Markers of subclinical cardiovascular disease in healthy postmenopausal women

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Cardiovascular disease is the leading cause of death in all continents

Member State

http://www.who.int

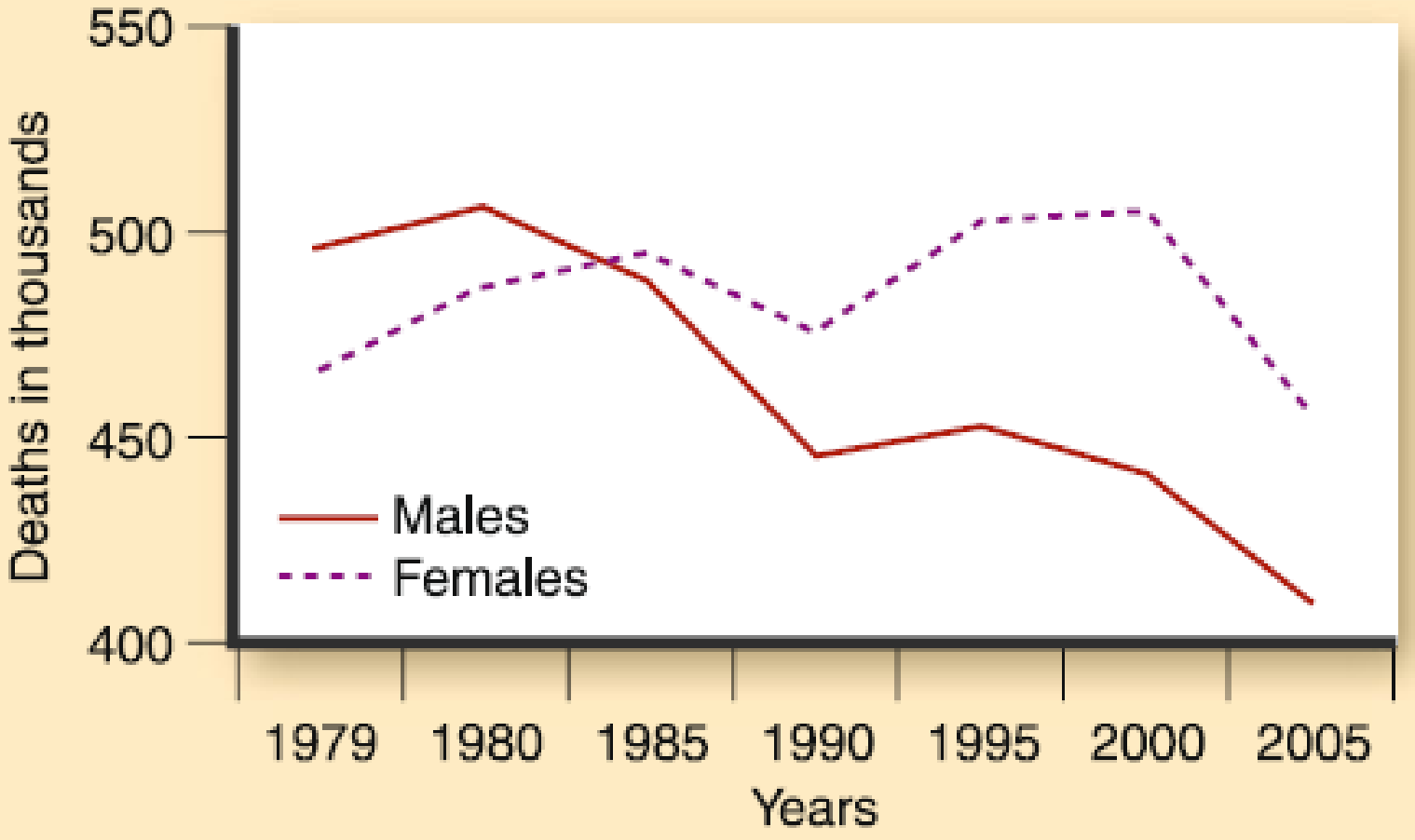
World Health Statistics 2009

World Health Organization

WHO REGION	Age-standardized mortality rates by cause [f,g] (per 100 000 population)			
	Non-communicable	of which: Cardio-vascular	Cancer	Injuries
	2004			
African Region	841	390	147	126
Region of the Americas	499	202	130	66
South-East Asia Region	701	365	107	131
European Region	590	332	142	79
Eastern Mediterranean Region	790	458	101	109
Western Pacific Region	557	243	139	68

CVD mortality

- Declined in men
- Continues to be high in women



Jennifer L. Jarvie • JoAnne M. Foody

Curr Cardiol Rep (2010) 12:488–496

Coronary artery disease mortality begins to increase 10 years after menopause and becomes higher compared to men

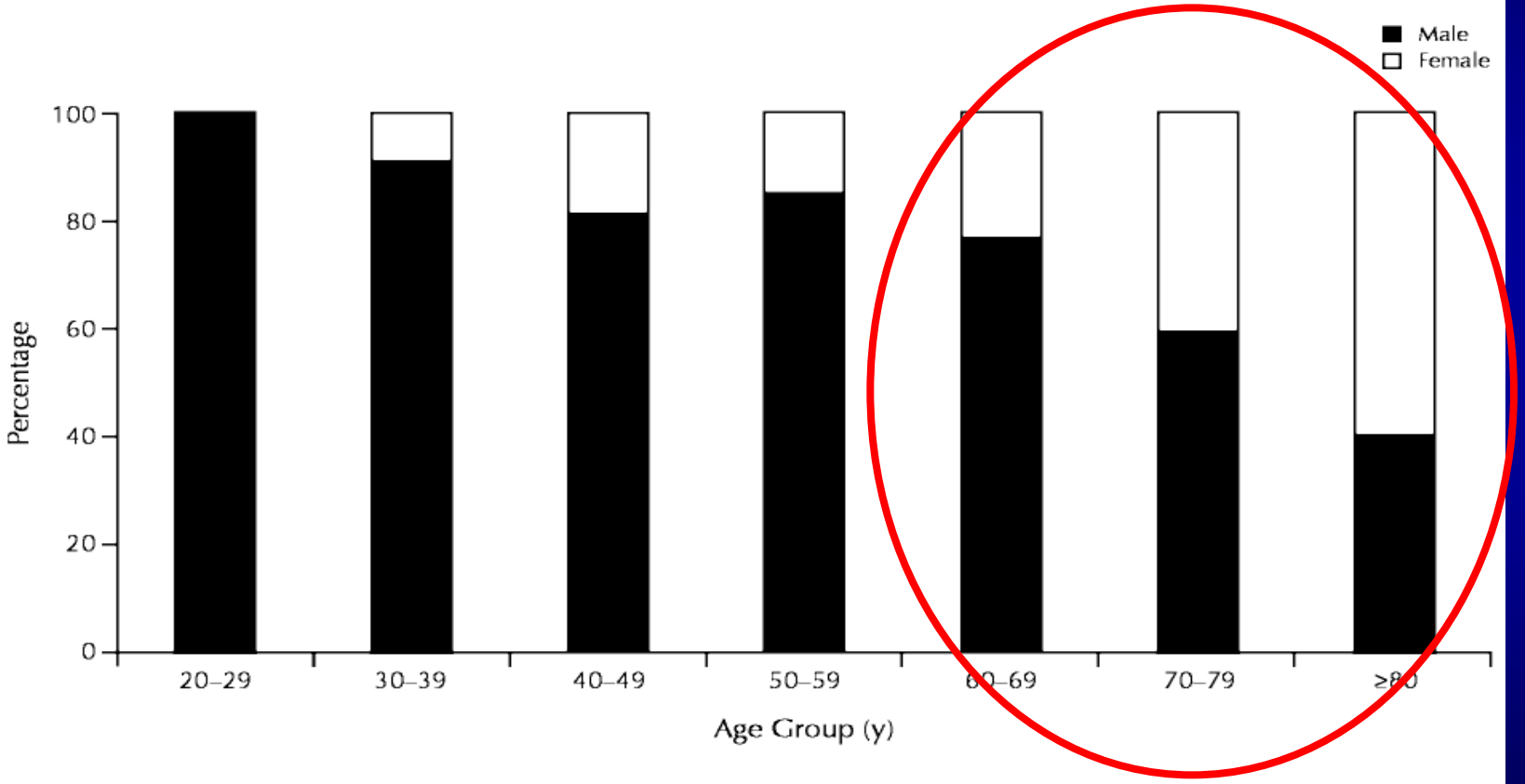


Figure 2. Sex distribution of mortality due to coronary heart disease, by age group, 2006. Reprinted with permission.[3]

Evangelista O et al, Gender Med 2009;6:17-36

CVD prevention is more effective in men than in women

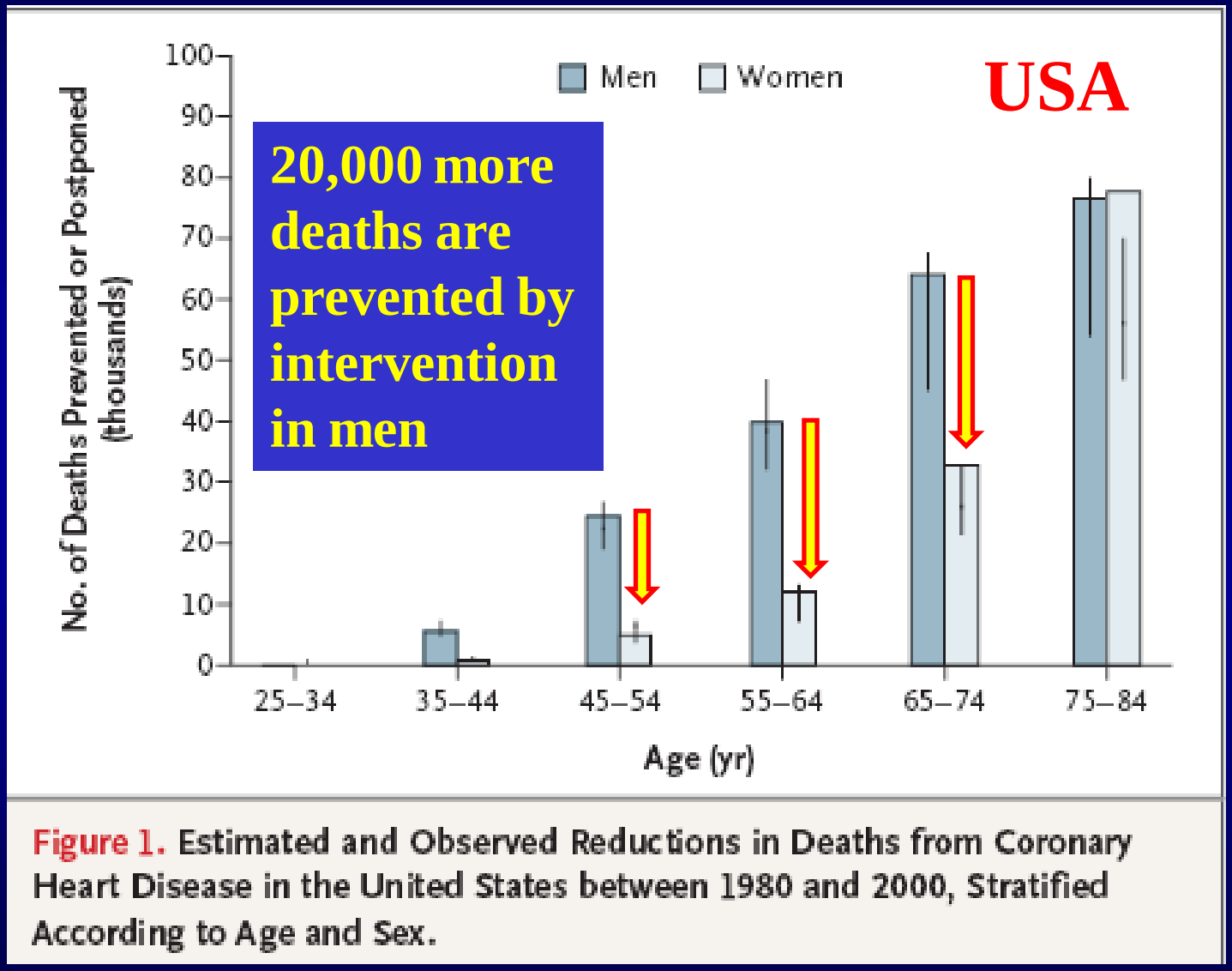


Figure 1. Estimated and Observed Reductions in Deaths from Coronary Heart Disease in the United States between 1980 and 2000, Stratified According to Age and Sex.

Ford ES et al, N Engl J Med 2007

Why cardiovascular mortality is higher in women compared to men?

