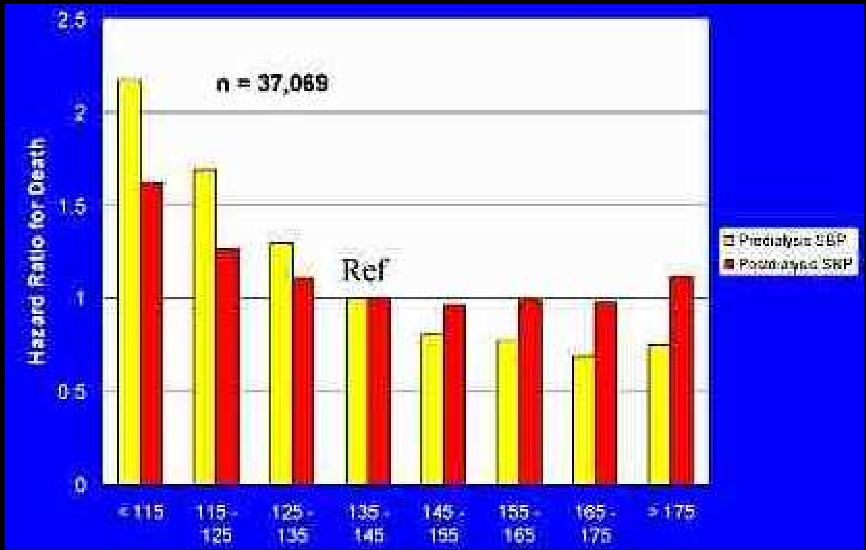
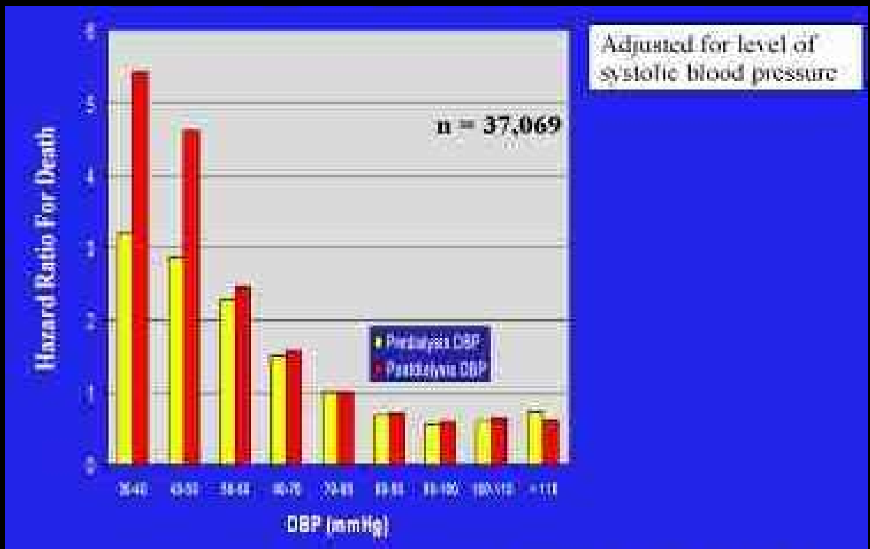
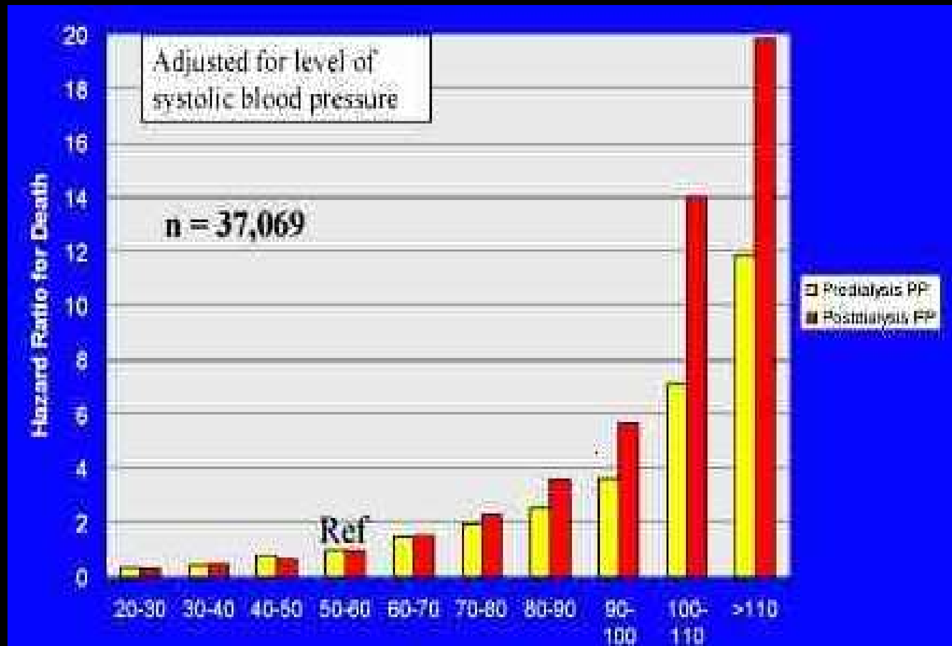
Targeting vascular damage (stiffness, calcifications) in CKD:

beyond blood pressure

Should we still measure BP in dialysis?

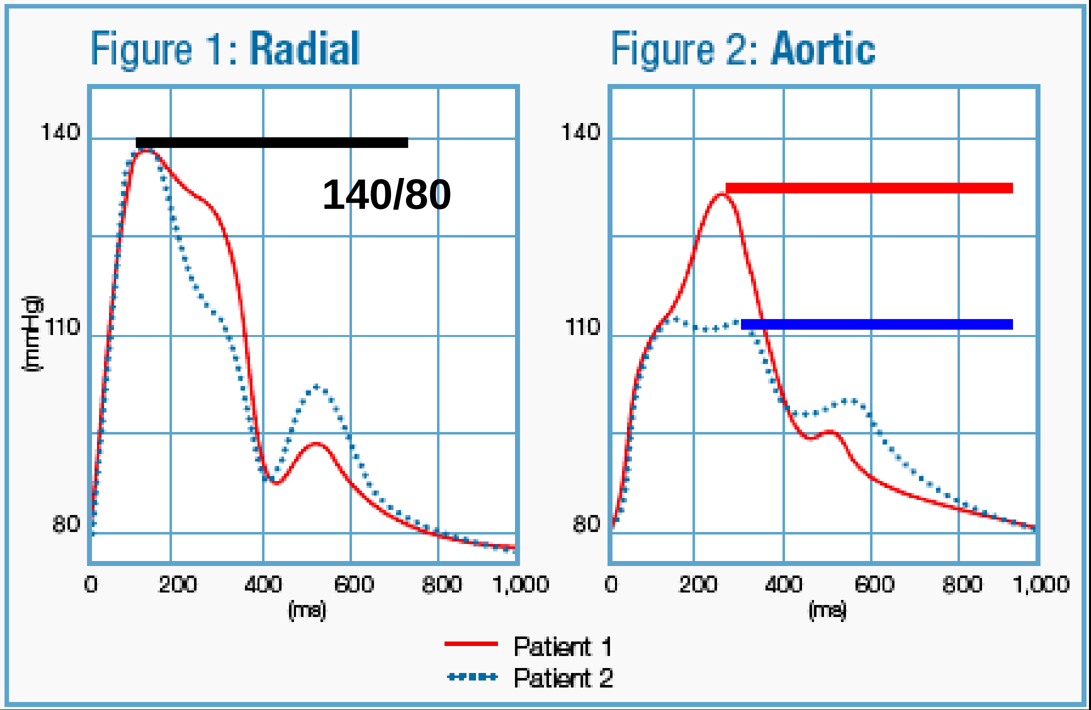






Clinical Problems with cuff BP

Case #1: Variances in Cuff BP vs. Central BP

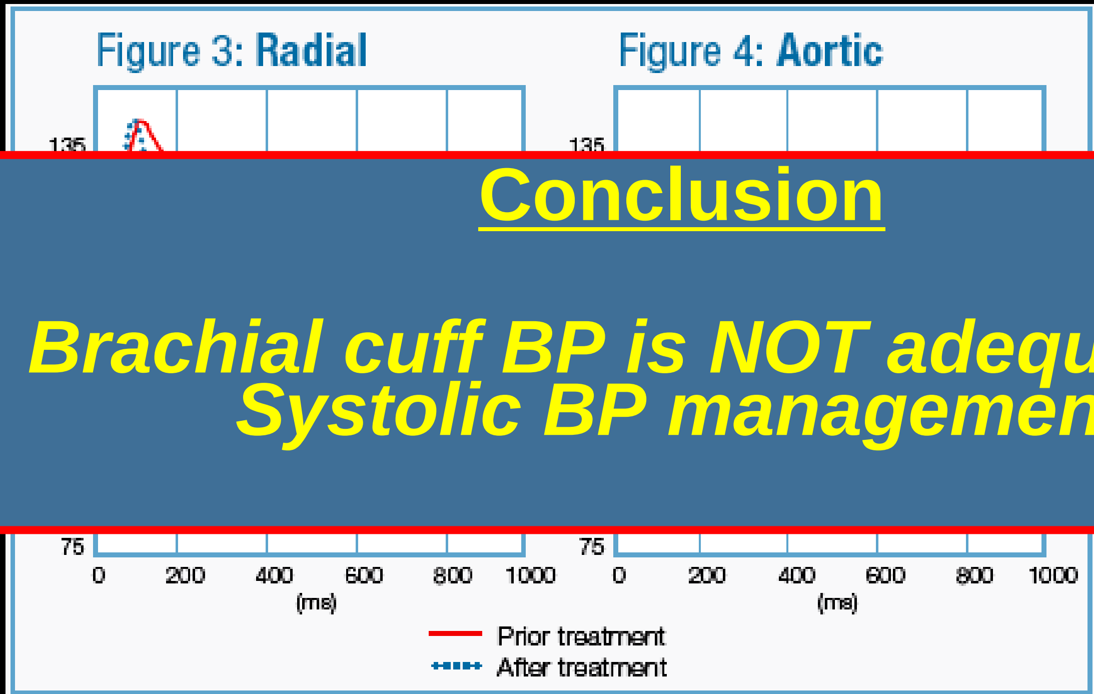


TWO PATIENTS … in the periphery, both (red & blue) have <u>identical</u> <u>BP</u> (140/80)

- **BUT...... Centrally there is a <u>critical Systolic BP (Sp) difference</u> between patients:**
- **WHY the different <u>Aortic</u> Sp?… the patients have different Arterial Stiffness !**

Clinical Problems with cuff BP

Case #2: Variances in Cuff BP vs. Central BP



Conclusion

Brachial cuff BP is NOT adequate for Systolic BP management

SAME PATIENT - before & after drug intervention (GTN for angina)

- **<u>There is No change</u> in Cuff Sp …but … . a <u>Big change</u> Aortic Sp**
- **Hypertension, Diabetes, Renal, Heart Failure => ALL require CV drug therapies.**

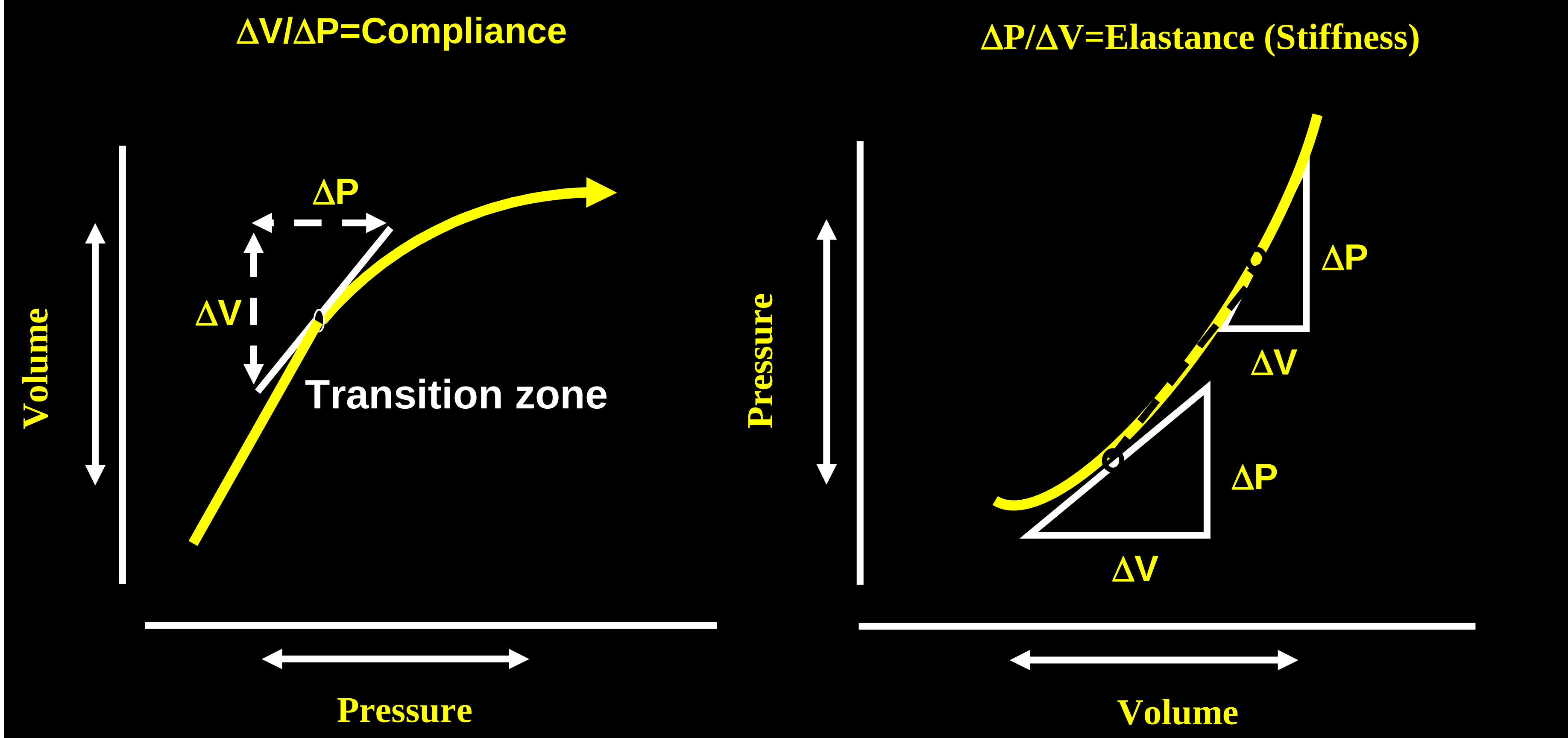
NON-INVASIVE METHODS FOR THE EVALUATION OF VASCULAR FUNCTION

- **ASSESSMENT OF ARTERIAL STIFFNESS:**
  - PWV
  - relating change in diameter/area to distending pressure
  - arterial pressure waveform analysis.
- **ENDOTHELIAL FUNCTION MEASUREMENT:**
  - endothelium-dependent (flow mediated)
  - endothelium-independent (NTG)
  - vascular responses of the brachial artery by high-resolution imaging

i) PWV = distance / ΔTA - ΔTB

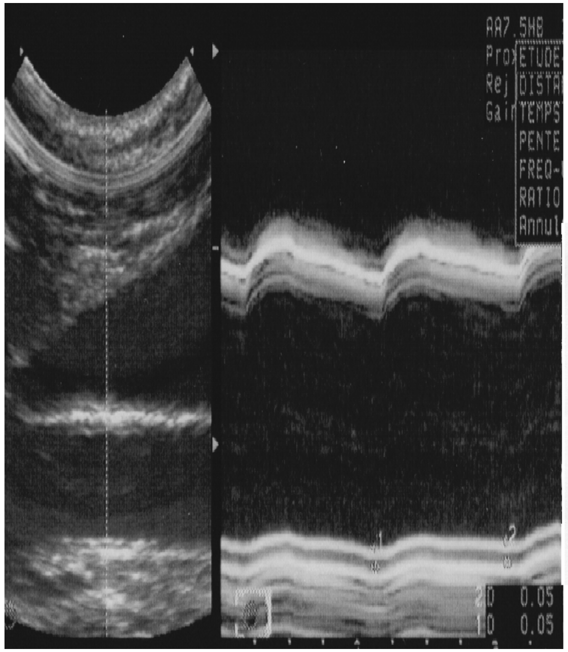
ΔTA / ΔTB = differences between the ECG and tonometer waveforms

ii) The volume – pressure relationship

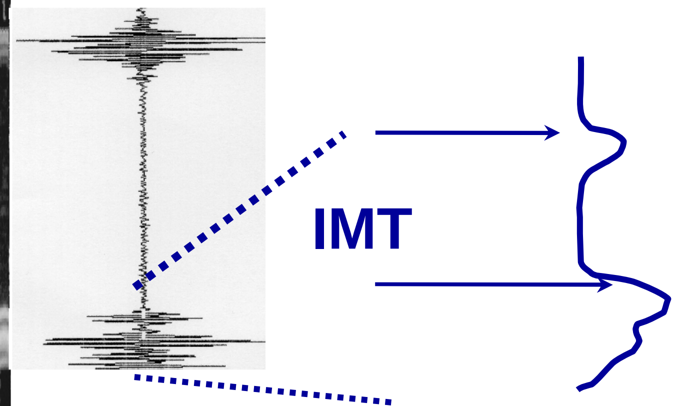


Distensibility = 2(ΔD/D)/(SBP - DBP), where D is carotid diastolic diameter and ΔD is change in artery diameter during systole. The stiffness parameter ß = ln(SBP/DBP)]/(D/D).

