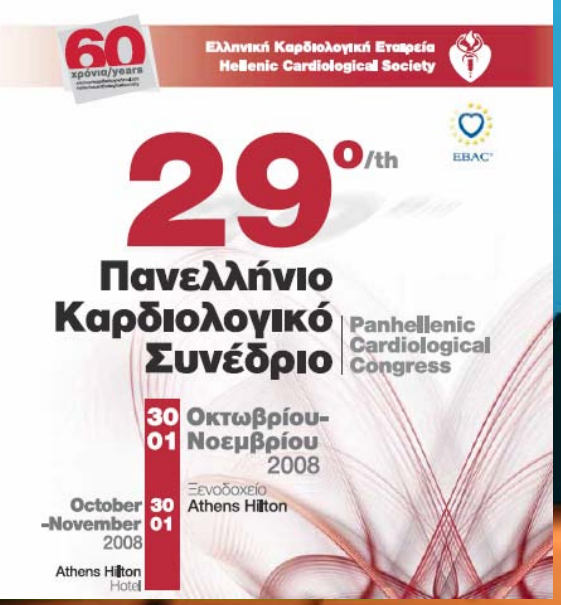
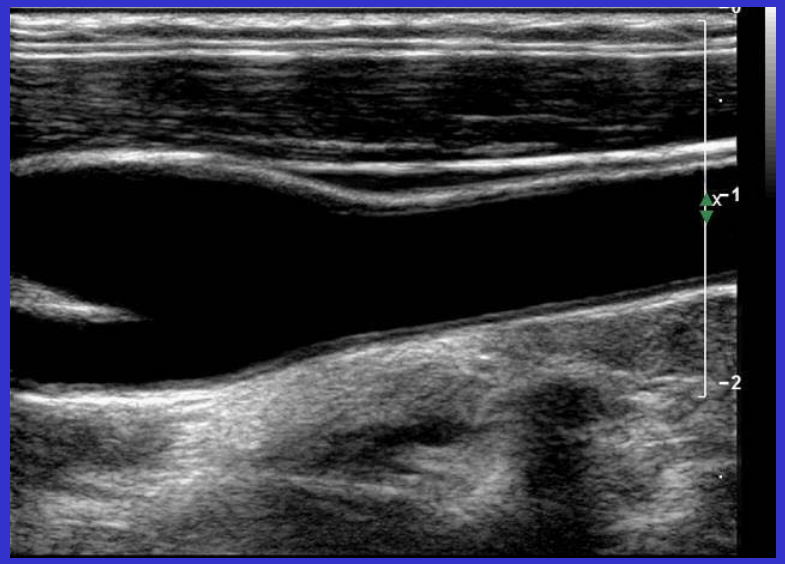


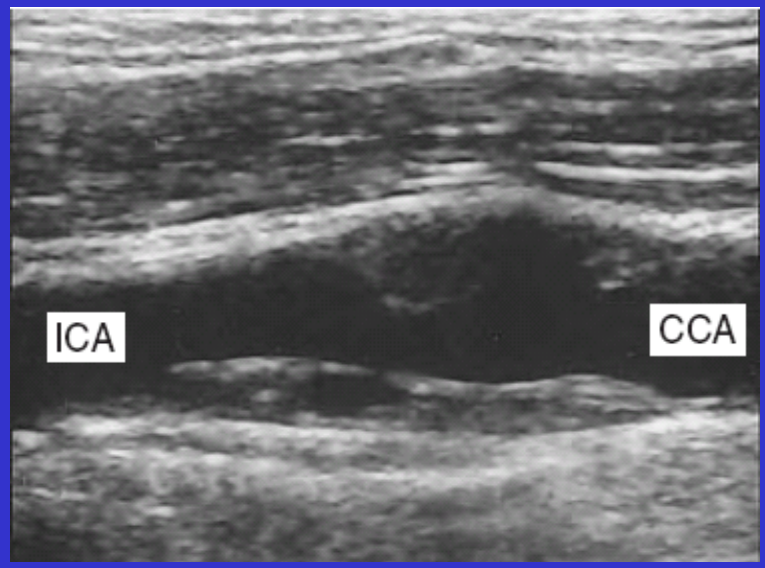
Πρώιμη αγγειακή γήρανση στην υπέρταση: διάγνωση και αντιμετώπιση

Χαράλαμπος Βλαχόπουλος

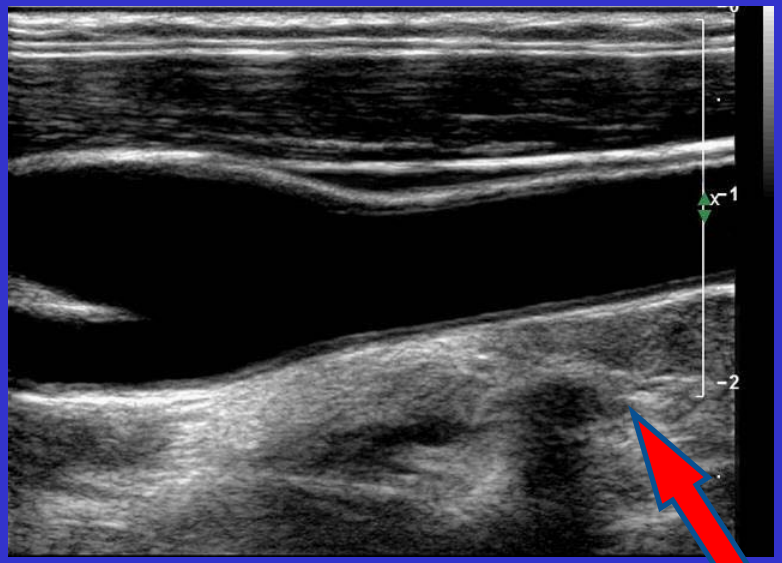
1η Καρδιολογική Κλινική Πανεπιστημίου Αθηνών
Ιπποκράτειο Γ.Ν.Α.

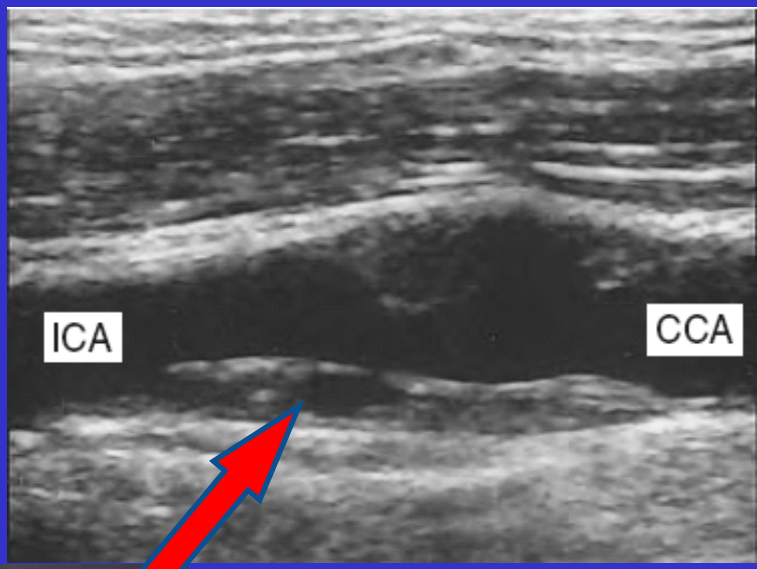
Οι προβλεπόμενες αρτηριακές αλλαγές με βάση την ηλικία και τους παράγοντες κινδύνου ...



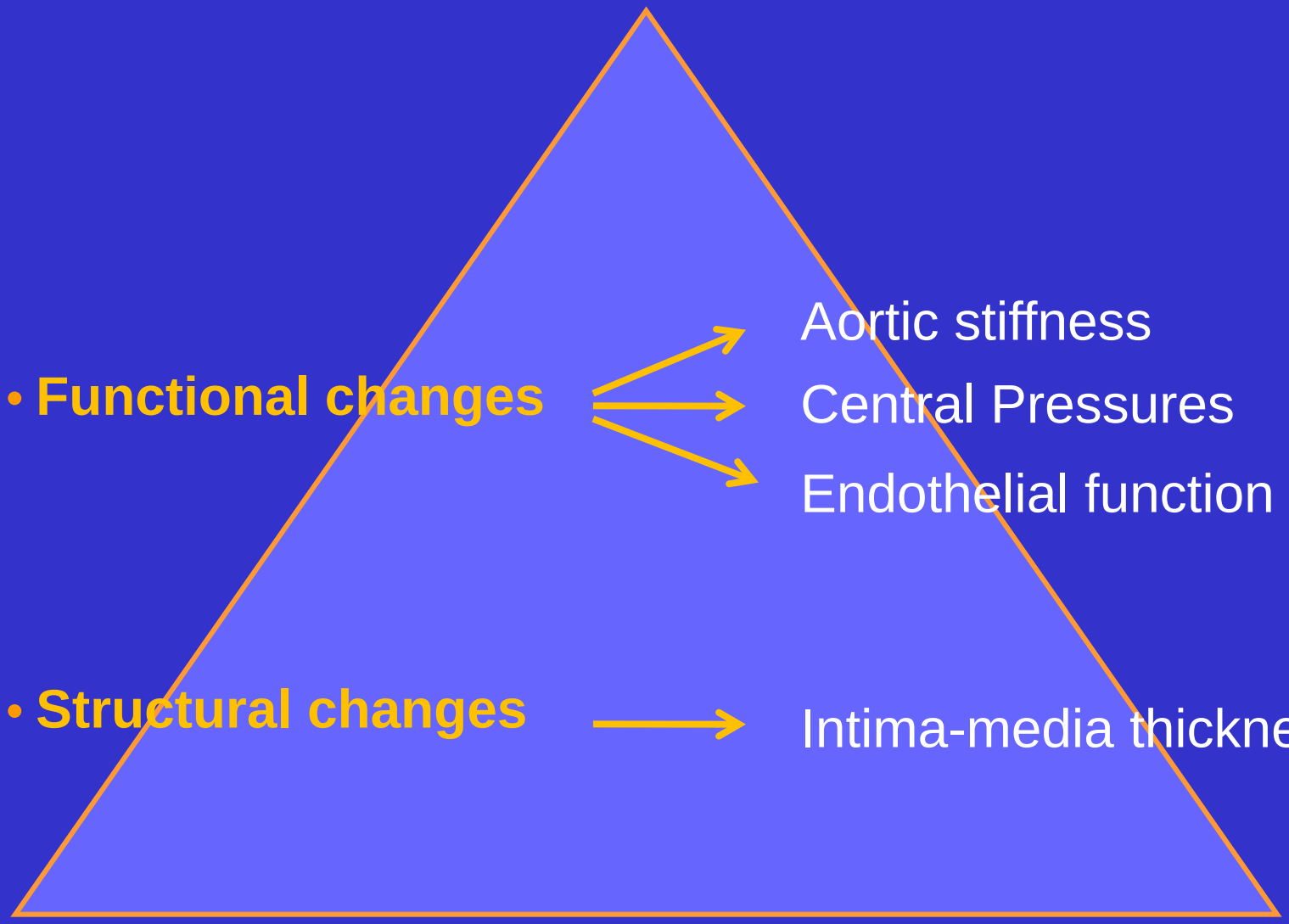


…δεν αντιστοιχούν πάντα στη βιολογική ηλικία !!!





