Alterations of Cardiovascular System after Menopause

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Men vs. Women and pre-post Menopause

Whether higher cardiovascular risk is a function of aging, a consequence of menopause and its associated loss of endogenous estrogen or both has been debated.

목차

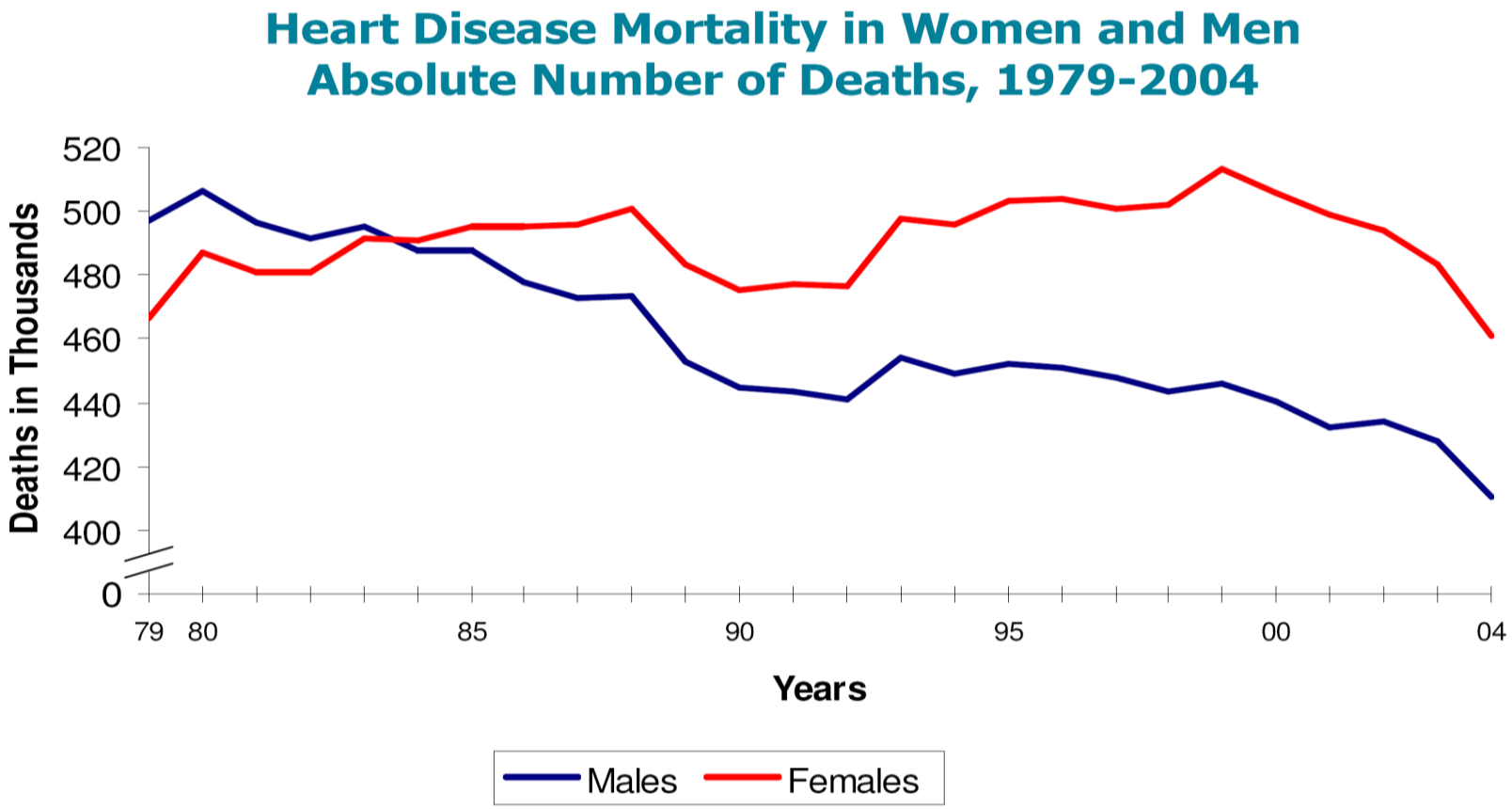
- **Evidence of higher cardiovascular risk in women after menopause**
- **Alterations of cardiovascular system after menopause**
  - -- Cardiac change
  - -- Coronary artery disease
  - -- Endothelial function
  - -- IMT and aortic stiffness
  - -- Hypertension
- **Take home message**

Menopause

- Average age at menopause: 51.4 years
- Women in developed countries live over 1/3 of their lives in the postmenopausal state

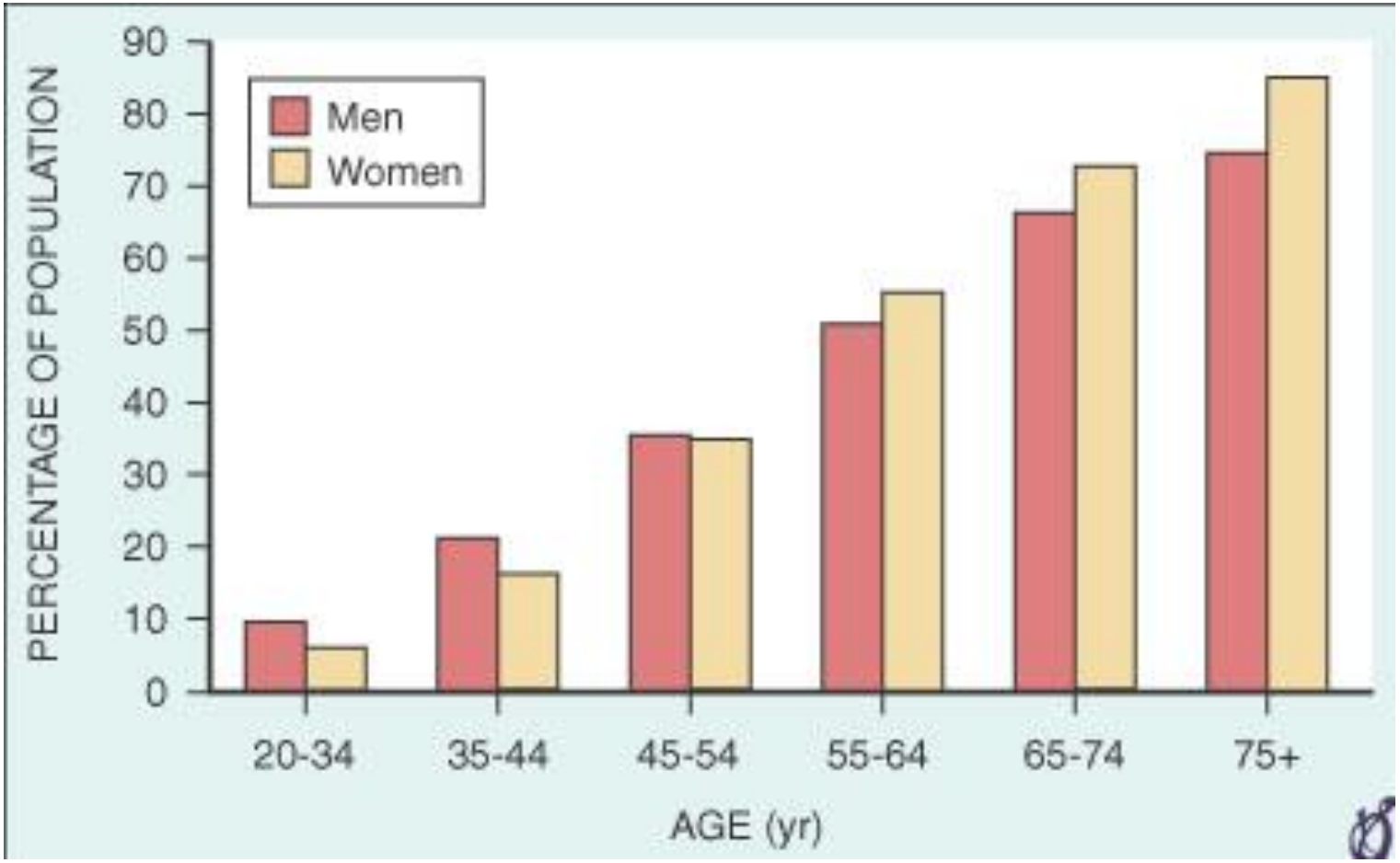
- Global population of postmenopausal women:
  from 467 million in 1990 to 1,200 million in 2030
- Understanding the impact of menopause on women's health is becoming increasingly important

More Women Die From Heart Disease Than Men



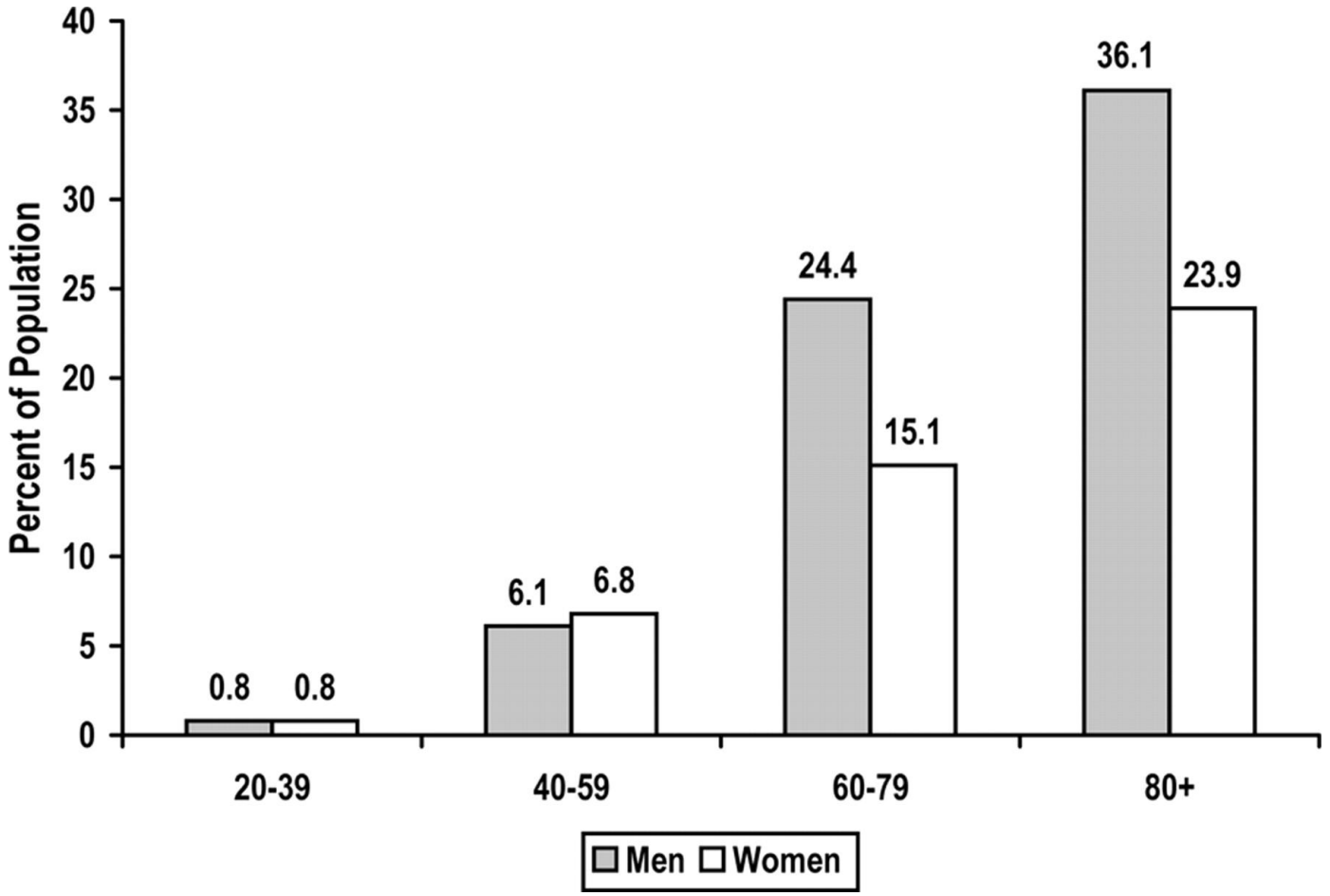
American Heart Association. Heart Disease and Stroke Statistics-2009 update

Estimated Prevalence of Cardiovascular Disease in Americans 20 years of age and older



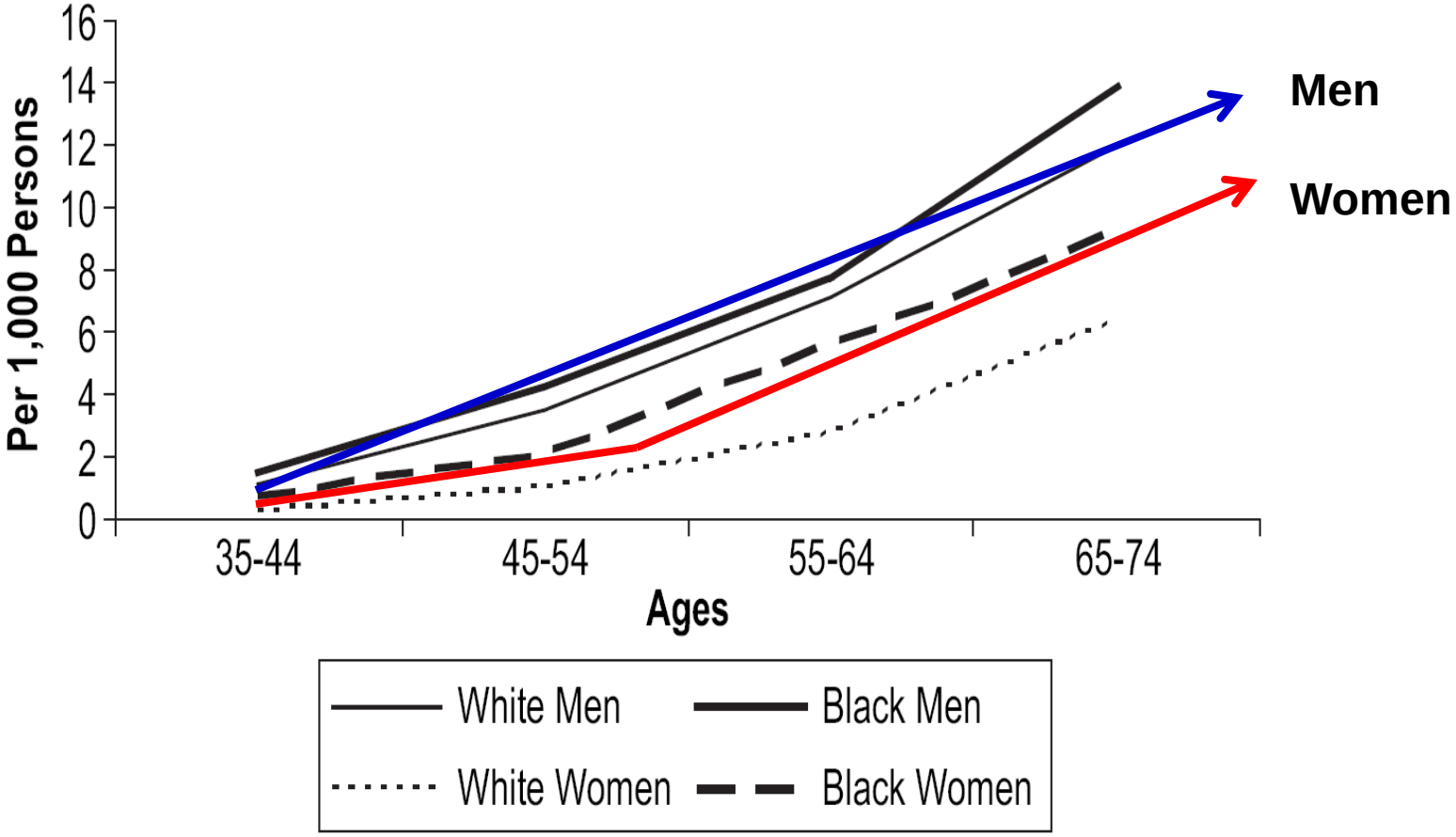
American Heart Association: Heart Disease and Stroke Statisticsw-2006 update

Prevalence of CHD by age and sex



Lloyd-Jones, D. et al. Circulation 2009;119:e21-e181

Annual Rate of First Myocardial Infarctions by Age, Sex, and Race

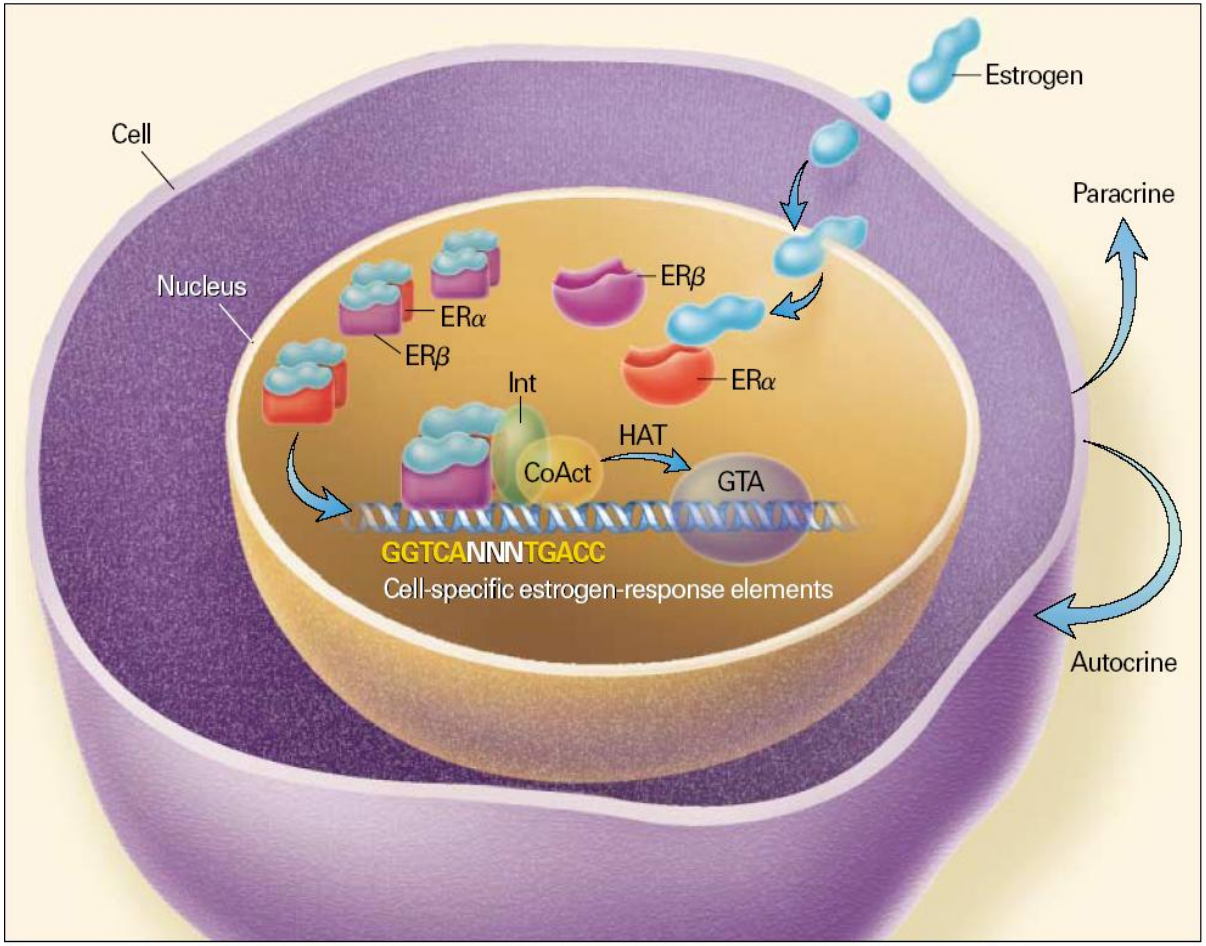


Why CV Risk Increased After Menopause

- The mechanisms underlying the increased cardiovascular risk after menopause are incompletely known.

