Early Detection of Damaged Organ

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  - Confirm the diagnosis of HT
    ambulatory blood pressure monitoring (ABPM)
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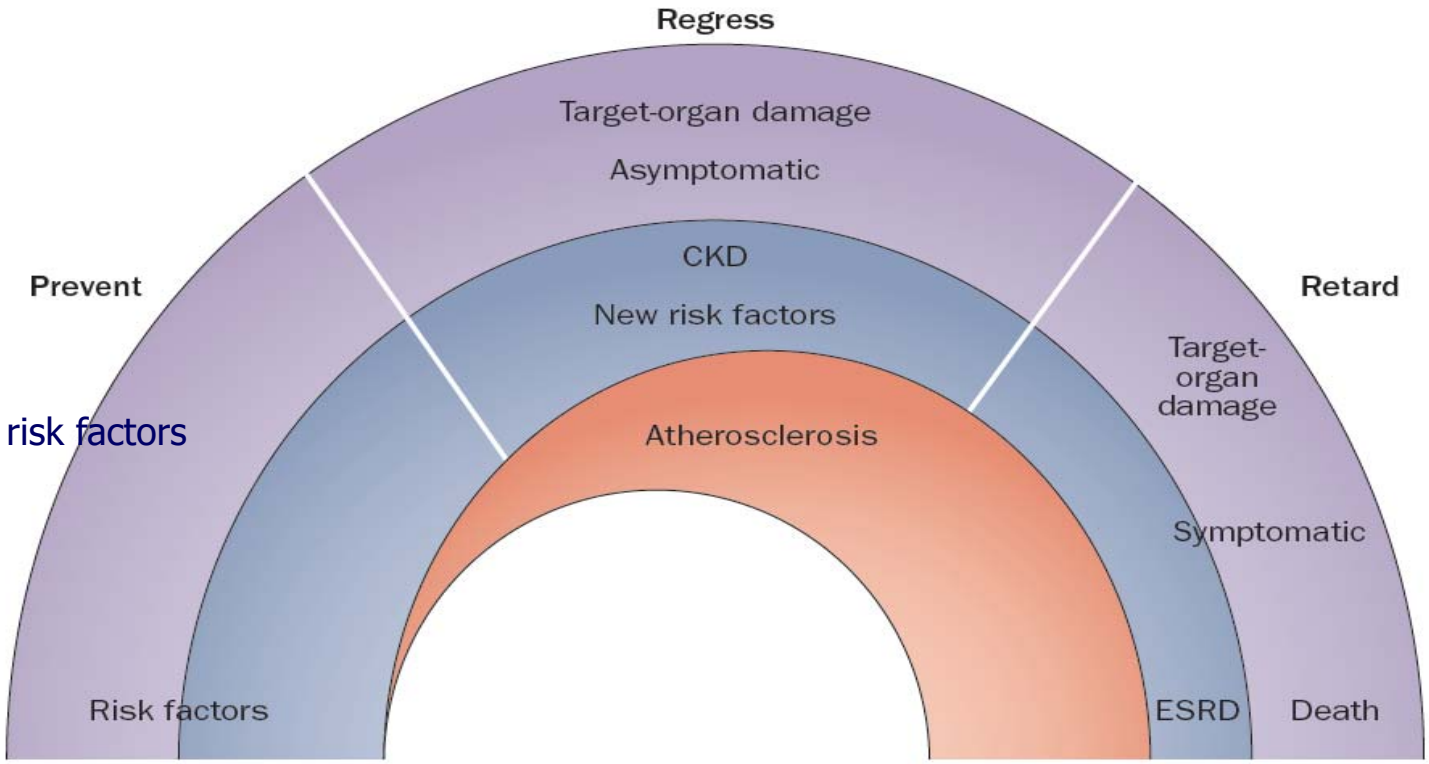
- Early detection of end organ damage
  - Pulse wave velocity (PWV)
  - Carotid intima-media thickness (CIMT)
  - Coronary artery calcification (CAC)

Cardiovascular (Cardiorenal) continuum

Cumulative burden of hypertension



[Ruilope LM, *Nat. Rev. Cardiol*. 2011]

Office vs 24h BP measurements in high-risk patients

BP Control: 24-h BP measurements < 130/ 80 mmHg

N=4,729

Office BP (mmHg)	% of patients with whose 24-h BP is actually controlled*		
	Patients with established CHD‡	Patients with history of stroke‡	Patients with diabetes mellitus‡
<120/80	88.4 (114 of 129)	82.9 (56 of 68)	81.8 (118 of 144)
120–129/80–84	75.6 (98 of 130)	73.2 (66 of 90)	74.3 (169 of 228)
130–139/85–89	65.1 (146 of 224)	59.7 (73 of 123)	57.1 (233 of 408)
140–159/90–99	45.2 (181 of 401)	43.0 (112 of 260)	43.2 (493 of 1,142)
≥160/100	25.3 (52 of 205)	23.7 (30 of 126)	22.3 (139 of 624)
Total	46.1 (502 of 1,089)	43.1 (287 of 667)	38.3 (975 of 2,546)

[J. R. *et al. Am. J. Med.* 2009]

NHS
National Institute for
Health and Clinical Excellence

clinic BP measurement

'Real' BP ?

Issue date: August 2011

Hypertension

Clinical management of primary hypertension in adults

This guideline partially updates and replaces NICE clinical guideline 34

NICE clinical guideline 127
Developed by the Newcastle Guideline Development and Research Unit and updated by the National Clinical Guideline Centre (formerly the National Collaborating Centre for Chronic Conditions) and the British Hypertension Society

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Diagnosing hypertension

- If the clinic blood pressure is 140/90 mmHg or higher, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension. **[new 2011]**
- When using ABPM to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00).
  Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension. **[new 2011]**
- When using home blood pressure monitoring (HBPM) to confirm a diagnosis of hypertension, ensure that:
  - for each blood pressure recording, two consecutive measurements are taken, at least 1 minute apart and with the person seated **and**
  - blood pressure is recorded twice daily, ideally in the morning and evening **and**
  - blood pressure recording continues for at least 4 days, ideally for 7 days.

  Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of hypertension. **[new 2011]**

Updated recommendation in NICE guideline 2011

Diagnosing hypertension

- If Clinic BP ≥ 140/90 mmHg → offer ABPM to confirm the diagnosis of HT [new 2011]
- When using ABPM to confirm a diagnosis of HT

  - at least 2 measurements/hr during the person's usual waking hrs (ie: 08:00 - 22:00)

  - use the average value of at least 14 measurements taken during the person's usual waking hours [new 2011]

- When using home blood pressure monitoring to confirm a diagnosis of HT, ensure that:

  - for each BP recording, two consecutive measurements are taken, at least 1 minute apart and with the person seated **and**

  - BP is recorded twice daily, ideally in the morning and evening **and**

  - BP recording continues for at least 4 days, ideally for 7 days

  Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of HT [new 2011]

Out-of-office monitoring in NICE guideline 2011

Does the use of HBPM or ABPM improve response to treatment ?

- Increasing use of HBPM and for the diagnosis of HT
- Few data of utility of HBPM or ABPM
  - monitoring BP control or indicators of clinical outcome in treated HT compared with clinic BP monitoring

NICE guideline 2011

CV death and ABPM vs HBPM vs Clinic BP

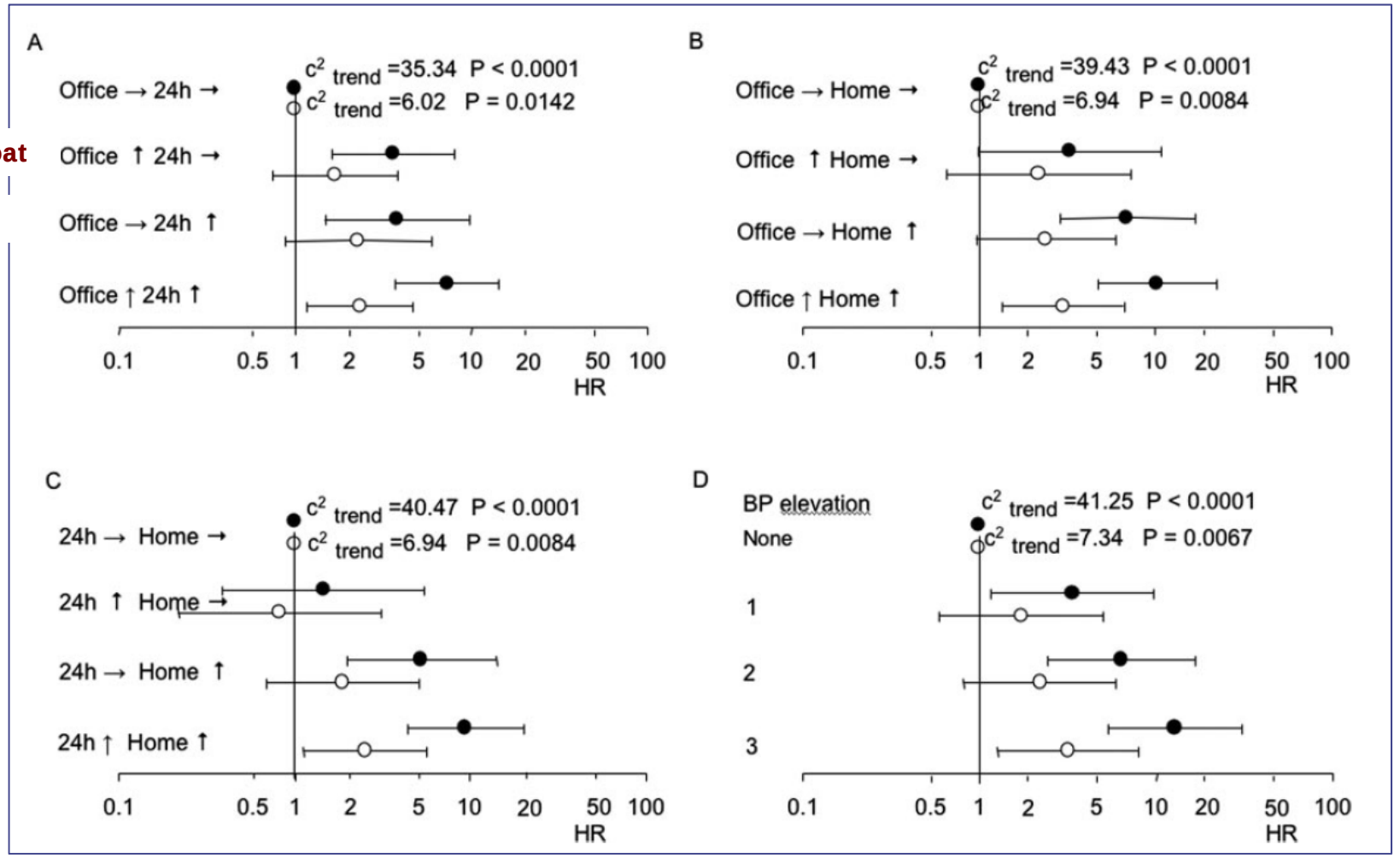
In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study