Βιοδείκτες αγγειακής ηλικίας



Criteria of a Biomarker

A theoretical basis

High reproducibility

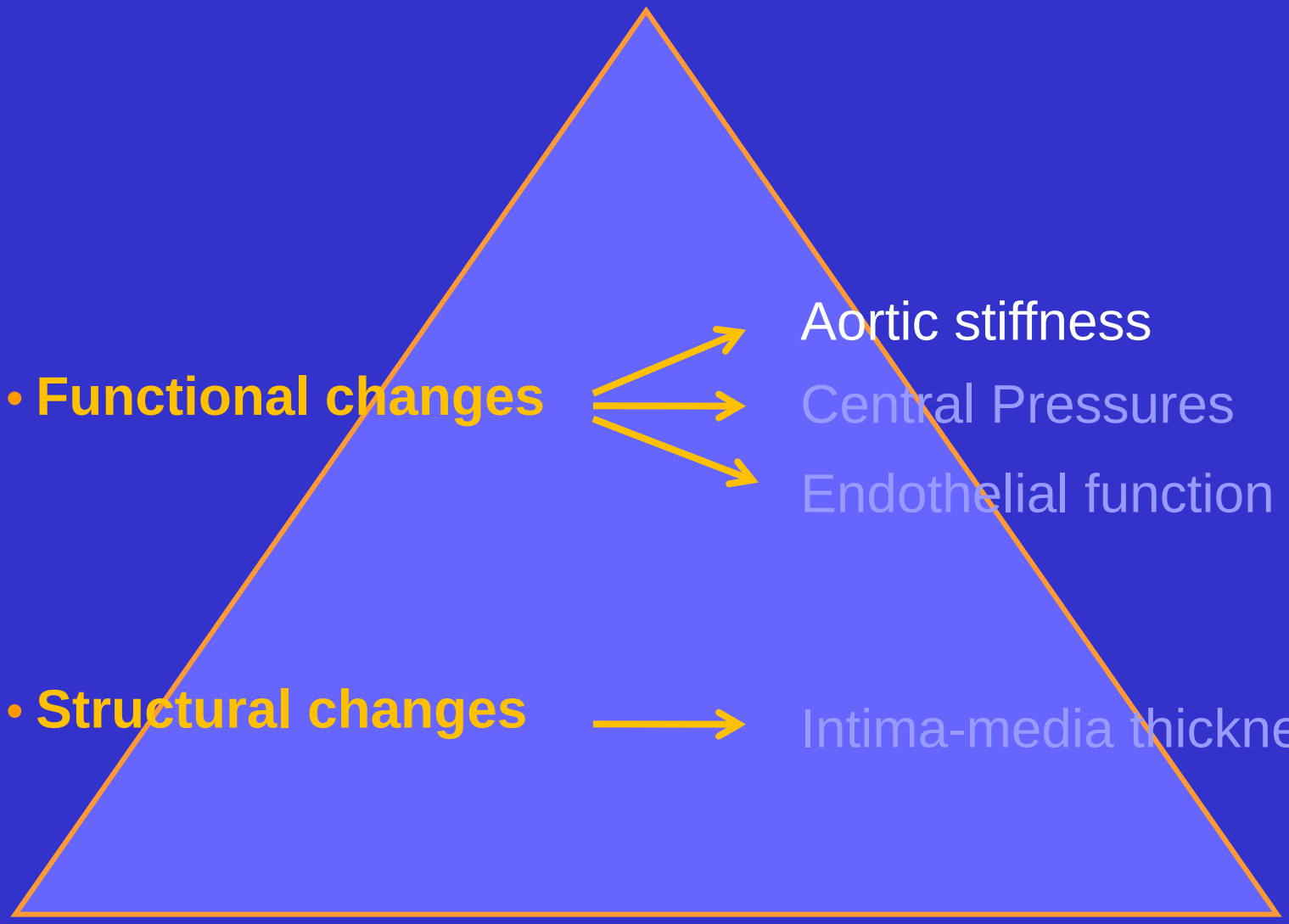
Ease of use

Incremental value

Ability to monitor and guide therapy

R Vasan 2006

Βιοδείκτες αγγειακής ηλικίας



Aortic stiffness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

Aortic stiffness

European Heart Journal Advance Access published September 25, 2006

European Heart Journal
doi:10.1093/eurheartj/ehl254

Special article

Expert consensus document on arterial stiffness: methodological issues and clinical applications

Stephane Laurent[1*], John Cockcroft[2], Luc Van Bortel[3], Pierre Boutouyrie[1], Cristina Giannattasio[4], Daniel Hayoz[5], Bruno Pannier[6], Charalambos Vlachopoulos[7], Ian Wilkinson[8], and Harry Struijker-Boudier[9] on behalf of the European Network for Non-invasive Investigation of Large Arteries

Incremental value

Ability to monitor and guide therapy

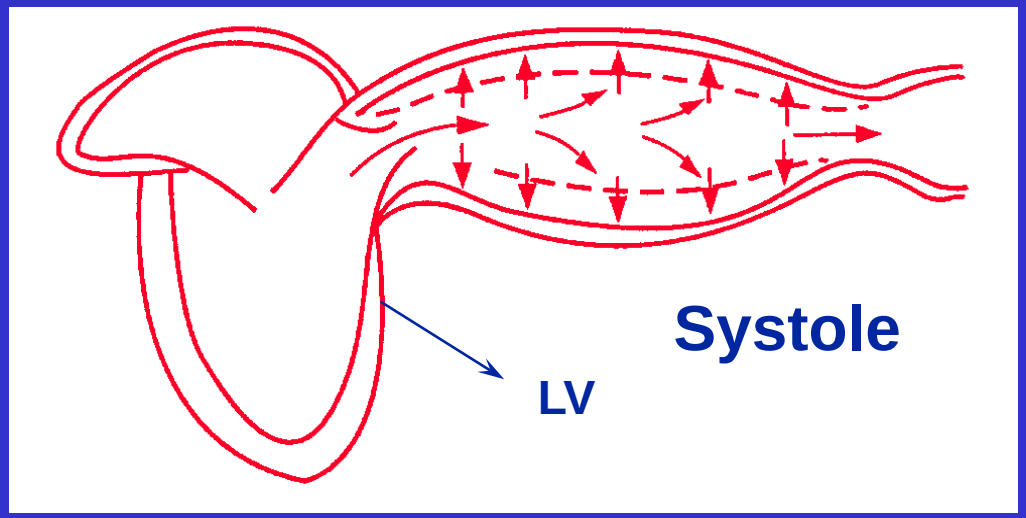
Theoretical basis

Left ventricular ejection generates a pulse wave which will propagate along the arterial walls at certain speed

Blood = incompressible fluid

Artery = elastic conduit

} ⟹ Propagation along the arterial tree



The propagation velocity is determined by:

The elastic and geometric properties of the arterial wall
The characteristics of the arterial wall structure

Aortic stiffness

A theoretical basis

High reproducibility

Ease of use

Incremental value

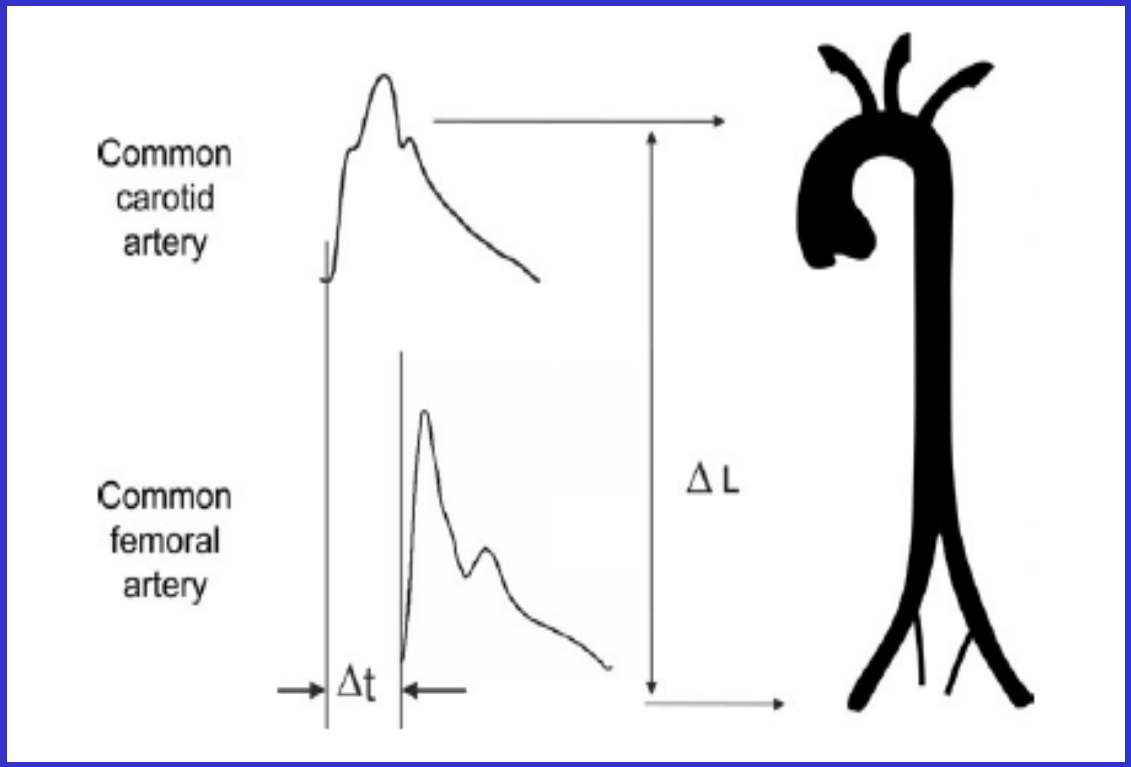
Ability to monitor and guide therapy

Aortic stiffness - Evaluation

Pulse Wave Velocity

Complior

Carotid-Femoral (aortic) Pulse Wave Velocity measurement using the foot-to-foot velocity method



PWV = d (m) / Δt (sec)

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

Aortic stiffness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

Aortic stiffness – Prognostic role of PWV

Longitudinal studies reporting the independent predictive value of PWV

First author, yr	Events	Type of patients
Willum-Hansen T, 2006	CV events, CV mortality	General population
Mattace –Rasso FU, 2006	CV events	General population
Shokawa T, 2005	CV mortality	General population
Boutouyrie P, 2002	Coronary events	Essential Hypertension
Laurent S, 2001	All cause and CV mortality	Essential Hypertension
Laurent S, 2003	Fatal strokes	Essential Hypertension
Sutton-Tyrrell K, 2005	CV events	Elderly subjects
Meaume S, 2001	CV mortality	Elderly subjects
Blacher J, 1999	All cause and CV mortality	ESRD
Shoji T, 2001	CV mortality	ESRD
Cruickshank K, 2002	All cause and CV mortality	DM II

Aortic stiffness - Prognostic role of PWV

1.51

TABLE 5. Relative Risk of Cardiovascular Mortality According to Cardiovascular Risk Factors in Multivariate Analysis: Various Models Including PWV, PP, or SBP

Parameters	OR	Lower 95% CI	Higher 95% CI	*P*
Model 1 CHI^2=97				
Previous CVD, yes/no	8.33	4.33	16.02	<0.0001
Age, 10 y	1.69	1.25	2.30	<0.001
PWV, 5 m/s	1.51	1.08	2.11	0.03
Model 2 CHI^2=95				
Previous CVD, yes/no	8.09	4.19	15.61	<0.0001
Age, 10 y	1.72	1.27	2.34	<0.0001
PP, 10 mm Hg	1.19	0.99	1.42	0.06
Model 3 CHI^2=96				
Previous CVD, yes/no	8.32	4.33	16.02	<0.0001
Age, 10 y	1.82	1.36	2.45	<0.0001
SBP, 10 mm Hg	1.15	1.02	1.30	0.03

Diabetes (yes/no), included in each of the 3 models, was not significantly associated with cardiovascular mortality.