1. Estrogen protection is lost after the menopause

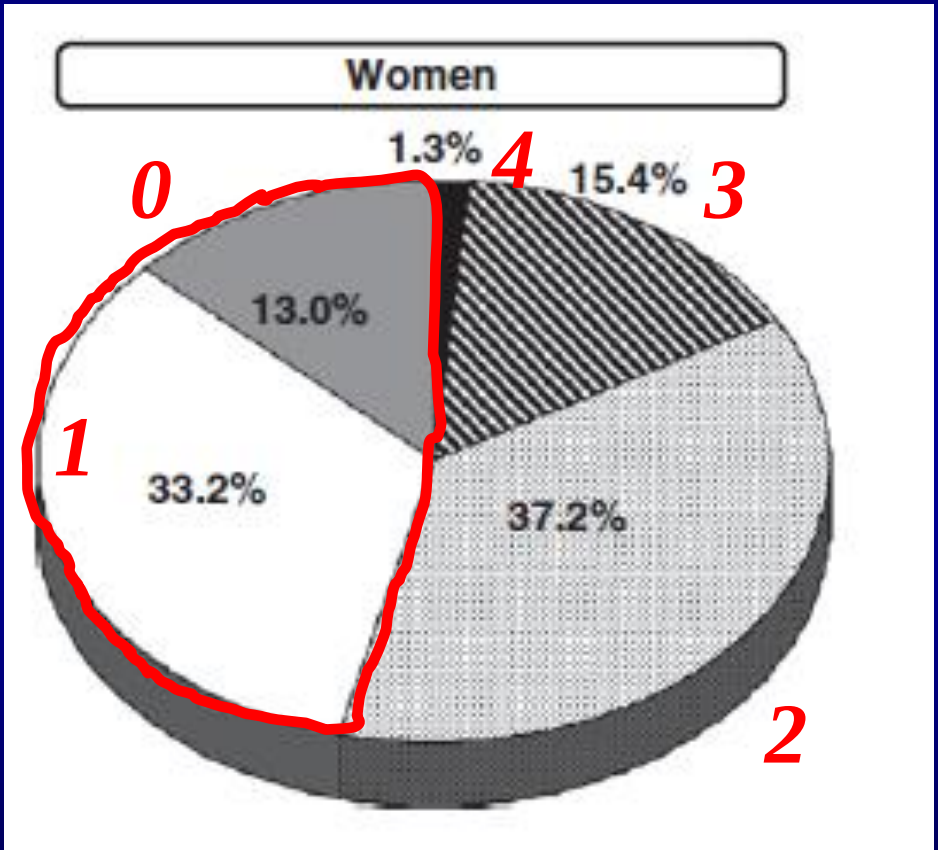
2. Traditional cardiovascular risk factors in CVD prediction models may not have the same impact in women

- Age
- Smoking
- Cholesterol
- Blood pressure

3. Primary prevention policies targeted to men

CVD prediction models are not accurate in women

50% of women with prevalent coronary artery disease had a "low risk" CVD profile



Number of traditional risk factors present in women with established CVD

Khot UN et al. JAMA 2003

- **Traditional risk factors can not accurately predict CVD risk in women**

➔ ***The best way to predict CVD risk is to identify the disease per se at an early stage***

Methods of assessing subclinical CVD disease

Non-invasive / U/S or CT-scan

- Intima Media Thickness (IMT)
- Atherosclerotic plaque
- Coronary artery calcium score (CACS)

→ Arterial structure

- Pulse Wave Velocity
- Ankle / Brachial index (ABI)

→ Arterial stiffness and blood flow

- Flow mediated dilation (FMD)

→ Endothelial function

Intima – media thickness

- Distance between inner echogenic line representing blood interface and outer echogenic line representing adventitial junction
- Normal: < 0.9 mm

Atherosclerotic plaque

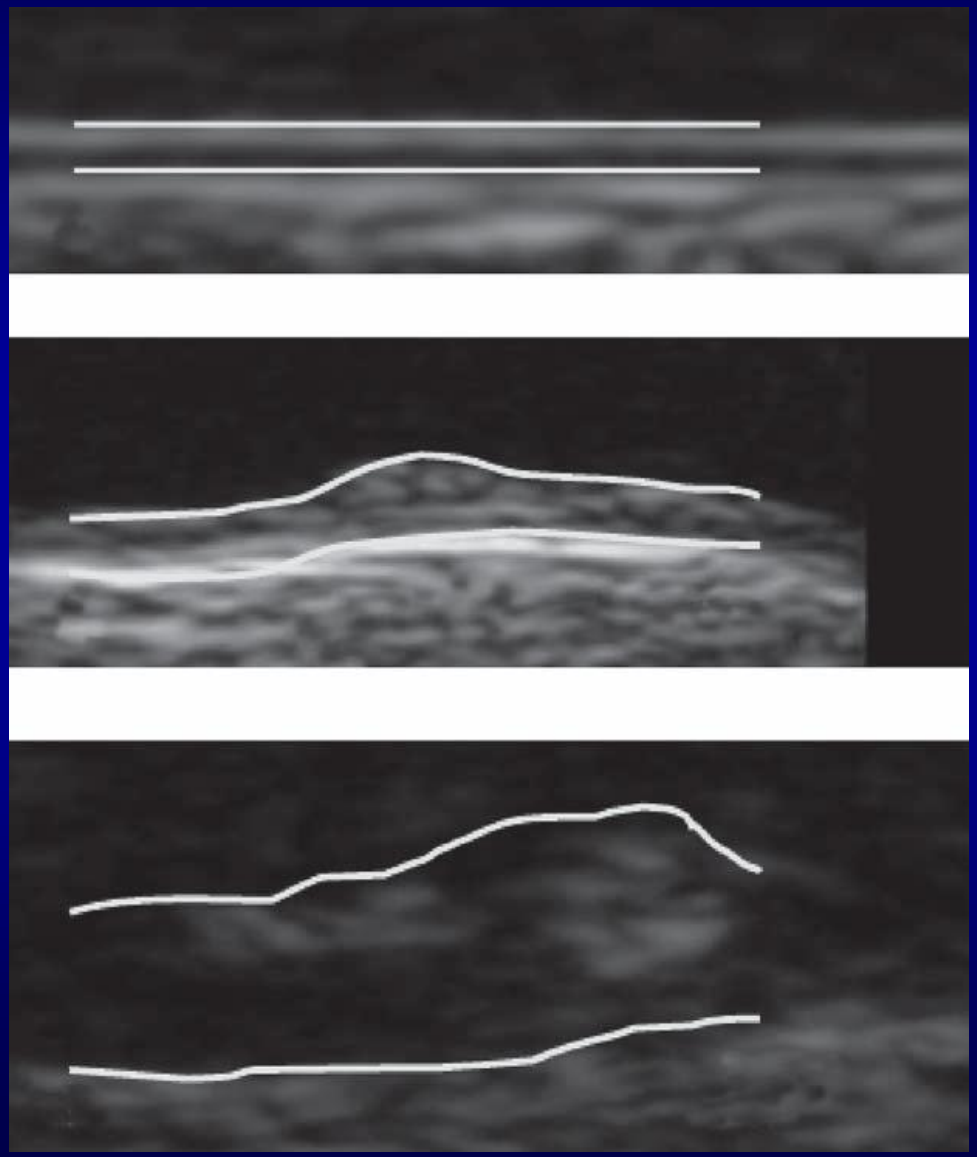
- Focal thickening of at least 0.5mm or IMT > 1.5 mm