N= 2051, follow-up of 148 months

CV DEATHS

White-coat

Masked



[Mancia G et al, *Hypertension*. 2006]

Role of ABPM or HBPM on early detection of damaged organ

- Ohsama study: ABPM vs HBPM vs clinic BP
- HBPM: maximum home SBP
- Masked HT

Ambulatory vs home vs clinic blood pressure

Ambulatory Versus Home Versus Clinic Blood Pressure

The Association With Subclinical Cerebrovascular Diseases: The Ohasama Study

Azusa Hara, Kazushi Tanaka, Takayoshi Ohkubo, Takeo Kondo, Masahiro Kikuya, Hirohito Metoki, Takanao Hashimoto, Michihiro Satoh, Ryusuke Inoue, Kei Asayama, Taku Obara, Takuo Hirose, Shin-Ichi Izumi, Hiroshi Satoh, Yutaka Imai

See Editorial Commentary, pp XX–XX

Abstract—The usefulness of ambulatory, home, and casual/clinic blood pressure measurements to predict subclinical cerebrovascular diseases (silent cerebrovascular lesions and carotid atherosclerosis) was compared in a general population. Data on ambulatory, home, and casual/clinic blood pressures and brain MRI to detect silent cerebrovascular lesions were obtained in 1007 subjects aged ≥55 years in a general population of Ohasama, Japan. Of the 1007 subjects, 583 underwent evaluation of the extent of carotid atherosclerosis. Twenty-four–hour, daytime, and nighttime ambulatory and home blood pressure levels were closely associated with the risk of silent cerebrovascular lesions and carotid atherosclerosis (all $P<0.05$). When home and one of the ambulatory blood pressure values were simultaneously included in the same regression model, each of the ambulatory blood pressure values remained a significant predictor of silent cerebrovascular lesions, whereas home blood pressure lost its predictive value. Of the ambulatory blood pressure values, nighttime blood pressure was the strongest predictor of silent cerebrovascular lesions. The home blood pressure value was more closely associated with the risk of carotid atherosclerosis than any of the ambulatory blood pressure values when home and one of the ambulatory blood pressure values were simultaneously included in the same regression model. The casual/clinic blood pressure value had no significant association with the risk of subclinical cerebrovascular diseases. Although the clinical indications for ambulatory blood pressure monitoring and home blood pressure measurements may overlap, the clinical significance of each method for predicting target organ damage may differ for different target organs. (***Hypertension***. **2012;59:00-00.)** • **Online Data Supplement**

Ambulatory vs home vs clinic blood pressure

Usefulness of ABPM, HBPM, clinic BP (CBP) to predict subclinical cerebrovascular dis.
- silent cerebrovascular lesions (SCLs), carotid atherosclerosis (CAS)

ABP, HBP, CBP and brain MRI to detect SCLs
- N= 1007 (aged ≥ 55 year-old) in a general population of Ohasama, Japan.

Evaluation of CAS extent : mean IMT > 0.9 mm or focal carotid plaque (+)
- N= 583 of 1007

ABPM
: daytime and nighttime - according to the diary
BP measurement- every 30 min

HBP - HEM701C (Omron Healthcare Co. Ltd, Japan)
: measured BP every morning within 1 h of waking in the sitting position
after an interval of rest of more than 2 min
record the results over a 4-week period

[Hara A et al, *Hypertension*. 2012]

Results

- 24 hr, daytime, nighttime ABP and HBP
  : closely associated with risk of SCLs and CAS (all P<0.05)

- Each of the ABP values : significant predictor of SCLs
  Nighttime BP: strongest predictor of SCLs

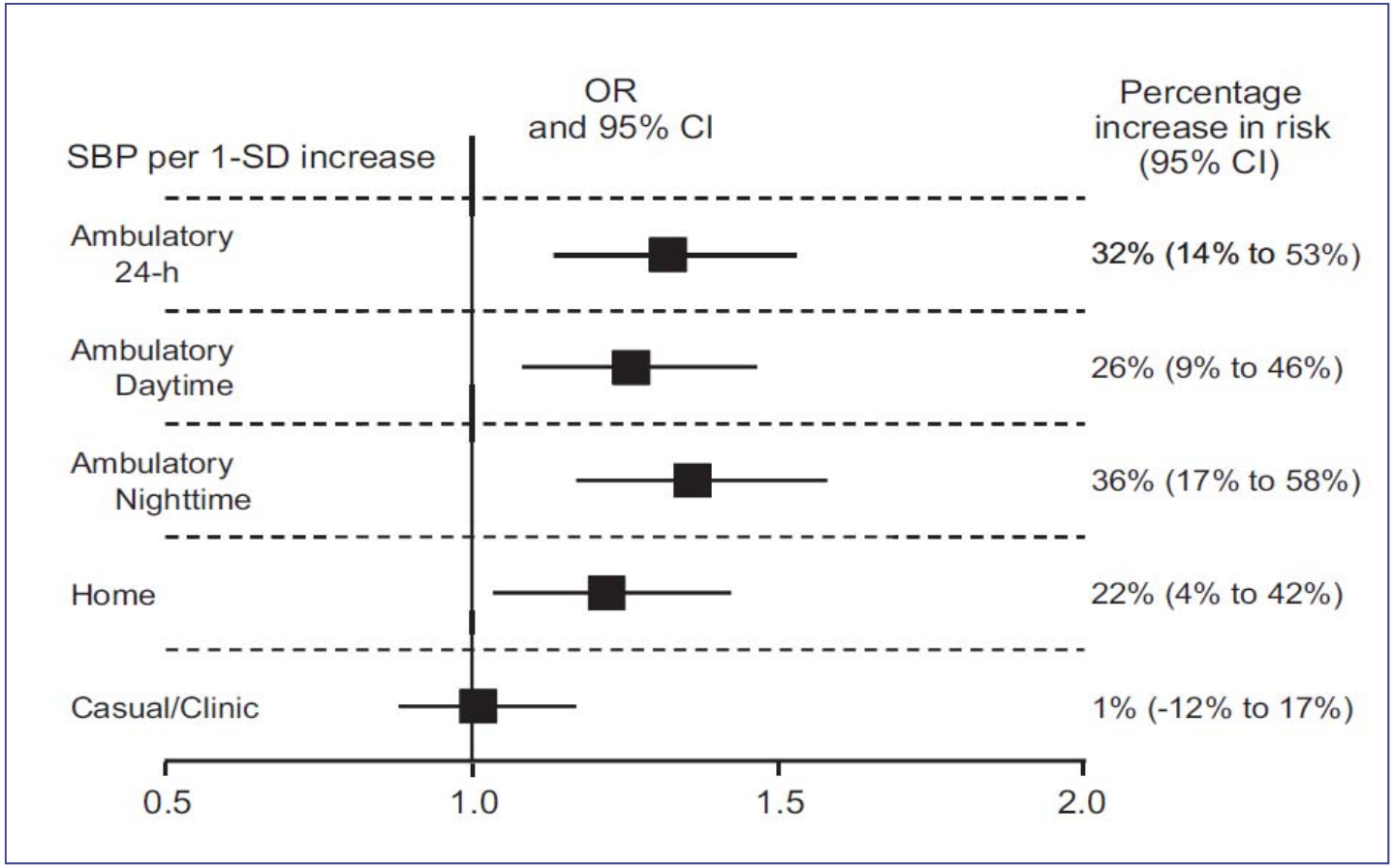
- HBP value : more closely associated with the risk of CAS

- CBP: no significant association with the risk of subclinical cerebrovascular dis

- Clinical significance of each method for predicting TOD
  - may differ for different target organs

[Hara A et al, *Hypertension*. 2012]

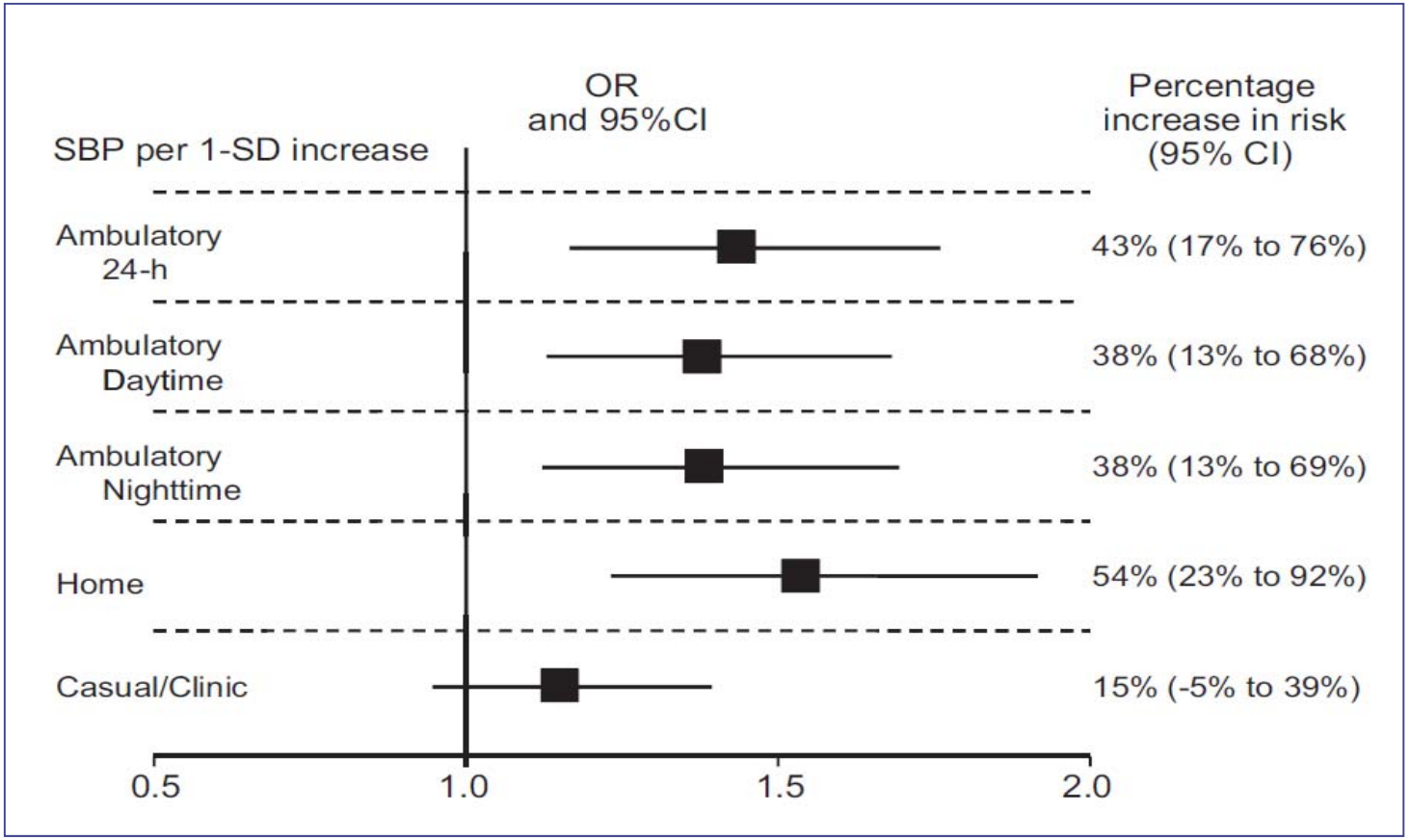
Risk of SCLs per 1-SD increase in SBP



Adjusted for age, sex, BMI, smoking, drinking status, anti-HT medication, and history of cardiovascular dis., hypercholesterolemia, or diabetes mellitus.