Echotracking is 3 to 10 x more precise than usual image based techniques



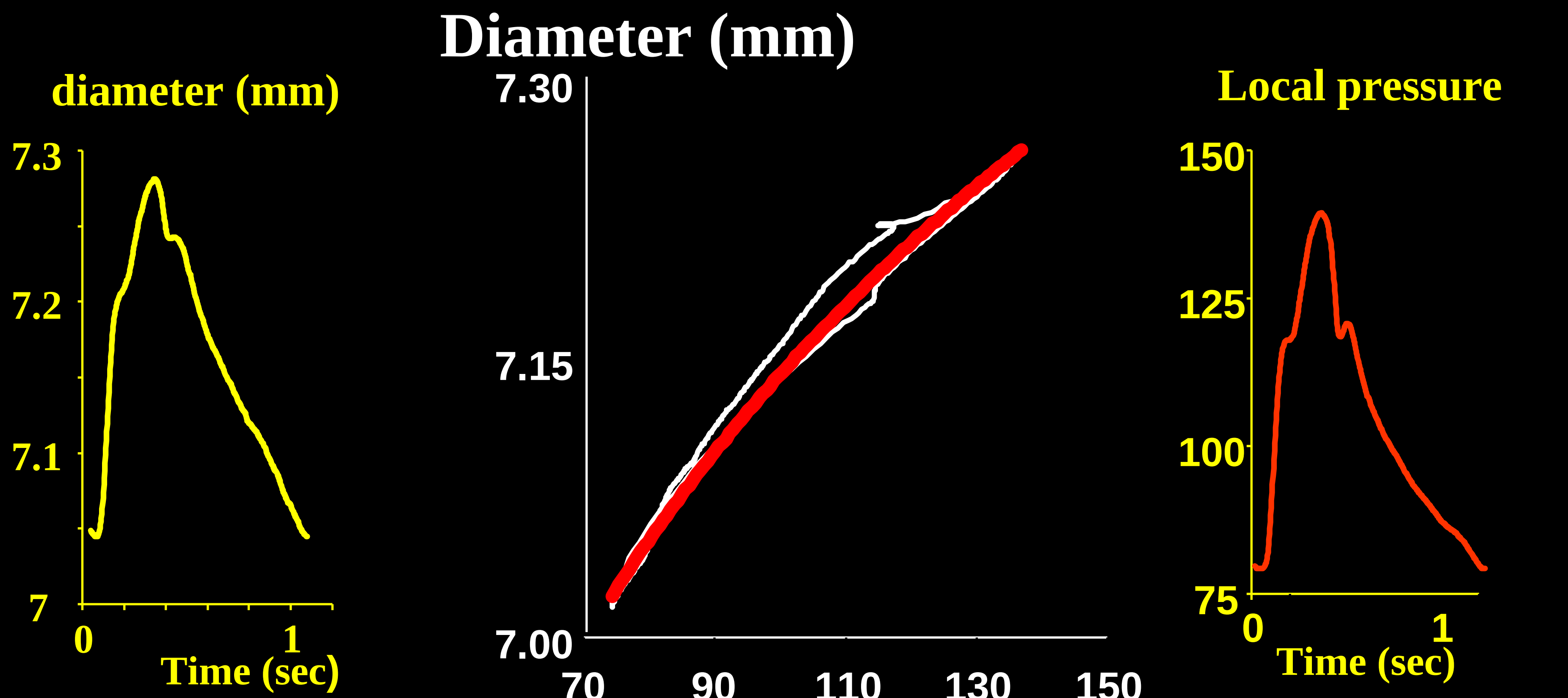
Signal averaging
10-10 000 RF lines



2 D   TM   RF Signal

Spatial resolution	200-400 µm	20-40 µm

The diameter-pressure curve



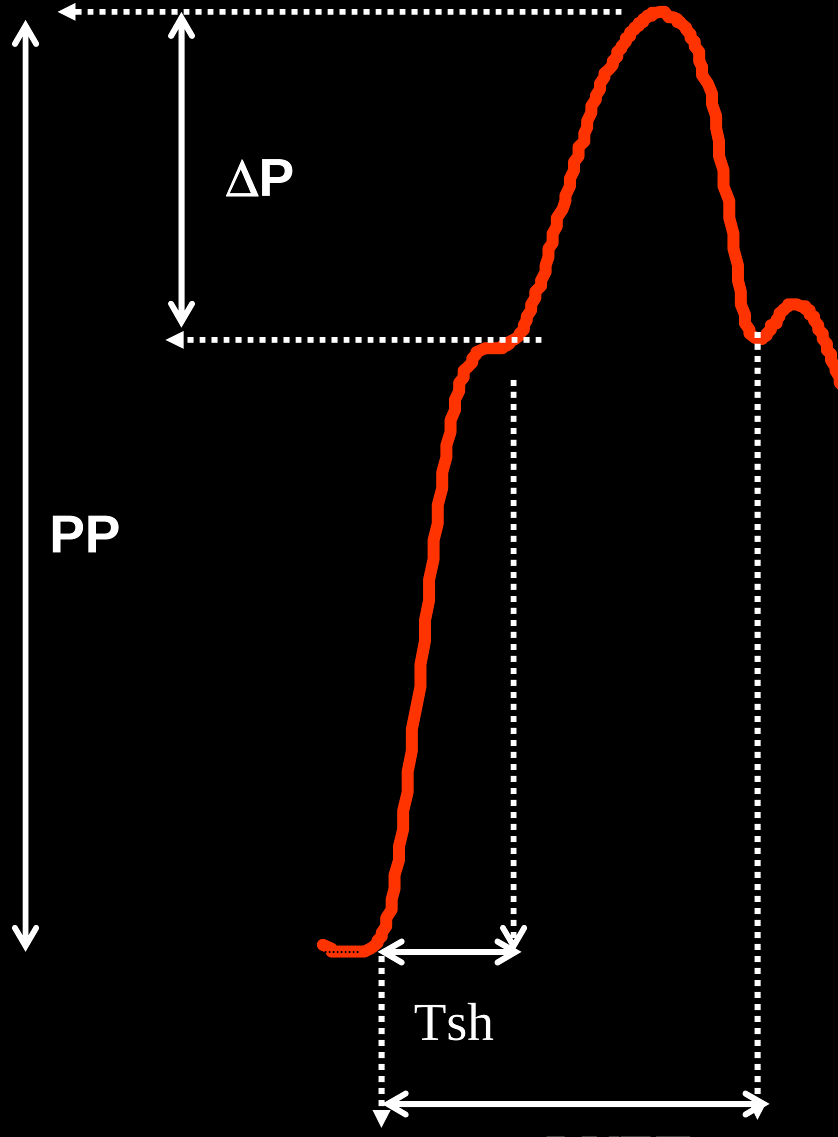
High-definition echotracking devices

- Wall Track system
- NIUS system

Aplanation Tonometry

- Millar Instruments

Aortic arterial pressure waveforme



ΔP = augmented pressure

PP = pulse pressure

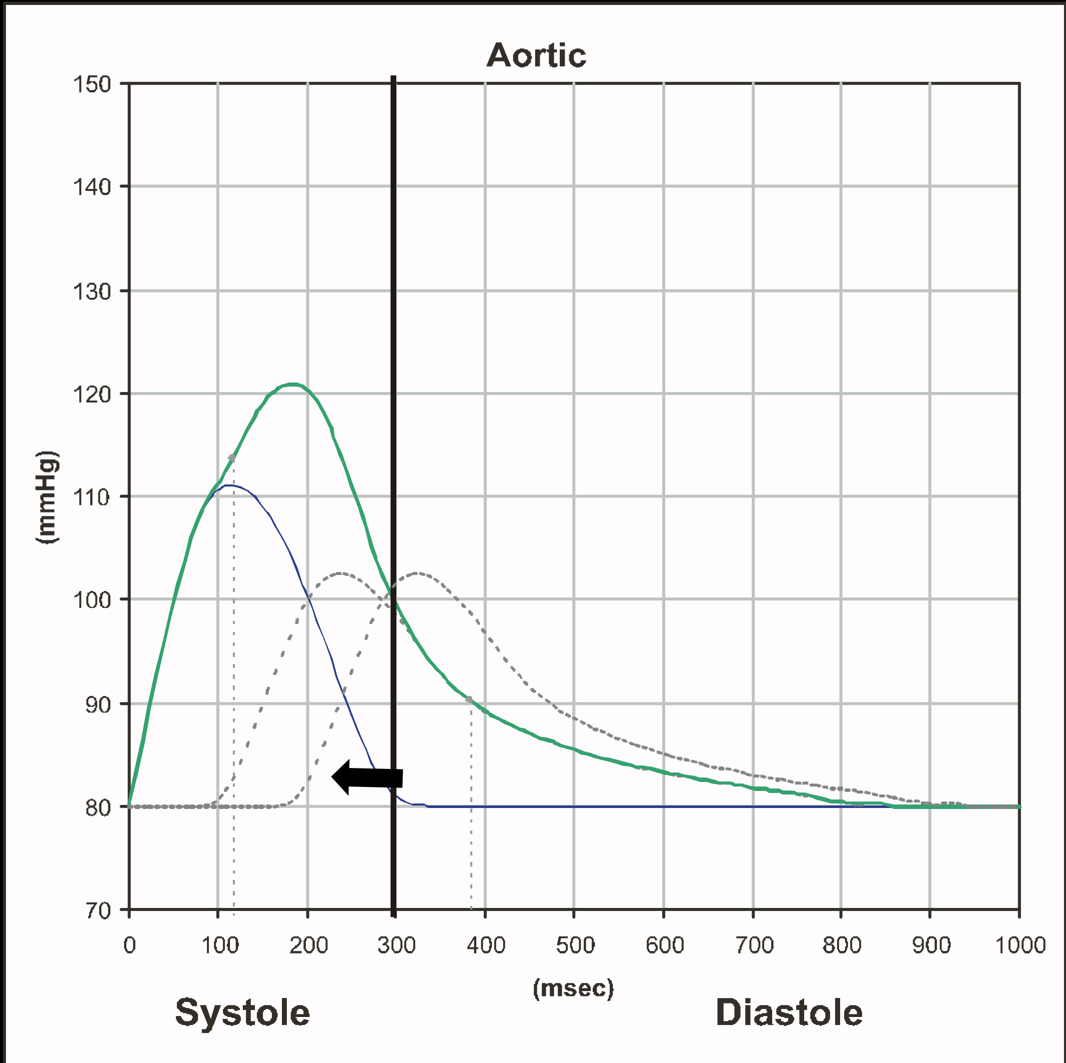
Augmentation index=ΔP/ PP

Tsh = time to shoulder

LVET = LV ejection time

Composite measure – related to:
1) Stiffness
2) Peripheral reflective properties

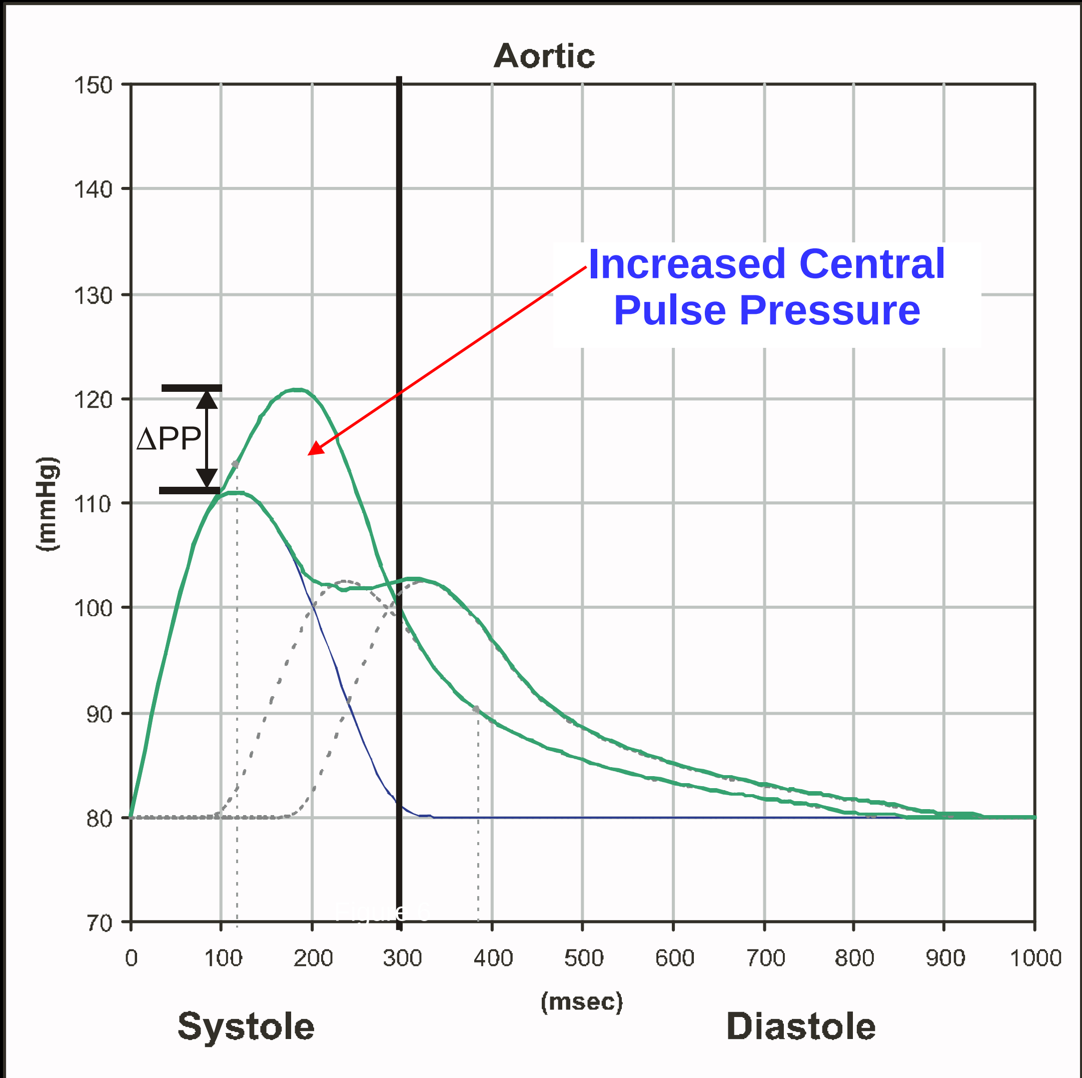
Pressure Wave Reflection at the Heart



If the patient's arteries get stiffer….

- **PWV ⇧**
- **the reflected wave arrives sooner back at the heart**
- **There are <u>three</u> important clinical implications**

Pressure Wave Reflection at the Heart



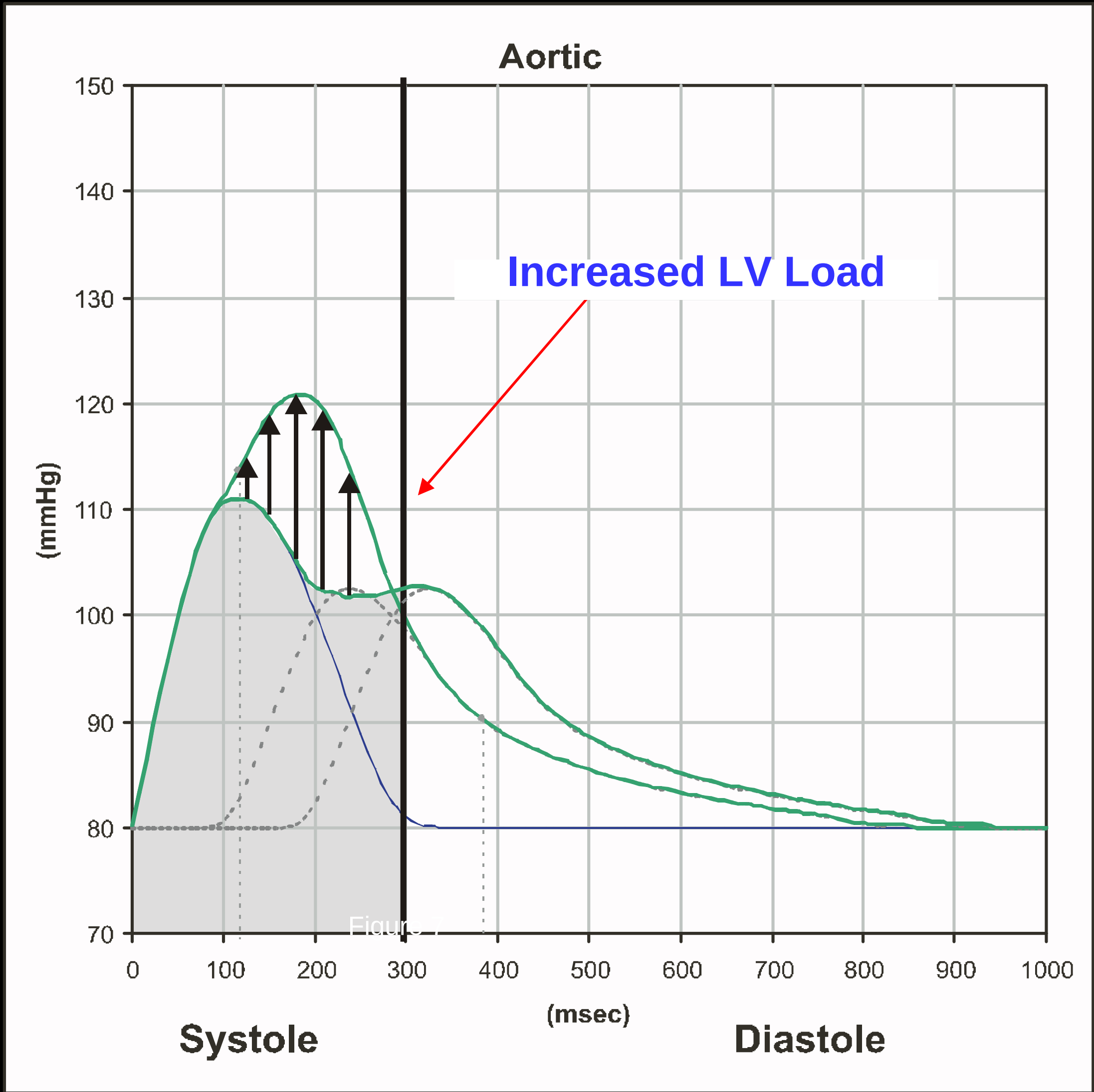
First

- increase in central PP
- *i.e.* increase in (pulsatile) stress on (cerebral) blood vessels

=

- increased <u>stroke risk</u>

Pressure Wave Reflection at the Heart



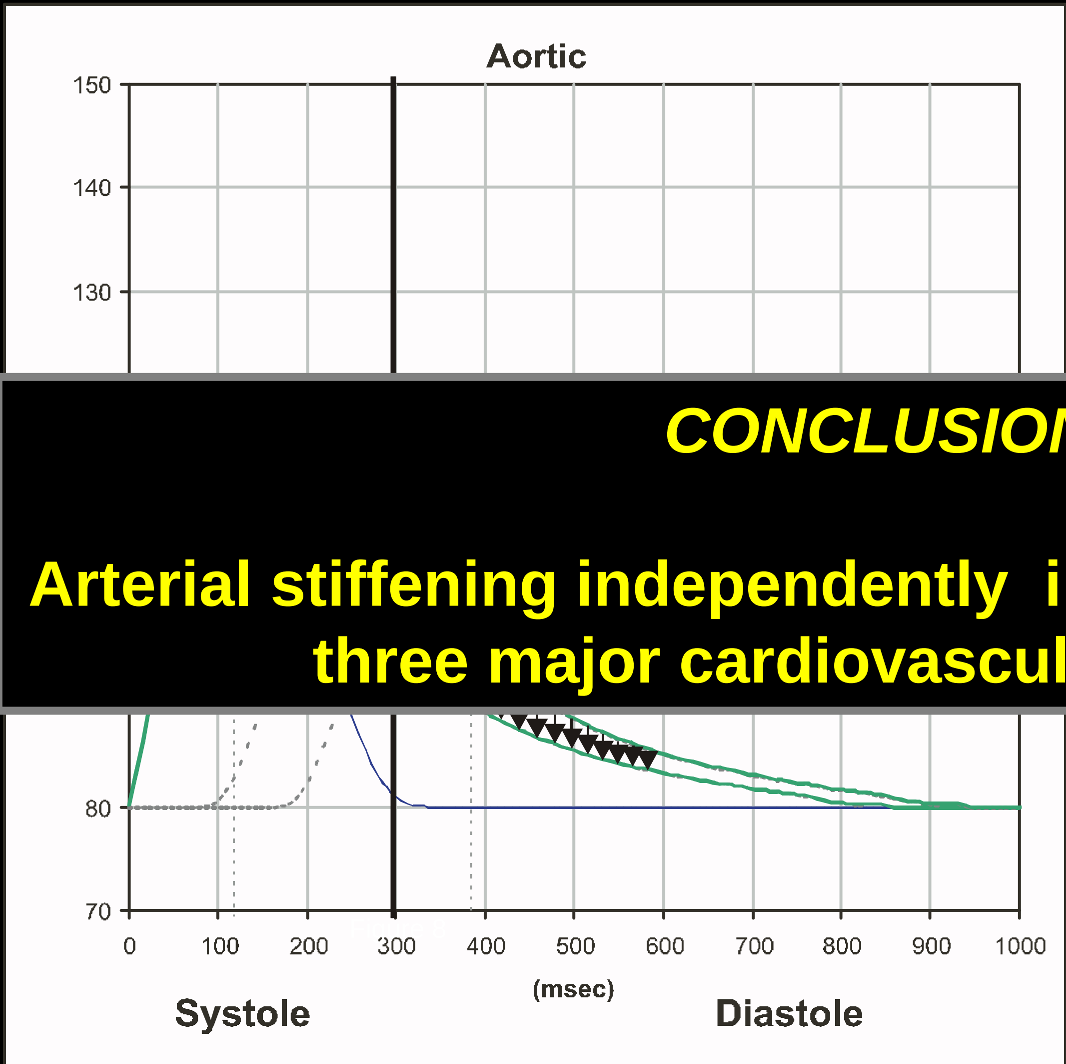
Second

- increase in **LV load**

=

- **increased <u>LV mass</u>**

Pressure Wave Reflection at the Heart



Third

- reduced

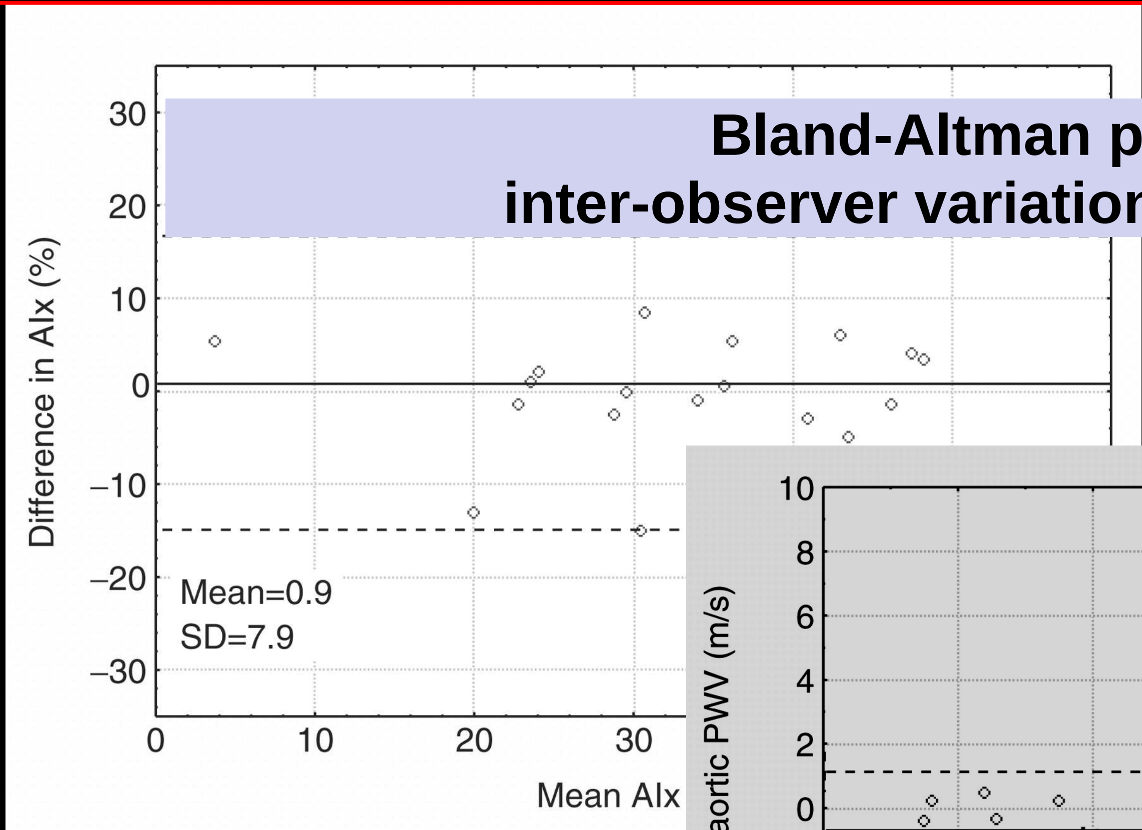
- myocardial ischemia.

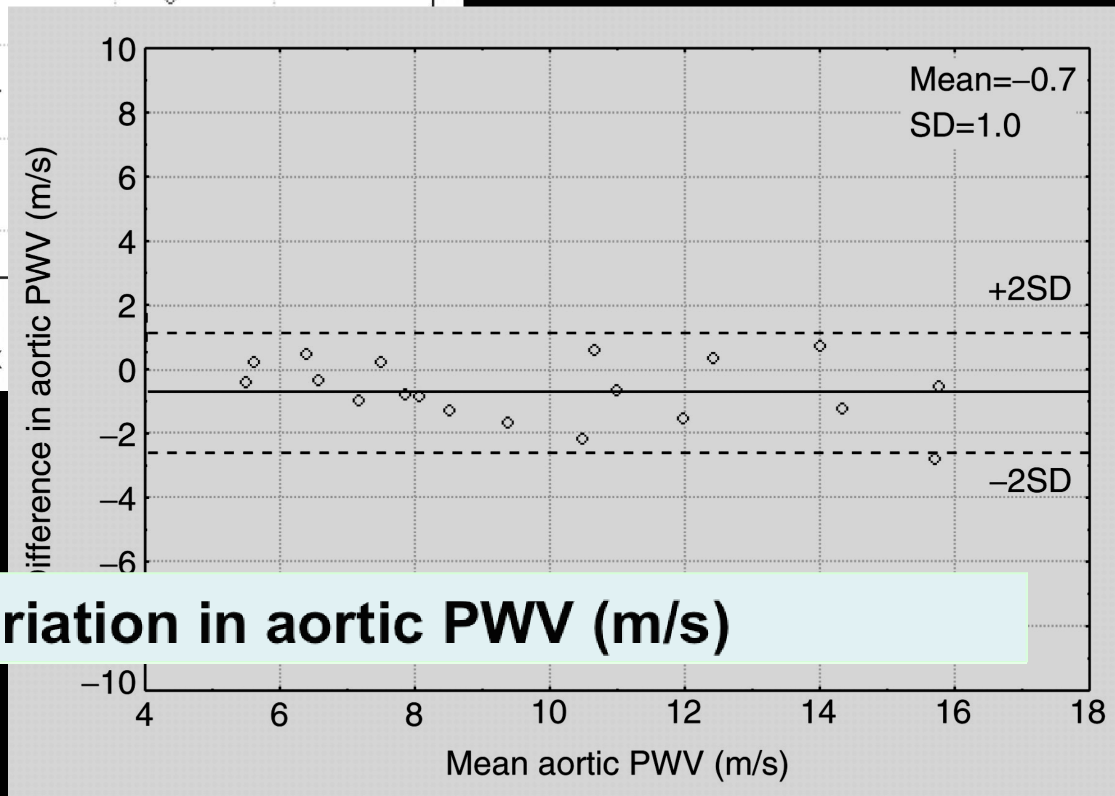
CONCLUSION:

Arterial stiffening independently increases the risk of all three major cardiovascular outcomes.

EXCELLENT REPRODUCIBILITY WITH PWV AND AIx

Bland-Altman plot:
inter-observer variation in AIx (%)



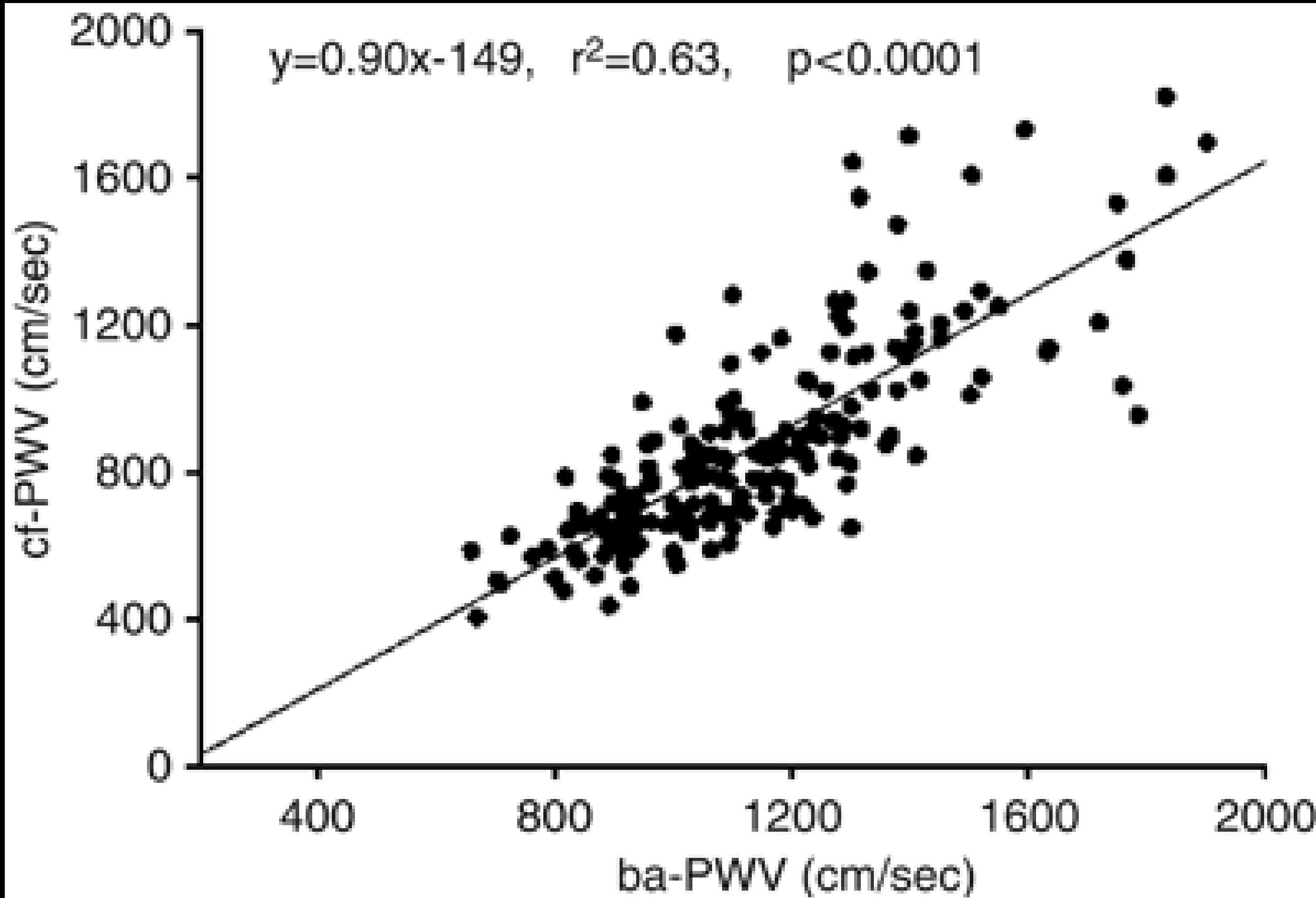


day-to-day variation in aortic PWV (m/s)

Frimodt-Moller, M. et al.
NDT. 2008 23:594-600;

Brachial-ankle vs carotid-femoral PWV as a determinant of CDV structure and function

Yu et al, *JHH* 2008



baPWV > cfPWV as a determinant of CDV structure and function ?