Stages of Atheromatosis

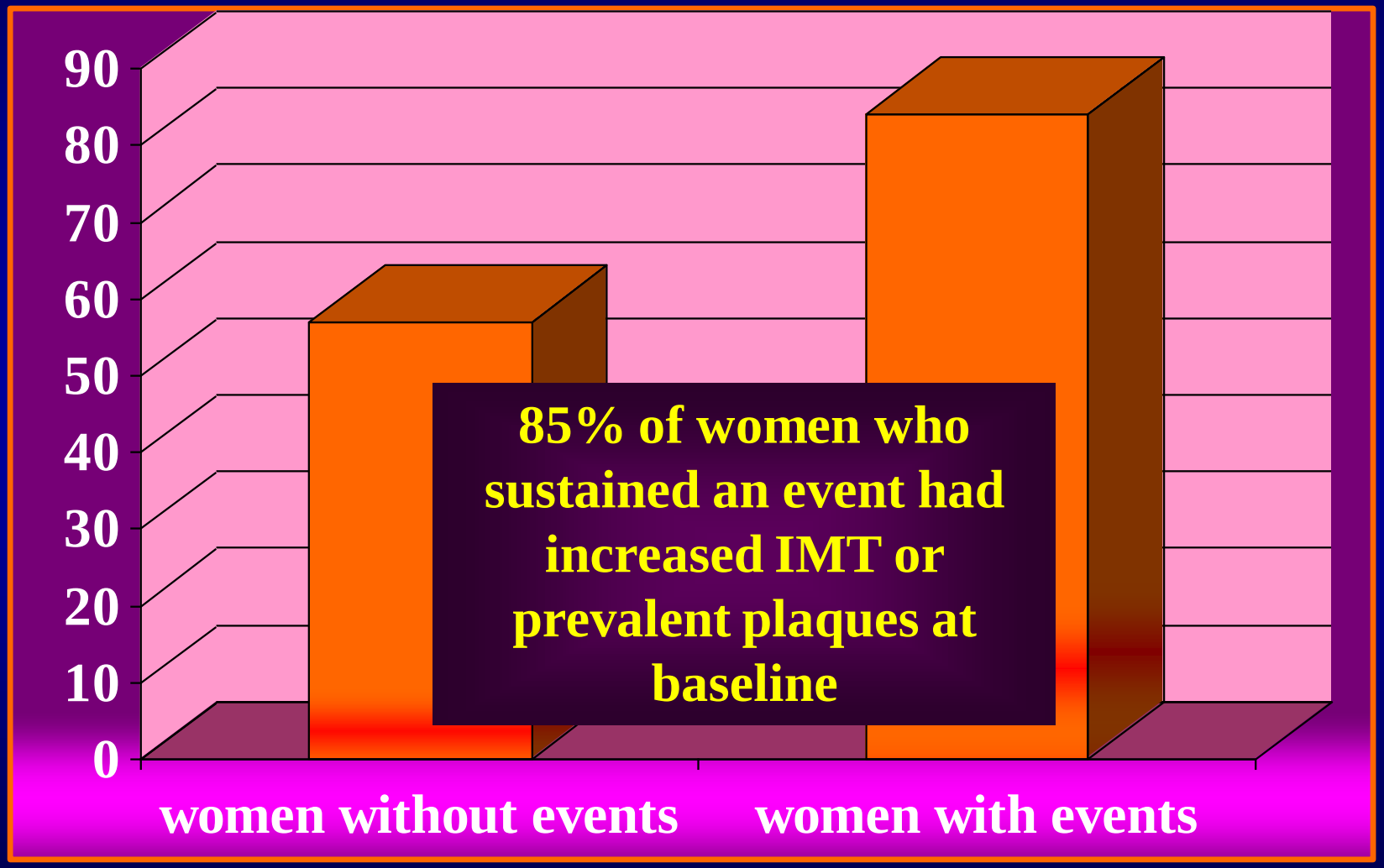
Normal IMT

Thick IMT

Atherosclerotic plaque

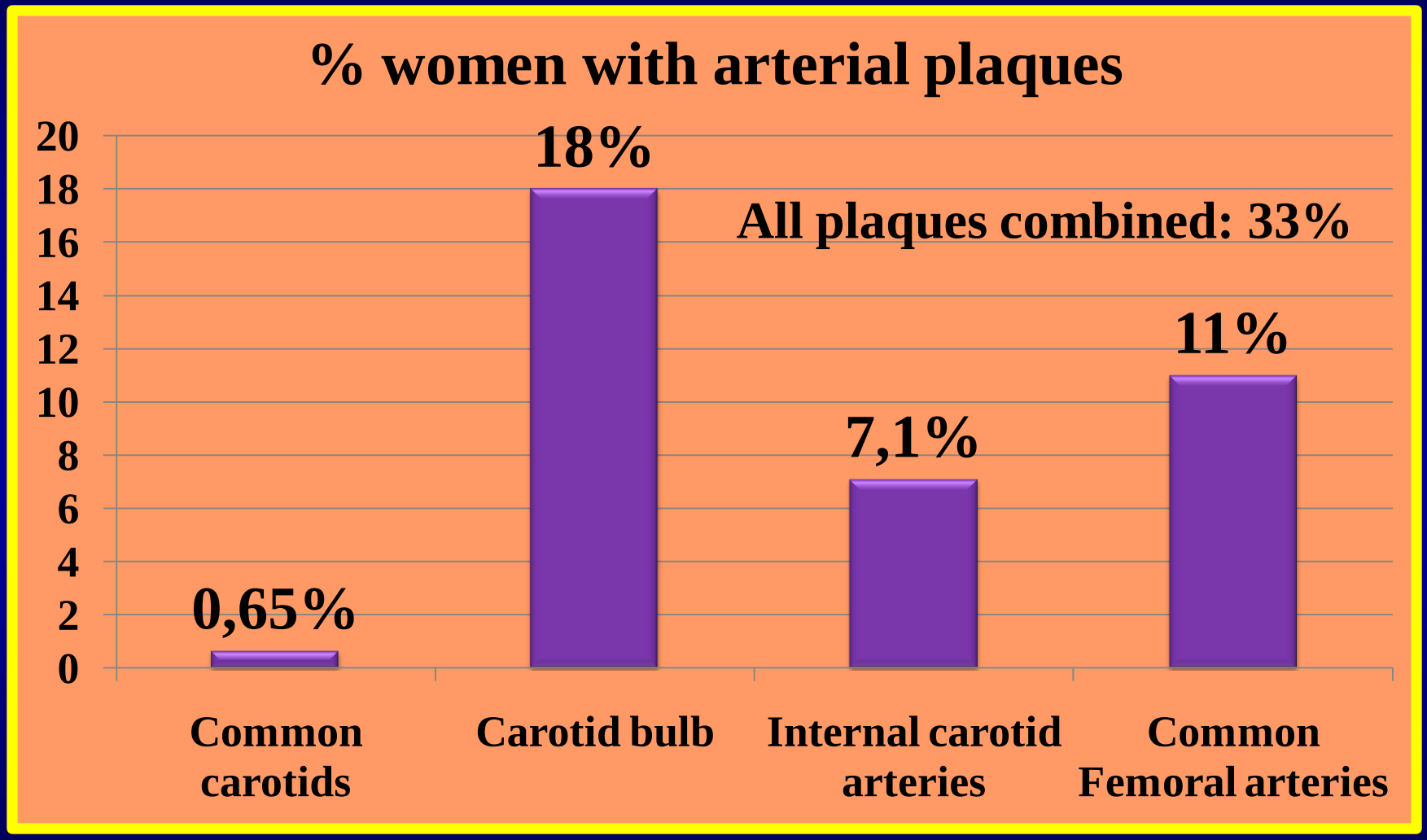


Increased IMT is a strong predictor of future cardiovascular events



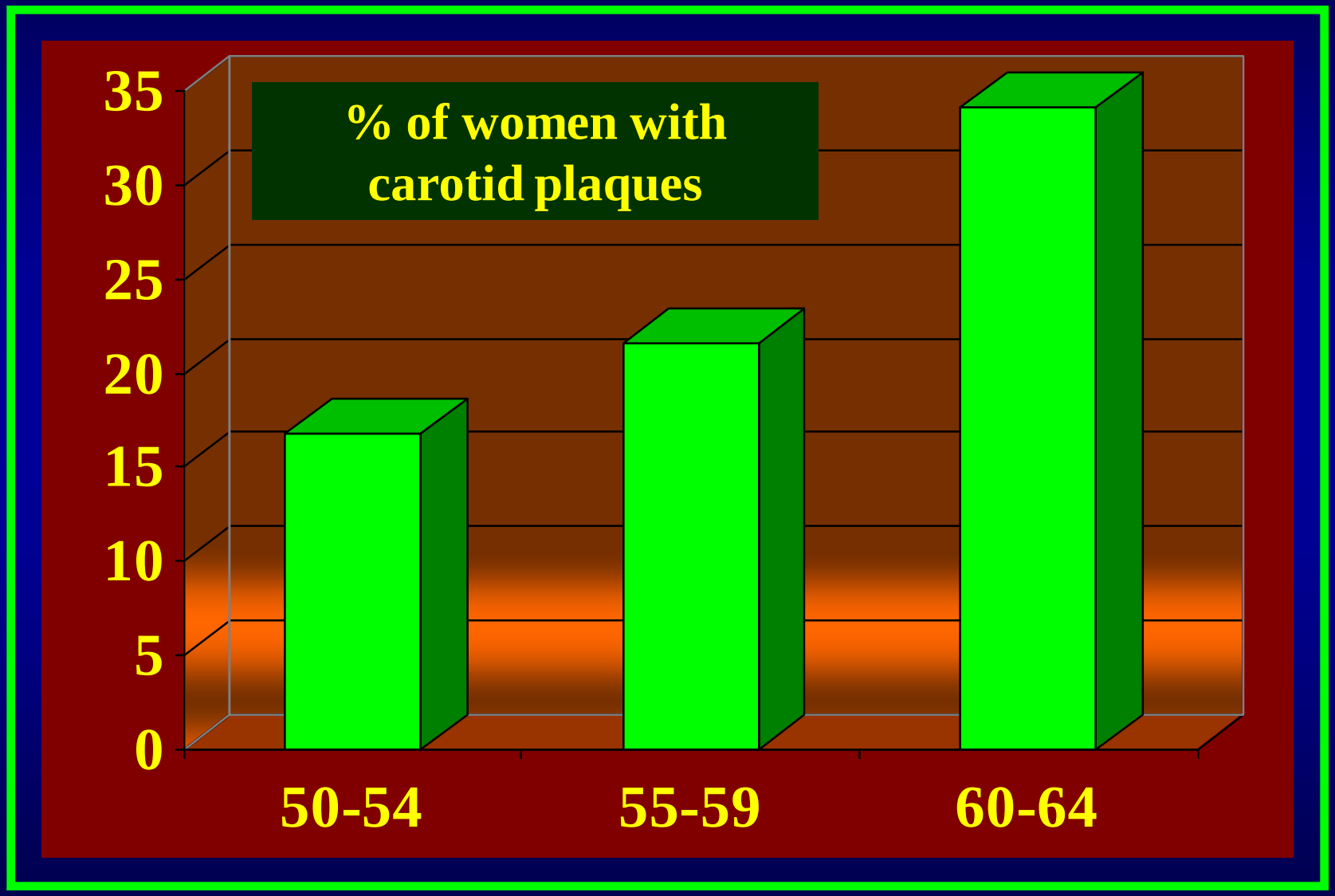
Corrado E et al, Menopause 2008;15:240

1 out of 3 healthy recently menopausal women has a carotid or femoral atherosclerotic plaque



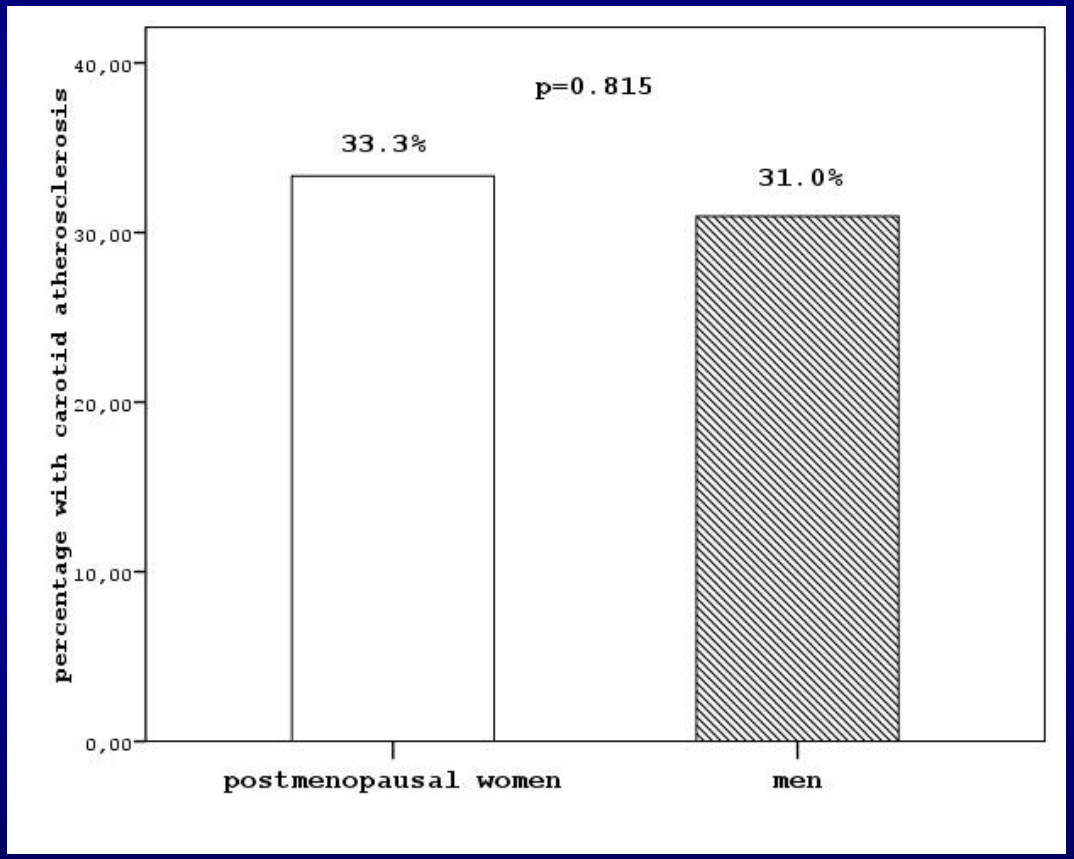
Lambrinoudaki I, Stamatelopoulos K et al, Metabolism (in press)

The prevalence of subclinical atherosclerosis increases rapidly after menopause



Yu RHY et al, Maturitas 2009;63:233

Healthy women within the first 10 years after menopause have the same prevalence of subclinical atheromatosis as men



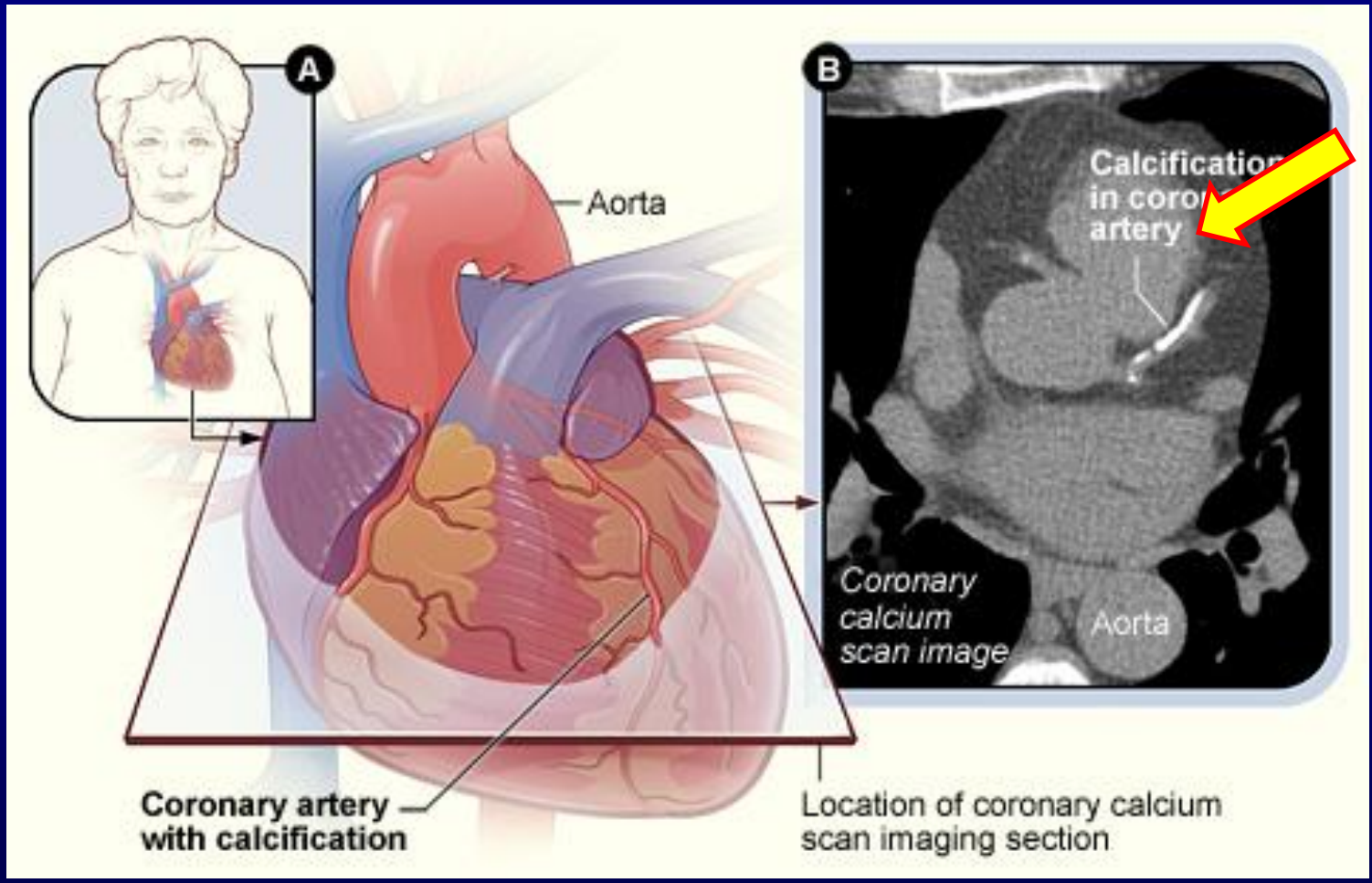
Menopause Clinic, University of Athens, Heart Score

