Arterial stiffness as a new target in hypertension:

choosing the right therapeutic strategy for optimal cardiovascular protection.

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Institut national
de la santé et de la recherche médicale

1- Arterial stiffness: An independent determinant of Cardiovascular Risk

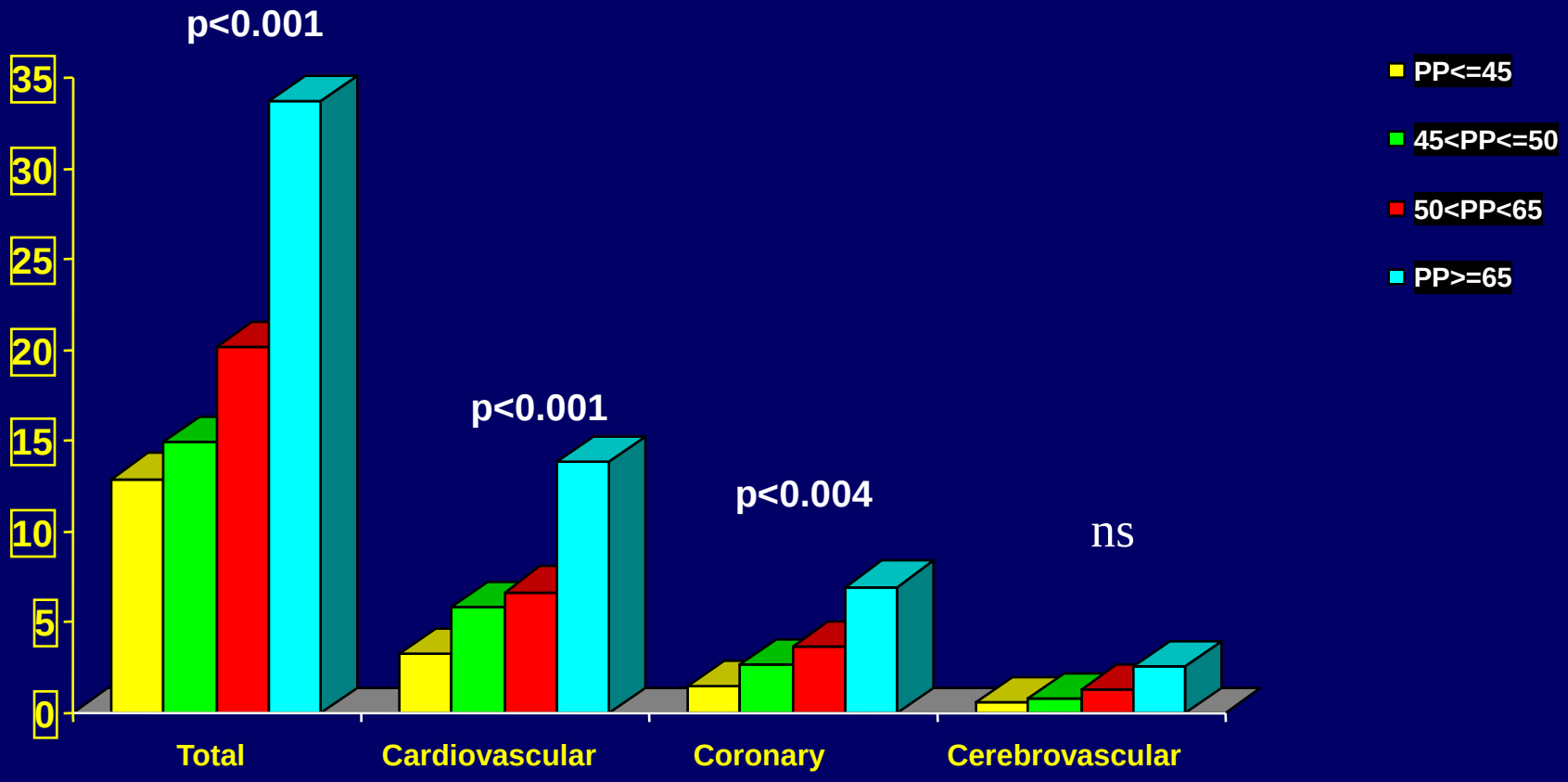
2- Effects of drugs on Arterial Stiffness

3- Role of the RAAS

Arterial stiffness: An independent determinant of Cardiovascular Risk

- Peripheral PP
- Central PP
- Augmentation Index
- PWV

20 years mortality according to the PP levels
The IPC study



Benetos et al, *Hypertension* 1997

Aortic Pulse Pressure Is Related to the Presence and Extent of Coronary Artery Disease in Men Undergoing Diagnostic Coronary Angiography: A Multicenter Study

Nicolas Danchin, Athanase Benetos, Marilucy Lopez-Sublet, Thibaud Demicheli, Michel Safar, and Jean-Jacques Mourad, on behalf of the ESCAPP Investigators

Background: In the general population, pulse pressure (PP) is a correlate of cardiovascular outcomes. Few data are available regarding the links between PP and documented coronary artery disease (CAD).

Methods: From July 2000 to January 2002, a total of 1337 patients referred for a first diagnostic coronary angiogram at 75 participating centers were prospectively included. Of these individuals, 280 patients receiving no hypertensive therapy constituted the study population. Pulse pressure was recorded in the aortic root before angiography, and baseline characteristics, medical history, treatment used, and data from coronary angiography were recorded.

Results: In the whole population, aortic PP strongly correlated with the presence and extent of CAD in univariate analyses. However, the correlation disappeared in multivariate analysis, and a strong interaction with gender was found. In women (n = 82), aortic PP was not an independent predictor of CAD. However, in men (n = 198) an independent correlation between aortic PP and CAD was found, together with age and hypercholesterolemia. In addition, PP was strongly correlated with the extent of CAD (no disease, 51 ± 16 mm Hg; one or two stenoses, 54 ± 18 mm Hg; and more than two stenoses: 64 ± 20 mm Hg).

Conclusions: In this multicenter study, aortic PP was significantly correlated with the presence and extent of CAD in patients without antihypertensive therapy. This correlation, however, was independent of other risk factors for CAD in men but not in women. Am J Hypertens 2004;17:129–133 © 2004 American Journal of Hypertension, Ltd.

Key Words: Pulse pressure, coronary artery disease, gender.

There is ample epidemiologic evidence that brachial pulse pressure (PP) is an independent correlate of cardiovascular outcomes in the general population.[1–7] Specifically, it was shown that PP was a strong predictor of cardiac risk, whereas mean arterial pressure was a stronger predictor of cerebral events.[4] Few studies, involving only a limited number of patients, have investigated the relation between PP and angiographically documented coronary artery disease (CAD).[8–11]

In the present multicenter study, we sought to determine whether aortic PP measured at the time of a first diagnostic coronary angiogram was related to the presence and extent of CAD in patients who did not receive antihypertensive therapy.

Methods

Patients

From July 2000 to January 2002, a total of 1337 patients ≥40 years of age who were referred for a first diagnostic coronary angiogram at the 75 participating institutions were recruited. There was one investigator in each center, and the patients were recruited consecutively on the basis of the investigator's availability. We excluded patients who had already undergone any coronary angiography, those who were not in sinus rhythm, those with significant aortic valve disease (aortic stenosis with peak to peak gradient >25 mm Hg, aortic regurgitation greater than grade 1), those with a recent (<5 days myo-

Central Pulse Pressure and Mortality in End-Stage Renal Disease

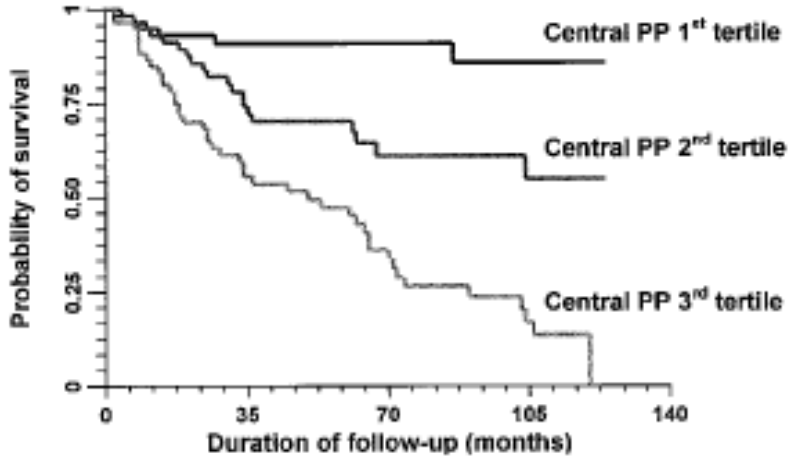
Michel E. Safar, Jacques Blacher, Bruno Pannier, Alain P. Guerin, Sylvain J. Marchais, Pierre-Marie Guyonvarc'h, Gérard M. London

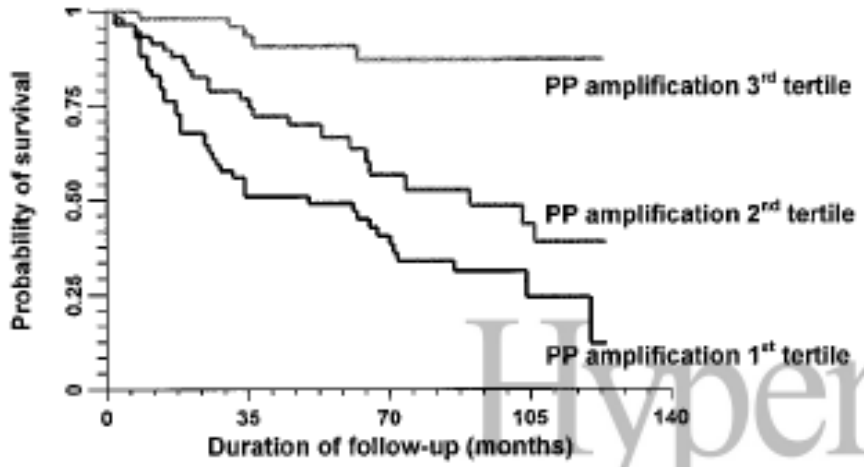
Abstract—Damage of large arteries is a major factor in the high cardiovascular morbidity and mortality of patients with end-stage renal disease (ESRD). Increased aortic pulse wave velocity (PWV) and brachial pulse pressure (PP) are the principal arterial markers of cardiovascular mortality described in these patients. Whether central (carotid) PP and brachial-carotid PP amplification may predict all-cause (including cardiovascular) mortality has never been investigated. A cohort of 180 patients with ESRD who were undergoing hemodialysis was studied between January 1990 and March 2000. The mean duration of follow-up was 52±36 months (mean±SD). Mean age at entry was 51.5±16.3 years. Seventy deaths occurred, including both cardiovascular and noncardiovascular fatal events. At entry, patients underwent carotid PP measurements (pulse wave analysis), echocardiography, and aortic PWV (Doppler ultrasonography), together with standard clinical and biochemical analyses. On the basis of Cox analyses, after adjustment of age, time on dialysis before inclusion, and previous cardiovascular events, 3 factors emerged as predictors of all-cause mortality: carotid PP, brachial/carotid PP, and aortic PWV. Adjusted hazard ratios for 1-SD increments were 1.4 (1.1 to 1.8) for carotid PP, 0.5 (0.3 to 0.8) for brachial/carotid PP, and 1.3 (1.0 to 1.7) for PWV. Brachial blood pressure, including PP, had no predictive value for mortality after adjustment. These results provide the first direct evidence that in patients with ESRD, the carotid PP level and, mostly, the disappearance of PP amplification are strong independent predictors of all-cause (including cardiovascular) mortality. (*Hypertension*. 2002;39:735-738.)

Key Words: renal disease ■ blood pressure ■ pulse ■ aorta ■ mortality

Central pulse pressure in ESRD patients

Hypertension 2002





Probabilities of survival in the study population according to the level of central PP and PP amplification divided into tertiles. Comparisons between survival curves were highly significant ($P<0.001$ for both).

