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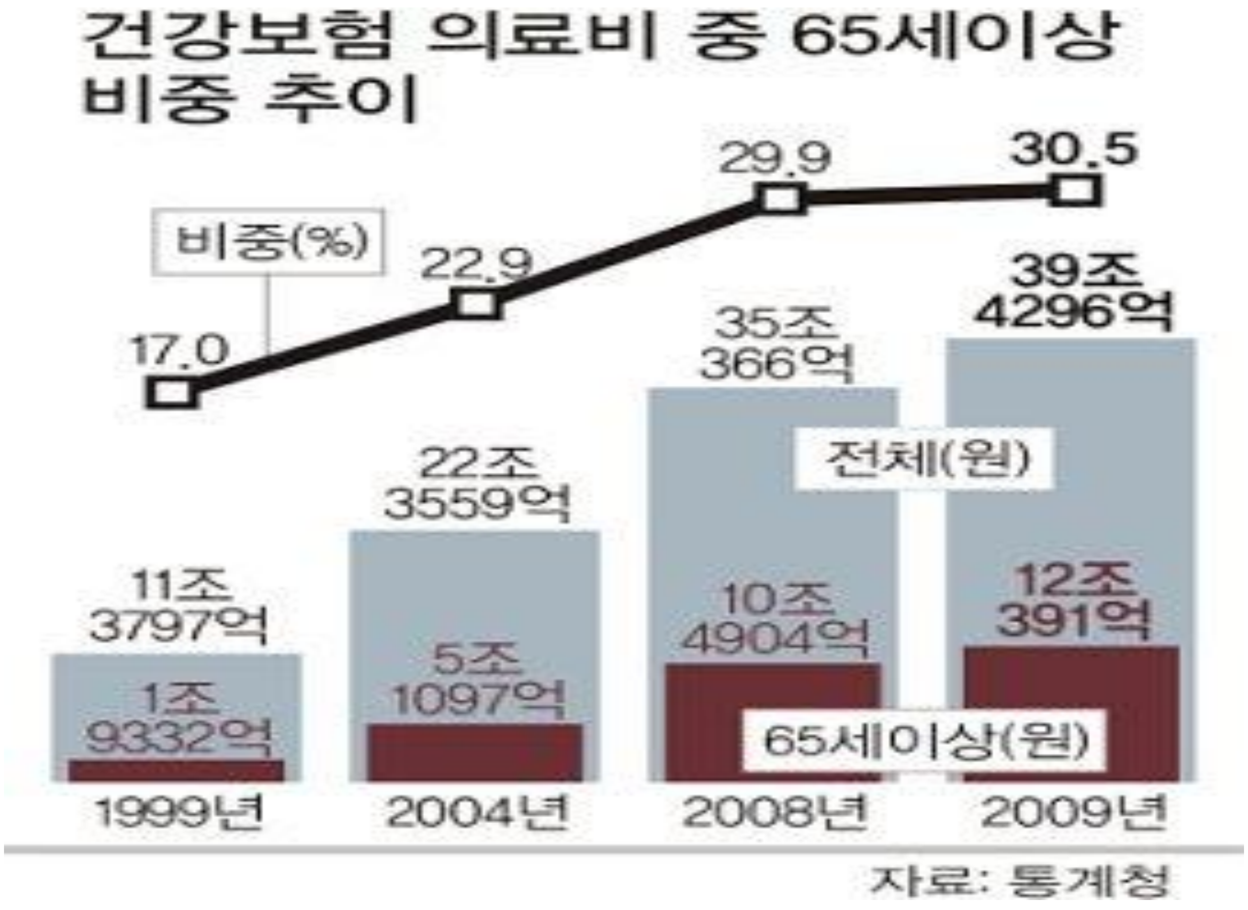
How to Stop Vascular Aging in the Hypertensive Elderly?

김 광 일

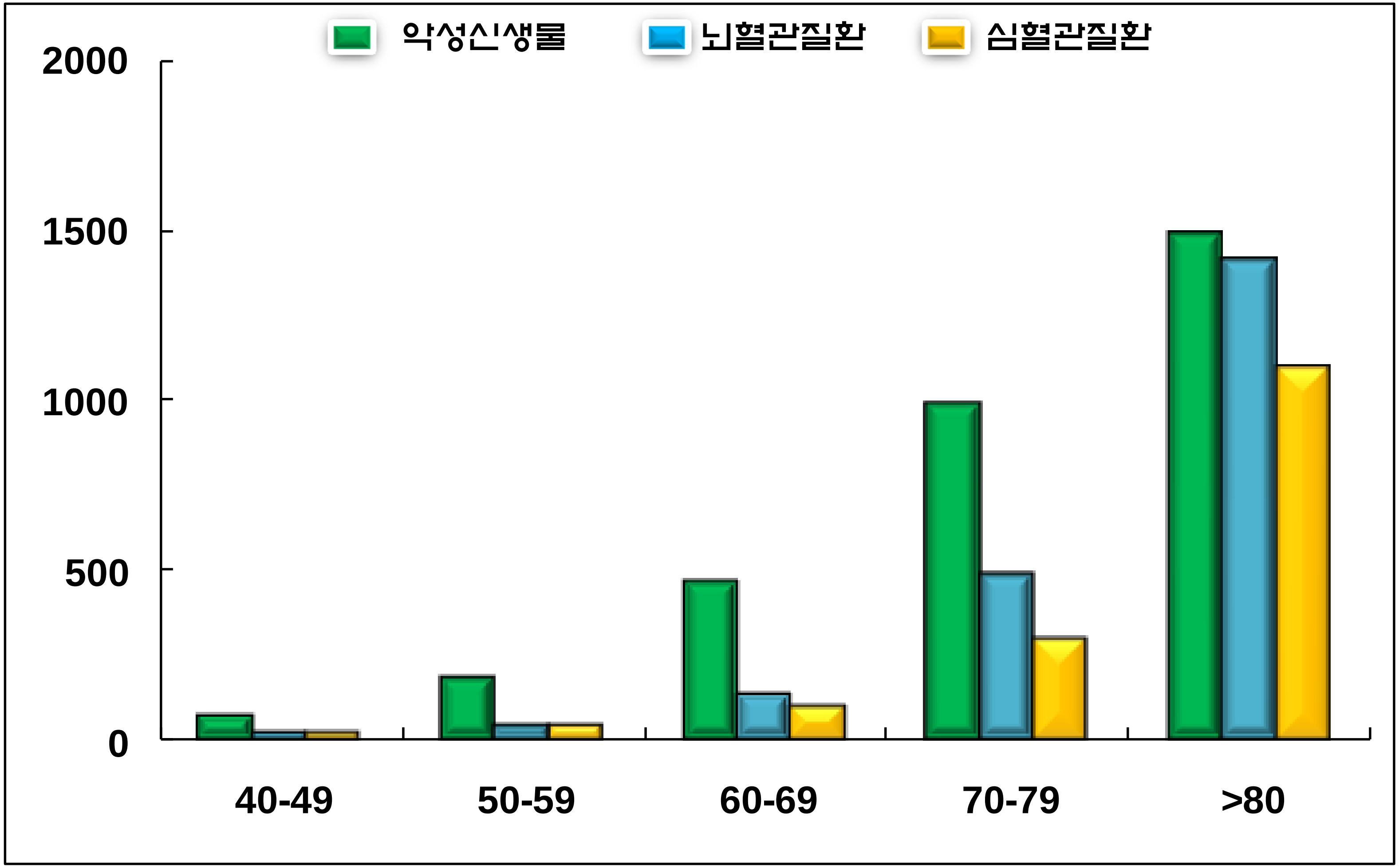
서울대학교 의과대학 내과
분당서울대학교 병원 내과

고령사회는 피할 수 없는 미래

노인인구의 증가: 의료비 상승



연령별 사망원인 통계 (통계청 자료)



인구 10만 명당 사망자수

How can we evaluate the status of vascular aging in the elderly patients ?

What is the biomarker of vascular aging?

Perceived age as clinically useful biomarker of ageing

	≥80 (n=345)			
	1st third	2nd third	3rd third	P value*
Perceived age	75.9	81.0	85.1	—
Person year	658.7	587.4	517.1	—
Deaths	42	74	69	—
Mortality rates per 100 years	6.4	12.6	13.3	<0.001
Strength score	3.1	2.7	2.3	<0.001
Grip strength	19.9	17.3	15.5	<0.001
MMSE	26.2	25.2	23.5	<0.001
Cognitive score	1.9	0.5	-0.3	<0.001
Telomere length:				
Hph I/Mnl I	4.9	4.7	4.5	<0.001
Hinf I/Rsa I	6.1	5.8	5.6	<0.001

Christensen et al, BMJ 2009

Criteria for biomarker of aging

- It must predict the rate of aging. (It must be a better predictor of life span than chronological age.)
- It must monitor a basic process that underlies the aging process, and not the effects of disease.
- It must be able to be tested repeatedly without harming the person, for example, a blood test or an imaging technique.
- It must be something that acts in both humans and laboratory animals, such as mice, so that it can be tested in animals before being validated in humans.

