Clinical management of peri-post menopausal symptoms with a nutraceutical combination

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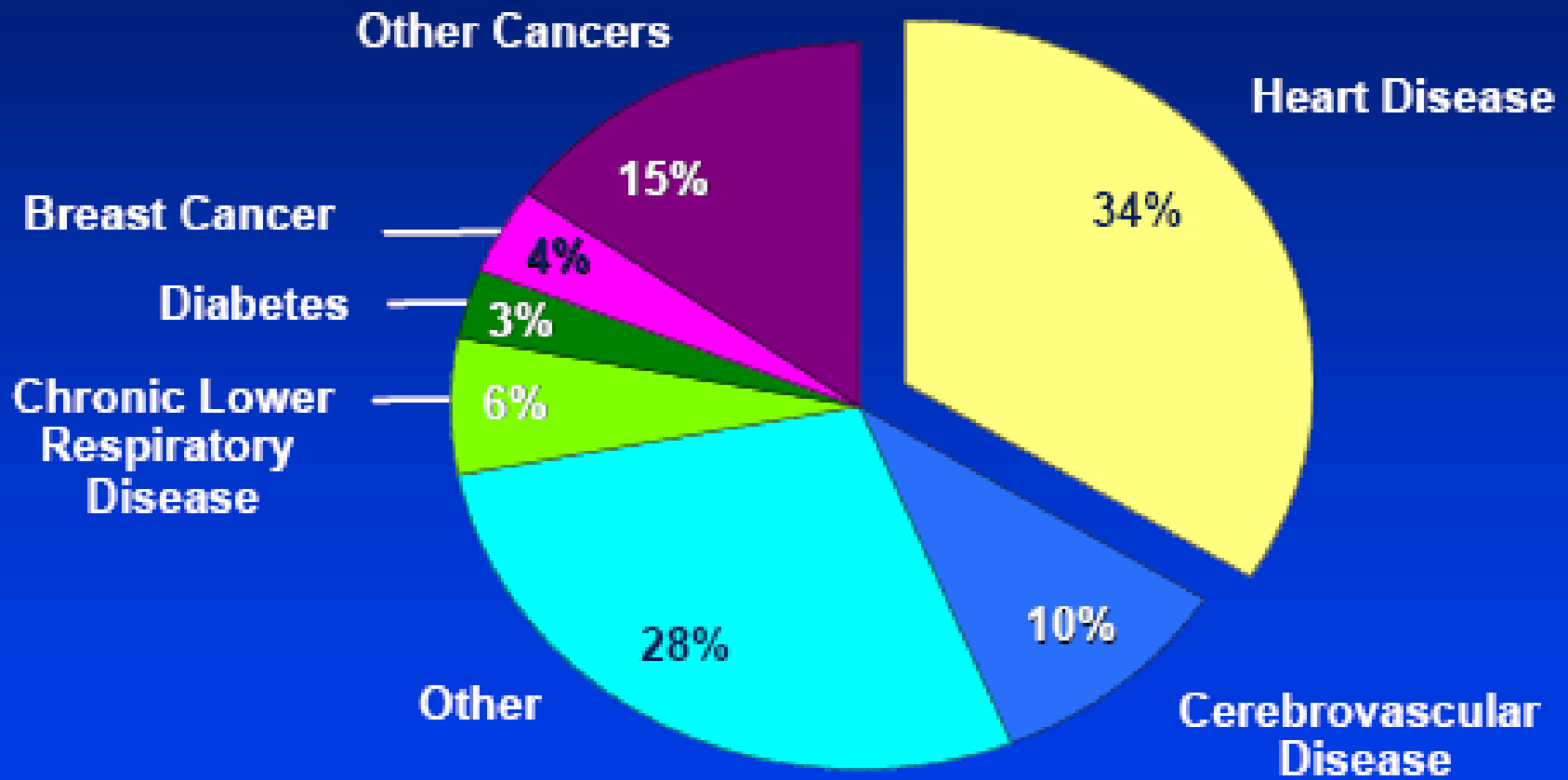
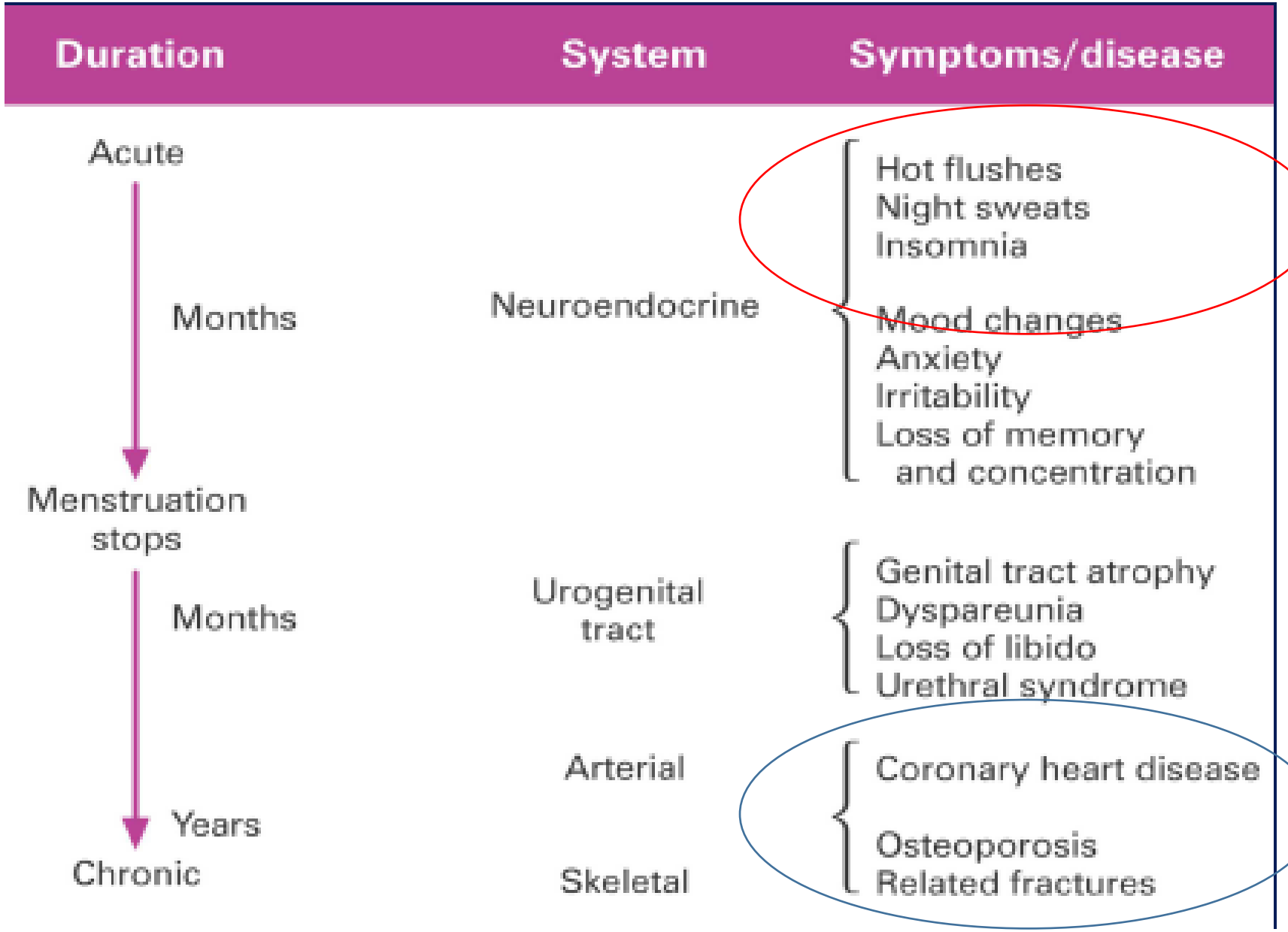
Causes of Death Among Women*