Aortic Pressure Augmentation Predicts Adverse Cardiovascular Events in Patients With Established Coronary Artery Disease

Julio A. Chirinos, Juan P. Zambrano, Simon Chakko, Anila Veerani, Alan Schob, Howard J. Willens, Guido Perez, Armando J. Mendez

Abstract—Pulse pressure (PP), a marker of arterial stiffness, predicts cardiovascular risk. We aimed to determine whether augmentation pressure (AP) derived from the aortic pressure waveform predicts major adverse cardiovascular events (MACE) and death independently of PP in patients with established coronary artery disease (CAD). We prospectively followed-up 297 males undergoing coronary angiography for 1186±424 days. Ascending aortic pressure tracings obtained during catheterization were used to calculate AP (difference between the second and the first systolic peak). Augmentation index (AIx) was defined as AP as a percentage of PP. We evaluated whether AP and AIx can predict the risk of MACE (unstable angina, acute myocardial infarction, coronary revascularization, stroke, or death) and death using Cox regression. All models evaluating AP included PP to assess whether AP adds to the information already provided by PP. Both AP and AIx significantly predicted MACE. The hazard ratio (HR) per 10 mm Hg increase in AP was 1.20 (95% confidence interval [CI], 1.08 to 1.34; $P<0.001$); the HR for each 10% increase in AIx was 1.28 (95% CI, 1.11 to 1.48; $P=0.004$). After adjusting for other univariate predictors of MACE, age, and other potential confounders, AP remained a significant predictor of MACE (HR per 10 mm Hg increase=1.19; 95% CI, 1.06 to 1.34; $P=0.002$), as did AIx (adjusted HR, 1.28; 95% CI, 1.09 to 1.50; $P=0.003$). AP was a significant predictor of death (HR per 10 mm Hg increase=1.18; 95% CI, 1.02 to 1.39; $P=0.03$). Higher AIx was associated with a trend toward increased mortality (HR=1.22; 95% CI, 0.98 to 1.52; $P=0.056$). Aortic AP predicts adverse outcomes in patients with CAD independently of PP and other risk markers. (***Hypertension*. 2005;45:980-985.**)

Key Words: arterial stiffness ■ cardiovascular events ■ coronary angiography ■ coronary artery disease ■ prospective study

Augmentation pressure and cardio-vascular events in CAD patients

Chirinos et al, Hypertension, 2005

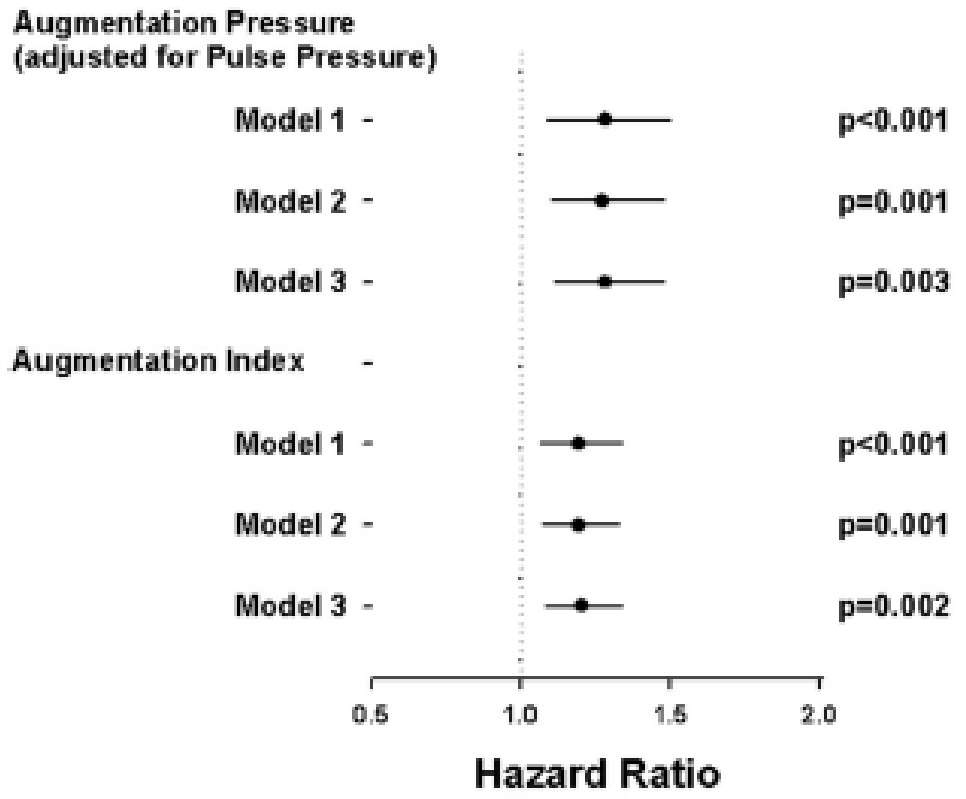
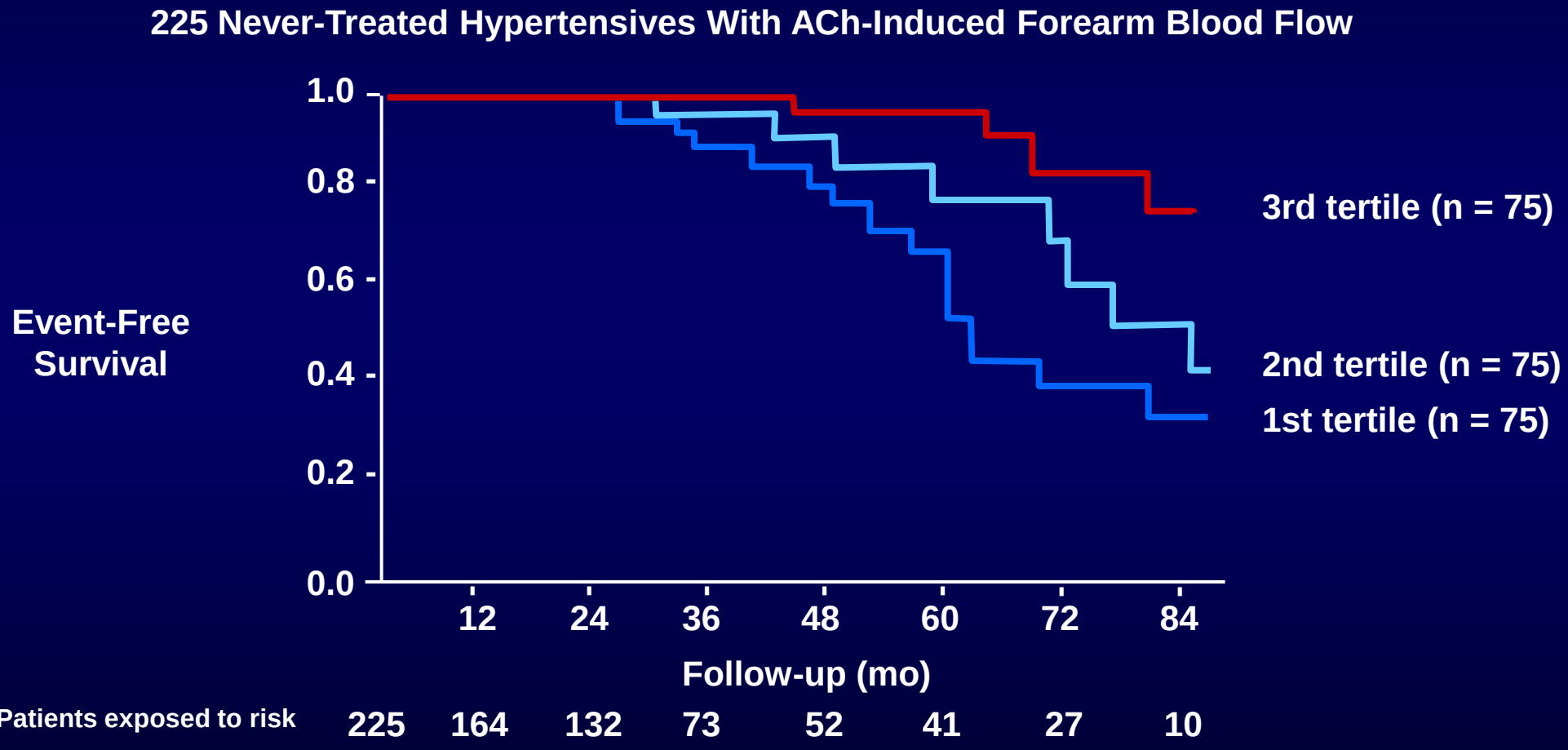


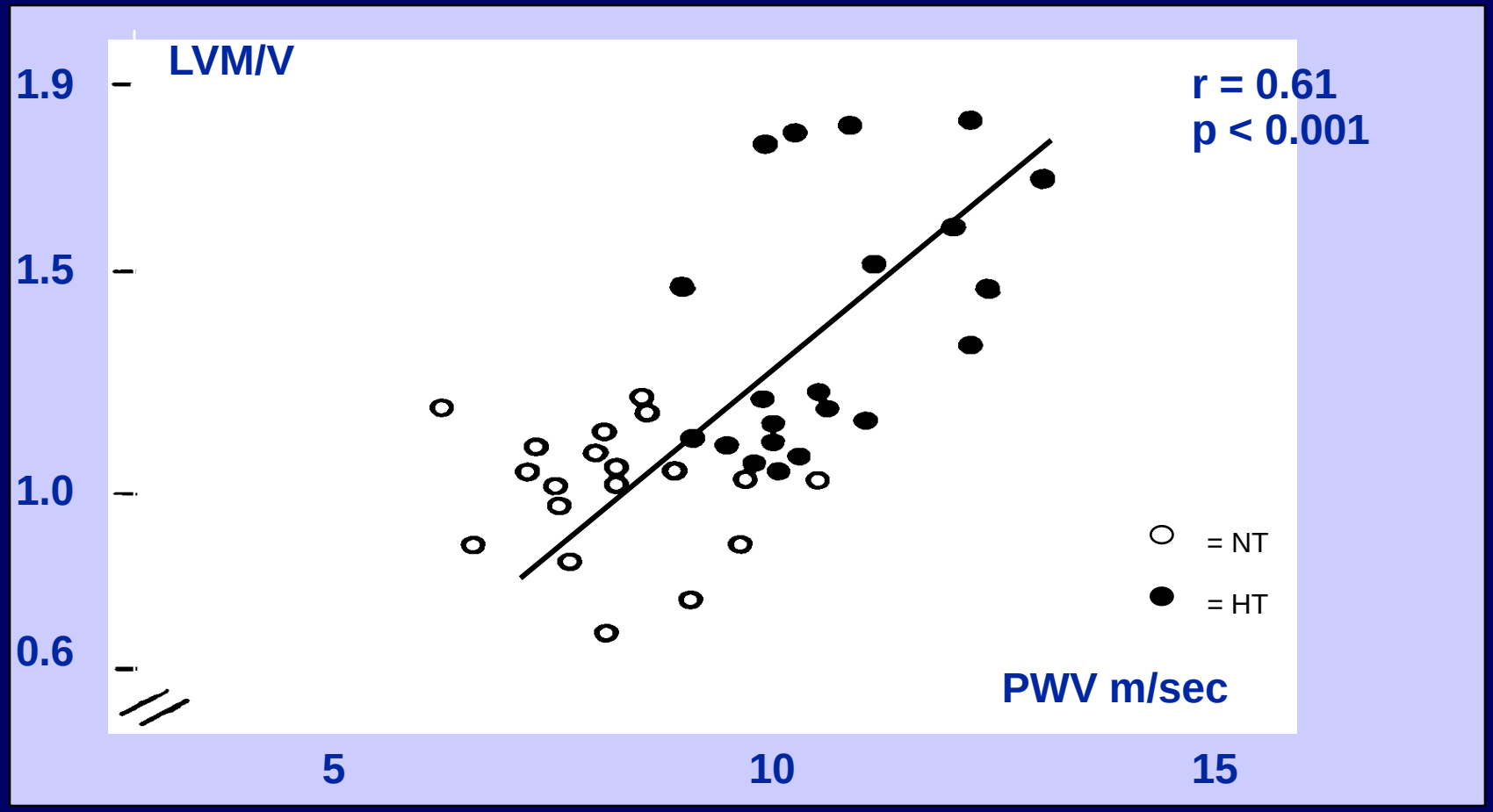
Figure 2. Augmentation pressure and augmentation index as predictors of major adverse cardiovascular outcomes. Hazard ratios and 95% confidence intervals for each 10-mm Hg increase in augmentation pressure (adjusted for pulse pressure) or 10% increase in augmentation index (AIx). Both augmentation pressure and AIx were adjusted for mean aortic pressure, heart rate, and ejection fraction in all models. Model 2 also included univariate predictors of major adverse cardiovascular events shown in Table 2. Model 3 included variables in model 2, age, height, and other potential confounders (angiotensin-converting enzyme inhibitor, β-blocker, statin use, high-density lipoprotein

Endothelial Dysfunction and Prognosis in Hypertensives



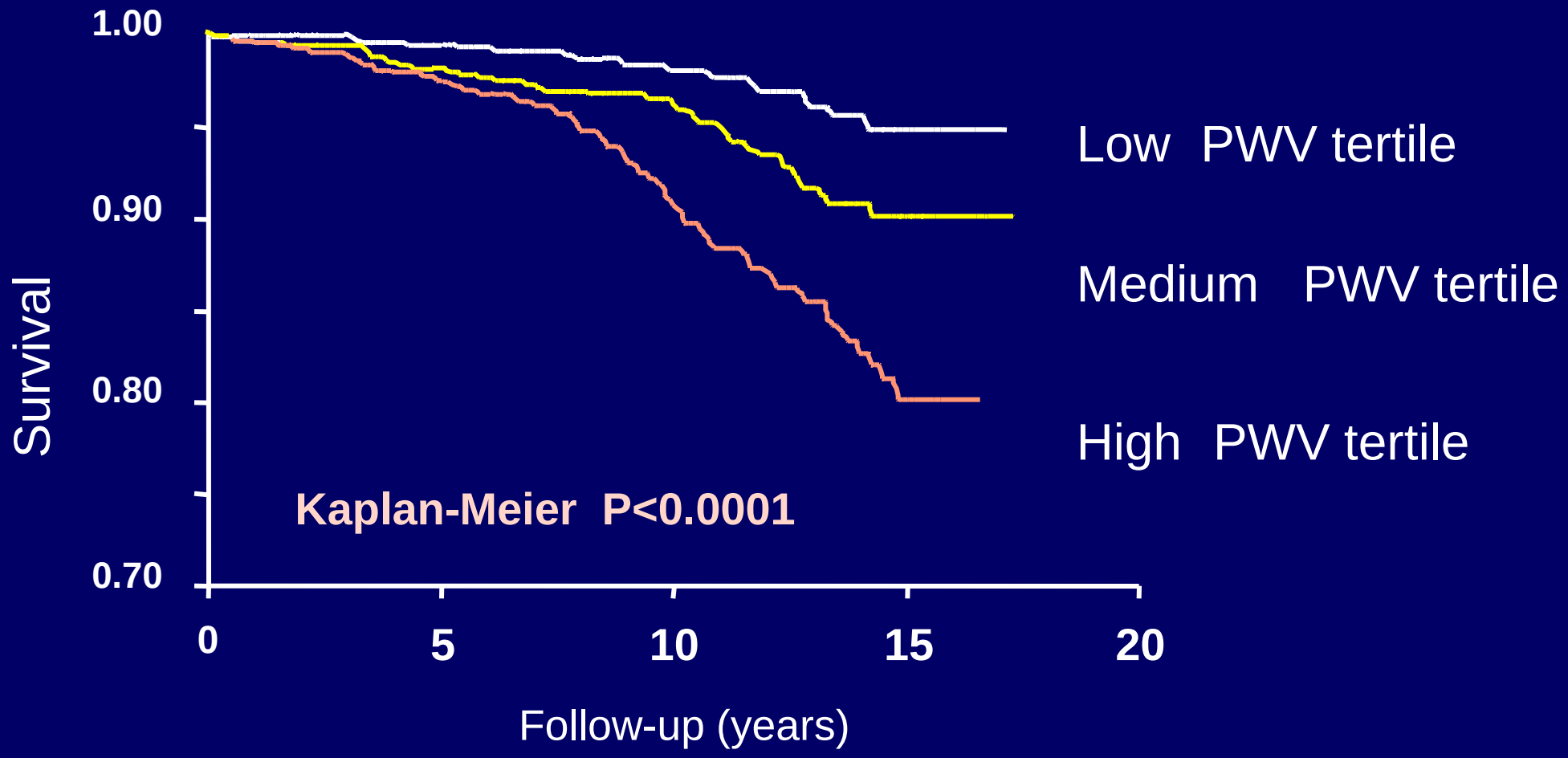
Perticone F et al. *Circulation.* 2001;104:191-196.