- Aging process vs. Menopause (estrogen deficiency) ?

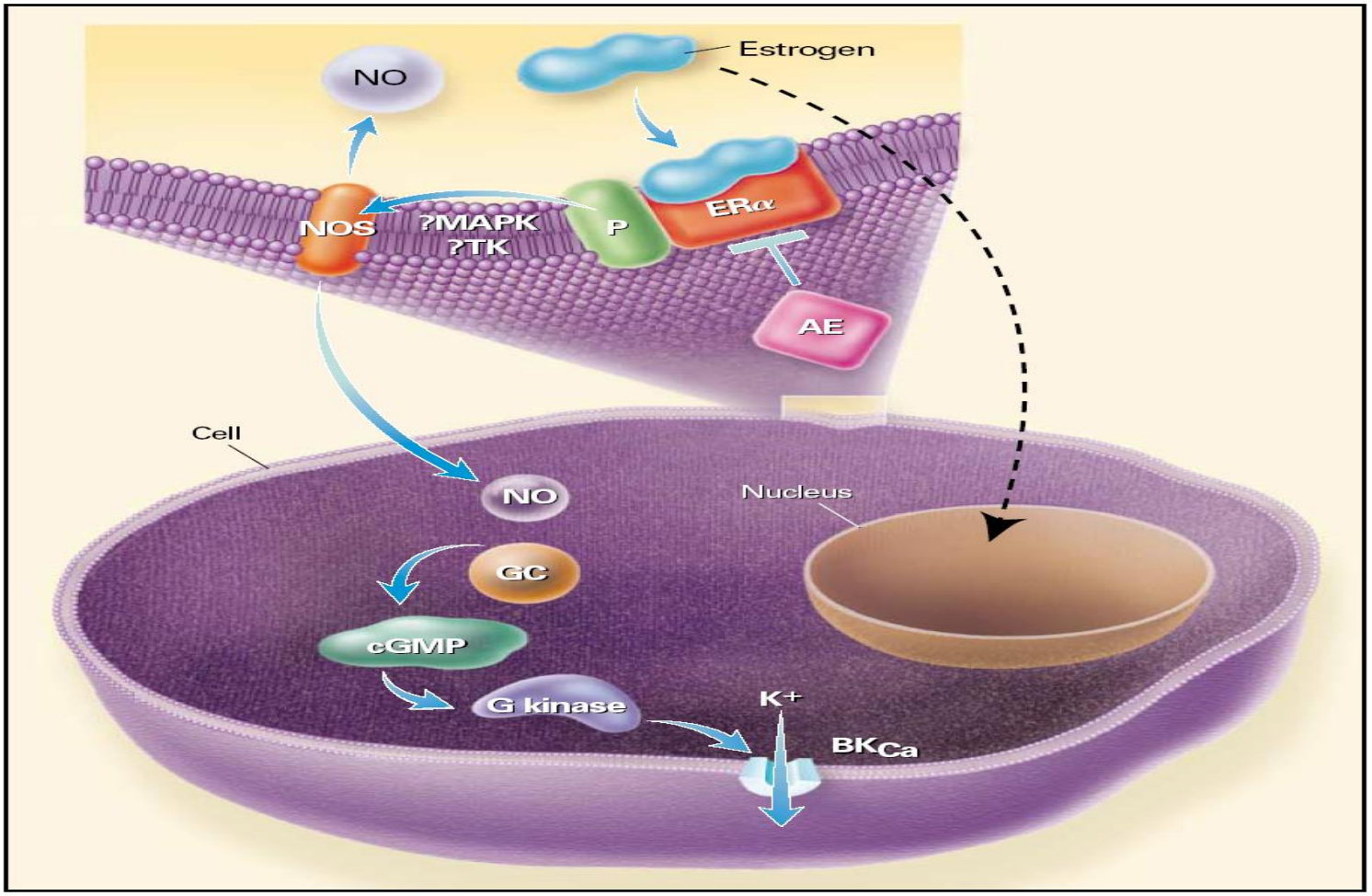
Vascular Genomic Effects of Estrogen



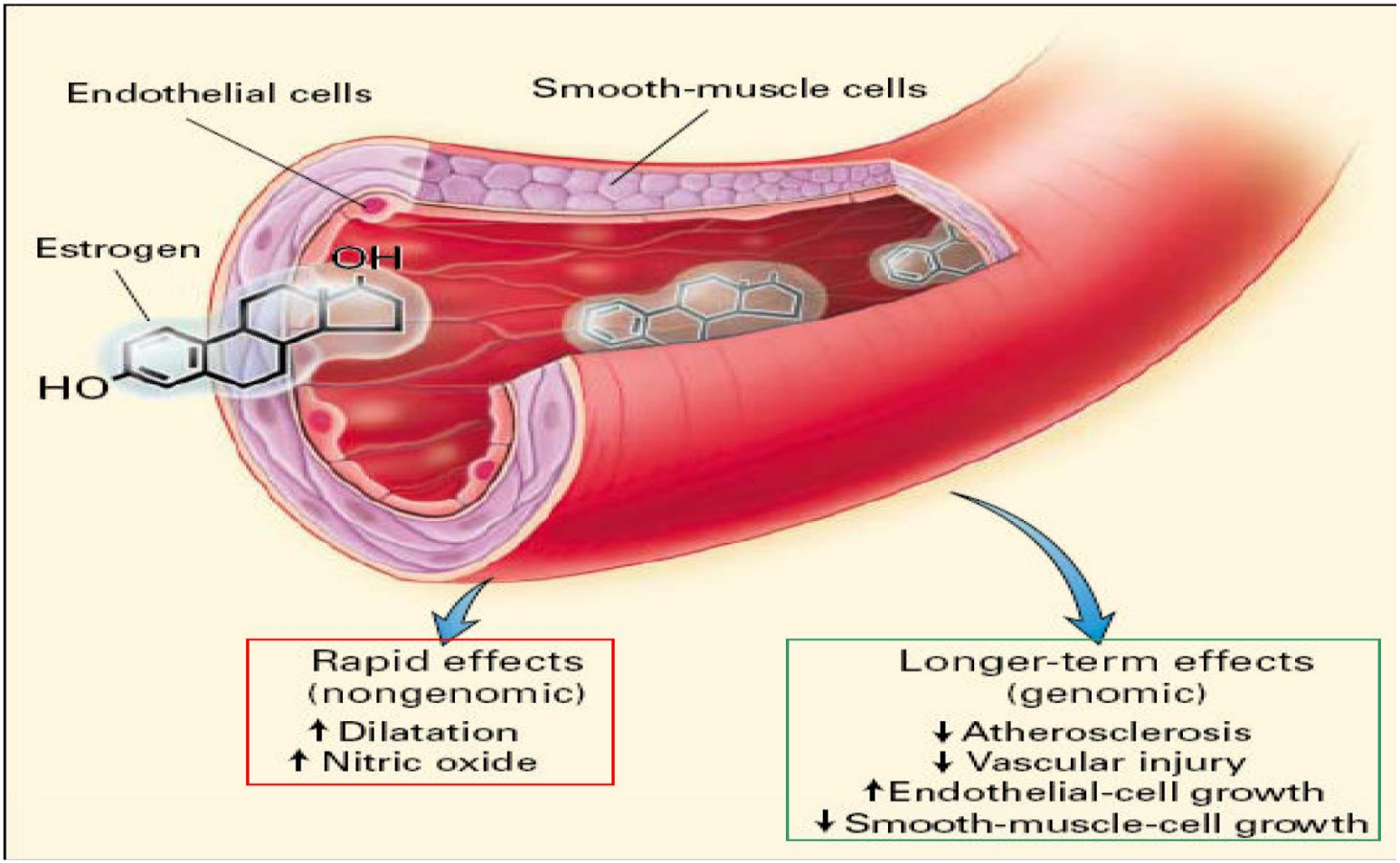
Ligand binding→

Activate or suppress gene transcription

Vascular Non-genomic Effects of Estrogen



Direct Effects of Estrogen on Blood Vessels



N Med J med 1999;340:1801

Cardiac change after menopause

Alterations of Cardiac System After Menopause

- Blunted day-night blood pressure reduction
- Impaired LV systolic performance
- Concentric LV geometric pattern

Blunted day-Night BP Reduction

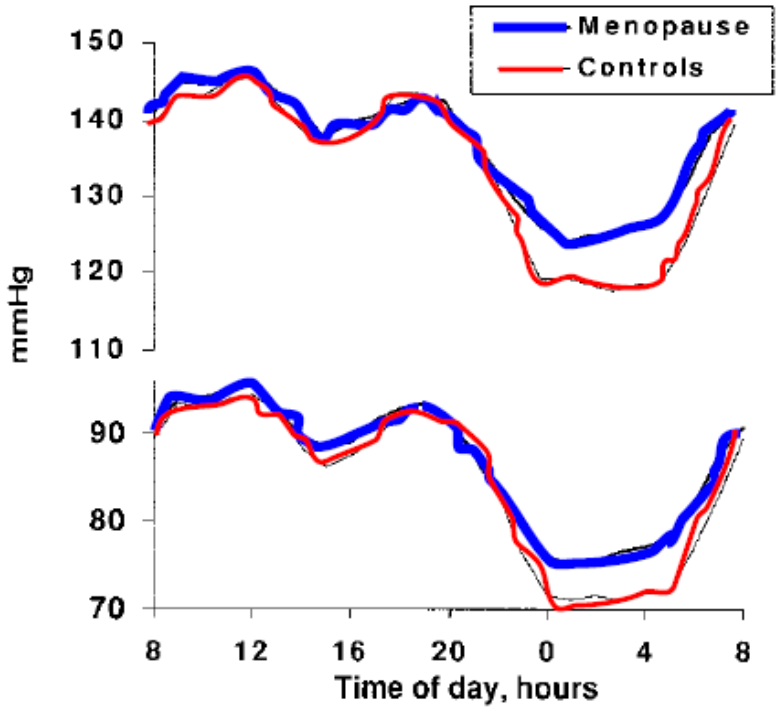


Figure 1. Twenty-four–hour BP profile in 76 postmenopausal women and 76 age- and BP-matched premenopausal women with essential hypertension.

Cir 1998;32:764-769.

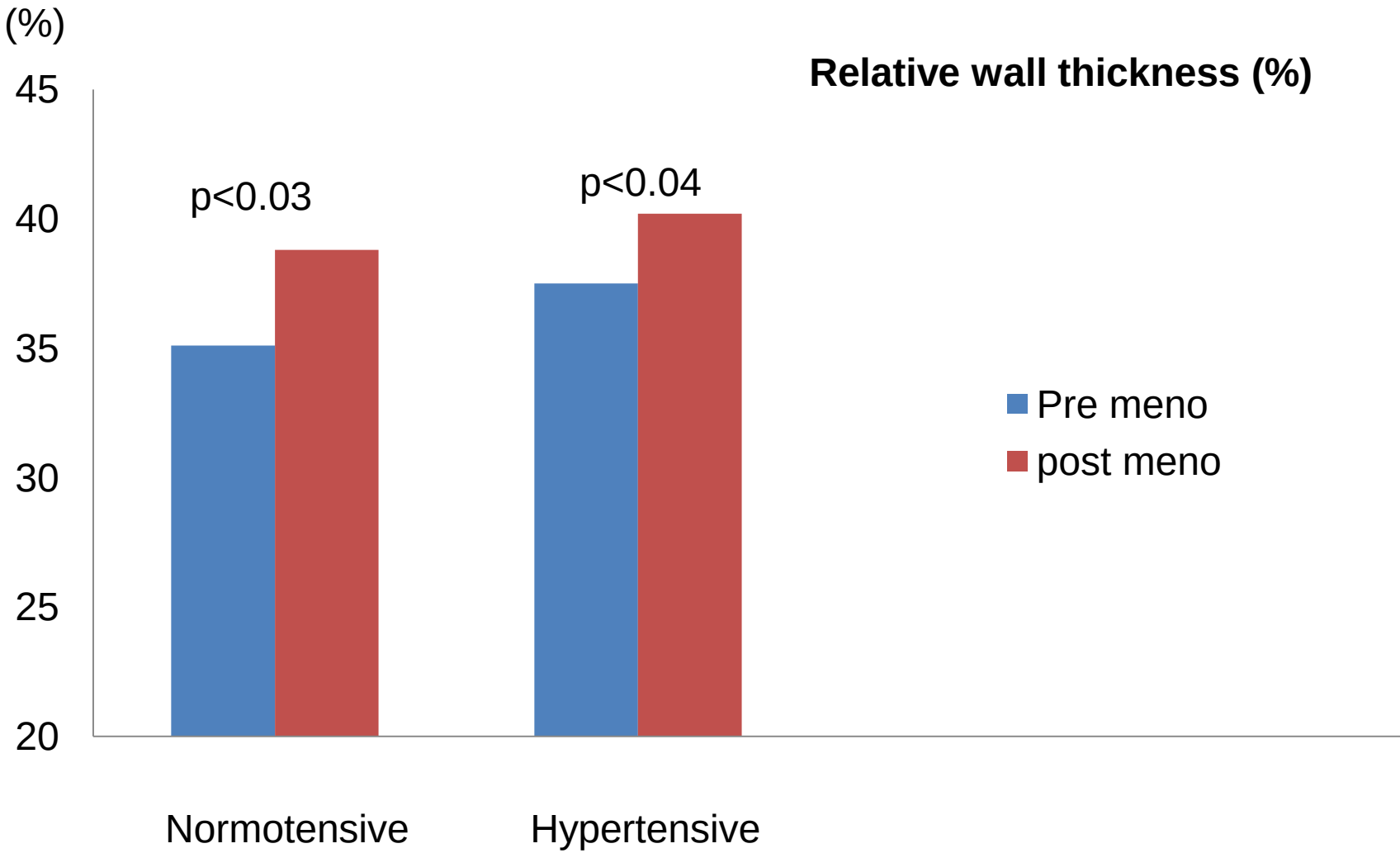
Blunted day-Night BP Reduction

TABLE 2 Hemodynamics at Rest, Ambulatory Blood Pressure, and Laboratory Parameters in Pre- and Postmenopausal Women

	Premenopausal	Postmenopausal	p Value
Hemodynamics at rest			
Systolic blood pressure (mm Hg)	108 ± 13	108 ± 12	NS
Diastolic blood pressure (mm Hg)	71 ± 8	72 ± 7	NS
Heart rate (beats/min)	67 ± 9	67 ± 9	NS
Cardiac index (L/min·m^2)	3.10 ± 0.71	2.64 ± 0.73	<0.01
Peripheral resistance index (dyne·s·m^2/cm^5)	2262 ± 661	2722 ± 757	<0.01
Ambulatory blood pressure (mm Hg)			
Daytime systolic blood pressure	119 ± 11	119 ± 12	NS
Daytime diastolic blood pressure	74 ± 7	76 ± 7	NS
Systolic blood pressure during sleep	100 ± 10	104 ± 13	<0.05
Diastolic blood pressure during sleep	59 ± 8	63 ± 8	<0.05
Systolic nocturnal decrease	19 ± 8	15 ± 8	<0.01
Diastolic nocturnal decrease	15 ± 6	12 ± 6	0.05
Biochemical and hematologic data			
Follicular stimulating hormone (mIU/ml)	17 ± 21	67 ± 31	<0.01
Estradiol (pg/ml)	81 ± 78	22 ± 36	<0.01
Hematocrit (%)	38 ± 3	40 ± 2	<0.01
Total cholesterol (mg/dl)	192 ± 34	207 ± 44	<0.05
Triglycerides (mg/dl)	83 ± 40	94 ± 69	NS
Plasma renin activity (mg/ml/h)	1.92 ± 4.17	2.05 ± 3.62	NS
Creatinine (mg/dl)	0.85 ± 0.12	0.87 ± 0.11	NS
Urinary sodium excretion (mEq/24 h)	107 ± 45	110 ± 47	NS

Am J Cardio 2002;89:830

Concentric LV geometric pattern



Hypertension 1998;32:764-769.

Concentric LV geometric pattern

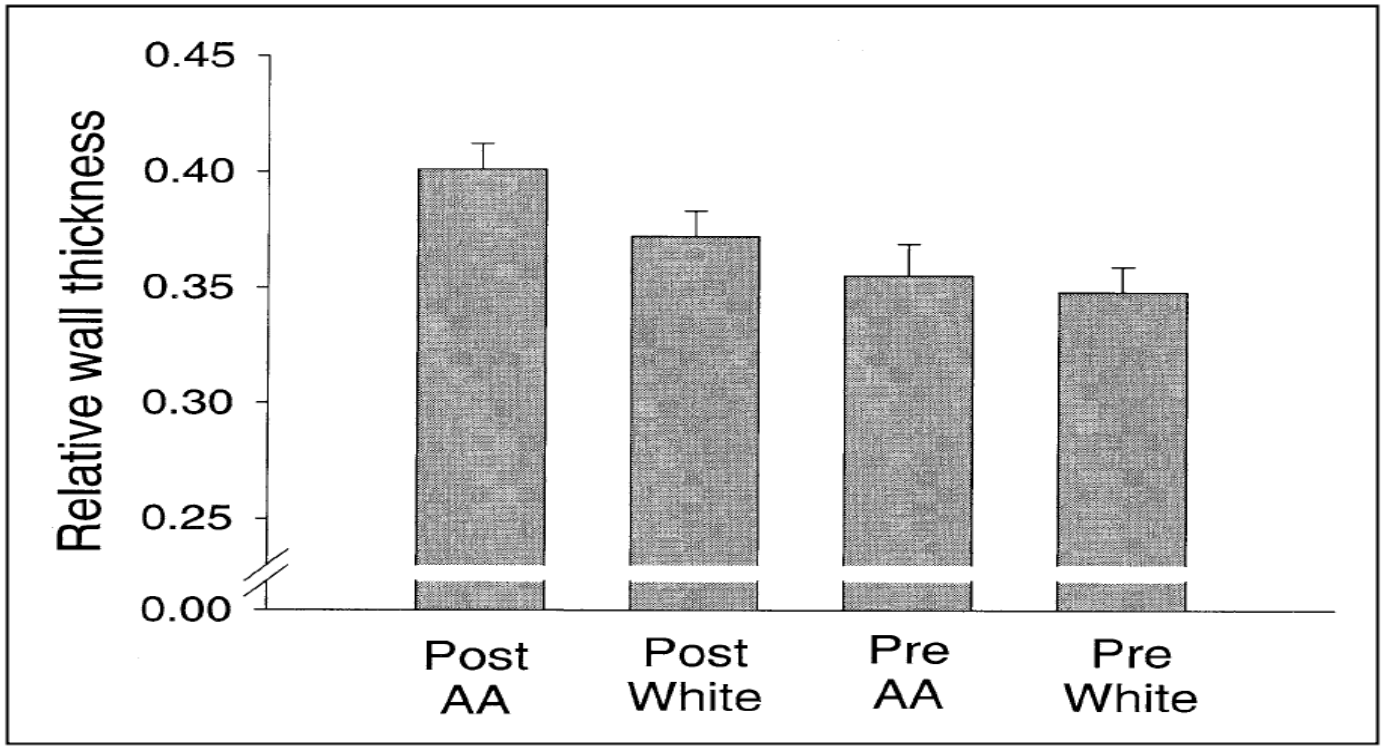


FIGURE 1. Left ventricular wall thickness in subgroups by menopause status and ethnicity. AA = African-American; Post = postmenopausal; Pre = premenopausal. Values represent mean ± SE.