Laurent S, et al. *Hypertension 2001;37:1236*

Aortic stiffness

A theoretical basis

High reproducibility

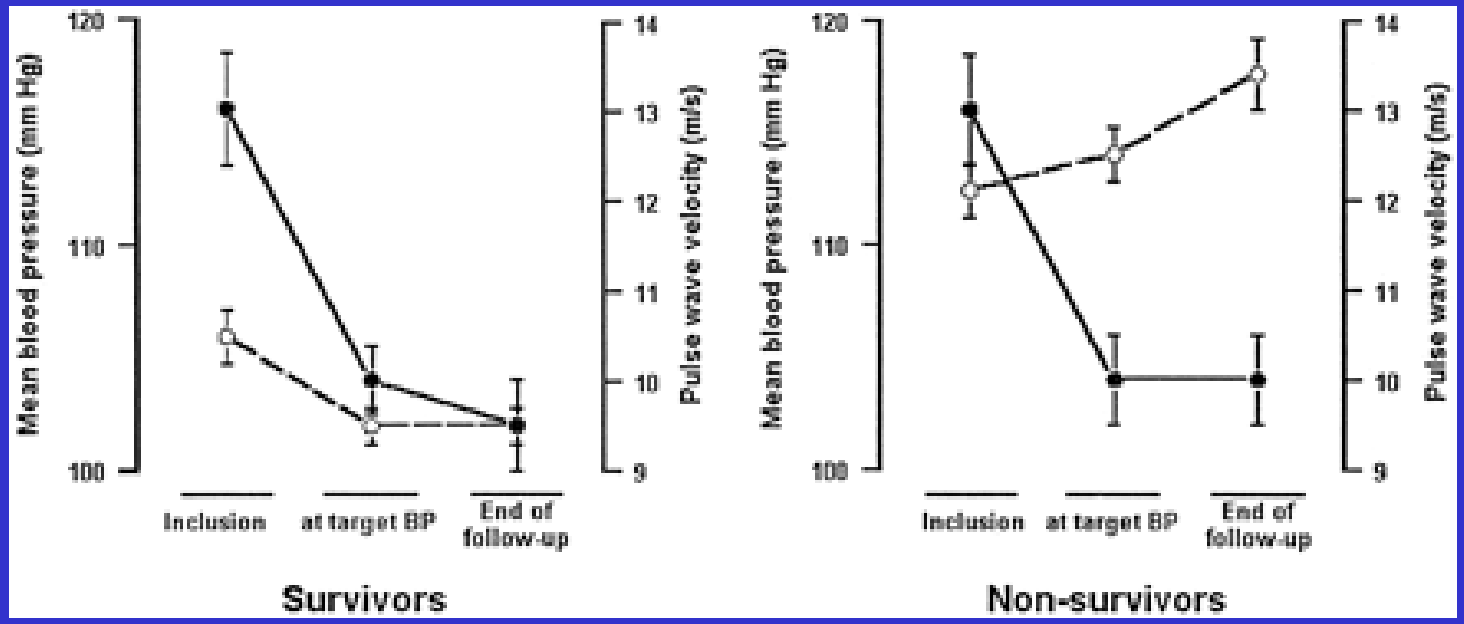
Ease of use

Incremental value

Ability to monitor and guide therapy

Prognostic role of PWV – changes with therapy

Despite similar reduction in MBP, only those who survived reduced aortic pulse wave velocity



Guerin AP, et al. *Circulation* 2001;103:987-992

Arterial stiffness: Where do we stand today?

European Heart Journal
doi:10.1093/eurheartj/ehm236

ESC and ESH Guidelines

2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

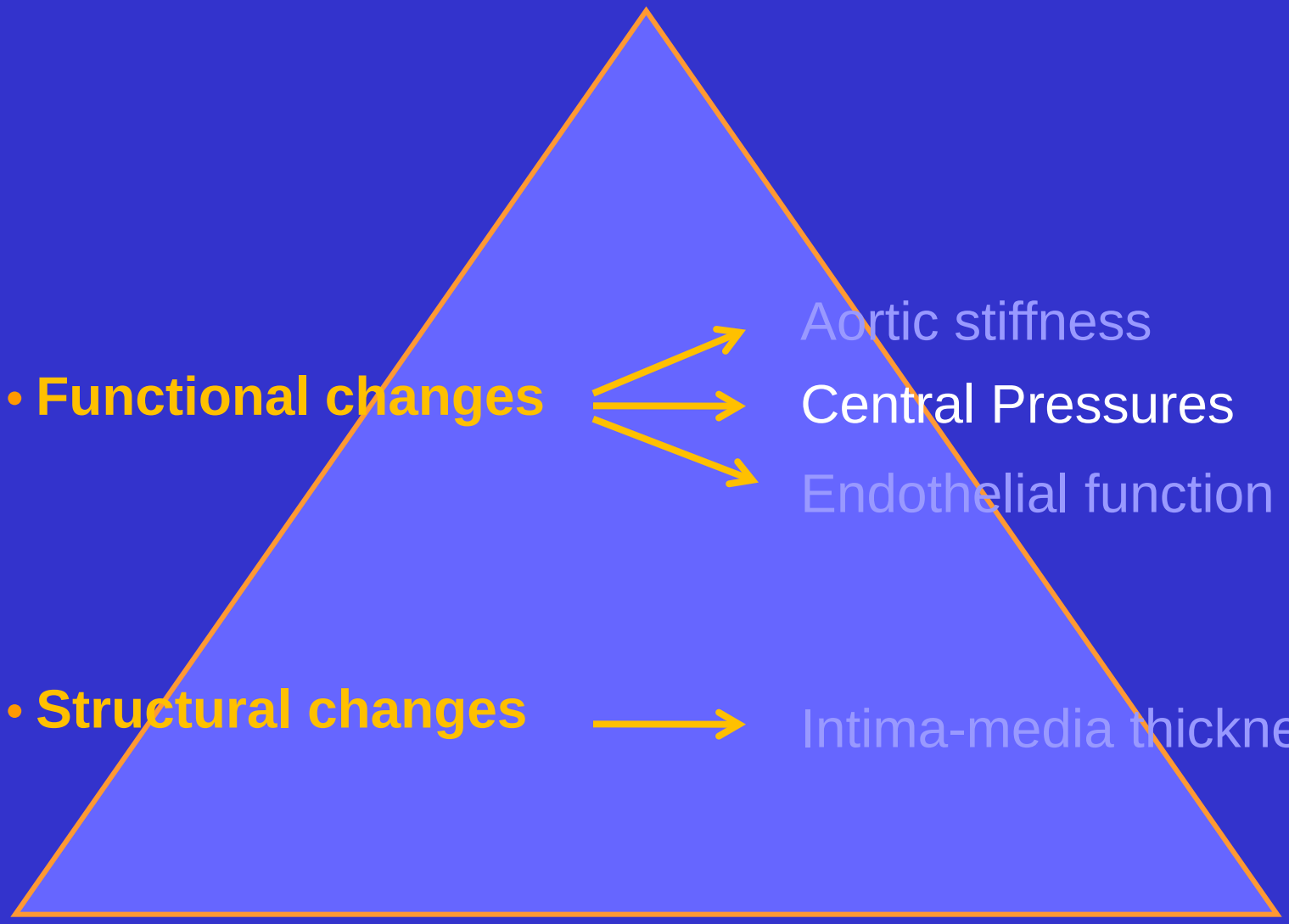
Recommended tests

- Echocardiogram
- Carotid ultrasound
- Quantitative proteinuria (if dipstick test positive)
- Ankle-brachial BP Index
- Fundoscopy
- Glucose tolerance test (if fasting plasma glucose >5.6 mmol/L (100 mg/dL)
- Home and 24 h ambulatory BP monitoring
- Pulse wave velocity measurement (where available)

Table 4 Availability, prognostic value and cost of some markers of organ damage (scored from 0 to 4 pluses)

Markers	CV predictive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid Intima-Media Thickness	+++	+++	++
Arterial stiffness (Pulse wave velocity)	+++	+	++
Ankle-Brachial Index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/Vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/White matter lesions	?	++	++++
Est. Glomerular Filtration Rate or Creatinine Clearance	+++	++++	+
Microalbuminuria	+++	++++	+

Βιοδείκτες αγγειακής ηλικίας



Central Pressures and Indices

Central Blood Pressure Measurements and Antihypertensive Therapy

A Consensus Document

Enrico Agabiti-Rosei, Giuseppe Mancia, Michael F. O'Rourke, Mary J. Roman, Michel E. Safar, Harold Smulyan, Ji-Guang Wang, Ian B. Wilkinson, Bryan Williams, Charalambos Vlachopoulos