*Percentage of total deaths in 1999 among women aged 65 years and older.

Anderson RN. *Natl Vital Stat Rep.* 2001;49:1-13.


Duration
System
Symptoms/disease
Acute
Months
Menstruation stops
Months
Years
Chronic
Neuroendocrine
Hot flushes
Night sweats
Insomnia
Mood changes
Anxiety
Irritability
Loss of memory and concentration
Urogenital tract
Genital tract atrophy
Dyspareunia
Loss of libido
Urethral syndrome
Arterial
Coronary heart disease
Skeletal
Osteoporosis
Related fractures

Hormonal modifications

In **pre-menopausal period** women face important hormonal modifications:

- **Decrease of Progesterone levels**
- **Related Hyperestrogenism**
- **Increase of FSH (**follicle-stimulating hormone)

⇨

- ✓ Anovulation
- ✓ Irregular periods
- ✓ Early episodes of hot flashes and serious sweats

Important metabolic changes:

- Fat deposition towards androgenic type
- **Alteration of lipid metabolism**
- Alteration of glucose metabolism
- Alteration of bone metabolism

⇩

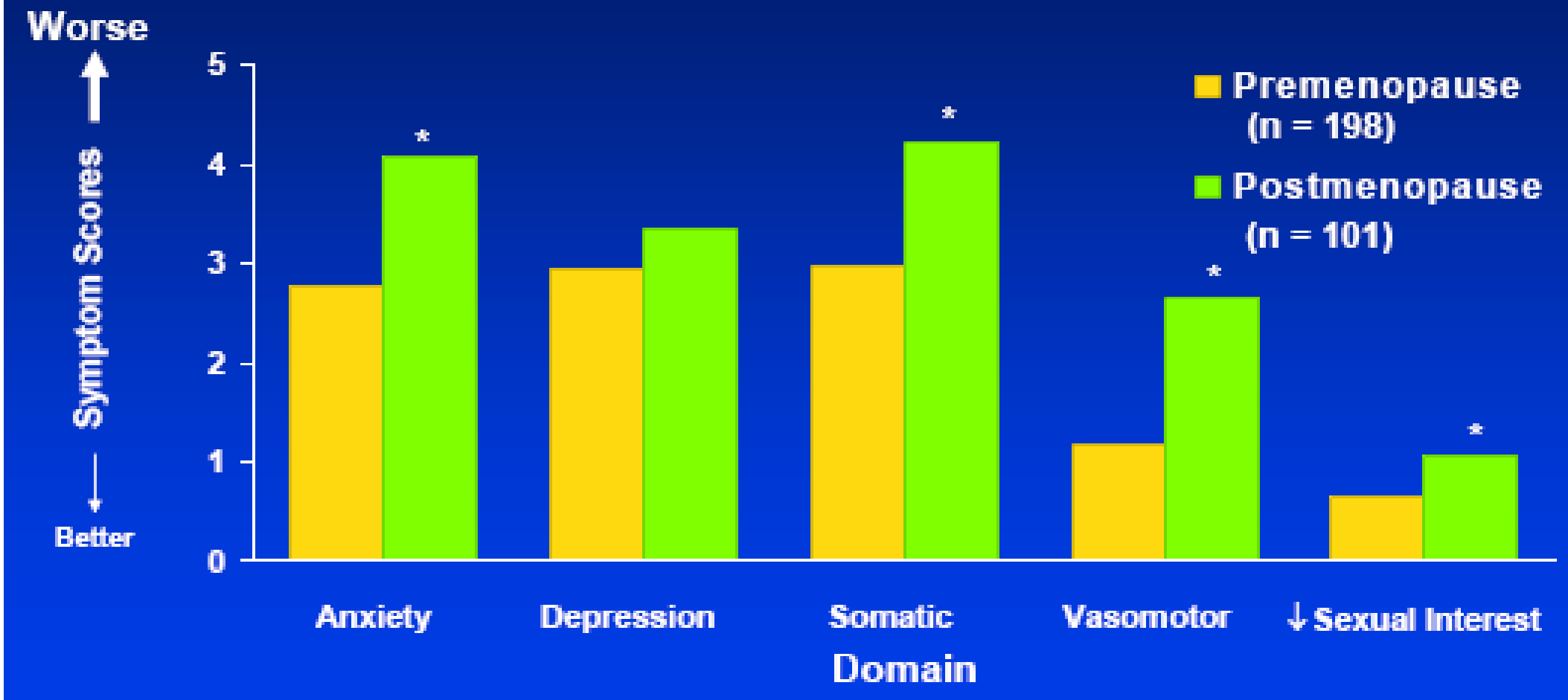
Long-term consequences on Cardiovascular and Osteo-articular apparatus