Potential biomarkers of ageing

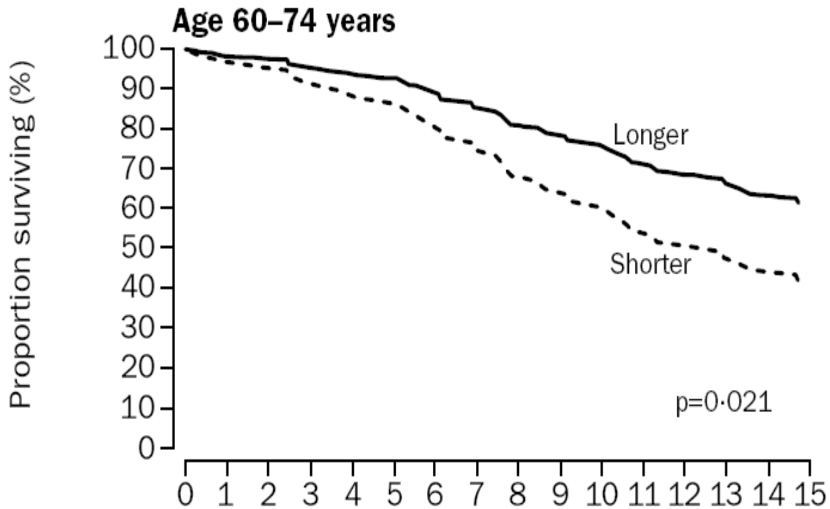
Underlying biological process	Possible biomarker	Change with age	Validated in studies		
			Cell culture/ animal	Human	
				Cross-sectional	Longitudinal
Oxidative stress	8-OHdG (DNA)	Increase	+	+	-
	MDA	Increase	+	+	-
	HNE	Increase	+	+	-
	oxLDL (lipids)	Increase	+	+	-
	Carbonyl groups (proteins)	Increase	+	-	-
Protein glycation	CML	Increase	+	+	-
	Pentosidine	Increase	+	+	-
Inflammation	IL-6	Increase	+	+	+
	CMV-positive CD8 T-cells	Increase	+	+	-
Replicative senescence	Senescence-associated β-Gal	Increase	+	-	-
	$P16^{INK4a}$	Increase	+	-	-
Telomeres	Telomere length	Decrease	+	+	-
Hormones	Growth hormone	Decrease	+	+	-
	IGF	Decrease	+	+	-
	DHEA	Decrease	+	+	+
	Oestrogen	Decrease	+	+	+
	Testosterone	Decrease	+	+	-

Simm et al, Biol. Chem 2008

Telomere length in blood DNA & survival

Number at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Longer	72	71	69	67	60	56	52	51	50	46	45	42	41	36	35	34
Shorter	71	69	63	59	57	56	51	46	43	40	37	34	31	27	25	23

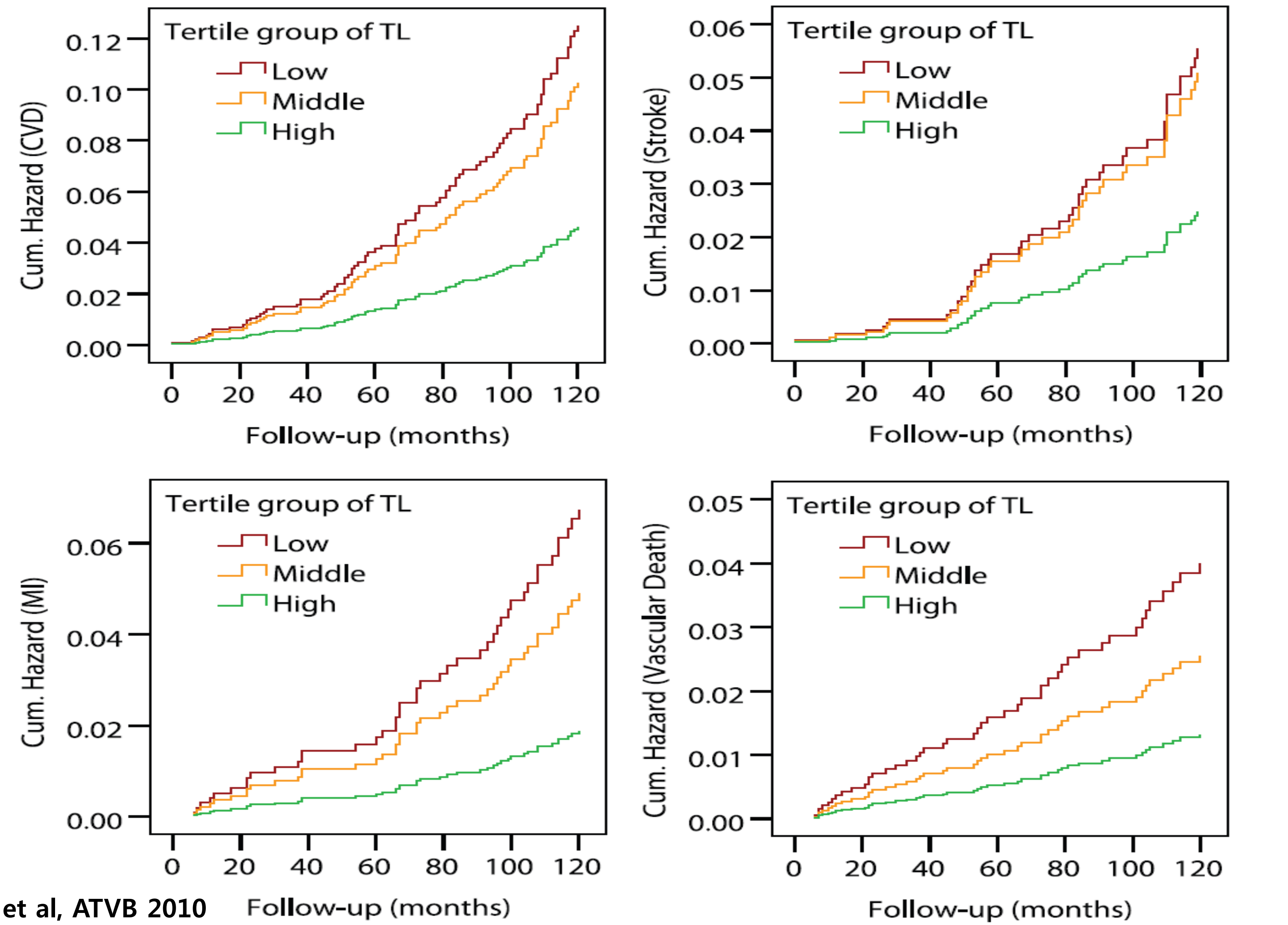


Number at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Longer	48	48	47	46	44	41	39	39	38	36	35	33	33	31	30	29
Shorter	45	44	44	42	41	41	39	35	32	32	30	28	26	25	23	22

Cawthon, et al, Lancet 2003

Clinical outcome according to telomere length



Willeit et al, ATVB 2010

Telomere length & risk of CHD

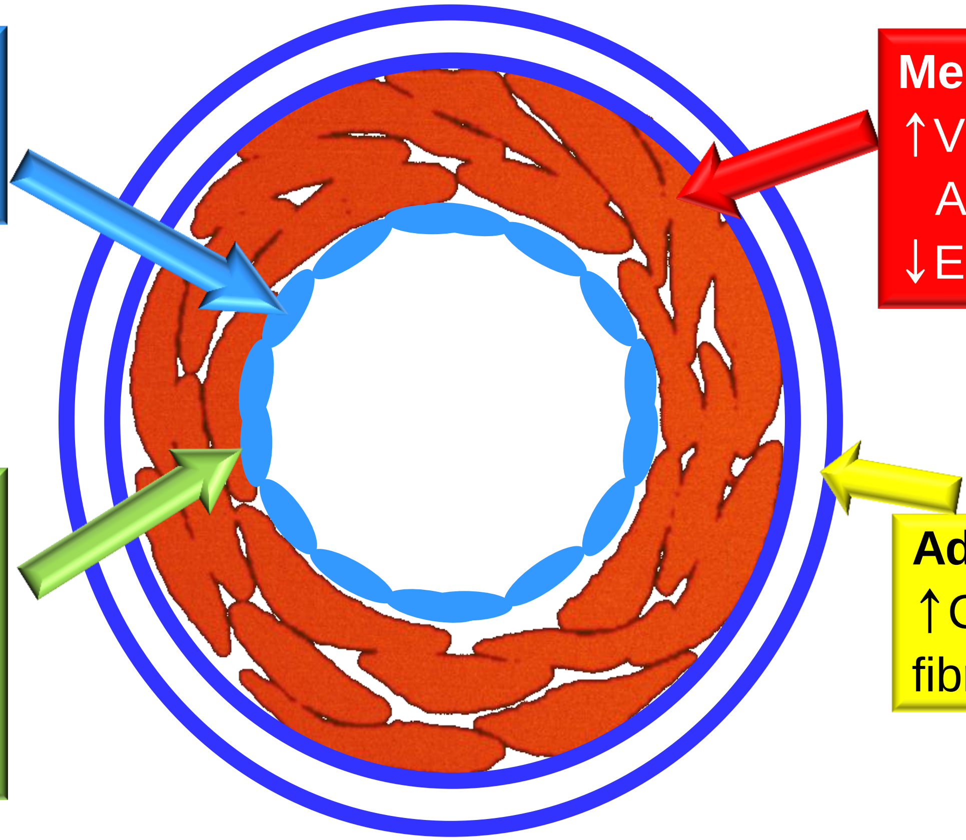
	Cases	Controls	OR (95% CI)	p
All individuals				
Highest tertile	123 (25%)	355 (34%)	(ref)	
Middle tertile	186 (38%)	355 (34%)	1·51 (1·15–1·98)	0·0029
Lowest tertile	175 (36%)	348 (33%)	1·44 (1·10–1·90)	0·0090
Individuals who received placebo				
Highest tertile	62 (21%)	180 (35%)	(ref)	
Middle tertile	118 (41%)	176 (34%)	1·93 (1·33–2·81)	0·0005
Lowest tertile	109 (38%)	161 (31%)	1·95 (1·33–2·84)	0·0006
Individuals who received pravastatin				
Highest tertile	61 (31%)	175 (32%)	(ref)	
Middle tertile	68 (35%)	179 (33%)	1·12 (0·75–1·69)	0·5755
Lowest tertile	66 (34%)	187 (35%)	1·02 (0·68–1·53)	0·9380