July 2007

Hypertension

Journal of the American Heart Association

American Heart Association®

Learn and Live℠

Incremental value

Ability to monitor and guide therapy

Central Pressures and Indices

A theoretical basis

High reproducibility

Ease of use

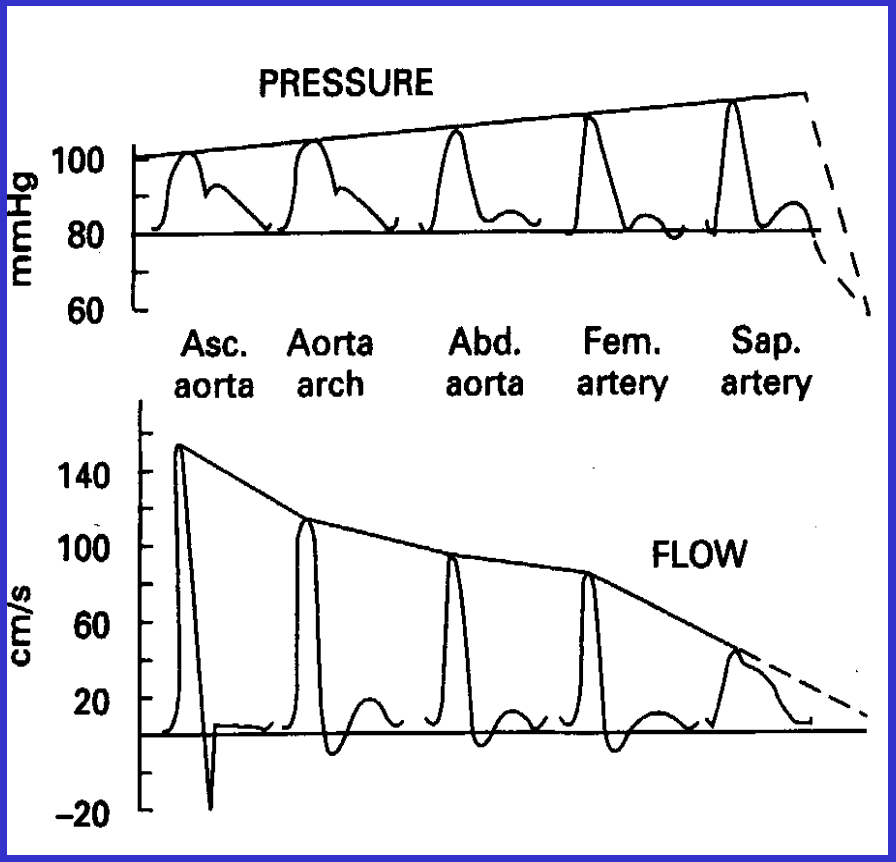
Incremental value

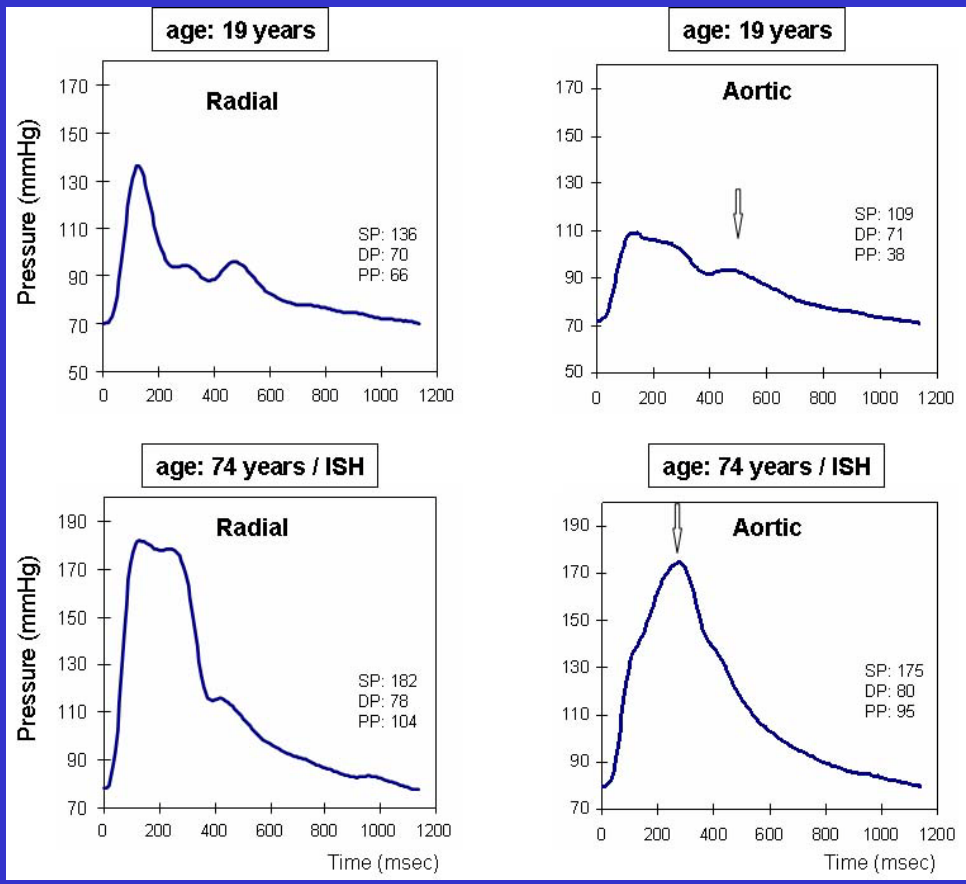
Ability to monitor and guide therapy

CBPs: theoretical basis

- amplification

- peripheral BP may overestimate central SP and PP, especially in young subjects





CBPs: theoretical basis

- **Aortic systolic BP=LV systolic P**

  reflects LV afterload

- **Aortic diastolic BP throughout diastole**

  determines coronary filling

- **Elastic-type arteries (aorta-carotids)**

  degenerate with aging and hypertension

Central BPs are physiologically more relevant than peripheral BPs to the pathogenesis of CV disease

Central Pressures and Indices

A theoretical basis

High reproducibility

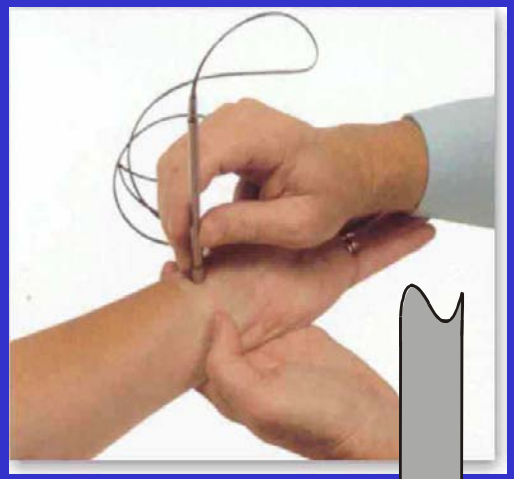
Ease of use

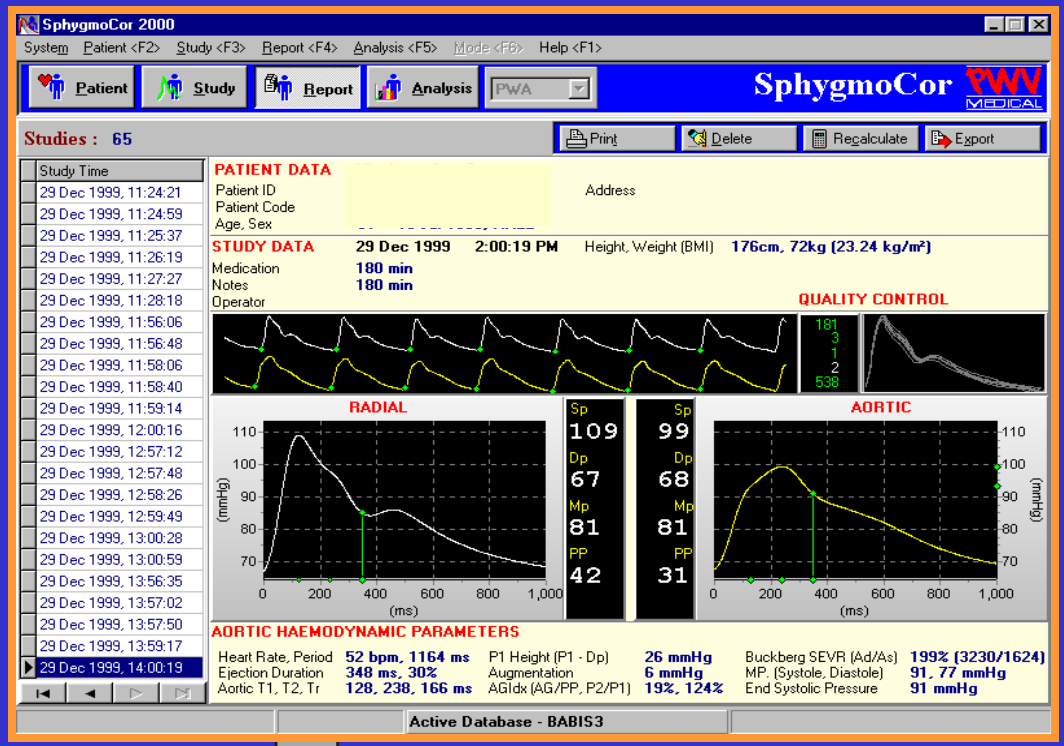
Incremental value

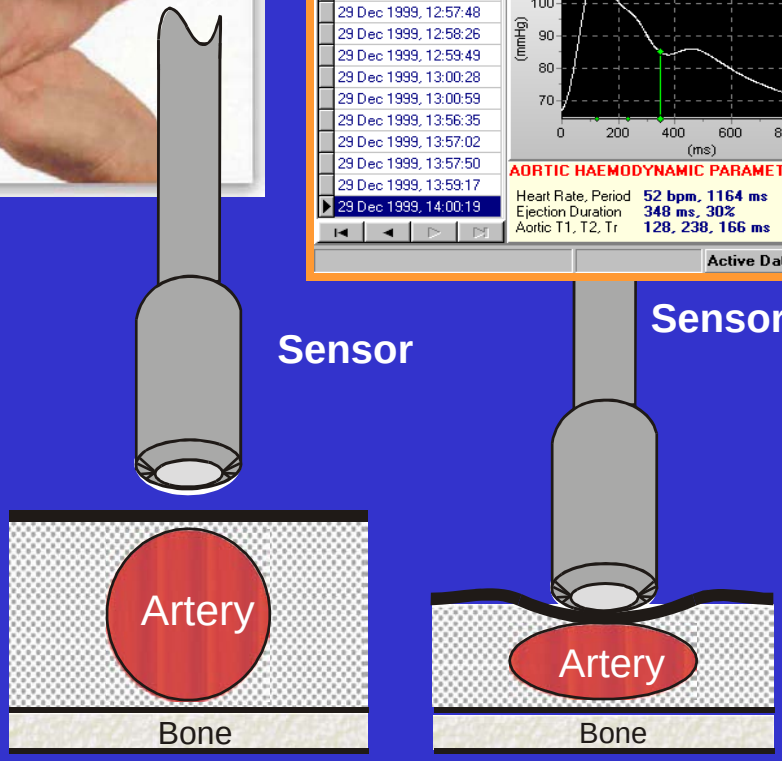
Ability to monitor and guide therapy

Central Pressure Measurement

Sphygmocor







Central Pressures and Indices

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

CBPs/indices as predictors of events

Longitudinal studies

First author	Year, country	Population	Design	Parameter	End-point
Nakayama *	2000, Japan	CAD-PTCA	Longitudinal (3-month FU)	Aortic fractional PP	restenosis
Lu *	2001, China	CAD-PTCA	Longitudinal (6-month FU)	Aortic PP	restenosis
London †	2001, France	ESRD	Longitudinal (52-month FU)	Carotid AIx	CV mortality
Safar †	2002, France	ESRD	Longitudinal (52-month FU)	Carotid PP, PP amplification	All-cause and CV mortality
Ueda*	2004, Japan	CAD-PTCA	Longitudinal (6-month FU)	Aortic AIx	restenosis
Chirinos *†	2005, USA	CAD	Longitudinal (3.2-year FU)	Aortic AP	CV mortality and events
Weber †	2005, Austria	CAD-PTCA	Longitudinal (2-year FU)	Aortic AIx	CV mortality and events
Dart	2006, Australia	Elderly female hypertensives	Longitudinal (4.1-year FU)	Carotid AIx, Brachial BP	CV mortality and events
Williams †	2006 CAFE study	Hypertensives	Longitudinal (up to 4-year FU)	Aortic PP	CV mortality and events during treatment
Roman †	2005 and 2007, USA	High-risk pts	Longitudinal (4.8-year FU)	Aortic PP	CV mortality and events
Jankowski *†	2008, Poland	Pts undergoing angiography	Longitudinal (4.5-year FU)	Pulsatility	CV mortality and events

* Measured invasively

Negative value

Incremental value

Central Pressures and Indices

A theoretical basis

High reproducibility

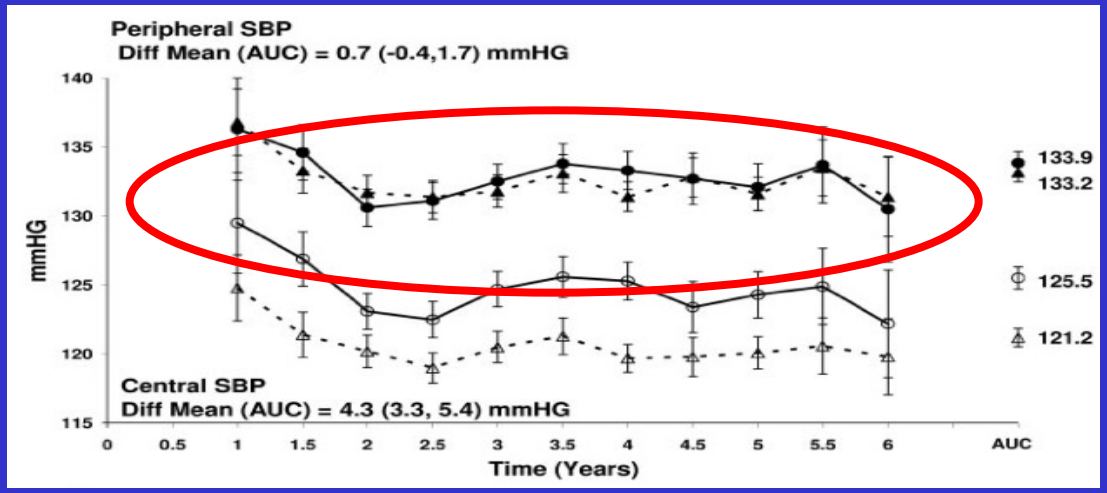
Ease of use

Incremental value

Ability to monitor and guide therapy

CBPs: Ability to monitor and guide therapy

CAFÉ Study



- BP-lowering drugs can have substantially different effects on central aortic pressures and hemodynamics despite a similar impact on brachial BP

- Central aortic pressure is an independent determinant of outcome

- Central aortic pressure may comprise a treatment target

Williams B, et al. Circulation 2006

CBs: Implementation in clinical practice

Need for reference values/cut-offs

Published:

ACCT 2005

EPOGH 2006

Ongoing:

European Network on Large Artery Investigation

NIA

Framingham

CBPs: Where do we stand today?

European Heart Journal
doi:10.1093/eurheartj/ehm236

ESC and ESH Guidelines

2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

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 pressures may be differently affected by antihypertensive drugs.[163] The need for invasive measurement of central blood pressure has confined this issue to research. However, recently a method has been described to non-invasively estimate 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 as opposed to peripheral blood pressure needs to be further confirmed in more large-scale observational and interventional studies.