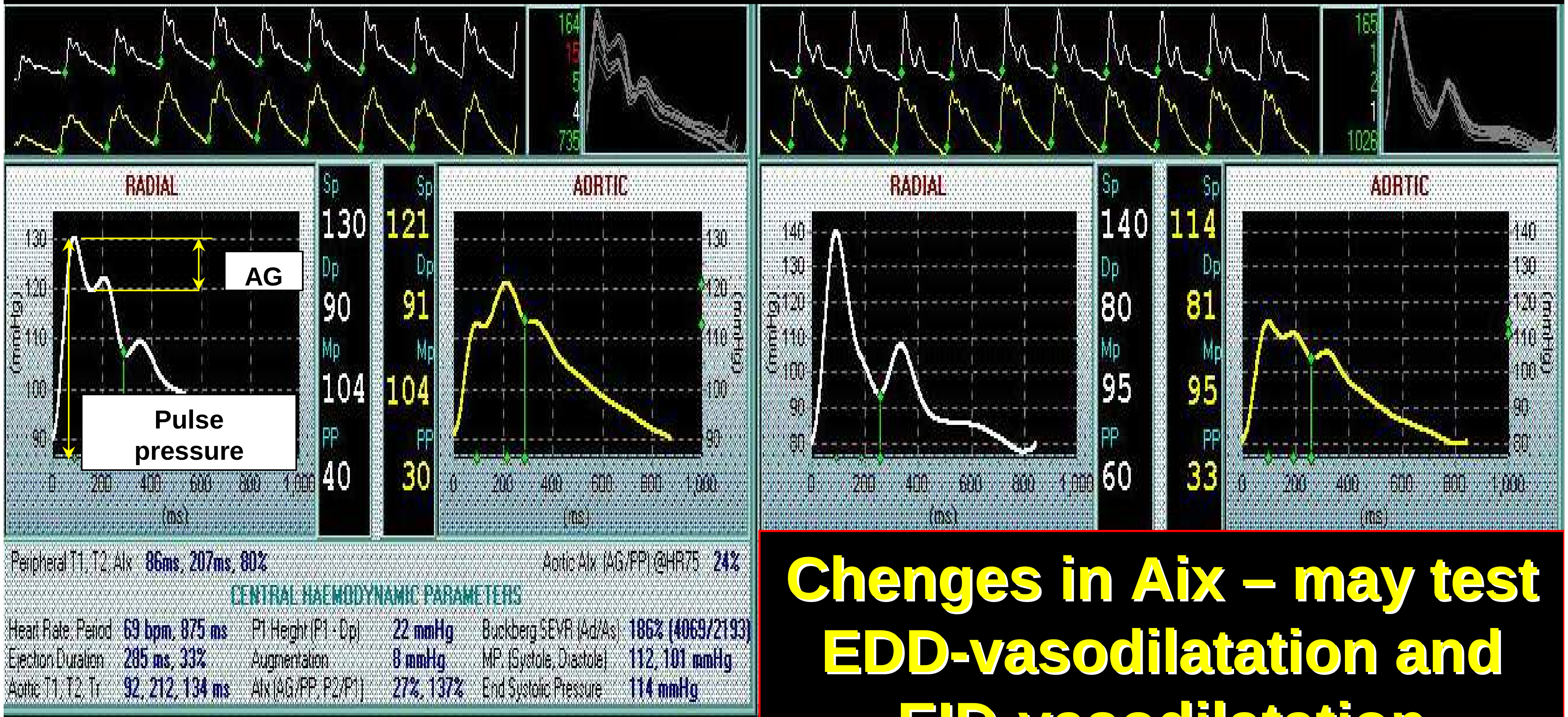
Yu et al, *JHH* 2008

	ba-PWV	*cf-PWV*	P-*value*
Cardiac structure			
LVM	0.29**	0.22**	0.0219
IVS	0.43**	0.36**	0.0165
PWT	0.46**	0.32**	<0.0001
LAD	0.35**	0.29**	0.0386
Cardiac function			
LVEF	0.02	0.03	0.3907
Ees	0.37**	0.39**	0.2726
IVRT	0.34**	0.27**	0.0202
Peak E	−0.12	−0.13*	0.3898
Peak A	0.46**	0.43**	0.1734
E/A ratio	−0.43**	−0.41**	0.2683
Arterial structure			
Carotid	0.51**	0.47**	0.0981
IMT	0.34**	0.34**	0.5000
Aorta	0.25**	0.21**	0.1264
Arterial function			
Incre-M	0.54**	0.48**	0.0014
Ea	0.41**	0.33**	0.0081
AI	0.38**	0.32**	0.0368

Endothelial function testing

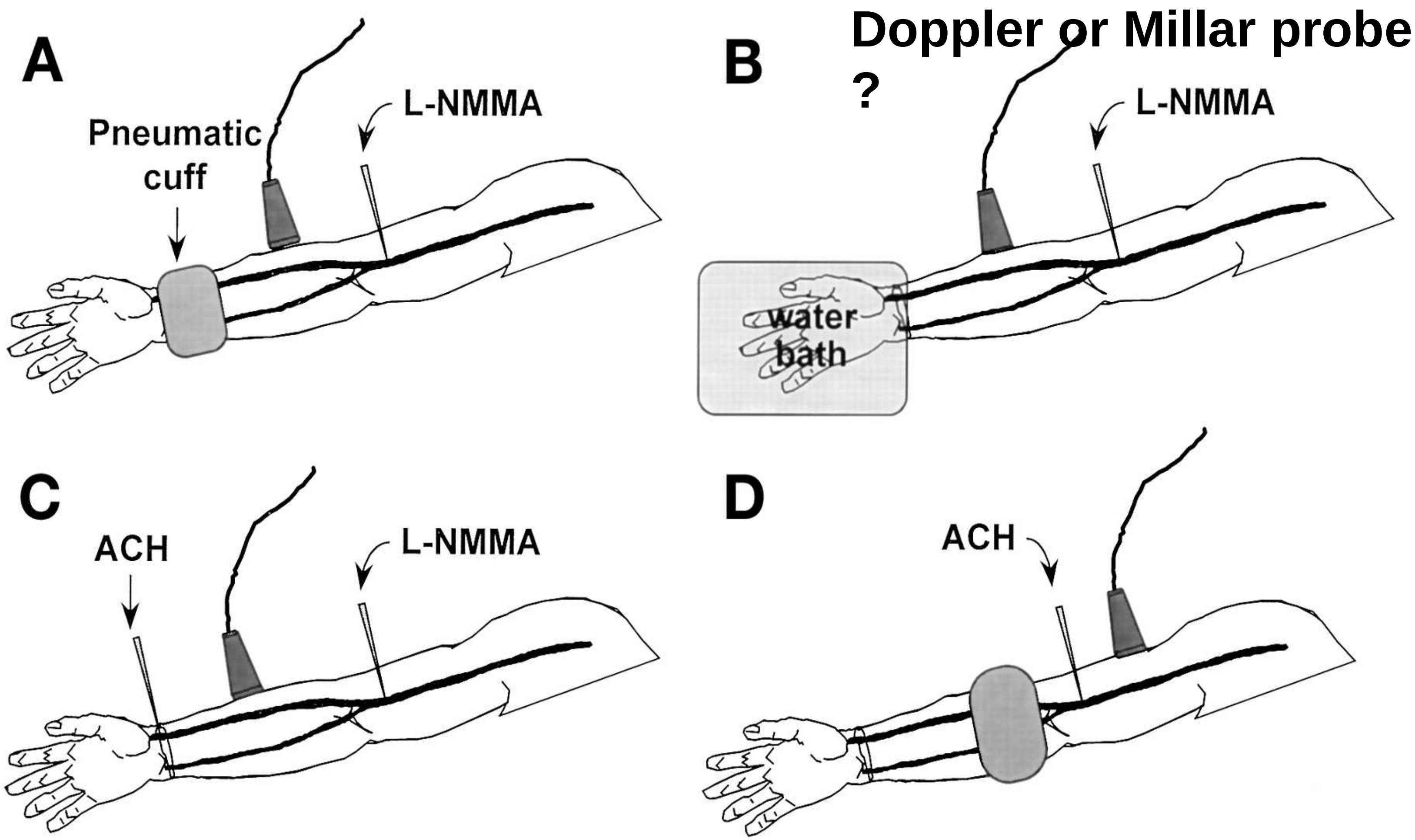
Pulse waveforms from a hemodialysis patient before (left panel, "stiff" pattern) and after (right panel, "normal" pattern) nitroglycerin administration.

AIx improved from +24% to –11%



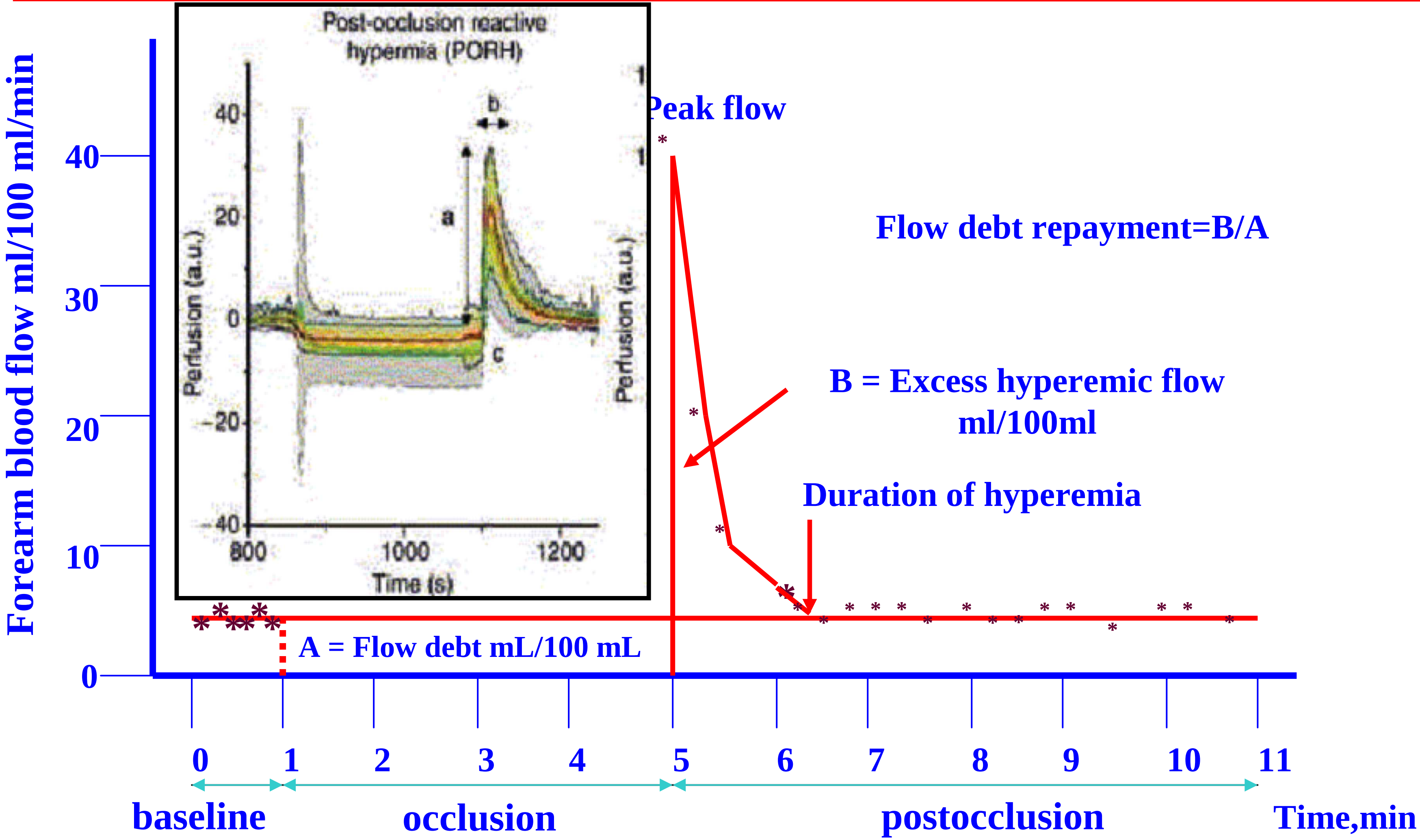
Chenges in Aix – may test EDD-vasodilatation and EID-vasodilatation

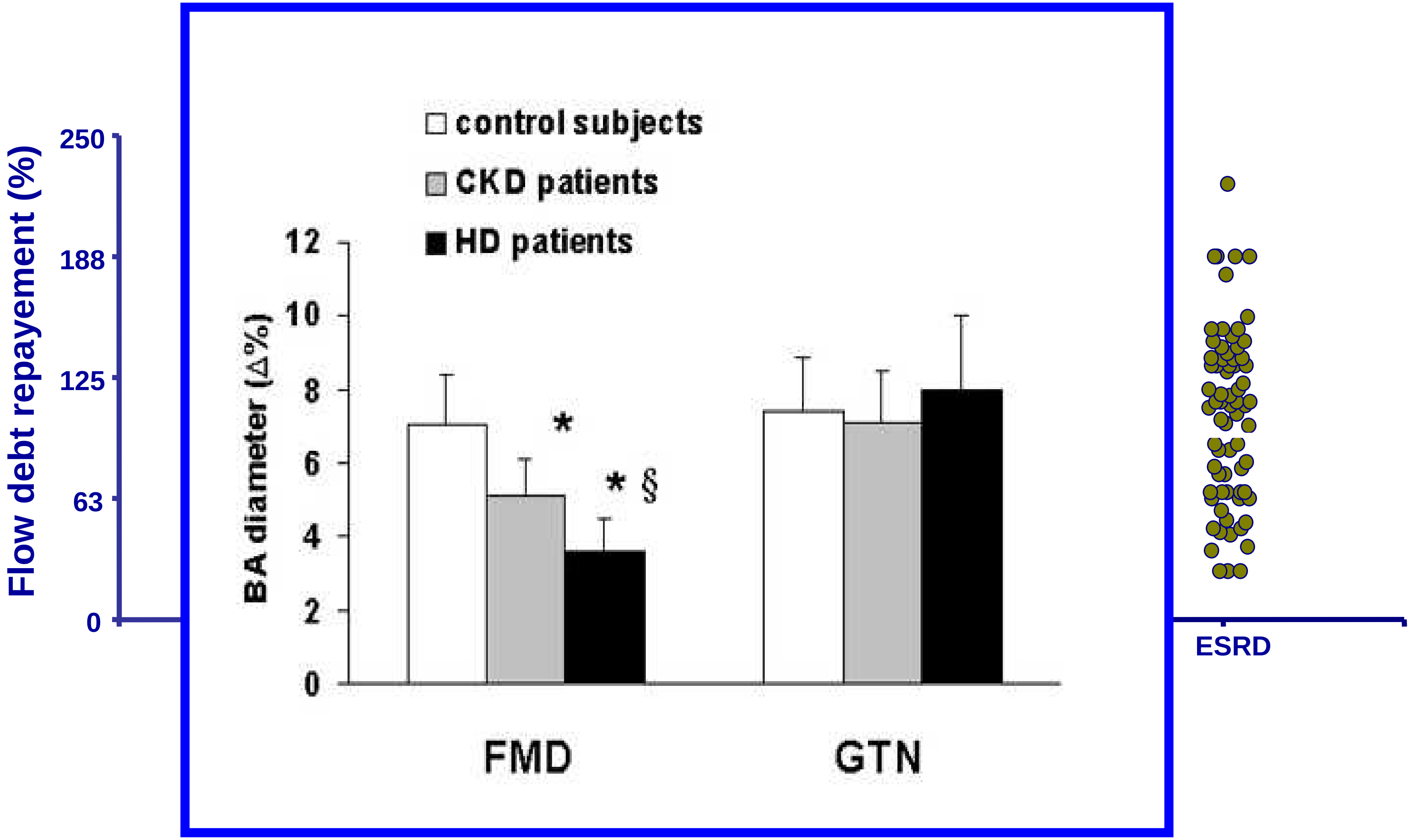
Methods of stimulating increased blood flow



Mullen, M. J. et al. Circ Res 2001;88:145-151

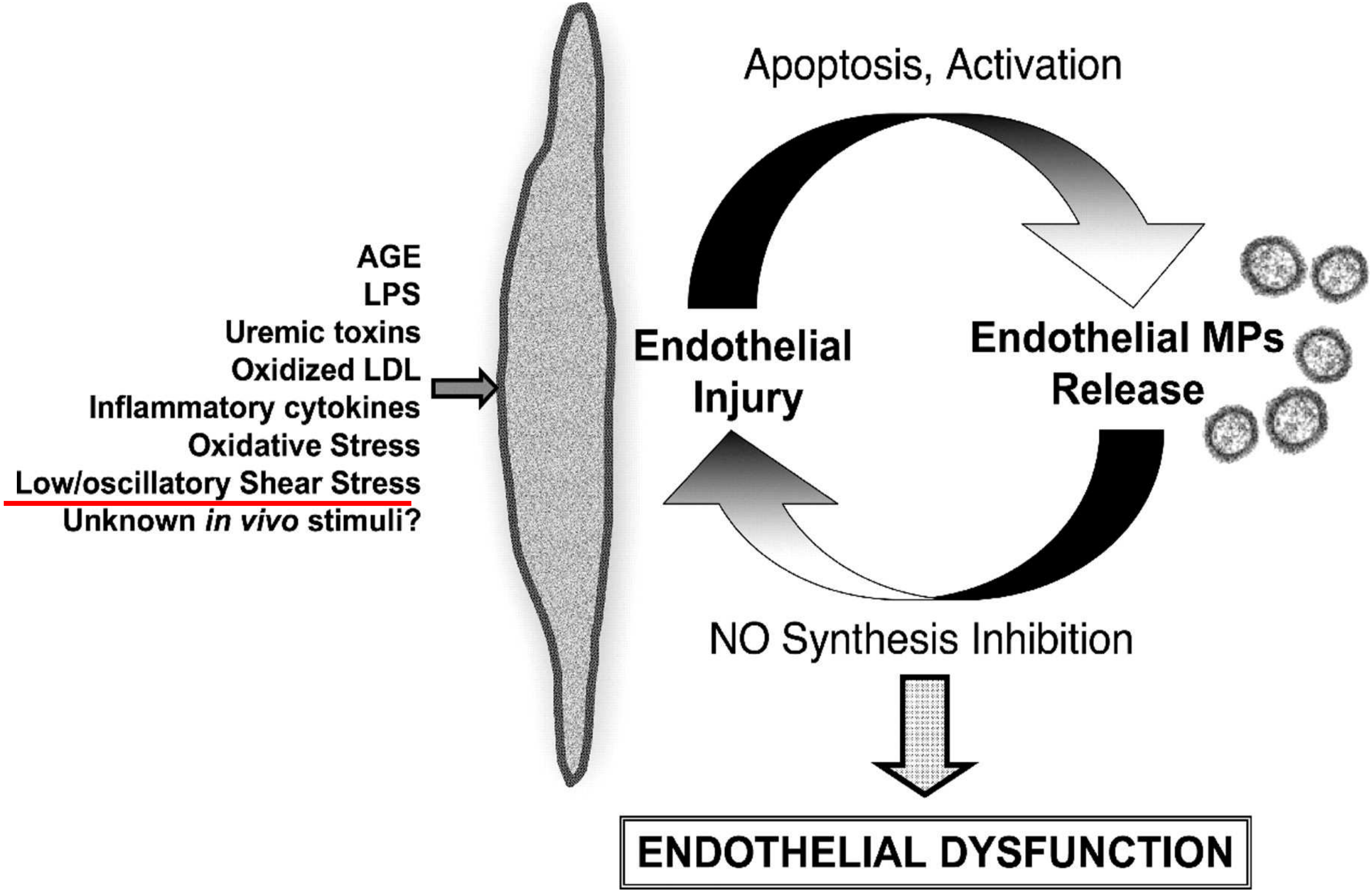
Schematic representation of reactive hyperemic response in the human forearm after five minutes of ischemia



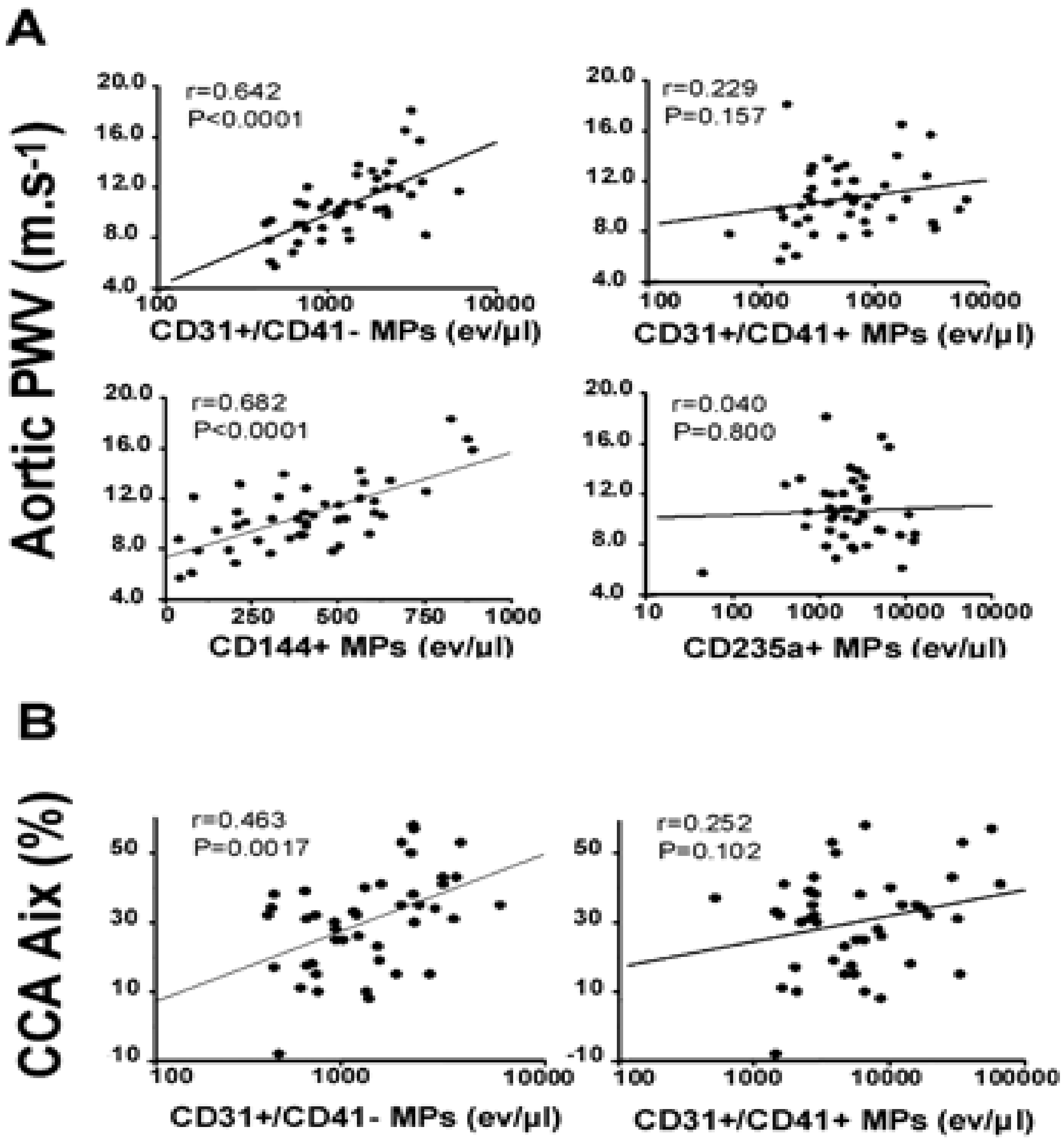


Pannier B et al. Kidney Int 2001

Uraemia – stiffness - endothelial dysfuction - microparticles



Boulanger, C. M. et al. Hypertension 2006;48:180-186

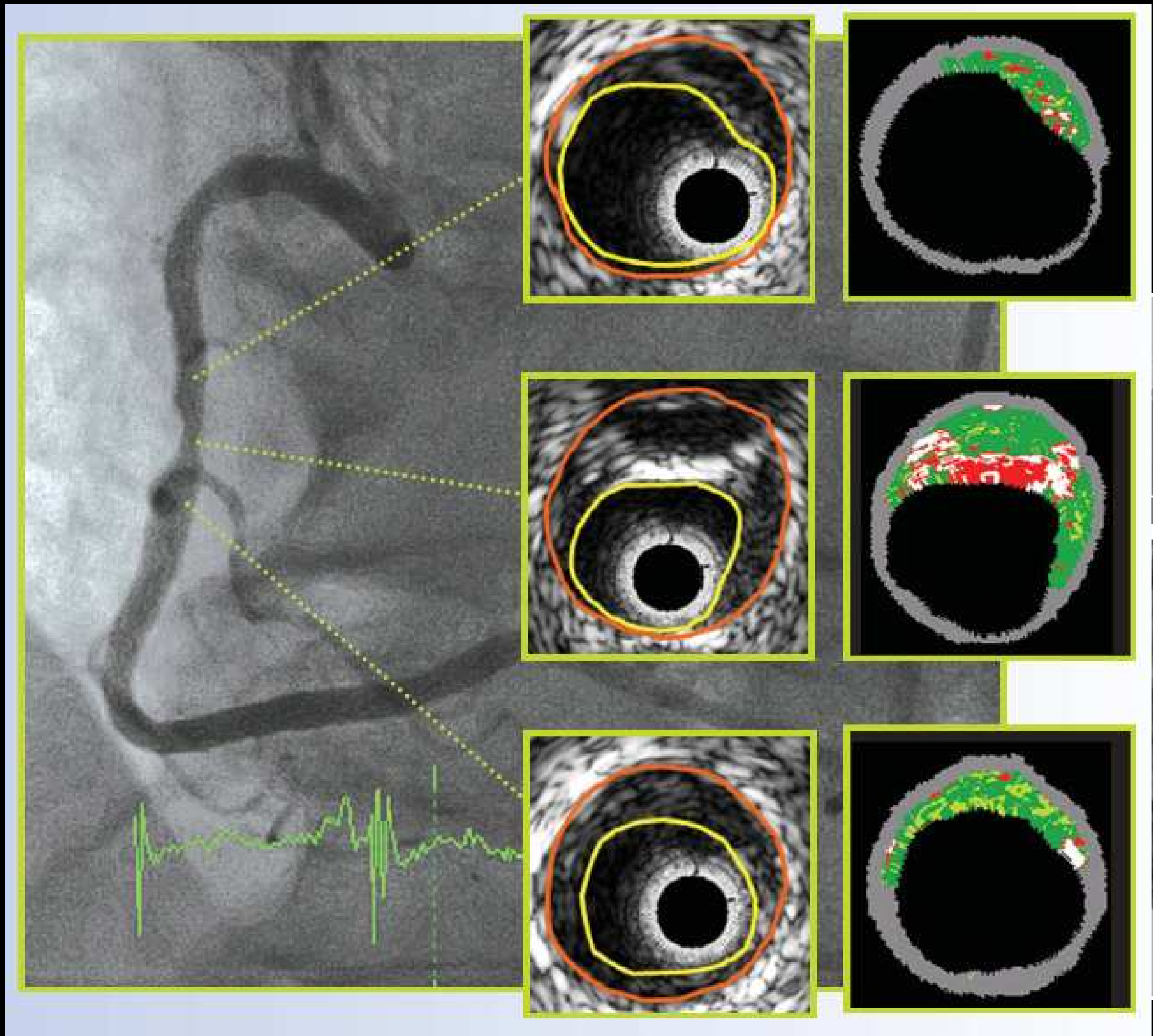

A
Aortic PWV (m.S-1)
r=0.642
P<0.0001
CD31+/CD41- MPs (ev/μl)
r=0.229
P=0.157
CD31+/CD41+ MPs (ev/μl)
r=0.682
P<0.0001
CD144+ MPs (ev/μl)
r=0.040
P=0.800
CD235a+ MPs (ev/μl)
B
CCA Aix (%)
r=0.463
P=0.0017
CD31+/CD41- MPs (ev/μl)
r=0.252
P=0.102
CD31+/CD41+ MPs (ev/μl)