[Hara A et al, *Hypertension*. 2012]

Risk of carotid atherosclerosis per 1-SD increase in SBP



Adjusted for age, sex, BMI, smoking, drinking status, anti-HT medication, and history of cardiovascular dis., hypercholesterolemia, or diabetes mellitus.

[Hara A et al, *Hypertension*. 2012]

Strength of this Ohasama study

- First study

  compare ABP, HBP, CBP values for their associations with

  the risk of subclinical cerebrovascular dis. in a large general population

- Advantage of ABP and HBP over CBP measurements

  - absence of the white-coat effect

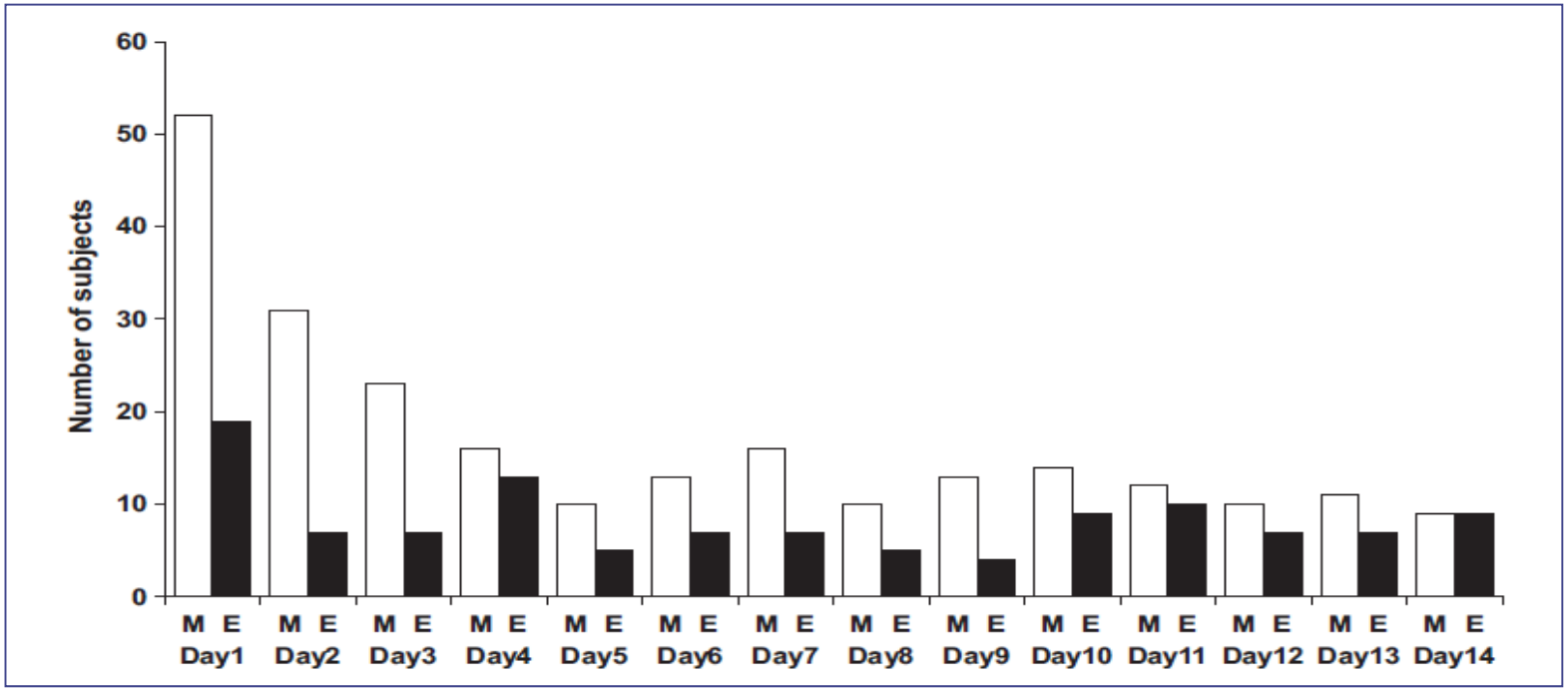
  - lack of digit preference & observer bias when automated devices are used

  - better correlation to target organ damage and prognosis

[Hara A et al, *Hypertension*. 2012]

Maximum value of home blood pressure

- Novel indicator of target organ damage in hypertension
  - n=356 (never treated hypertensives), age: 66.6± 11.0 year-old, M:F= 47:53



[Matsui Y et al, *Hypertension.* 2011]

Maximum home SBP and TOD

multivariate regression analyses between maximum home SBP and TOD

	Total Population (n=356)		Subgroup Analysis: Mean Home BP <135/85 mm Hg (n=135)		Subgroup Analysis: Mean Home BP ≥135/85 mm Hg (n=221)	
Dependent Variable	β (SE)	P	β (SE)	P	β (SE)	P
LVMI*, g/m^2	* age, sex, habitual drinking, mean office SBP adjusted					
Maximum home SBP, mm Hg	0.598 (0.094)	<0.001	0.512 (0.188)	0.007	0.655 (0.145)	<0.001
	Model R^2=0.32		Model R^2=0.21		Model R^2=0.24	
Carotid IMT†, mm	† age, sex, HT duration, DM, mean office SBP adjusted					
Maximum home SBP, mm Hg	0.003 (<0.001)	<0.001	0.003 (0.001)	0.006	0.003 (0.001)	<0.001
	Model R^2=0.27		Model R^2=0.26		Model R^2=0.24	
Log UACR‡, mg/gCr	‡ age, sex, DM, mean office SBP adjusted					
Maximum home SBP, mm Hg	0.004 (0.002)	0.02	0.001 (0.003)	0.68	0.003 (0.002)	0.18
	Model R^2=0.20		Model R^2=0.15		Model R^2=0.17	

Transient high BP readings at home - not noise,
: should be taken seriously as meaningful indicators for hypertensive TOD

[Matsui Y et al, 2011]

Masked hypertension

- Inverse of white-coat hypertension: masked hypertension
  : clinic BP <140/90 mmHg, and 24-h or home BP value above normal values

- First described by Pickering approximately 20 years ago

- Available data are consistent with regard to the prevalence, association with other risk factors, organ damage, and prognostic significance of masked HT

[Mancia G et al, *Nat. Rev. Cardiol*. 2011]

Masked HT: prevalence and patients at risk

- Prevalence of masked HT: about 9% in the whole population

  Sega, R. Circulation 2001, Mancia, G. Hypretension 2006

- Approximate 1/7 pt with normal clinic BP: to have elevated ABP or HBP

- Characterized by clinic BP are higher than those of normotensives

  Mancia, G. Hypretension 2006

- Demographic and clinical profile of pts who are prone to develop masked HT
  - young individuals (age <50 years)
  - pts with transiently elevated BP (particularly in stressful conditions)
  - Pts with high-normal clinic BP

[Mancia G et al, *Nat. Rev. Cardiol*. 2011]

Masked HT: pathogenesis

- Sustained activation of the sympathetic nervous system
  : impairment of baroreflex-mediated cardiovascular control
  that affects, in a fairly selective fashion, control of heart rate

  Grassi, G. Hypertension, 2007

- An increased reactivity to stressful stimuli

  Papadopoulos D J. Clin. Invest. 2007

- Smoking and excessive alcohol intake
  : via adrenergic activation, endothelial dysfunction, or both

  Schnall PI ,Hypertension , 1992, Mann S J, JAMA 1991

- Mechanisms for normal BP in the clinic in combination with elevated BP load during 24-h or home BP measurement
  : still remain unknown

[Mancia G et al, *Nat. Rev. Cardiol*. 2011]

Masked HT: clinical importance

- Masked HT
  - clearly associated with a higher prevalence of organ damage
    (such as LVH, ↑ in carotid IMT)

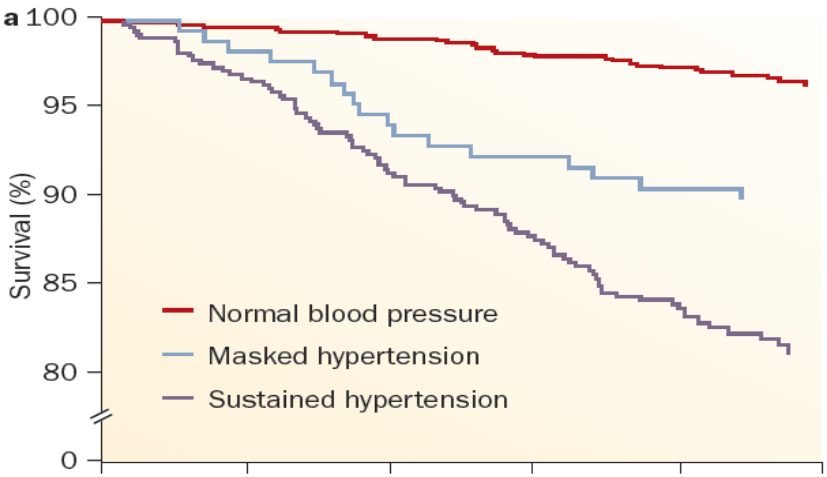
  - increased cardiovascular risk and all-cause mortality
    : RR- 1.5 (PAMELA study, Ohasama study)
    : masked HT= sustained HT (SHEAF study)

  - associated with increased prevalence and severity of metabolic risk factors
    and greater risks of developing sustained hypertension and diabetes

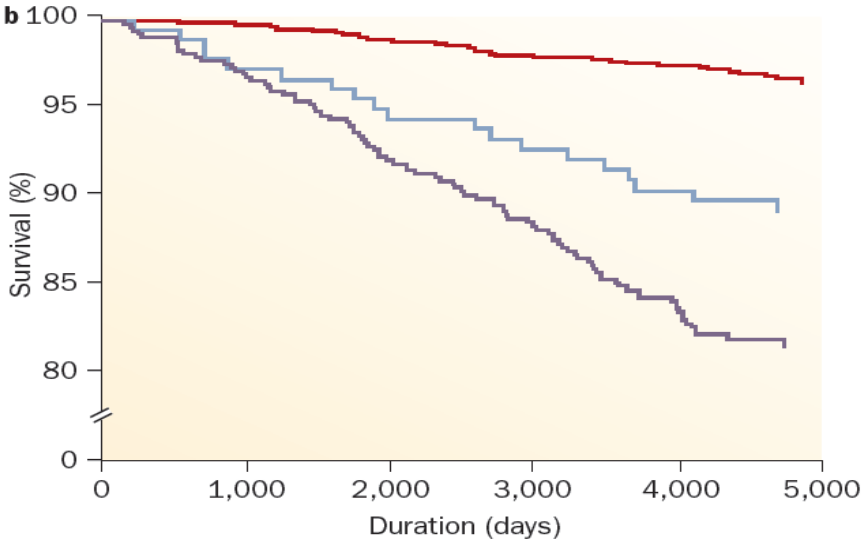
[Mancia G et al, *Nat. Rev. Cardiol*. 2011]

Survival: normotensives, masked HT, sustained HT

Clinic BP and 24h ABP



Clinic BP and Home BP



Verdecchia, P. et al . J. hypertensi 2001, Mancia G et al, Nat Rev Cardiol. 2011

Masked HT: clinical importance

- Detection: not easy in clinical practice
  - requires the collection of HBP or ABPM in all pts,
    even if normotensives in the clinical setting.