Am J Cardio 2002;89:830

Reduced LV systolic performance

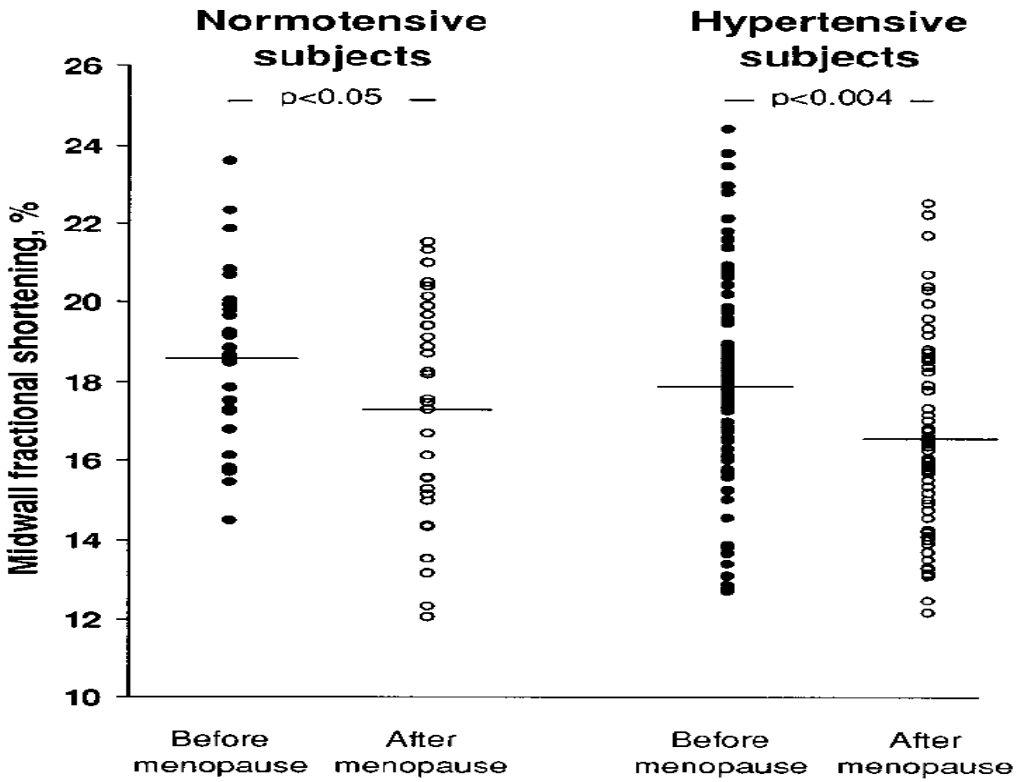


Figure 2. LV fractional shortening assessed at the midwall level in age- and BP-matched premenopausal (●) and postmenopausal (○) women.

Hypertension 1998;32:764-769.

CAD in pre, post menopausal women

European Heart Journal (2008) **29**, 1359–1369
doi:10.1093/eurheartj/ehn142

CLINICAL RESEARCH
Coronary heart disease

Sex differences in atheroma burden and endothelial function in patients with early coronary atherosclerosis

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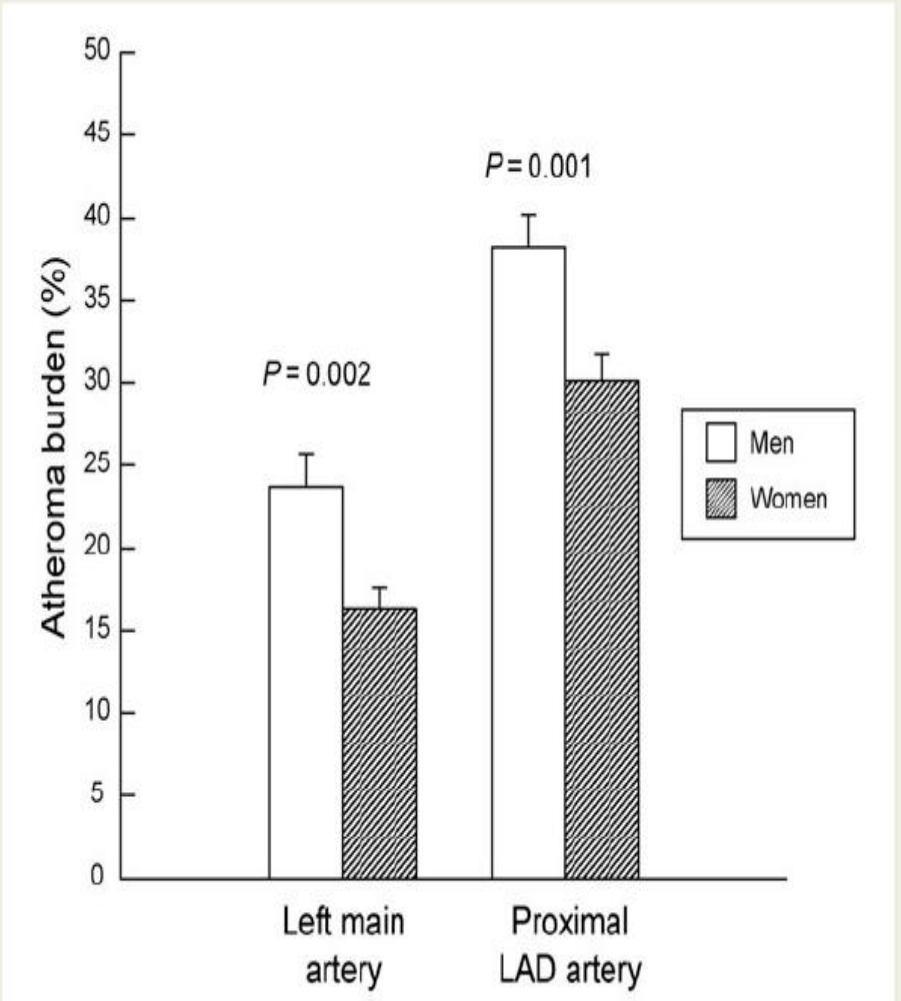
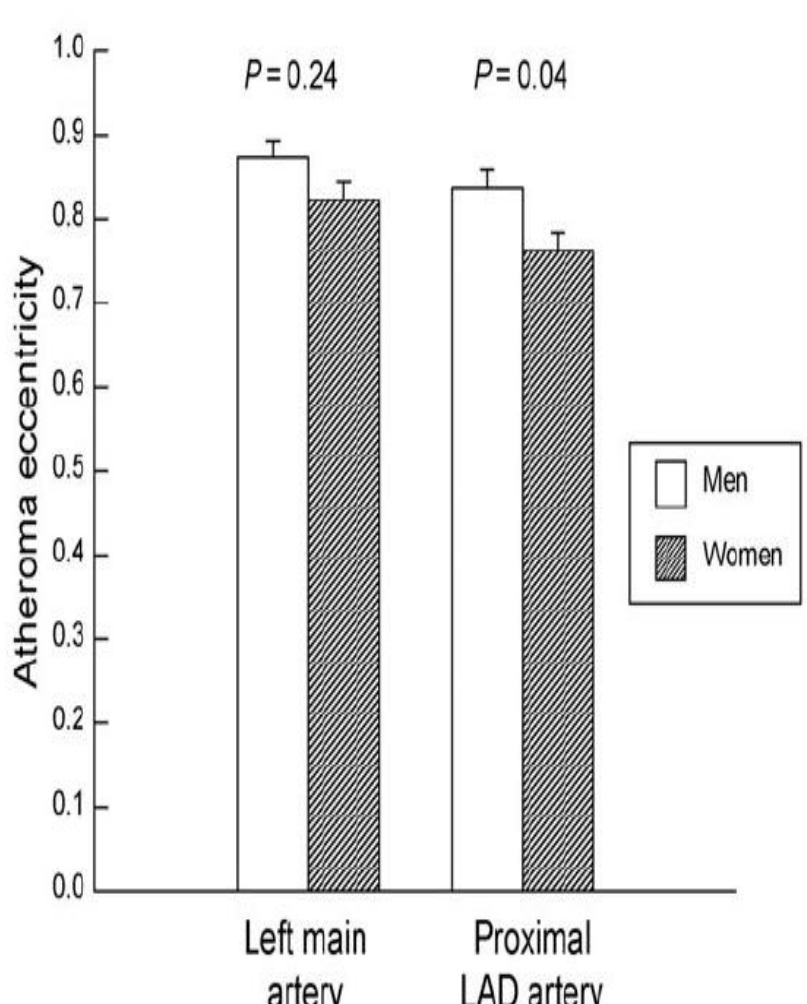
Table 1 Patient characteristics[a]

Characteristic	Patients		*P*-value
	Men ($n = 53$)	Women ($n = 89$)	
Age (year)	45.2 ± 11.0	51.7 ± 11.5	0.001
Hypertension	30 (56.6)	44 (49.4)	0.41
Diabetes mellitus	3 (5.7)	10 (11.2)	0.27
Hyperlipidemia	32 (60.4)	54 (60.7)	0.74
Current smoking	8 (15.1)	10 (11.2)	0.20
Body mass index (kg/m^2)	28.23 ± 4.42	30.14 ± 6.78	0.04
Mean arterial pressure (mmHg)	96.56 ± 14.00	99.29 ± 15.23	0.31
Ejection fraction (%)	65.18 ± 4.28	64.10 ± 5.62	0.24
Creatinine (mg/dL)	1.10 ± 0.21	0.91 ± 0.13	<0.001
Haemoglobin (g/dL)	13.98 ± 1.04	12.96 ± 1.11	<0.001
Glucose (mg/dL)	94 (89–101)	94 (86–104)	0.56
Total cholesterol (mg/dL)	175.28 ± 36.48	190.44 ± 37.57	0.02
LDL cholesterol (mg/dL)	106.73 ± 32.08	109.09 ± 33.10	0.68
HDL cholesterol (mg/dL)	41.48 ± 10.33	57.98 ± 16.41	<0.001
Triglycerides (mg/dL)	129 (86–166)	98 (64–147)	0.05
C-reactive protein (mg/dL)	0.16 (0.07–0.40)	0.36 (0.14–0.90)	0.01
Medications			
Aspirin	31 (58.5)	45 (50.6)	0.36
β-Blockers	17 (32.1)	28 (31.5)	0.94
ACE inhibitors	13 (24.5)	17 (19.1)	0.44
Calcium-channel antagonists	20 (37.7)	35 (39.3)	0.85
Lipid-lowering agents	23 (43.4)	35 (39.3)	0.63

ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Values are no. of patients (%), mean ± SD, or median (interquartile range).

Atheroma Between Gender





Epicardial and Microvascular Function Between Gender

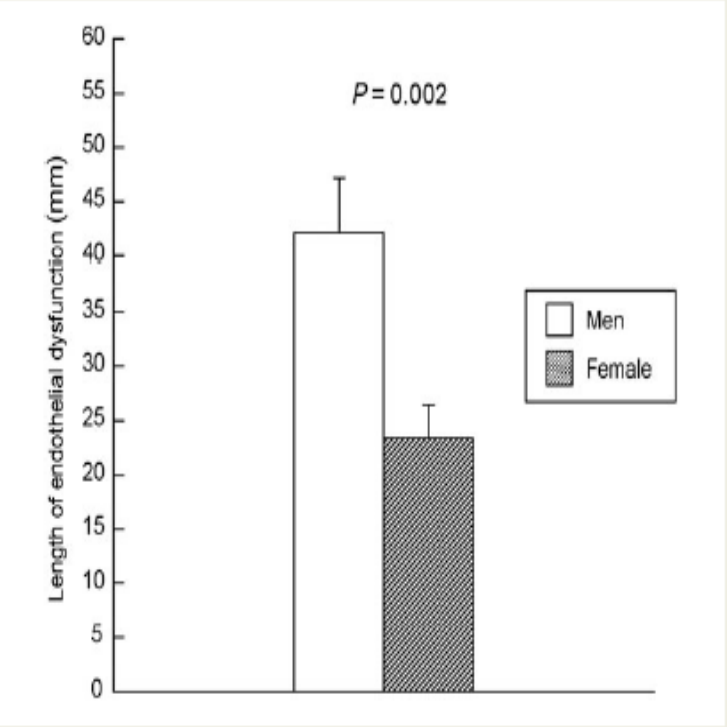


Figure 2 Graph shows the length of the coronary segments with epicardial endothelial dysfunction after intracoronary acetylcholine infusion. The segments were significantly longer in men than women ($P = 0.002$). Data are expressed as mean ± SEM.

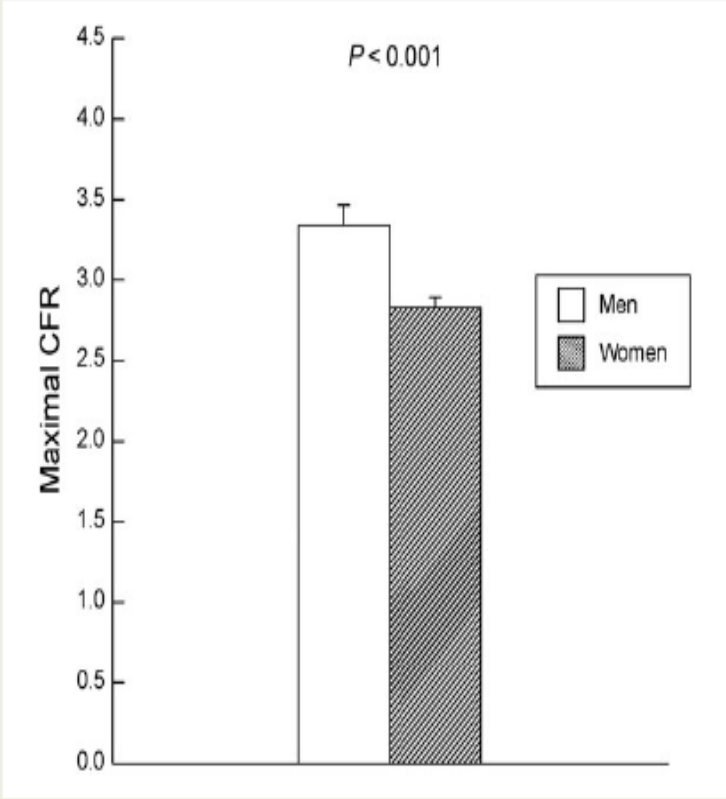
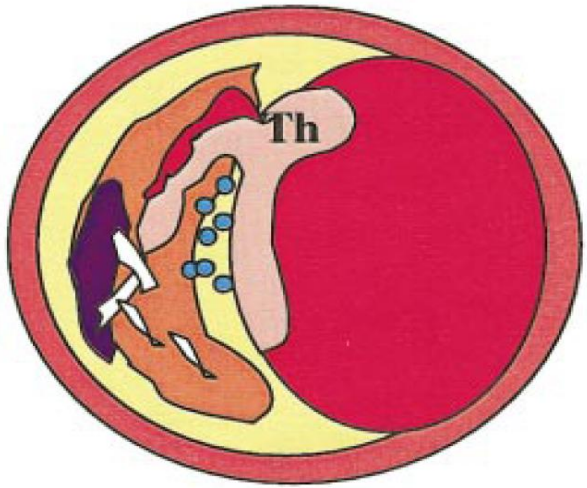


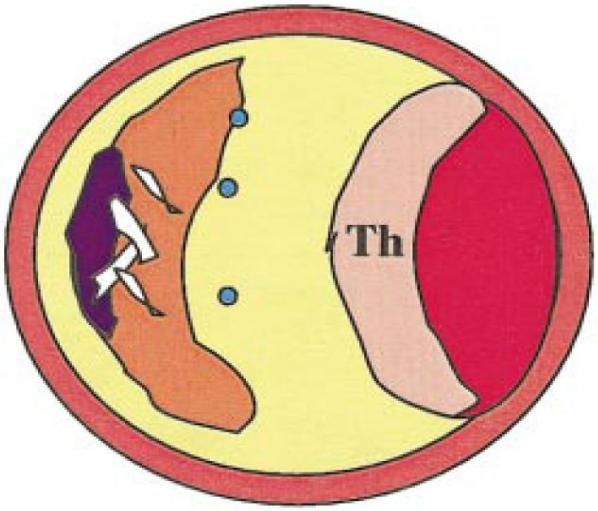
Figure 3 Maximal coronary flow reserve (CFR) after intracoronary infusion of adenosine was significantly decreased in women compared with men ($P < 0.001$). Data are expressed as mean ± SEM.