PWV is an independent determinant of LV hypertrophy



Bouthier et al, Am Heart J 1985

PWV and all-cause mortality in hypertensive subjects



Laurent S. et al. *Hypertension*, 2001

Arterial stiffness is associated with cardiovascular events in well functioning older adults

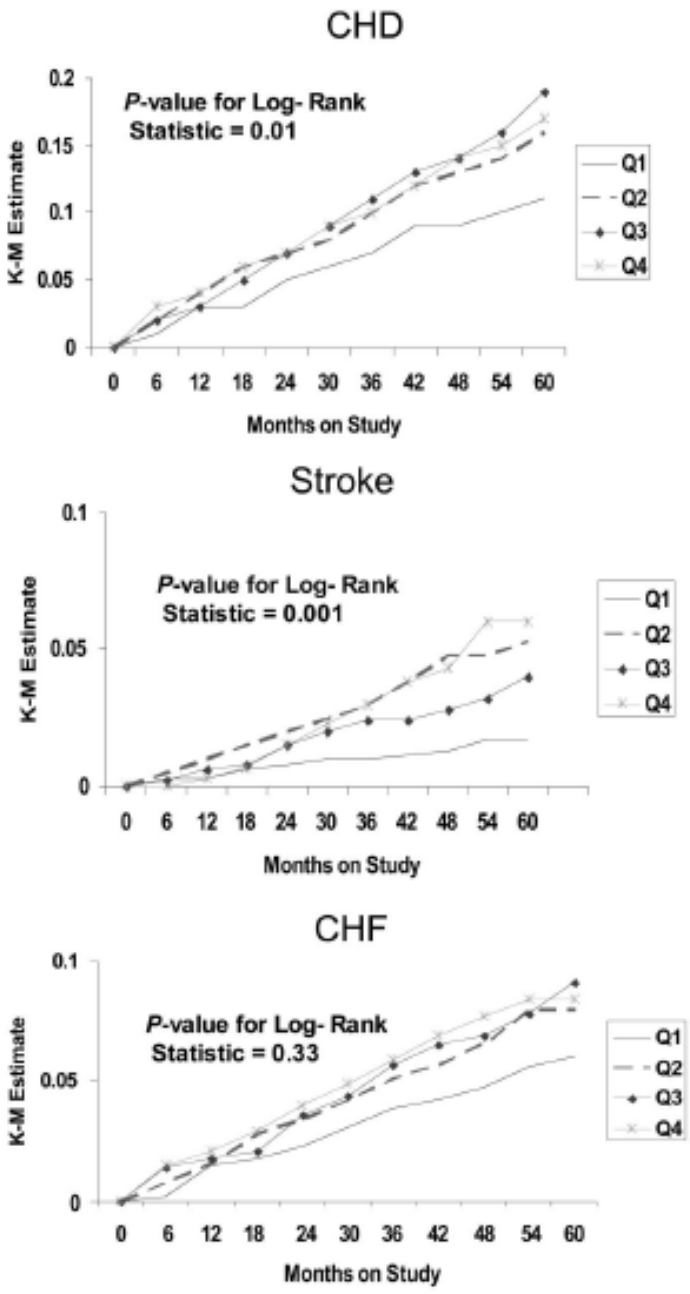
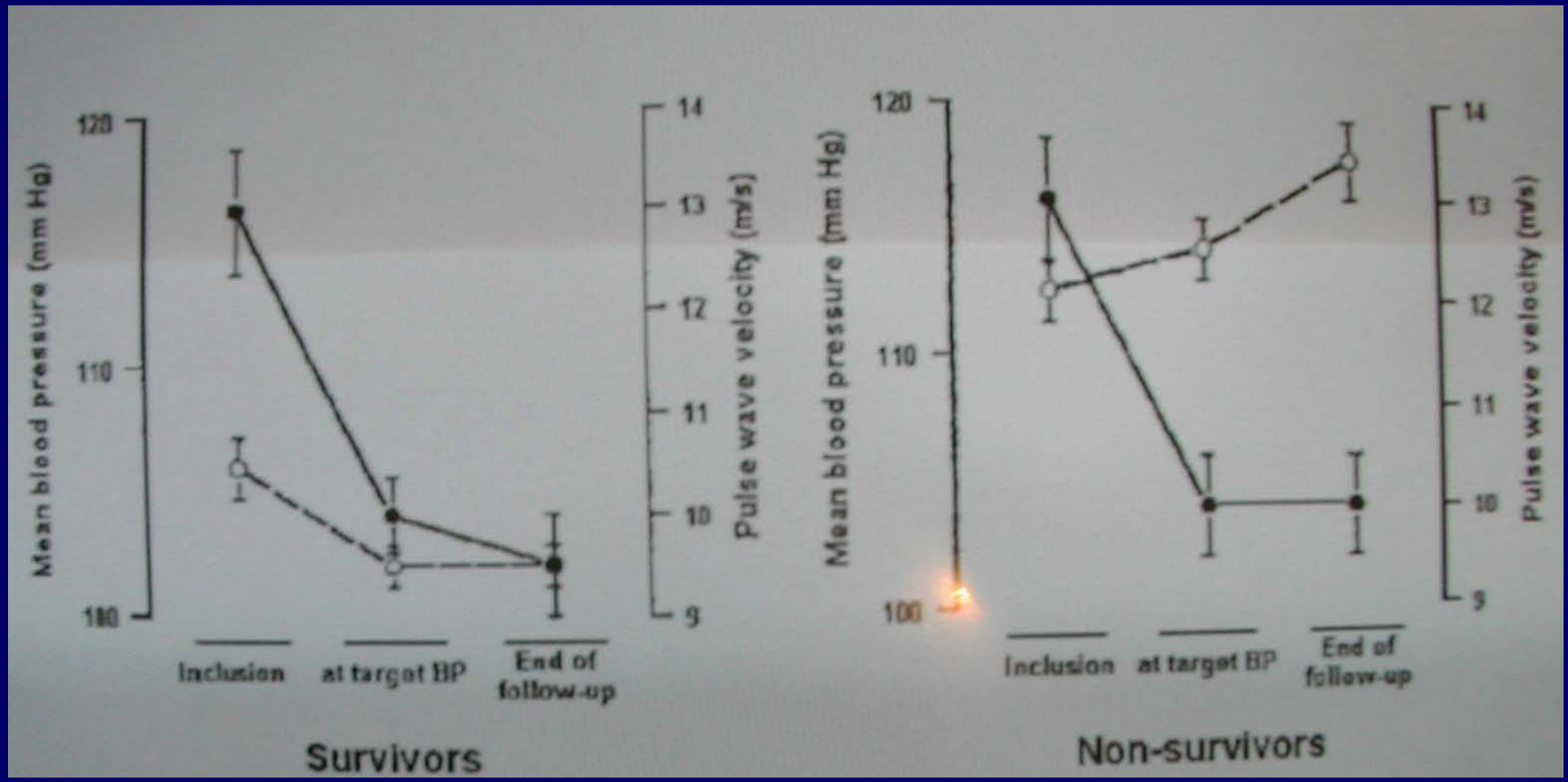


Figure 2. Kaplan-Meier estimates of CHD (top), stroke (middle), and CHF (bottom) by aPWV quartile.

Sutton-Tyrrell et al, *Circulation* 2005

Impact of aortic stiffness attenuation on survival of patients with end stage renal failure



Guerin A, et al; *Circulation 2001*

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Blood Pressure Response Under Chronic Antihypertensive Drug Therapy

The Role of Aortic Stiffness in the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind) Study

Athanase Protogerou, MD,* Jacques Blacher, MD, PhD,† George S. Stergiou, MD,* Apostolos Achimastos, MD,* Michel E. Safar, MD†

Athens, Greece; and Paris, France

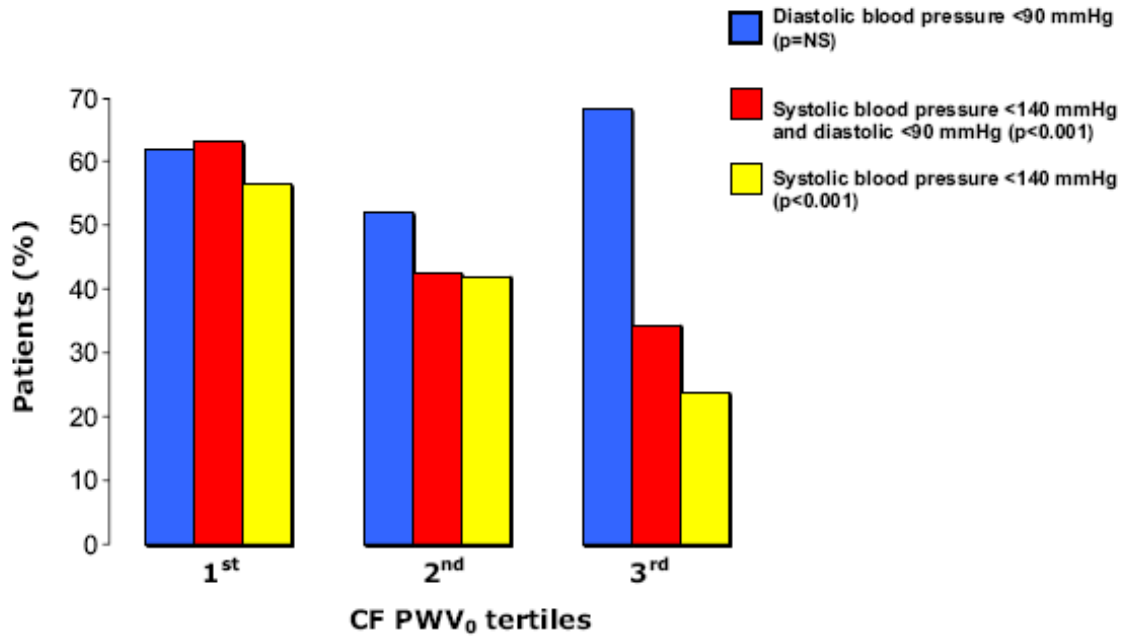


Figure 1 **Percentage of Patients* With Effective Blood Pressure Control After 12 Months of Treatment**

*Population with increased dosage (n = 154), similar results were found in the whole population (n =375) after 3 months (i.e., before dosage increase) and at 12 months. CF PWV_0 = baseline carotid-femoral pulse wave velocity.

1- Arterial stiffness: An independent determinant of Cardiovascular Risk

2- Effects of drugs on Arterial Stiffness

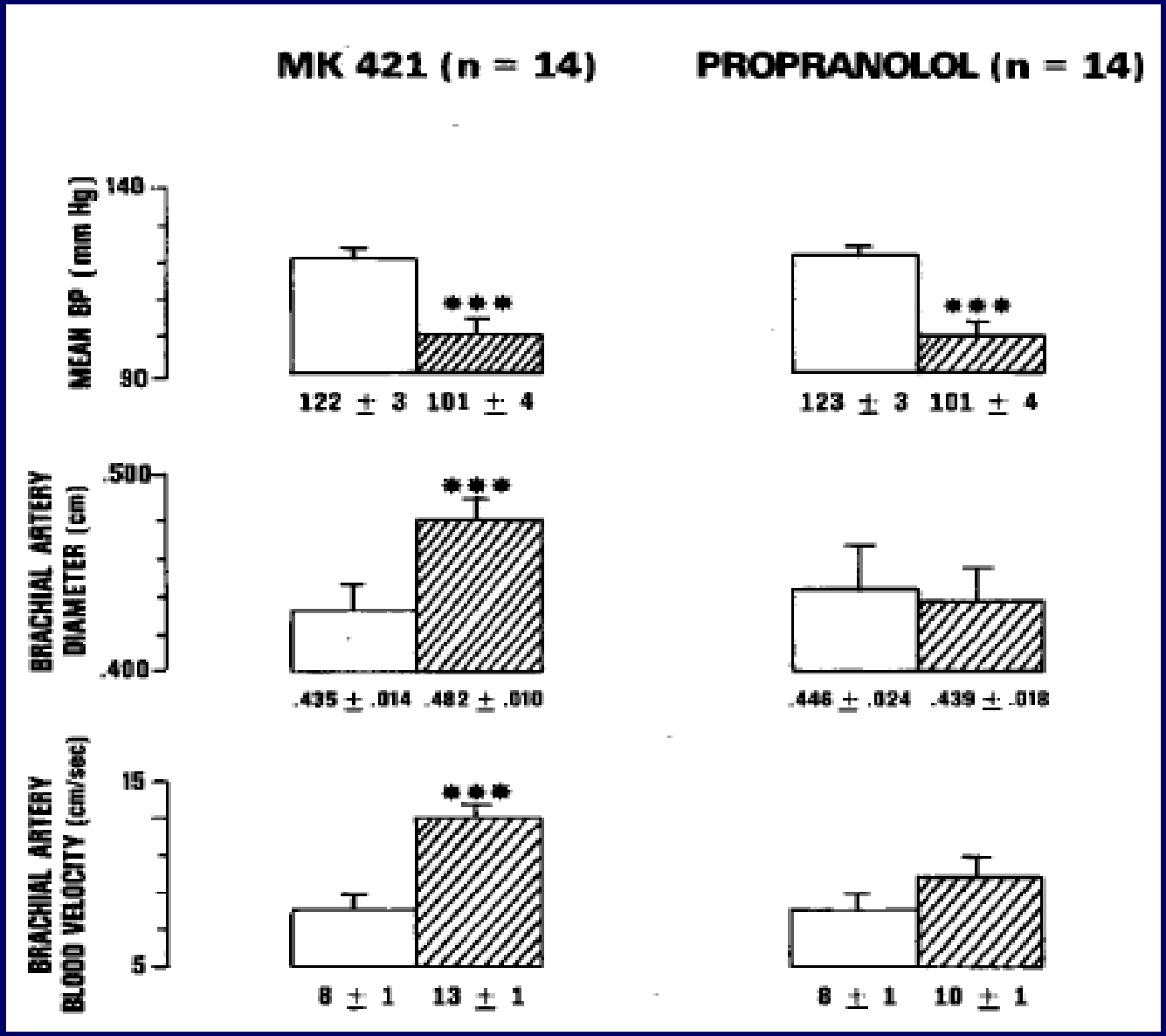
3- Role of the RAAS

Comparison of Oral MK 421 and Propranolol in Mild to Moderate Essential Hypertension and Their Effects on Arterial and Venous Vessels of the Forearm

