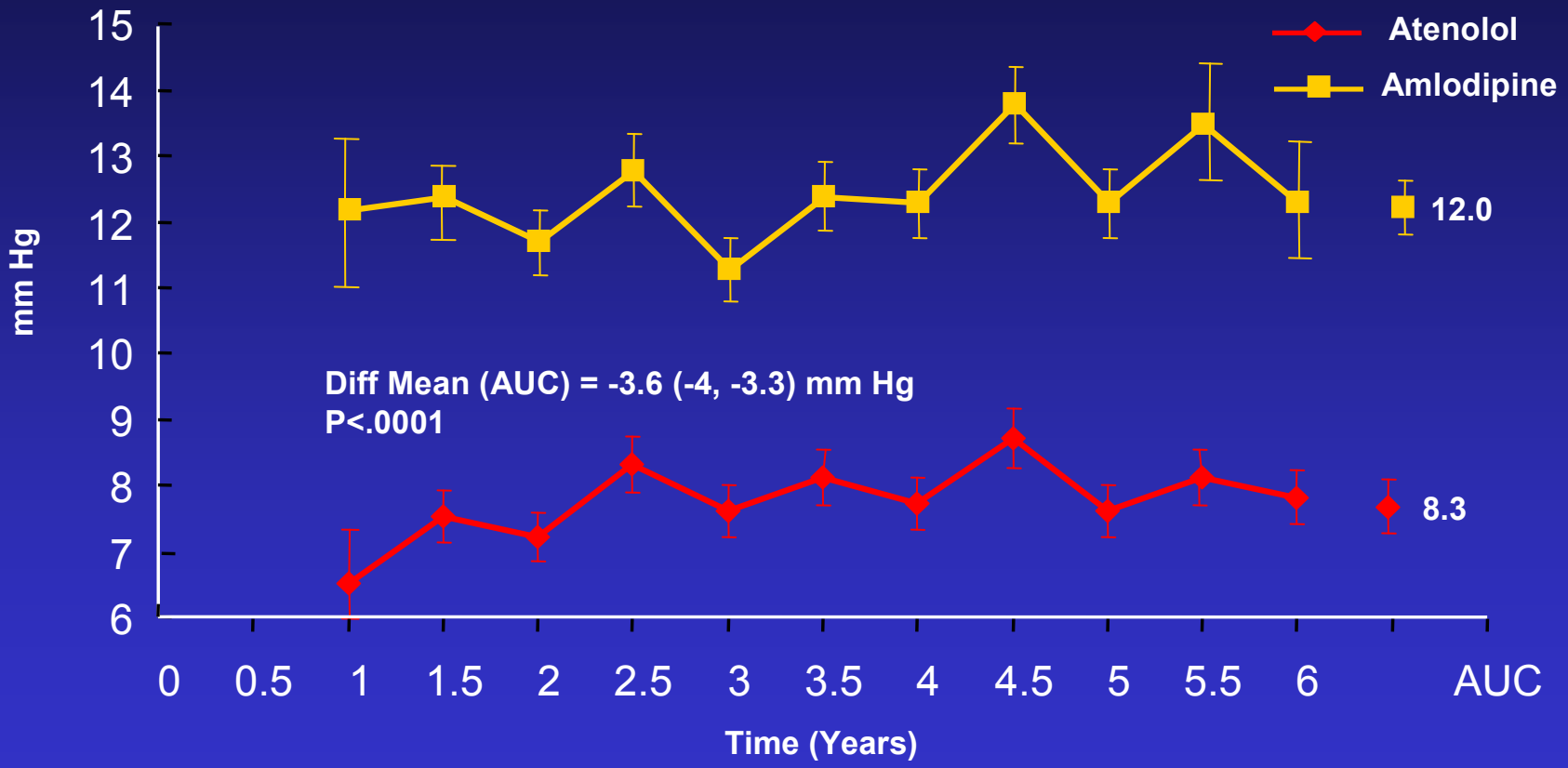
Primary outcome

Brachial and Central Aortic Systolic Blood Pressure (+ 95% CI)