Brouilette et al, Lancet 2007; WOSCOPS Study group

Mechanism of vascular aging

Endothelial Cells:
Endothelial dysfunction
Increased permeability

Intima:
↑Collagen, AGEs, Mø, leukocytes, ICAM, MMPs, TGFβ, VSMC
↓Elastin



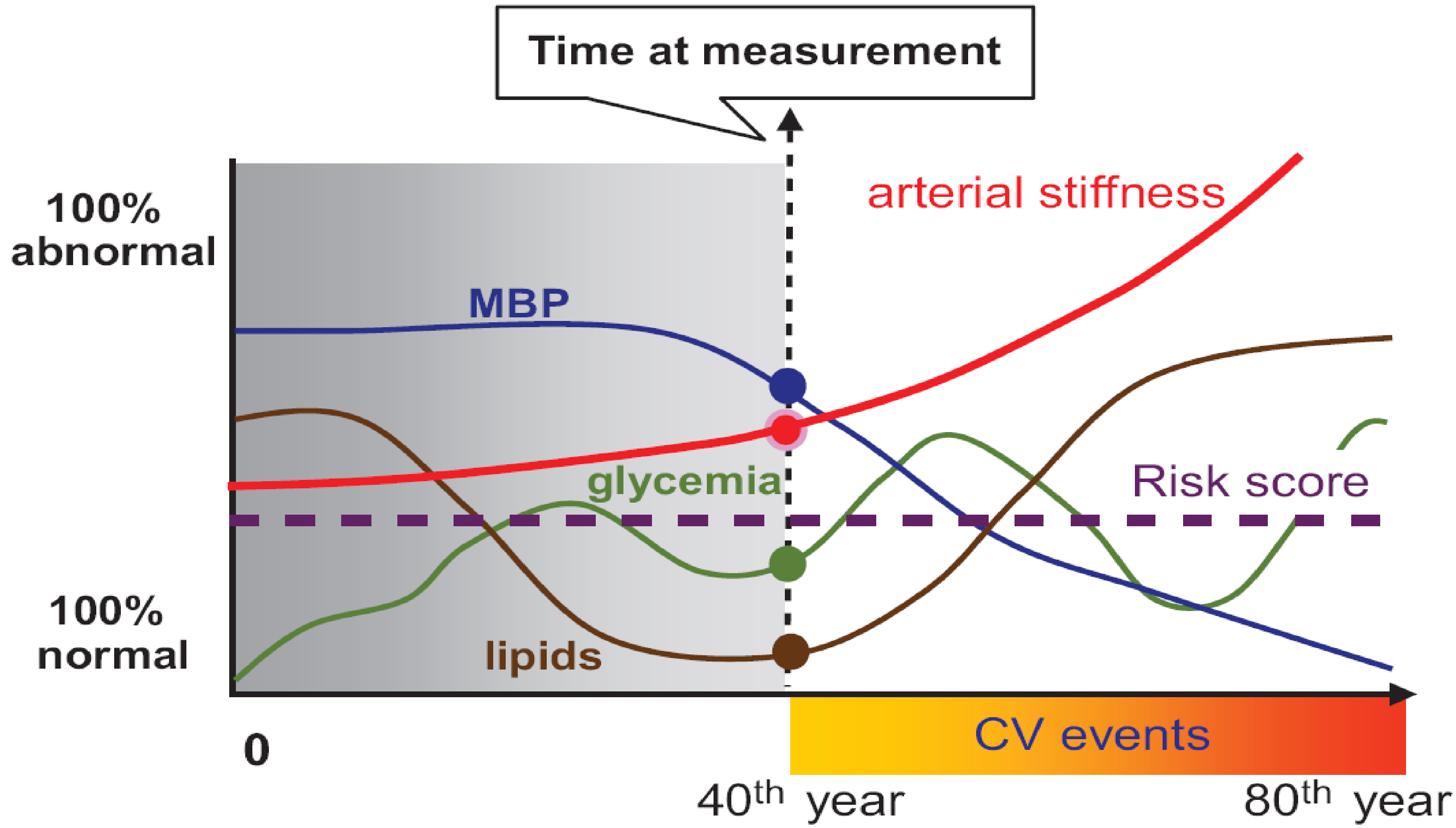
Media:
↑VSMC, collagen, AGEs, MMPs
↓Elastin

Adventitia:
↑Collagen
fibroblast

↑ Systolic and pulse pressures
↑ Vascular stiffness indices, pulse wave velocity
Altered central arterial pressure wave contour
Net effect: ↑ LV pulsatile load (afterload)