Every woman was matched to a man according to traditional CVD risk factors

- Age
- Blood pressure
- Smoking
- Central obesity
- BMI
- Cholesterol levels

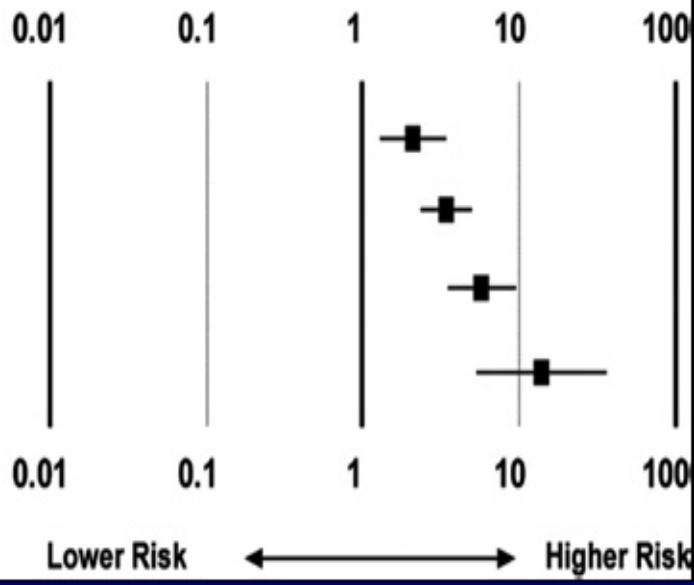
Arterial structure:

Coronary artery calcium score (CAC-Score) assessment by CT-scan



Coronary artery calcium score is a strong predictor of cardiac events

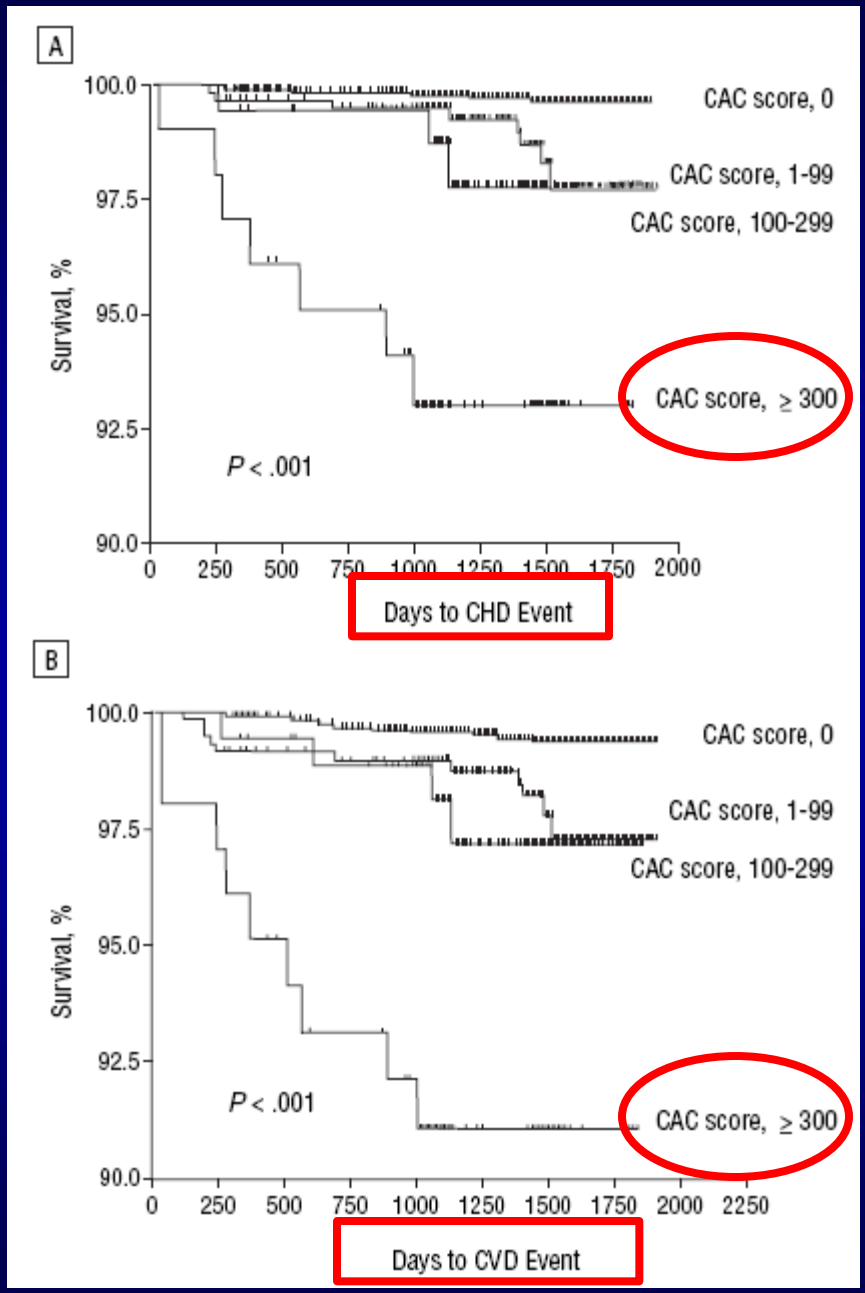
Summary RR Ratio	CACS	RR	(95% CI)	Events / N: Higher Risk	Events / N: Low Risk*	p
Average Risk	1-112	1.9	(1.3-2.8)	67 / 9,514	45 / 12,163	0.001
Moderate Risk	100-400	4.3	(3.1-6.1)	110 / 5,209	49 / 11,817	<0.0001
High Risk	400-999	7.2	(5.2-9.9)	182 / 3,940	49 / 8,649	<0.0001
Very High Risk	1,000	10.8	(4.2-27.7)	14 / 196	6 / 905	<0.0001



Greenland et al. JACC 2007

- **MESA sub-study: non-diabetic women aged 45-79 classified as low risk**

CAC-score group	CVD mortality (4 year follow-up)
High	10%
Low	2.5%



Lakoski s et al.
Arch Intern Med 2007

Markers of arterial stiffness / blood flow

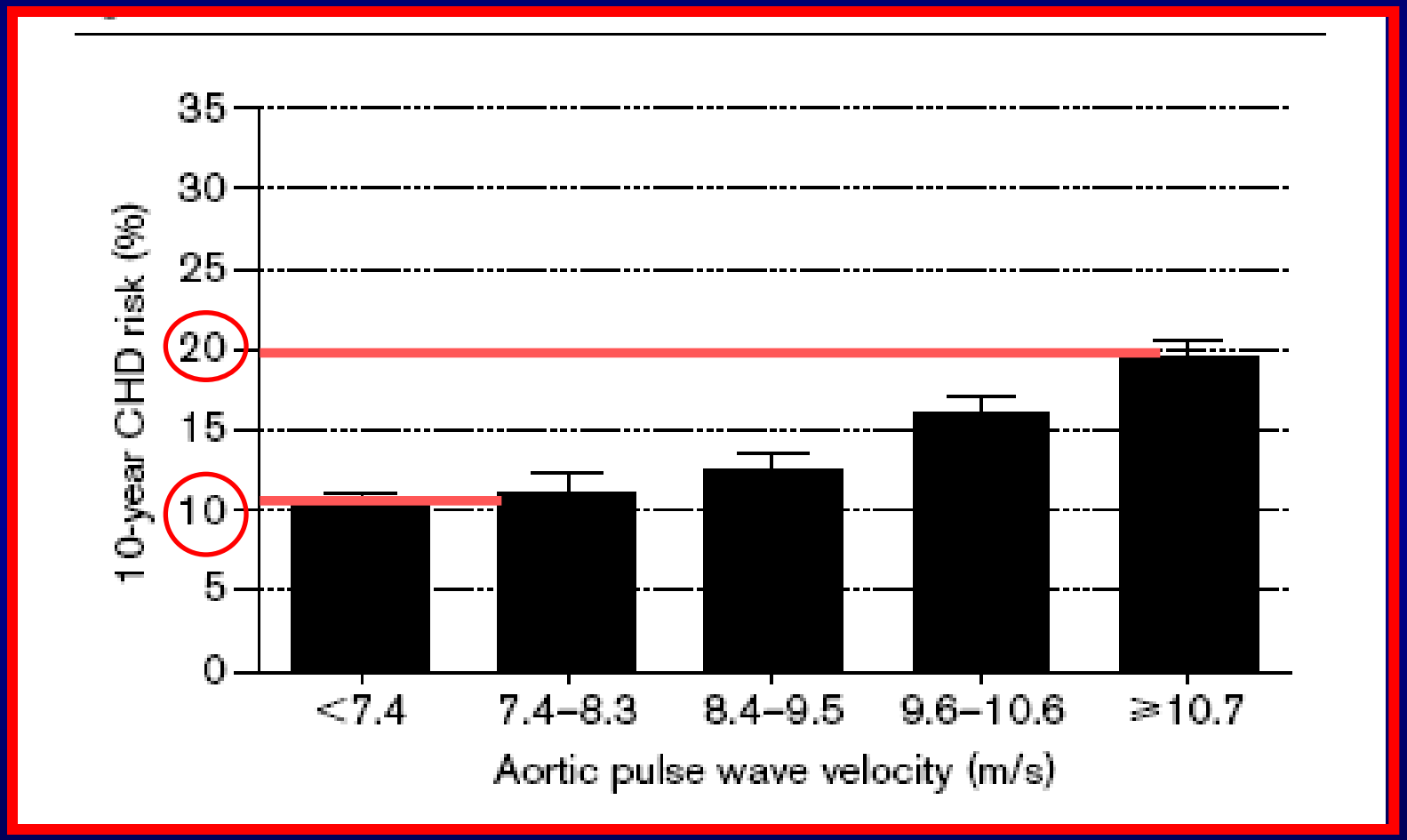
Pulse wave velocity (PWV)

- Speed of pulse transmission from heart to periphery
- High PWV → stiff arteries

Ankle – Brachial Index (ABI)

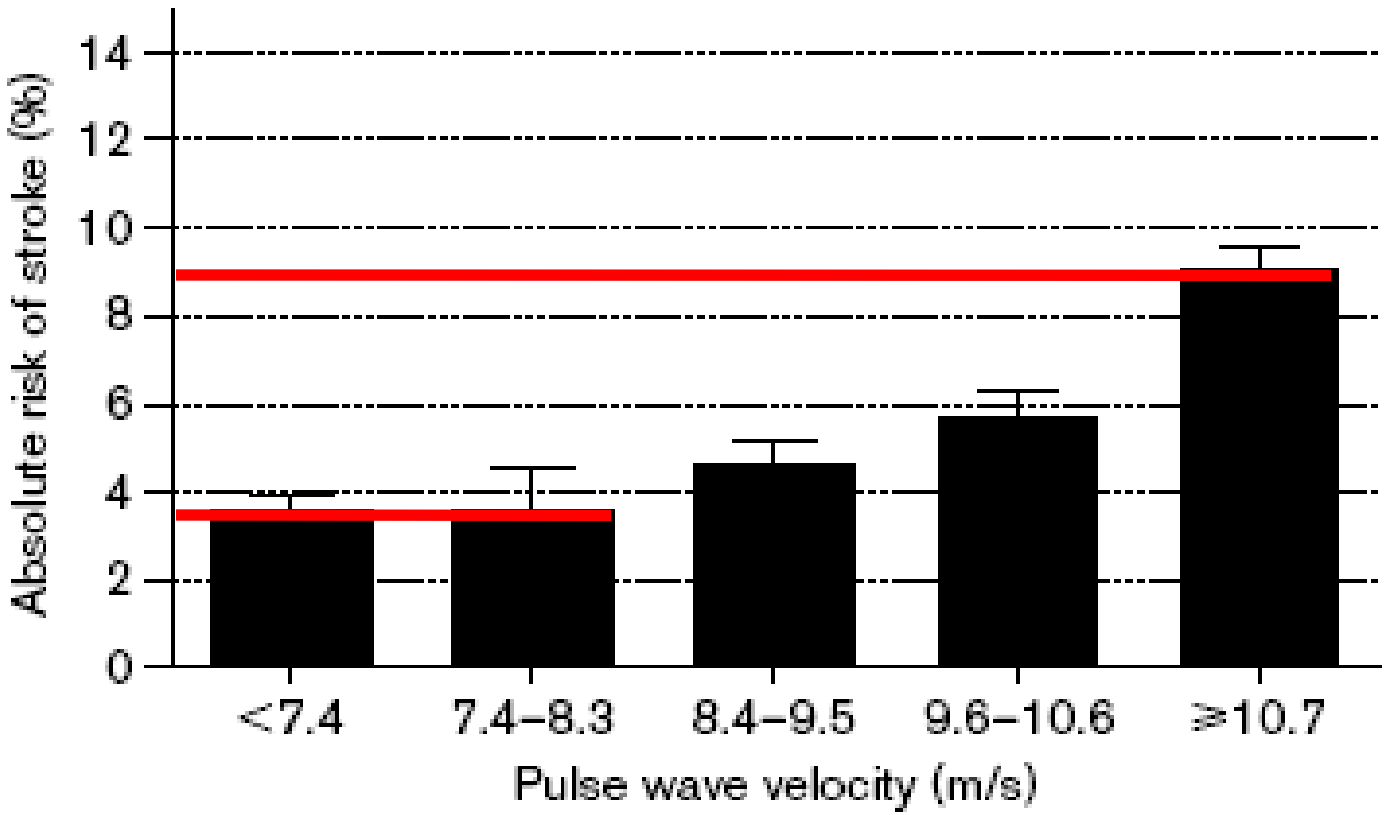
- Ankle blood pressure / brachial blood pressure
- Low ABI → peripheral arterial stenosis