Gender Differences in Physiology in Myocardial Infarction

Plaque Rupture



Plaque Erosion



Young women
Smoker

Virmani et al. ATVB 2000;20:1262

Effect of Menopause on Plaque Morphologic Characteristics in Coronary Atherosclerosis

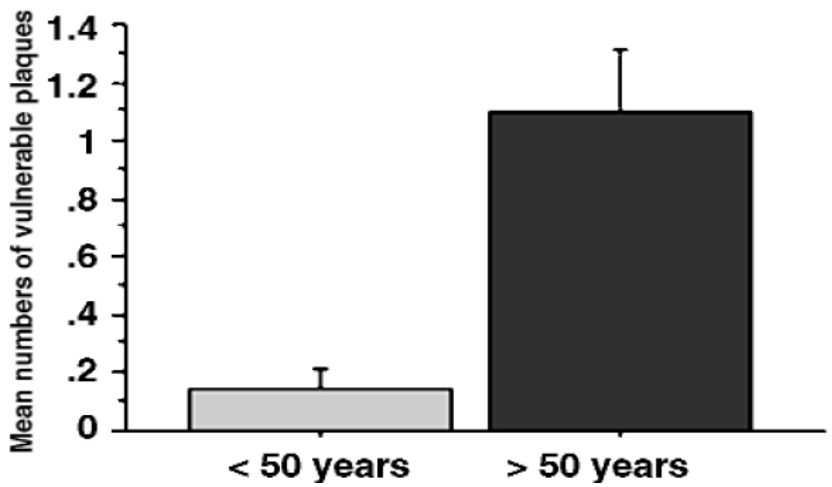
Table I. Mechanism of death and risk factors in 51 women who died suddenly from severe coronary artery disease

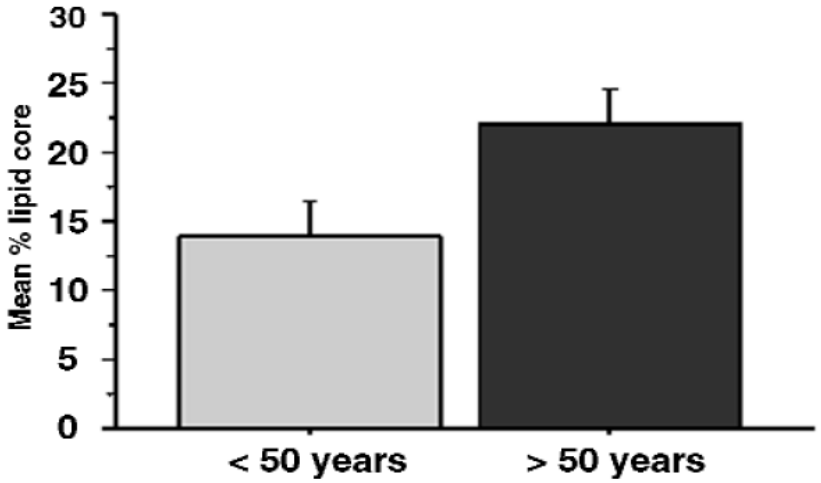
Mechanism of death (n)	Age >50 y (%)	TC (mg/dL)	Body mass index	Glycohemoglobin (mean %)	Cigarette smokers (n)
Plaque erosion (n = 18)	3 (17%)	191 ± 68	27 ± 4.3	6.7 ± 0.7	14 (78%)
Plaque rupture (n = 8)	7 (87%)	272 ± 61	31 ± 4.4	8.8 ± 4.4	4 (50%)
Stable plaque, no infarct (n = 7)	2 (29%)	178 ± 57	30 ± 10.6	8.0 ± 4.5	2 (29%)
Stable plaque, healed infarct (n = 18)	9 (50%)	198 ± 61	28 ± 9.0	10.2 ± 5.0	9 (50%)
P value	.001, rupture vs erosion; .03, rupture vs stable plaque, no infarct	.01, rupture vs stable plaque; .01, rupture vs stable plaque, healed infarct; .02, rupture vs erosion	.02, rupture vs eroded plaque	.001, stable plaque, healed infarct vs eroded plaque	

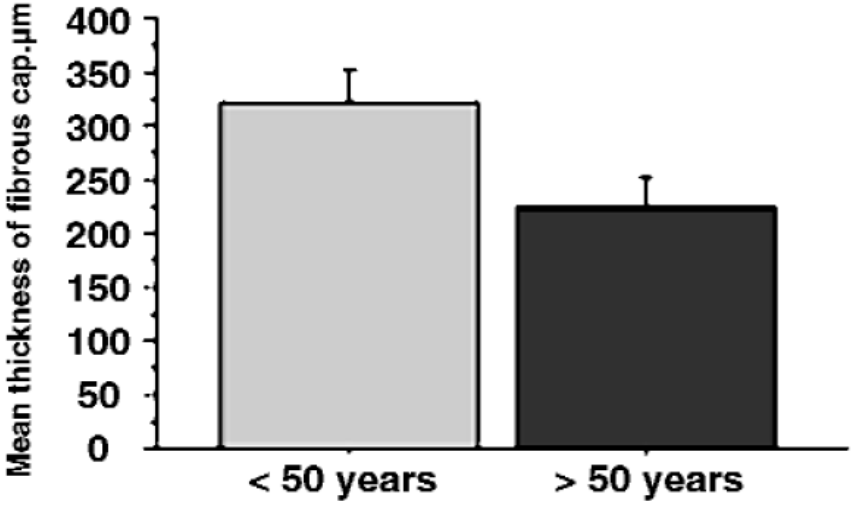
51 women who died suddenly from severe CAD

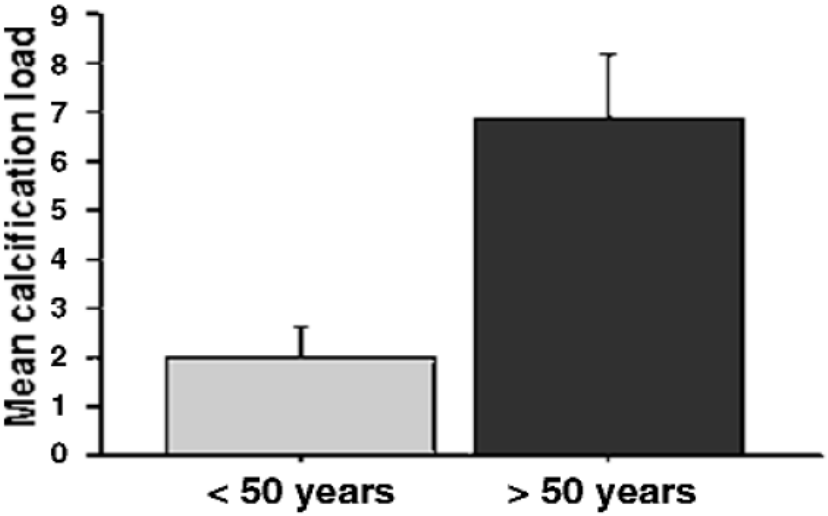
Burke AP, Virmani R. Am H J 2001;141:S58

Effect of Menopause on Plaque Morphologic Characteristics in Coronary Atherosclerosis



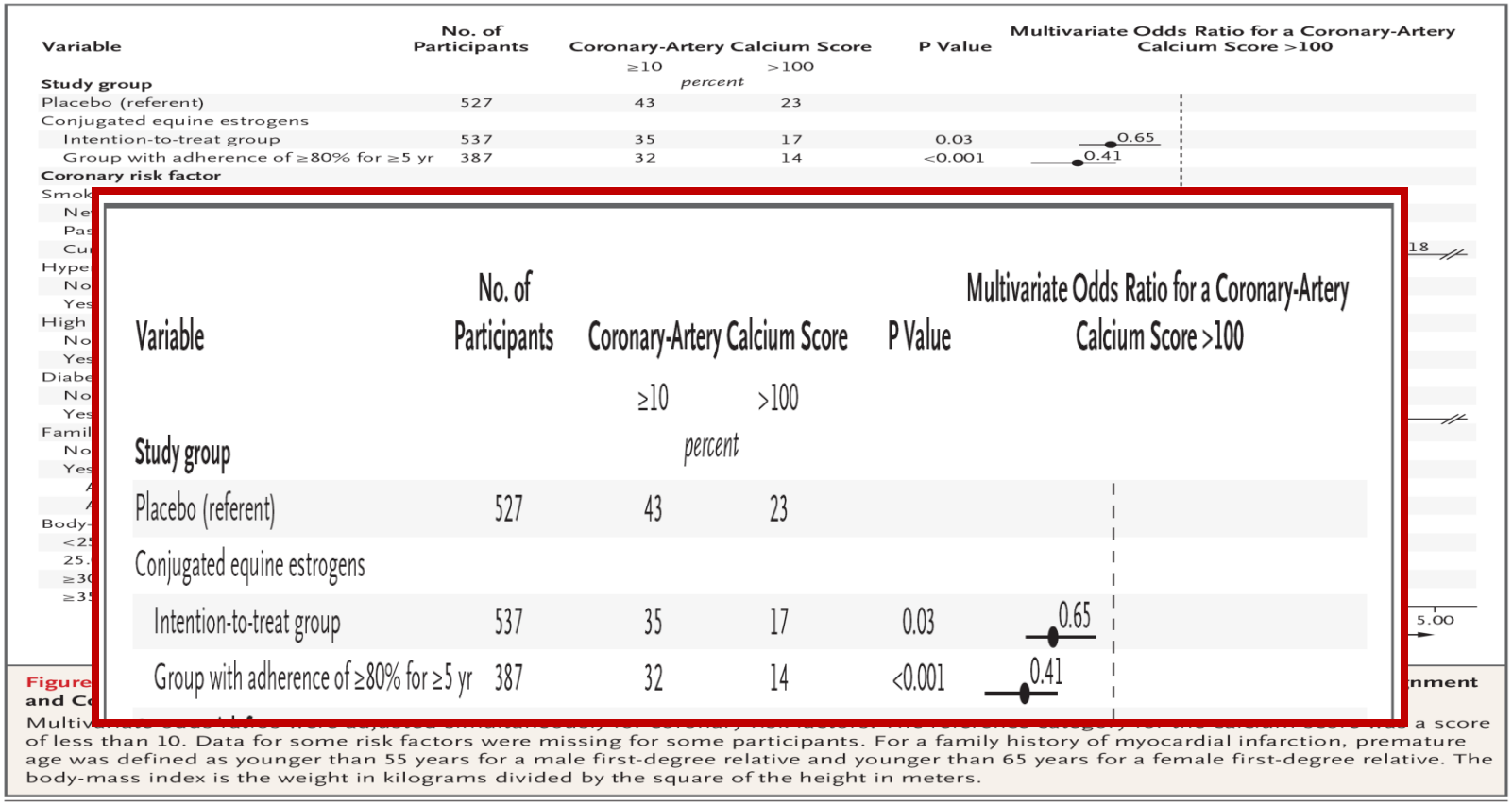






51 women who died suddenly from severe CAD
Burke AP, Virmani R. Am H J 2001;141:S58

Estrogen Therapy and Coronary Artery Calcification



Variable	No. of Participants	Coronary-Artery Calcium Score ≥10 (percent)	Coronary-Artery Calcium Score >100 (percent)	P Value	Multivariate Odds Ratio for a Coronary-Artery Calcium Score >100
Study group					
Placebo (referent)	527	43	23		
Conjugated equine estrogens					
Intention-to-treat group	537	35	17	0.03	0.65
Group with adherence of ≥80% for ≥5 yr	387	32	14	<0.001	0.41

Figure … and C…

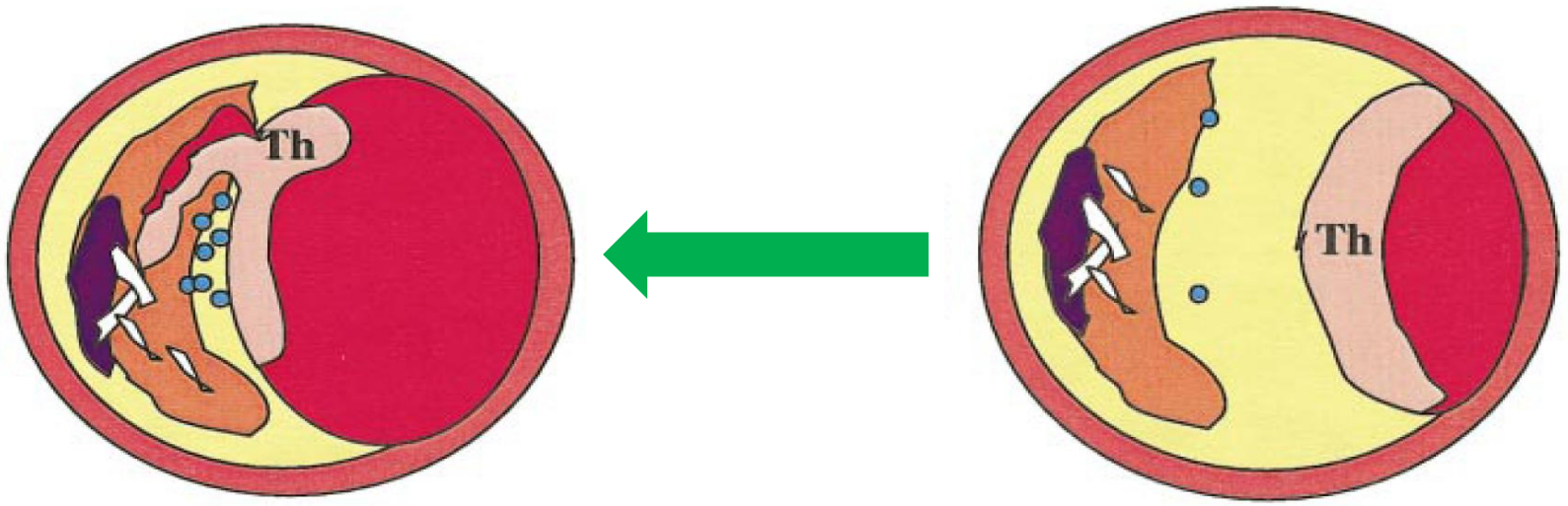
Multiv… a score of less than 10. Data for some risk factors were missing for some participants. For a family history of myocardial infarction, premature age was defined as younger than 55 years for a male first-degree relative and younger than 65 years for a female first-degree relative. The body-mass index is the weight in kilograms divided by the square of the height in meters.

Women's Health Initiative Trial, Conjugated equine estrogen (0.625mg/d), Undergone hysterectomy

Gender Differences in Physiology in Myocardial Infarction

Plaque Rupture

Plaque Erosion



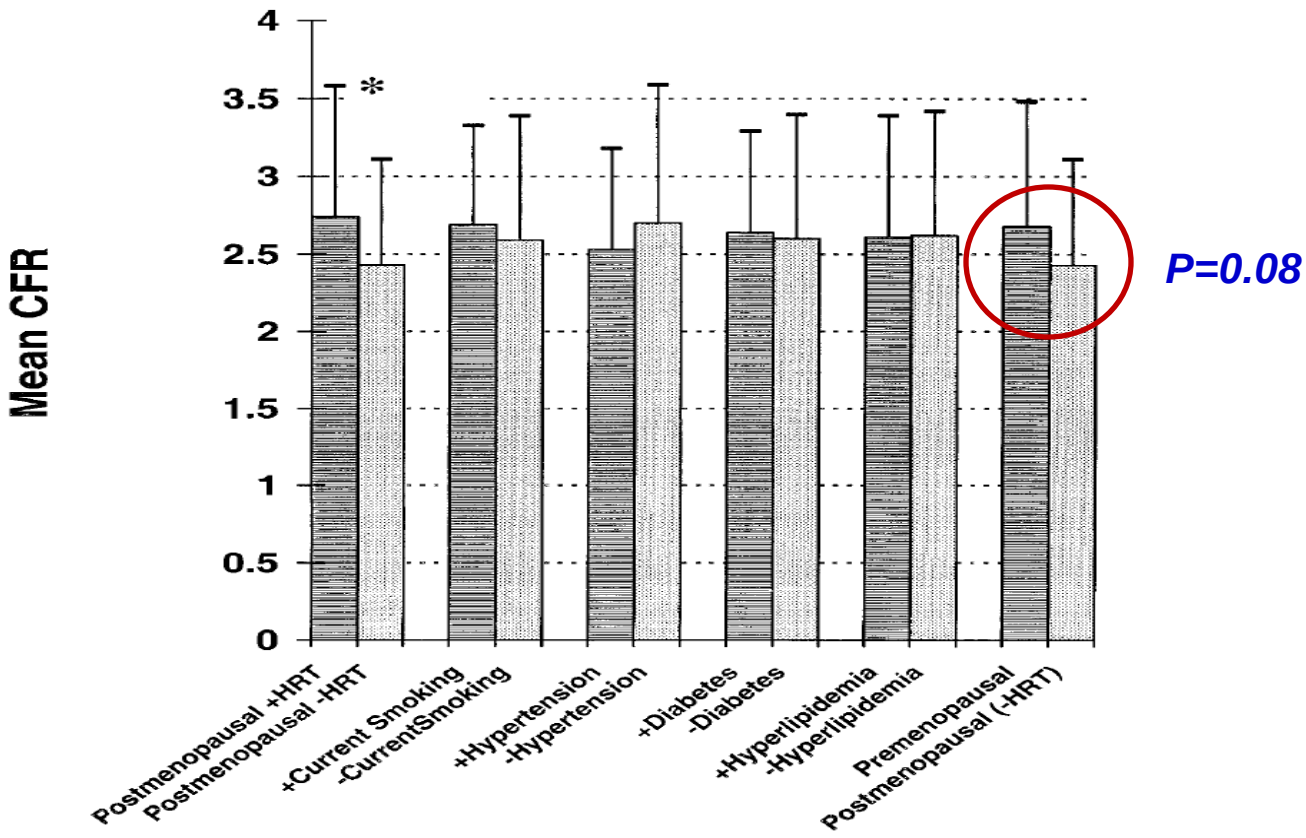
Older Women

Young women
Smoker

Virmani et al. ATVB 2000;20:1262

Microvascular dysfunction after menopause

Figure 1



Coronary flow velocity reserve in women with and those without traditional cardiac risk factors. Error bars denote standard deviation. *CFR,* Coronary flow velocity reserve; *HRT,* hormone replacement therapy in post-menopausal women. *Asterisk,* $P = .017$.