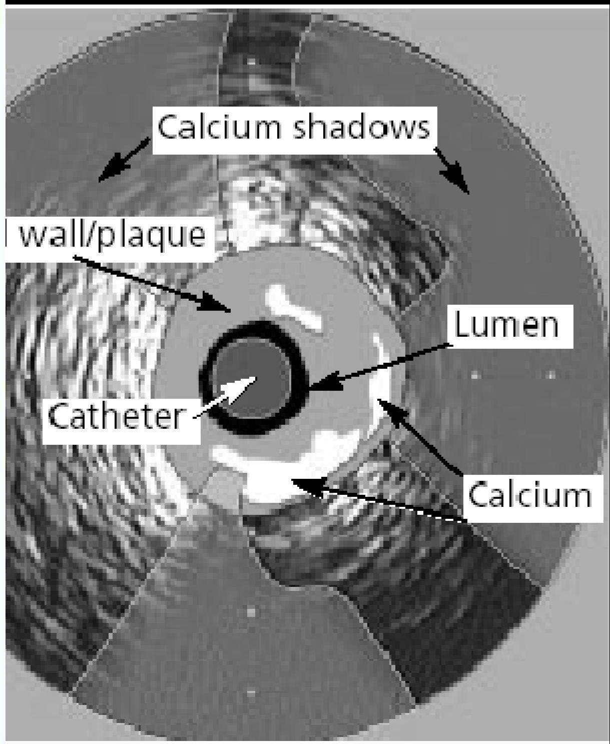
Philosophy and pathophisiology

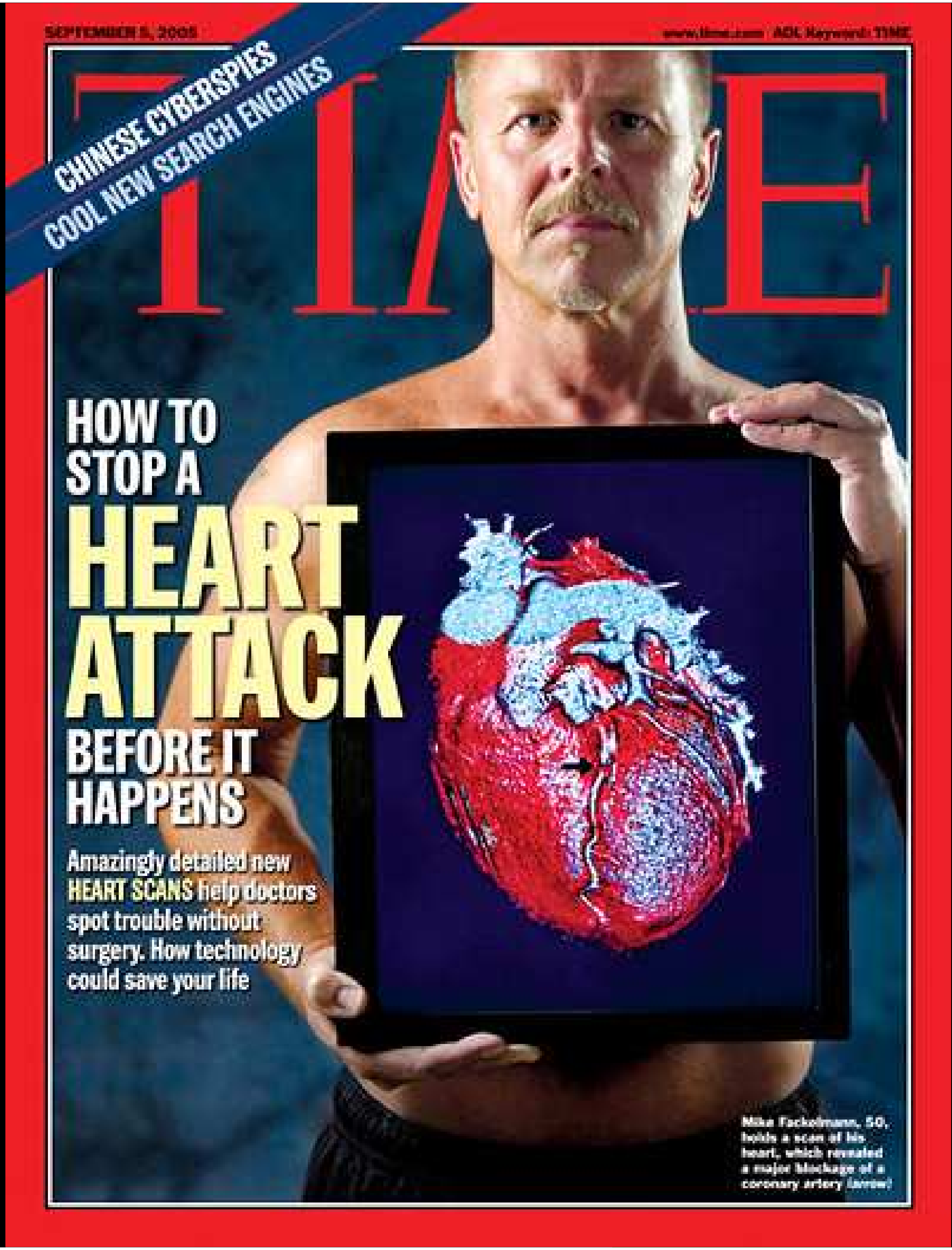
- Central arteries
  - “lower” stiffness
  - High sensitivity to ageing (VC?) and BP
- Peripheral arteries
  - “higher” stiffness
  - Sensitive mainly to vasoactive substances of endothelial origin
- PWA + baPWV + cfPWV = best approach ?

to be continued…

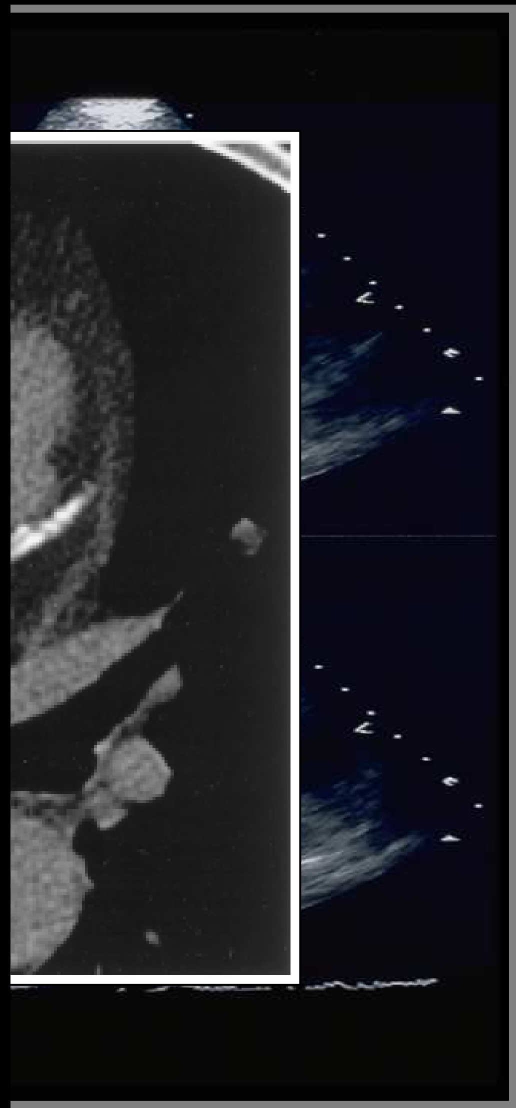
Virtual Histology of Atherosclerotic Plaques Using Intravascular Ultrasound





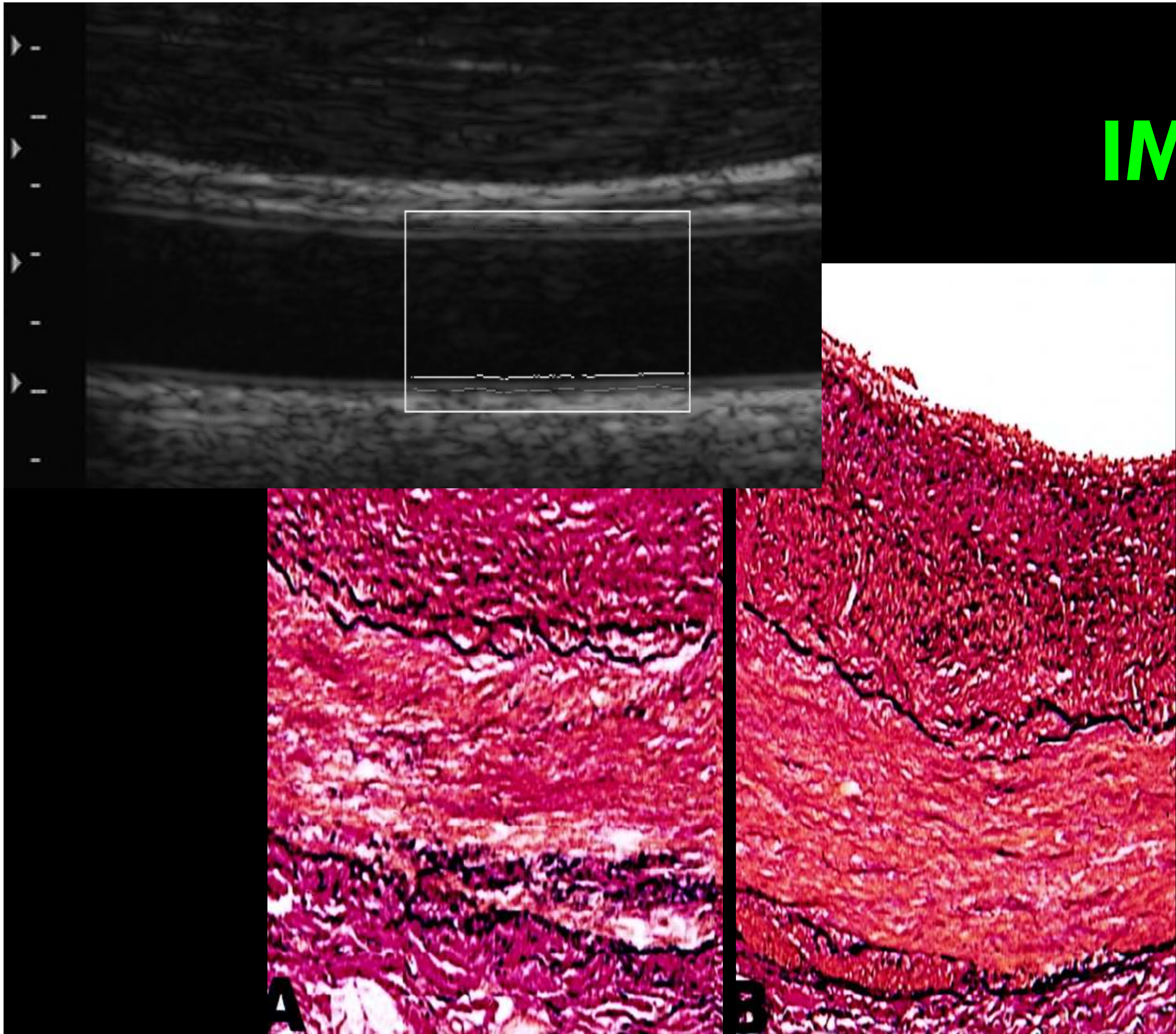


TIONS
ice ?



Raggi P et al *AJKD* 2004;43(3):572-9.

IMT



INTIMA

MEDIA

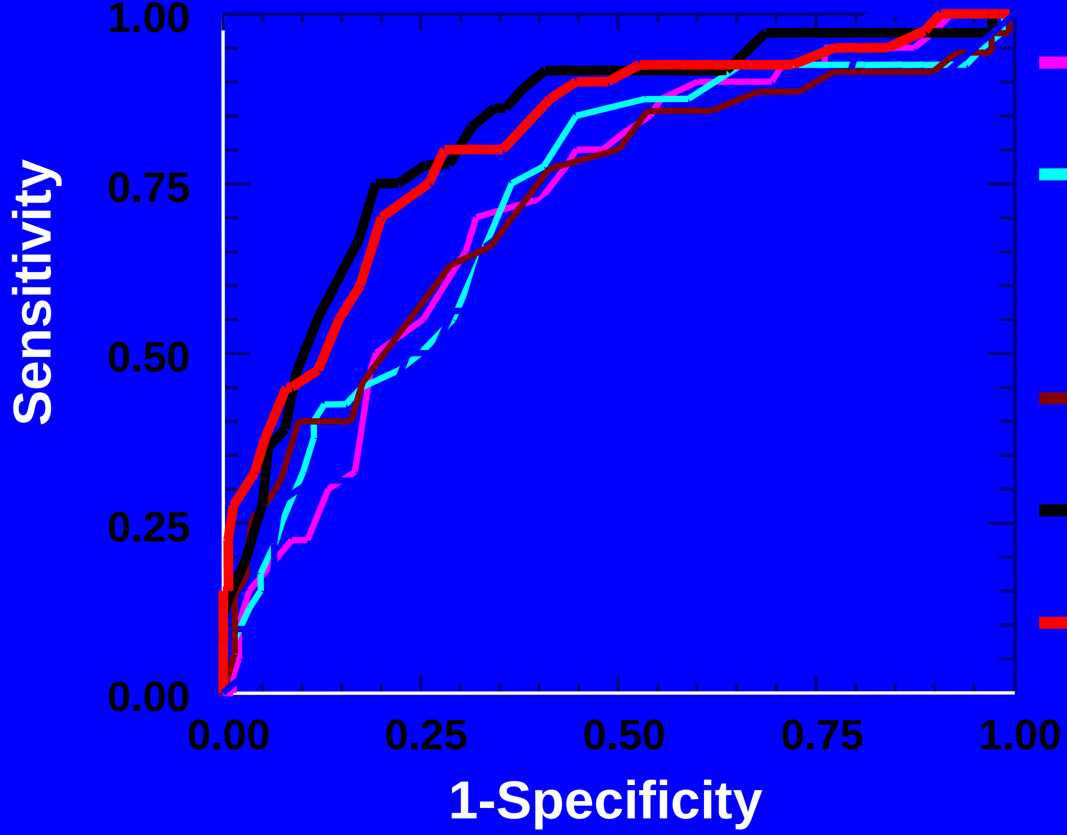
Non-CRF

CRF

Schwarz et al, NDT 2000;15:218-23

WHICH ONE IS THE MOST RELEVANT

?



Criterions

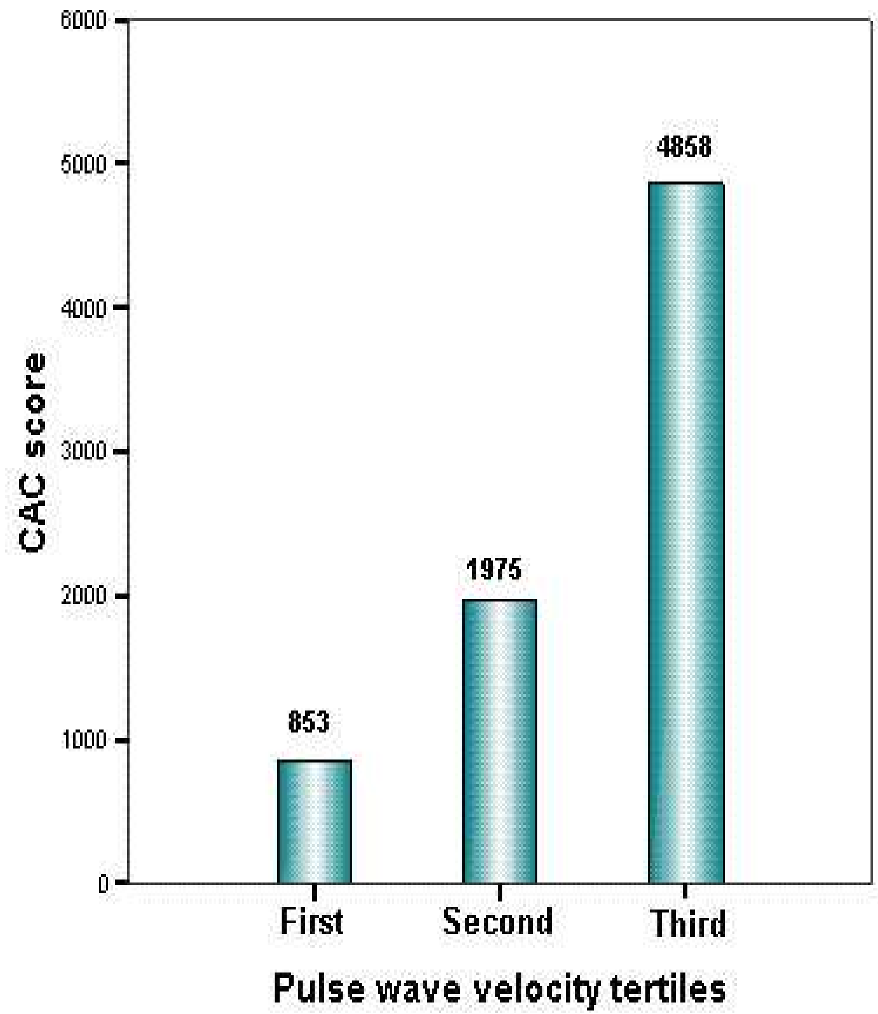
- Age; AUC 72±5%
- Pulse Pressure; AUC 72±5%
- Carotid IMT;AUC 68±6%
- LVmassix; AUC 72±5%
- Calcification score; AUC 82±4%
- Aortic PWV; AUC 82±4%

Calcification score: cut-off 390;sensitivity 83%;specificity69%; PPV41%;NPV94%
Aortic PWV: cut-off 10.75 m/s;sensitivity 84%;specificity 73%;PPV72%; NPV93%

G. London 2006

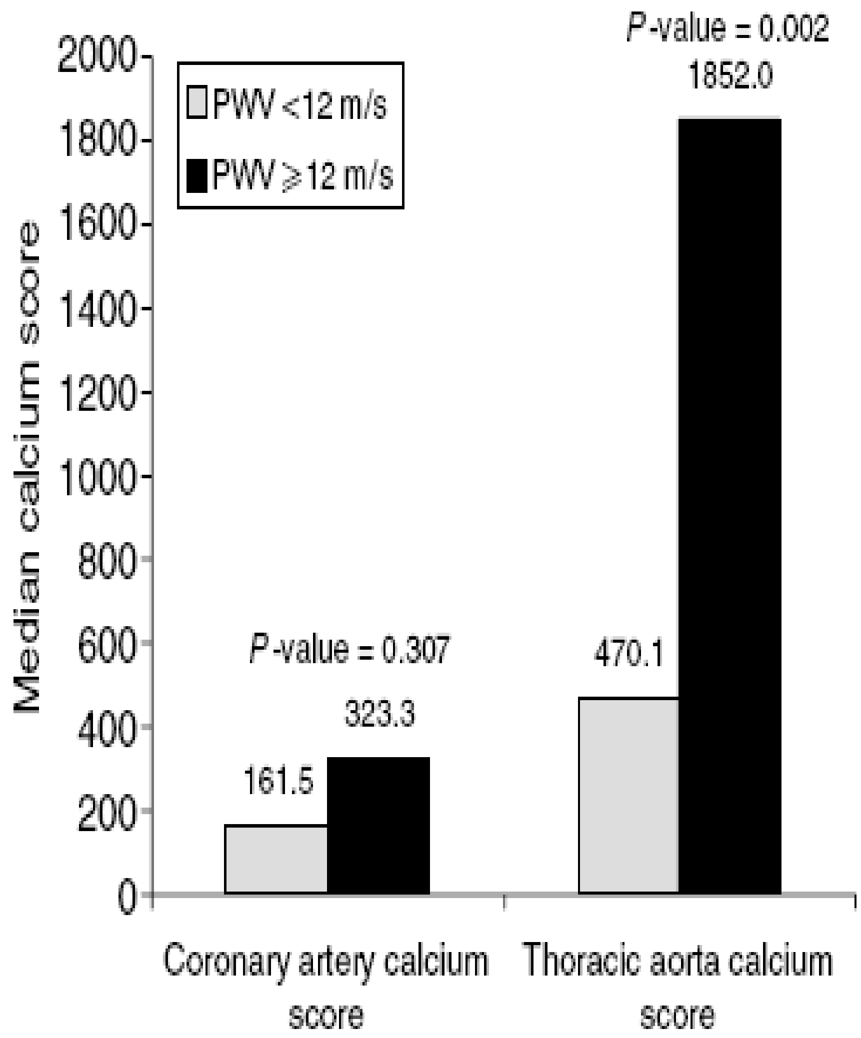
CAC and PWV in CKD

AA Haydar, A. Covic, S. Colhoun et al
Kidney Int. 2004



VC and PWV

P Raggi et al
Kidney Int. 2007



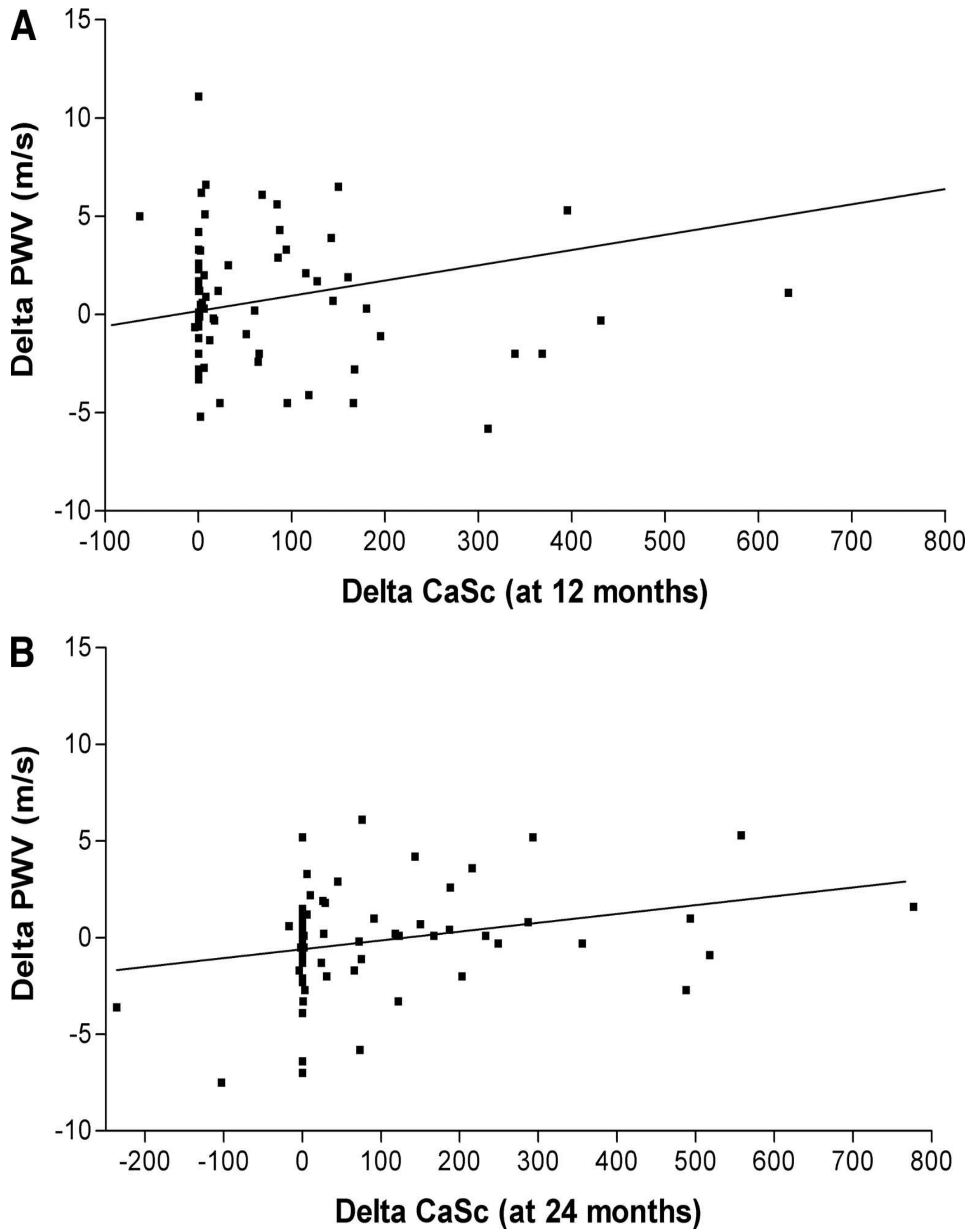
Scatter plot of change in CaSc against change in PWV

at 12 mo (r = 0.52, P < 0.001)

and

at 24 mo (r = 0.33, P = 0.003)

Sigrist, M. K. et al. *CJASN*



PWV, Aix, etc
are they useful?