Subjects with abnormally high PWV have a 2-fold increase in the 10-year risk of coronary heart disease



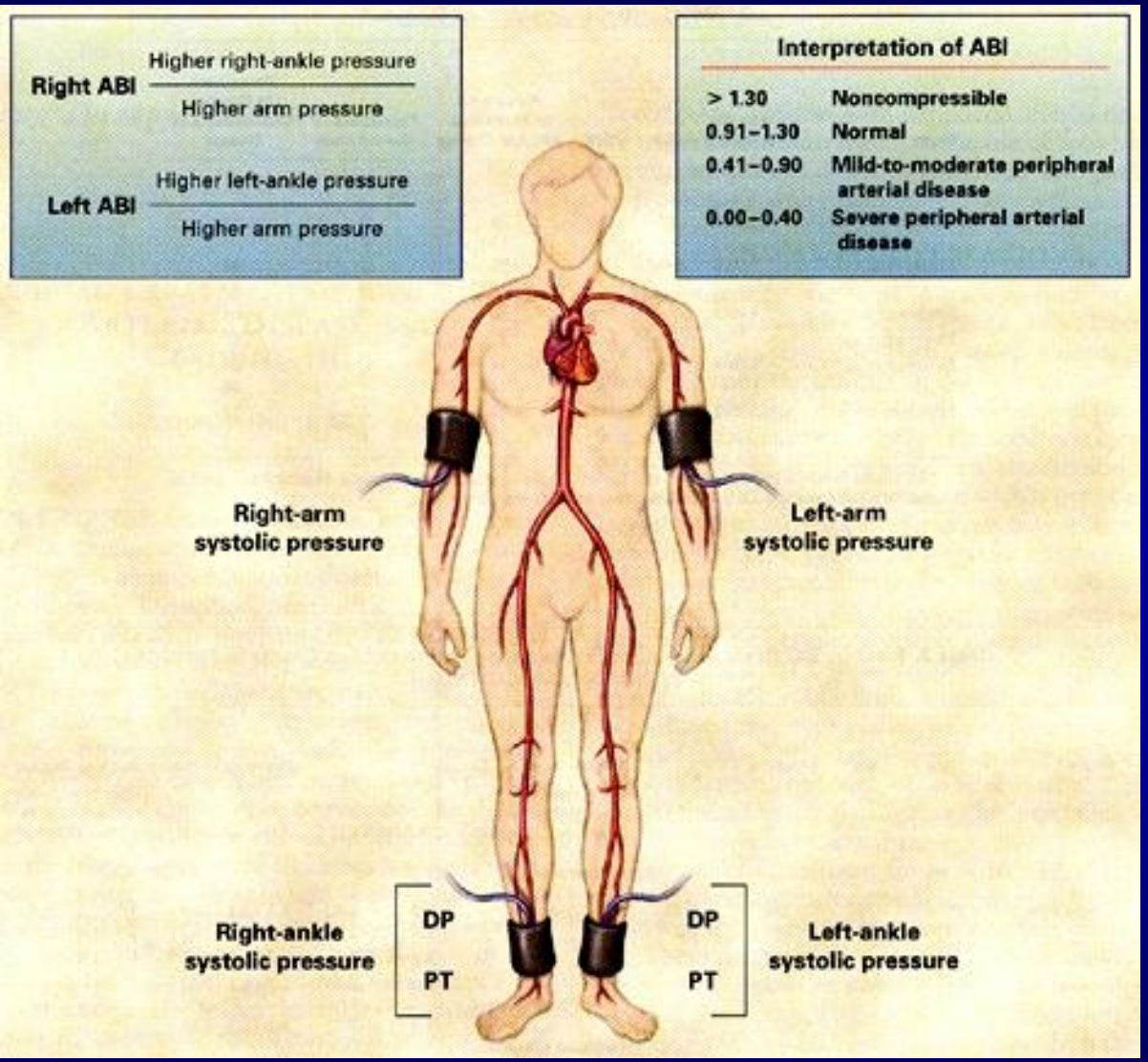
Lebrun CEI et al, J Hypertension 2002;20:2165

Subjects with abnormally high PWV have a 3-fold increase in the 10-year risk of stroke



Lebrun CEI et al, J Hypertension 2002;20:2165

Ankle – Brachial Index (ABI)



ABI < 0.90

arterial stenosis > 50%

- **95% sensitivity**
- **100% specificity**

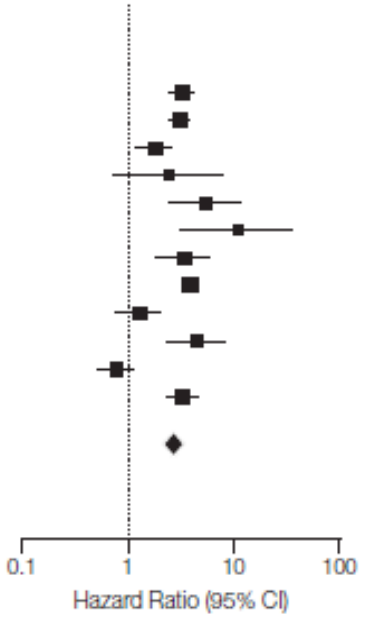
Hiatt, WR. N Engl J Med 2001; 344:1608

TASC working group. J VASC Surg 2000

ABI is a strong predictor of cardiovascular events in women

Study	No. of Women		No. of Deaths		Hazard Ratio (95% CI)
	ABI ≤0.90	ABI, 1.11-1.40	ABI ≤0.90	ABI, 1.11-1.40	
ARIC,[9] 2007	268	4441	66	393	3.17 (2.44-4.11)
Cardiovascular Health,[10] 1999	297	1134	159	280	3.05 (2.51-3.71)
Edinburgh Artery,[13] 1996	133	192	50	46	1.77 (1.19-2.64)
Framingham Offspring,[19] 2002	46	887	3	27	2.38 (0.72-7.86)
Hoorn,[21] 1999	23	62	15	11	5.42 (2.48-11.84)
InCHIANTI,[22] 2004	37	176	8	4	10.50 (3.16-34.88)
Limburg PAOD,[14] 2004	84	486	18	33	3.34 (1.88-5.94)
Rotterdam,[16] 2004	657	1496	383	324	3.75 (3.23-4.36)
San Diego,[23] 1992	47	81	29	45	1.25 (0.78-2.00)
San Luis Valley Diabetes,[24] 1995	19	364	11	63	4.37 (2.30-8.30)
Strong Heart,[12] 2004	143	1540	24	325	0.77 (0.51-1.16)
Women's Health and Aging,[25] 2000	147	296	78	62	3.22 (2.30-4.50)
Overall	1901	11157	844	1613	2.71 (2.03-3.62)

Test for heterogeneity: $\chi^2_{11} = 78.97$; $P<.001$; $I^2 = 86.1\%$
Test for overall effect: $z = 6.73$; $P<.001$



ABI < 0.9 → **RR of CVD death: 2.7**

Ankle Brachial Index Collaboration. JAMA 2008

PRACTICE GUIDELINE

Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update

A Guideline From the American Heart Association

At risk (≥1 major risk factor[s])	Cigarette smoking
	SBP ≥120 mm Hg, DBP ≥80 mm Hg, or treated hypertension
	Total cholesterol ≥200 mg/dL, HDL-C <50 mg/dL, or treated for dyslipidemia
	Obesity, particularly central adiposity
	Poor diet
	Physical inactivity
	Family history of premature CVD occurring in first-degree relatives in men <55 y of age or in women <65 y of age
	Metabolic syndrome
	Evidence of advanced subclinical atherosclerosis (eg, coronary calcification, carotid plaque, or thickened IMT)
	Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
	Systemic autoimmune collagen-vascular disease (eg, lupus or rheumatoid arthritis)
	History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension

Prevention guidelines

include the presence of subclinical atherosclerosis in the risk assessment of the asymptomatic woman

- **Who should be screened?**
- **What markers should be assessed?**

2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

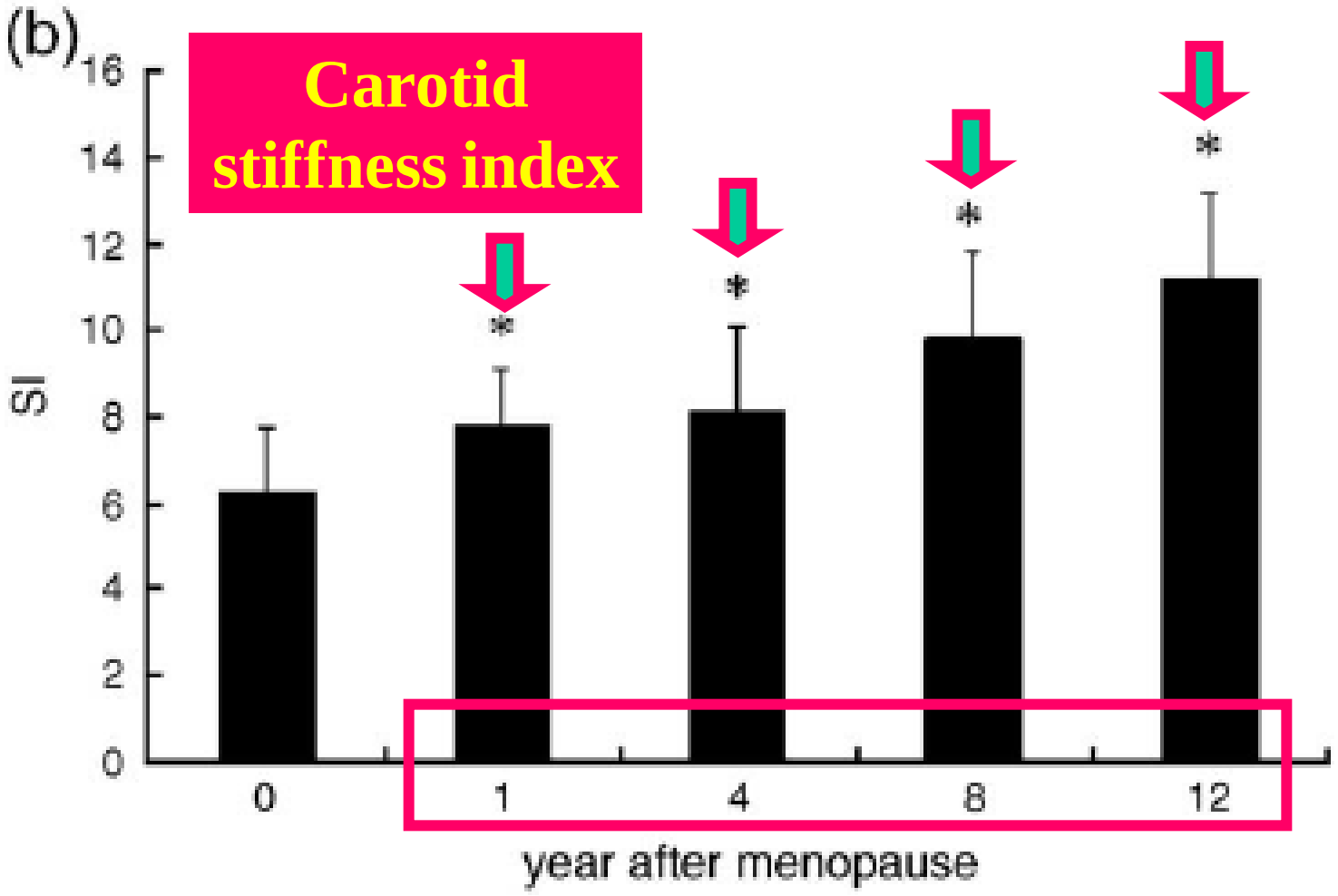
- **IMT , ABI, CACS ➔*CLASS IIa (level of evidence B)***:
  - Asymptomatic adults at intermediate risk (10% to 20% 10-year risk) ⇨ >1 risk factors
  - in all asymptomatic adults with diabetes, 40 years of age and older.