Atenolol	86	243	324	356	445	372	462	270	339	128	85	1031
Amlodipine	88	248	329	369	475	406	508	278	390	126	101	1042

Difference Between Brachial and Central Aortic Systolic BP by Treatment Arm



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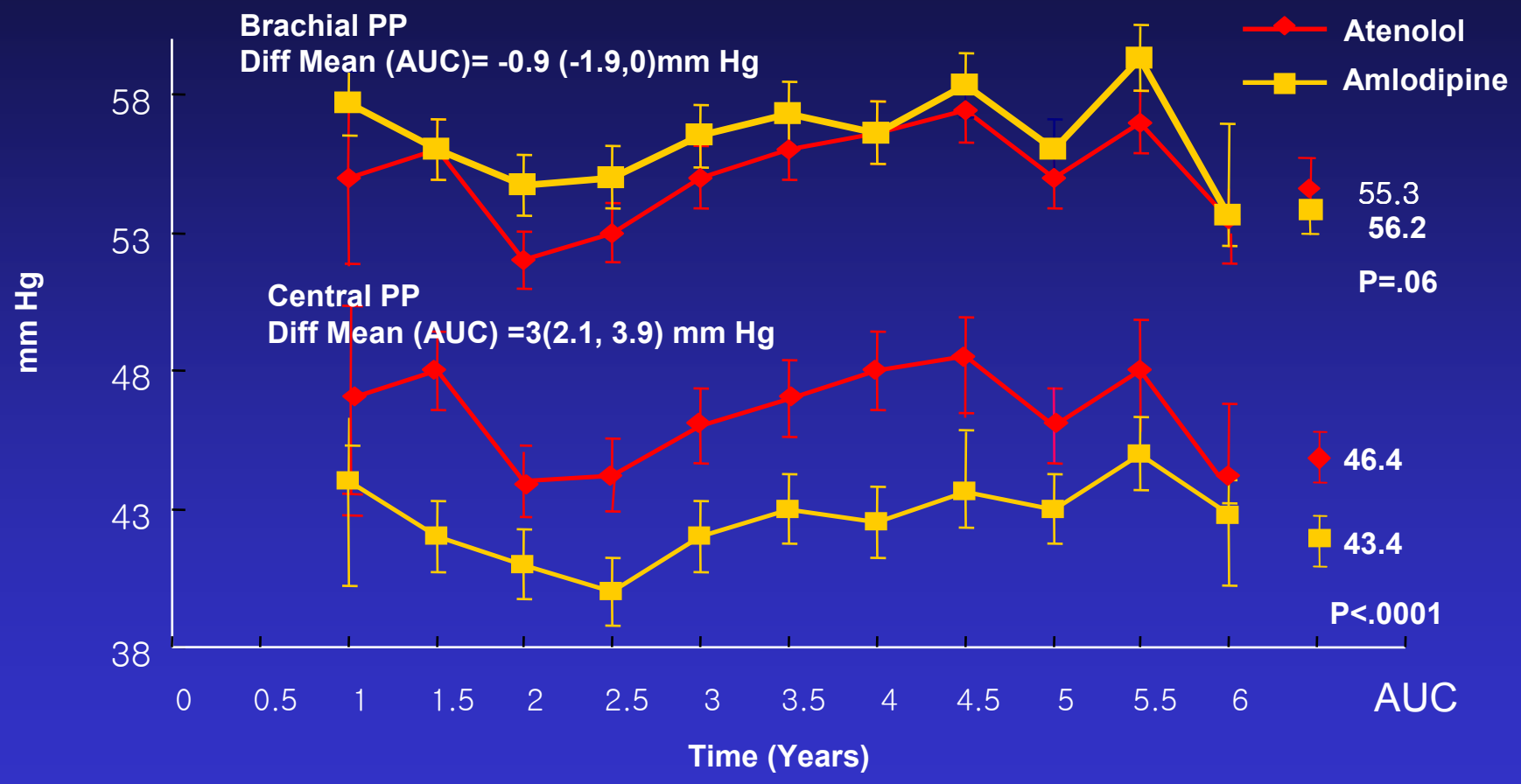
Brachial and Central Aortic Pulse Pressure by Treatment Arm