" Though a wider use of PWV and AIx measurements may add further precision to the assessment of arterial damage, the availability of these techniques is largely limited to research centres."

CBPs: Where do we stand today?

Central Blood Pressure Measurements and Antihypertensive Therapy

A Consensus Document

Enrico Agabiti-Rosei, Giuseppe Mancia, Michael F. O'Rourke, Mary J. Roman, Michel E. Safar, Harold Smulyan, Ji-Guang Wang, Ian B. Wilkinson, Bryan Williams, Charalambos Vlachopoulos

Hypertension
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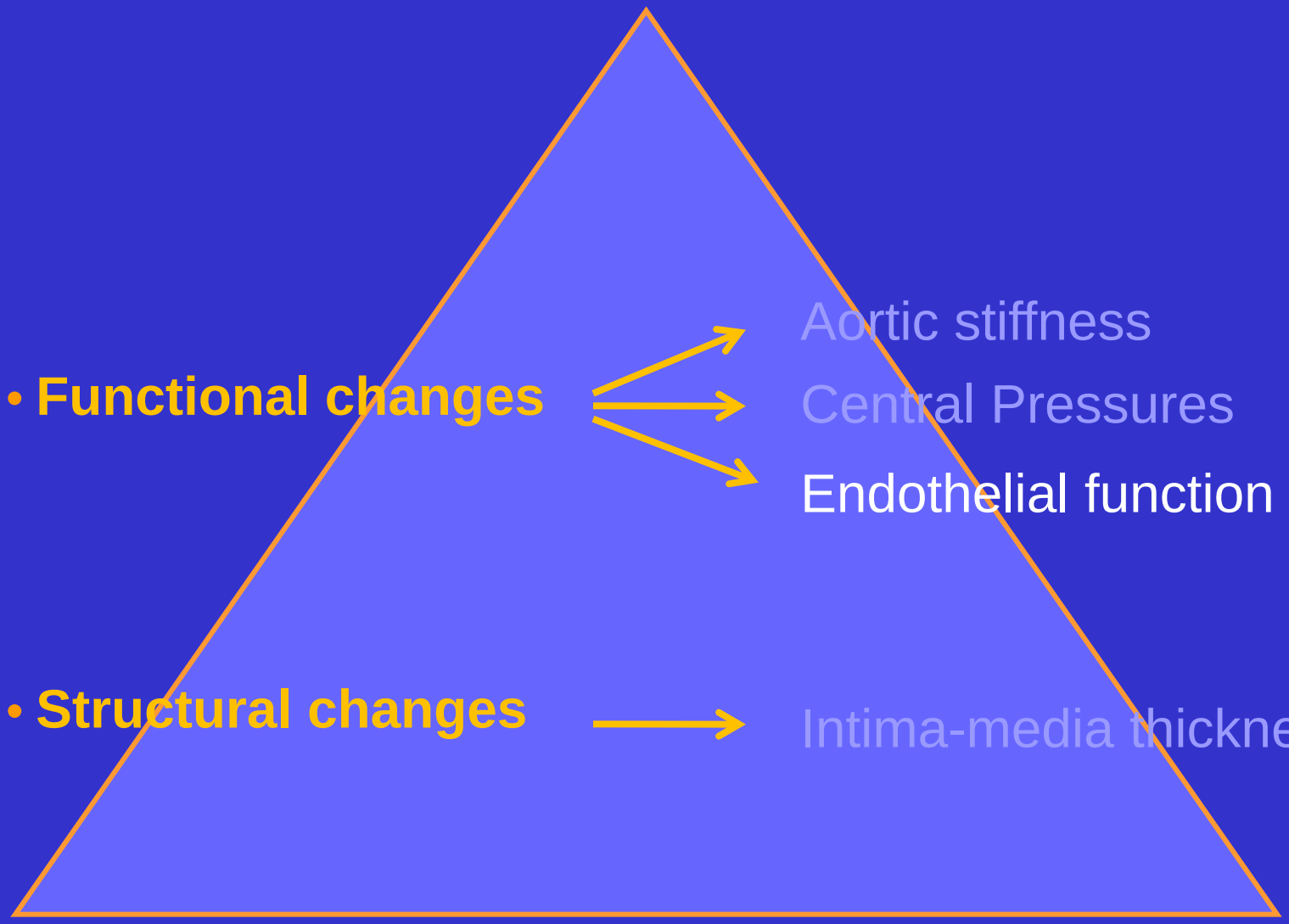
is desirable. Inclusion of a parameter in patient assessment and management should serve various purposes, such as advancement of science, physician education, and practicality of use in a range of settings, whereas cost should also be taken into consideration. Assessment of central pressures meets these criteria to a varying degree at present. *Definition of terms such as central and peripheral BP, arterial stiffness, wave reflections, and systolic BP and PP amplification should be readily available to both clinicians and researchers and introduced in the guidelines on hypertension and cardiovascular risk.* Although brachial BP remains our point of reference, there is a definite sense that efforts to investigate

Βιοδείκτες αγγειακής ηλικίας



Flow-mediated Dilatation

A theoretical basis

High reproducibility

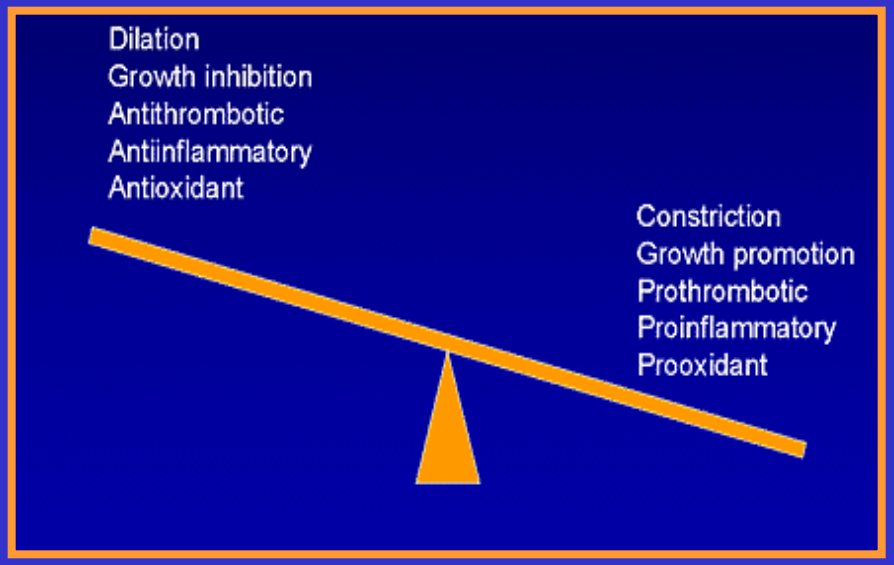
Ease of use

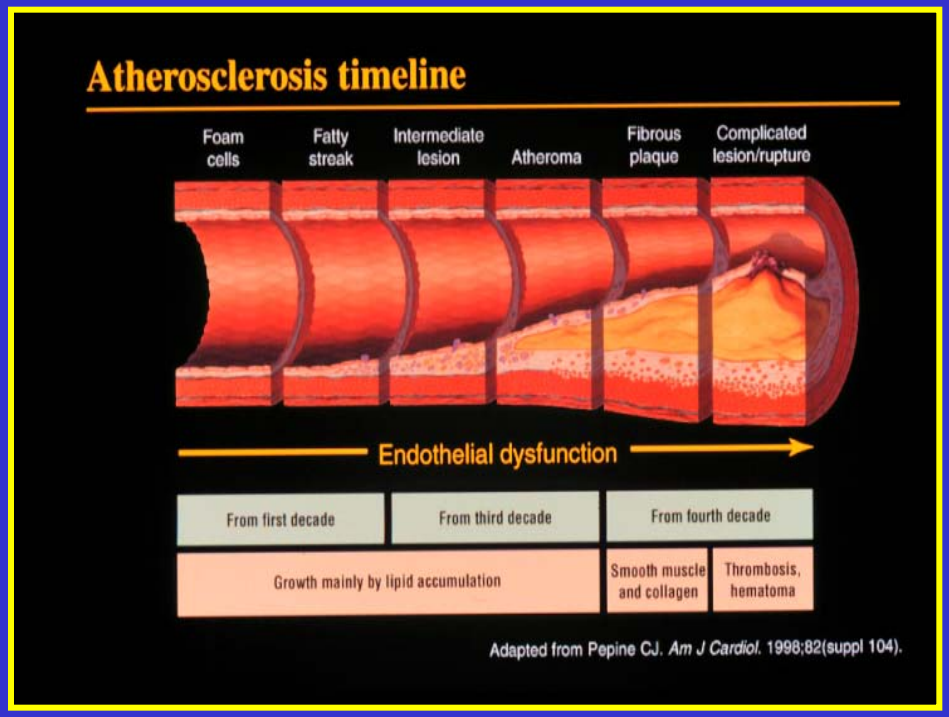
Incremental value

Ability to monitor and guide therapy

FMD: theoretical basis

ENDOTHELIUM





Flow-mediated Dilatation

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High reproducibility

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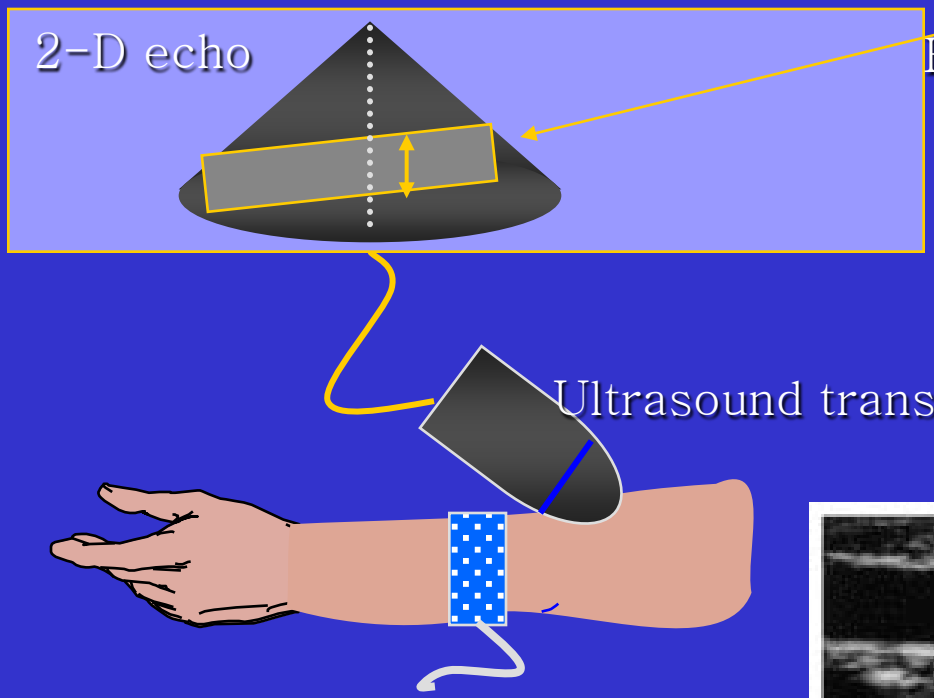
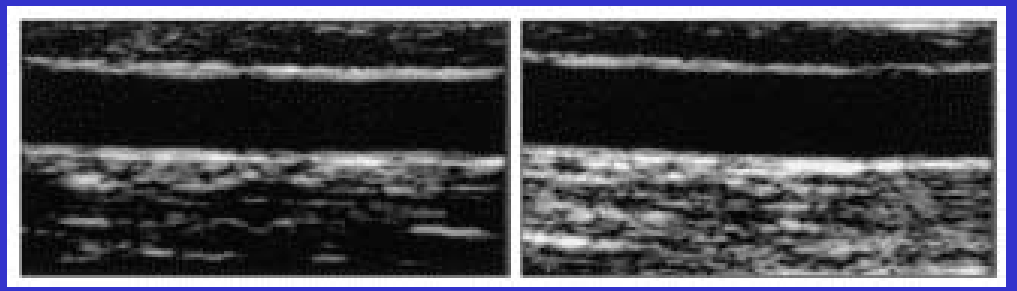
Incremental value