Greenland P et al. Circulation 2010

“Female”cardiovascular risk factors and subclinical CVD

- Menopausal age
- Systolic blood pressure
- Metabolic syndrome
- Hot flushes
- Sex hormones
- Osteoporosis

Arterial stiffness associates linearly with menopausal age



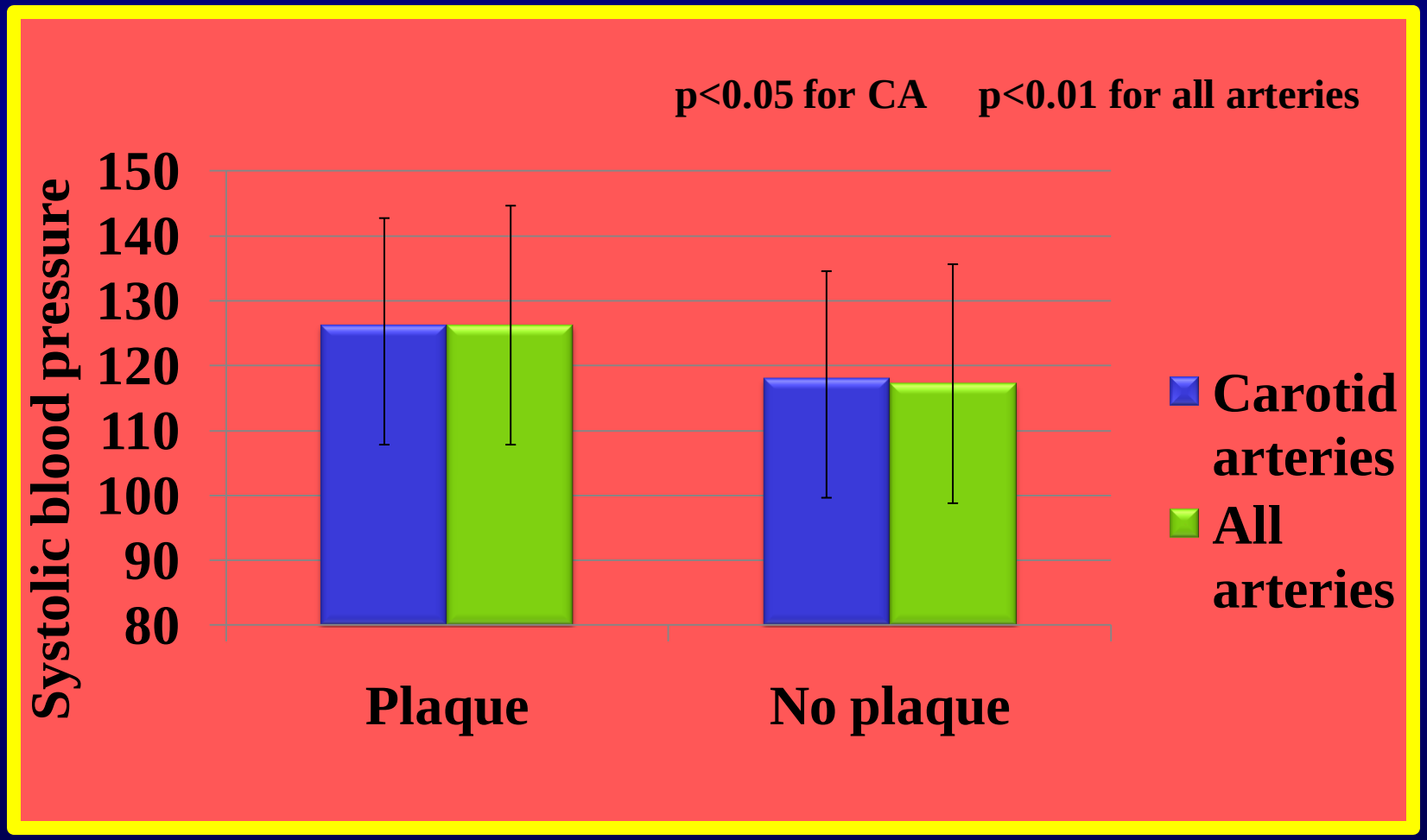
Itsumi S et al, Life Sciences 2006;78:1696

Menopausal age predicts subclinical atherosclerosis in healthy recently menopausal women

	EXP(B)	*p-value*
Age (years)	0.431	0.511
Years since menopause	**1.266**	**0.007**
(kg/m^2)	0.346	0.556
Smoking	1.292	0.541
TG (mg/dl)	1.110	0.292
HDL-C (mg/dl)	0.422	0.516
LDL-C (mg/dl)	0.107	0.744
HOMA-IR	1.365	0.243
Insulin (μU/ml)	2.142	0.143
SBP (mmHg)	**1.040**	**0.021**
DBP (mmHg)	0.326	0.568

Menopause Clinic, University of Athens, Heart Score

Postmenopausal women with atherosclerotic plaques have higher systolic blood pressure



Menopause Clinic, University of Athens, Heart Score

Systolic blood pressure: risk factor for CVD

- **Women: higher systolic blood pressure compared to men**
- **WHI: 17% systolic hypertension with normal diastolic pressure**
- **Treatment of systolic hypertension: 36 - 42% reduction in stroke risk**

Guidelines for the Primary Prevention of Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Stroke 2011;42;517-584;

Sylvia Wassertheil-Smoller

Nutrition, Metabolism & Cardiovascular Diseases (2010) 20, 419—425

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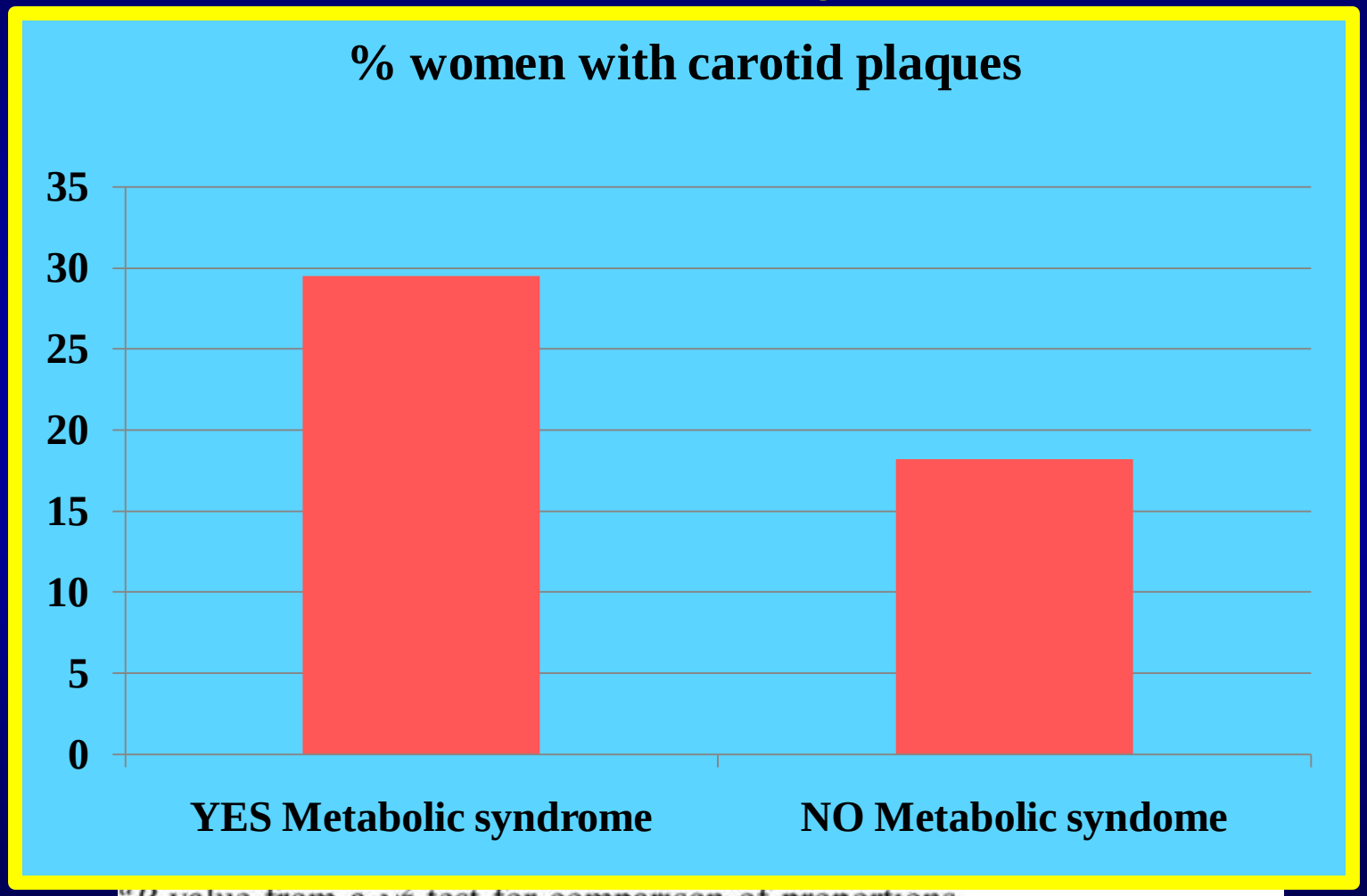
Menopause Clinic, University of Athens, Heart Score

Atherosclerotic plaques are twice as frequent in postmenopausal women with the metabolic syndrome

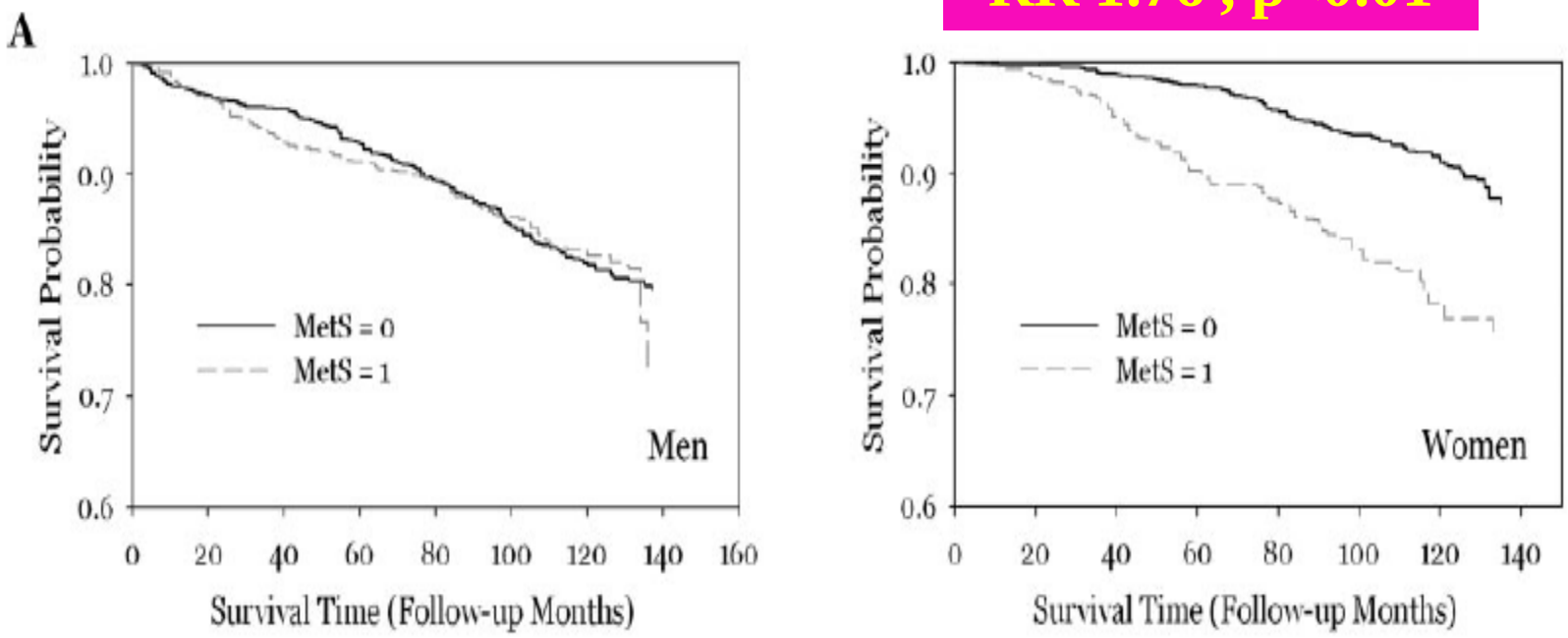


"*P* value from a χ^2 test for comparison of proportions.

Yu, Ruby et al, Menopause 2008; 15(1):185-192.