Symptoms, disorders and risks during menopause

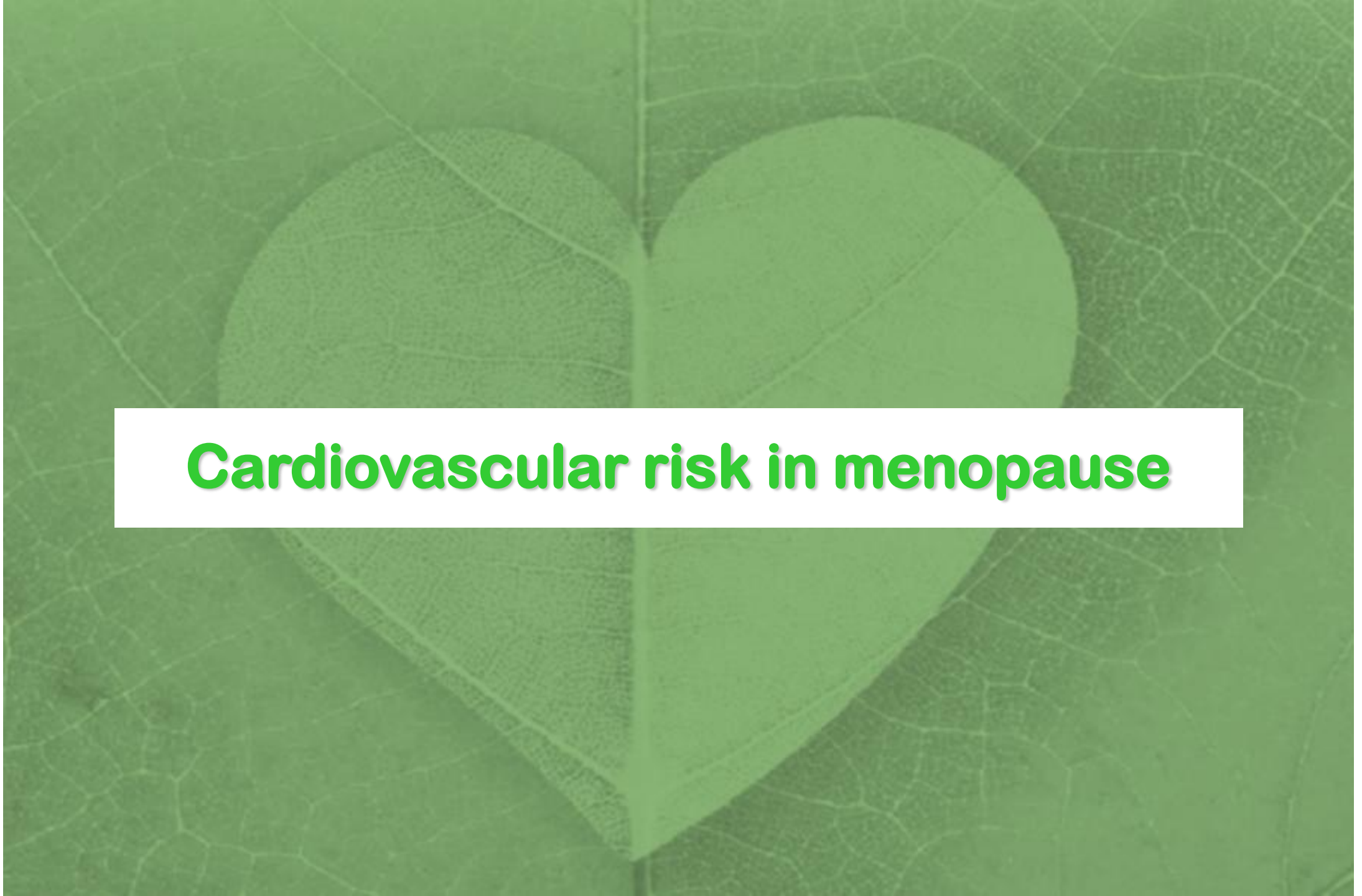
Symptoms / risks	Frequency (in percentage)
Hot flashes	86,8%
Night sweats	82,1%
Insomnia	67,8%
Irritability	65,2%
Depression	47,5%
Anxiety	56,8%
Vaginal dryness	>50%
Fatigue	49,4%
Paraesthesias	34,5%
Vertigo	32,8%
Arthritis	20,9%
Hypertension	20,4%
Osteoporosis	13,3%