Ability to monitor and guide therapy

FMD





Basal diameter

Diameter at 60s hyperemia

$$\text{FMD (\%)} = 100\% \times \frac{\text{Post-ischemic diameter (60}^{\text{th}}\text{ sec)-resting diameter}}{\text{resting diameter}}$$

Corretti M, et al. JACC 2002

FMD: reproducibility

- Highly operator dependent

- Though not reproducible as biochemical biomarkers, has an acceptable coefficient of variation ≈ 20%

Anderson T. Circulation 2007

Flow-mediated Dilatation

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

FMD: ease of use

	Scientific Rationale and Physiology of FMD	
Training	Basic knowledge of ultrasound equipment, two-dimensional and Doppler analysis	Qualification criteria
	Demonstrate technical tips and pitfalls	Training period with close supervision and feedback
	Ergonomic issues	Formal observer-specific reproducibility assessment
	Qualification criteria	Minimum number of studies:
	Training period with close supervision	At least 100 supervised scans prior to scanning independently
	Periodic review of scan performance	All observers from a given study measure 100 studies together prior to reading independently
	Minimum number of studies:	At least 100 scans per year to maintain competency
	At least 100 supervised scans prior to scanning independently	
	At least 100 scans per year to maintain competency	
Reproducibility	Image variability	Multisite studies should have core reading laboratory, intra- and interobserver variability, temporal variability
	In single-site study, each sonographer scans the same participants to assess for systematic differences	

An art form in itself!

The learning curve typically requires several months, depends on the technical skill of the individual, and the frequency with which the technique is performed

Corretti et al. JACC 2002

Flow-mediated Dilatation

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

FMD as a predictor of events

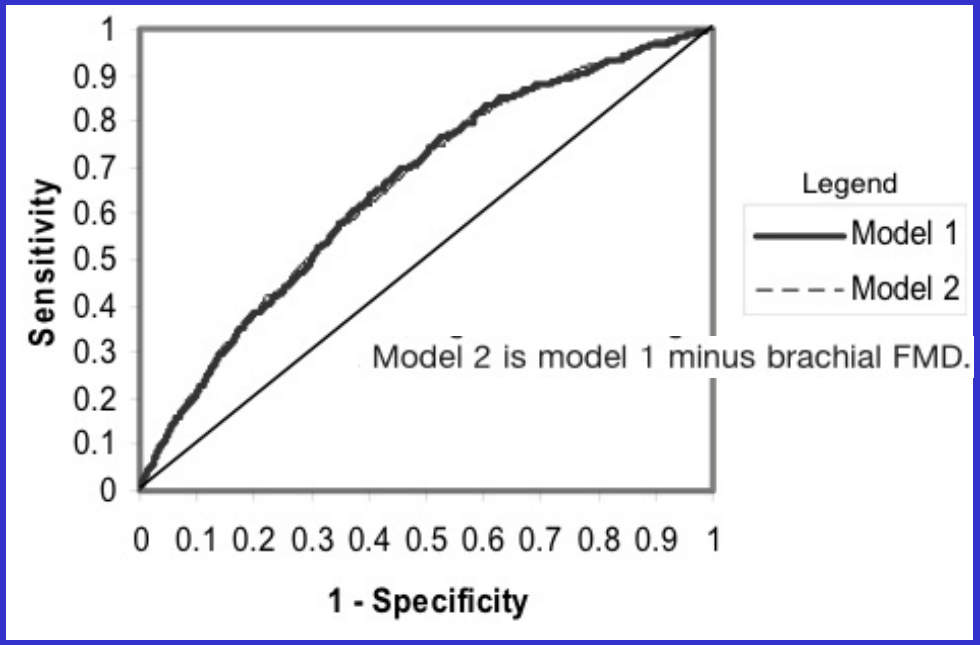
Longitudinal studies

First author	Year	Population	Follow Up	End-point
Neunteufl	2000	Chest pain (73 pts)	5 years	Death, CHD events
Gocke	2002	Vascular surgery (187 pts)	1 month	CHD events, stroke
Modena	2002	Hypertensive, postmenopausal women (400 pts)	67 months	Non-fatal CV events
Gocke	2003	Vascular surgery (199 pts)	1.2 years	CHD evens, stroke
Brevetti	2003	PAD (131 pts)	23 months	CHD, CV and peripheral vascular events
Chan	2003	CHD (152 pts)	34 months	CHD, CV and peripheral vascular events
Fathi	2004	High risk of CHD (444 pts)	24 months	CHD events, stroke
Frick	2005	Chest pain (398 men)	39 months	CHD events
Meyer	2005	CHF, UNOS status 2(75 pts)	up to 3 years	Conversion to UNOS status 1, or death
Katz	2005	CHF, NYHA II-III (149 pts)	28 month	Death, urgent cardiac transplantation
Yeboah	2007	Older pts (2792 pts)	5 years	CV events

Incremental value

FMD: incremental predictive value

FMD adds very little (≈ 1%) to the prognostic accuracy in older patients



Yeboah et al. Circulation 2007

- **Subjects with high CVD risk have stiff arteries. Stiff arteries *don't* dilate**

Thus, in high risk patients FMD may not reflect endothelial dysfunction completely

Flow-mediated Dilatation

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

FMD: ability to monitor and guide therapy

- Limited data on the effect of therapy (based on events) Modena et al. JACC 2002
- Allows the study of interventions over a period of ***months***, not necessarily years
- More rapid evaluation of the novel therapies

FMD: Where do we stand today?

European Heart Journal
doi:10.1093/eurheartj/ehm236

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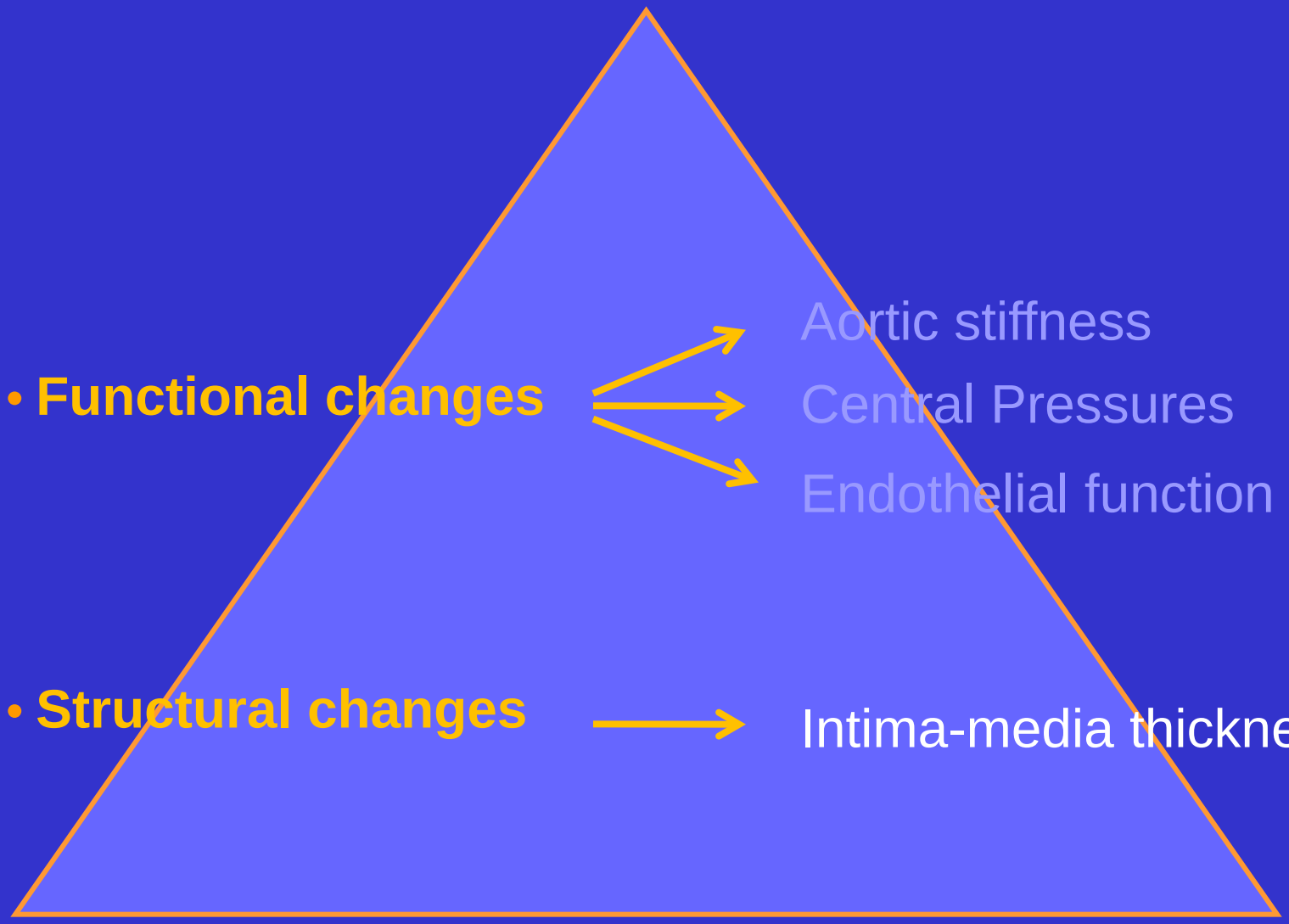
"Assessment of endothelial function *cannot* be advocated as currently useful in the clinical evaluation of the hypertensive patient."