Atenolol	86	243	324	356	445	372	462	270	339	128	85	1031
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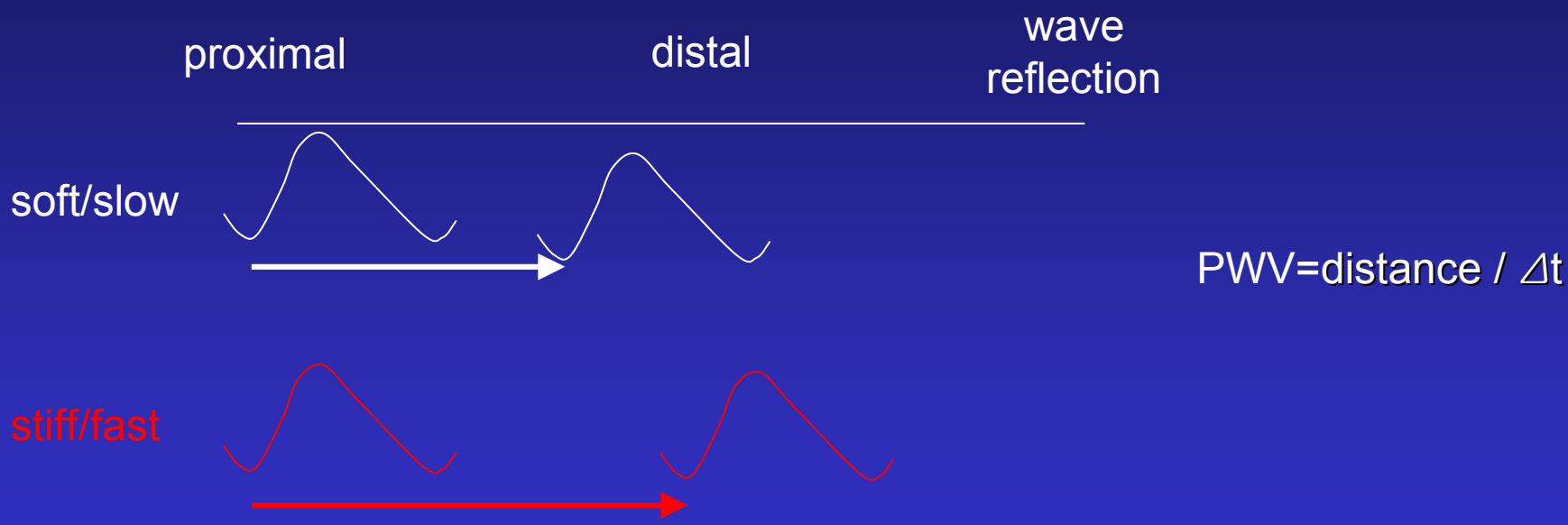
Pulse Wave Velocity