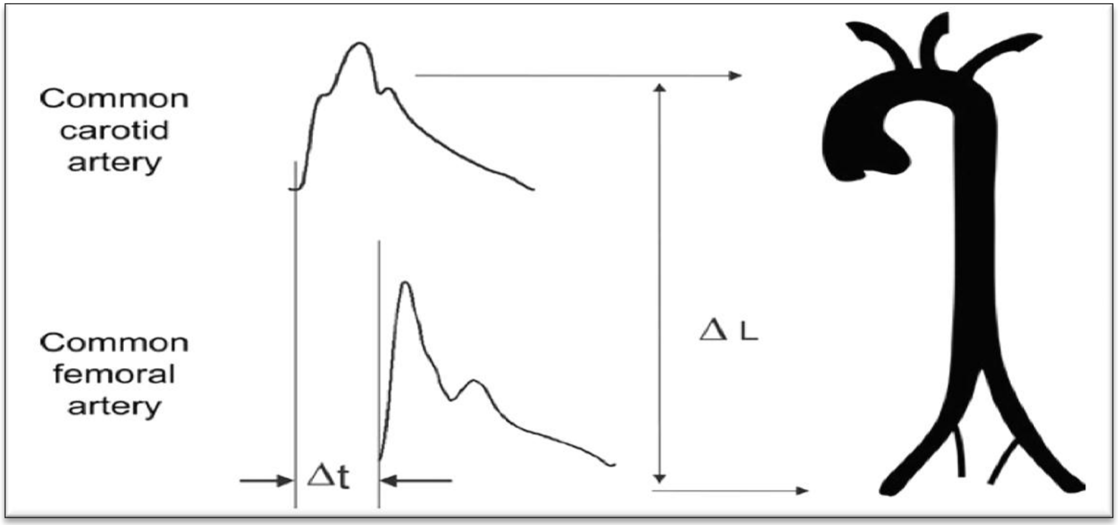
Zieman et al, ATVB 2005

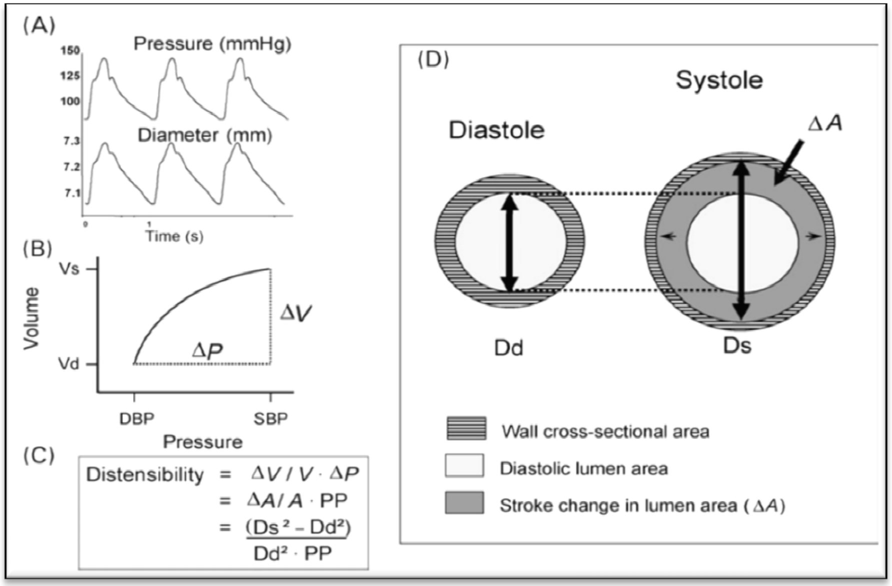
Arterial stiffness as a marker of aging

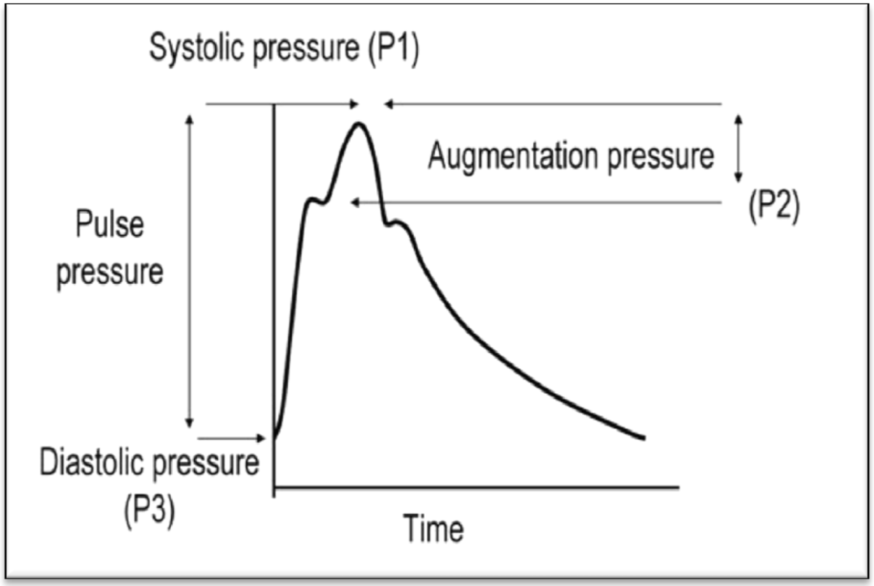


Nilsson, et al, Hypertension 2009

Measurement of arterial stiffness

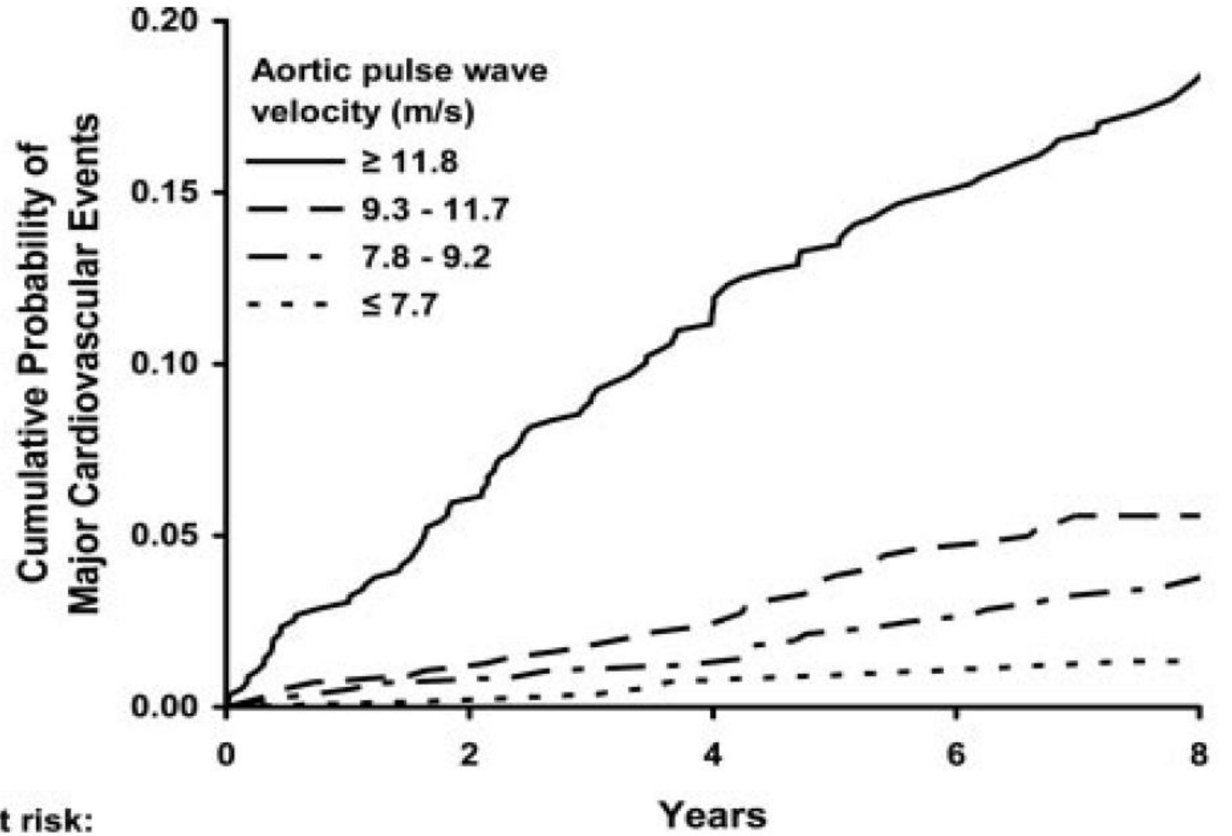






Laurent et al, EHJ 2006

Arterial Stiffness & Cardiovascular Events

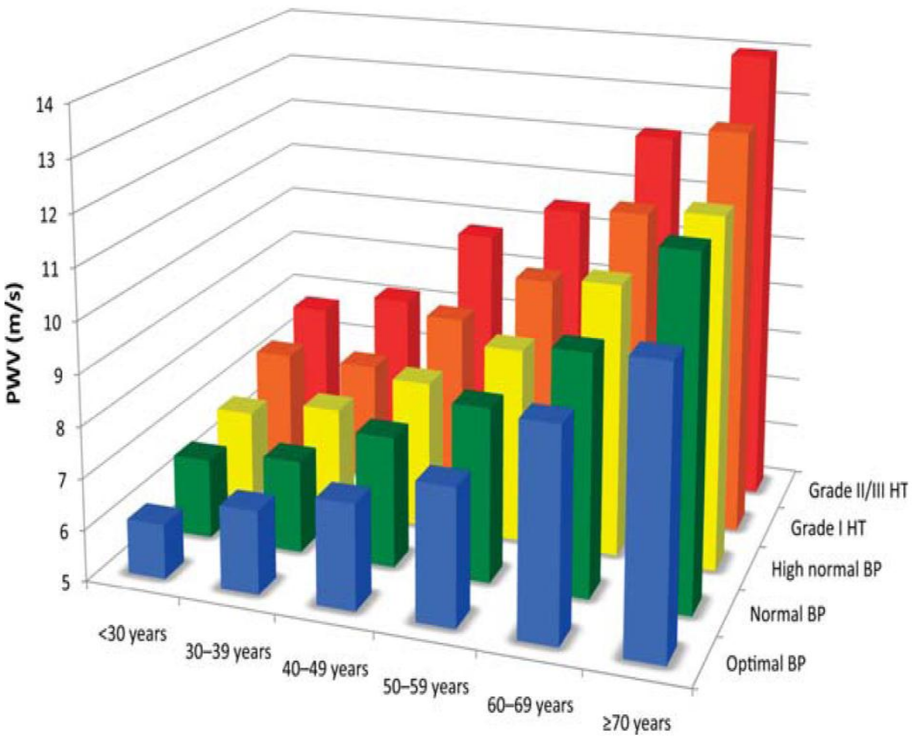


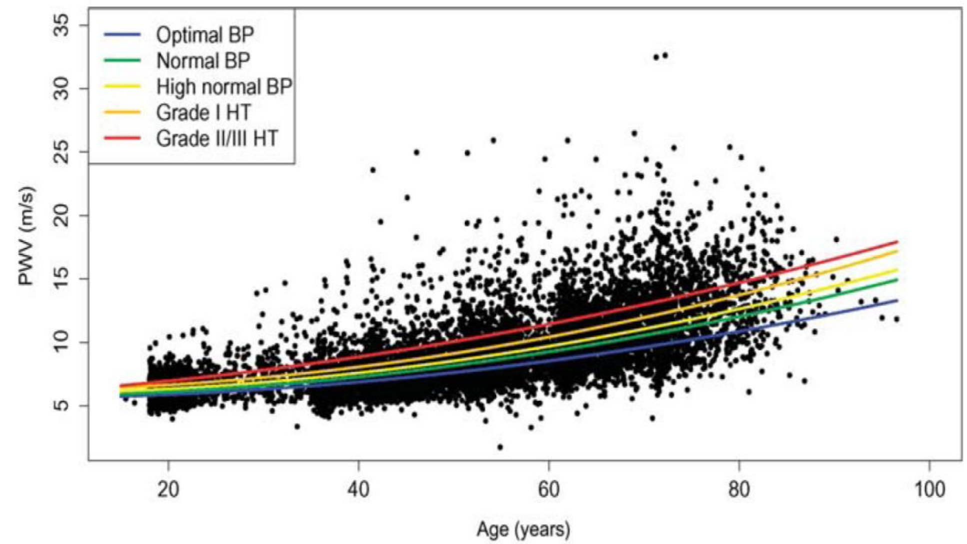
Number at risk:
Aortic pulse wave velocity (m/s)