Βιοδείκτες αγγειακής ηλικίας



Intima-Media Thickness

A theoretical basis

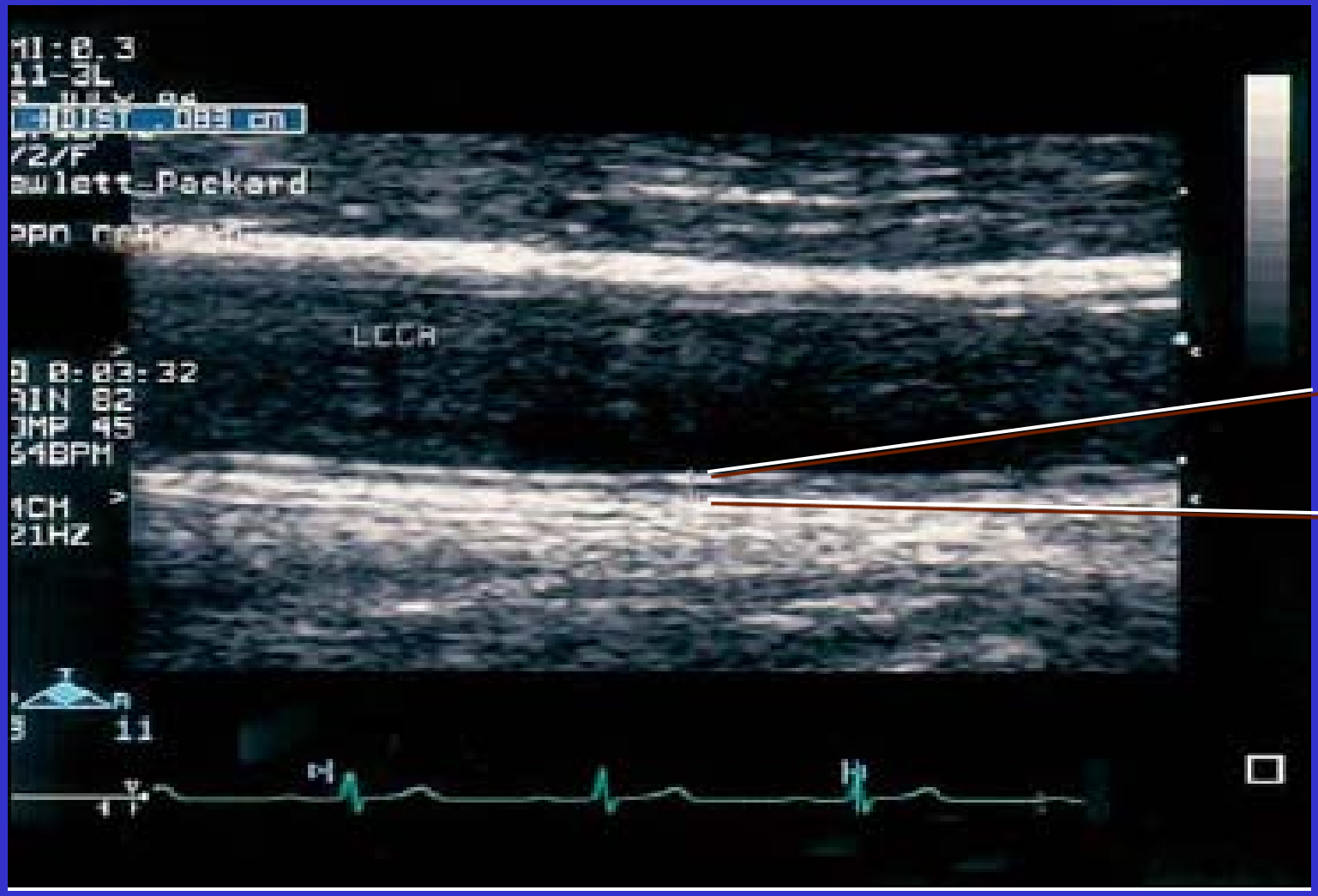
High reproducibility

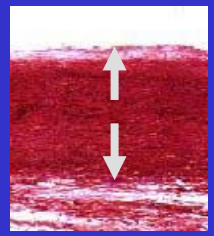
Ease of use

Incremental value

Ability to monitor and guide therapy

IMT: theoretical basis





IMT: theoretical basis

- Male gender, age increase IMT values (men>women, 0.6%/year)
- Increased IMT due to:
  - Intima thickening (atherosclerosis, age-dependent fibromuscular hyperplasia)
  - Media thickening (smooth muscle - hypertension, atherosclerosis)

Intima-Media Thickness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

IMT: reproducibility

- Acceptable reproducibility
- Acceptable operator dependency
- Variability is less for the CCA than for the ICA
- Overall, a reliable and reproducible method for use in population studies

Intima-Media Thickness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

IMT: ease of use

- Medium level of difficulty to master
- Has a moderate learning curve
- Methodological Considerations

  Where should we measure ? (left, right, both? far vs. near? CCA, bulb, ICA?)

  How should we measure? (short- or long-axis)

  Mean IMT or Mean Maximum IMT ?

  Should we include plaques in measurements ?

Intima-Media Thickness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

IMT: Longitudinal studies

First author	Year	Population	Follow Up	End-point
Salonen	1993	1,257 middle-aged eastern Finnish men	1 month to 2.5 years	Fatal and nonfatal MI
Chambless	1997	12,841 subjects (45-64 y)	4-7 years	Fatal and nonfatal CHD events
O'Leary	1999	4,476 subjects (>65 y)	6.2 years	MI, stroke, combined end point (MI or stroke)
Iglesias del Sol	2002	2,073 subjects (>55 y)	4.6 years	Fatal and nonfatal MI
Lacroix	2003	123 PCI patients	0.9 years	Worsnening or reccurence of cardiac symptoms
Aboyans	2005	609 CABG patients	3.5 years	MI, stroke, CV death, CABG, PAD
Rosvall	2005	5,163 subjects (58 y)	7 years	Fatal and nonfatal stroke
Lorenz	2006	5,056 subjects (19-90 y)	4.2 years	MI, stroke, combined end point (MI, stroke, death)

Incremental value

Intima-Media Thickness

A theoretical basis

High reproducibility

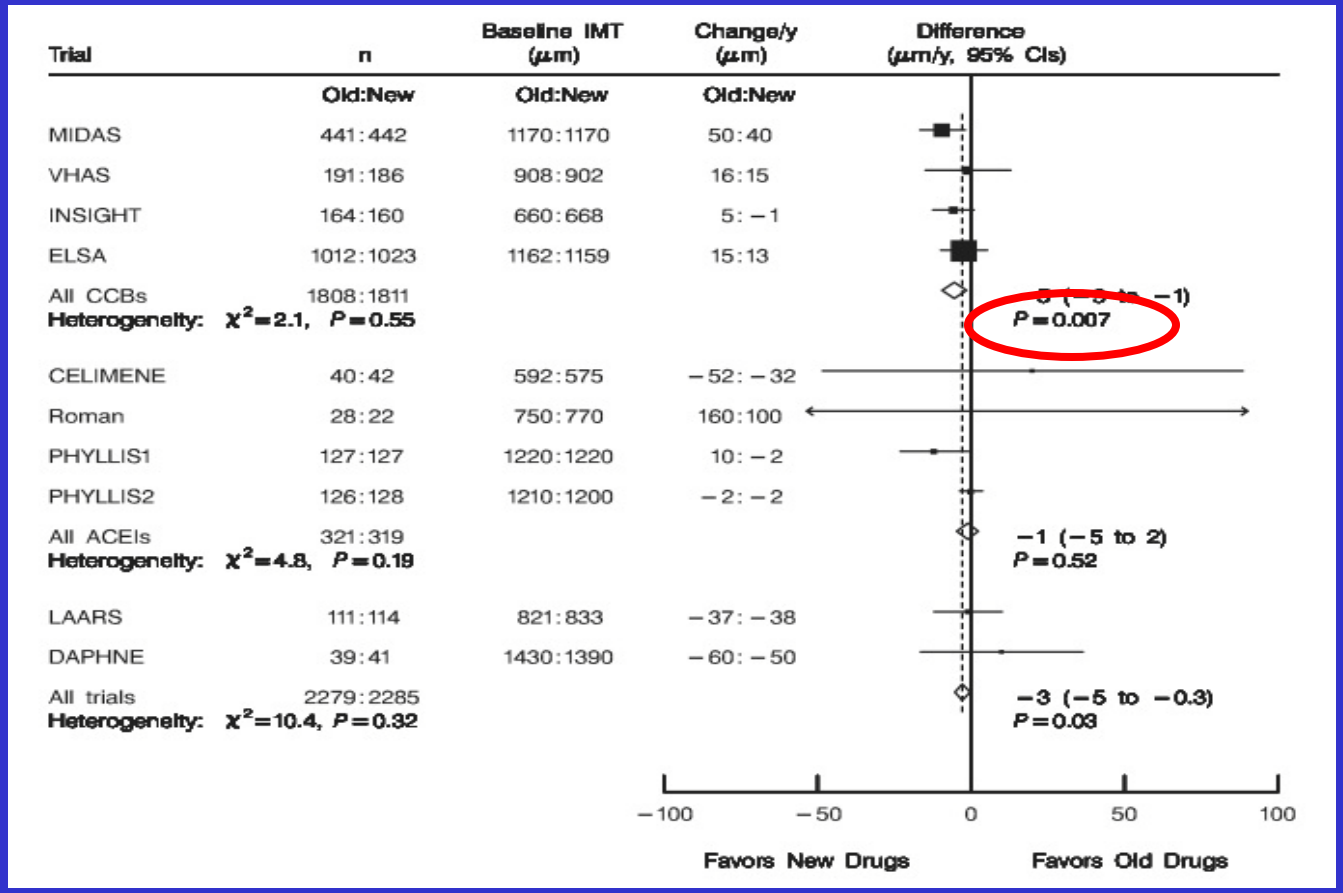
Ease of use

Incremental value

Ability to monitor and guide therapy

IMT: ability to monitor and guide therapy

Meta-analysis of 4 trials, 3619 hypertensives



CCBs reduced IMT (by 5*μ*m/year) more than diuretics, β blockers, ACEIs *for the same reduction in BP*

Wang et al. Stroke 2006

IMT: Where do we stand today?

European Heart Journal
doi:10.1093/eurheartj/ehm236

ESC and ESH Guidelines

2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

"U/S scanning of carotid arteries is recommended when detection of vascular hypertrophy or asymptomatic atherosclerosis is deemed useful."

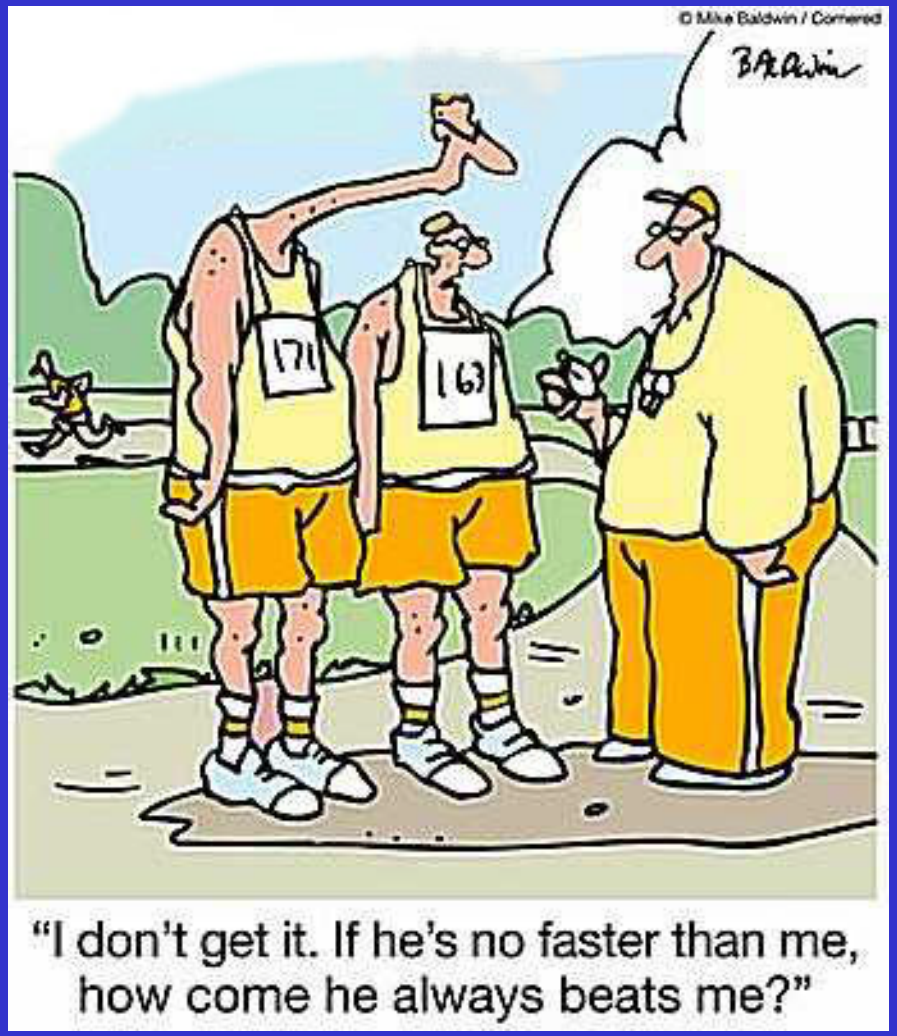
Recommended tests

- Echocardiogram
- Carotid ultrasound
- Quantitative proteinuria (if dipstick test positive)
- Ankle-brachial BP Index
- Fundoscopy
- Glucose tolerance test (if fasting plasma glucose >5.6 mmol/L (100 mg/dL)
- Home and 24 h ambulatory BP monitoring
- Pulse wave velocity measurement (where available)