- One practical suggestion: to suspect the presence of masked HT
  - despite normal clinic BP values, pts with the presence of end-organ damage

- In these patients, performance of home or 24-h ambulatory blood-pressure monitoring is highly recommended.

Summary-I

- Potential role of ABPM or HBPM on early detection of TOD

  Recent data suggests

  HBPM or ABPM might be useful for

  early detection of TOD in HT compared with clinic BP monitoring

End organ damage in arterial hypertension

Vasculopathy
Endothelial dysfunction
Remodeling
Generalized atherosclerosis
Atheroscleortic stenosis
Aortic aneurysm

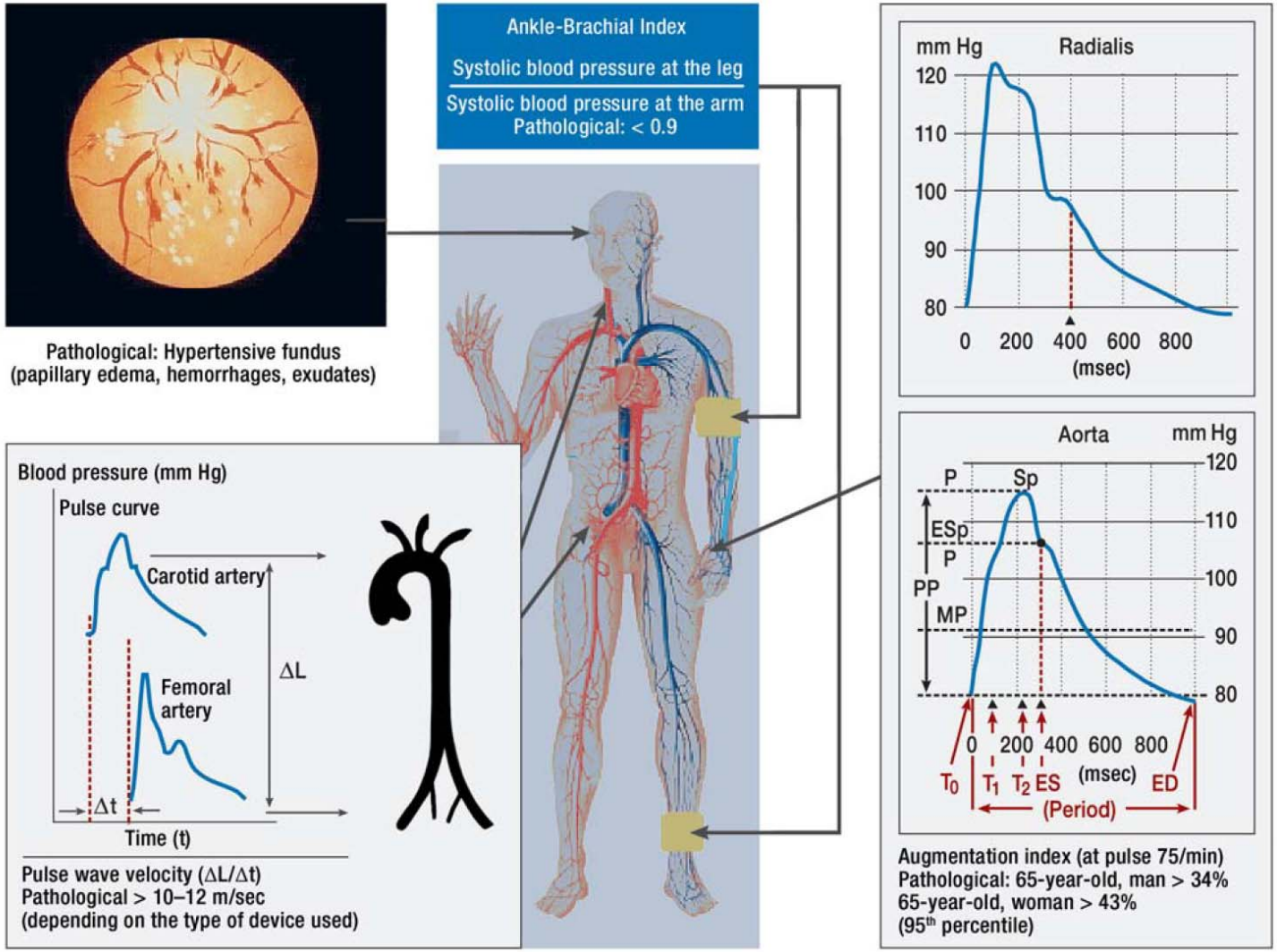
Cerebrovascular damage
Acute hypertensive encephalopathy
Stroke
Intracerebral hemorrhage
Lacunar infarction
Vascular dementia
Retinopathy

Heart disease
Left ventricular hypertrophy
Atrial fibrillation
Coronary microangiopathy
Coroanry heart disease, Myocardial infarction
Heart failure

Nephropathy
Albunimuria
Proteinuria
Chronic renal insufficiency
Renal failure

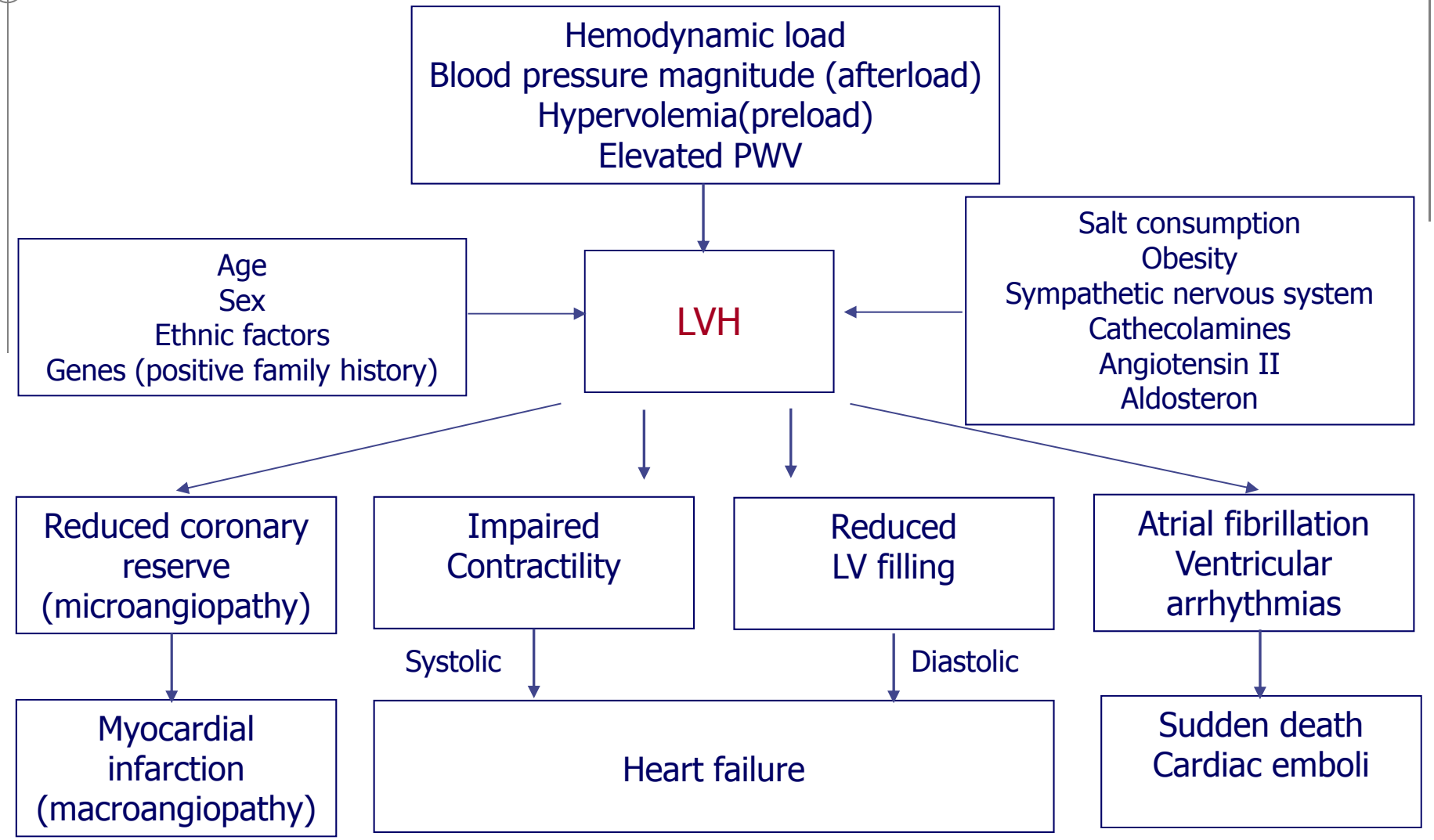
[Schmieder RE, 2010]

Generalized vasculopathy



[Schmieder RE, 2010]

Hypertensive heart disease



[Schmieder RE, 2010]

Diagnosis of early hypertensive end organ damage

Definitions of subclinical organ damage associated with HT: 2007 ESC guideline

Electrocardiographic left ventricular hypertrophy Sokolow-Lyon ≥ 38 mm, Cornell > 2440 mm×msec
Echocardiographic left ventricular hypertrophy LVMI ≥ 125 g/m^2 for men and ≥ 110 g/m^2 for women
Carotid intima-media thickness (Carotid IMT) > 0.9 mm or plaque
Carotid-femoral pulse wave velocity > 12 m/sec
Ankle-Brachial BP Index < 0.9
Serum creatinine elevated Men: 1.3–1.5mg/dl (115–33 µmol/l), Women:1.2–1.4mg/dl (107–24 µmol/l)
Elevated albumin excretion Microalbuminuria: 30–300 mg/24 hours, Albumin-creatinine ratio: men ≥ 22, women ≥ 31 mg/g creatinine
Low estimated glomerular filtration rate (< 60 ml/min/1.73 m^2) or creatinine clearance < 60 ml/min