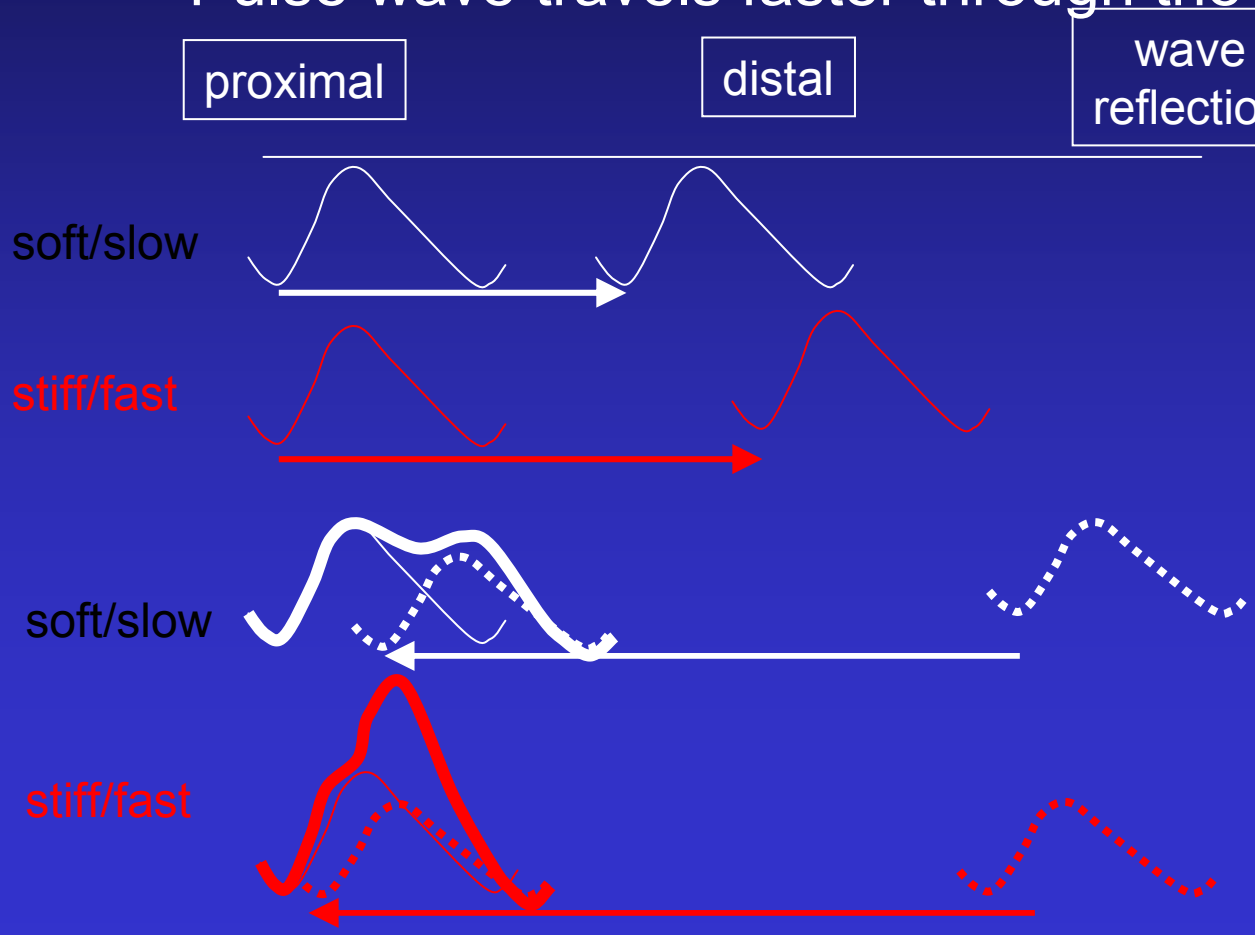
- Pulse wave travels faster through the stiffer artery.



PWV=distance / ⊿t

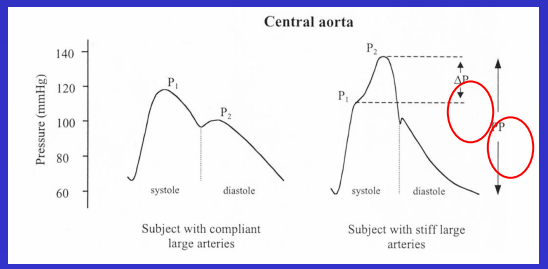
Pulse Wave Analysis & AI

- Pulse wave travels faster through the stiffer artery.