Estronet Study 2006

Effect of Menopause on QOL: Greene Climacteric Scale

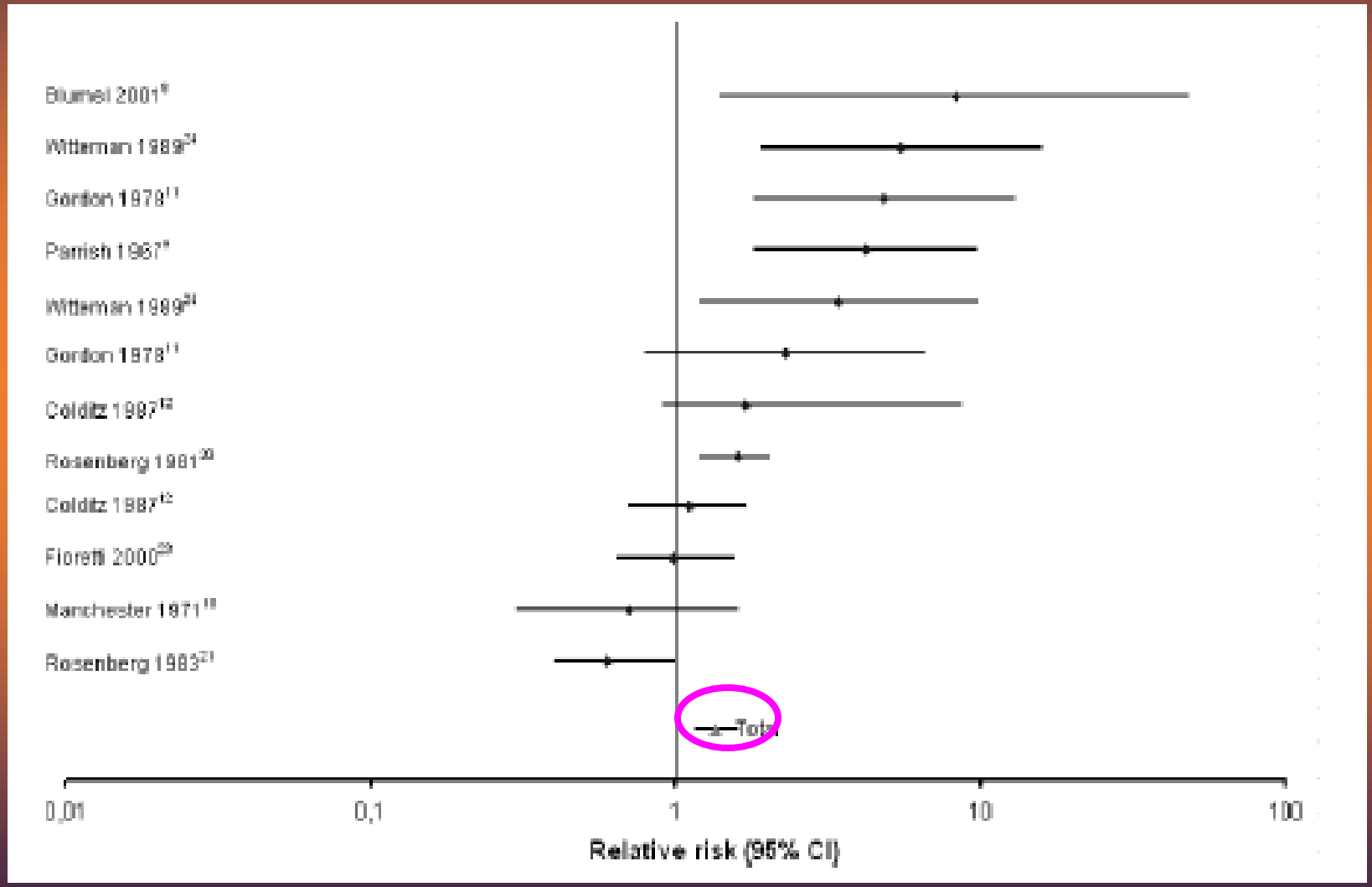


n = 493: 101 premenopausal; 95 perimenopausal; 198 postmenopausal; 95 hysterectomized. Age range, 45–65 years.
*$P < .05$ vs premenopause. Barentsen R, et al. *Maturitas*. 2001;38:123-8.


Cardiovascular risk in menopause

Postmenopausal status and cardiovascular disease risk, overall analysis.

Premenopausal status is the reference.



Menopause, Vol. 13, No. 2, 2006

Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis