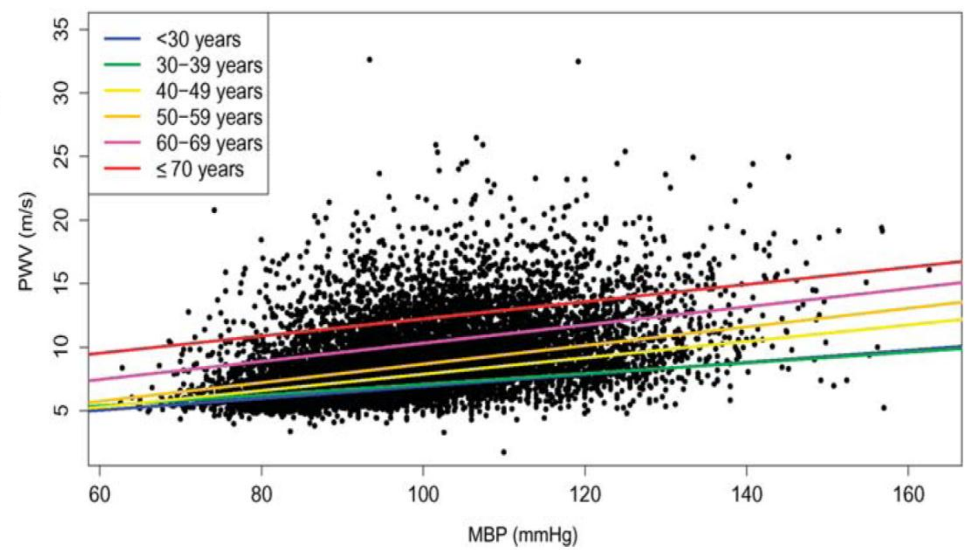
≥ 11.8	560	513	462	424	161
9.3 - 11.7	555	542	529	502	246
7.8 - 9.2	573	561	551	537	278
≤ 7.7	544	541	535	531	275

Mitchell et al, Circulation 2010

Normal & reference values for PWV

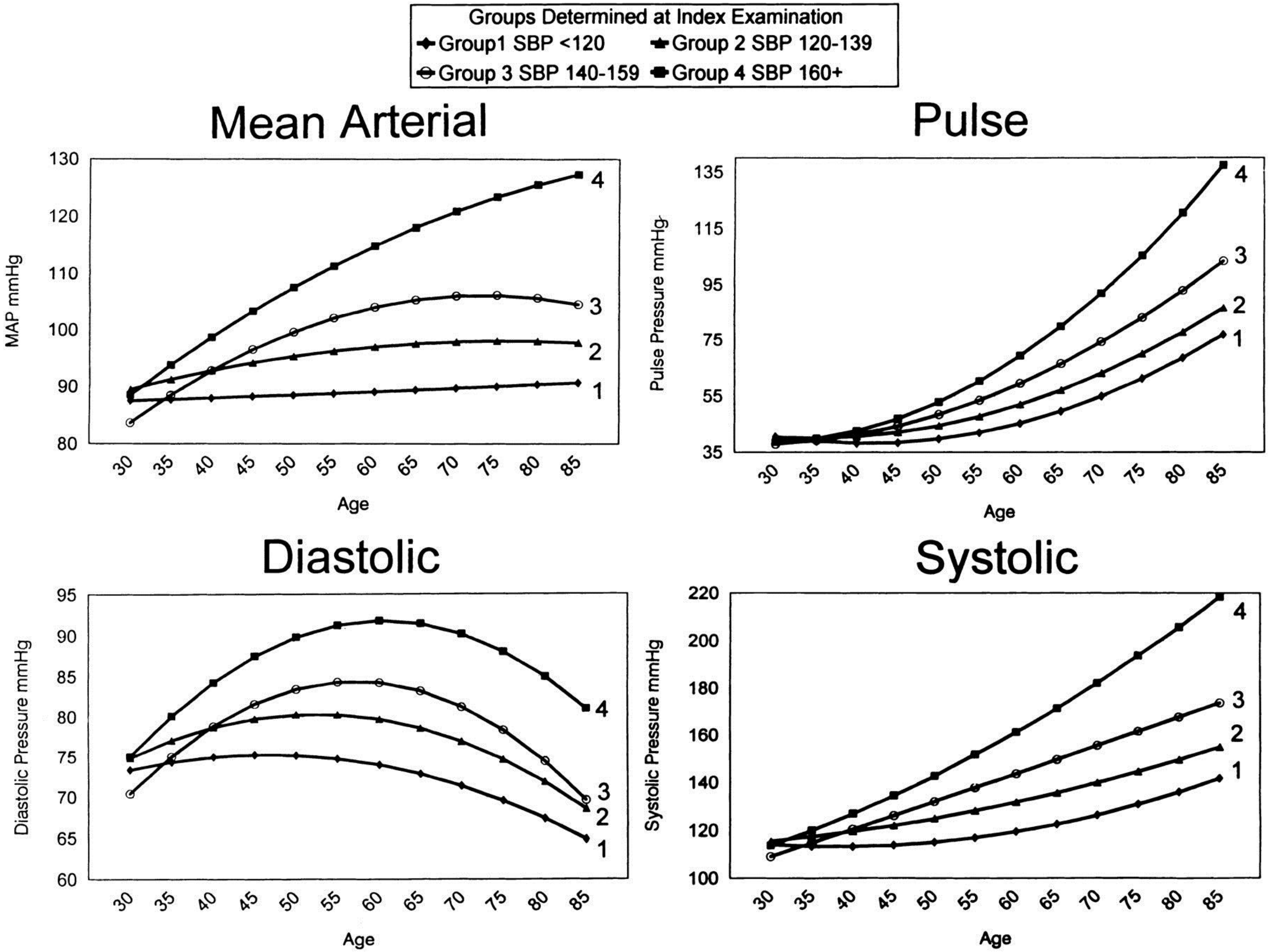






P. Boutouyrie and S.J. Vermeersch, EHJ 2010

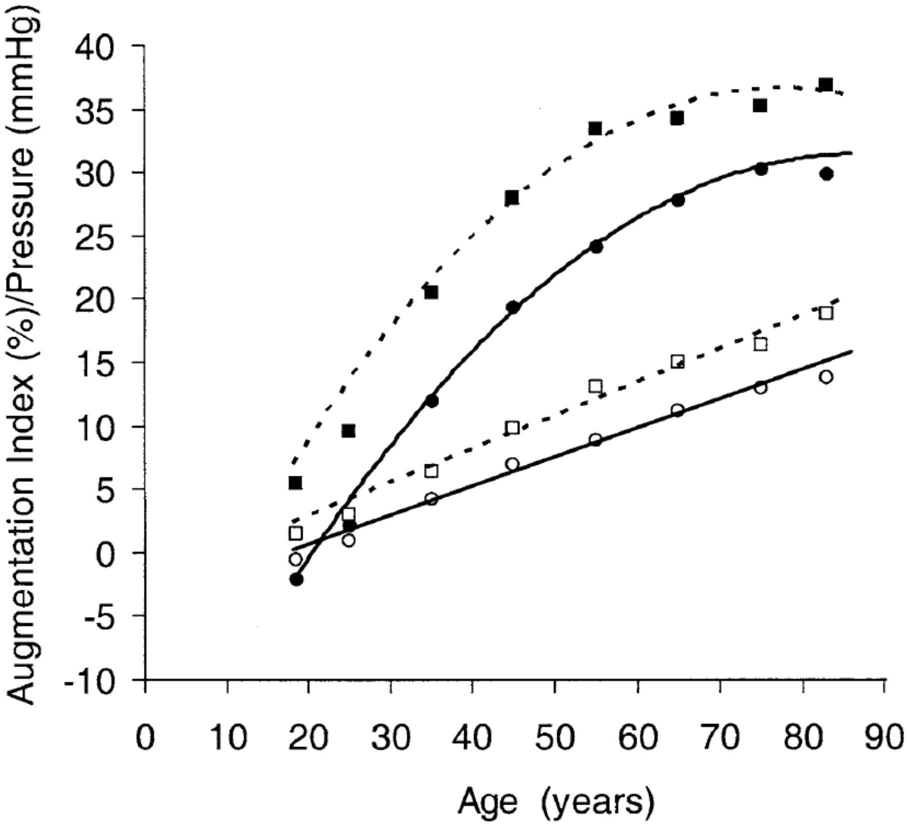
Arterial pressure components by age: Group averaged individual regression analysis