[Mancia G et al, 2009]

PWV

Increased arterial stiffness: independent predictor of adverse CV outcomes
including mortality, MI, stroke, Af, cognitive decline, renal dysfunction

GENOA study cohort
N= 812, mean age: 58 years, F:58%, hypertensives: 71%

Burden of subclinical disease

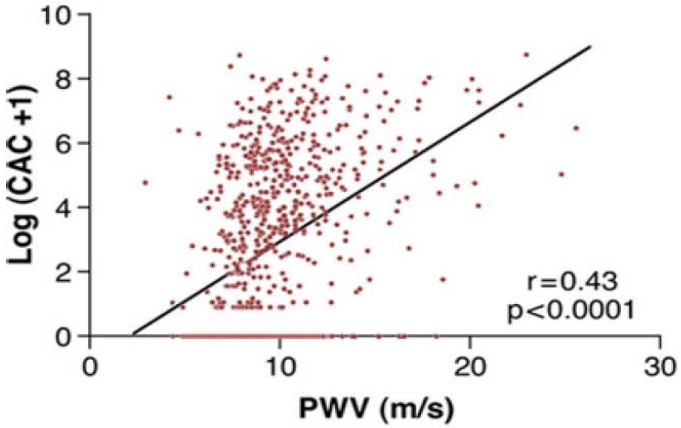
higher PWV (1 m/s increase) was significantly associated

with higher log (CAC+1)	($\beta \pm SE$ = 0.14±0.04 ; p=0.0003),
lower ABI	($\beta \pm SE$= -0.005 ±0.002;p=0.02),
greater log (WMH)	($\beta \pm SE$=0.03±0.009; p=0.002),
but not with log (UACR±1)	(p= 0.66)

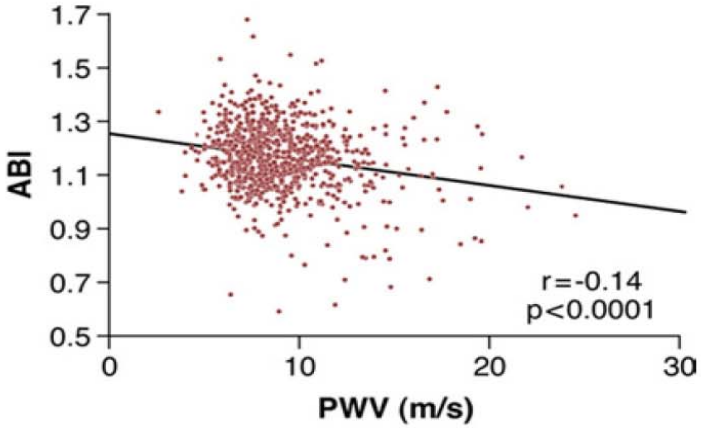
[Coutinho T et al, 2011]

Subclinical atherosclerosis and arteriosclerosis

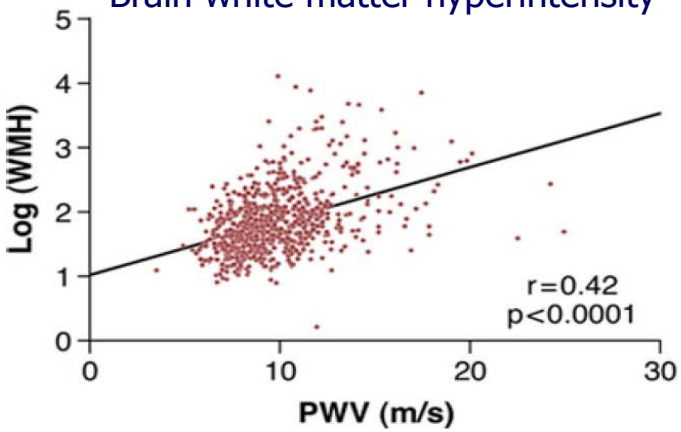
CAC: coronary artery calcification



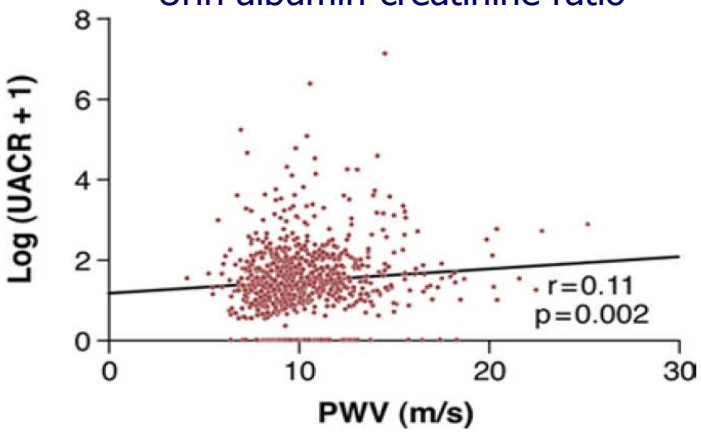
Ankle-brachial index



Brain white matter hyperintensity



Urin albumin-creatinine ratio



Higher aPWV was independently associated with greater burden of subclinical disease in coronary, lower extremity, and cerebral arterial beds.

[Coutinho T et al, 2011]

- Further prospective studies are needed
  - temporality of association b/t arterial stiffness and TOD

- Randomized clinical trials
  - improvement of arterial stiffness could prevent or slow the progression of TOD in HT patients

[Coutinho T et al, 2011]

CIMT and presence or absence of plaque improves prediction of CHD Risk

Baseline characteristics: Atherosclerosis Risk In Communities (ARIC) study, 1987-99
n= 13,415. mean age: 54.0 year-old, mean FU duration: 15.1 years

Traditional CV risk (TRF) vs add CIMT and pretense of plaque → improved CHD prediction ?

	Men (n = 5,682)	Women (n = 7,463)	Entire Sample (n = 13,145)
Age, yrs	54.42 (5.8)	53.75 (5.7)	54.0 (5.8)
Body mass index, kg/m^2	27.23 (4.0)	27.46 (5.8)	27.36 (5.1)
Systolic blood pressure, mm Hg	122.1 (17.7)	119.7 (19.1)	120.72 (18.6)
Diastolic blood pressure, mm Hg	75.5 (11.2)	71.9 (10.9)	73.46 (11.2)
Total cholesterol, mg/dl	210.2 (39.4)	217.0 (42.1)	214.0 (41.1)
Triglycerides, mg/dl	130.4 (67.0)	117.1 (60.5)	122.9 (63.7)
HDL cholesterol, mg/dl	45.3 (13.9)	58.2 (17.2)	52.6 (17.1)
LDL cholesterol, mg/dl	138.8 (37.2)	135.4 (40.2)	136.8 (39.0)
CIMT 25th percentile (unadjusted), mm	0.65	0.58	0.61
CIMT 75th percentile (unadjusted), mm	0.84	0.74	0.78
Fasting glucose, mg/dl	106.3 (28.0)	104.1 (32.6)	105.0 (30.7)
Whites	77.7%	72.6%	74.8%
Diabetes mellitus	10.3%	10.0%	10.1%
Current tobacco use	27.6%	25.0%	26.1%
Former tobacco use	43.2%	22.48%	31.5%
Cholesterol-lowering medication use	2.3%	2.6%	2.4%
Aspirin use (%)	41.1%	49.4%	45.8%
Statin use (%)	0.3%	0.6%	0.5%

[Nambi V et al, 2010]

Adjusted area under curve (AUC) for different model: Compared with with TRF-Only

Model	Overall	Men	Women
TRF only	0.742	0.674	0.759
TRF+CIMT	0.750 (0.005 to 0.012)	0.690 (0.009 to 0.022)	0.762 (−0.002 to 0.006)
TRF+plaque	0.751 (0.006 to 0.013)	0.686 (0.005 to 0.017)	0.770 (0.005 to 0.016)
TRF+CIMT+plaque	0.755 (0.008 to 0.017)	0.694 (0.011 to 0.027)	0.770 (0.005 to 0.017)
TRF+CIMT+plaque vs. TRF+IMT	(0.001 to 0.006)	(−0.001 to 0.006)	(0.003 to 0.012)
TRF+IMT+plaque vs. TRF+plaque	(0.001 to 0.005)	(0.002 to 0.011)	(−0.002 to 0.002)

AUC = area under the curve; CI = confidence interval; CIMT = carotid intima-media thickness; TRF = traditional risk factors.

[Folak JF et al, 2011]