ALAIN Ch. SIMON, MD, JAIME A. LEVENSON, MD, JEAN D. BOUTHIER, MD, ATHANASE BENETOS, MD, APOSTOLOS ACHIMASTOS, MD, MARIE FOUCHARD, MD, BRIGITTE C. MAAREK, MD, and MICHEL E. SAFAR, MD

Am J Cardiol, 1984

Enalapril vs Propranolol on large artery geometry and mechanics



Simon A, Am J Cardiol, 1984

Enalapril vs Propranolol on large artery geometry and mechanics

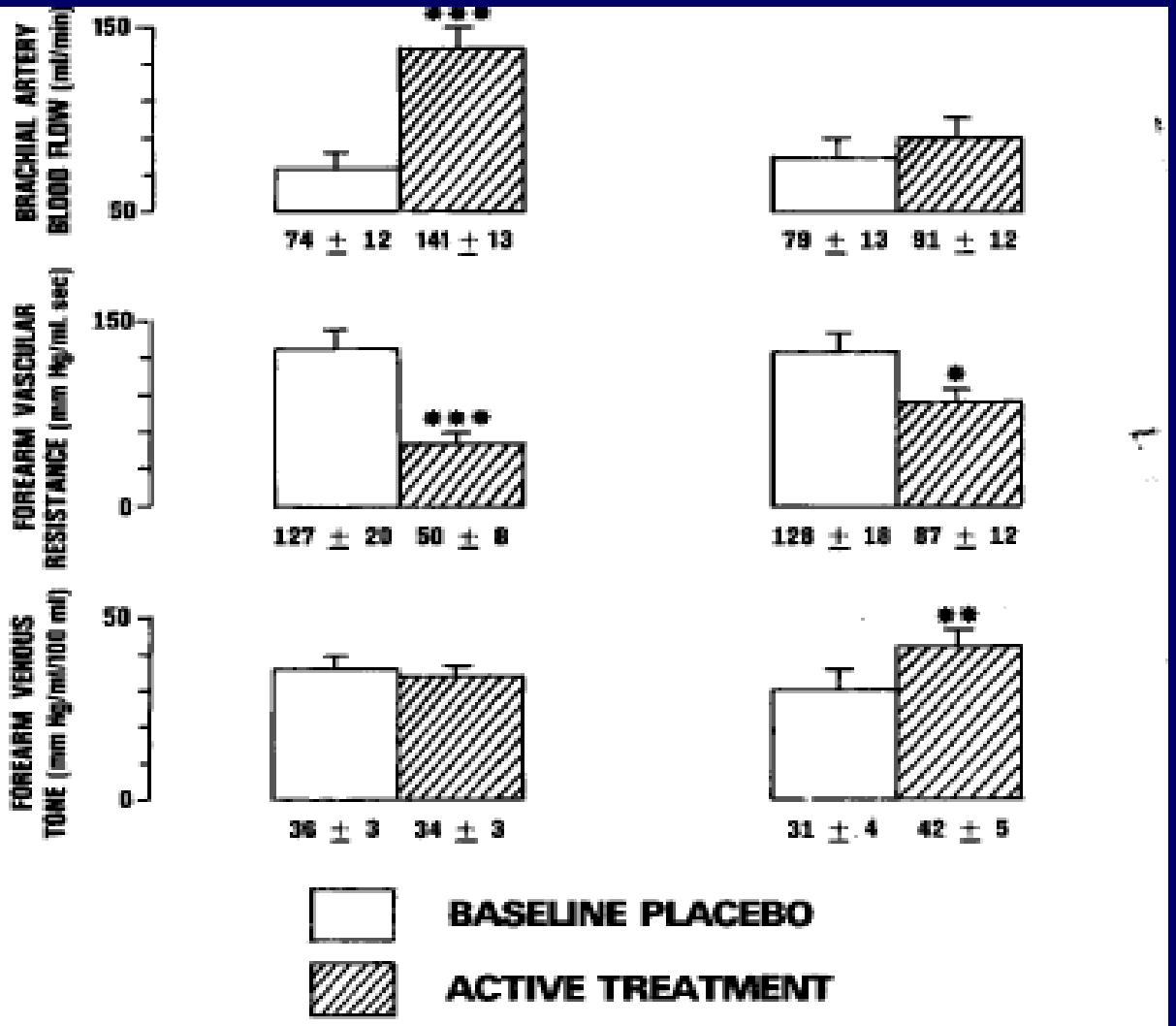


FIGURE 3. Changes in forearm circulation after treatment with MK 421 and propranolol. Values are mean ± standard error of the mean. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. BP = blood pressure.

Simon A, Am J Cardiol, 1984

Vascular effects of intravenous infusion of the angiotensin converting enzyme inhibitor perindoprilat

Athanase Benetos, Jean Philippe Santoni and Michel E. Safar

This study was aimed at evaluating the hemodynamic changes after acute inhibition of the renin–angiotensin system in hypertensive patients. Twenty-one subjects with essential hypertension were randomized into three groups of seven subjects each. In group I, the direct vascular vasodilator dihydralazine was administered at a dose of 4 μg/kg per min. Groups II and III received a continuous intravenous infusion of the angiotensin converting enzyme (ACE) inhibitor perindoprilat at a dose of 1 μg/kg per min and 2.5 μg/kg per min, respectively. Brachial artery hemodynamics and aortic distensibility were evaluated non-invasively. Vascular reactivity was evaluated by the cold-pressor test. In all three groups, an identical decrease in blood pressure was observed ($P < 0.001$), followed by a slight (but not significant) decrease in the heart rate in both perindoprilat groups, and an important tachycardia in the dihydralazine group ($P < 0.001$). Brachial artery diameter was increased in the high-dose perindoprilat group from 0.437 ± 0.014 to 0.479 ± 0.013 cm ($P < 0.02$), but remained unchanged in the two other groups. No significant changes in brachial artery mean blood velocity and blood flow were observed. In group III, aortic distensibility increased almost twice as much as in the two other groups, but this difference was not statistically significant. The pressor response to the cold-pressor test was not modified in the three groups; the heart rate response was almost completely abolished in groups II and III, but increased in the dihydralazine group ($P < 0.01$). These results suggest that (1) intravenous administration of perindoprilat decreases blood pressure without increasing the heart rate, and inhibits tachycardia during the cold-pressor test, and (2) since only higher doses of ACE inhibitor may be capable of inducing vasodilatation in the large arteries, despite having an identical hypotensive effect and the same degree of plasma ACE inhibition, the two different doses of perindoprilat induced different vascular effects. We propose that higher doses of perindoprilat may be necessary in order to inhibit vascular ACE, or to stimulate vasodilating systems.

Journal of Hypertension 1990, **8**:819–826

Keywords: Arterial compliance, vascular renin, angiotensin system, angiotensin converting enzyme inhibition, vascular reactivity.

Vasodilating effects of Dihydralazine and Perindopril

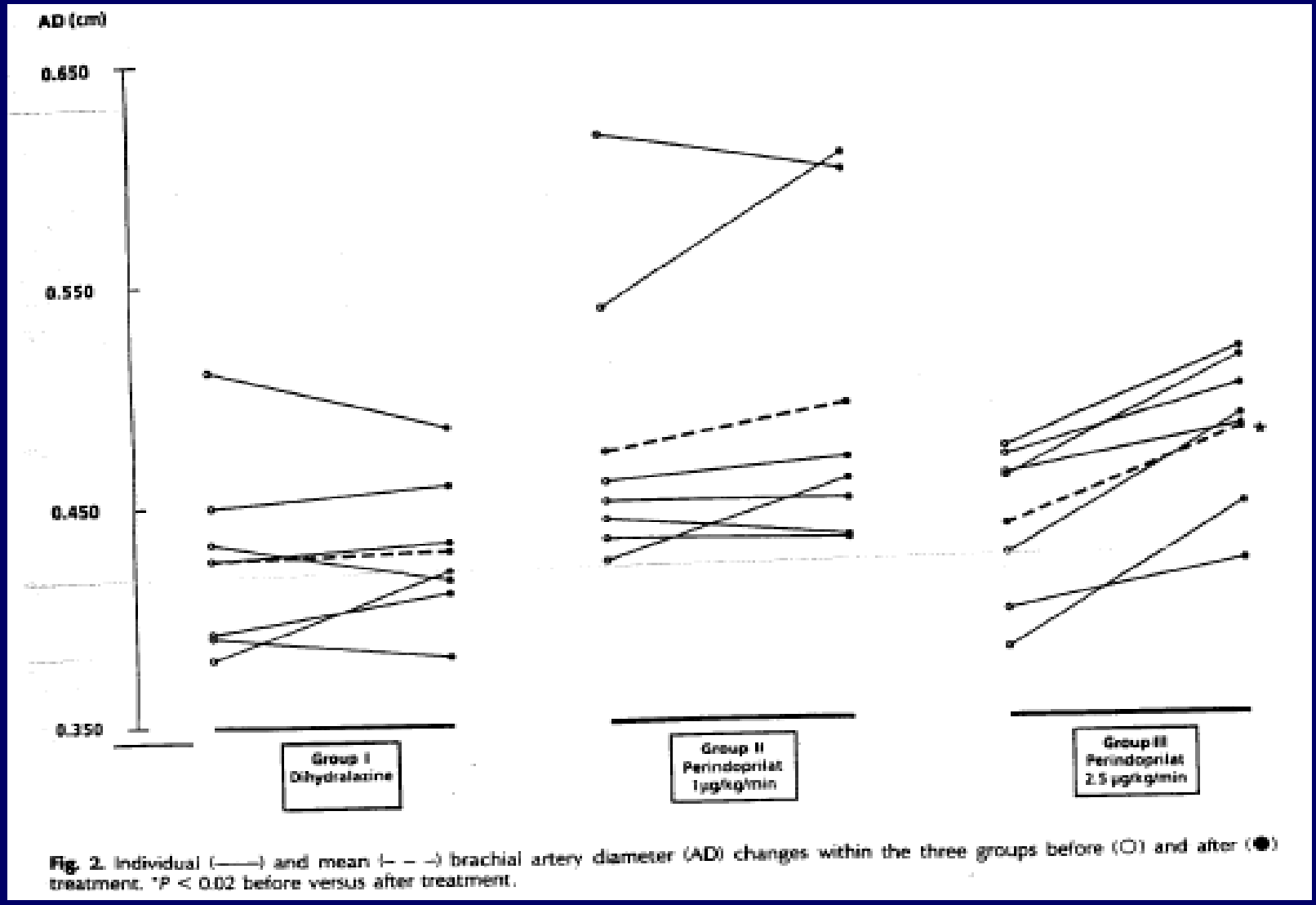


Fig. 2. Individual (——) and mean (– – –) brachial artery diameter (AD) changes within the three groups before (○) and after (●) treatment. *$P < 0.02$ before versus after treatment.