The presence of metabolic syndrome is associated with higher all-cause mortality ONLY in women

RR 1.76 , p<0.01



Lin JW et al, J Clin Endocrinol Metab 2010

The presence of metabolic syndrome increases cardiovascular mortality by 6-fold in postmenopausal women under 65 years

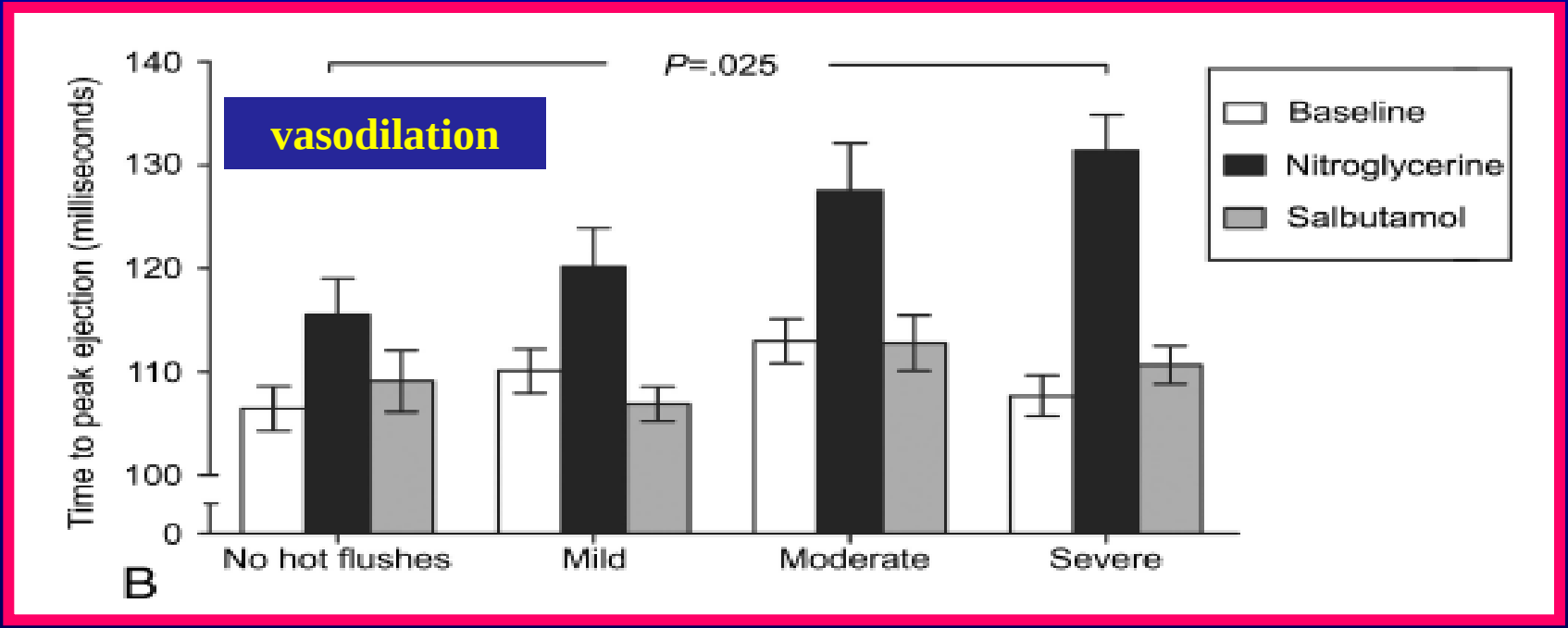
	Men				Women			
	Univariate		Adjusted		Univariate		Adjusted	
Mortality cause	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age ≥65 yr								
All causes[a]	0.66 (0.44–0.99)	0.04	0.73 (0.49–1.09)	0.12	2.35 (1.55–3.58)	<0.001	1.87 (1.22–2.85)	0.005
Cardiovascular disease[a]	0.60 (0.36–1.00)	0.05	0.66 (0.40–1.08)	0.10	2.48 (1.57–3.92)	0.002	1.71 (1.08–2.71)	0.02
Cardiac disease[a]	0.60 (0.33–1.06)	0.08	0.64 (0.36–1.12)	0.12	2.40 (1.50–3.85)	<0.001	1.64 (1.03–2.61)	0.04
Noncardiovascular disease[a]	0.71 (0.41–1.24)	0.22	0.80 (0.46–1.40)	0.43	2.24 (1.22–4.11)	0.01	2.01 (1.04–3.88)	0.04
Age <65 yr								
All causes[a]	1.09 (0.46–2.56)	0.84	1.06 (0.47–2.41)	0.89	1.85 (0.91–3.77)	0.09	1.48 (0.68–3.23)	0.31
Cardiovascular disease[a]	2.03 (0.62–6.67)	0.24	1.98 (0.60–6.48)	0.26	10.7 (1.74–66.0)	0.01	5.83 (1.38–24.7)	0.02
Cardiac disease[a]	2.01 (0.59–6.86)	0.26	1.95 (0.57–6.67)	0.28	13.5 (1.56–118.0)	0.02	4.43 (1.09–18.0)	0.04

!!!

Lin JW et al, J Clin Endocrinol Metab 2010

Women with hot flushes are

- more prone to subclinical atherosclerotic disease
- more responsive to vasodilatory agents compared to women with no hot flushes
- These women may benefit more by HRT compared to asymptomatic women



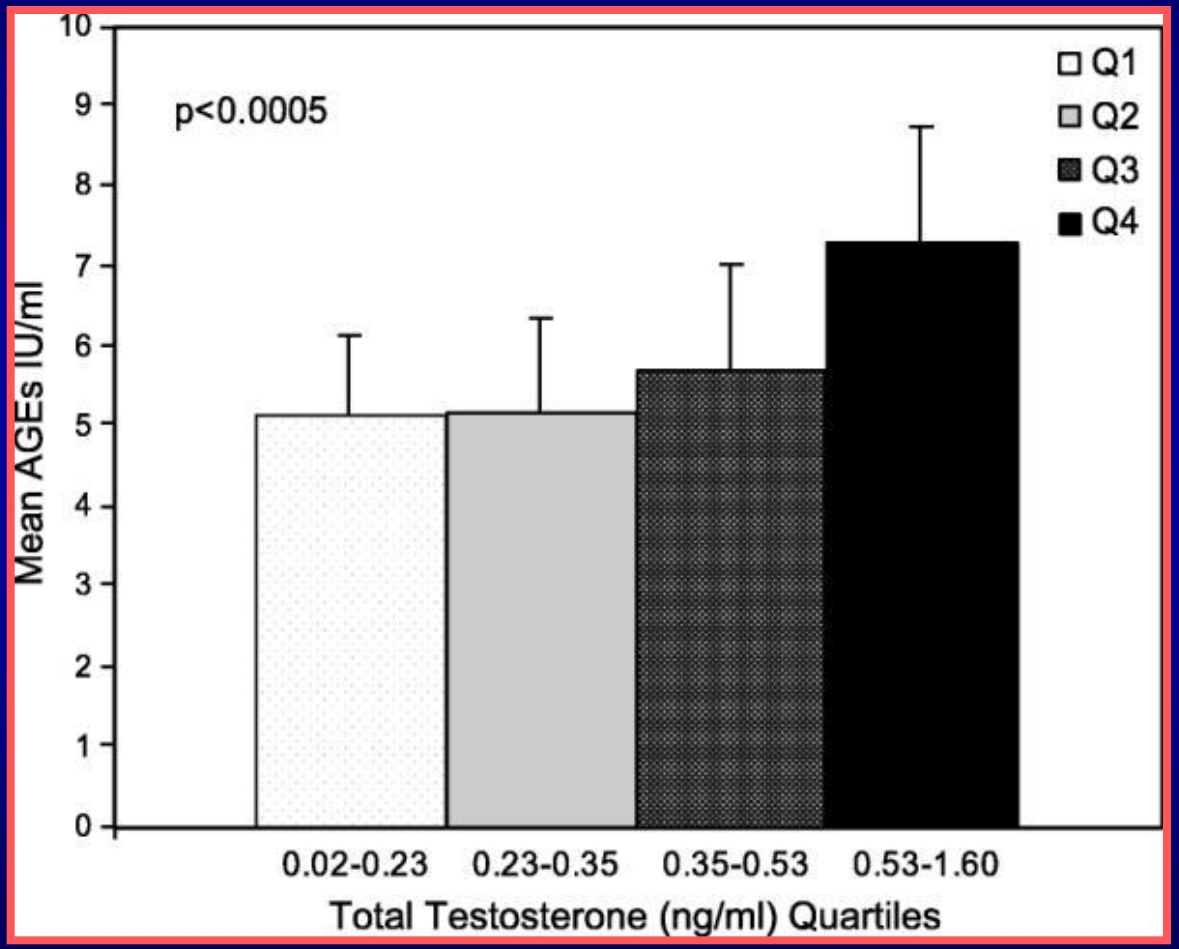
Tuomikoski P et al. Obstet Gynecol 2009;113:902

Thurston RC et al, Circulation 2008;118:1234

Allison MA et al, Menopause 2010:17:1136-45

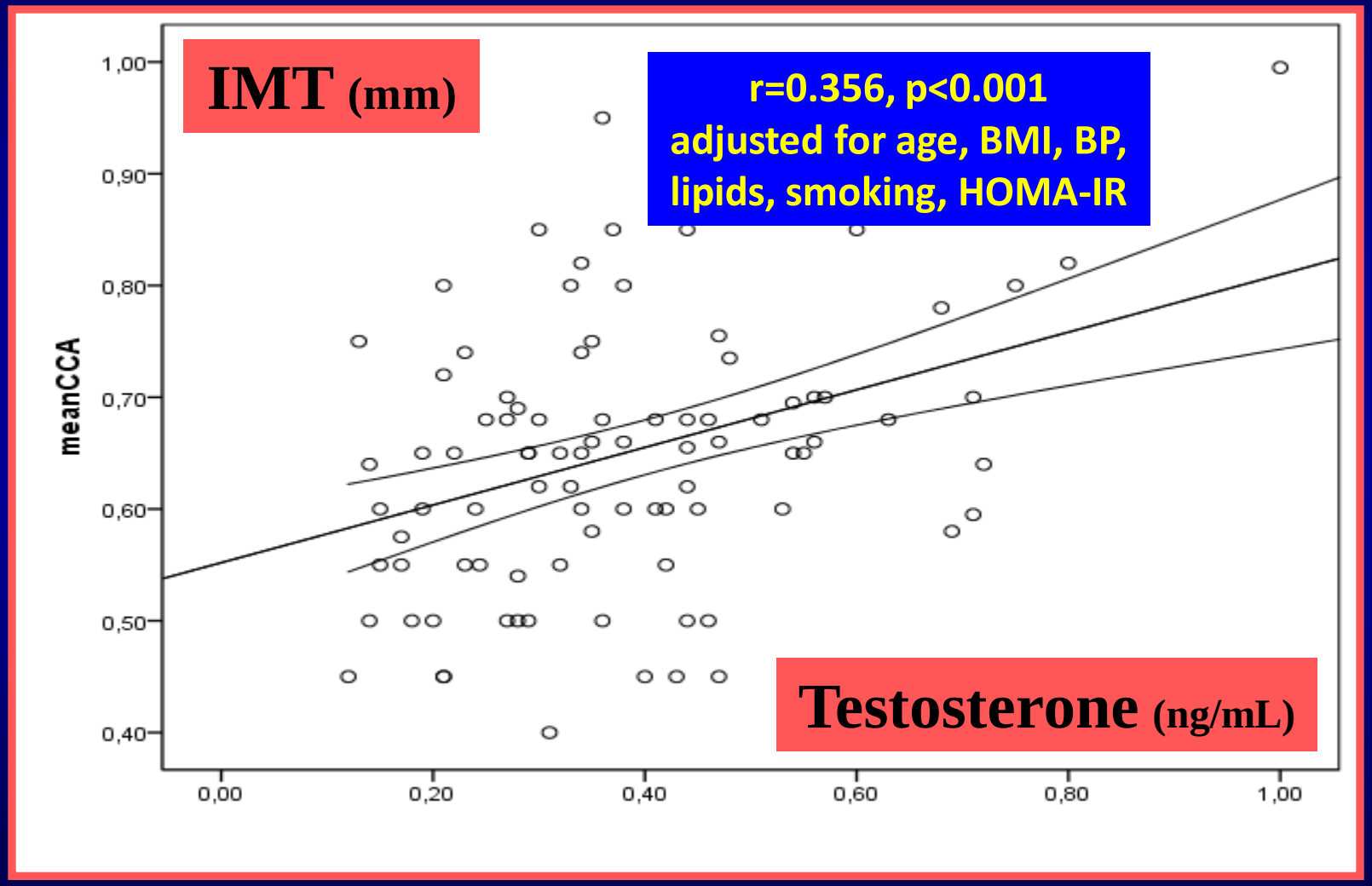
Endogenous androgens are positively associated with pro-atherogenic activity in healthy postmenopausal women