Number and percent re-classfied in CHD risk category and observed CHD risk

- CIMT and plaque information added to TRF(traditional risk) prediction models

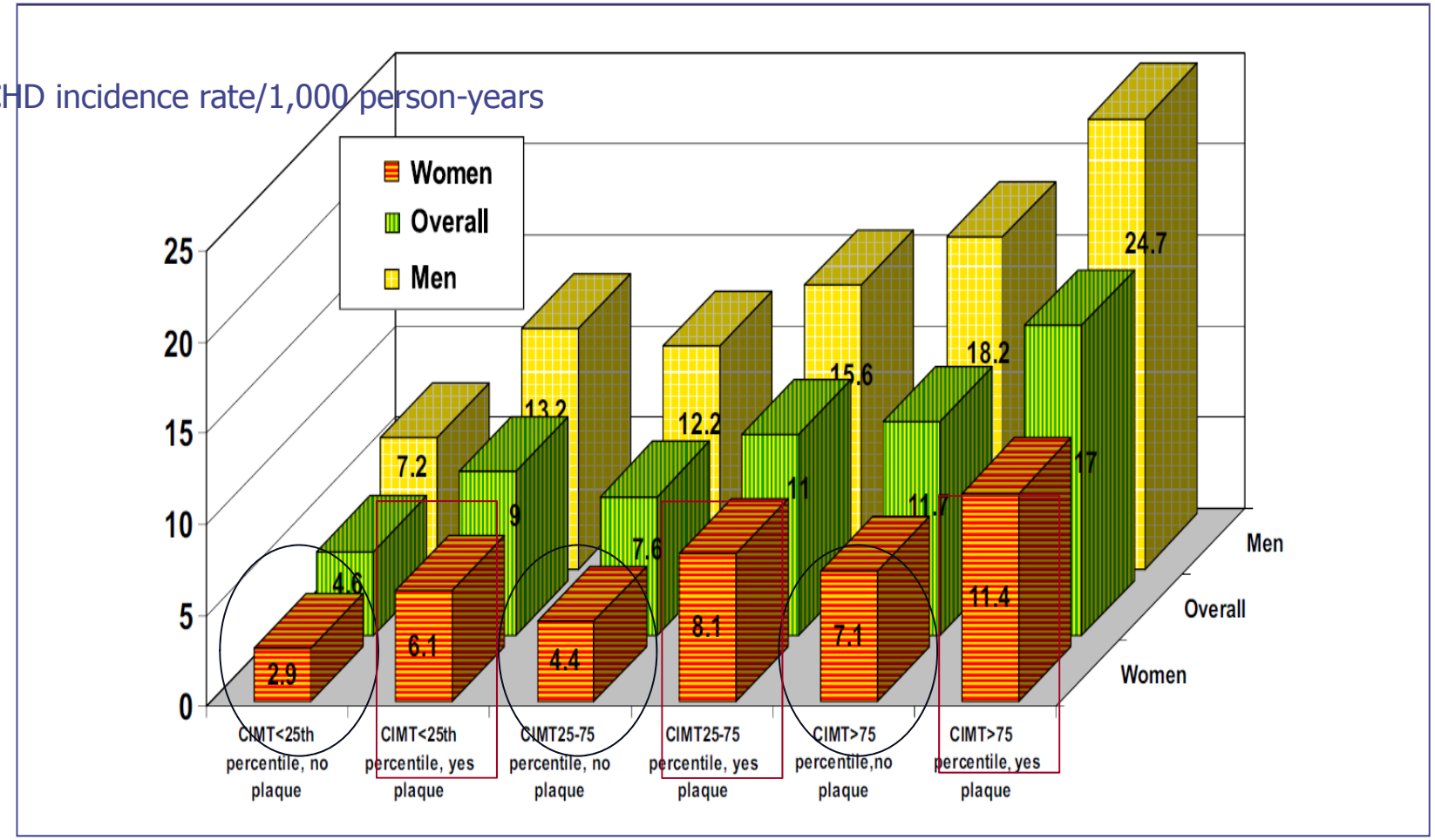
	CHD Risk by TRF + CIMT + Plaque				
CHD Risk by TRF Only	<5%	5%–10%	10%–20%	>20%	All
≤5%, low risk	5,305 (94.9)	287 (5.1)	0 (0.00)	0 (0.00)	5,592 (74.9)
	2	6	—	—	2
5%–10%, low-intermediate risk	316 (26.9)	704 (59.8)	157 (13.3)	0 (0.00)	1,177 (15.8)
	5	9	12	—	8
10%–20%, high-intermediate risk	0 (0.00)	132 (25.3)	321 (61.6)	68 (13.1)	521 (7.0)
	—	6	14	32	14
>20%, high risk	0 (0.00)	0 (0.00)	43 (24.9)	130 (75.1)	173 (2.3)
	—	—	8	37	30
All	5,621 (75.3)	1,123 (15.1)	521 (7.0)	198 (2.7)	7,463 (100.0)
	2	8	3	35	4

Values are n (%) and Kaplan-Meier 10-year risk (%). *All observed risks have been interpolated to 10-year event rates by Kaplan-Meier risk estimates using the actual observed events over a mean follow-up of 15.7 years.

Net reclassification index (NRI) in intermediate group

	Overall		Men		Women	
Model	NRI	Clinical NRI	NRI	Clinical NRI	NRI	Clinical NRI
TRF vs. TRF + CIMT	7.1 (2.2 to 10.6)	16.7 (9.3 to 22.4)	8.9 (3.4 to 15.1)	15.8 (8.6 to 24.6)	6.1 (−2.3 to 9.4)	15.9 (1 to 23.3)
TRF vs. TRF + plaque	7.7 (2.3 to 11.4)	17.7 (10.9 to 24.7)	4.2 (0.2 to 12.2)	10.5 (4.5 to 20.5)	10.2 (0.7 to 15.4)	25.6 (7.8 to 37.6)
TRF vs. TRF + CIMT + plaque	9.9 (3.8 to 13.5)	21.7 (13.4 to 28.2)	8.9 (4.1 to 17.1)	16.4 (9.5 to 27)	9.8 (1.1 to 15.4)	25.4 (9 to 37)
TRF + CIMT vs. TRF + CIMT + plaque	2.8 (−1.2 to 6.4)	10.6 (3.8 to 16.5)	0.03 (−2.6 to 6.3)	5.1 (0.3 to 13.2)	3.6 (−1.7 to 11.6)	12.8 (2.5 to 28.6)
TRF + plaque vs. TRF + CIMT + plaque	2.1 (−1.1 to 5.3)	7.9 (2.6 to 13.3)	4.8 (−0 to 10)	10.7 (4.3 to 19)	−0.3 (−3.7 to 3.6)	2.5 (−3.5 to 10.3)

CIMT and presence or absence of plaque improves prediction of CHD Risk



[Nambi V et al, 2010]

CIMT and Cardiovascular Events

Framingham Offspring Study cohort
N= 2965, mean FU: 7.2 years → CVD (+), n=296

mean IMT of common carotid artery, maximum IMT in internal carotid artery

Re-classification of CHD risk using 8-year Framingham risk score after adding IMT

Characteristic	No CVD at Follow-up (N = 2669)	CVD at Follow-up (N = 296)
Duration of follow-up — yr	7.5±1.7	4.6±2.8
Age — yr	57.3±9.5	62.9±9.5
Female sex — no. (%)	1501 (56.2)	128 (43.2)
Systolic blood pressure — mm Hg	126.8±18.4	136.8±19.2
Treatment for high blood pressure — no. (%)	598 (22.4)	126 (42.6)
Cholesterol — mg/dl		
Total	206.1±39.1	211.1±41.4
HDL	52.3±16.3	46.2±12.9
Diabetes — no. (%)	205 (7.7)	52 (17.6)
Cigarette smoking — no. (%)	377 (14.1)	64 (21.6)
Intima–media thickness†		
Mean CCA thickness — mm	0.59±0.13	0.66±0.15
Maximum ICA thickness — mm	1.30±0.79	1.90±1.00
ICA thickness >1.5 mm, indicating plaque — no. (%)	727 (27.4)	177 (59.6)

[Folak JF et al, 2011]

Hazard Ration for Cardiovascular disease

with and without Internal Carotid Artery (ICA) Intima–Media Thicknesses

Risk Factor	Model with Risk Factors Only		Model with Risk Factors and ICA Intima–Media Thickness		Model with Risk Factors and ICA Intima–Media Thickness >1.5 mm	
	Hazard Ratio or C Statistic (95% CI)	P Value	Hazard Ratio or C Statistic (95% CI)	P Value	Hazard Ratio or C Statistic (95% CI)	P Value
Sex, female vs. male	0.74 (0.57–0.95)	0.02	0.78 (0.61–1.01)	0.06	0.79 (0.61–1.02)	0.07
Age, per increase of 1 yr	1.05 (1.04–1.07)	<0.001	1.05 (1.03–1.06)	<0.001	1.04 (1.03–1.06)	<0.001
Systolic pressure, per increase of 1 mm Hg	1.01 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.002
Treatment for high blood pressure, yes vs. no	1.55 (1.21–2.00)	<0.001	1.51 (1.18–1.95)	0.001	1.47 (1.14–1.89)	0.003
Cholesterol, per increase of 1 mg/dl						
Total	1.00 (1.00–1.01)	0.02	1.00 (1.00–1.01)	0.03	1.00 (1.00–1.01)	0.03
HDL	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
Diabetes, yes vs. no	1.44 (1.06–1.97)	0.02	1.41 (1.03–1.92)	0.03	1.38 (1.01–1.88)	0.04
Cigarette smoking, yes vs. no	2.23 (1.67–2.98)	<0.001	2.10 (1.57–2.81)	<0.001	1.97 (1.47–2.64)	<0.001
ICA intima–media thickness						
Per increase of 1 mm			1.26 (1.16–1.36)	<0.001		
Per increase of 1 SD			1.21 (1.13–1.29)	<0.001		
Thickness ≥1.5 mm, representing plaque					1.92 (1.49–2.47)	<0.001
C statistic	0.748 (0.719–0.776)		0.758 (0.730–0.785)		0.762 (0.734–0.789)	

[Folak JF et al, 2011]

Net Reclassification Index

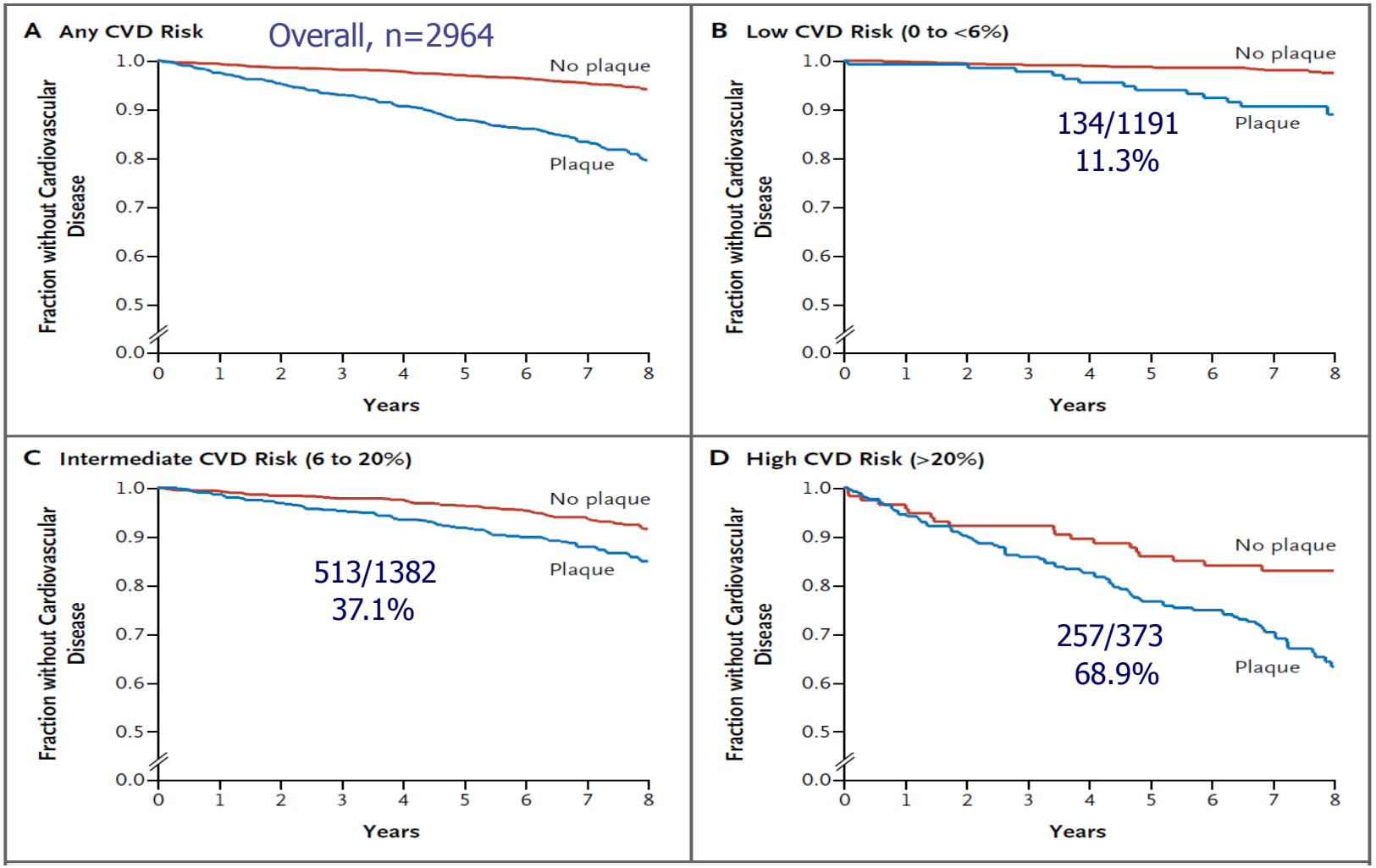
Reclassification of Framingham risk score categories after addition of IMT of ICA