Reis et al. WISE study. Am H J 2001;141:735

Endothelial function in menopausal women

Endothelial Dysfunction: The Risk of Risk Factors

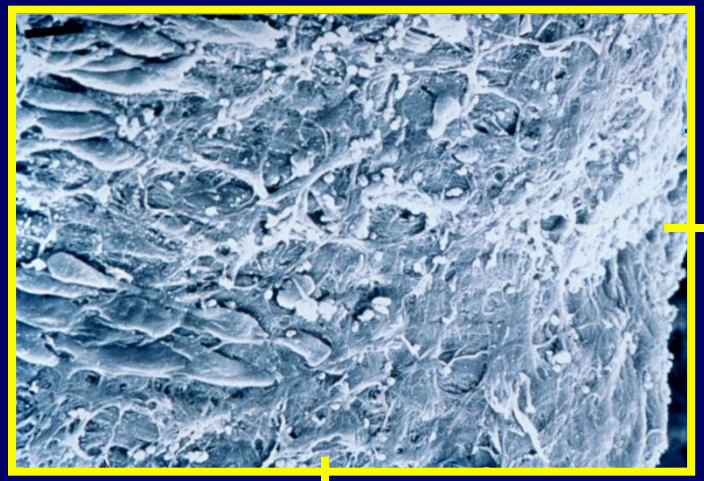
Smoking

Hypertension

Hypercholesterolemia

Diabetes

New risk factors



Genomic predisposition

Endothelial dysfunction: The risk of the risk factors

Dementia

Heart failure

Stroke

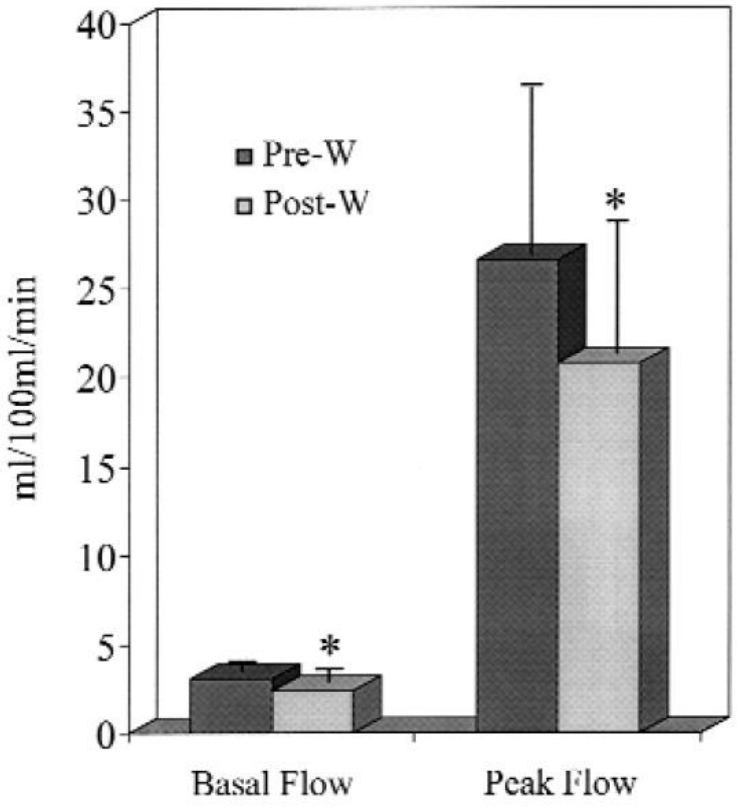
Acute Coronary syndrome

Sudden death

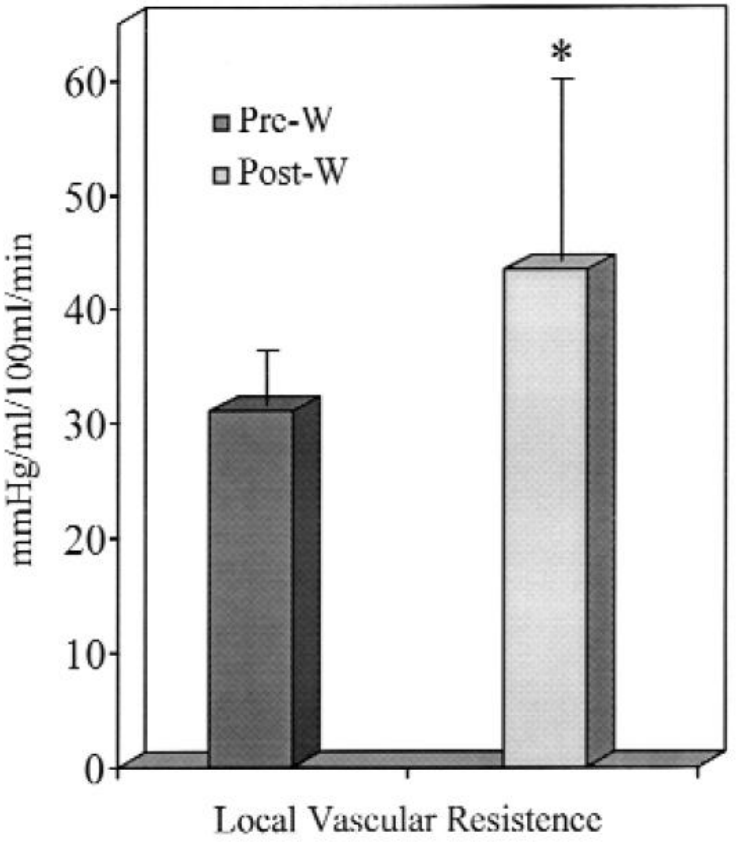
Impotence

Sleep apnea

Impaired Forearm Blood Flow and Vasodilator Reserve in Healthy Postmenopausal Women



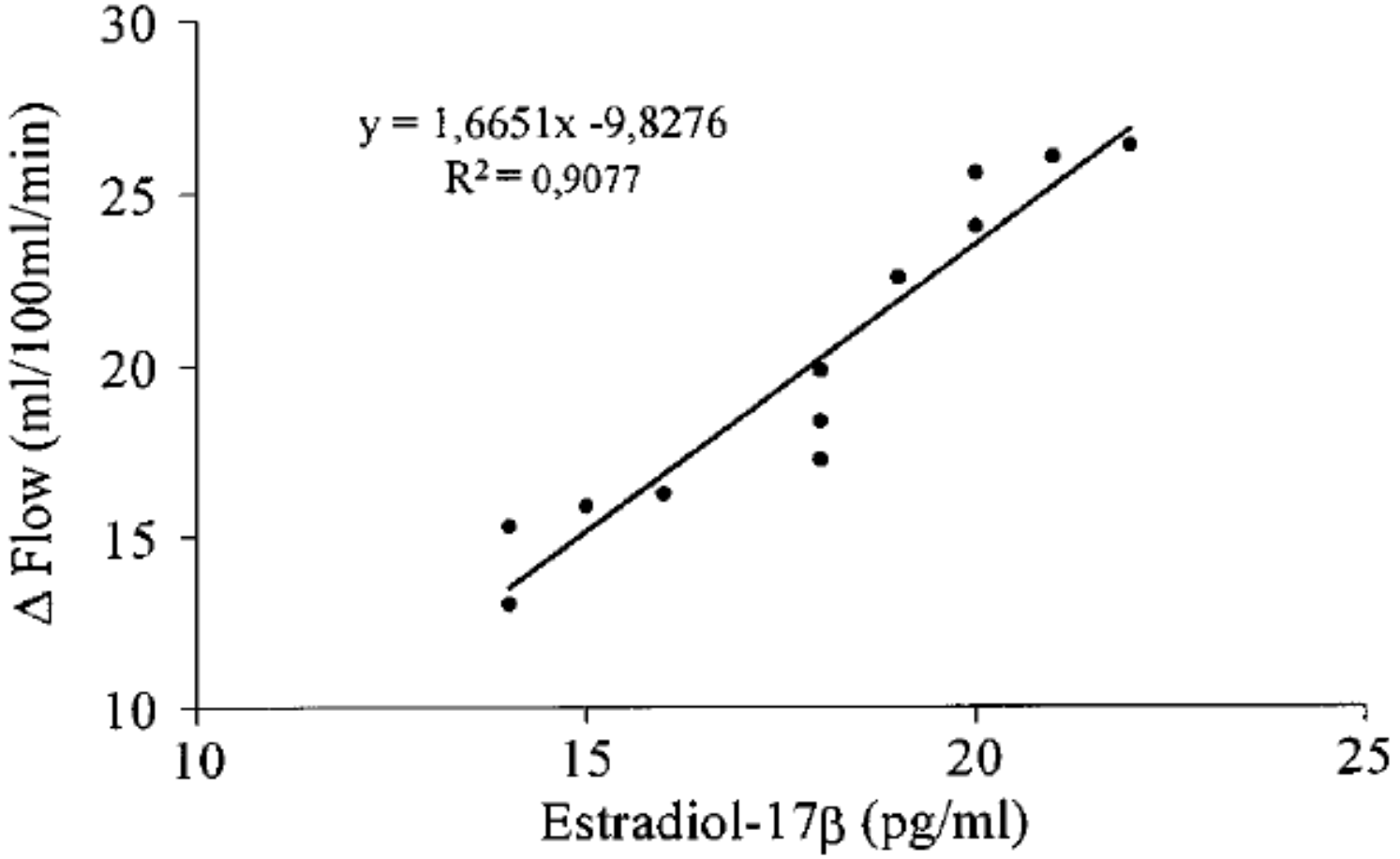
Forearm blood flow



Vascular Resistence

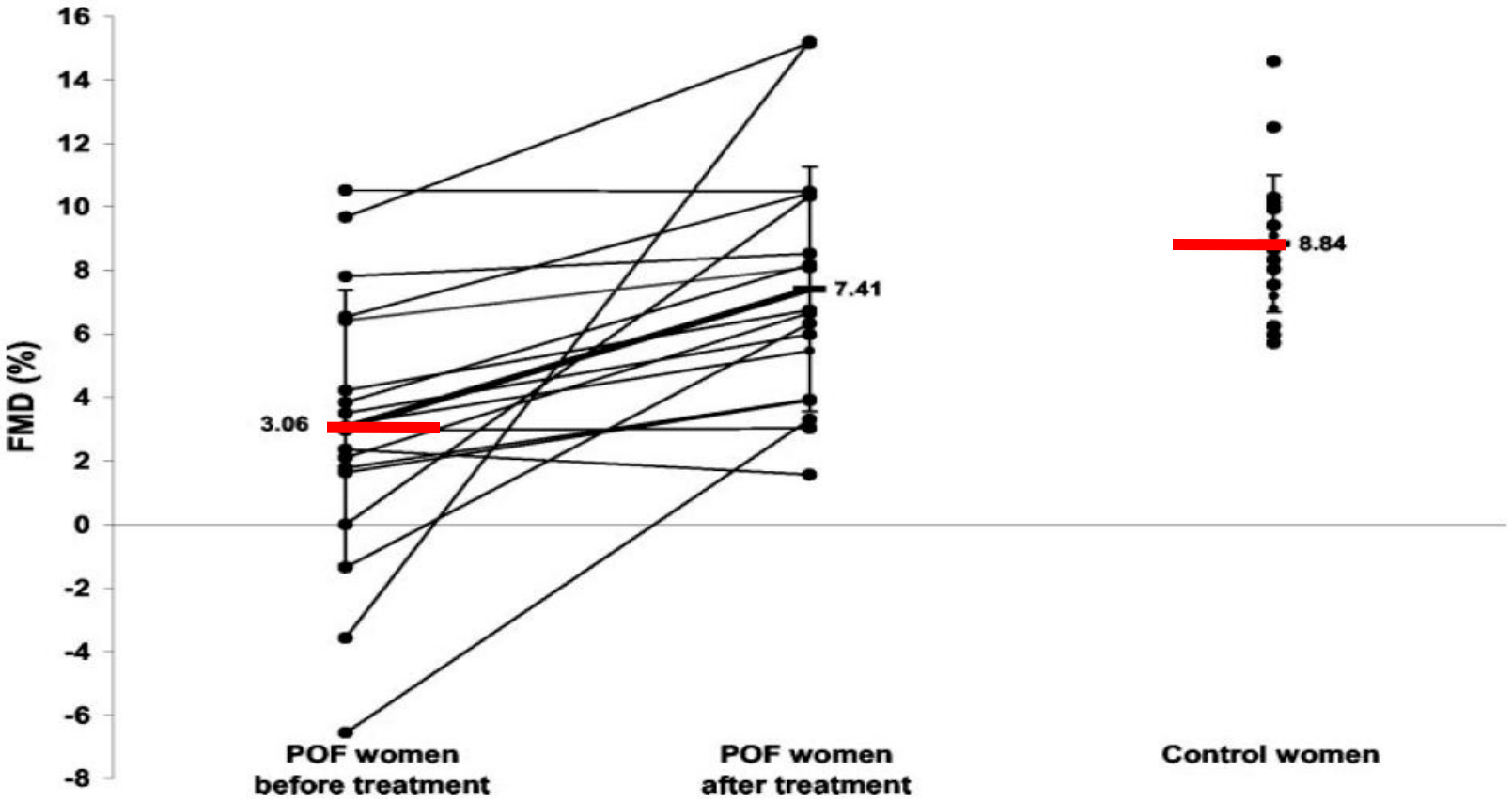
Mercuro G. et al. Am Heart J 1999;137:692

Impaired Forearm Blood Flow and Vasodilator Reserve in Healthy Postmenopausal Women



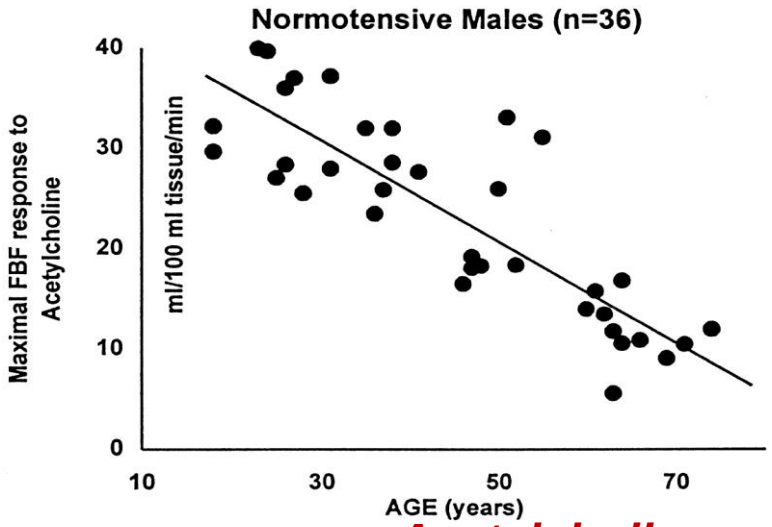
Mercuro G. et al. Am Heart J 1999;137:692

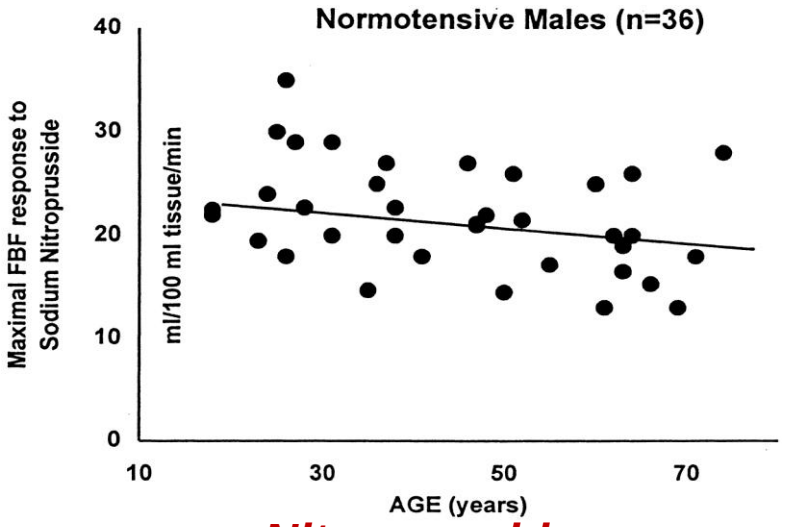
Impaired Endothelial Function in young women with premature ovarian failure



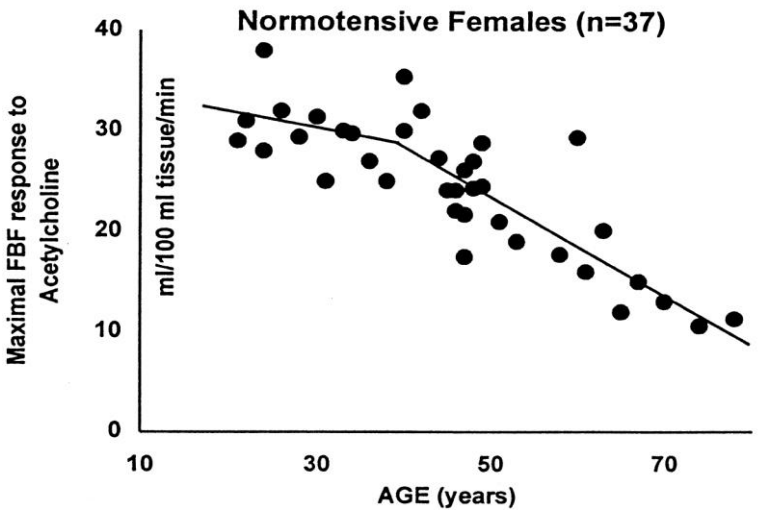
Kalantaridous et al. J Clin Endocrinol Metab 2004;89:3907

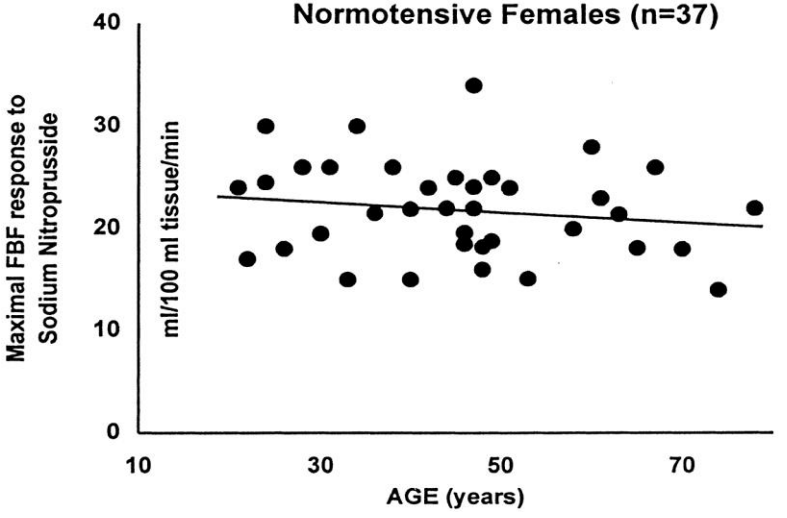
Menopause is associated with endothelial dysfunction in women





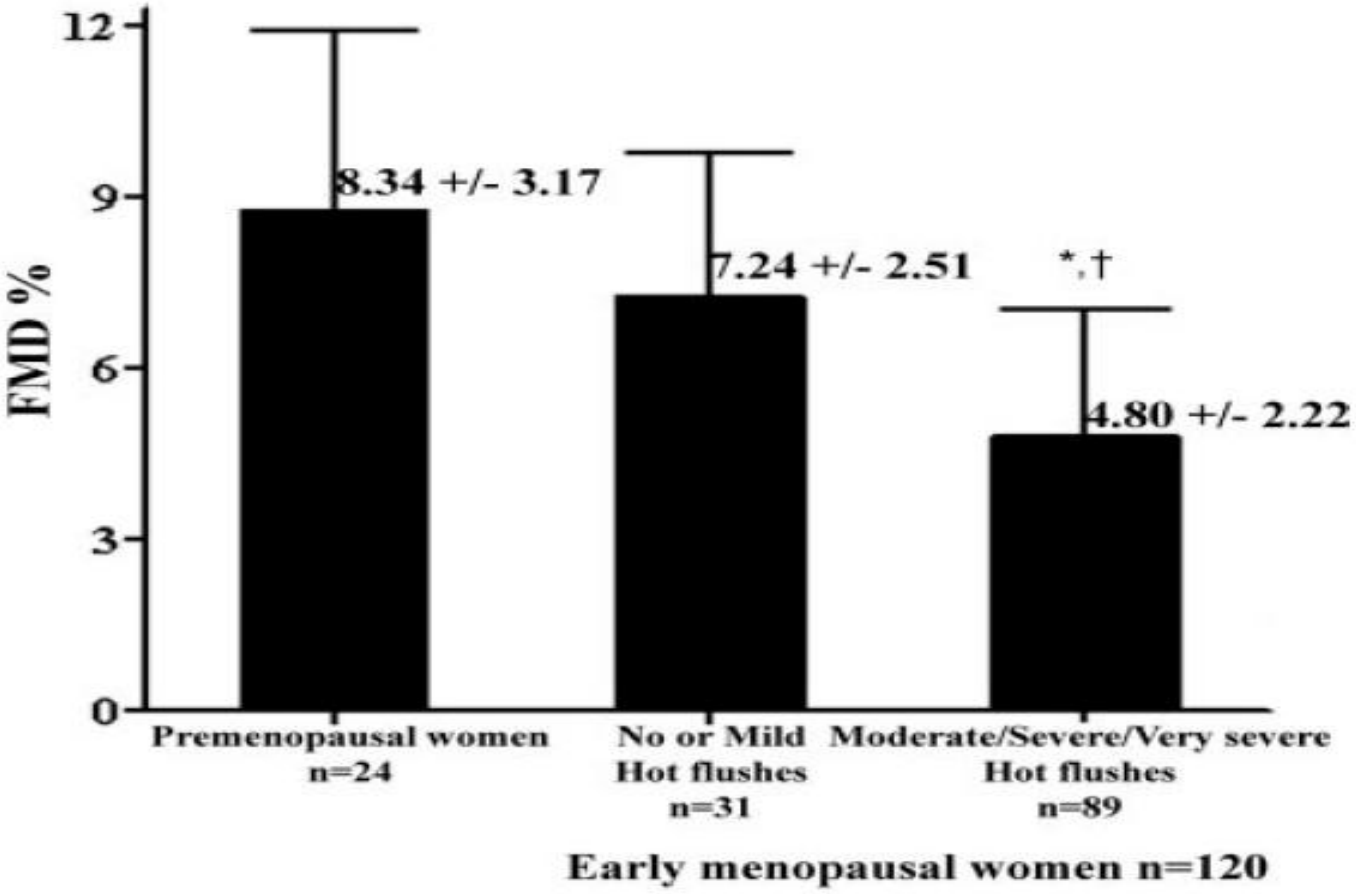
Acetylcholine ***Nitroprusside***





Taddei, S. et al. Hypertension 1996;28:576-582

FMD and Early Menopause



Bechlioulis et al. J Clin endocrinol Metab 2010;95:1199

Menopause tends to downregulate NO-cGMP pathway resulting in endothelial dysfunction

Table 1

Platelet nitric oxide levels in platelet rich plasma and plasma nitric oxide levels, c-GMP and estradiol levels in study and control groups.