- For early menopause and cardiovascular disease, the pooled relative risk estimate was 1.25 (95% CI, 1.15-1.35).
- In the stratified analysis, the pooled effect was 1.38 (95% CI, 1.21-1.58) after controlling for age and smoking.
- The pooled effect of bilateral oophorectomy on cardiovascular disease was 4.55 (95% CI, 2.56-8.01).

Atsma F.Menopause, Vol. 13, No. 2, 2006

It is not only a matter of age:

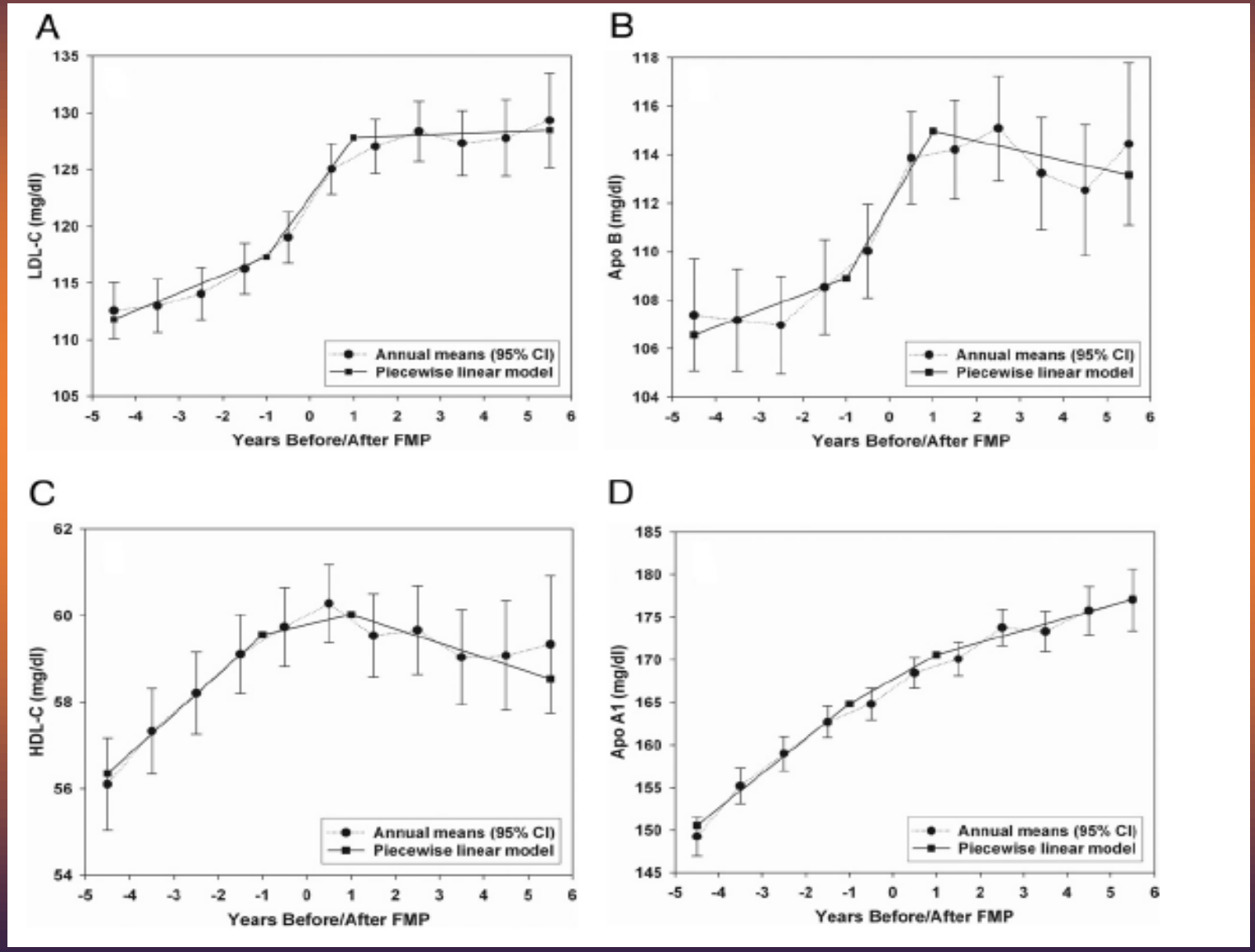
menopause represents the “trigger” for a multi level metabolic changes ……..