Original Risk Category		Reclassification		
		Low Risk	Intermediate Risk	High Risk
		number of participants		
Participants without cardiovascular events		NRI : 1.8 %		
Low risk	< 6%	1125	31	0
Intermediate risk	6-20 %	85	1126	45
High risk	> 20%	0	40	234
Participants with cardiovascular events		NRI : 5.8 %		
Low risk	< 6%	27	8	0
Intermediate risk	6-20 %	1	112	13
High risk	> 20%	0	5	94

NRI: Overall 7.6 %, $p<0.001$

[Folak JF et al, 2011]

Plaque vs New onset CVD



[Folak JF et al, 2011]

Subclinical coronary atherosclerosis vs cardiovascular risk in different stages of HT

Population-based Heinz Nixdorf Recall Study cohort.
N= 4181, median FU: 7.18 years, Cross sectional longitudinal outcome study

115 primary end points (2.8%: fatal and nonfatal myocardial infarction)
152 secondary end points (3.6%: stroke and coronary revascularization)

cross-sectional relationship and longitudinal outcome
between JNC VII BP categories and coronary artery calcification (CAC)

[Erbel R et al, 2012]

Hazard Ratio of primary and secondary end points

JNC 7 BP categories compared with normotensives

JNC 7 Categories	Crude Estimate (95% CI)	Adjusted Estimate (95% CI), Model 1*	Adjusted Estimate (95% CI), Model 2†
Men			
Normotension	1.0	1.0	1.0
Prehypertension	1.45 (1.10–2.09)	1.23 (0.87–1.74)	1.22 (0.87–1.72)
Stage 1 hypertension	3.19 (2.17–4.69)	2.09 (1.44–3.02)	1.96 (1.36–2.83)
Stage 2 hypertension	5.33 (3.75–7.59)	2.95 (2.09–4.15)	2.74 (1.94–3.86)
Women			
Normotension	1.0	1.0	1.0
Prehypertension	1.93 (1.52–2.47)	1.49 (1.18–1.88)	1.42 (1.13–1.79)
Stage 1 hypertension	2.49 (1.87–3.31)	1.65 (1.25–2.18)	1.55 (1.17–2.04)
Stage 2 hypertension	4.88 (3.93–6.05)	2.80 (2.25–3.48)	2.51 (2.02–3.13)

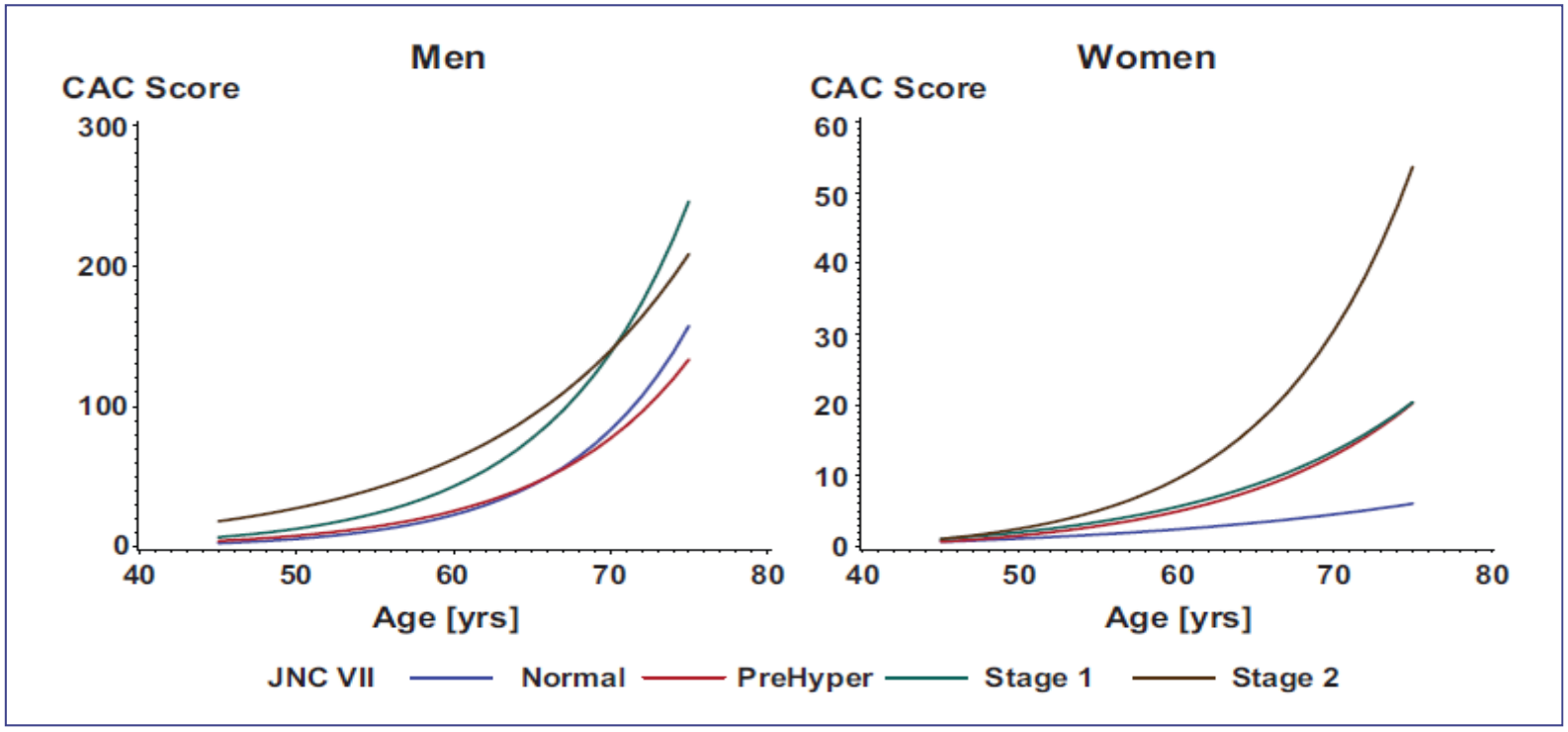
CAC indicates coronary artery calcification; JNC 7, Seventh Joint National Committee for Prevention Detection and Treatment of High Blood Pressure.

*Model 1 was adjusted for age.

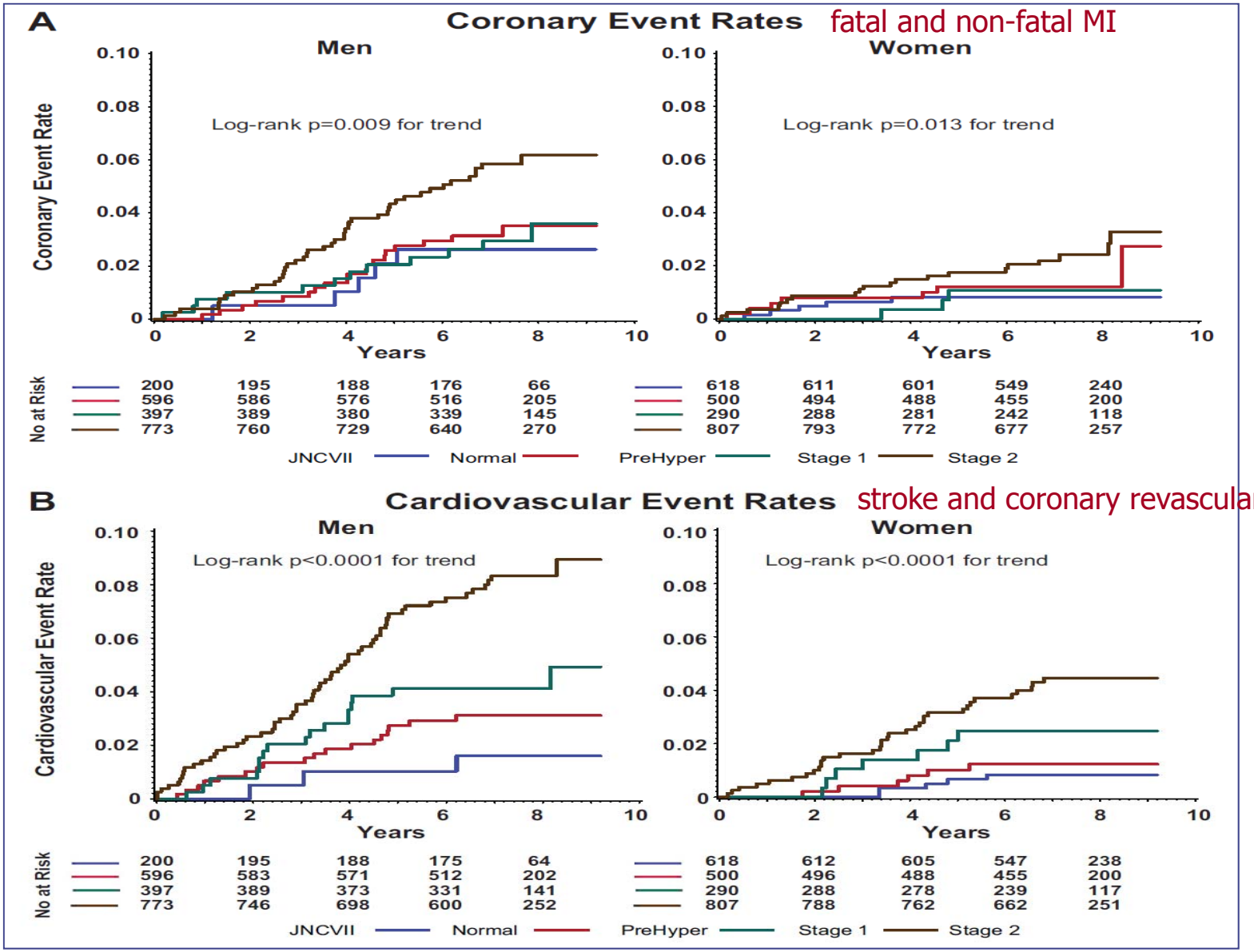
†Model 2 was adjusted for age, cholesterol, diabetes mellitus, and ever smoking.