Benetos A et al; *J. Hypertens* 1990

Differential Impact of Blood Pressure–Lowering Drugs on Central Aortic Pressure and Clinical Outcomes

Principal Results of the Conduit Artery Function Evaluation (CAFE) Study

The CAFE Investigators, for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators

CAFE Steering Committee and Writing Committee: Bryan Williams, MD, FRCP; Peter S. Lacy, PhD; Simon M. Thom, MD, FRCP; Kennedy Cruickshank, MD; Alice Stanton, MB, PhD, FRCPI; David Collier, MBBS, PhD; Alun D. Hughes, MBBS, PhD; H. Thurston, MD, FRCP

Study Advisor: Michael O'Rourke, MD, FRACP

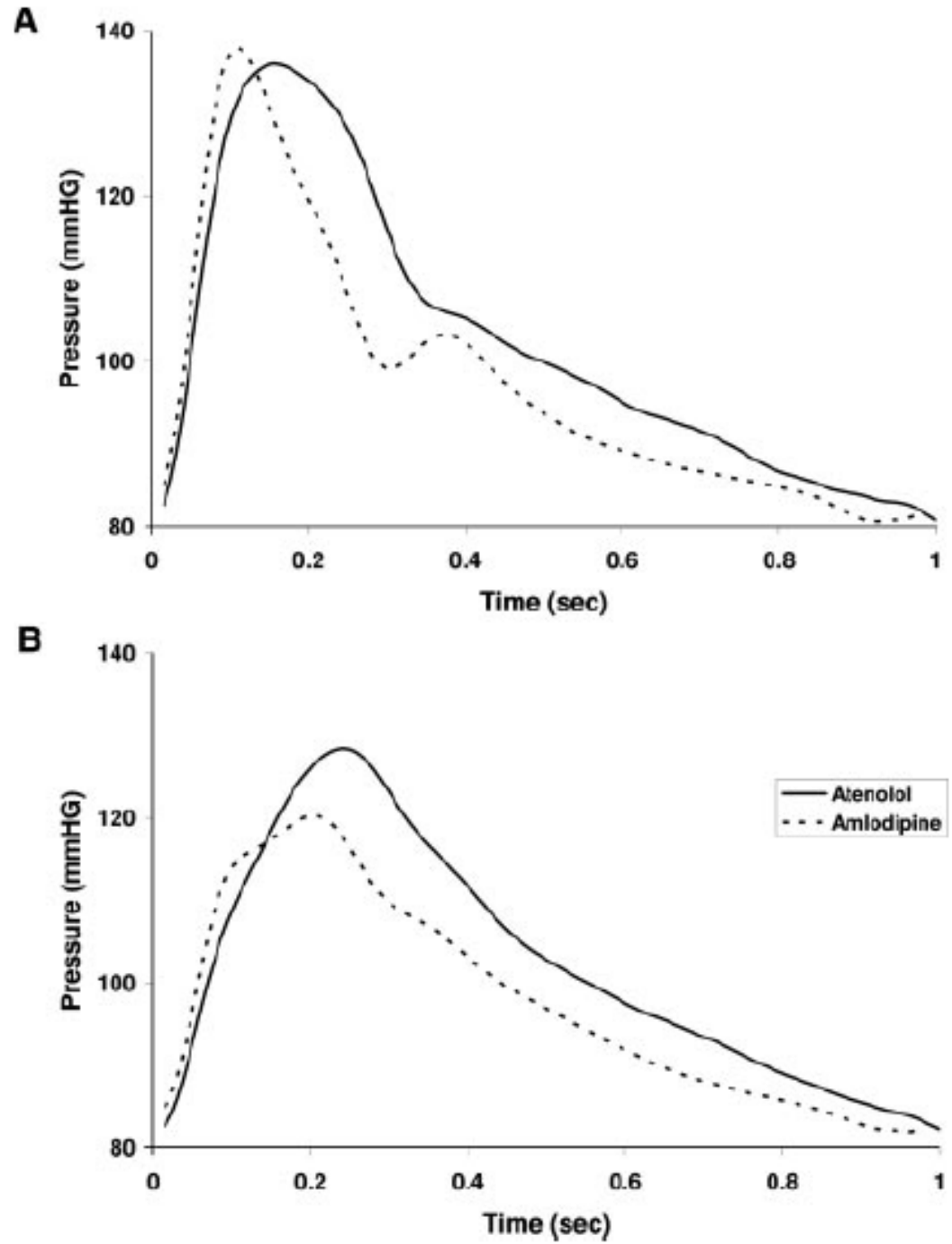
Background—Different blood pressure (BP)-lowering drugs could have different effects on central aortic pressures and thus cardiovascular outcome despite similar effects on brachial BP. The Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), examined the impact of 2 different BP lowering-regimens (atenolol±thiazide-based versus amlodipine±perindopril-based therapy) on derived central aortic pressures and hemodynamics.

Methods and Results—The CAFE study recruited 2199 patients in 5 ASCOT centers. Radial artery applanation tonometry and pulse wave analysis were used to derive central aortic pressures and hemodynamic indexes on repeated visits for up to 4 years. Most patients received combination therapy throughout the study. Despite similar brachial systolic BPs between treatment groups (Δ0.7 mm Hg; 95% CI, −0.4 to 1.7; $P=0.2$), there were substantial reductions in central aortic pressures with the amlodipine regimen (central aortic systolic BP, Δ4.3 mm Hg; 95% CI, 3.3 to 5.4; $P<0.0001$; central aortic pulse pressure, Δ3.0 mm Hg; 95% CI, 2.1 to 3.9; $P<0.0001$). Cox proportional-hazards modeling showed that central pulse pressure was significantly associated with a post hoc–defined composite outcome of total cardiovascular events/procedures and development of renal impairment in the CAFE cohort (unadjusted, $P<0.0001$; adjusted for baseline variables, $P<0.05$).

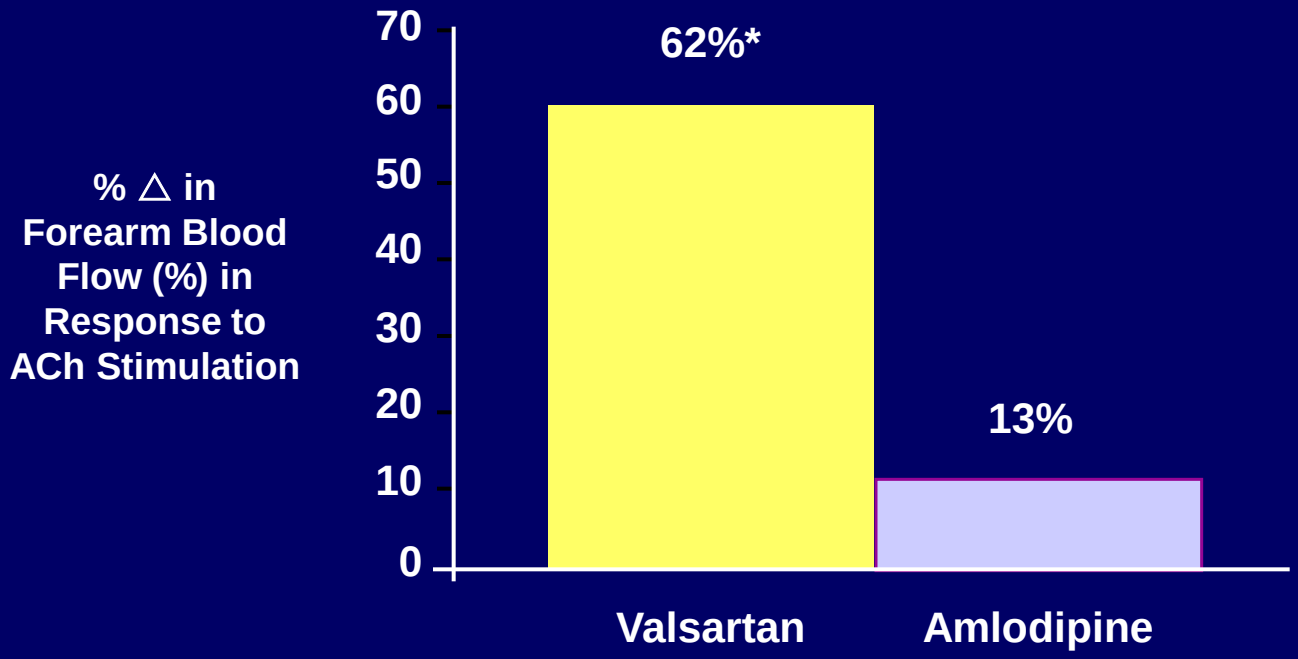
Conclusions—BP-lowering drugs can have substantially different effects on central aortic pressures and hemodynamics despite a similar impact on brachial BP. Moreover, central aortic pulse pressure may be a determinant of clinical outcomes, and differences in central aortic pressures may be a potential mechanism to explain the different clinical outcomes between the 2 BP treatment arms in ASCOT. (*Circulation*. 2006;113:1213-1225.)

Key Words: aorta ■ arteries ■ blood pressure ■ hemodynamics ■ hypertension

CAFE study


A
140
120
100
80
Pressure (mmHG)
0
0.2
0.4
0.6
0.8
1
Time (sec)
B
140
120
100
80
Pressure (mmHG)
0
0.2
0.4
0.6
0.8
1
Time (sec)
Atenolol
Amlodipine

Valsartan vs Amlodipine: Improvement in Endothelial Function

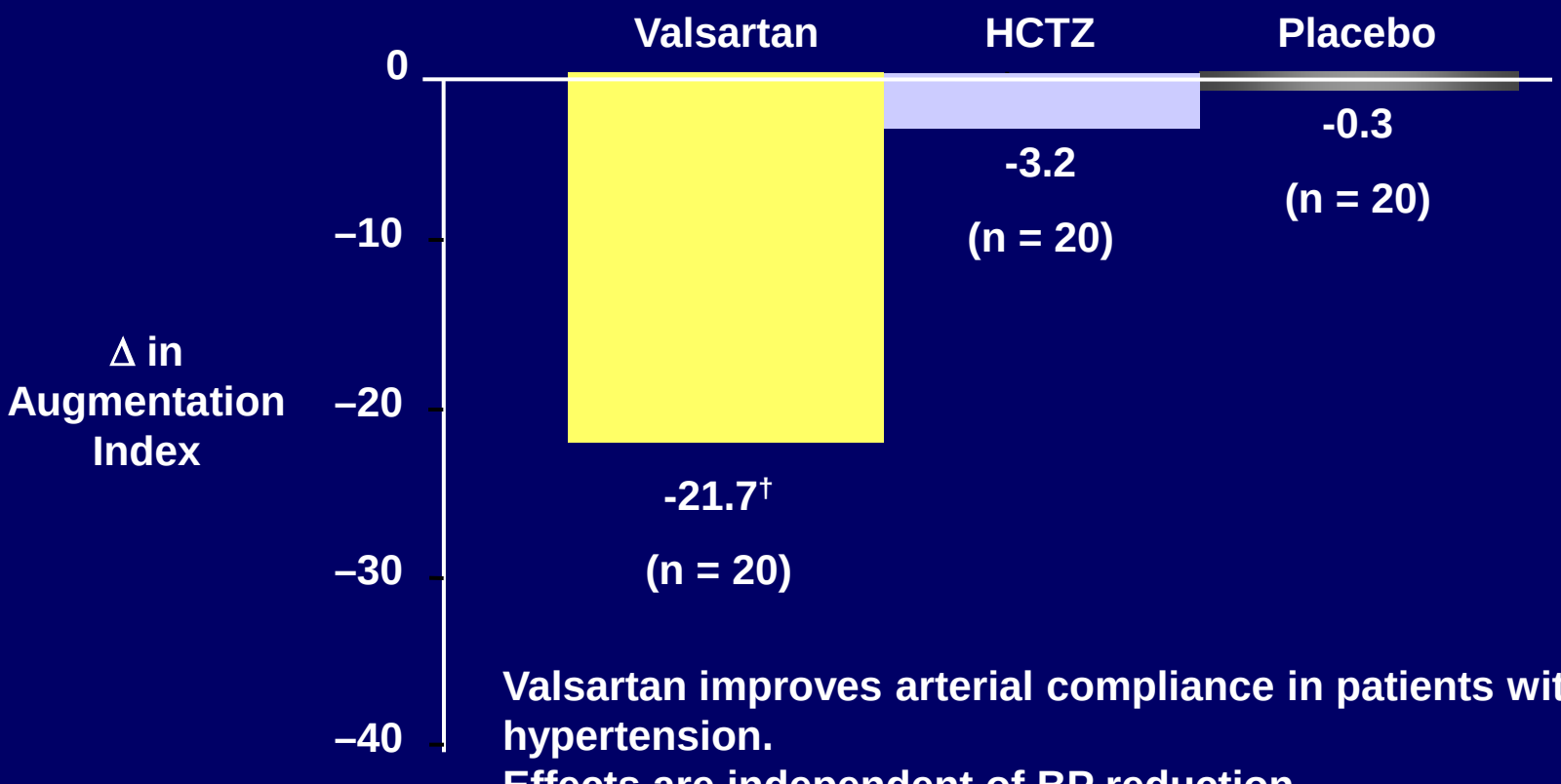


In this single-blind crossover study, 12 hypertensive patients were randomized to valsartan and amlodipine for 8-week treatment periods that were separated by a 2-week placebo washout. Intra-arterial infusions of ACh were used to assess stimulated endothelium-dependent nitric oxide release.

*P <0.05 vs baseline.

Tzemos N et al. *Am J Hypertens.* 2001;14:A66-A67.

Valsartan Improves Vessel Elasticity



Valsartan improves arterial compliance in patients with hypertension.
Effects are independent of BP reduction.