General population

CKD population

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

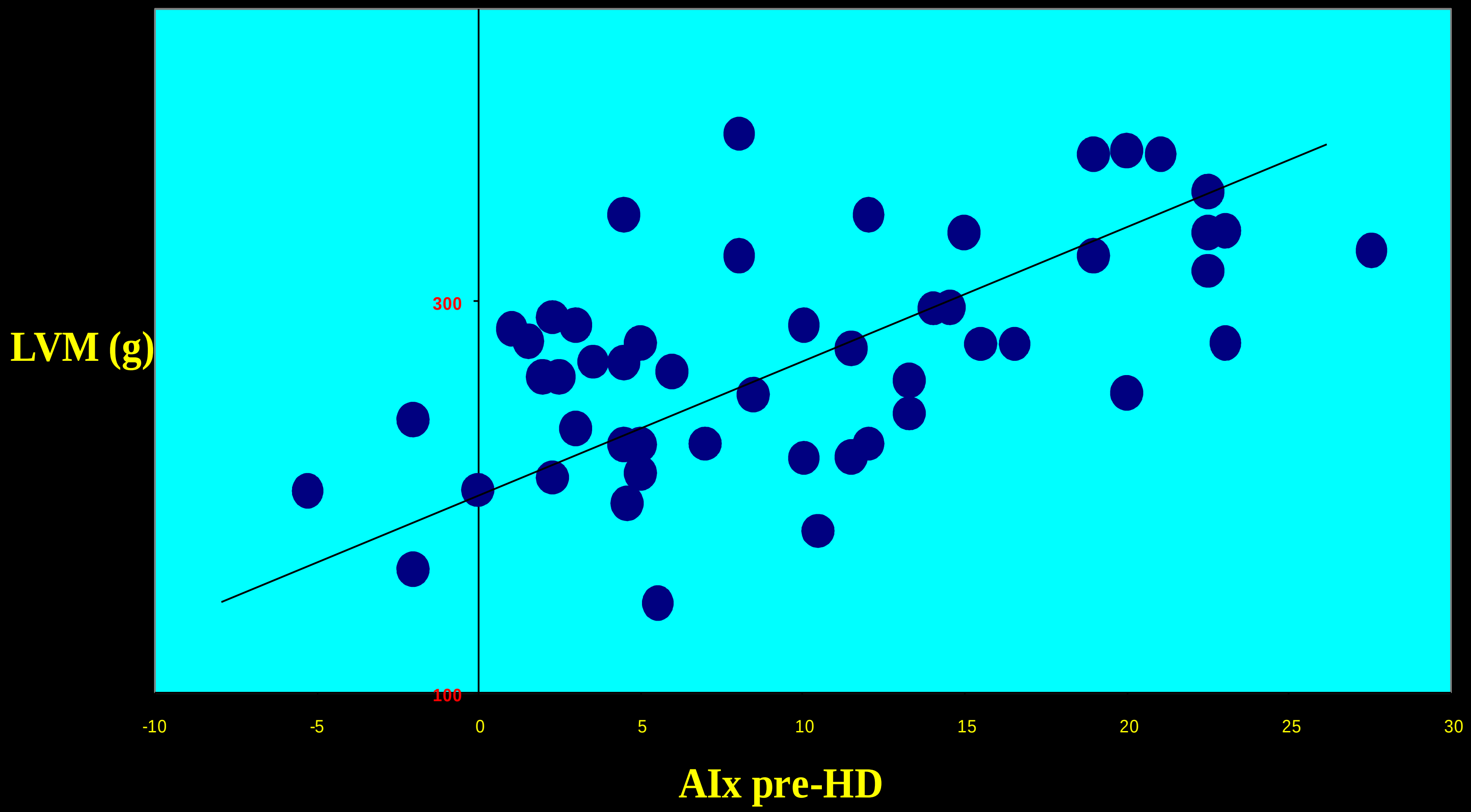
Laurent et al European Heart J. 2006

Measurement site	First author (year, country)	Events	Follow-up (years)	Type of patient (number)
Aortic PWV	Blacher (1999, Fr)	CV mortality	6.0	ESRD (241)
	Laurent (2001, Fr)	CV mortality	9.3	Hypertension (1980)
	Meaume (2001, Fr)	CV mortality	2.5	Elderly (>70) (141)
	Shoji (2001, Jp)	CV mortality	5.2	ESRD (265)
	Boutouyrie (2002, Fr)	CHD events	5.7	Hypertension (1045)
	Cruickshank (2002, GB)	All cause mortality	10.7	IGT (571)
	Laurent (2003, Fr)	Fatal strokes	7.9	Hypertension (1715)
	Sutton-Tyrrell (2005, USA)	CV mortality and events	4.6	Elderly (2488)
	Shokawa (2005, Jp)	CV mortality	10	General population (492)
	Willum-Hansen (2006, Dk)	CV mortality	9.4	General population (1678)
	Mattace-Raso (2006, Neth.)	CV mt, CHD	4.1	Elderly (2835)
Ascending aorta (invasive)	Stefanadis (2000, Gr)	Recurrent acute CHD	3	Acute CHD (54)
Carotid distensibility	Blacher (1998, Fr)	All cause mortality	2.1	ESRD (79)
	Barenbrock (2001, Ge)	CV events	7.9	ESRD (68)

IGT, impaired glucose tolerance; CHD, coronary heart disease. Countries: Dk, Denmark; Fr, France; GB, Great Britain; Ge, Germany; Gr, Greece; Jp, Japan; Ne,

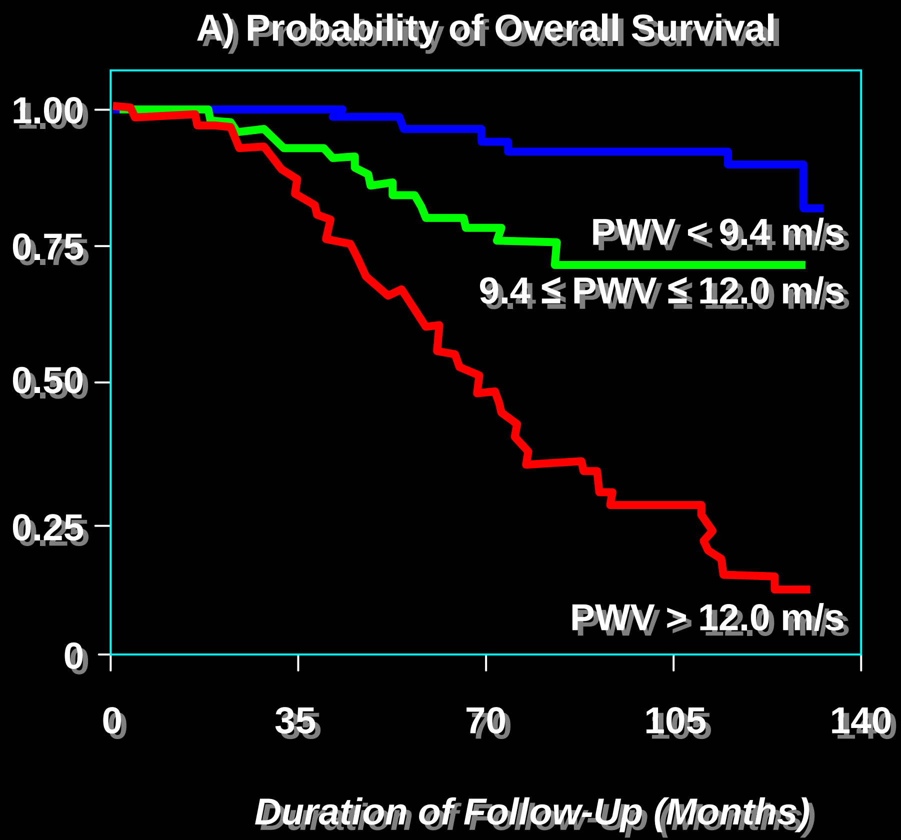
Central pulse pressure	Safar (2002, France)	All cause mortality	4.3	ESRD (180)
	Williams (2006, United Kingdom)	CV events	3.4	HT, ASCOT study (2073)
Carotid AIx	London (2001, France)	All cause and CV mortality	4.3	ESRD (180)
	Weber (2005, Austria)	Severe CV events	2	Undergoing PCI (262)
	Williams (2006, United Kingdom)	CV events	3.4	HT, ASCOT study (2073)

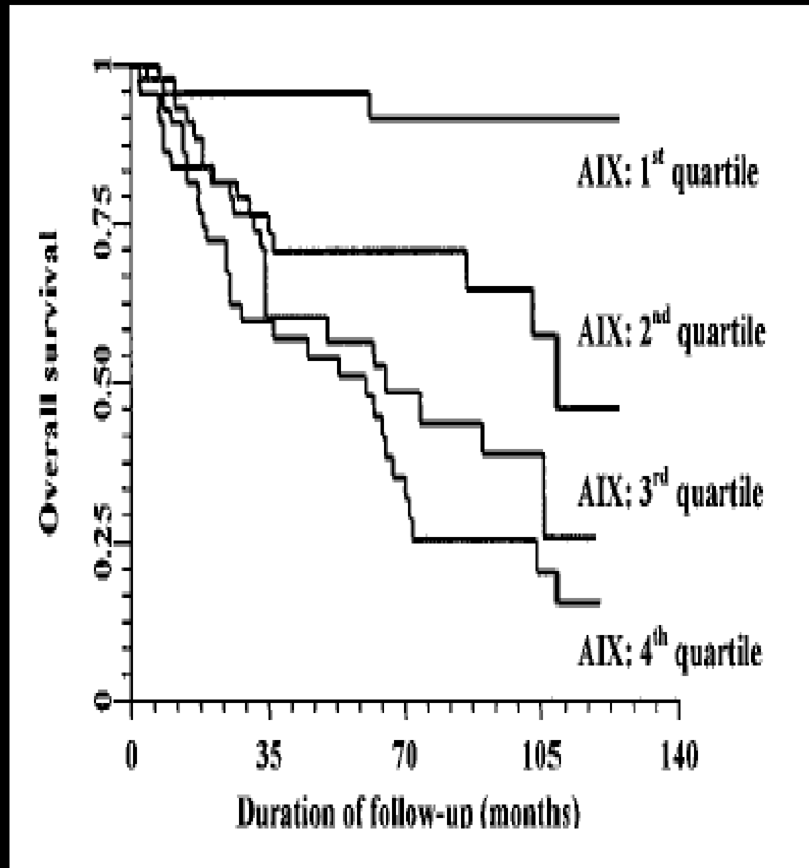
PWV, Aix, etc - are they <u>also</u> useful in CKD / dialysis populations ?



A. Covic, et al. *Kidney Int* 2000; 57(6):2634.

Aortic Stiffness and Mortality in ESRD: PWV and AIx





N = 241, F/U = 72+/-41 months

N = 189, F/U = 52+/-36 months

Blacher *Circulation*, 1999 (99): 2434

London et al, *Hypertension*, 2001, 38: 434

Nephrol Dial Transplant (2006) 21: 2859–2866
doi:10.1093/ndt/gfl307
Advance Access publication 19 July 2006

NDT
Nephrology Dialysis Transplantation

Original Article

Arterial wav
patients—onl

Adrian Covic[1], Ni
Radu Sascau[2] and

[1]Dialysis and Transpl
[3]Renal Unit, Guy's H

[redacted]

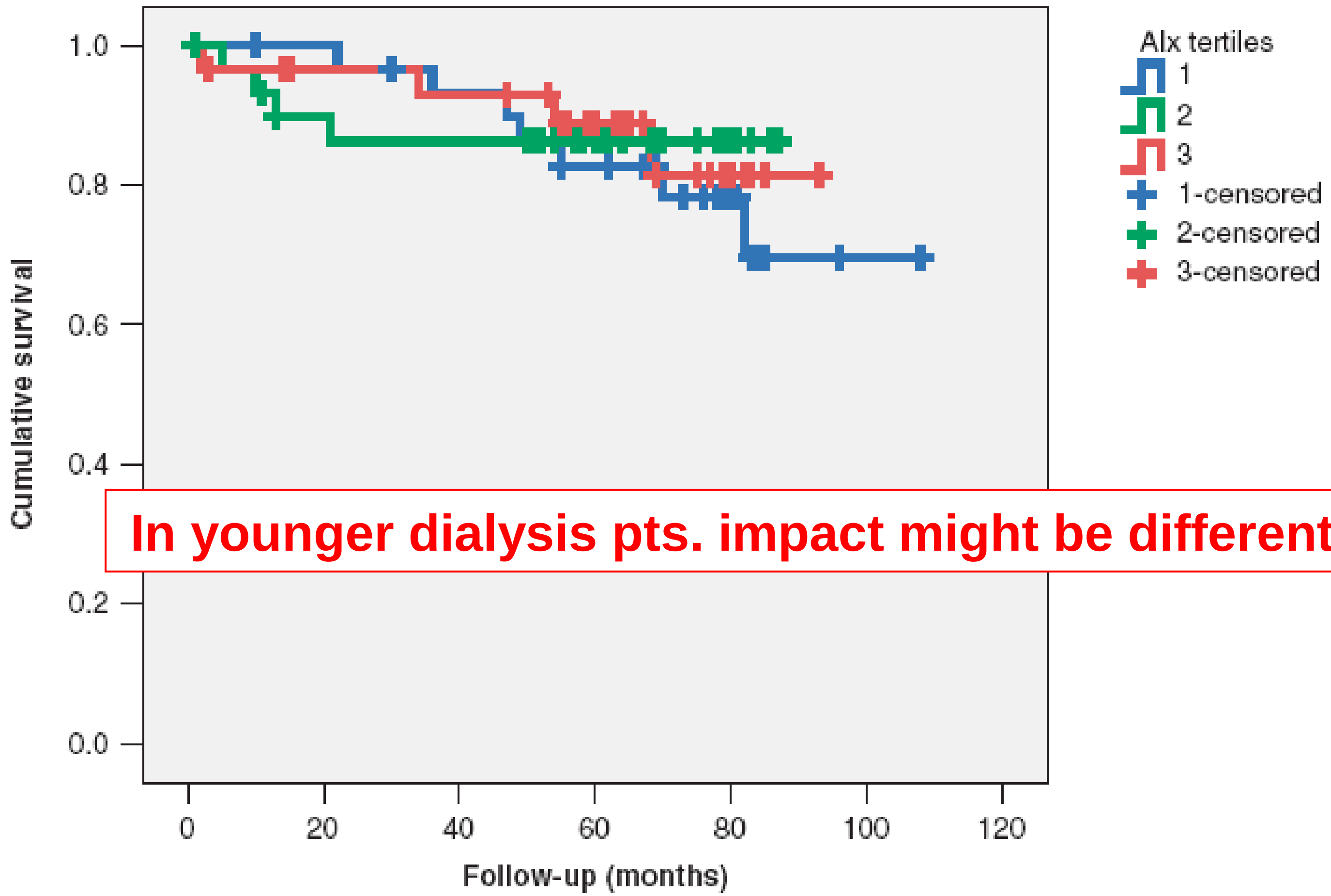
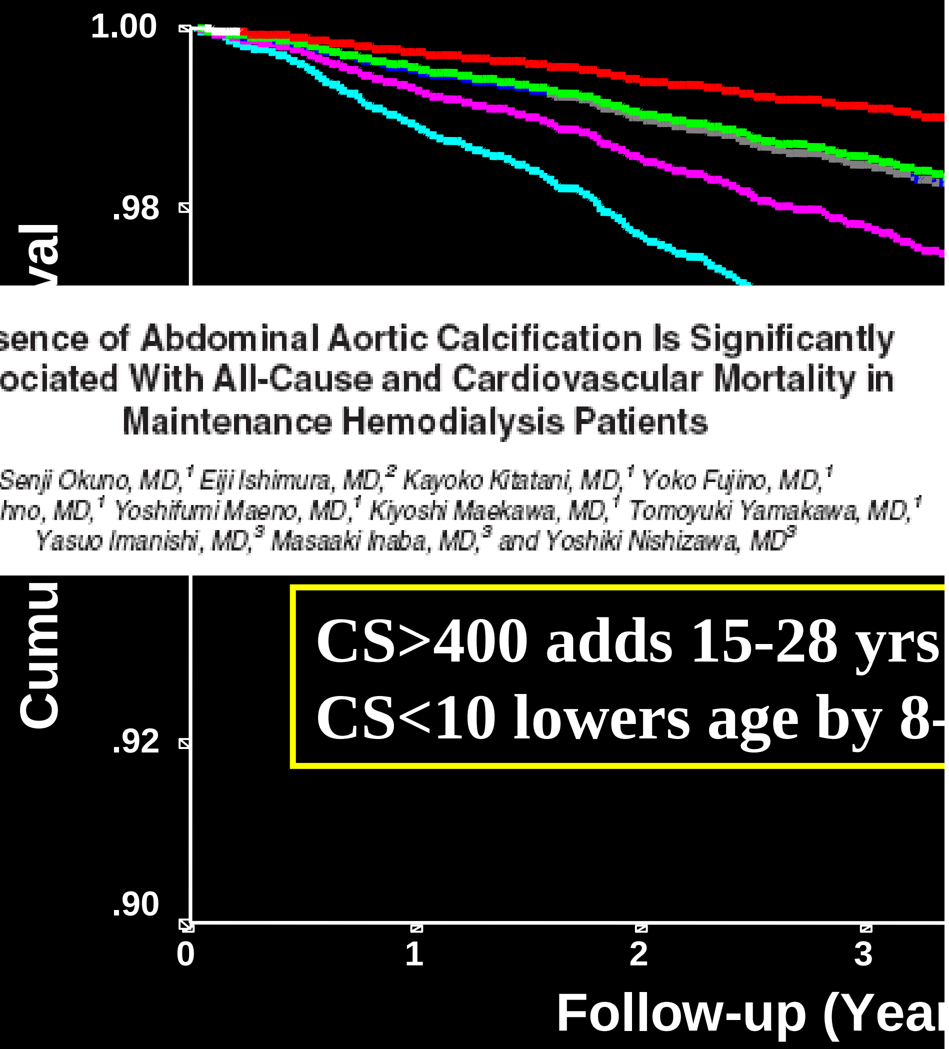


Fig. 1. Kaplan–Meier survival curves according to augmentation index tertiles (log rank test: $P = 0.78$).

In younger dialysis pts. impact might be different

VC Increases Mortality Risk – EBCT evaluation, or even simpler…

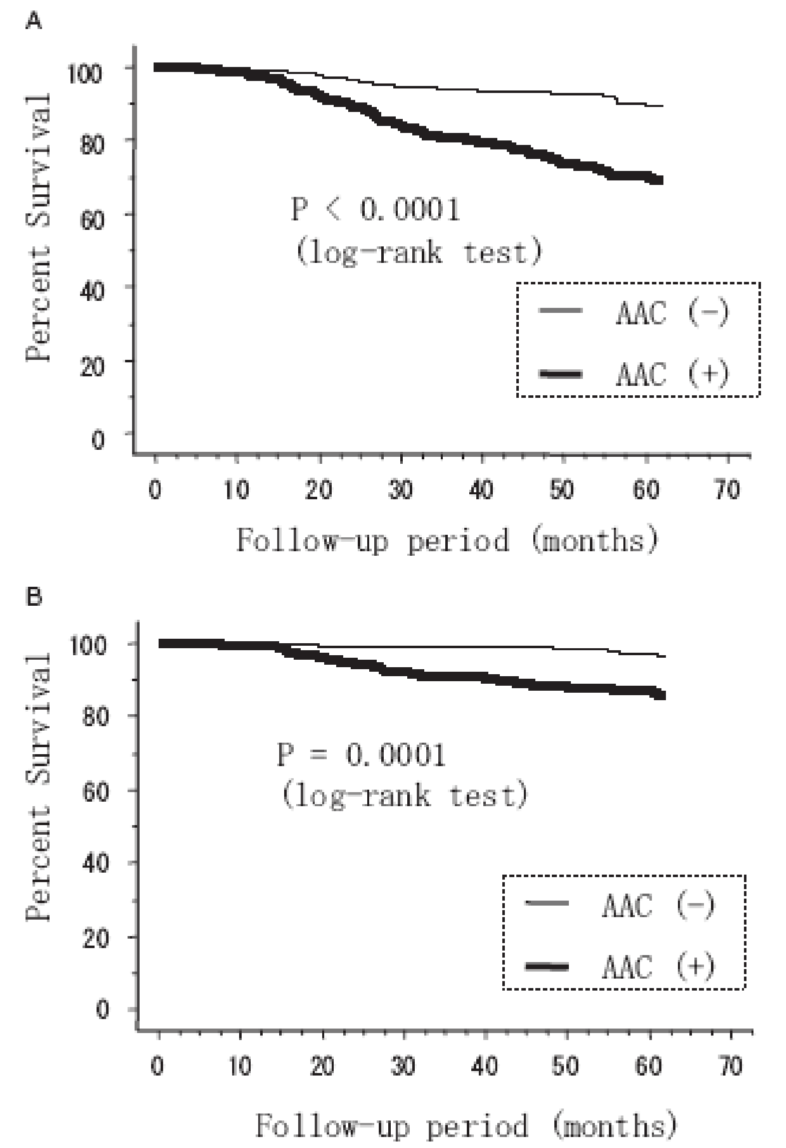


Presence of Abdominal Aortic Calcification Is Significantly Associated With All-Cause and Cardiovascular Mortality in Maintenance Hemodialysis Patients