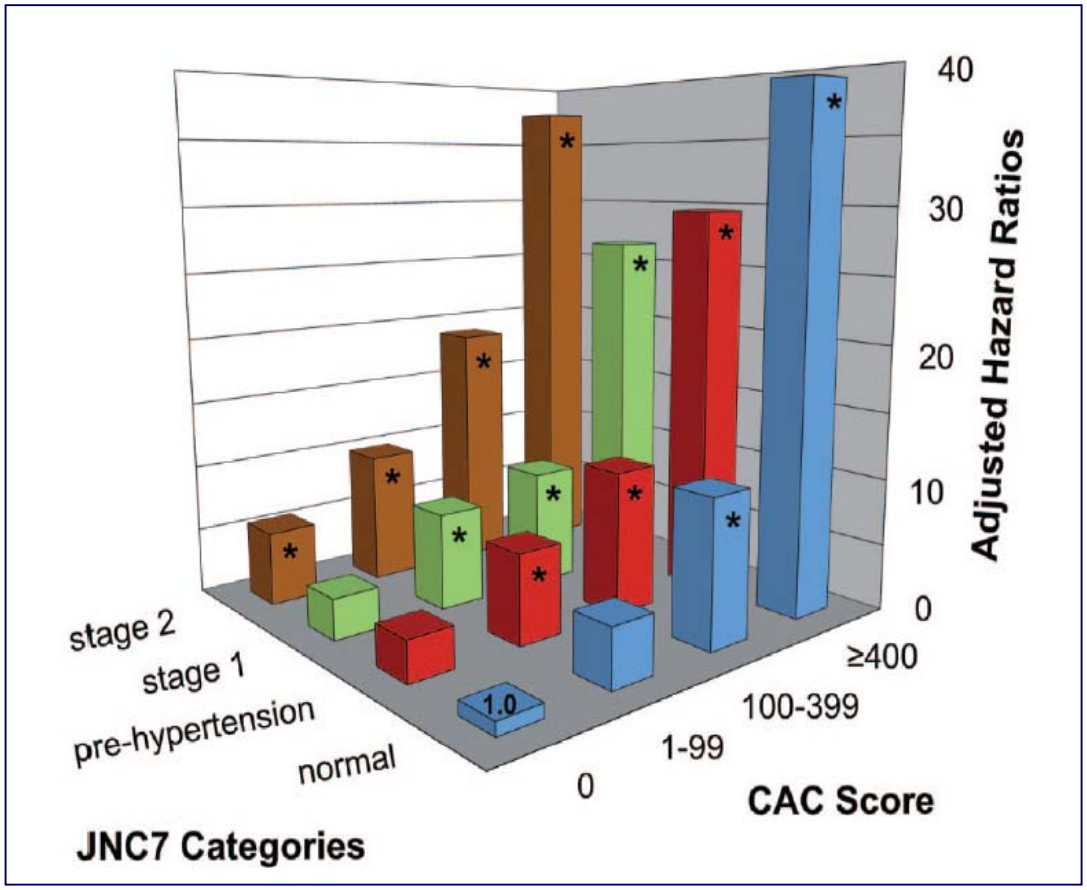
[Erbel R et al, 2012]

CAC score vs JNC VII BP categories



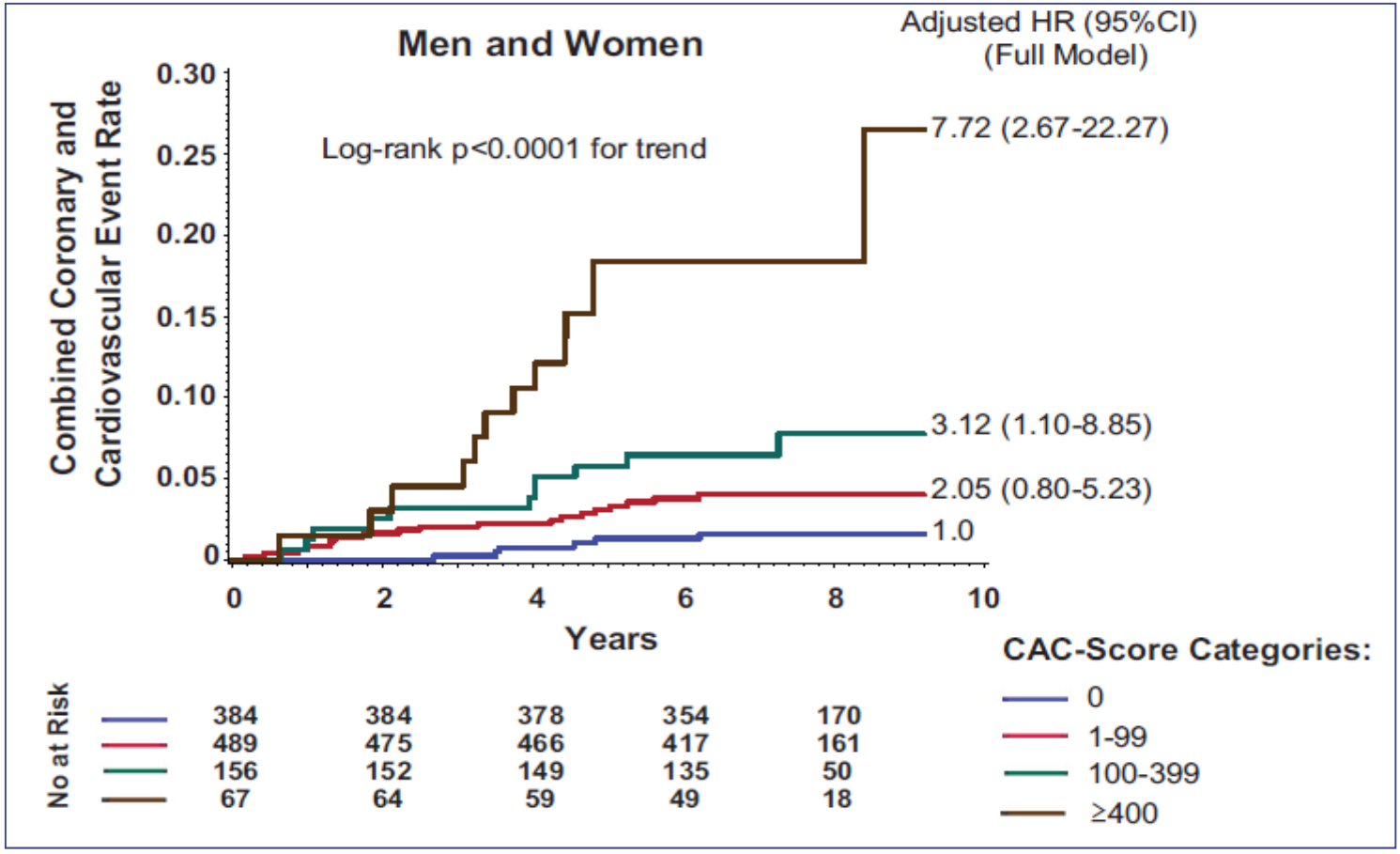
[Erbel R et al, 2012]


A
Coronary Event Rates
fatal and non-fatal MI
Men
Women
Coronary Event Rate
0.10
0.08
0.06
0.04
0.02
0
Log-rank p=0.009 for trend
Log-rank p=0.013 for trend
0 2 4 6 8 10
Years
No at Risk
200 195 188 176 66
596 586 576 516 205
397 389 380 339 145
773 760 729 640 270
618 611 601 549 240
500 494 488 455 200
290 288 281 242 118
807 793 772 677 257
JNCVII
Normal
PreHyper
Stage 1
Stage 2
B
Cardiovascular Event Rates
stroke and coronary revascularization
Men
Women
Cardiovascular Event Rate
Log-rank p<0.0001 for trend
Log-rank p<0.0001 for trend
Years
No at Risk
200 195 188 175 64
596 583 571 512 202
397 389 373 331 141
773 746 698 600 252
618 612 605 547 238
500 496 488 455 200
290 288 278 239 117
807 788 762 662 251
JNCVII
Normal
PreHyper
Stage 1
Stage 2



[Erbel R et al, 2012]

Combined Endpoint Event Rates in Prehypertension



Risk of myocardial infarction and stroke in HT but also in pre-HT depends on the degree of CAC

[Erbel R et al, 2012]

Summary-2

- PWV
  - independently associated with greater burden of subclinical disease in coronary, lower extremity and cerebral arterial beds.

- CMIT improves CHD risk prediction
  - adding plaque and CIMT to TRF
  - adding plaque and max. IMT of internal carotid artery

- CAC
  - cumulative event rates were determined by BP categories and CAC
  - risk of MI/ stroke in HT but also in pre-HT depends on the degree of CAC

Take home massage

- ABPM or HBPM
  - useful in early detection of TOD compared with clinic BP monitoring

- PWV, CIMT, CAC - useful biomarker of TOD

? Different clinical significance of each method for predicting TOD

- PWV : association with subclinical burden (cross-sectional study only)
- CIMT: useful for primary prevention (7.2 year, 10 year F/U data)
- CAC : useful in management for prehypertensives

Table 1. Baseline Characteristics of the Study Participants (n = 812 Unless Otherwise Specified)

	Mean/No.	± SD, %	Median (IQR)
Age, yrs	58.4	9.7	59.09 (51.10–65.33)
Men	344	42.4	
Body mass index, kg/m^2	30.3	5.8	29.60 (26.33–33.35)
Waist circumference, cm	99.6	156.0	99.3 (89.2–109.2)
Hypertension	577	71.1%	
Systolic blood pressure, mm Hg	130.9	16.3	129.00 (119.00–142.00)
Diastolic blood pressure, mm Hg	74.6	8.7	75.0 (69.0–80.0)
Total cholesterol, mg/dl	199.9	33.1	196.8 (127.0–394.5)
HDL cholesterol, mg/dl	52.7	15.5%	50.0 (24.9–115.3)
Statin use	217	26.72%	
Antihypertensive use	546	67.2%	
ACE inhibitor/ARB use	262	32.2%	
Calcium channel blocker use	104	12.8%	
Beta-blocker use	256	31.5%	
Diuretic use	291	35.8%	
Aspirin use	319	39.3%	
Diabetes	91	11.21%	
Smoking (past or current)	375	46.18%	
Estimated glomerular filtration rate, ml/min/1.73 m^2	65.0	13.3	65.2 (26.4–113.9)
Coronary artery calcification score (n = 791)	195.9	484.1	12.04 (0–144.60)
Ankle-brachial index (n = 773)	1.15	0.12	1.15 (1.01–1.23)
White matter hyperintensity volume, cm^3 (n = 638)	7.5	6.2	5.7 (4.3–7.9)
Urine albumin-creatinine ratio, mg/g (n = 760)	8.2	48.5	3.1 (0–1177.8)
Aortic pulse wave velocity, m/s	9.8	2.8	9.1 (7.90–10.98)
Coronary artery calcification present	492	60.6%	
Ankle-brachial index <0.9	27	3.3%	
White matter hyperintensity volume >5.7 cm^3	318	50%	
Urine albumin/creatinine ratio >10, mg/g	82	10.1%	

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

[Coutinho T et al, 2011]