Early clinical management of menopausal symptoms are requested

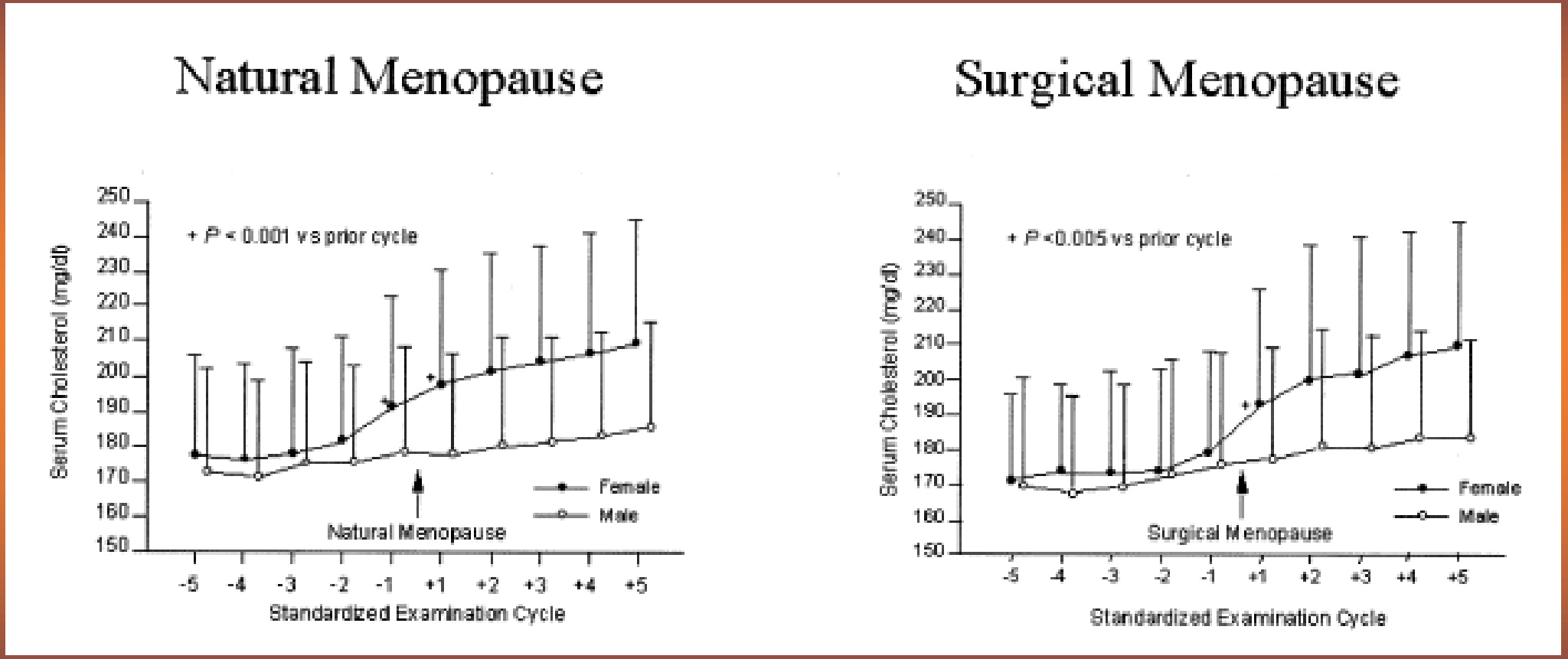
with the aim of prevention

Lipids Annual and Estimated Means