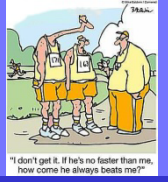
Table 4 Availability, prognostic value and cost of some markers of organ damage (scored from 0 to 4 pluses)

Markers	CV predictive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid Intima-Media Thickness	+++	+++	++
Arterial stiffness (Pulse wave velocity)	+++	+	++
Ankle-Brachial index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/Vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/White matter lesions	?	++	++++
Est. Glomerular Filtration Rate or Creatinine Clearance	+++	++++	+
Microalbuminuria	+++	++++	+

PWV, CBPs, FMD, IMT: and the winner is…



PWV, CBPs, FMD, IMT: and the winner is…



- Assess different aspects of arterial status: function structure

- PWV and CPBs integrate the overall status of the arterial tree and represent the load to the heart
- CBPs and FMD can detect *early* changes
- IMT, PWV and CBPs can detect the *cumulative (late)* effects
- Provide complementary information

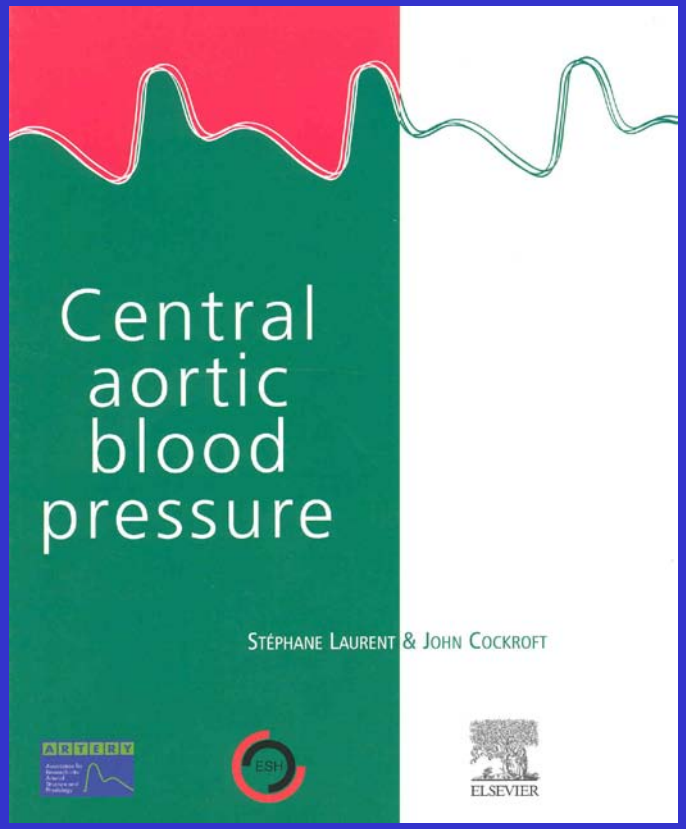
Biomarkers of Arterial Aging and Treatment ???

Biomarkers of Arterial Aging and Treatment

Table 2
Pharmacological treatment associated with a reduction in arterial stiffness (modified from [2])

Antihypertensive treatment ACE inhibitors AT1 blockers Aldosterone blockers Calcium channel blockers Diuretics β-Blockers
Treatment of congestive heart failure ACE inhibitors Nitrates
NO donors Nitrates Sinitrodil
Phosphodiesterase type-5 inhibitors Sildenafil
Hypolipidemic agents Statins Ezetimibe
Anti-inflammatory drugs TNFα antagonists
Antidiabetic agents Thiazolidinediones
AGE breakers Alagebrium (ALT-711)

Vlachopoulos C et al



Wilkinson I

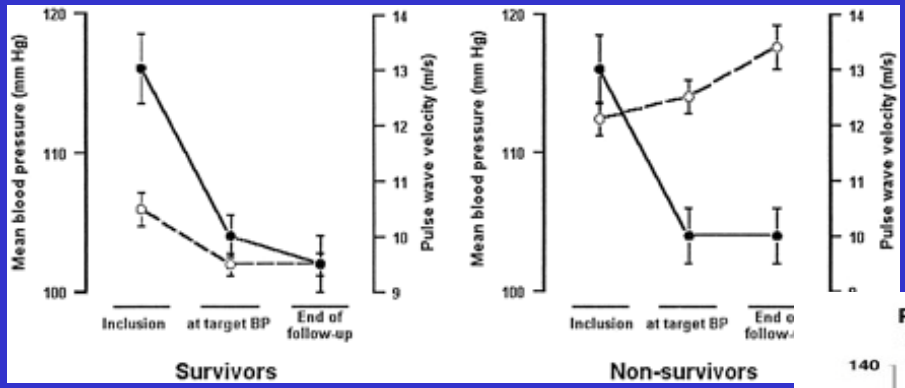
Comparative effect of drugs on central hemodynamic indices

	Aortic pulse wave velocity	Augmentation index
ACE inhibitors	↓	↓↓
Angiotensin receptor blockers	↓	↓↓
β-Blockers	↓↓	↑
Calcium channel blockers	↓	↓↓
Thiazide diuretics	↔	↓
Nitrates	↔	↓↓↓
PD5 inhibitors	↓	↓

ACE: angiotensin-converting enzyme; PD5: phosphodiesterase type 5.

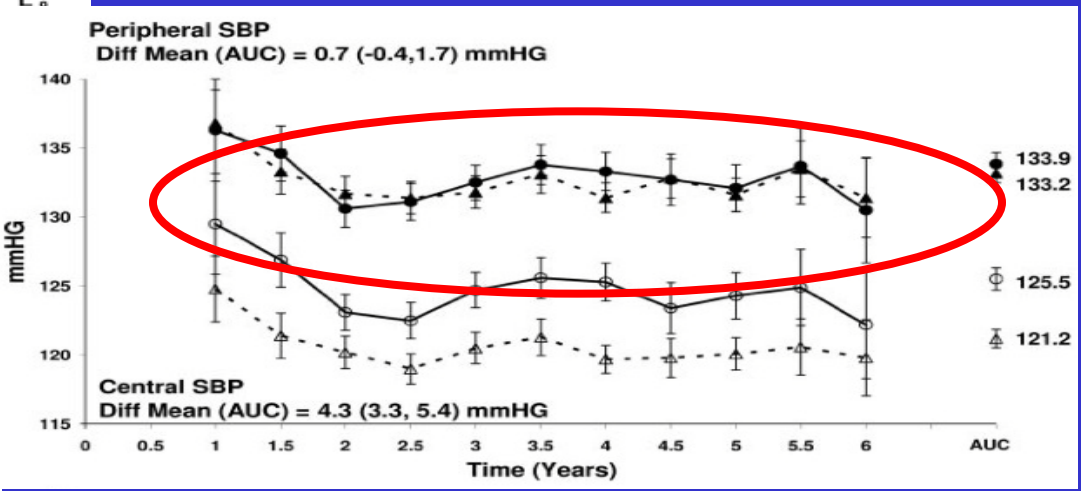
Biomarkers of Arterial Aging and Treatment

STIFFNESS



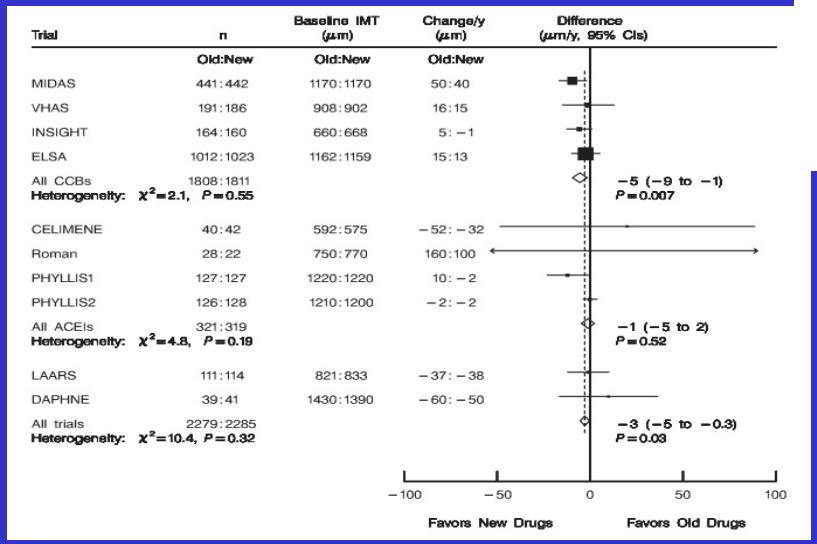
Guerin AP, et al. *Circulation* 2001;103:987-992

Central Pressures



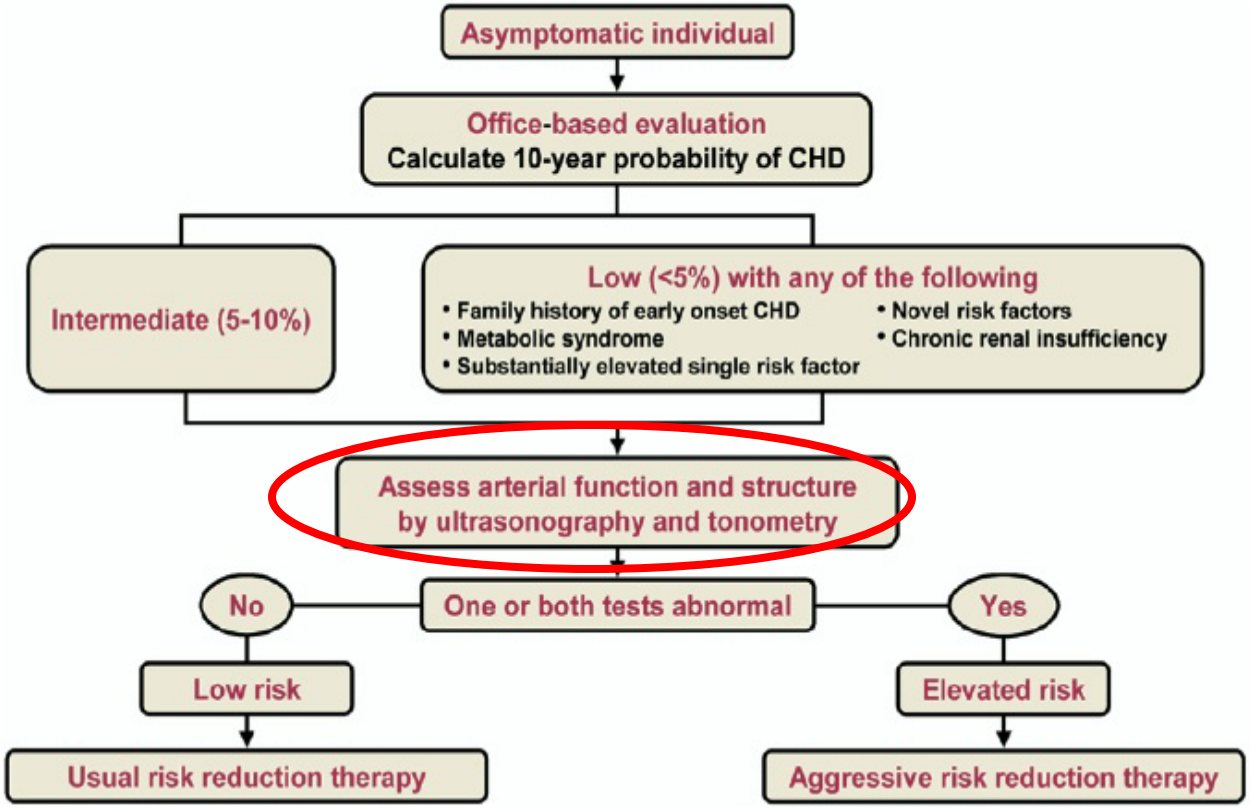
CAFÉ Study

IMT



Wang et al. Stroke 2006

CBPs, FMD, IMT: clinical tools or research toys?



Kullo and Malik. JACC 2007

Risk stratification

‘A man is as old as his arteries’

Thomas Sydenham

Chronological or vascular age?