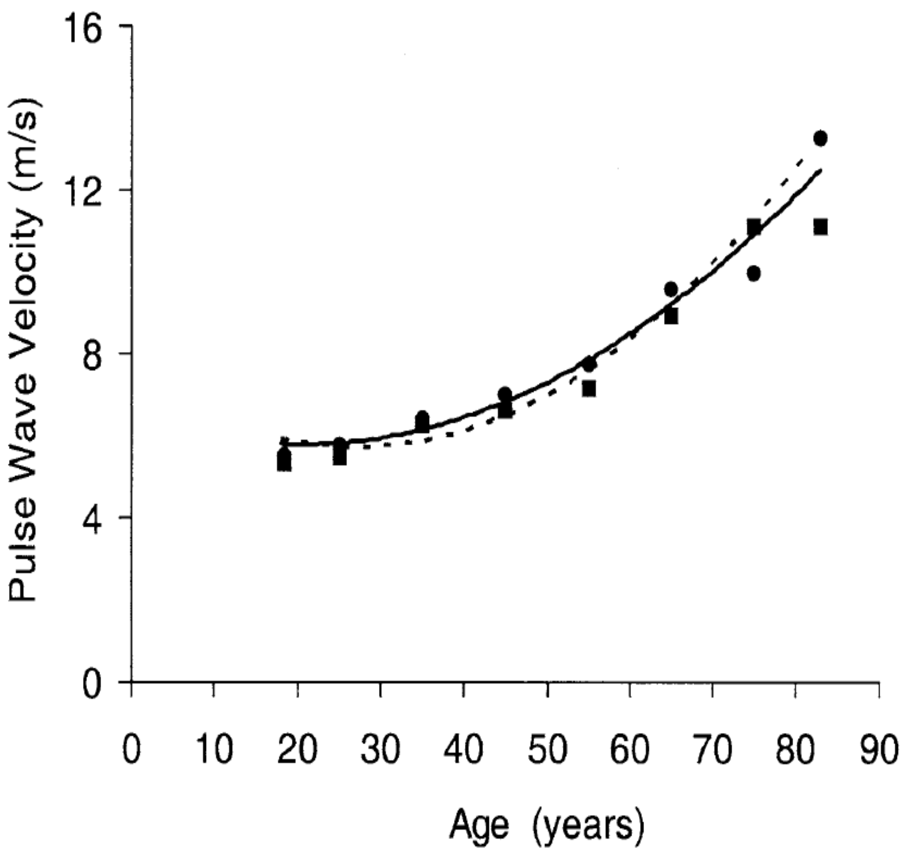
Franklin, et al. Circulation1997

Differential Effects of Aging on Wave Reflection & Pulse Wave Velocity

Augmentation index

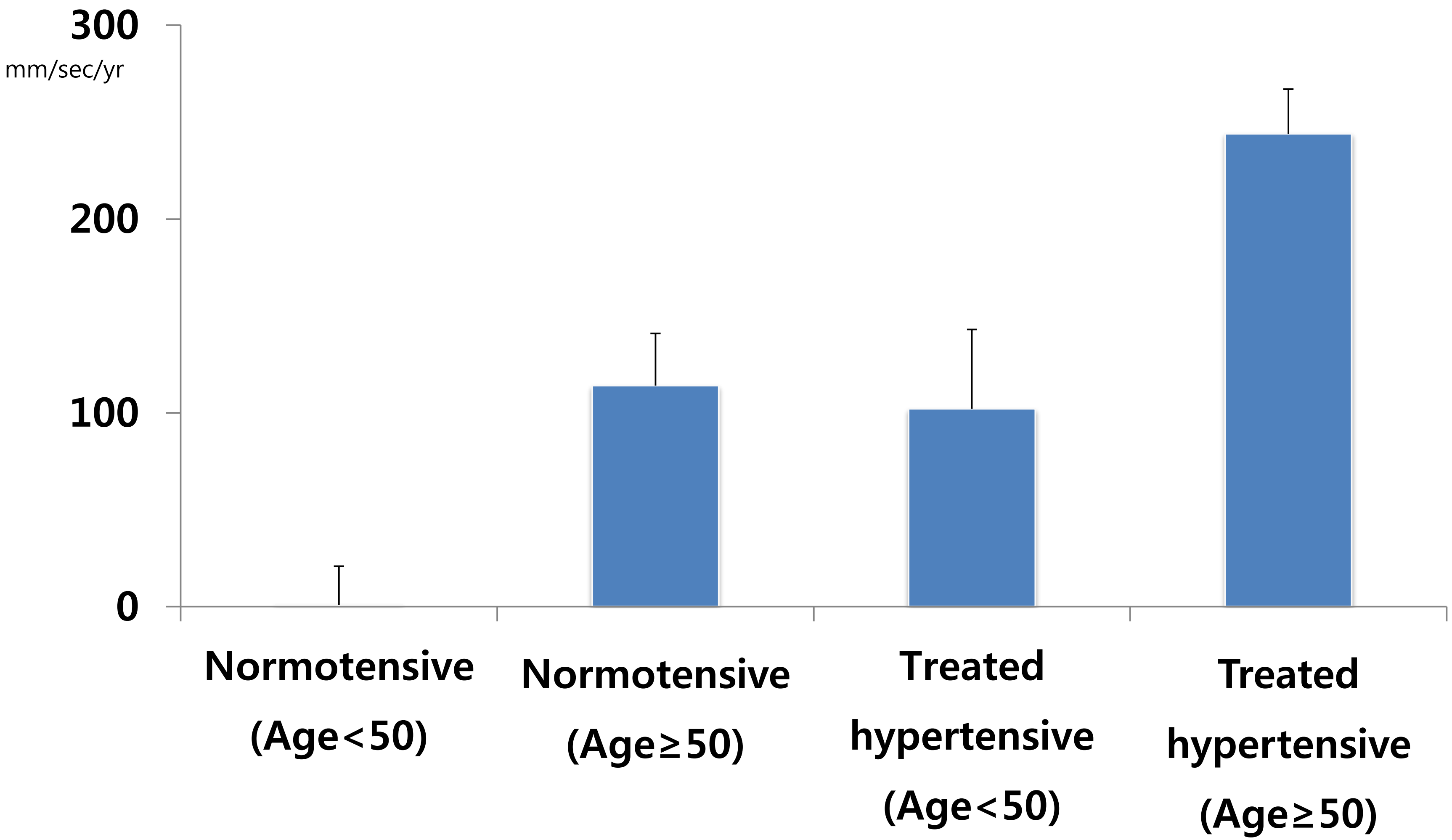


Pulse wave velocity



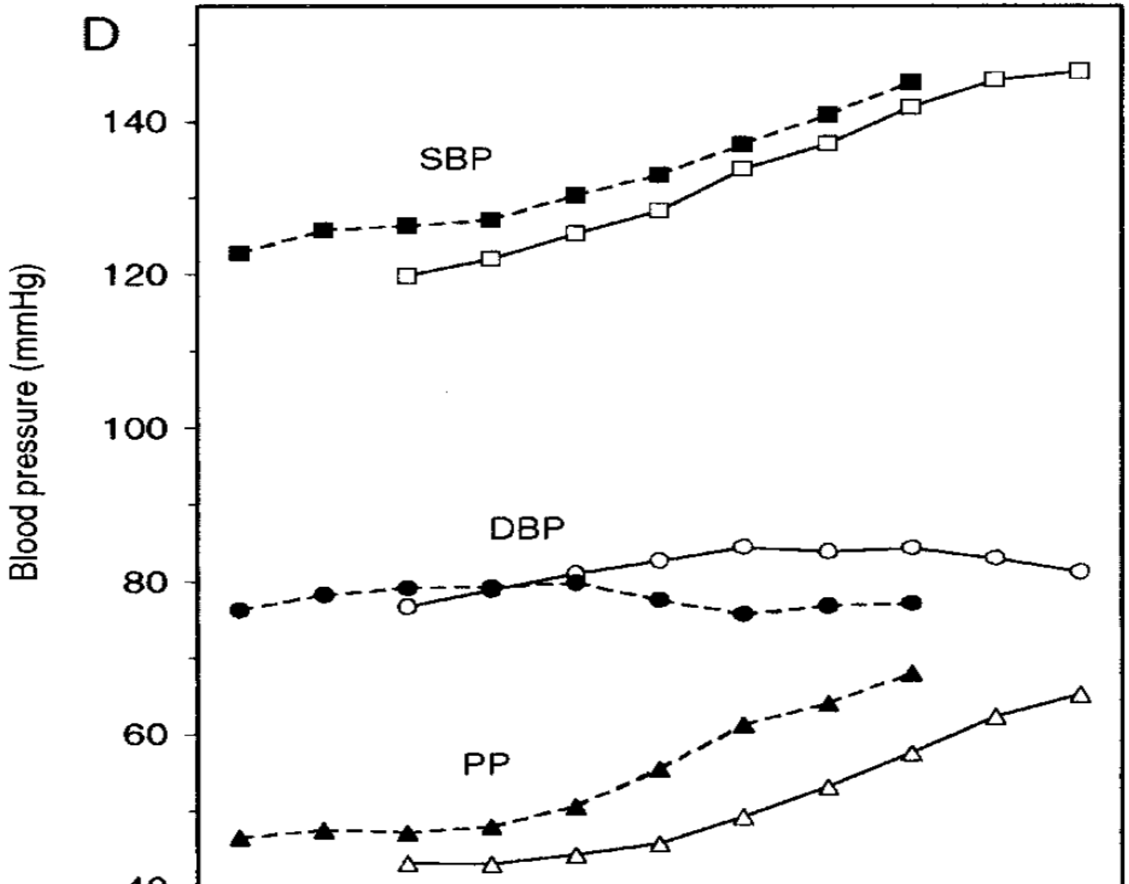
McEniery et al, JACC2005

Annual PWV progression



Benetos et al, Circulation 2002

Altered Age-Related Blood Pressure Pattern in Type 1 Diabetes



Age (years)	18-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Significance	-	-	**‡	**	**	*‡	‡	‡	†	-	-
Diabetes, n	417	280	284	256	202	149	115	50	22	-	-
Controls, n	-	-	684	705	683	719	667	402	359	261	209