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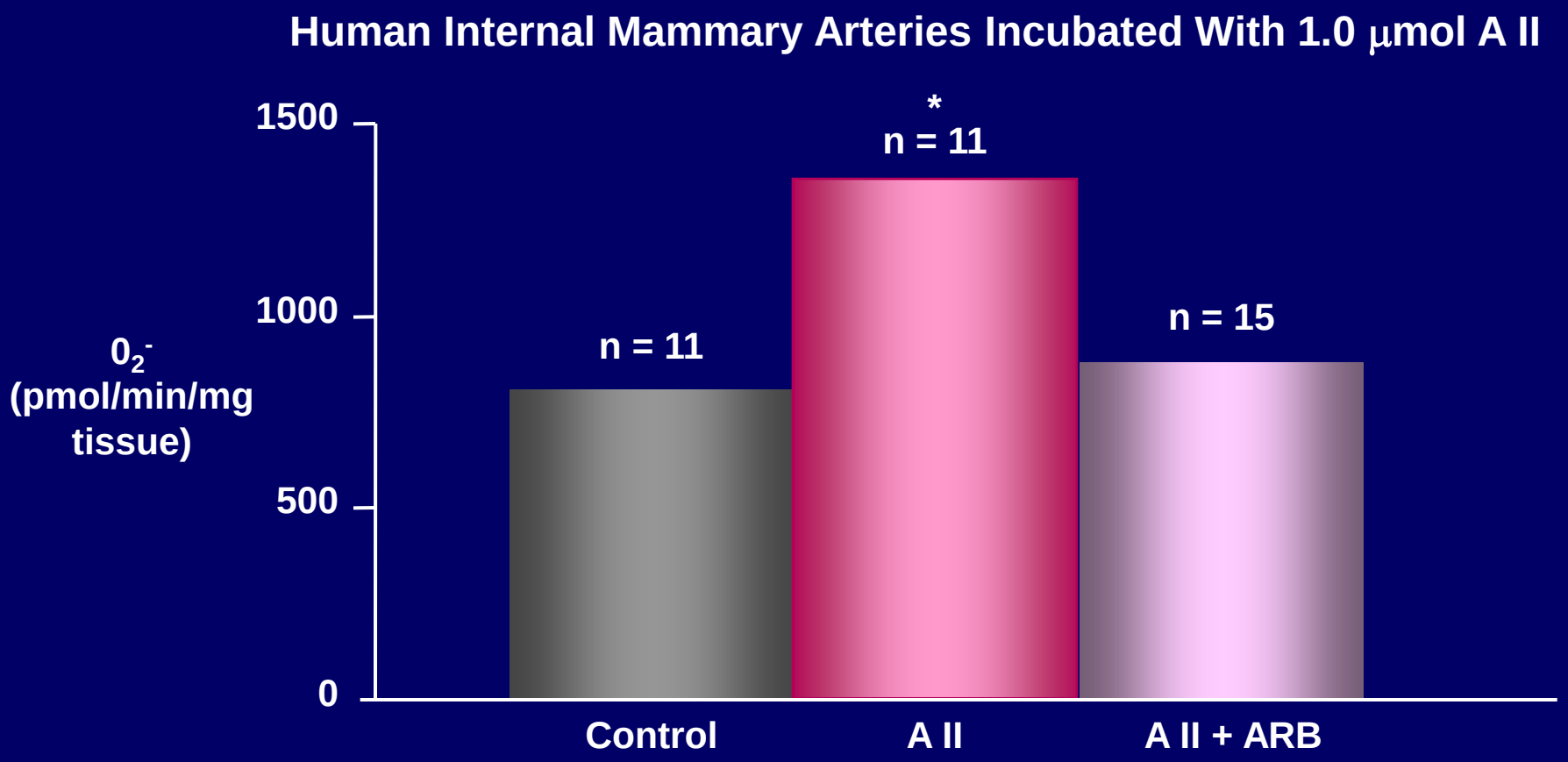
Klingbeil AU et al. *J Hypertens*. 2002;20:2423-2428.

A II Induces Superoxide Production in Human Vascular Tissue



**P* =0.001 vs control.

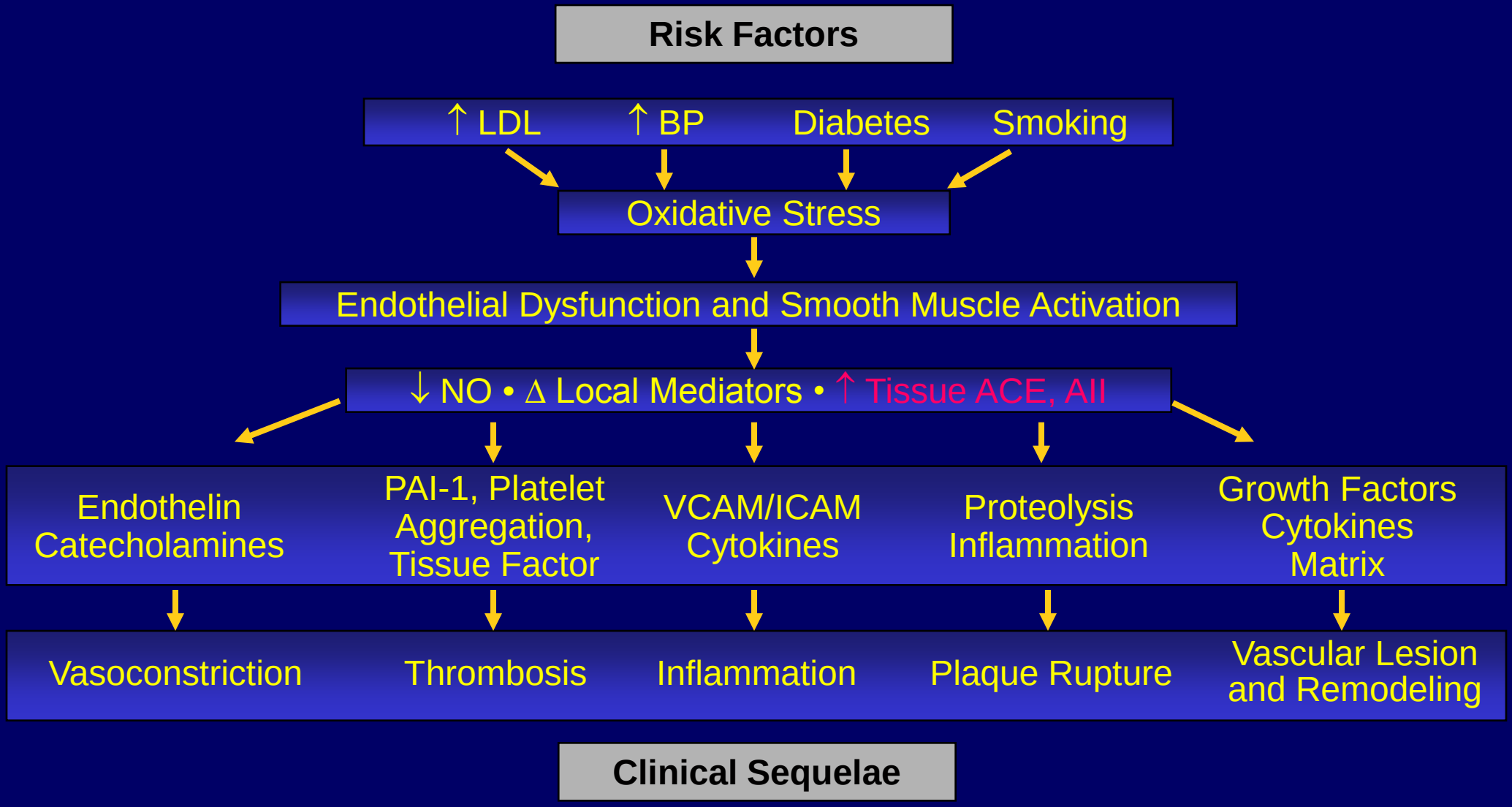
Berry C et al. *Circulation*. 2000;101:2206-2212.

1- Arterial stiffness: An independent determinant of Cardiovascular Risk

2- Effects of drugs on Arterial Stiffness

3- Role of the RAAS

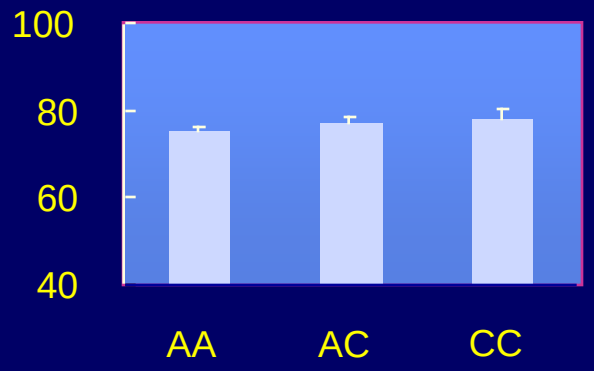
Role of A II in Vascular Disease



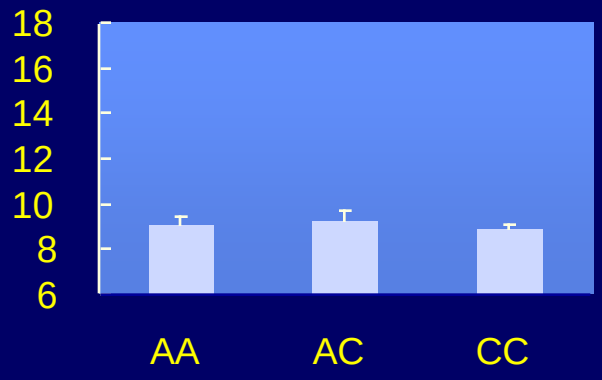
Dzau VJ. *Hypertension*. 2001;37:1047-1052.

DBP and PWV in normotensive and hypertensive subjects according to the AT_1R $A^{1166}C$ genotype

Normotensives

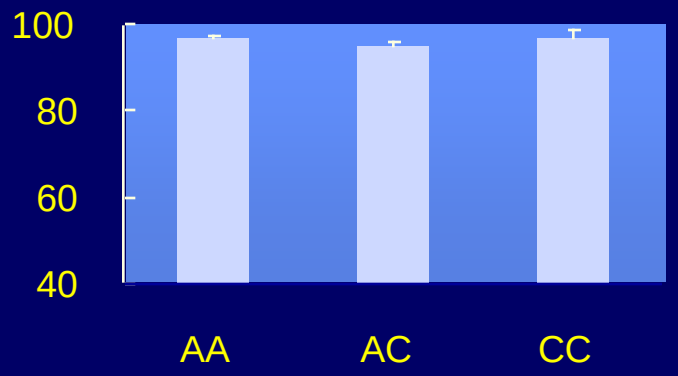


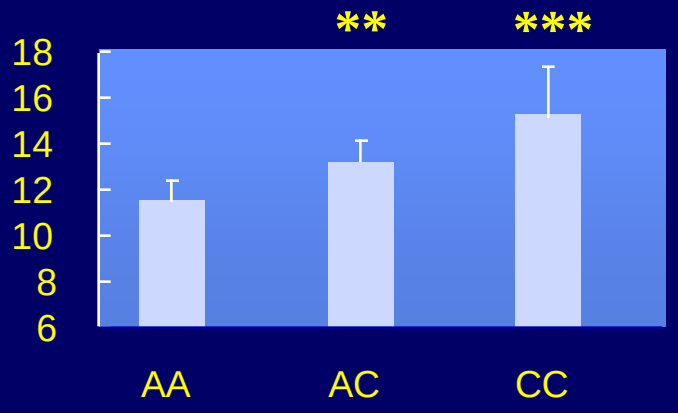
DBP (mmHg)



PWV ($m.sec^{-1}$)

Hypertensives

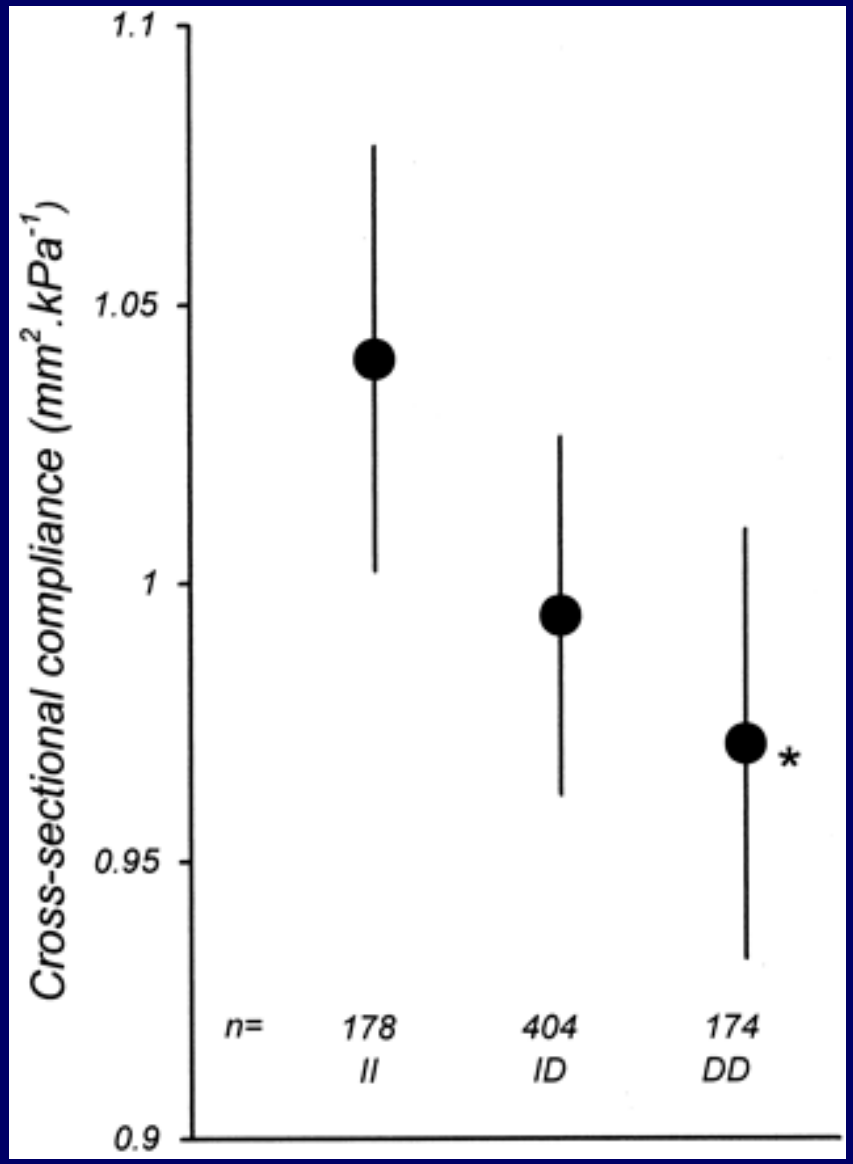




** : p < 0.01
*** : p < 0.001

Benetos et al; *Circulation* 1996

Carotid artery compliance according to the ACE I/D genotype



E. Blakestein et al, *Hypertension* 2001

Hemodynamic Parameters Before and After Perindopril Treatment According to Angiotensin II Type 1 Receptor $A^{1166}C$ Genotype

	AA		AC+CC		
Parameter	Base	Perind	Base	Perind	P
SBP (mm Hg)	155±3	146±3	159±6	140±3	<.05
DBP (mm Hg)	92±2	87±2*	96±3	85±2	<.05
MBP (mm Hg)	114±2	108±2	117±4	103±3	<.05
HR (bpm)	66±2	70±2	67±2	69±4	NS
PWV, m/s	12.5±0.4	11.5±0.3	14.4±1.0	11.5±0.7	<.001§

*P<.05, P<.01, P<.001, baseline vs treatment; §P<.02, after adjustment for age and changes in mean BP.