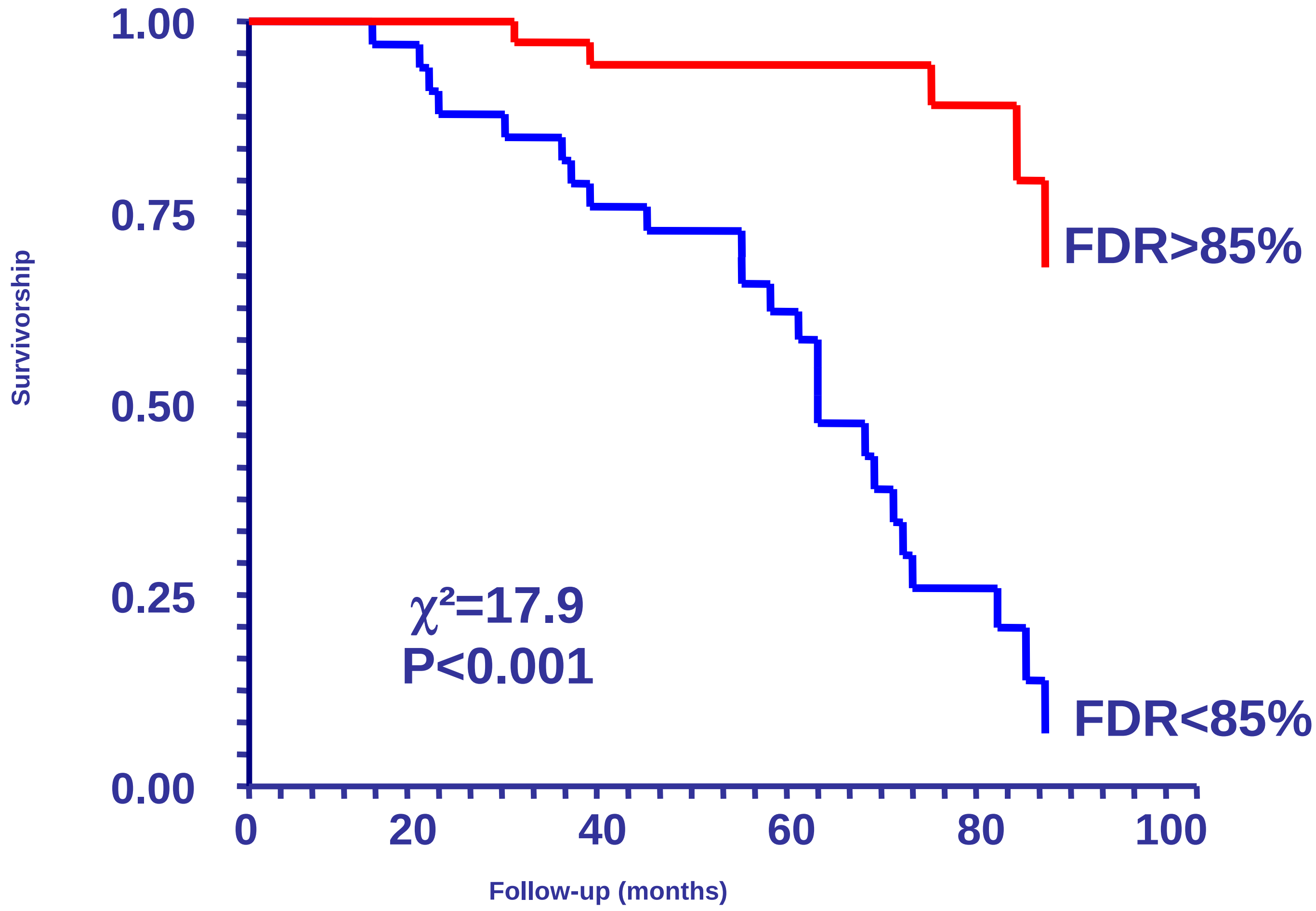
Senji Okuno, MD,[1] Eiji Ishimura, MD,[2] Kayoko Kitatani, MD,[1] Yoko Fujino, MD,[1] Kaori Kohno, MD,[1] Yoshifumi Maeno, MD,[1] Kiyoshi Maekawa, MD,[1] Tomoyuki Yamakawa, MD,[1] Yasuo Imanishi, MD,[3] Masaaki Inaba, MD,[3] and Yoshiki Nishizawa, MD[3]

CS>400 adds 15-28 yrs
CS<10 lowers age by 8-

Shaw L, Raggi P, Berman D, Callister TQ. *Radi*



Probability of survival in ESRD patients according to postischemic forearm flow debt repayement (FDR)



London GM et al. Kidney Int 2003

Review

Kidney & Blood Pressure Research

Kidney Blood Press Res **2007; 30(2) :97-107.**

Causes and Consequences of Increased Arterial Stiffness in Chronic Kidney Disease Patients

Paul Gusbeth-Tatomir Adrian Covic

Dialysis and Renal Transplantation Center, Parhon University Hospital, Iasi, Romania

The Official Journal of the National Kidney Foundation

VOL 45, NO 6, JUNE 2005

AJKD American Journal of Kidney Diseases

REVIEWS

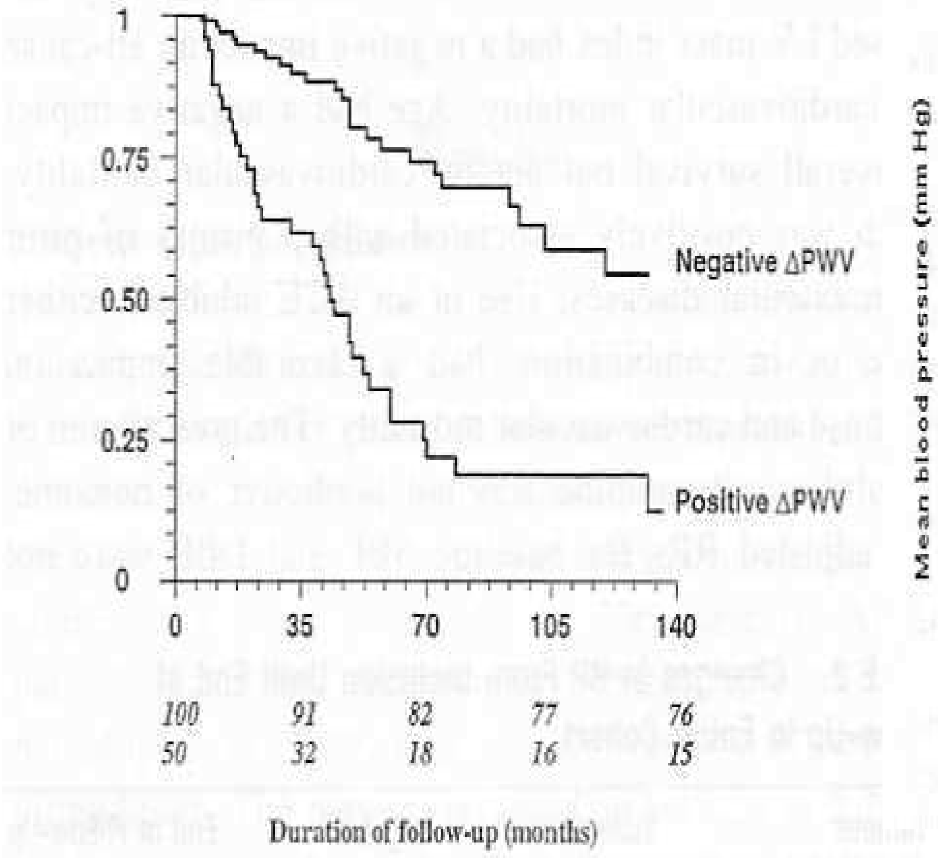
Arterial Stiffness in Renal Patients: An Update

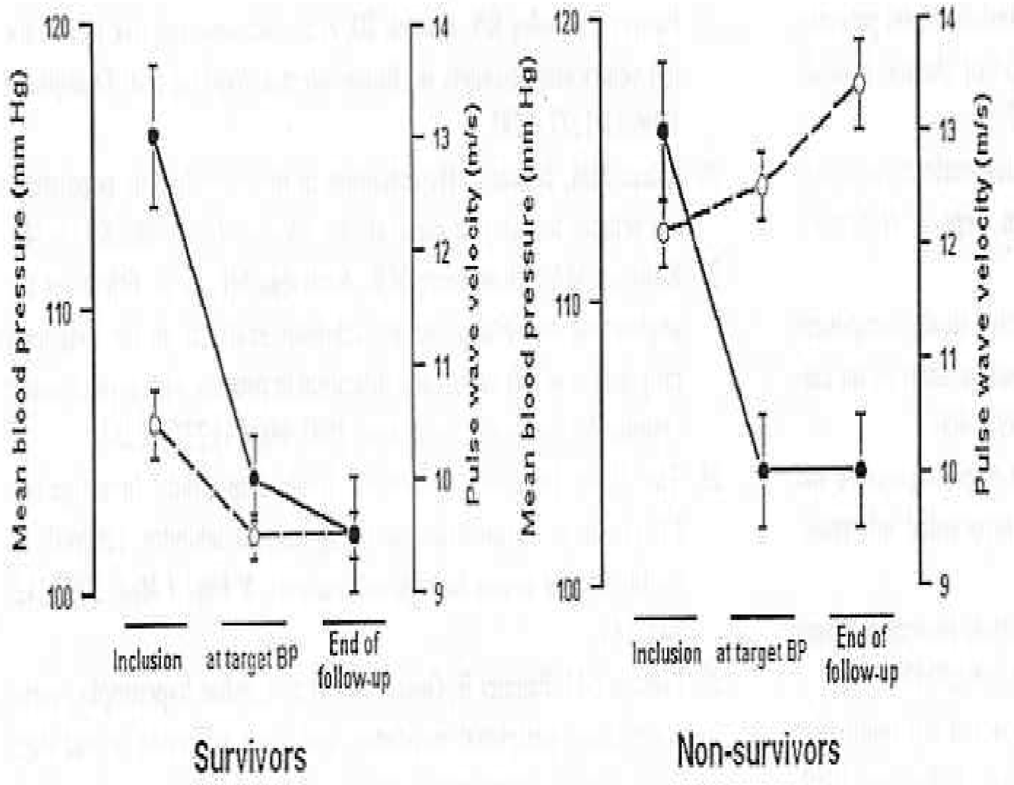
Adrian Covic, MD, PhD, Paul Gusbeth-Tatomir, MD, and David J.A. Goldsmith, MA, FRCP

How can we treat ?

Treatment is important ! Impact of change in PWV on survival

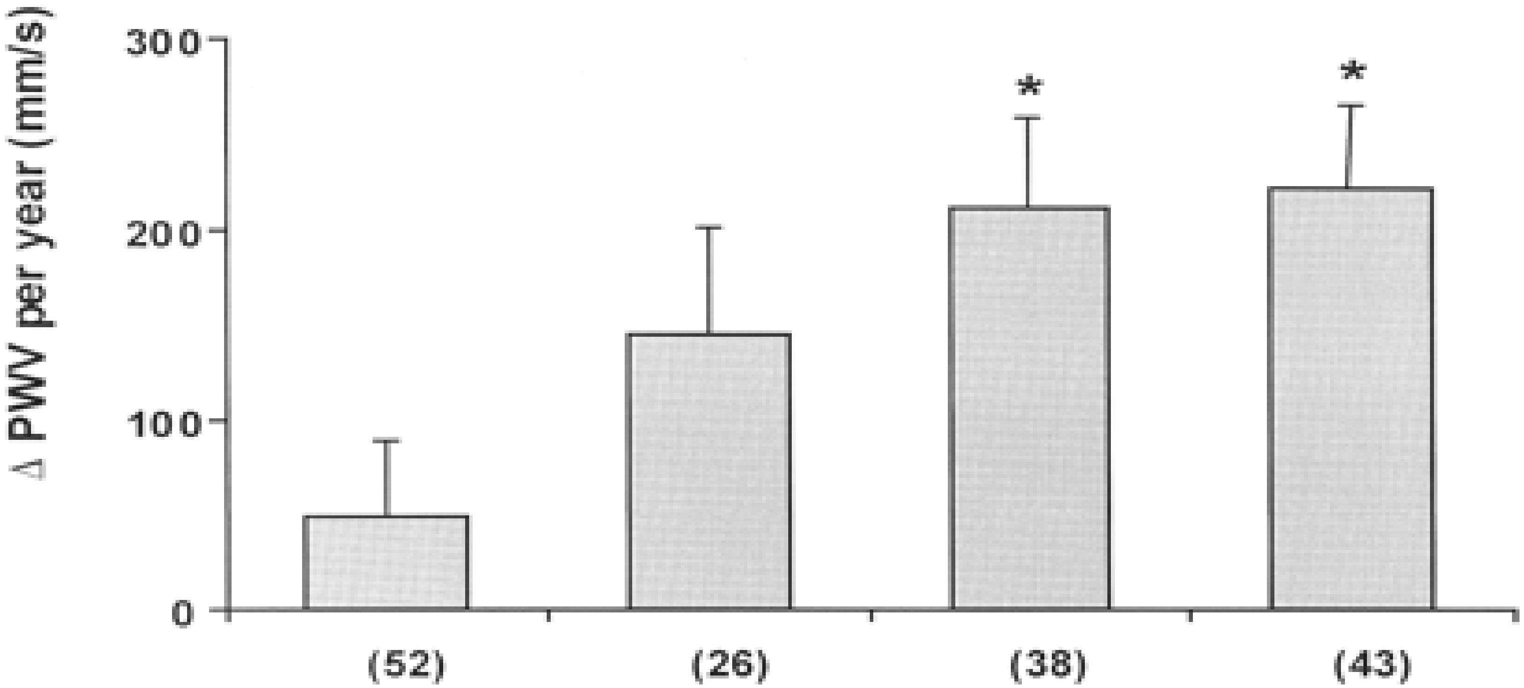
Guerin, *Circulation* 2001





SIMPLE THINGS: CONTROL BP
Annual PWV progression
(adjusted for initial PWV, age, HR, and sex)
in treated hypertensive subjects as a function of MAP control

(Benetos, *Circulation* **2002)**



V1	Controlled	Uncontrolled	Controlled	Uncontrolled
MAP mmHg	99.3 ± 0.7	114.2 ± 1.1	101.8 ± 0.9	117.0 ± 0.8
SBP/DBP mmHg	134.3/81.8	155.1/94.0	137.5/83.8	157.1/97.0
V2	Controlled	Controlled	Uncontrolled	Uncontrolled
MAP mmHg	98.5 ± 0.8	100.2 ± 1.2	115.7 ± 0.9	116.9 ± 0.9
SBP/DBP mmHg	136.2/79.7	139.5/80.4	161.9/93.2	161.7/94.6

Control BP, but all antihypertensives are equal?

Hypertension

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

Low doses of losartan and trandolapril improve arterial stiffness in hemodialysis patients.

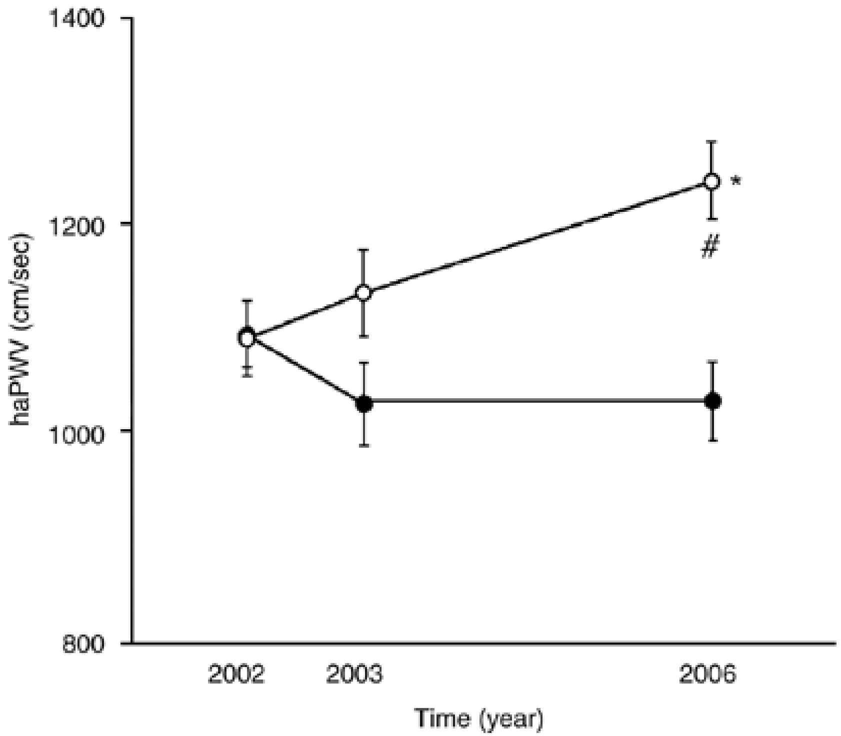
Ichihara et al. et al Am J Kidney Dis. 2005 May;45(5):866-74.

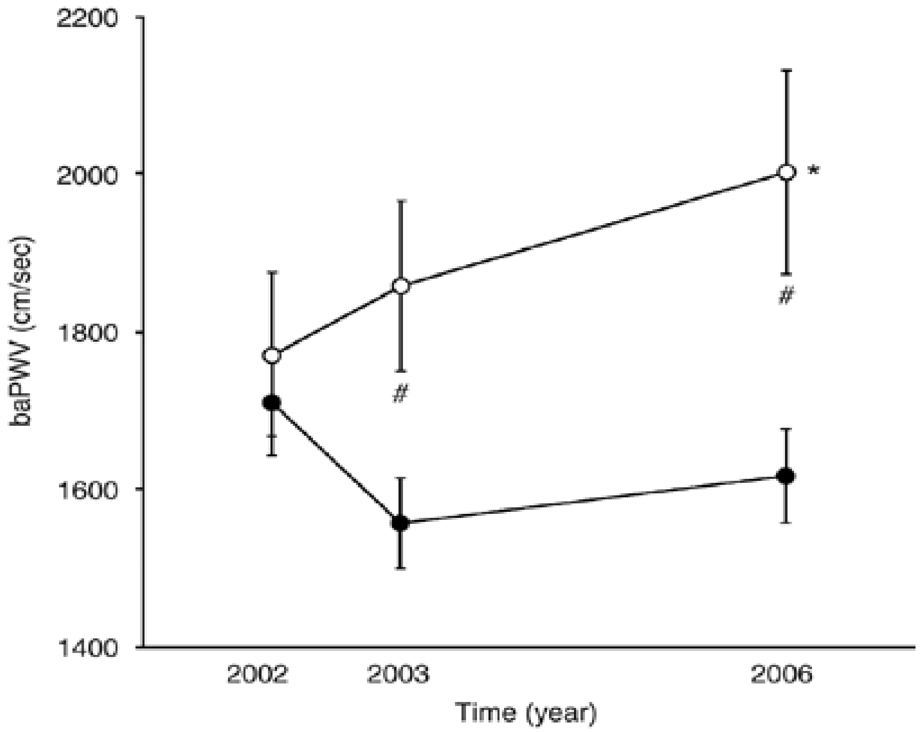
CONCLUSION: In hemodialysis patients, trandolapril is as effective as losartan in decreasing PWV independent of its depressor effect and in suppressing elevated IDL-C levels.

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

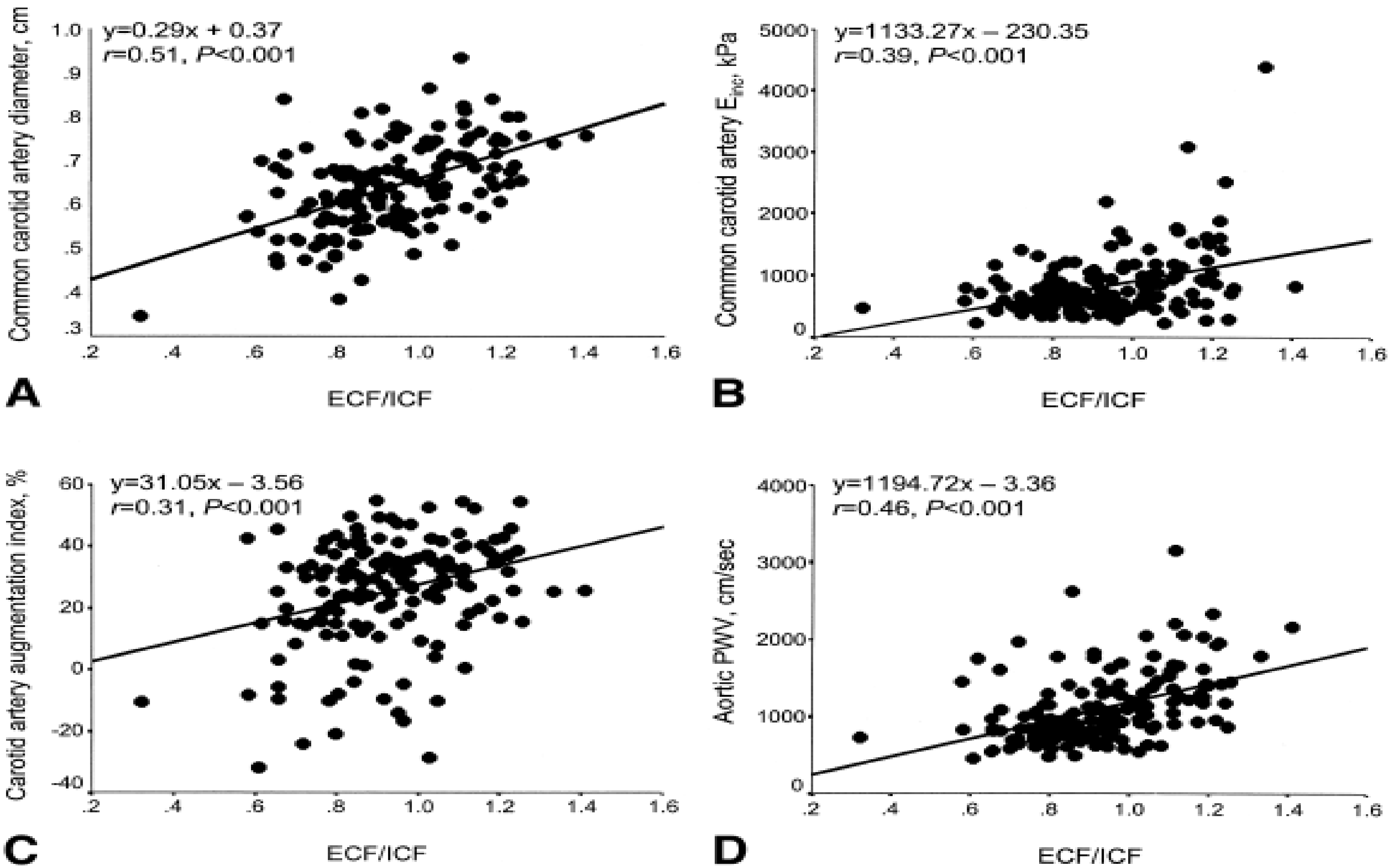
Vascular compliance changes under ACE-I in non-diabetic CKD
Mimura et al *JHH* 2008





Volume overload **is related to arterial stiffness**

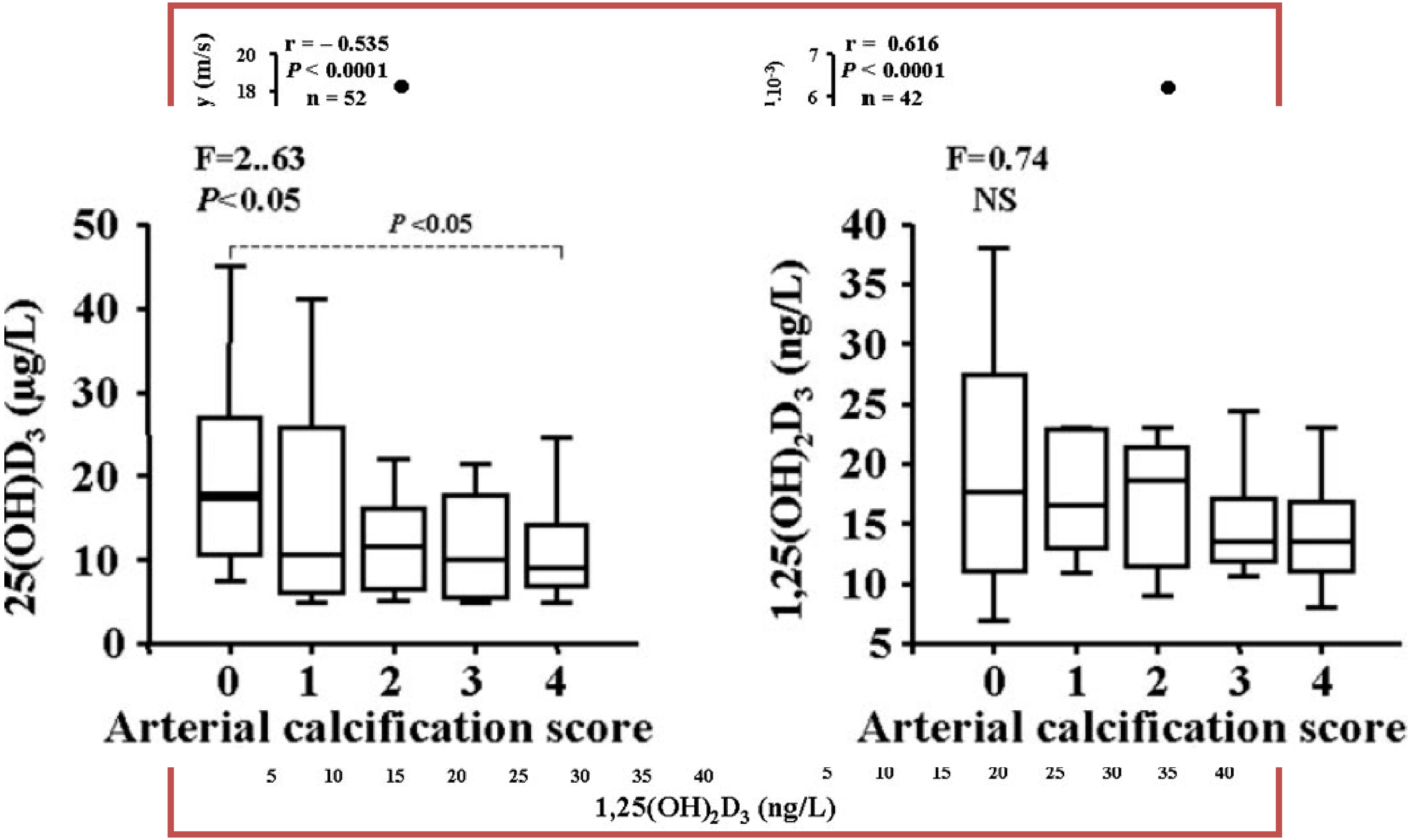
(Lin et al, *Am J Kidney Dis* **2003)**



Targeting VC and stiffness with the same strategies – is it possible?

- The case of vit D
- The case of P binder
- The case of statins

Effects of Vitamin D on Arterial Stiffness and VC



London J, et al. *J Am Soc Nephrol.* 2007;18(2):613-20.