Serum AGEs (advanced glycation end-products)



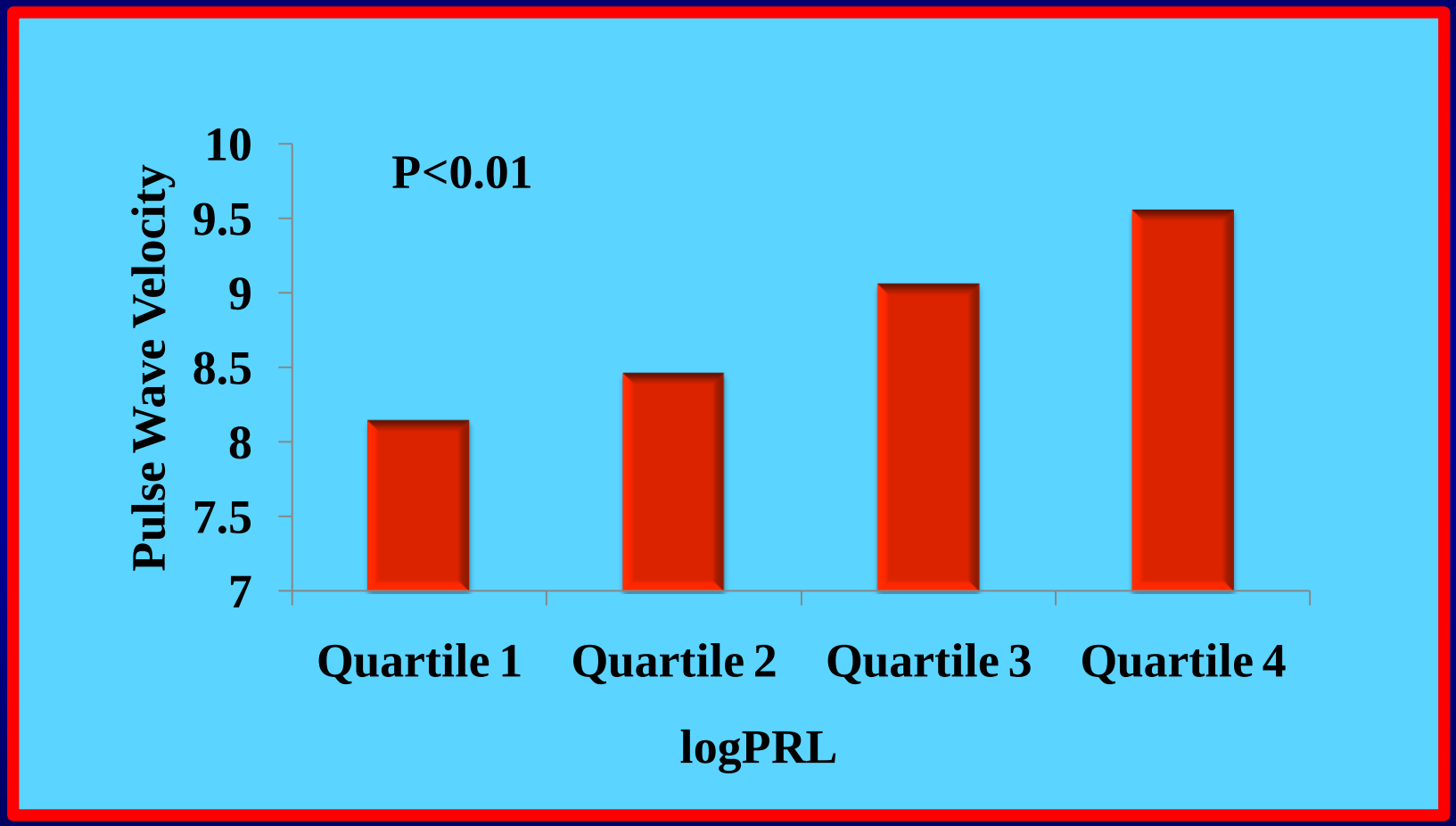
Diamanti-Kandarakis E, Lambrinoudaki I et al Menopause 2010 ;17:1182

Circulating testosterone is positively associated with carotid IMT in healthy recently menopausal women



Lambrinoudaki I, Stamatelopoulos K et al, Metabolism (in press)

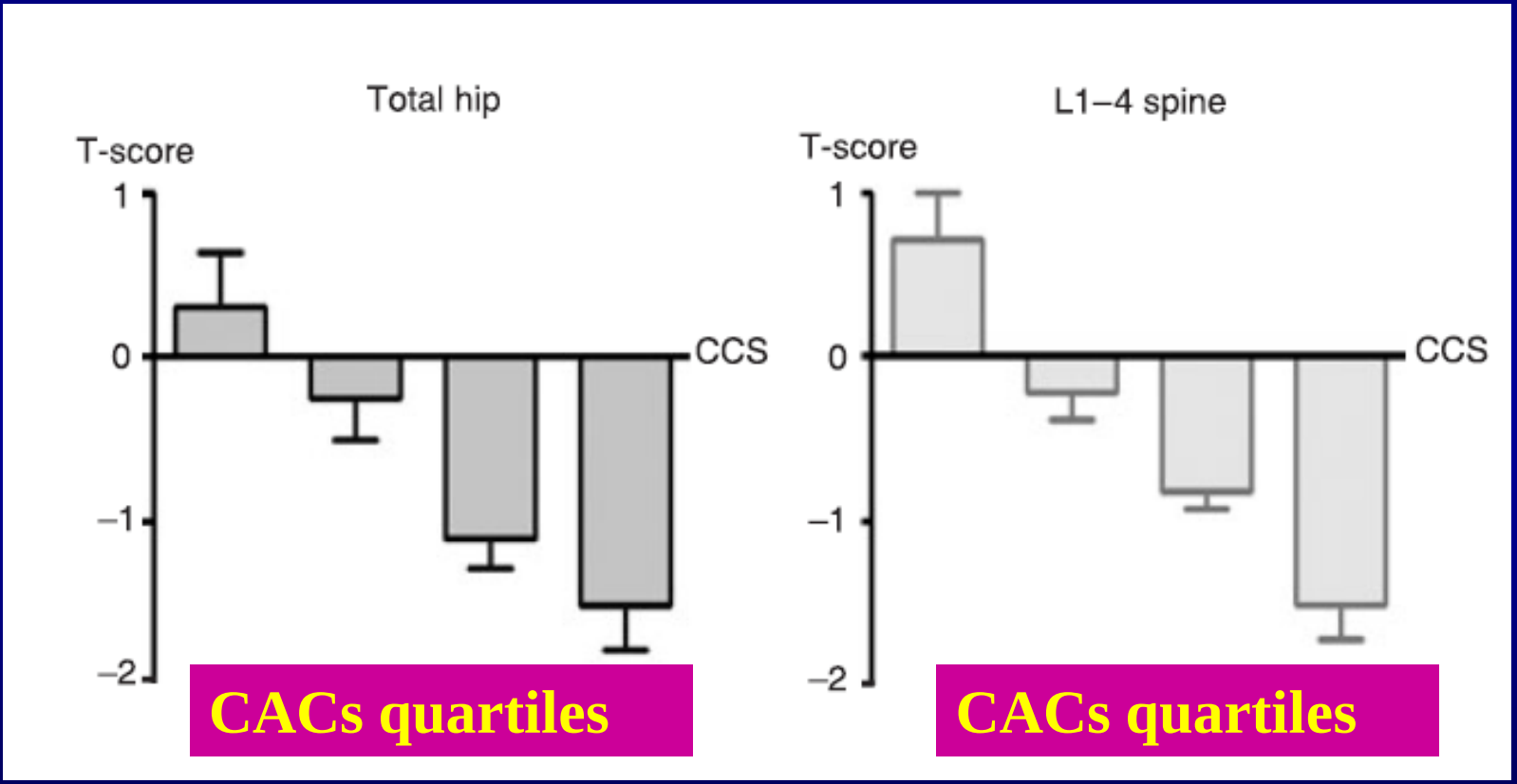
Women with higher serum prolactin have stiffer arteries compared to women with lower prolactin



Georgiopoulos G, Stamatelopoulos K, Lambrinoudaki I et al, Hypertension 2009;54:98

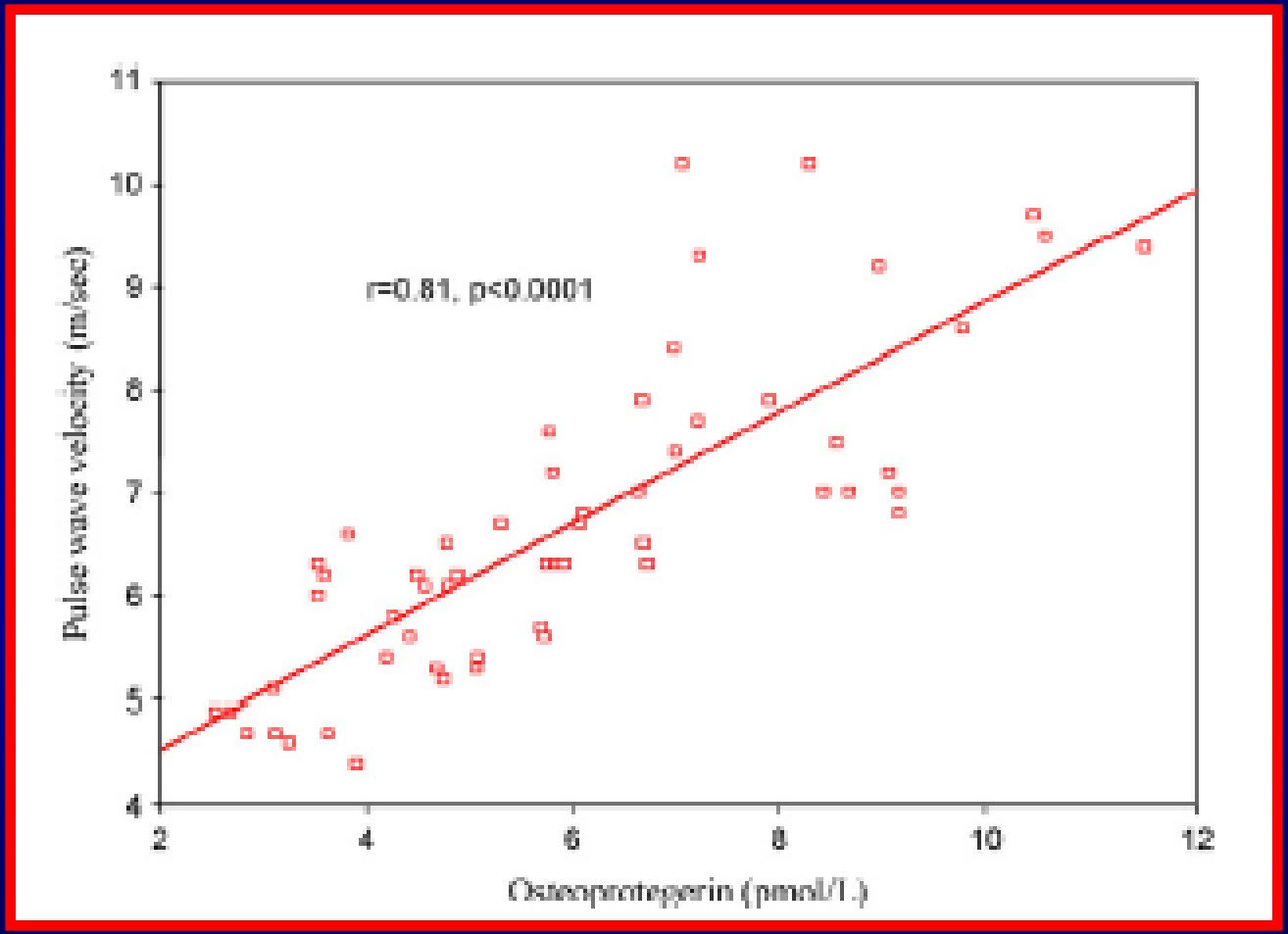
Subclinical CVD and osteoporosis

Low bone mineral density is associated with higher CAC score in postmenopausal women



Sung Hee Choi et al, Clin Endocrinol 2009;71:644

Serum osteoprotegerin correlates positively with arterial stiffness



Sharkorododsky et al. Atherosclerosis 2009

Conclusions

- CVD mortality is higher in postmenopausal women compared to men
- Traditional CVD risk prediction models have a lower performance in women
- Gender – specific risk factors may account for the difficulties in predicting CVD risk in women
- The prevalence of subclinical atherosclerosis in women equals that of men soon after menopause
- Assessment of subclinical atherosclerosis may help us to identify the woman at risk at an early point when preventive intervention is effective

…. see you in Athens in 2012

9TH EUROPEAN CONGRESS ON

MENOPAUSE AND ANDROPAUSE

ATHENS, GREECE, 28-31 MARCH, 2012