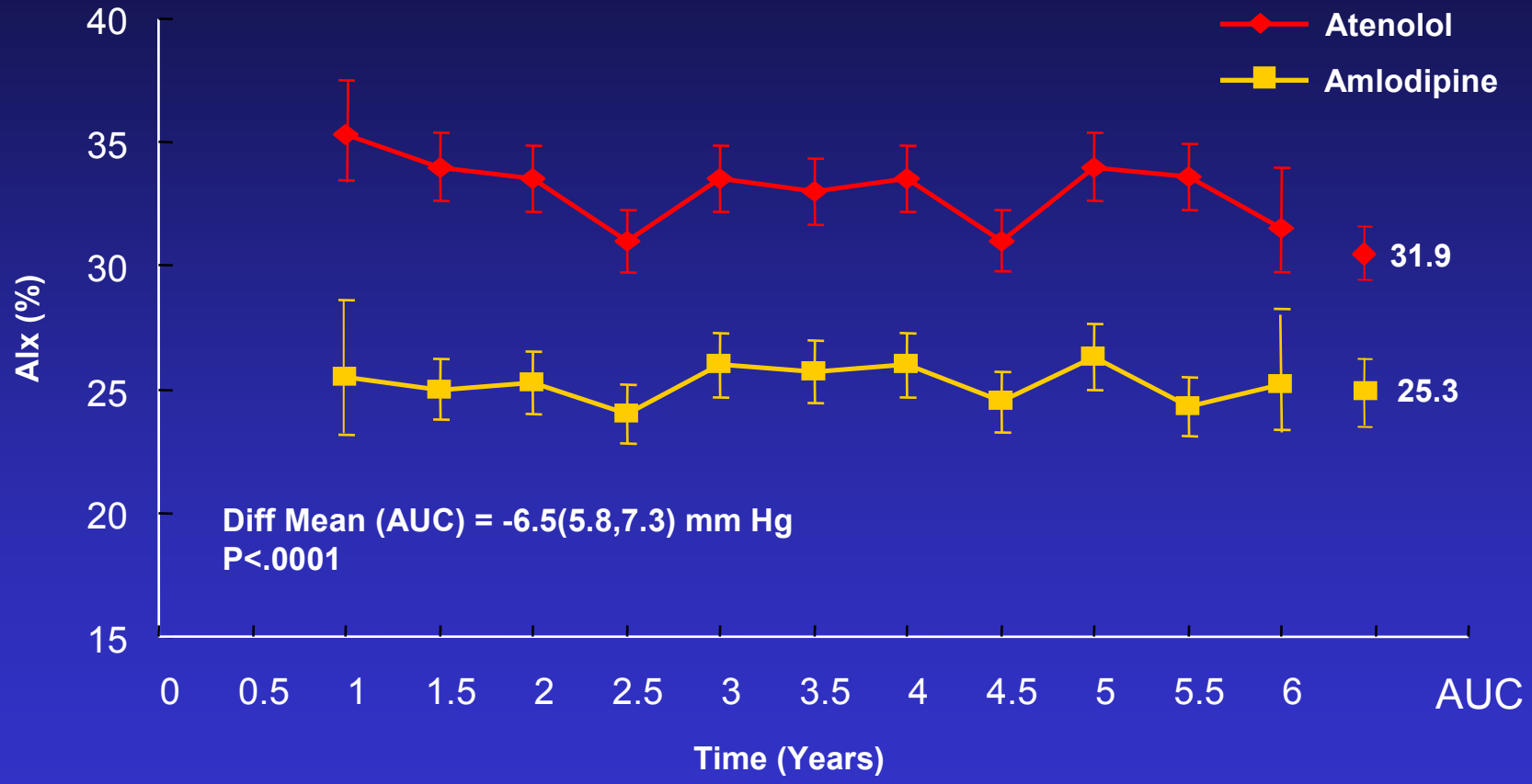


PWV=distance / ⊿t

AI,PP,PCA



Augmentation Index (%) by Treatment Arm



Atenolol	86	243	324	356	445	372	462	270	339	128	85	1031
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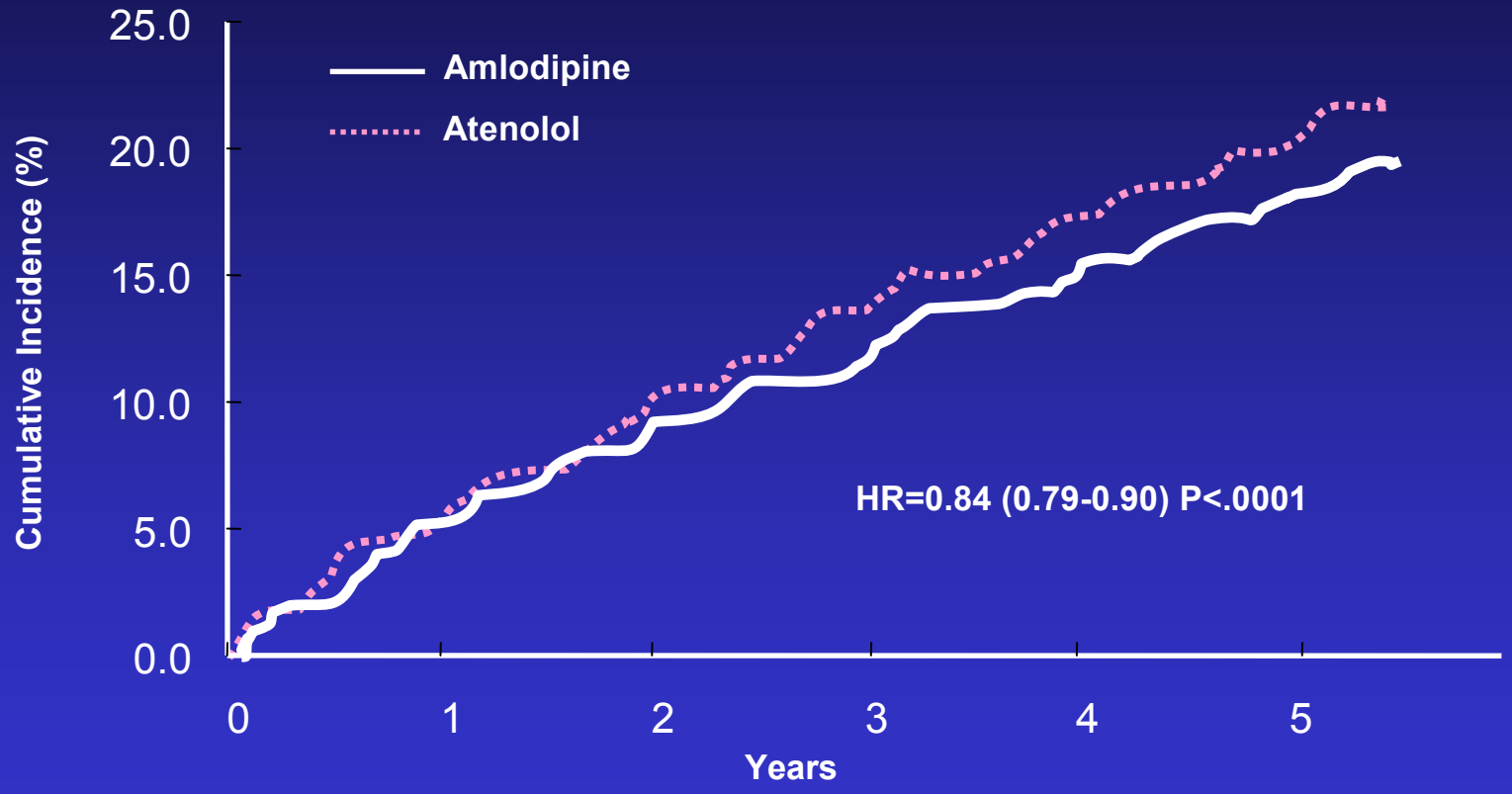
Results summary

- Atenolol-based therapy associated with higher Central aortic systolic pressure and higher central aortic pulse pressure, despite similar brachial pressures, when compared with amlodipine-based therapy

- AI (central aortic pressure wave attributable to wave reflection) increased by atenolol-based therapy compared with amolodipine-based thearpy

Secondary Endpoint regarding central aortic hemodynamic parameters and clinical outcomes