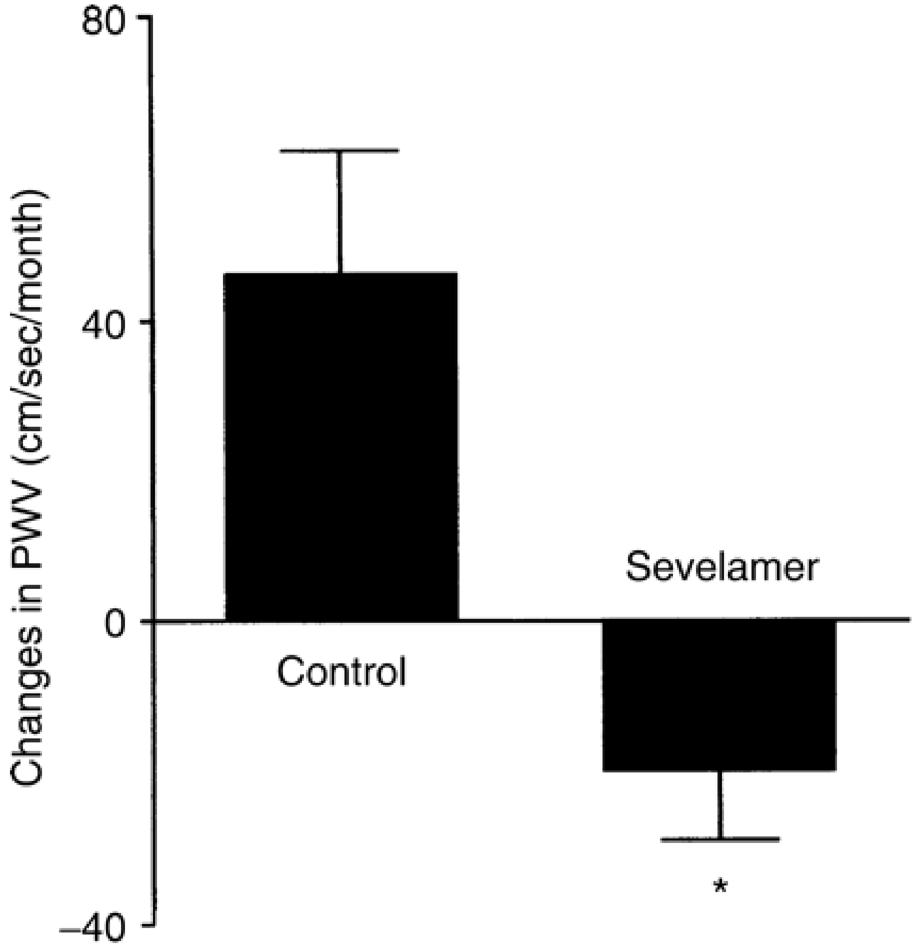
Nephrol Dial Transplant (2005) 20: 811–816
doi:10.1093/ndt/gfh656

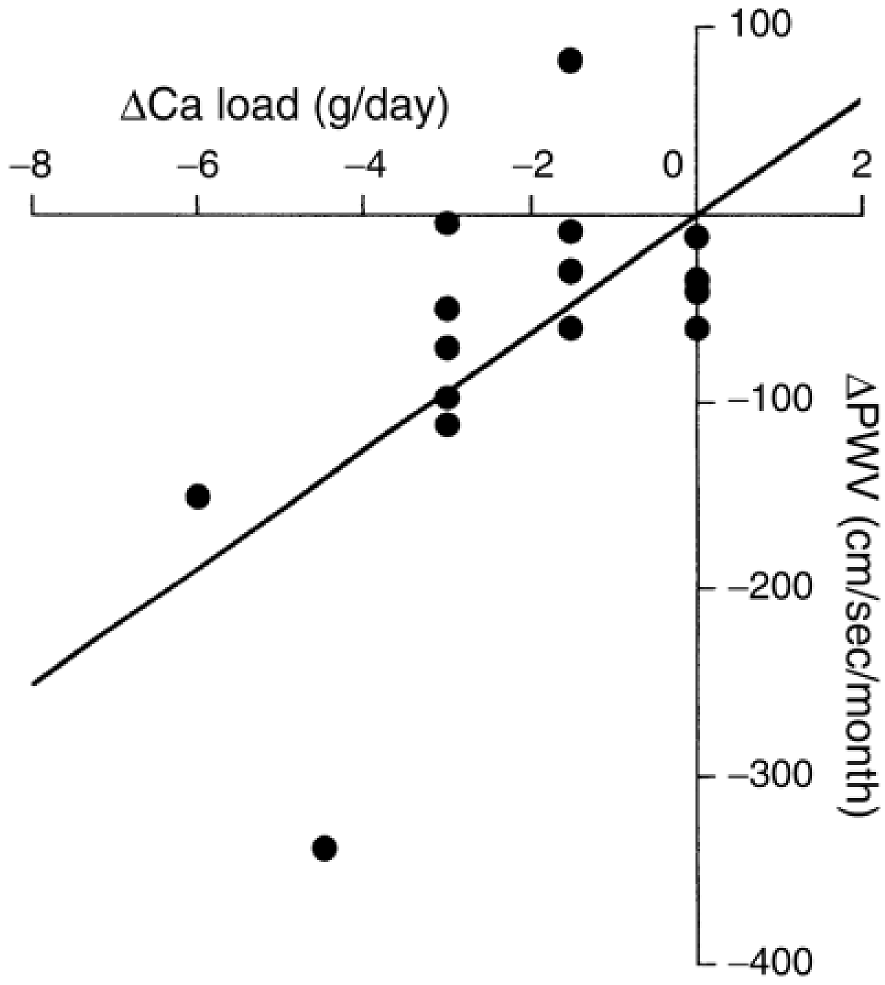
Preliminary Communication

Nephrology Dialysis Transplantation

New strategy to attenuate pulse wave velocity in haemodialysis patients

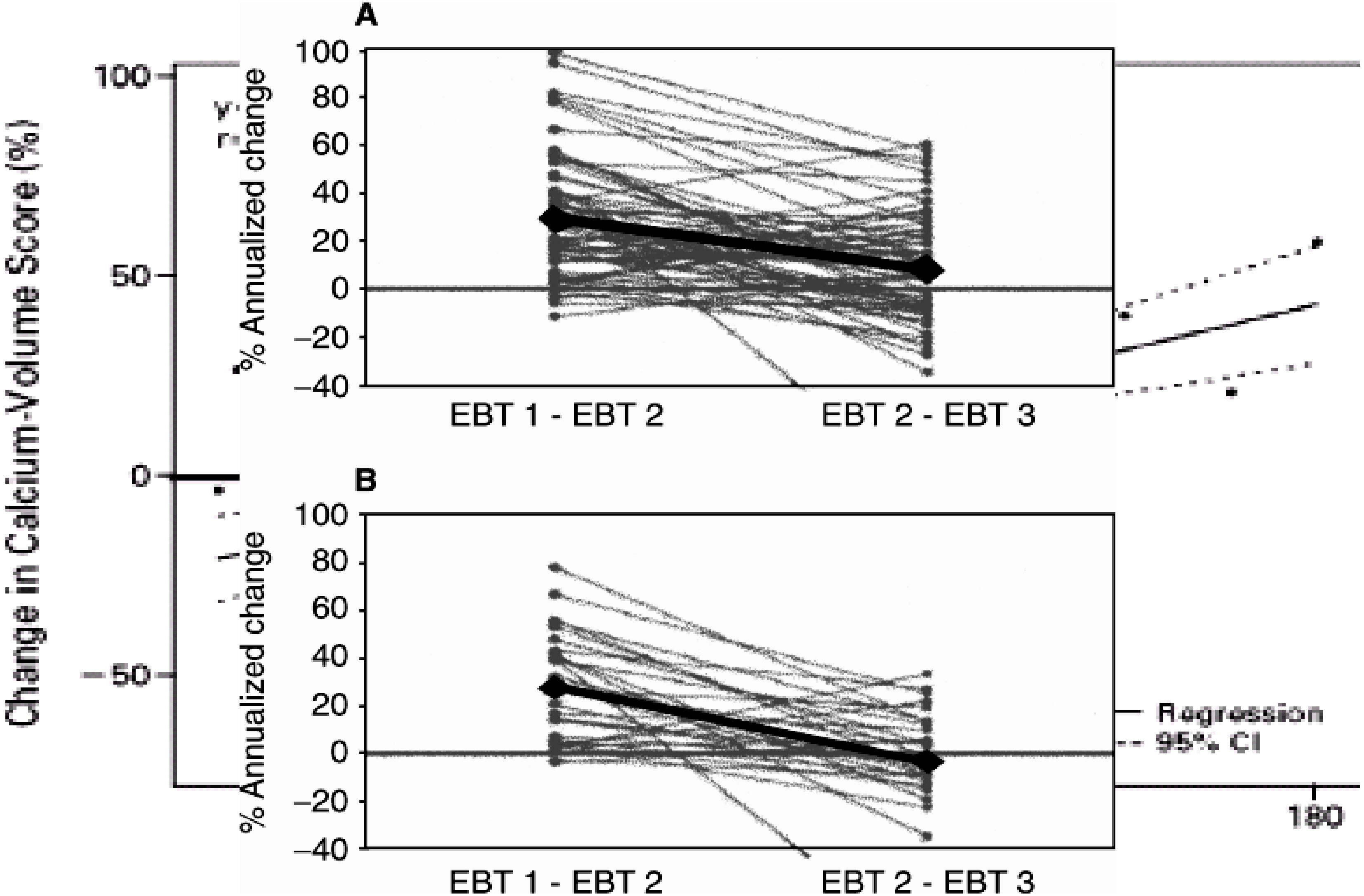
Tsuneo Takenaka[1] and Hiromichi Suzuki[2]





Statin therapy and VC

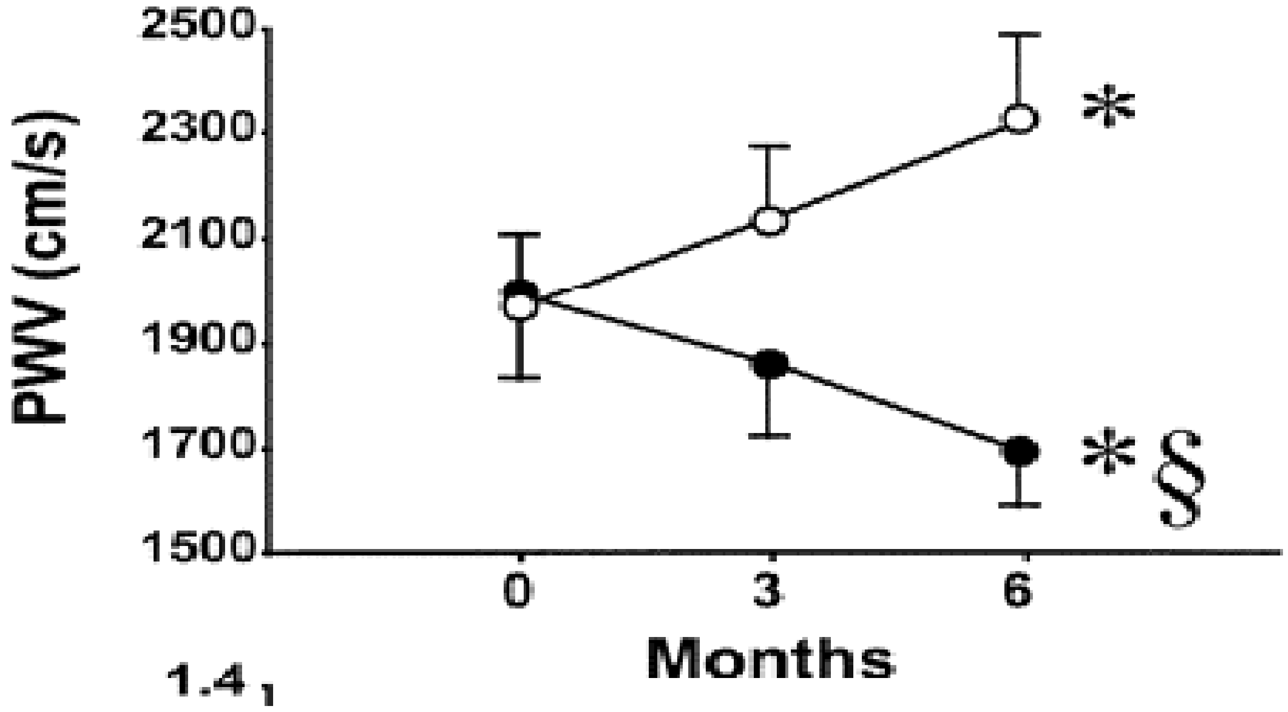
Callister, *N Engl J Med* 1998



Quinibi, *Kidney Int.,* 2005, 67 (suppl 95), S43-S50

Statins have a favorable effect on:

PWV, inflamation (CRP), oxidized lipids

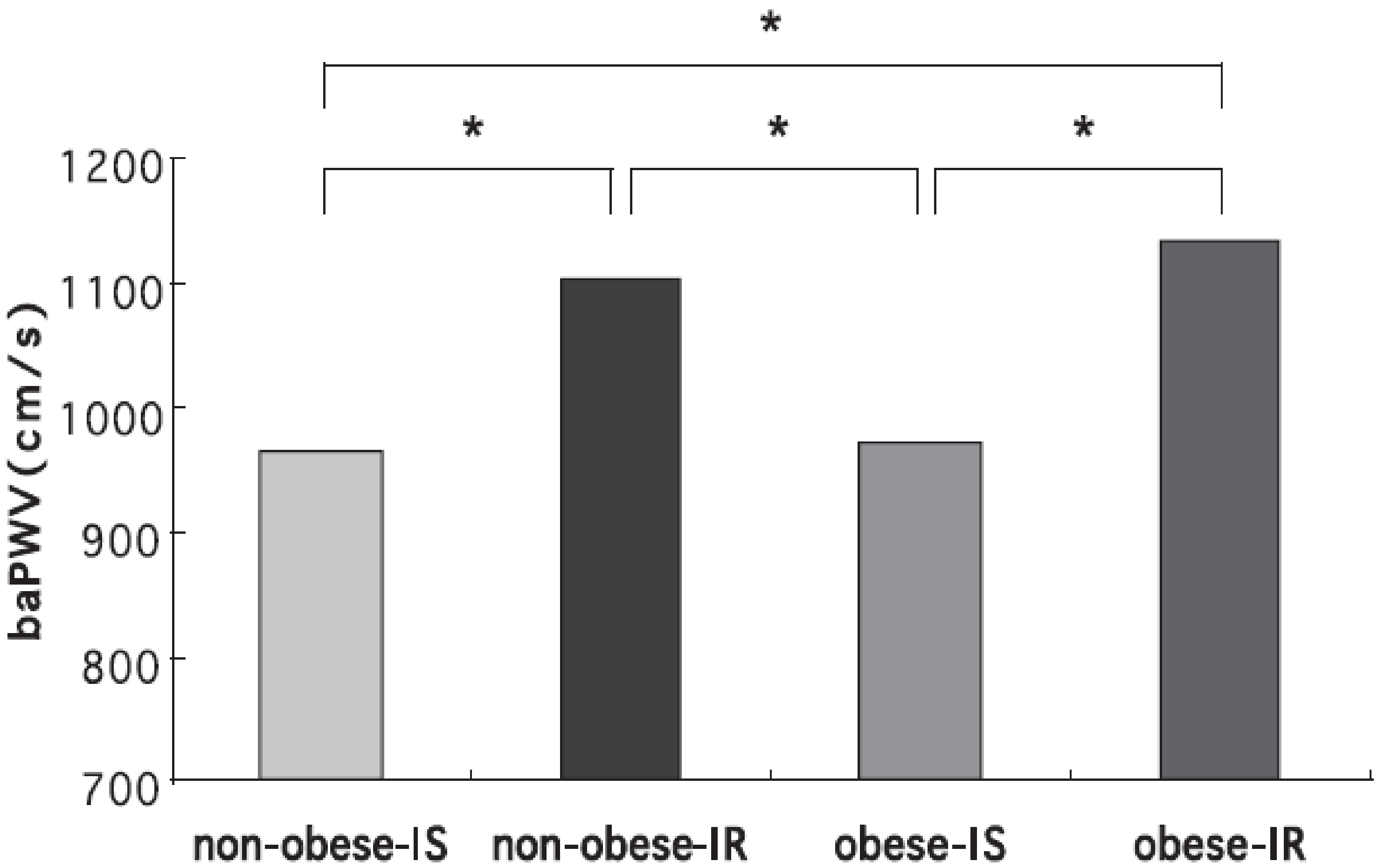


Changes in PWV and over 6 months in patients treated with placebo (open circles) and fluvastatin (closed circles).

(Ichihara, *Nephrol Dial Transplant* **2002)**

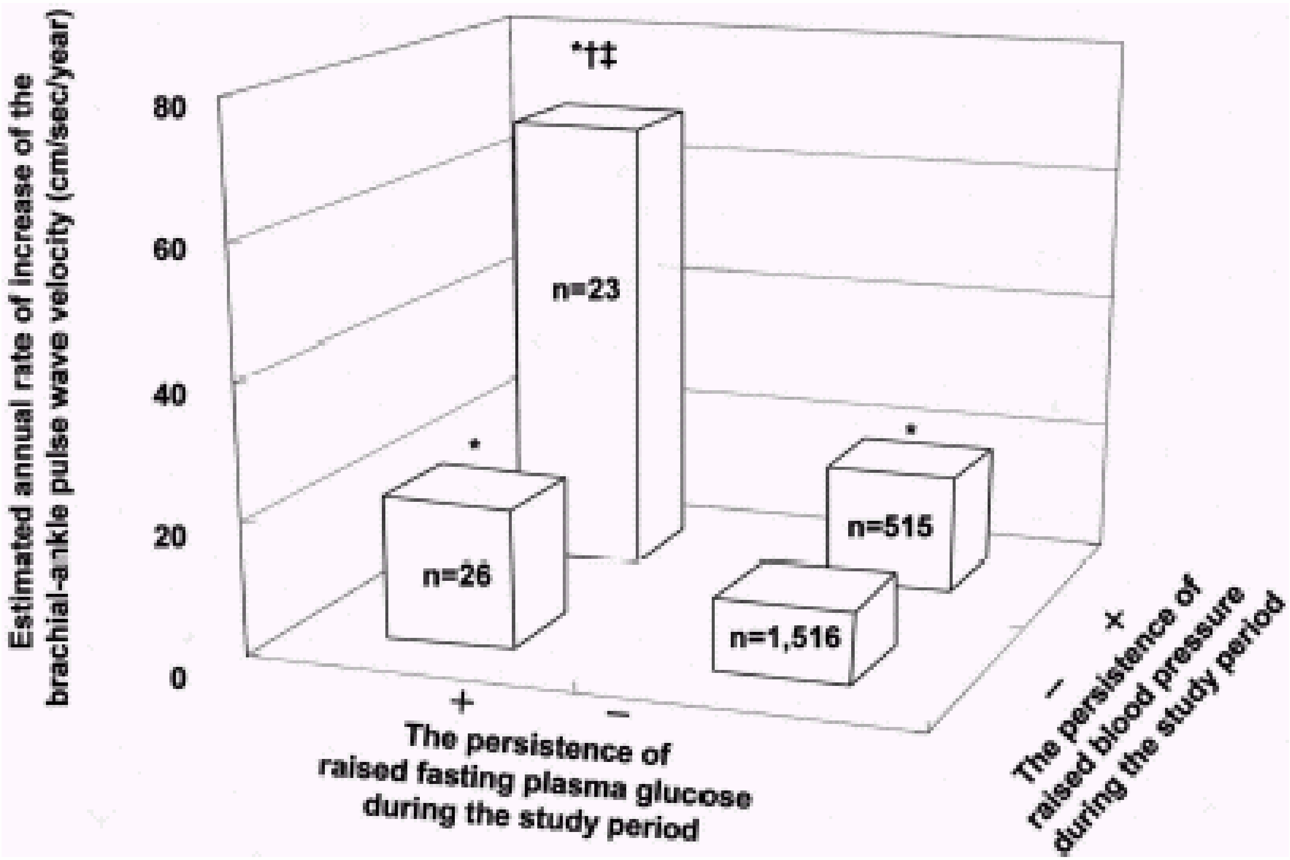
Other strategies

Pioglitazone in type 2 diabetic nephropathy – Nakamura, *Metabolism*, 2004, 53: 1382



Ji-Won Lee, Hypertension Research 2007; 30:5-11

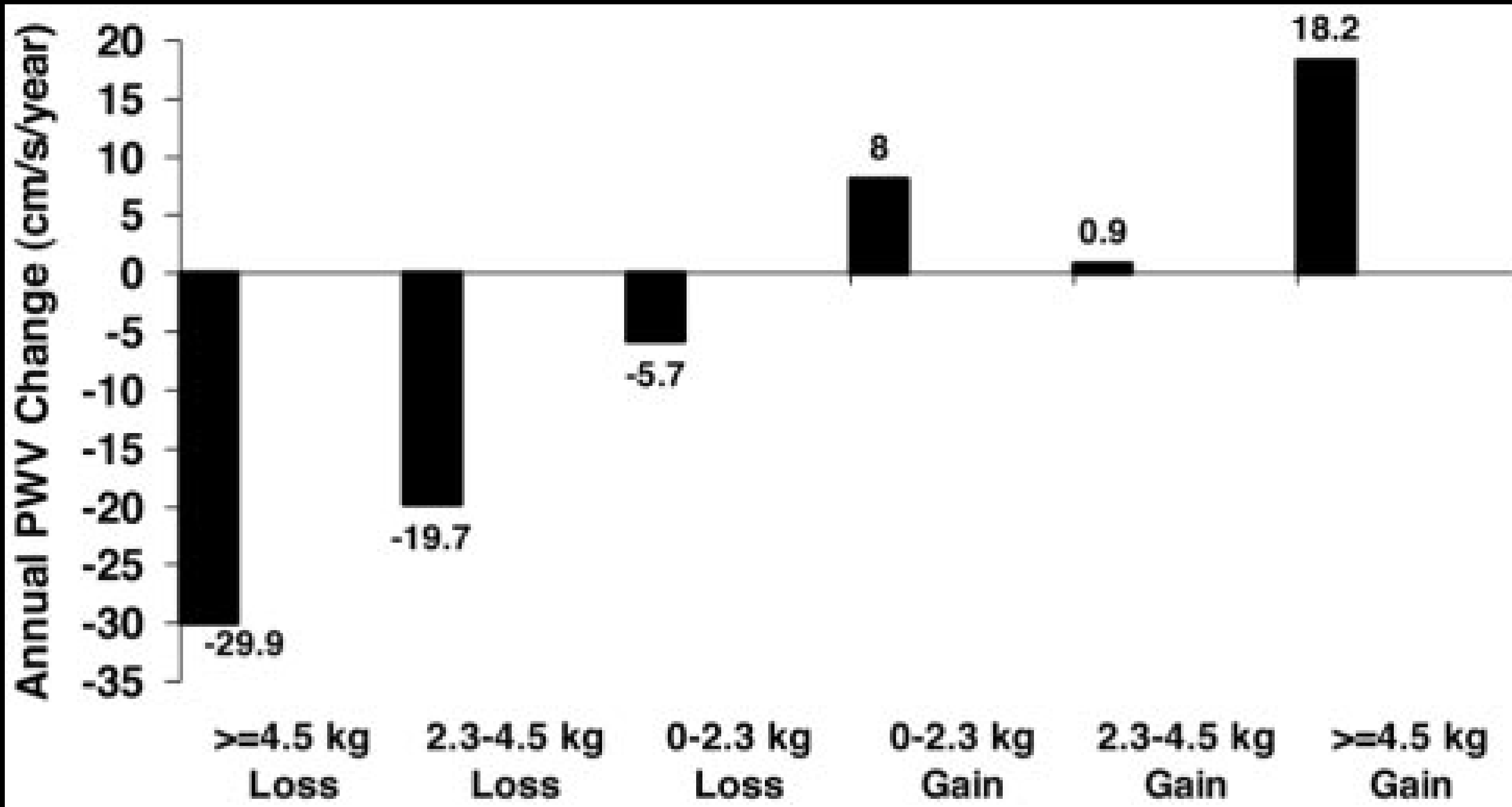
Glycemic control is always mandatory
Tomyiama, ***Hypertension*** 2006



Weight Change Is Associated With Change in Arterial Stiffness Among Healthy Young Adults

Wildman et al. *Hypertension.* 2005; 45:187-192.)