Benetos, A. et al. Hypertension 1996;28:1081-1084

Hemodynamic Parameters Before and After Nitrendipine Treatment According to Angiotensin II Type 1 Receptor $A^{1166}C$ Genotype

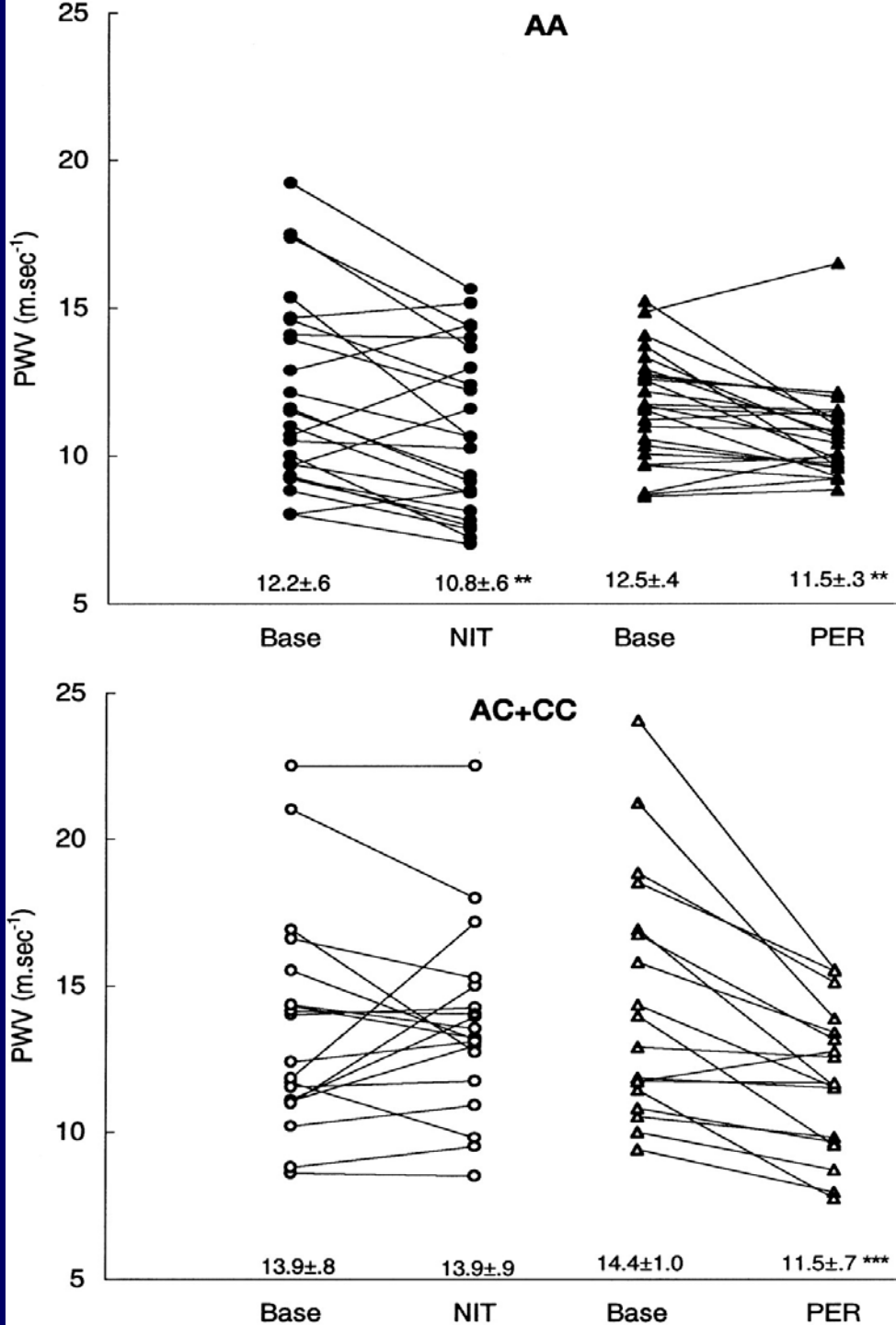
	AA		AC+CC		
Parameter	Base	Nitrend	Base	Nitrend	Inter *P*
SBP (mm Hg)	158±3	140±3	158±2	146±2*	NS
DBP (mm Hg)	96±2	87±2*	96±2	89±1*	NS
MBP (mm Hg)	119±2	106±2	117±2	109±2*	NS
HR, bpm	69±2	70±1	71±3	75±3	NS
PWV, m/s	12.2±0.6	10.8±0.6*	13.9±0.8	13.9±0.9	<.01

*$P<.01$, $P<.001$, baseline vs treatment; $P<.01$, after adjustment for age and changes in mean BP.

Benetos, A. et al. Hypertension 1996;28:1081-1084

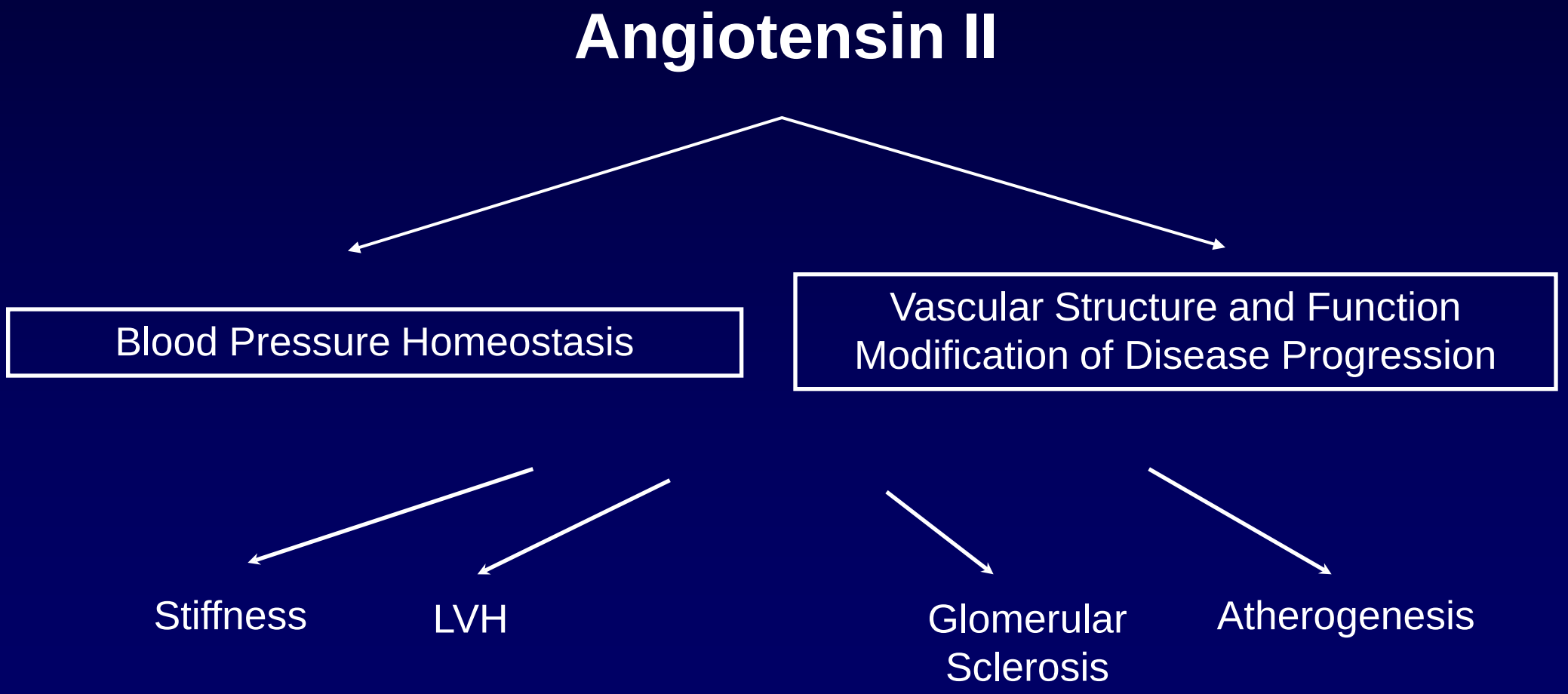
Changes of PWV after Perindopril or Nitrendipine

in AT1-R AA homozygotes (top) and AC+CC subjects (bottom)