Parameters	Study group ($n=50$) (mean ± S.E.M.)	Control group ($n=50$) (mean ± S.E.M.)	p-Value
Estradiol (pg/ml)	22.14 ± 2.77	50.62 ± 6.52	<0.01
Plasma NO (μM/L)	7.31 ± 1.11	11.15 ± 0.90	0.000
c-GMP (pmol/ml)	1.02 ± 0.15	2.22 ± 0.66	0.000

Table 3

Correlation of age and estrogen levels with lipid profile and nitric oxide–c-GMP levels.

	Study group		Control group	
	Age (years)	Estradiol levels	Age (years)	Estradiol levels
Plasma NO (μM/L)	$r=-0.09$, $p=0.54$	$r=0.389$, $p=0.021$	$r=0.269$, $p=0.11$	$r=0.466$, $p=0.002$
c-GMP (pmol/ml)	$r=0.080$, $p=0.58$	$r=0.293$, $p=0.08$	$r=0.210$, $p=0.18$	$r=0.352$, $p=-0.04$
Serum cholesterol	$r=0.231$, $p=0.16$	$r=-0.409$, $p=0.011$	$r=-0.088$, $p=0.63$	$r=-0.267$, $p=0.229$
Serum triglycerides	$r=0.262$, $p=0.11$	$r=0.186$, $p=0.316$	$r=0.093$, $p=0.62$	$r=0.172$, $p=0.443$
Serum LDL (mg/dl)	$r=0.162$, $p=0.38$	$r=-0.451$, $p=0.024$	$r=-0.131$, $p=0.55$	$r=-0.285$, $p=0.223$
Serum VLDL (mg/dl)	$r=0.28$, $p=0.08$	$r=0.196$, $p=0.298$	$r=0.065$, $p=0.72$	$r=0.094$, $p=0.671$
Serum HDL (mg/dl)	$r=0.027$, $p=0.87$	$r=0.060$, $p=0.75$	$r=-0.224$, $p=0.22$	$r=-0.120$, $p=0.568$
Serum apolipoprotein B	$r=-0.15$, $p=0.43$	$r=-0.214$, $p=0.303$	$r=0.062$, $p=0.724$	$r=0.214$, $p=0.266$

Salhotra S, et al. Maturitas 2009;62:166

Carotid IMT after menopause

Carotid IMT and Years Since Bilateral Oophorectomy

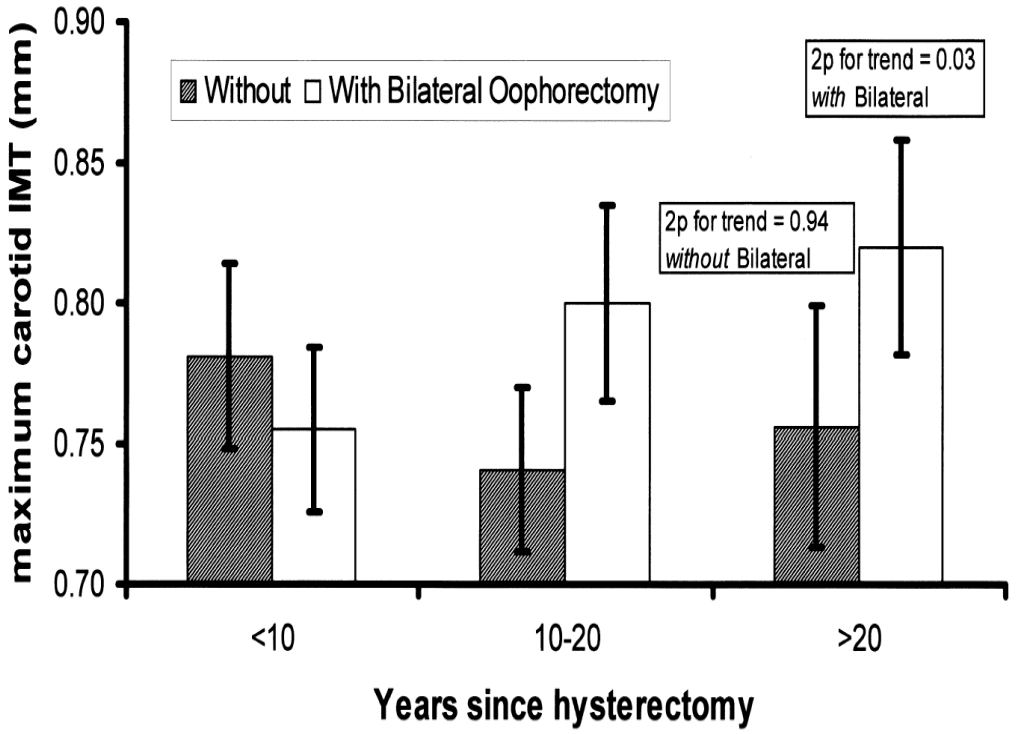
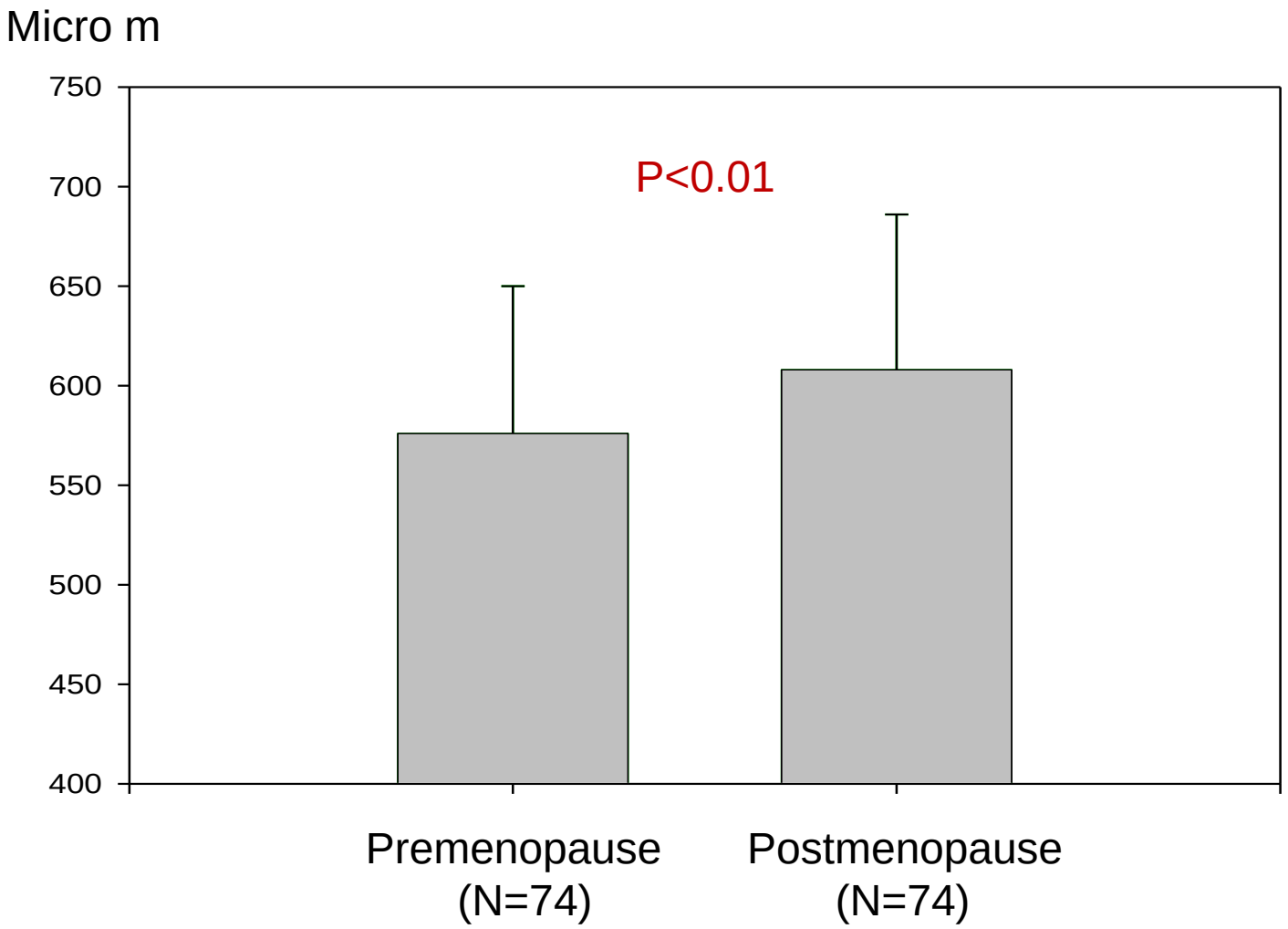


FIGURE 1. Carotid atherosclerosis and number of years since hysterectomy, The Los Angeles Atherosclerosis Study, 1995–1996. Error bars represent standard errors. The sample size in each group, according to years since hysterectomy, is as follows. Women without bilateral oophorectomy (hatched bars): <10, *n* = 12; 10–20, *n* = 22; >20, *n* = 8. Women with bilateral oophorectomy (white bars): <10, *n* = 21; 10–20, *n* = 19; >20, *n* = 15. IMT, intima-media thickness.

Dwyer KM, et al. Am J epidemiol 2002;156:438

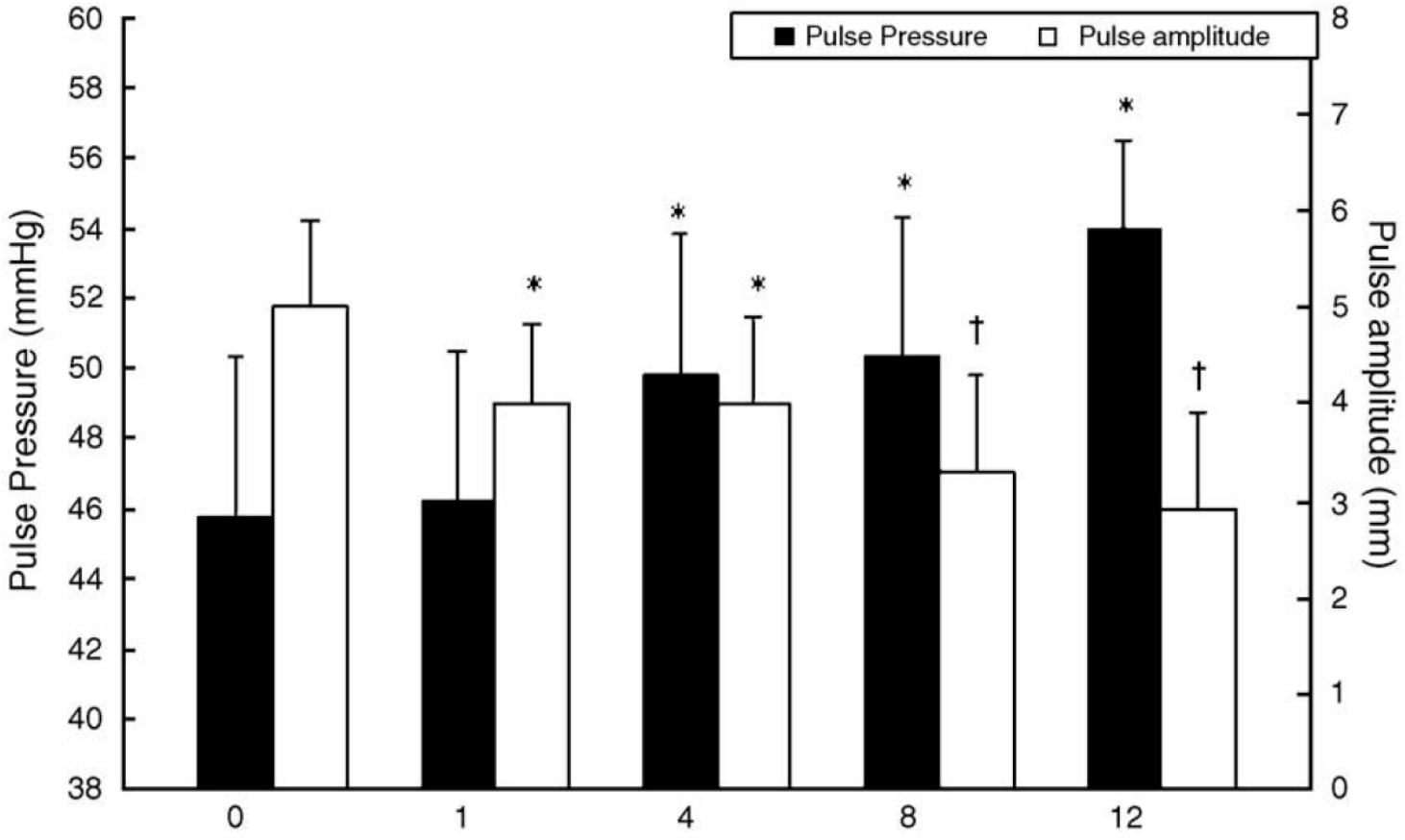
Common Carotid IMT After Menopause



Muscelli E, et al. Am J Hypertens 2009;22:364

Aortic Stiffness after menopause

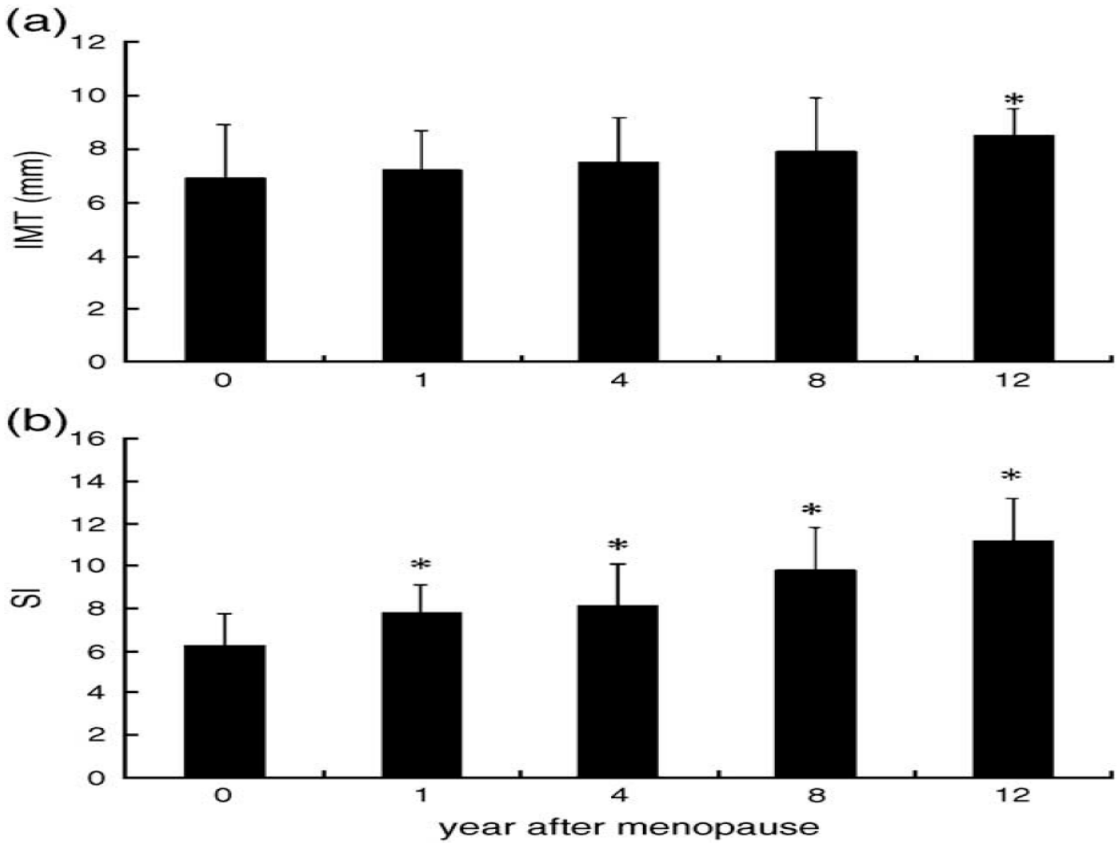
Pulse Pressure Changes after menopause



Small cross-sectional study: Women without diabetes, HTN, thromboembolic dz, cancer, or other chronic illness

Izumi S, et al. Life Sciences 2006;78:1696

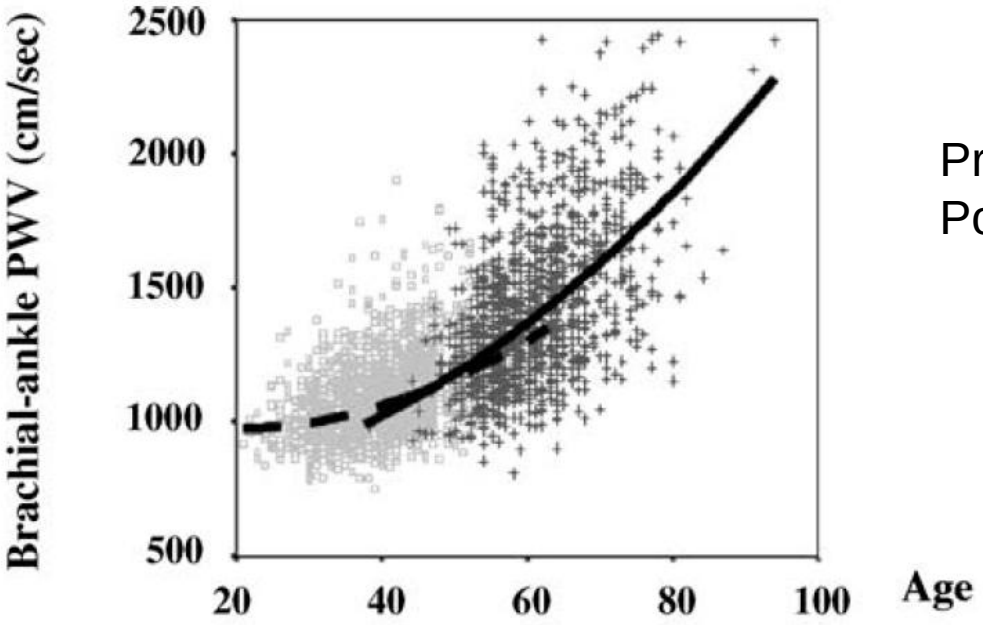
IMT and Stiffness Index (SI) in postmenopausal Women