Atenolol	9639	8808	8455	8118	6965
Amlodipine	9618	8692	8259	7872	6710

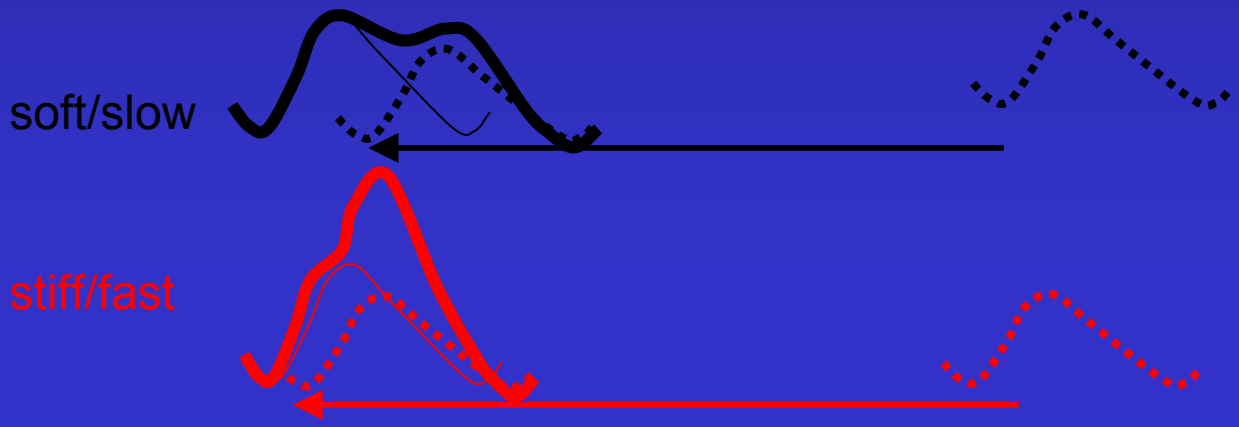
Impact of Blood Pressure and Central Aortic Hemodynamics on Clinical Outcomes in the CAFÉ Study (Hazard/10 mm Hg)

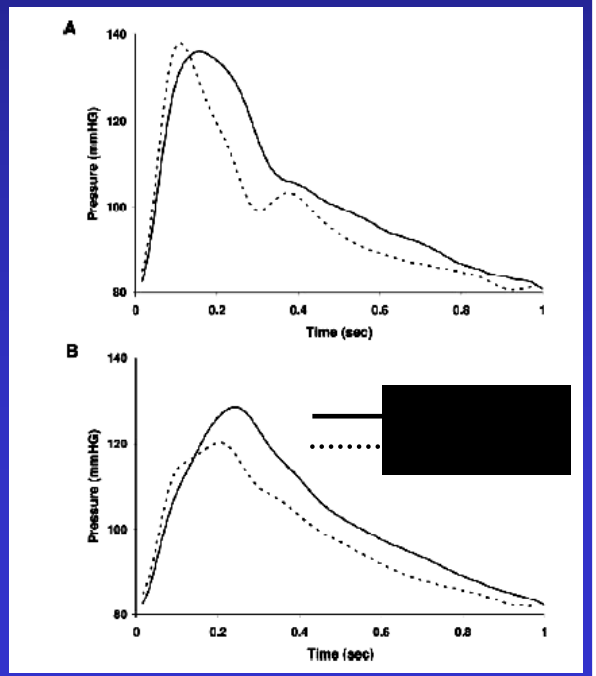
Updated Cox proportional hazard model for the composite endpoint, unadjusted

Factor	X^2	P	HR	CI
Peripheral PP	21.0	<.0001	1.21	1.12-1.30
Central PP	17.8	<.0001	1.20	1.11-1.30
Augmentation	7.10	.008	1.22	1.06-1.4
P_1 height	19.0	<.0001	1.37	1.20-1.54

Discussion

- Higher Central aortic systolic and pulse pressure may results from Increased pressure wave reflection
- Mechanisms of Differences in aortic systolic pressure wave reflections
  - Arterial pulse wave velocity (x)
  - Pressure wave reflection site
    - Relative vasoconstriction
    - Small artery remodeling
  - Timing of systolic ejection resulting from differences in heart rate





CAFÉ study Conclusion

- Despite similar brachial systolic blood pressure, amlodipine + perindopril-based treatment more effective than atenolol+thiazide-based treatment at lowering central aortic systolic blood pressure and central aortic pulse pressure
- Central aortic pressure may be an important independent determinant of clinical outcomes
- Results of the CAFÉ study suggest that the "central aortic blood pressure hypothesis" is a plausible mechanism to explain the better clinical outcomes for hypertensive patients treated with amlodipine+perindopril-based therapy in ASCOT

Beyond brachial blood pressure lowering effect!!