Benetos, A. et al. Hypertension 1996;28:1081-1084

Main effects of Angiotensin II on the CV system

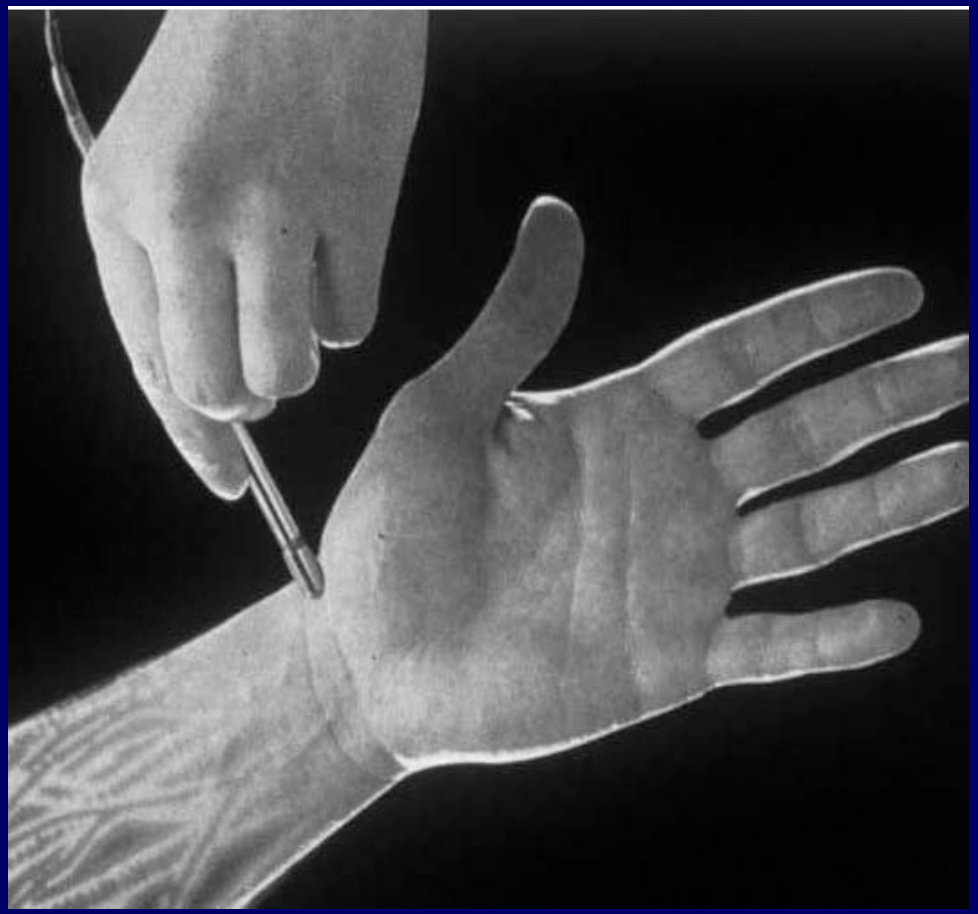


Optimal Cardiac, Vascular and Renal Protection in high risk patients

Earlier and more aggressive BP control

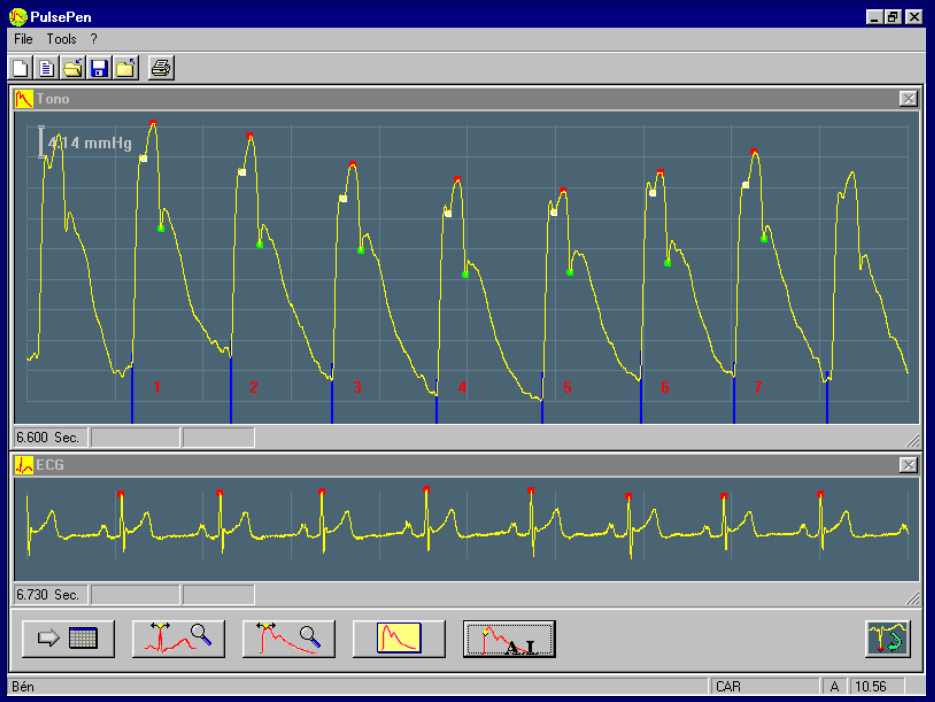
Pharmacologic blockade of the RAAS

Tonometrie d’applanation

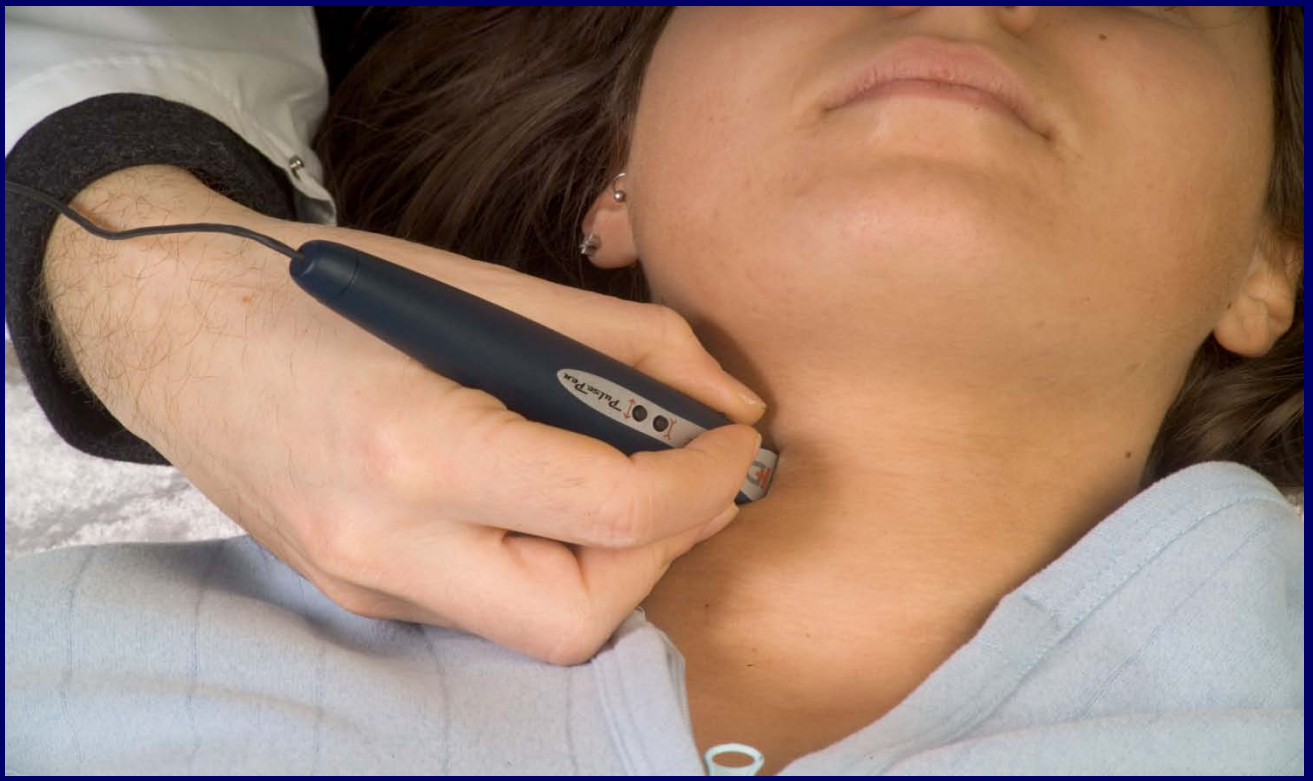


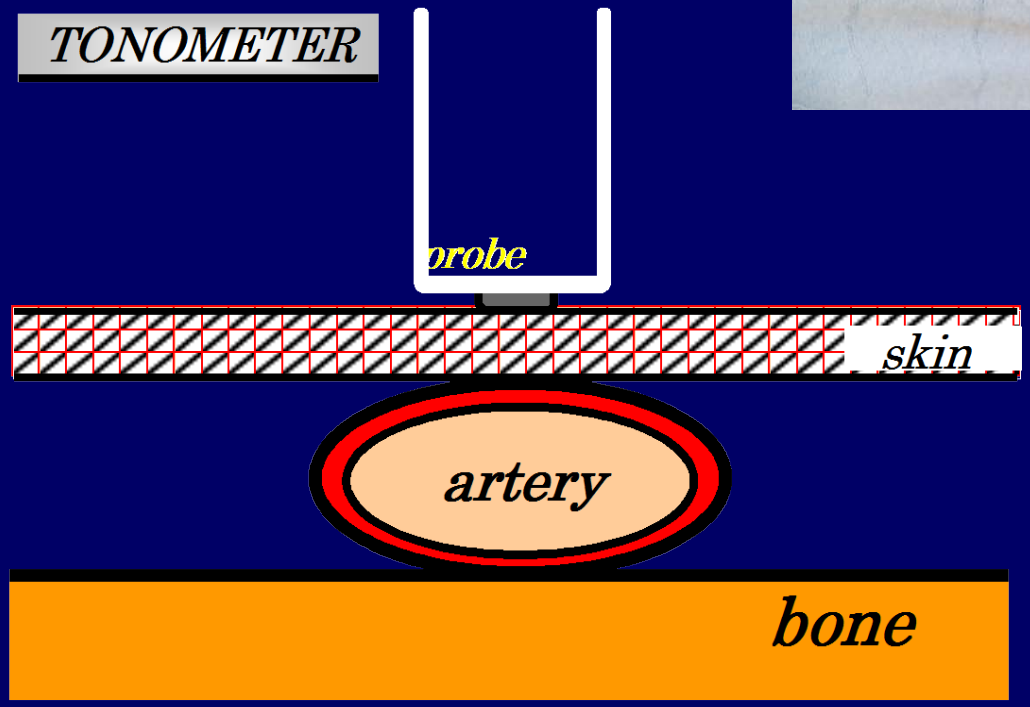

PulsePen

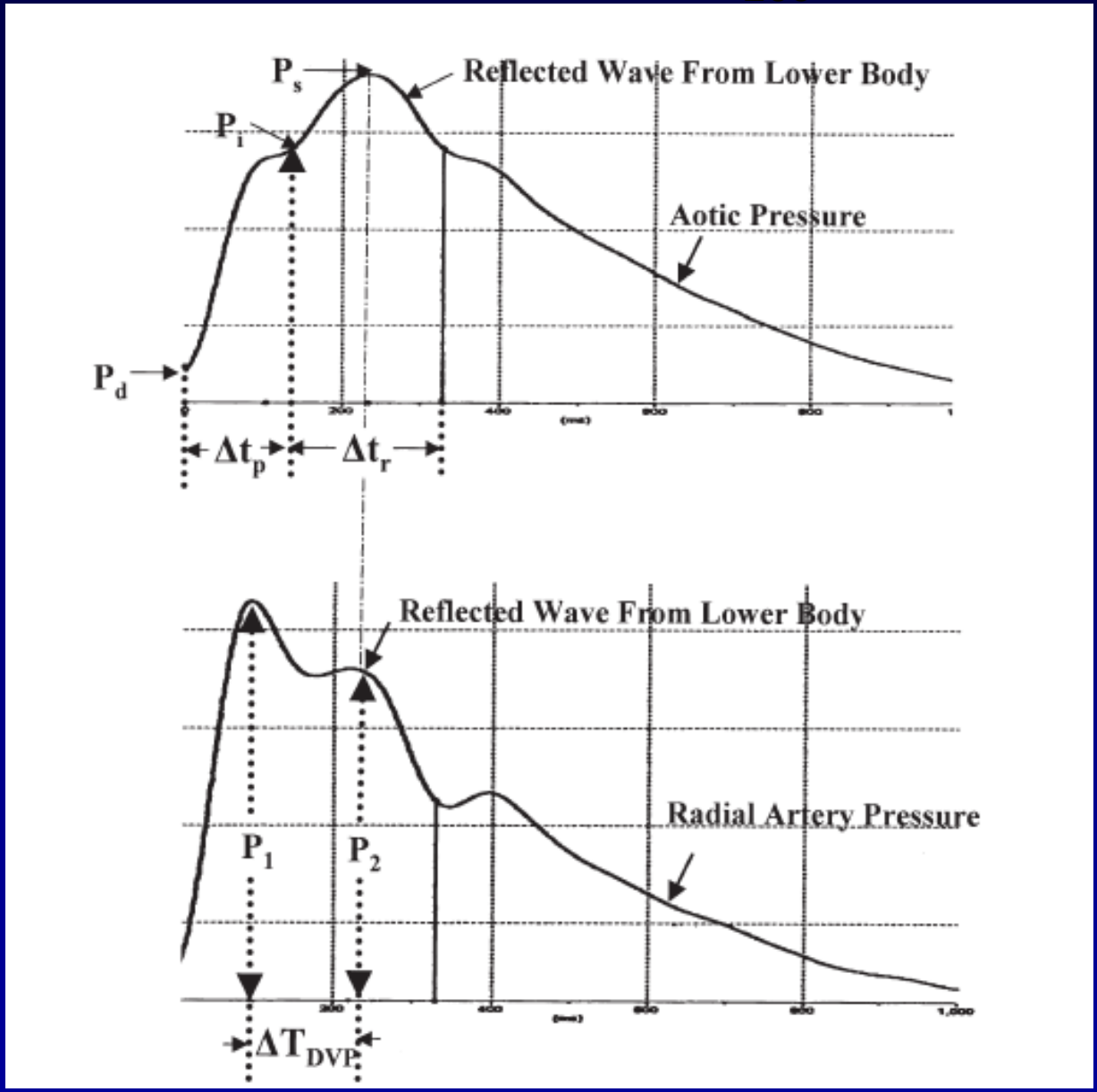

Архив Монитор Печатать Настройки Справка
Кольцо
Сигналы
F1 Справка
Alt+F3 Закрыть
F10 Меню
Alt+X Выход

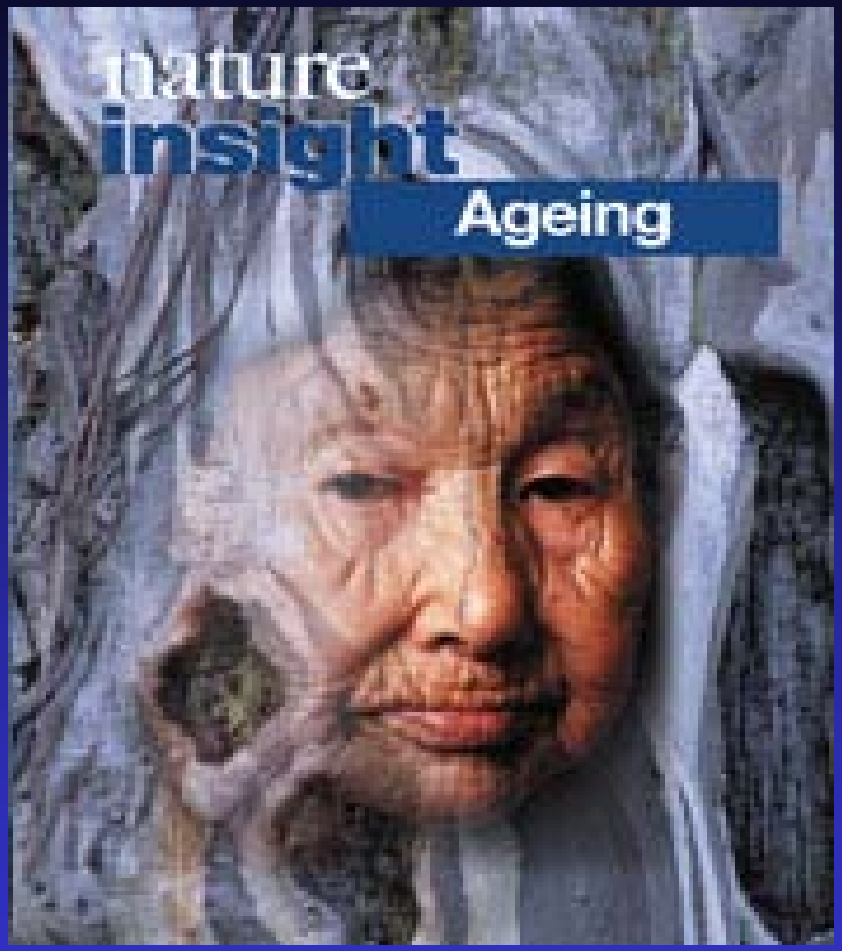

PulsePen
File Tools ?
Tono
114 mmHg
1
2
3
4
5
6
7
6.600 Sec.
ECG
6.730 Sec.
Bén
CAR
A
10.56


SphygmoCor
SOFTWARE GUIDE
MANUAL




TONOMETER
probe
skin
artery
bone


P_s
Reflected Wave From Lower Body
P_i
Aotic Pressure
P_d
Δt_p
Δt_r
Reflected Wave From Lower Body
Radial Artery Pressure
P_1
P_2
ΔT_{DVP}



- Thank you

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