Small cross-sectional study : Women without diabetes, HTN, thromboembolic dz, cancer, or other chronic illness

Izumi S, et al. Life Sciences 2006;78:1696

Menopause is an independent factor augmenting the age-related increase in arterial stiffness in the early postmenopausal phase

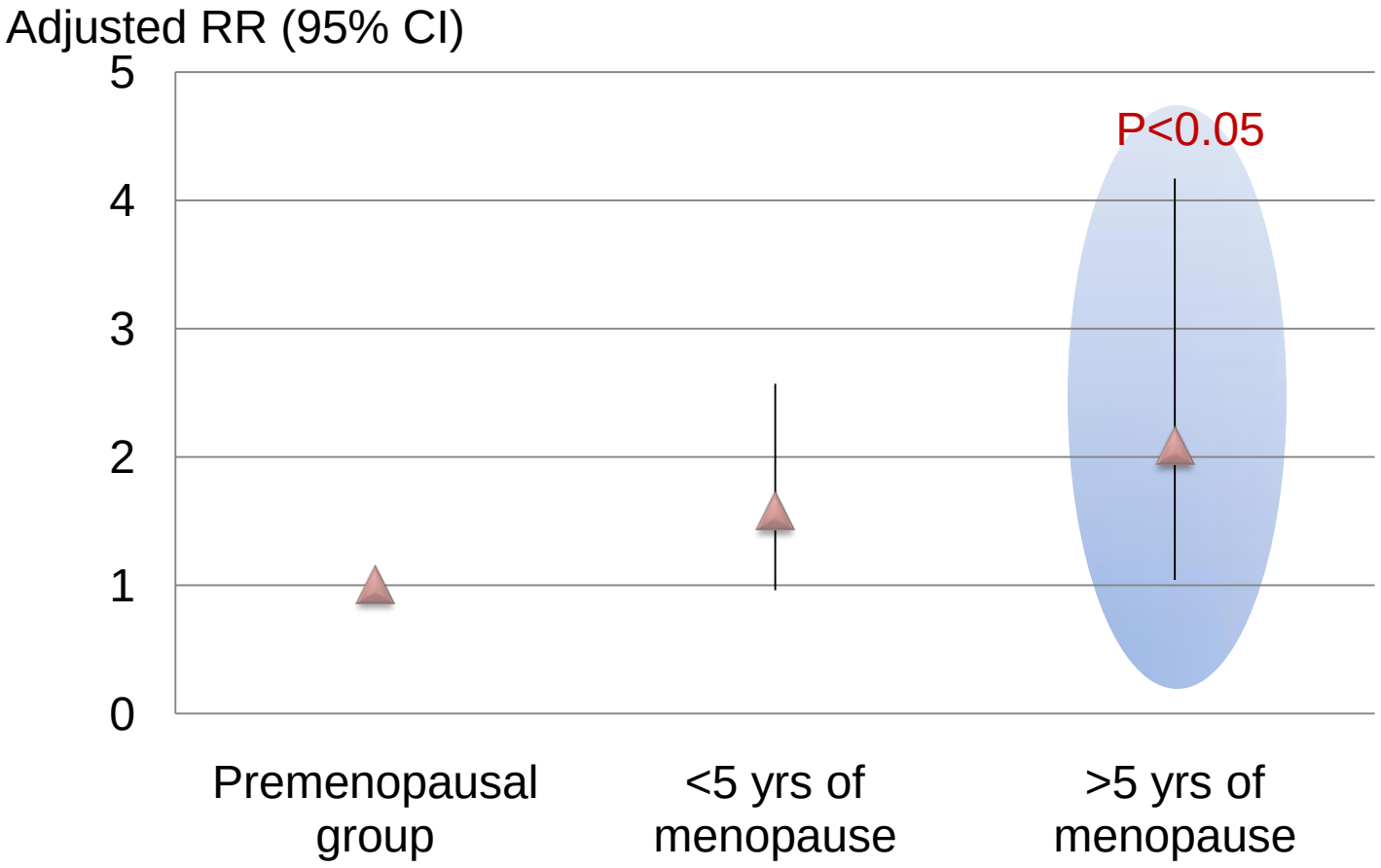


Premeno, n=1804
Postmeno, n=1345

Postmenopausal group:
brachial-ankle PWV=0.23 x age^2- 8.92 x age + 1058, r = 0.41, p< 0.01
Premenopausal group:
brachial-ankle PWV = 0.17 x age^2- 0.58 x age + 812, r = 0.56, p< 0.01

Zaydun G, et al. Atherosclerosis 2006;184:137

The >5 years postmenopausal category was a significant risk factor for belonging to the highest baPWV tertile, even after adjustments for age and other conventional atherosclerotic risk factors

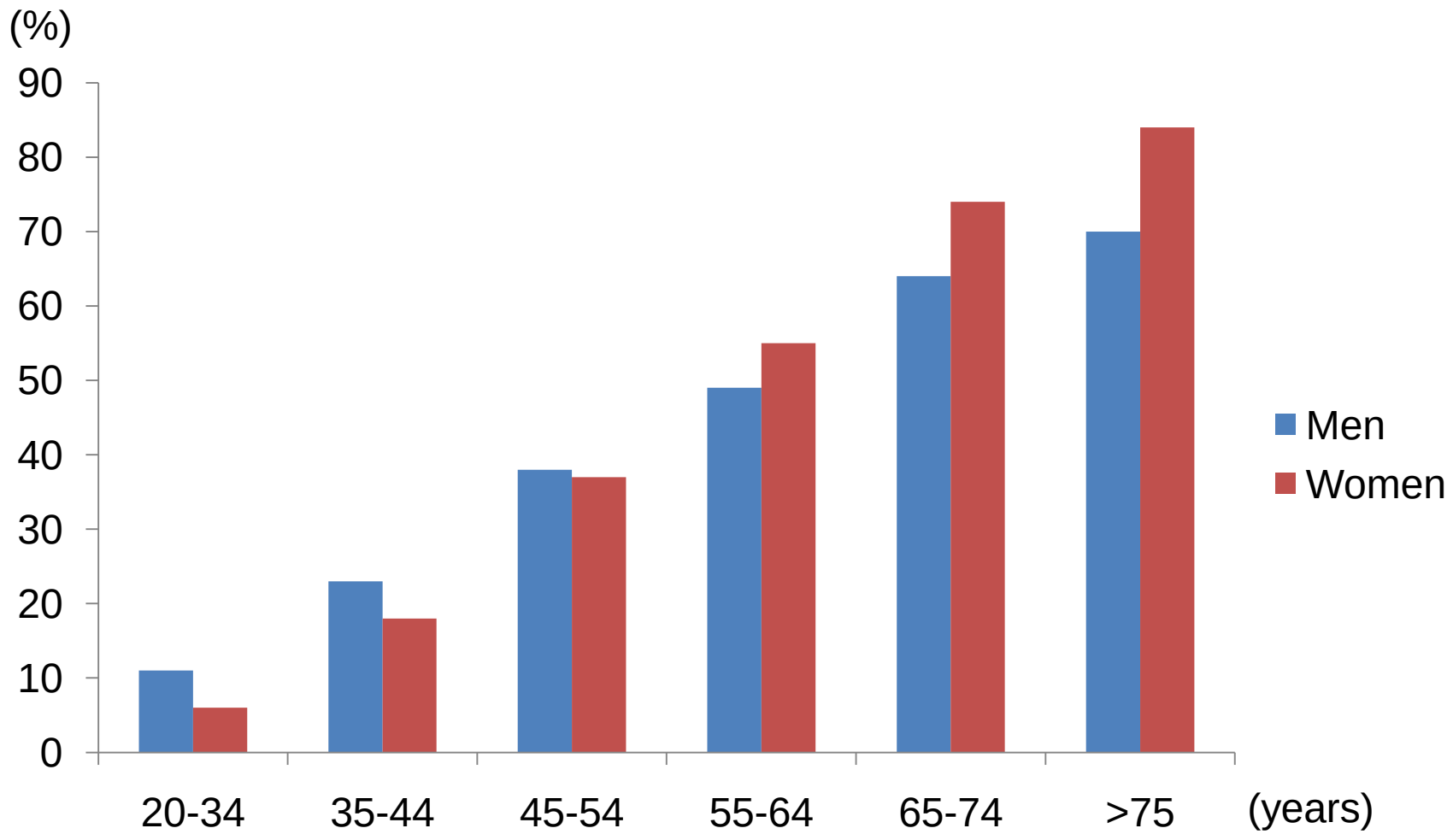


Subjects age between 45-56 years

Zaydun G, et al. Atherosclerosis 2006;184:137

HTN after menopause

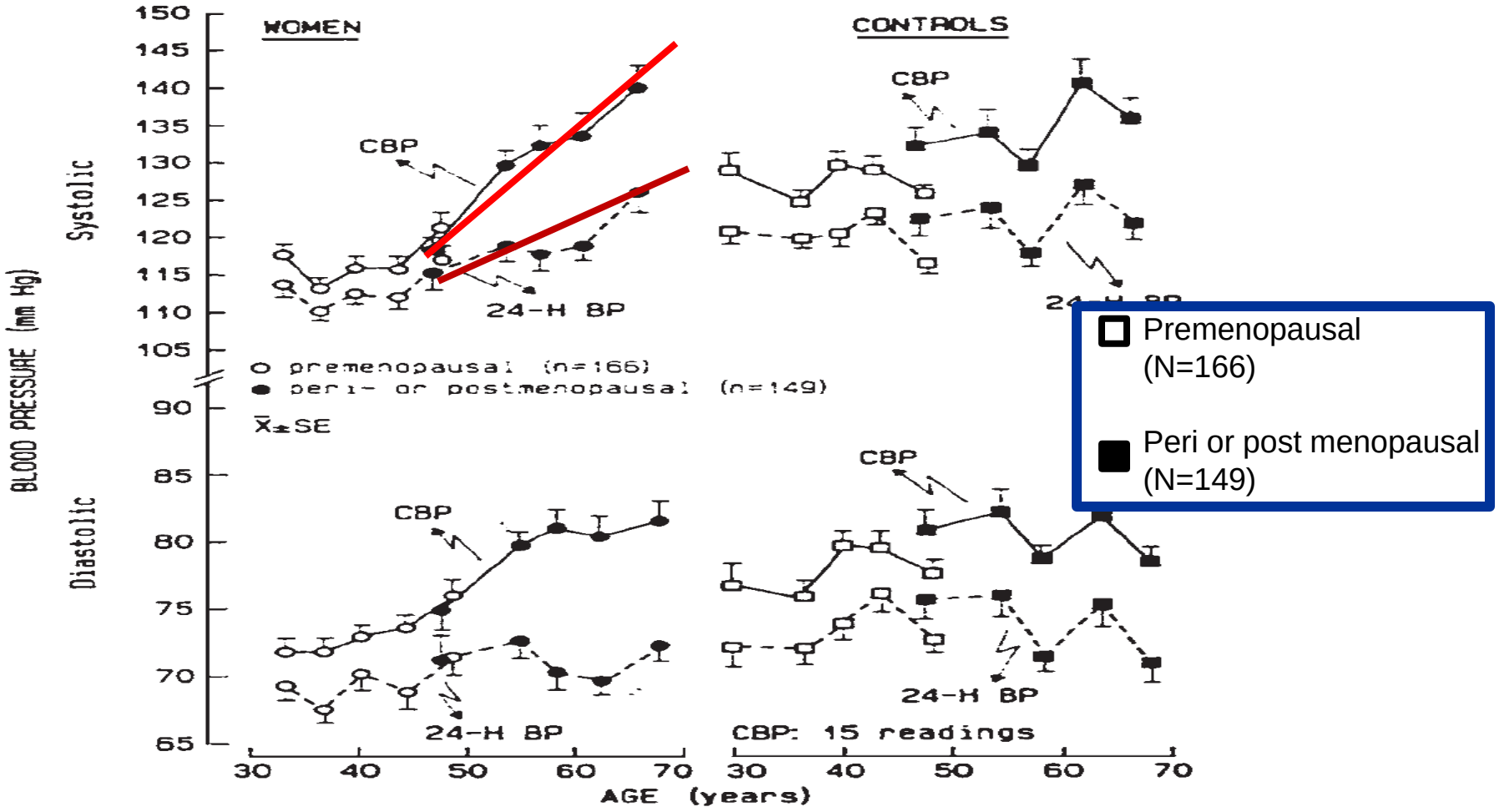
Sexual Dimorphism in Blood Pressure



Circulation 2008;117:e25

Menopause and Hypertension

Changes in BP from baseline to f/u (mean 5.2 years)



J Hum Hypertens 1997;11:507.

Menopause and Hypertension: An Age-Old Debate

Association with HTN	No association with HTN	Association wi… lowe…
– Cross-sectional study: Weiss 1972 (897), Staessen 1989 (462), Owens 1993 (34… Zanchet… (18… …ective study: …Staessen 1997 (315), Scuteri 2001 (226)	– Prospective study: Casiglia 1996 (568), Luoto … (3… … 1997 …3), Colditz 1987 (121,700)	…ective study: …van Beresteyn 1989 (193)

The Effect of menopause on BP is controversial.

Hypertension 2008;51:952.

Bilateral Oophorectomy increases BP Within a Few Weeks

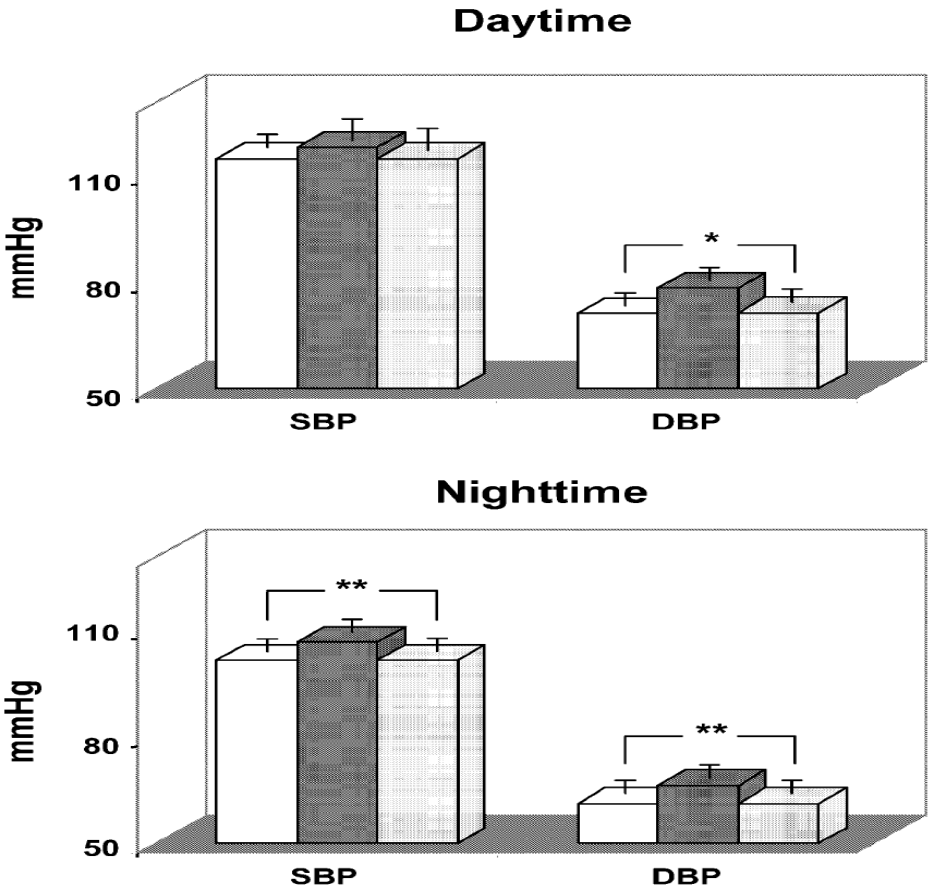
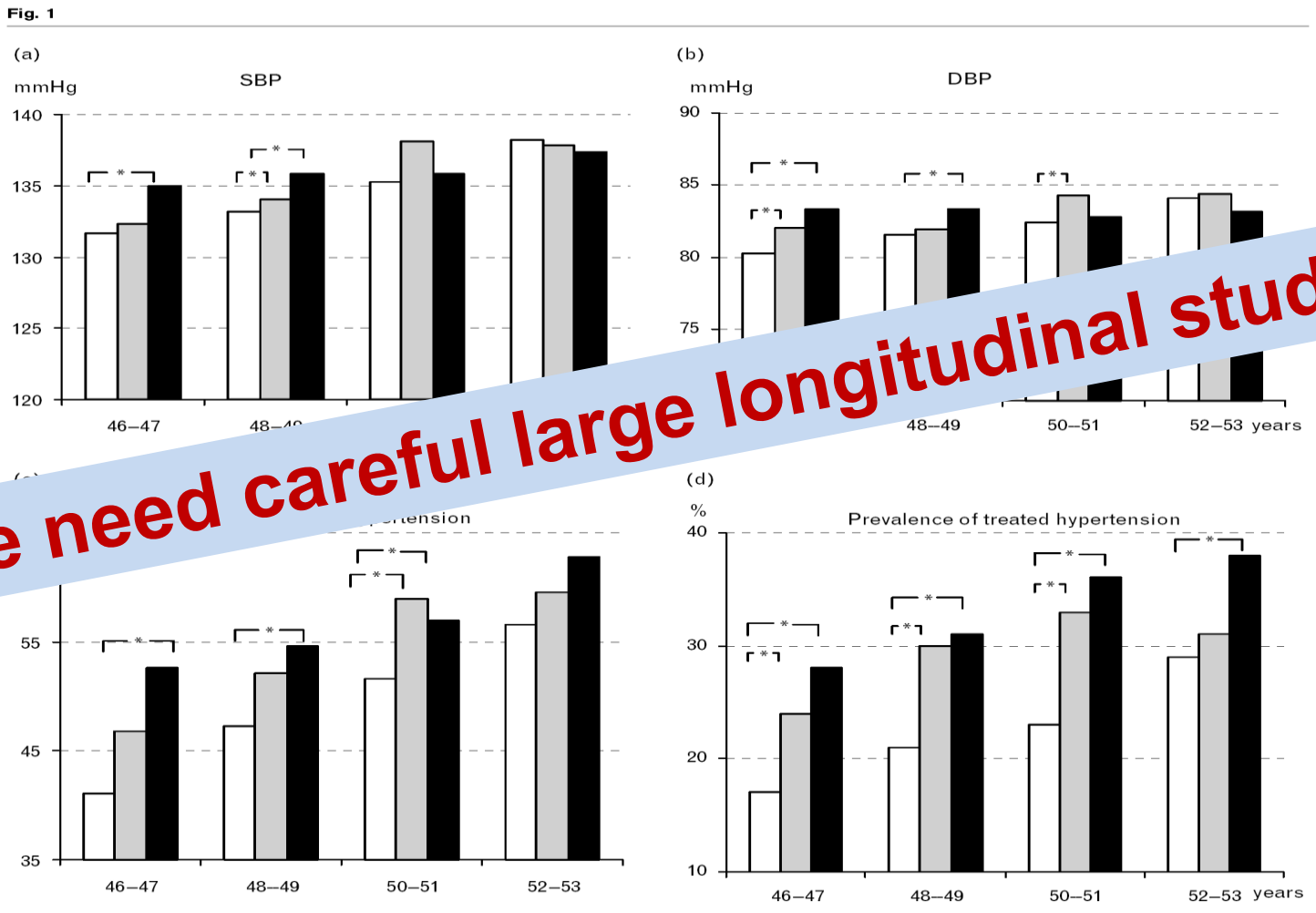


Fig. 2. Systolic and diastolic blood pressure at baseline (open bars), after oophorectomy (dark gray bars) and after 3 months of ERT (light gray bars) during daytime (top) and nighttime (bottom) period. (n=16) * $P < 0.05$, ** $P < 0.01$ vs. baseline and ERT.