Rönnback et al, Circulation 200

Impact of Cardiovascular Risk Factors on Aortic Stiffness & Wave Reflections

aPWV	Beta	R^2 Change	P	AIx	Beta	R^2 Change	P
Univariable models				Univariable models			
Age, gender	…	…	<0.001	Age, gender, height, HR	…	…	<0.001
Hypertension, yes/no	0.20	…	<0.001	Hypertension (yes/no)	0.08	…	<0.001
Hypercholesterolemia, yes/no	0.01	…	0.3	Hypercholesterolemia (yes/no)	0.04	…	<0.001
Smoking, yes/no	0.04	…	<0.001	Smoking (yes/no)	0.03	…	0.001
Diabetes, yes/no	0.08	…	<0.001	Diabetes (yes/no)	0.01	…	0.3
Multivariable model, adjusted $R^2 = 0.68$				Multivariable model, adjusted $R^2 = 0.74$			
Age	0.61	60.7	<0.001	Age	0.61	61	<0.001
MAP	0.19	4.6	<0.001	Gender	0.17	4.3	<0.001
Heart rate	0.10	0.8	<0.001	Heart rate	−0.24	3.3	<0.001
Gender	−0.08	0.8	<0.001	MAP	0.31	4.7	<0.001
Diabetes, yes/no	0.07	0.6	<0.001	Height	−0.12	0.8	<0.001
Hypertension, yes/no	0.06	0.2	<0.001	Hypertension (yes/no)	−0.06	0.2	<0.001
Smoker, yes/no	0.03	0.1	0.003	Smoker (yes/no)	0.03	0.1	0.002
Statin therapy, yes/no	0.03	<0.1	0.007	Hypercholesterolemia (yes/no)	0.02	0.1	0.004
Hypercholesterolemia, yes/no	−0.02	0.1	0.008				

McEniery et al, HT 2010

Non-pharmacological and pharmacological treatment associated with a reduction in arterial stiffness

Non-pharmacological	*Pharmacological*
Exercise training	Anti-hypertensive treatment
Dietary changes	Diuretics
Weight loss	Beta-blockers
Low-salt diet	ACE-inhibitors
Moderate alcohol consumption	AT1 blockers
Garlic powder	Calcium channel antagonists
Alpha-linoleic acid	Treatment of congestive heart failure
Fish oil	ACE-inhibitors
HRT	Nitrates
	Hypolipidaemic agents
	Statins
	Antidiabetic agents
	Thiazolidinediones
	AGE-breakers
	Alagebrium (ALT-711)

Laurent et al, EHJ 2006

TNF-α Antagonists Reduce Arterial Stiffness

Variable	Baseline: Anti-TNF (n=35)	Baseline: Control (n=25)	Baseline: *P*	Change: Anti-TNF (n=35)	Change: Control (n=25)	Change: *P*
Brachial SBP, mm Hg	129.8±20.5	132.0±17.0	0.65	−2.5±9.5	−2.6±10.1	0.97
Brachial DBP, mm Hg	79.1±10.7	79.2±8.7	0.97	−2.4±7.1	−2.1±7.4	0.91
Central SBP, mm Hg	120.6±20.5	121.7±17.5	0.83	−2.5±9.5	−3.5±9.6	0.70
Central PP, mm Hg	41.5±14.2	41.2±12.0	0.93	−1.0±7.8	−1.4±6.6	0.85
MAP, mm Hg	97.1±13.7	97.7±12.1	0.87	−2.1±7.9	−2.6±7.8	0.80
HR, bpm	64.9±10.0	63.1±9.7	0.48	−0.2±9.1	2.0±9.3	0.37
Central AP, mm Hg	9.6±7.3	8.4±6.5	0.52	0.7±3.4	0.6±3.1	0.91
AIx, %	23.0±12.4	19.8±12.5	0.33	0.1±7.1	−1.0±5.8	0.53
aPWV, m/s	7.45±1.44	7.47±1.29	0.96	−0.50±0.78	0.05±0.54	0.002

Variable	Regression Coefficient (CI)	*P*
Sex	−0.020 (−0.340, 0.299)	0.90
Age, y	−0.002 (−0.015, 0.011)	0.74
Anti-TNF-α therapy	−0.485 (−0.789, −0.165)	0.003
Δ MAP, mm Hg	0.029 (0.008, 0.050)	0.008