N = 152 white and black adults aged 20-to 40 years
mean annual PWV changes = 29.9 cm/s/year (regression) for those with 4.5 kg annual weight loss and 18.2 cm/s/year (progression) for those with 4.5 kg annual weight gain



OSA – non-dipping – autonomic neuropathy

Drager LF et al. *Chest 2007; 131(5) :1379*

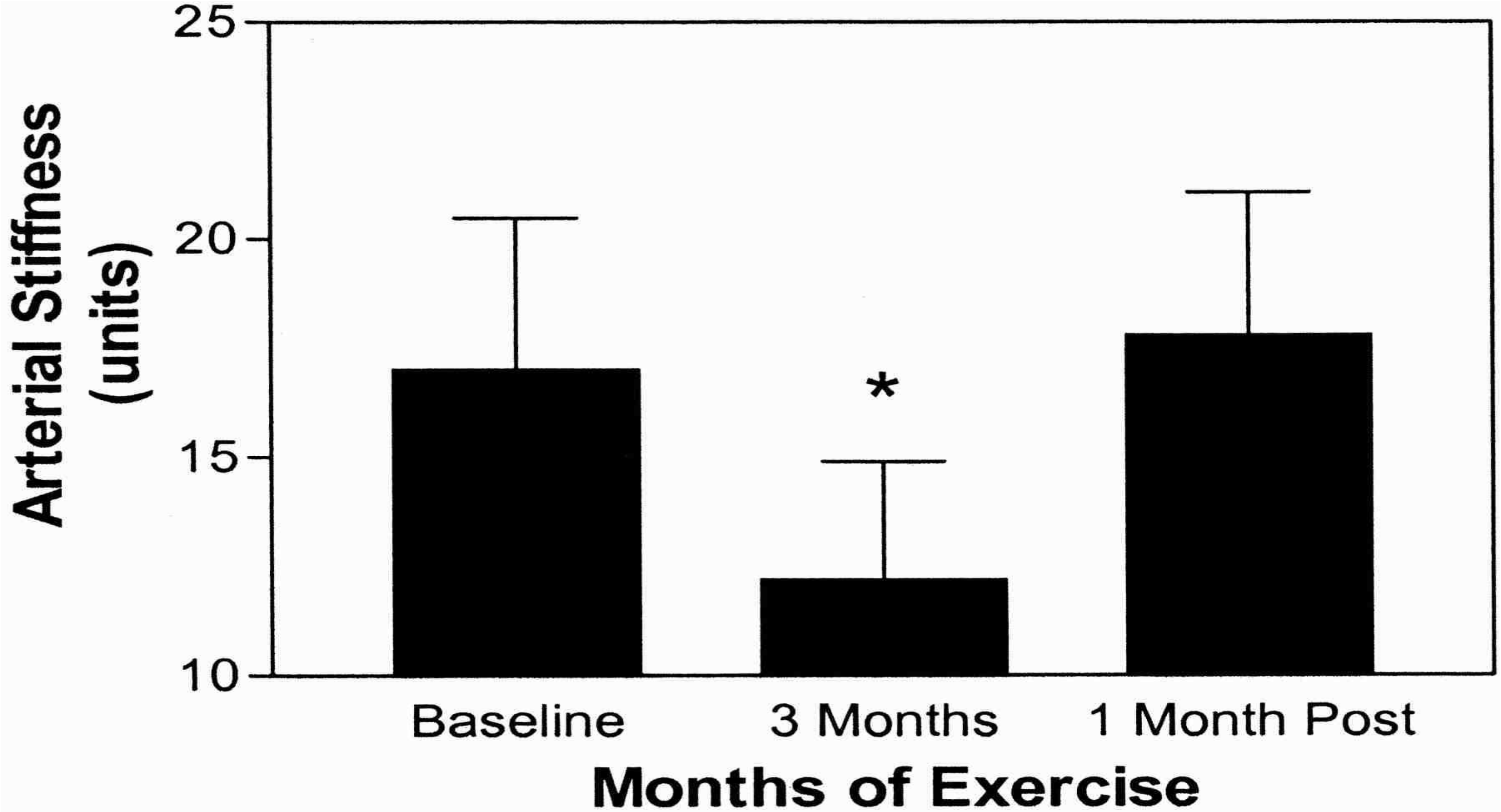
- Severe OSA - associated with arterial stiffness and heart structure abnormalities,
- Additive effects with HTA.

Jerrard-Dunne P et al. *J Hypertens 2007; 25:1233*

- A reverse-dipper pattern associated with increased PWV and with less day: night variability in heart rate

Other strategies

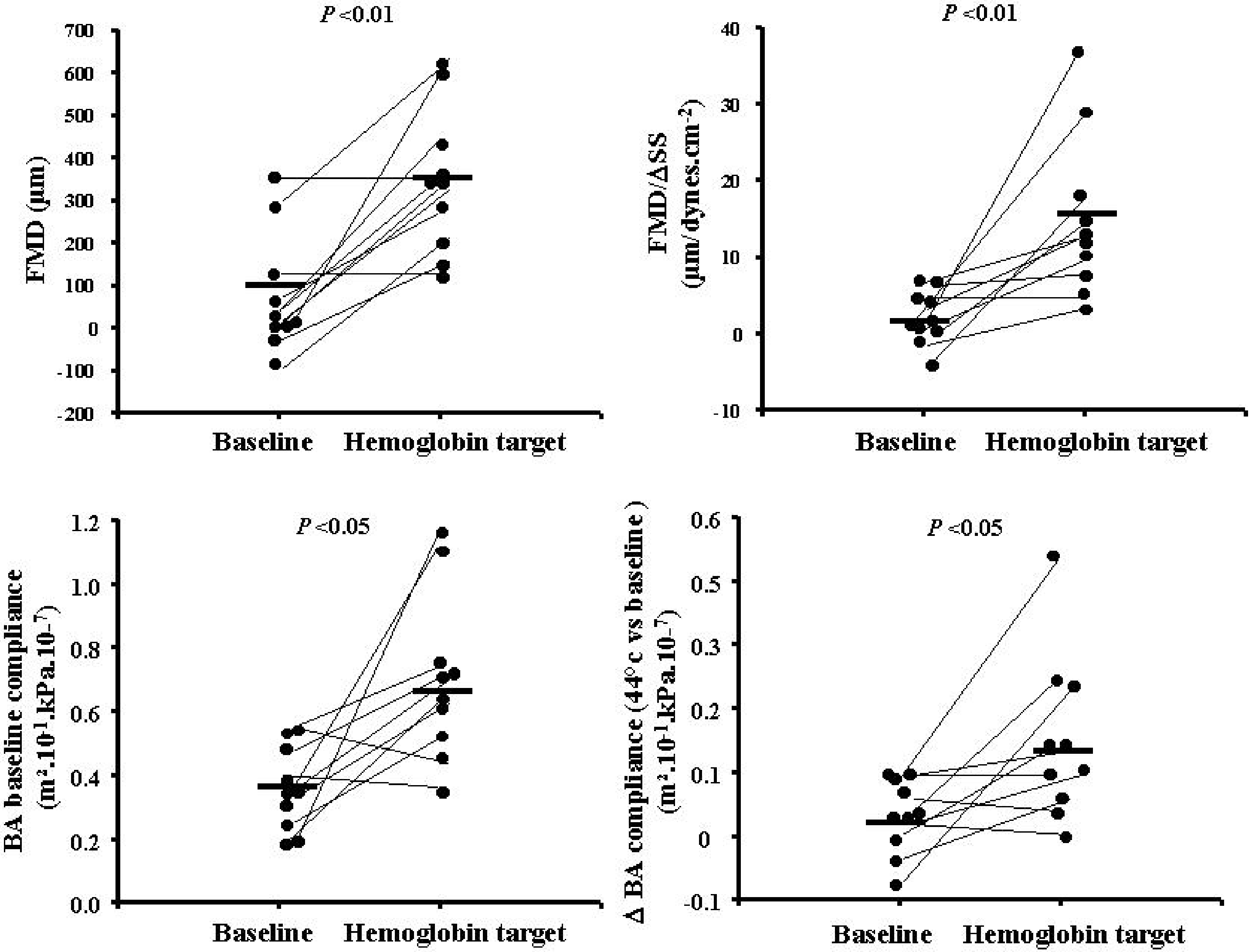
Stefan Mustata, et al. *JASN*., 2004; 15: 2713 - 2718.
Impact of an Exercise Program on Arterial Stiffness in Hemodialysis Patients



Cardiorespiratory Fitness, Physical Activity, and Arterial Stiffness The Northern Ireland Young Hearts Project Colin A et al *Hypertension*. *2004;* 44:721-726.

- N = 405 young men and women
- Findings suggest that arterial stiffness-related benefits of exercise are most likely to accrue if exercise prescription in young adults targets improvements in cardiorespiratory fitness.

Effects of anemia correction on FMD and brachial artery compliance



Verbeke et al JASN 2007

Choice of RRT

Does it matters?

Peritoneal Dialysis International, Vol. 24, pp. 365–372
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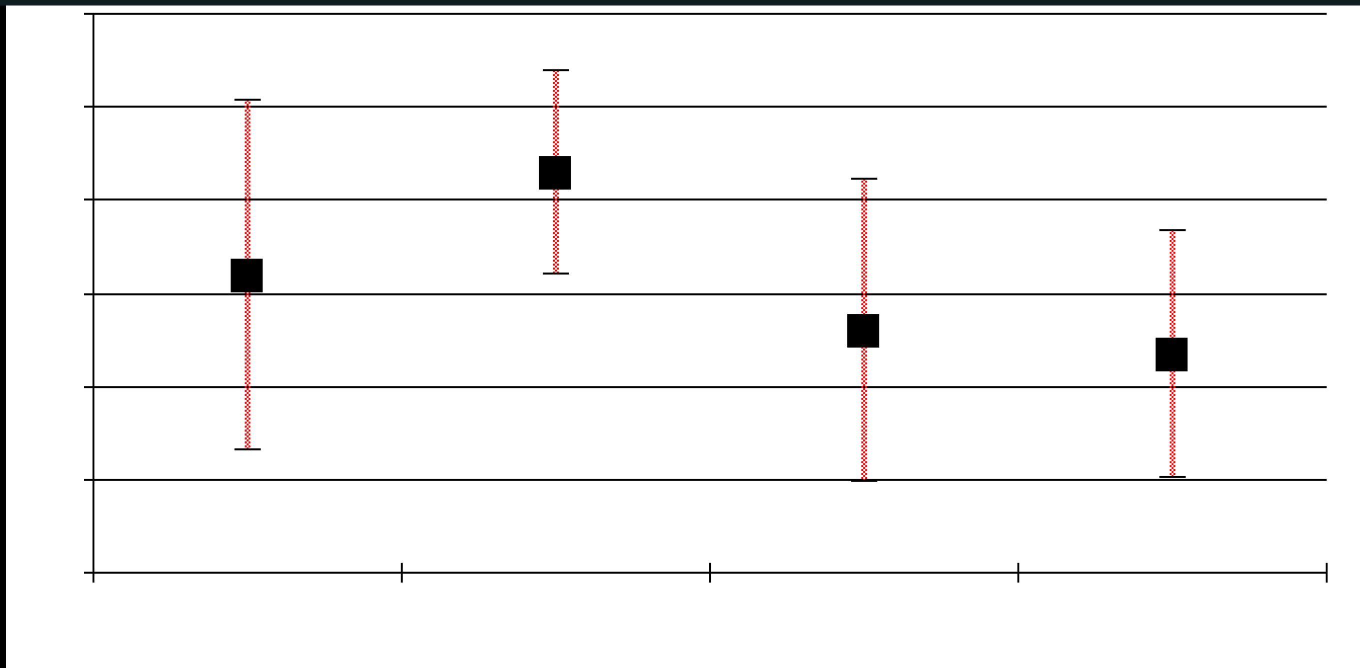
THE INFLUENCE OF DIALYTIC MODALITY ON ARTERIAL STIFFNESS, PULSE WAVE REFLECTIONS, AND VASOMOTOR FUNCTION

Adrian Covic,[1] David J.A. Goldsmith,[2] Laura Florea,[1] Paul Gusbeth–Tatomir,[1] and Maria Covic[1]

Avoid PD? Prefer RTx?



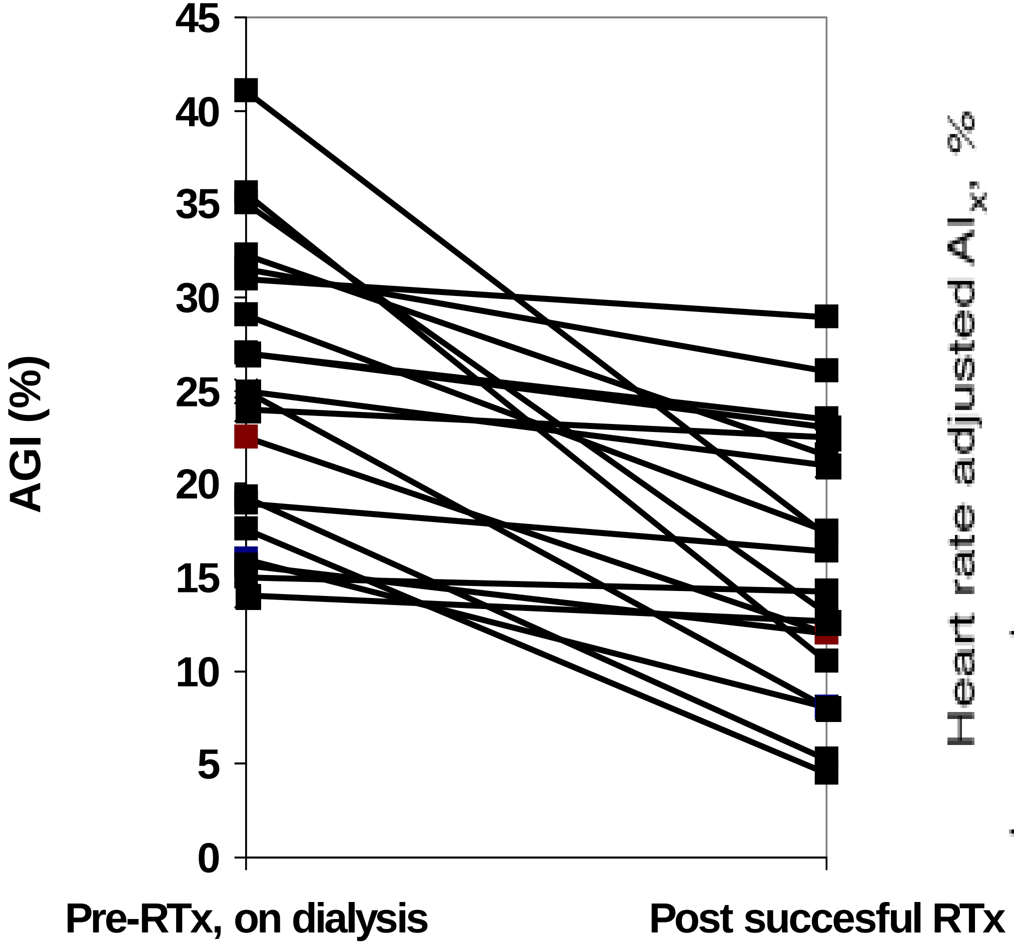
Successful Renal Transplantation Decreases Aortic Stiffness And Increases Vascular Reactivity In Dialysis Patients.

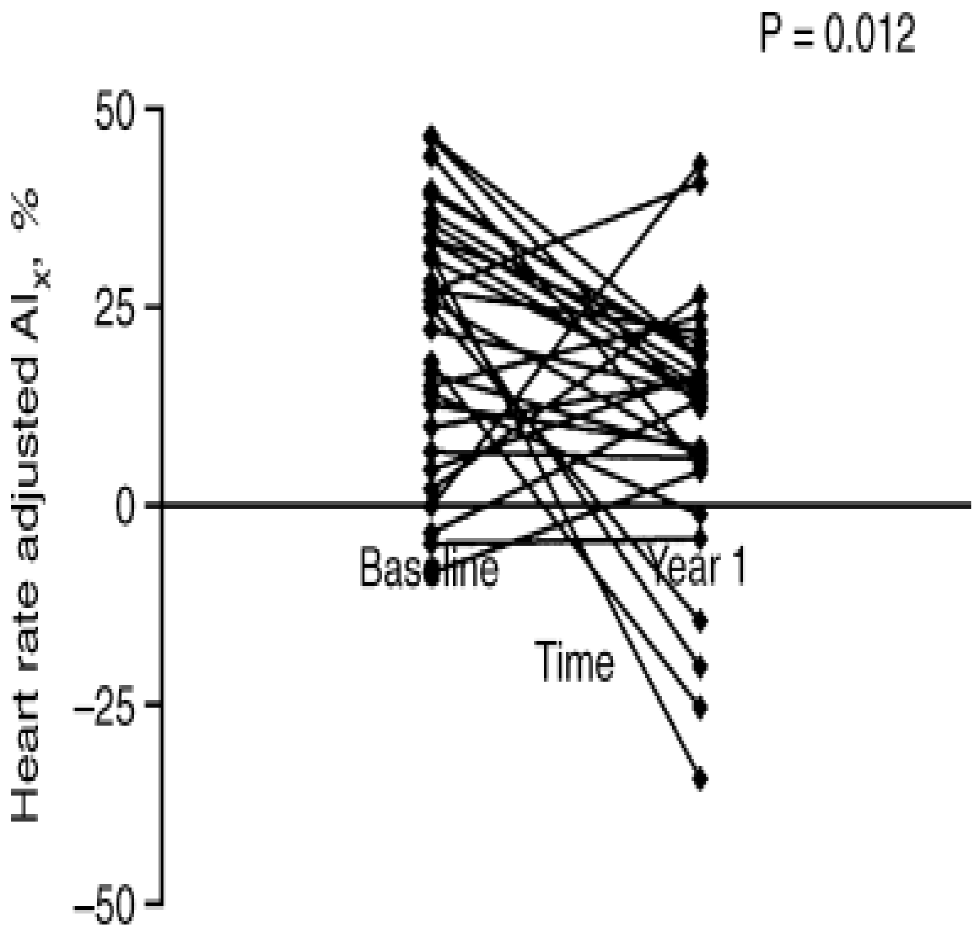
A. Covic et al., *Transplantation*, 2003, 76:1573)

- 21 HD patients studied 1/12 pre and 3/12 post live-related renal transplantation
  - compared to a group with essential HT
- Echo, PWA and PWV pre and post RTx

- **PWV fell significantly after RTx (**)**
- **Similar to age, gender and BP matched EHT controls (*)**

AIx





Covic, *Transplantation* 2003

Zoungas, *KI* 2004

Nephrol Dial Transplant (2007) 1 of 7
doi:10.1093/ndt/gfm379

NDT
Nephrology Dialysis Transplantation

Original Article

Arterial stiffness and wave reflections in renal transplant recipients

Francis Verbeke[1], Wim Van Biesen[1], Patrick Peeters[1], Luc M. Van Bortel[2] and Raymond C. Vanholder[1]

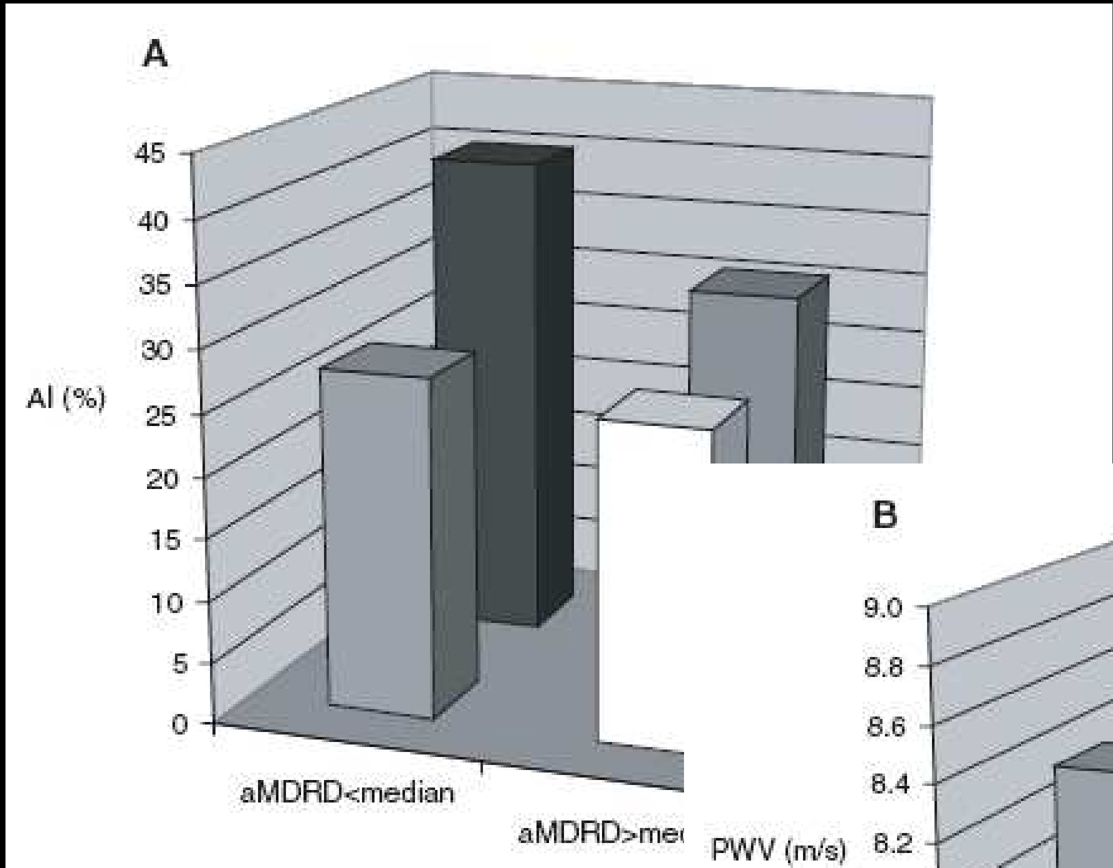
- **After correction for age, BP and anthropometry, AI and PWV remained 7.4% and 0.7 m/s higher in RTR than controls**
- **= difference in vascular age of >10 years.**

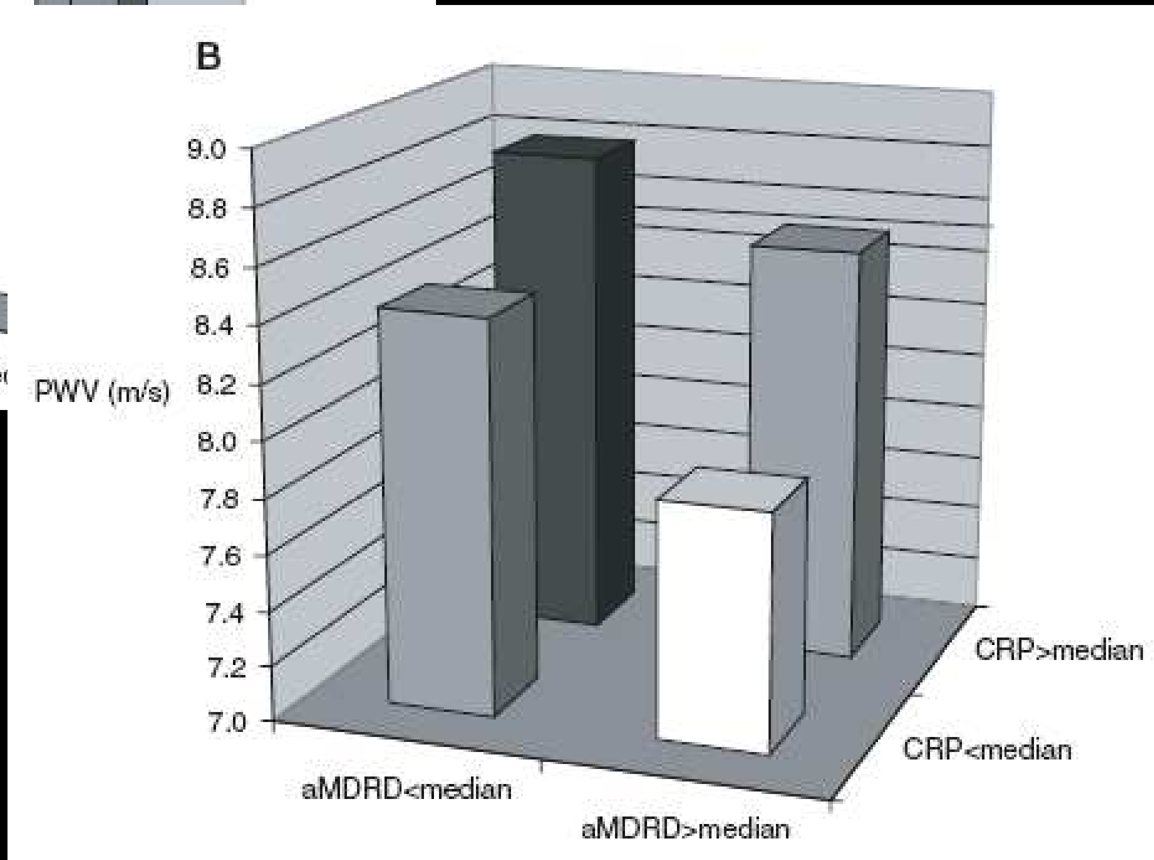
WHY SUCH A DIFFERENCE –

LESSONS TO BE LEARNED?

(multivariate analysis) - independent factors:

GFR and CRP





<u>Differences RTR vs controls</u>

- in GFR = 2/3 of the ↑

- in CRP = 1/3 of the ↑

in PWV and AI

Summary and Conclusions

- **Alterations in large artery structure, and function, are fundamental to hemodynamic changes in chronic kidney disease**
- **Calcification, Sodium-RAAS, inflammation and AGE's are likely to be major explanations of the changes**
- **Targets to prevent / retard vascular stiffening**

– Ovehydration / salt / renin-angiotensin-aldosterone	Y
– Inflammation / lipids	Y
– Wave reflections	Y
– Calcification	Y
– AGE's	(Y)