Maturitas 2004;47:131-138

SIMONA Epidemiological Study

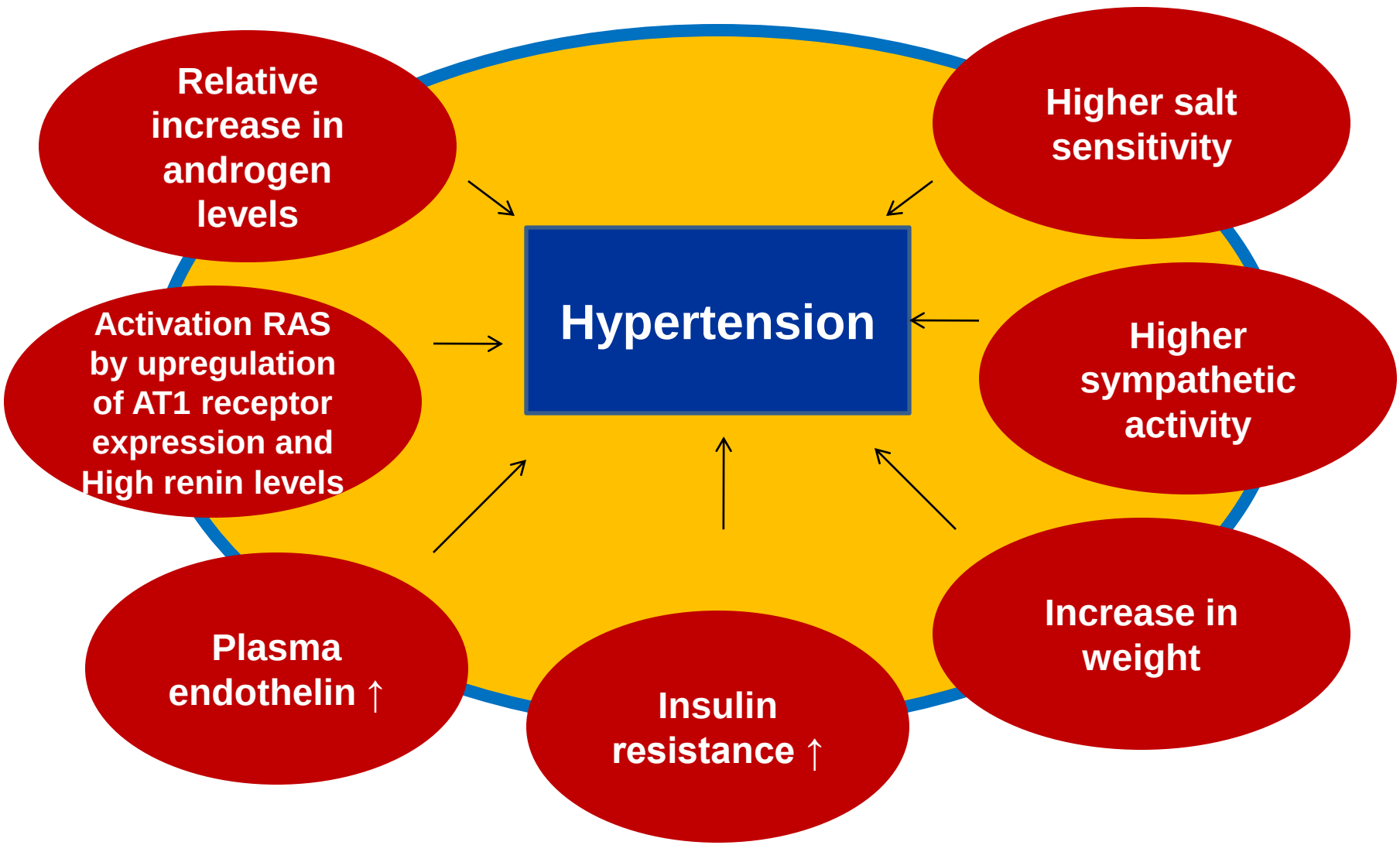


(a) Systolic blood pressure (SBP); (b) diastolic blood pressure (DBP); (c) prevalence of hypertension; and (d) prevalence of treated hypertension in premenopausal (white columns), perimenopausal (grey columns) and postmenopausal (black columns) women in four subsequent age strata. The asterisk indicates $P < 0.05$.

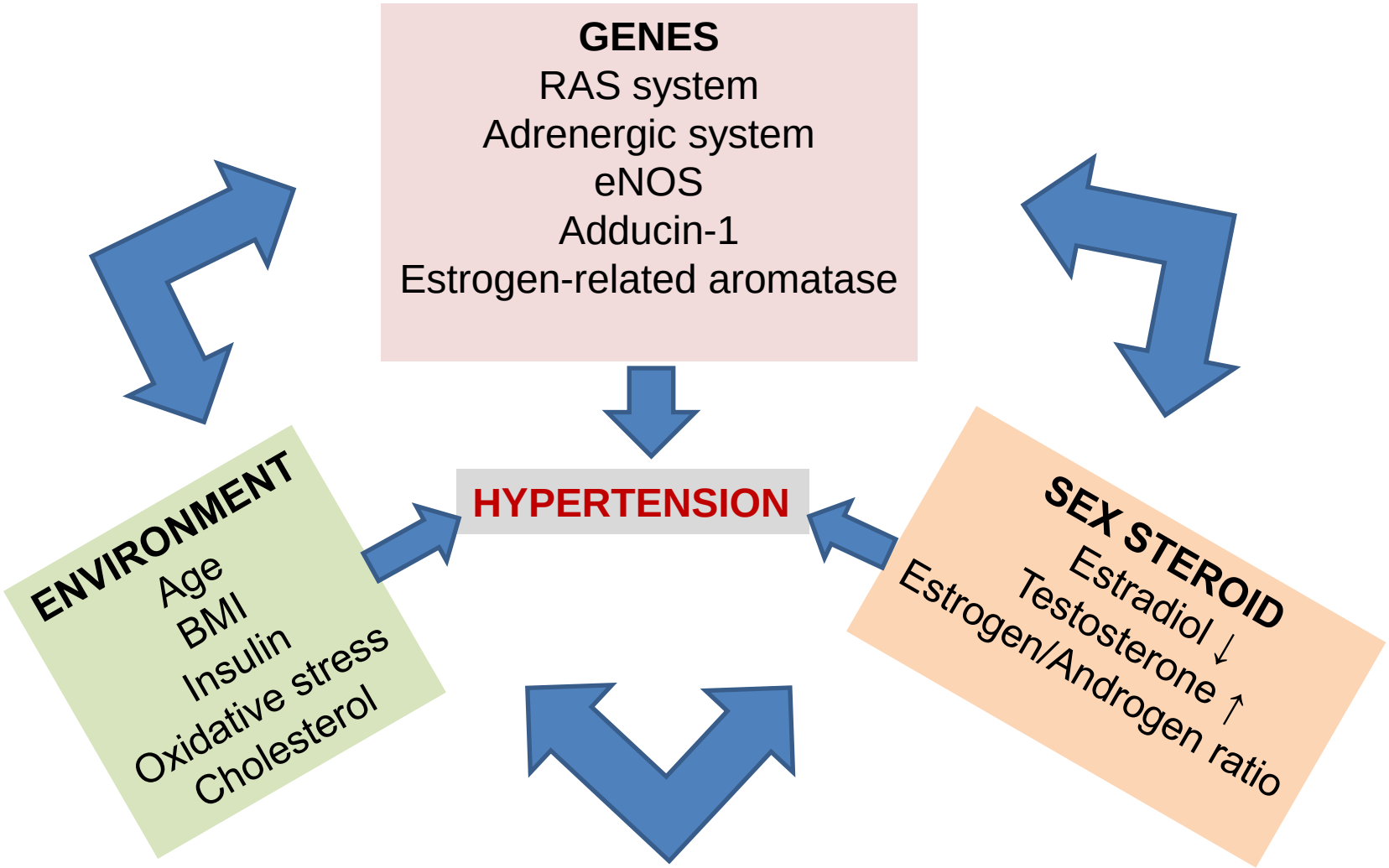
We need careful large longitudinal studies

18000 Italian women, J Hypertens. 2005;23:2269

Suggested Mechanisms of Estrogen Deficiency on Hypertension

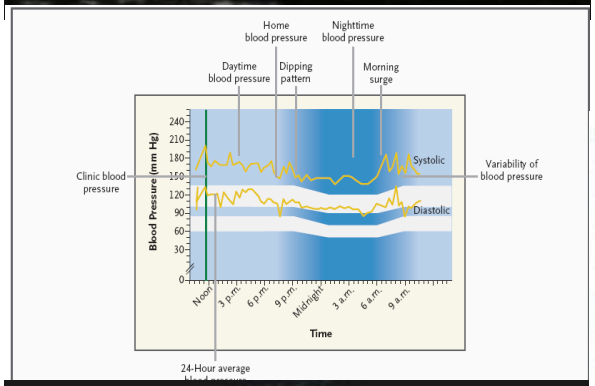


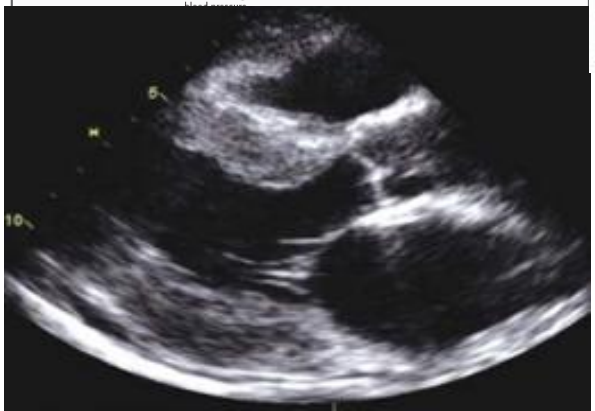
Factors Contributing to HTN in Postmenopausal Women

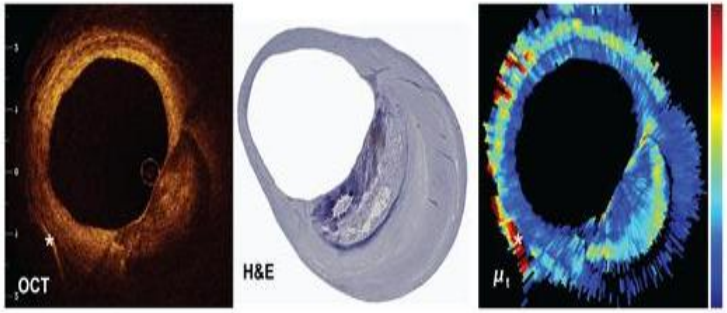


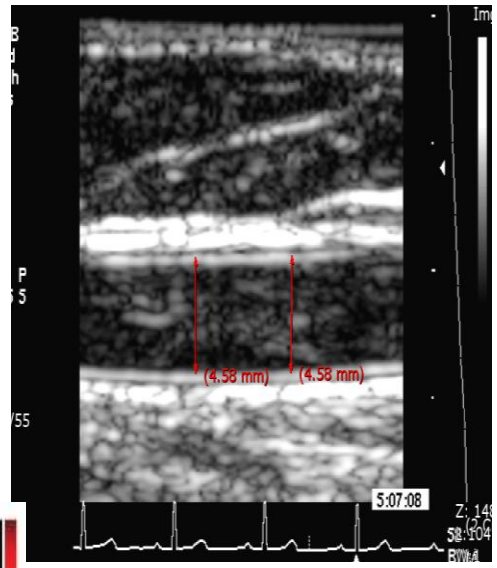
Hypertension 2008;51:952.

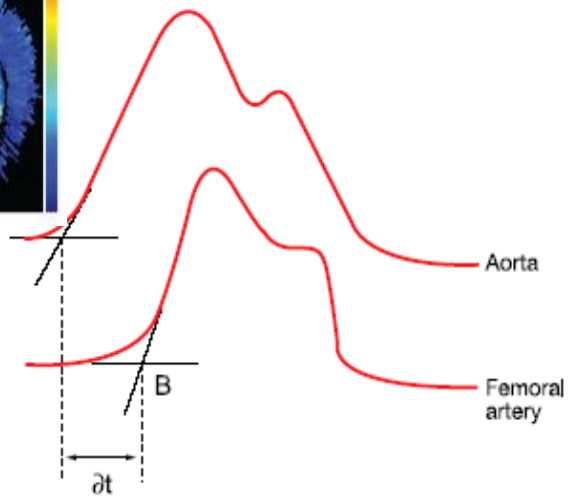
Take Home Messages (I)



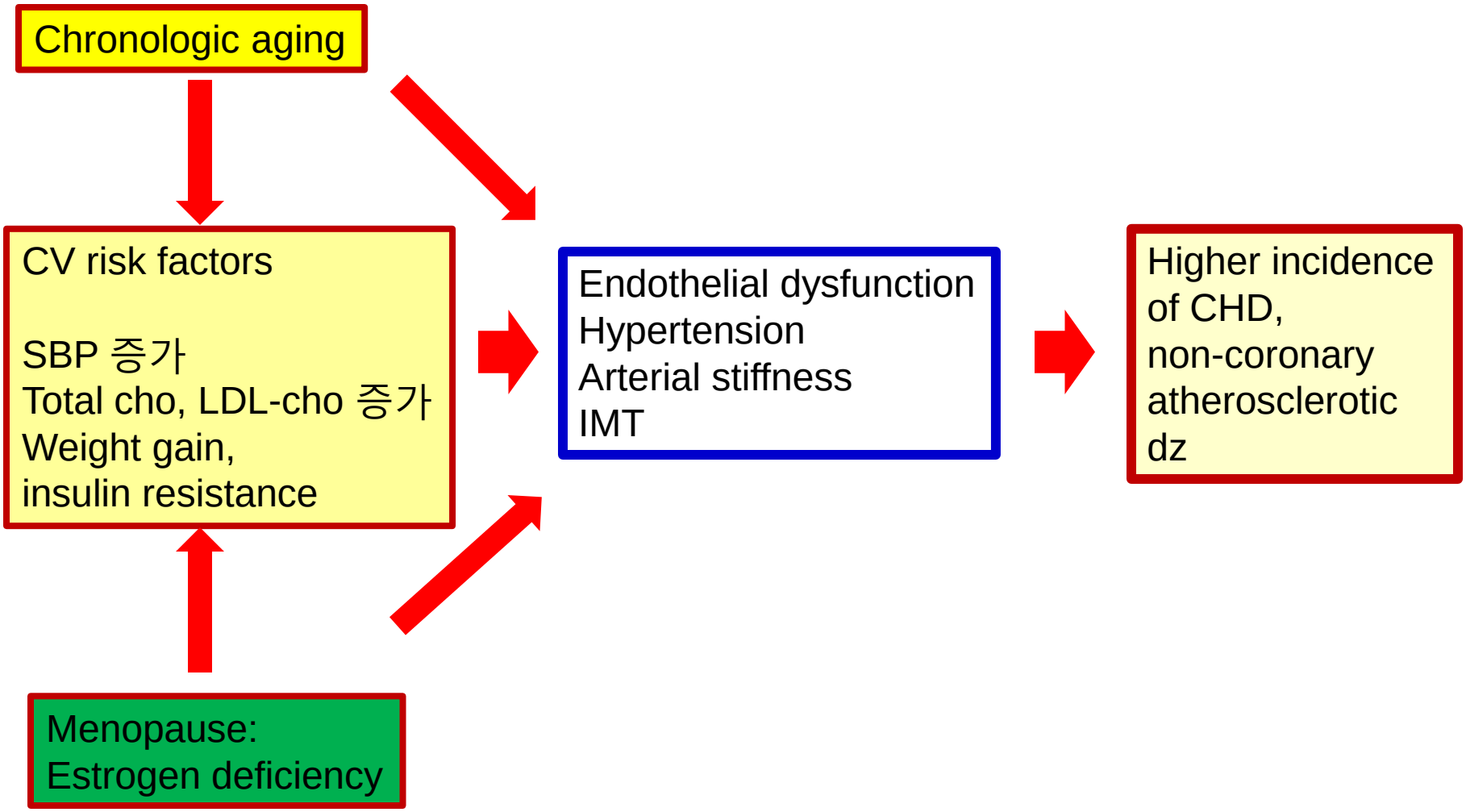








Take Home Messages (II)



Take Home Messages (III)

Chronologic aging

CV risk factors

SBP 증가
LDL-cho 증가
Insulin resistance

Frequent regular
Health check-up

BP control

ACE-I, ARB
Statin
Insulin resistance
control

Improvement of

Endothelial
dysfunction
Hypertension
Arterial stiffness
IMT

Prevention of
CHD and
Non-oronary
atherosclerotic
dz in post-
menopausal
women

Menopause:
Estrogen deficiency

HRT

ELITE study
KEEPS trial

HRT: Further Study

- ELITE Study (Early versus Late Intervention Trial with Estradiol): oral 17 estradiol, carotid IMT, perimenopausal women vs. those 6 years after menopause

- KEEPS trial (kronos Early Estrogen Prevention Study): carotid IMT or coronary calcium in women, enrolled who are within 36 months of final menstrual period

Pharmacologic Therapy in hypertensive Women

- Thiazide: (Class I, Level A): component of initial therapy

  high prevalence of salt-sensitive hypertension in postmenopausal women, JNC-7 guideline

High risk: CHD, cerebrovascular dz, peripheral dz, AAA, CKD, DM, 10-year Framingham risk ≥ 20%
Initital tx should be **β-blockers and/or ACE-I / ARB**

- ACE-inhibitor, ARB:

  useful to antagonize the activation of the RAS observed after menopause

  especially in postmenopausal women with the metabolic syndrome

  should not used in pregnant women

Evidenc-based guidelines for cardiovascular disease prevention in women
Circulation 2007;115;1481
2007 ESC/ESH guidelines for management of hypertenion
JNC-VII