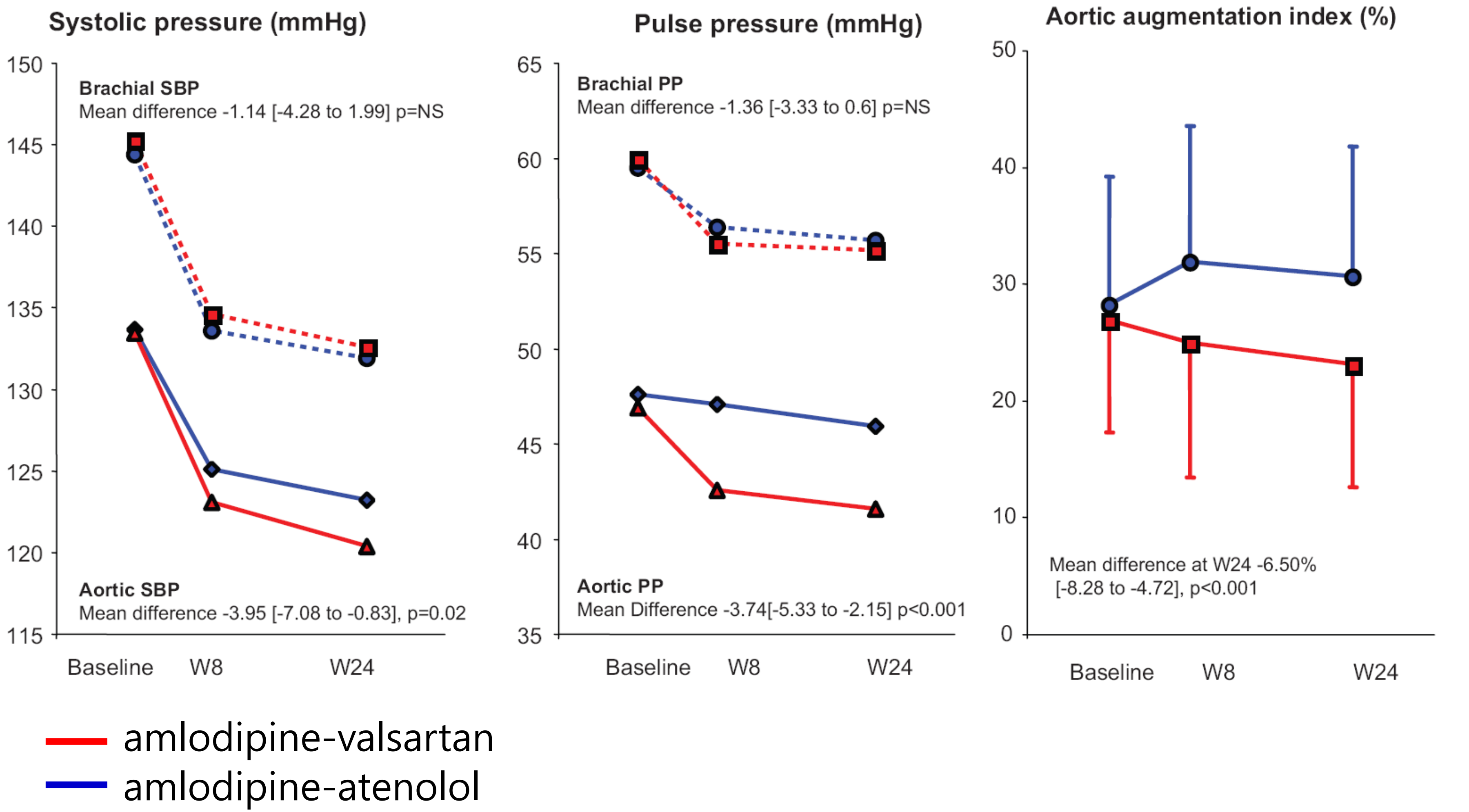
Angel et al, Hypertension 2010

Antihypertensive Drugs & Central Pressure in ISH

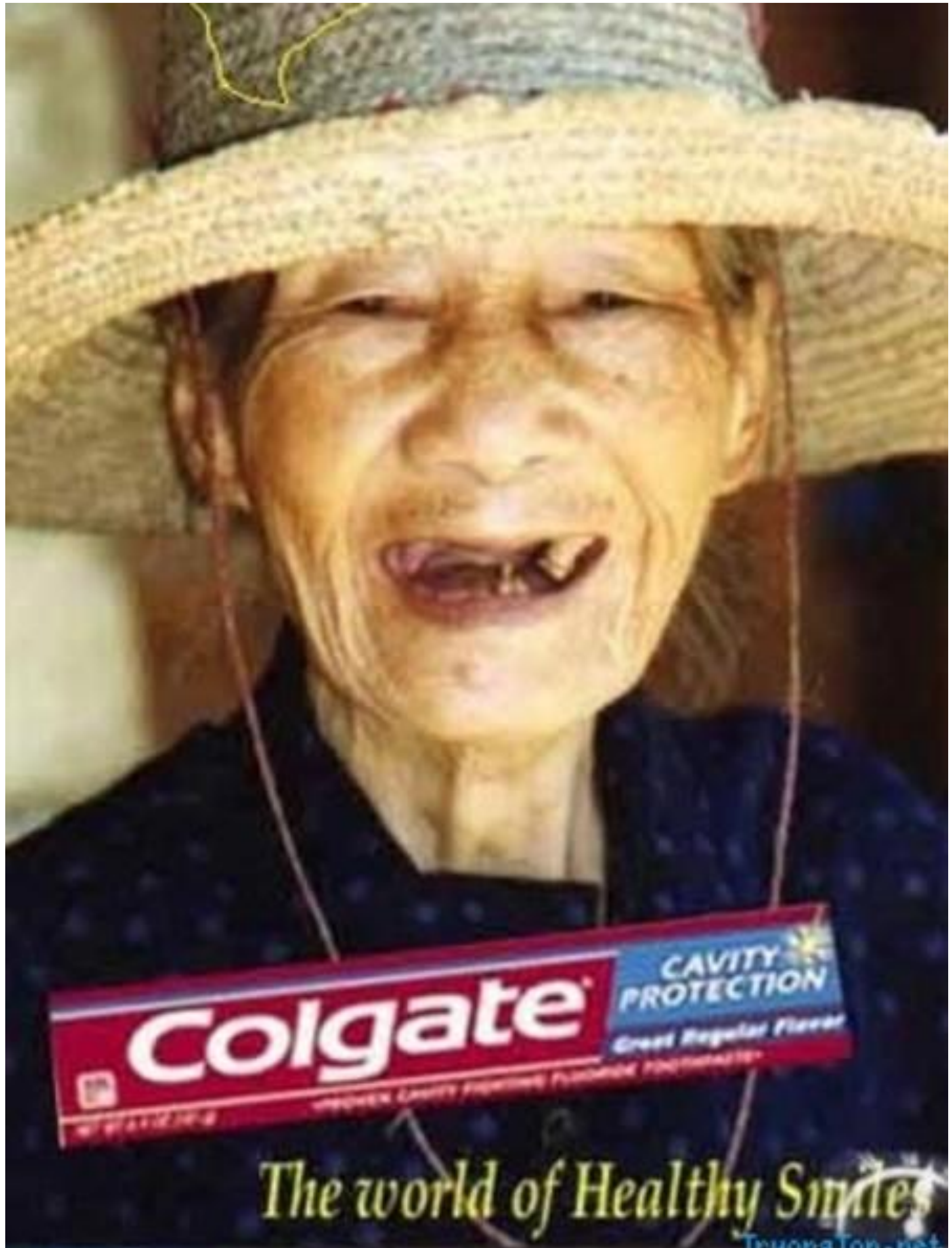
Parameter	Perindopril Placebo	Perindopril 10 wk	Atenolol Placebo	Atenolol 10 wk	Lercanidipine Placebo	Lercanidipine 10 wk	Bendrofluazide Placebo	Bendrofluazide 10 wk	2-Way ANOVA, Time, Drug
Peripheral SBP, mm Hg	153±3	136±4*	156±2	138±4*	146±2	133±3*	154±3	140±3*	<0.001, 0.1
Peripheral DBP, mm Hg	80±2	75±2*	84±2	76±3*	80±2	79±3	85±2	82±3	<0.001, 0.3
Peripheral PP, mm Hg	72±4	61±4*	72±3	62±3*	66±3	54±4*	69±4	58±4*	<0.001, 0.3
Central SBP, mm Hg	140±4	123±4*	144±3	130±4*	132±2	118±3*	139±2	126±2*	<0.001, 0.02‡
Central PP, mm Hg	58±4	46±3*	59±2	53±3	51±3	38±4*	53±4	42±3*	<0.001, 0.02‡§
P1 height, mm Hg	42±3	36±3*	42±2	35±2*	37±2	30±2*	39±2	32±2*	<0.001, 0.1
PP amplification	1.33±0.08	1.35±0.06	1.24±0.03	1.17±0.02*	1.31±0.04	1.42±0.06	1.33±0.04	1.38±0.04	0.2, 0.03‡
MAP, mm Hg	104±2	96±2*	108±2	97±3*	102±2	97±2	109±2	102±2*	<0.001, 0.1
HR, bpm	71±3	73±3	67±2	57±3*	73±2	75±3	75±3	77±3	0.4, 0.001†‡§
AP, mm Hg	15±2	10±2*	17±2	19±2	14±2	8±2*	13±2	11±2	0.002, 0.02‡
AIx, %	25±3	20±4	29±2	34±2*	26±2	19±3*	25±3	24±3	0.2, 0.03†‡§
Aortic PWV, m/s	9.01±0.59	9.34±0.47	9.64±0.50	8.82±0.46	9.54±0.60	9.79±0.89	10.25±0.28	10.55±0.57	0.9, 0.4

Mackenzie et al, Hypertension 2009

Central BP lowering efficacy



Boutouyrie et al, Hypertension 2010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CAVITY PROTECTION
Great Regular Flavor
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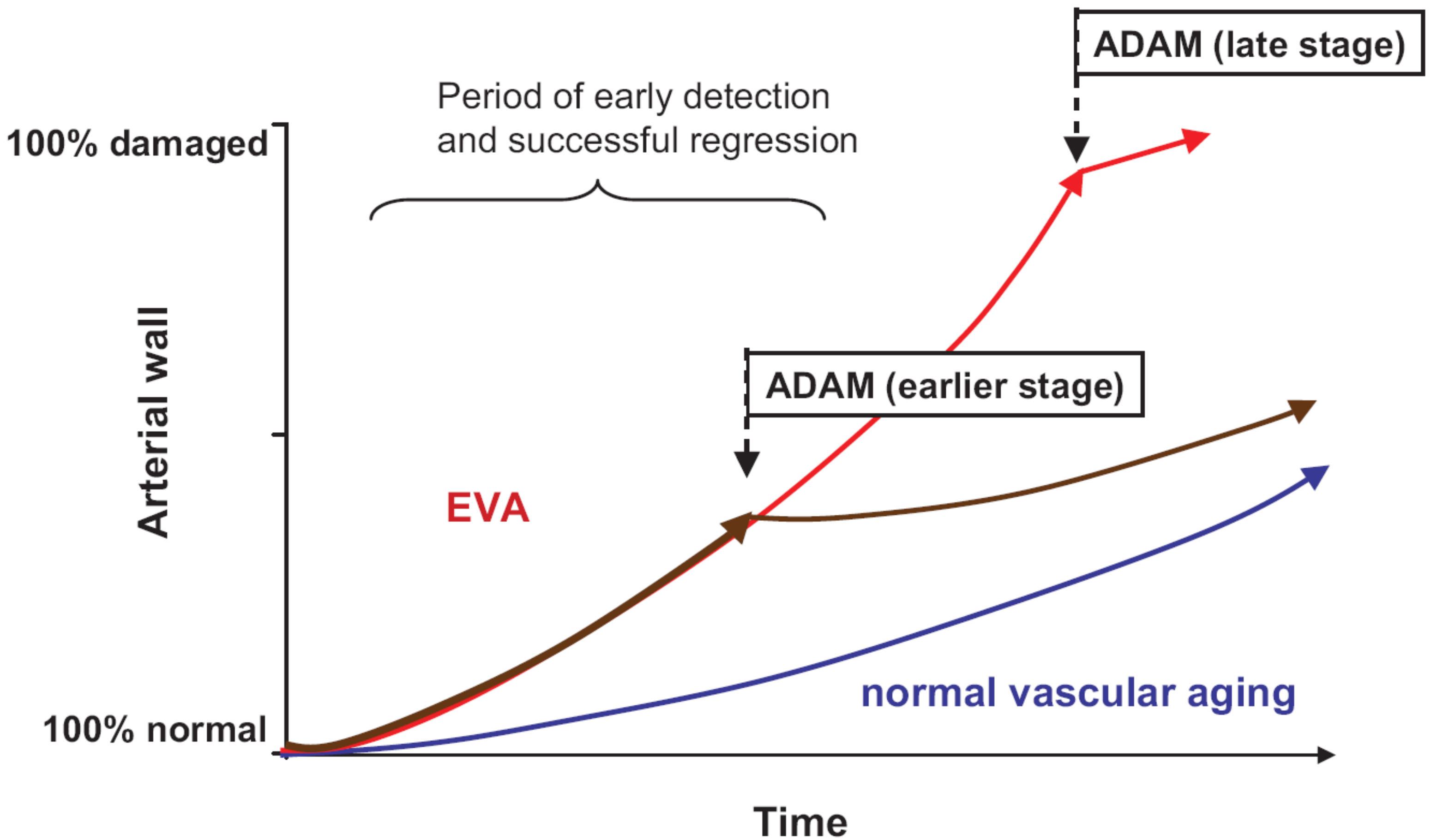
EVA & ADAM

EVA: Early vascular aging, ADMA: aggressive decrease of atherosclerosis modifiers



Nilsson, et al, Hypertension 2009

Thanks for your attention !