Matthews et al. JACC Vol. 54, No. 25, 2009 Menopause and Risk Factors



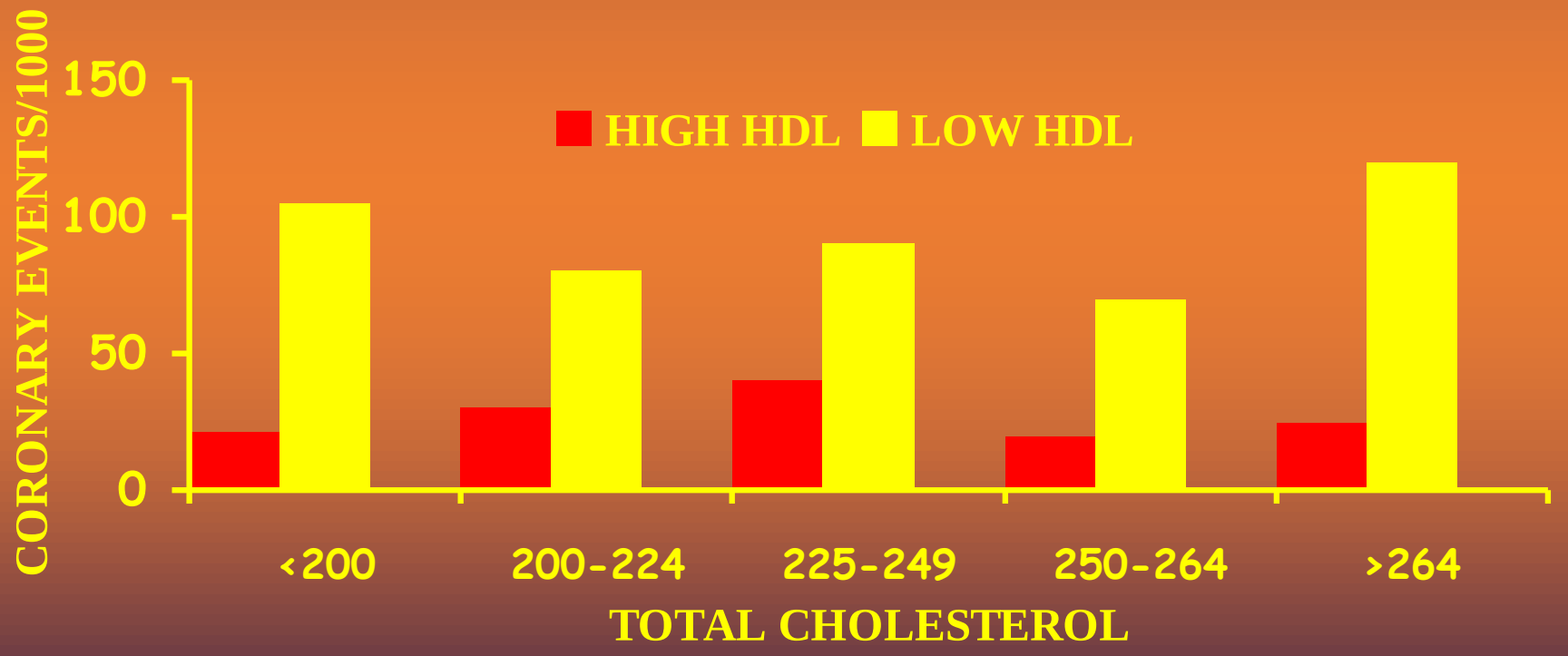
Effect of menopause on total cholesterol levels in women



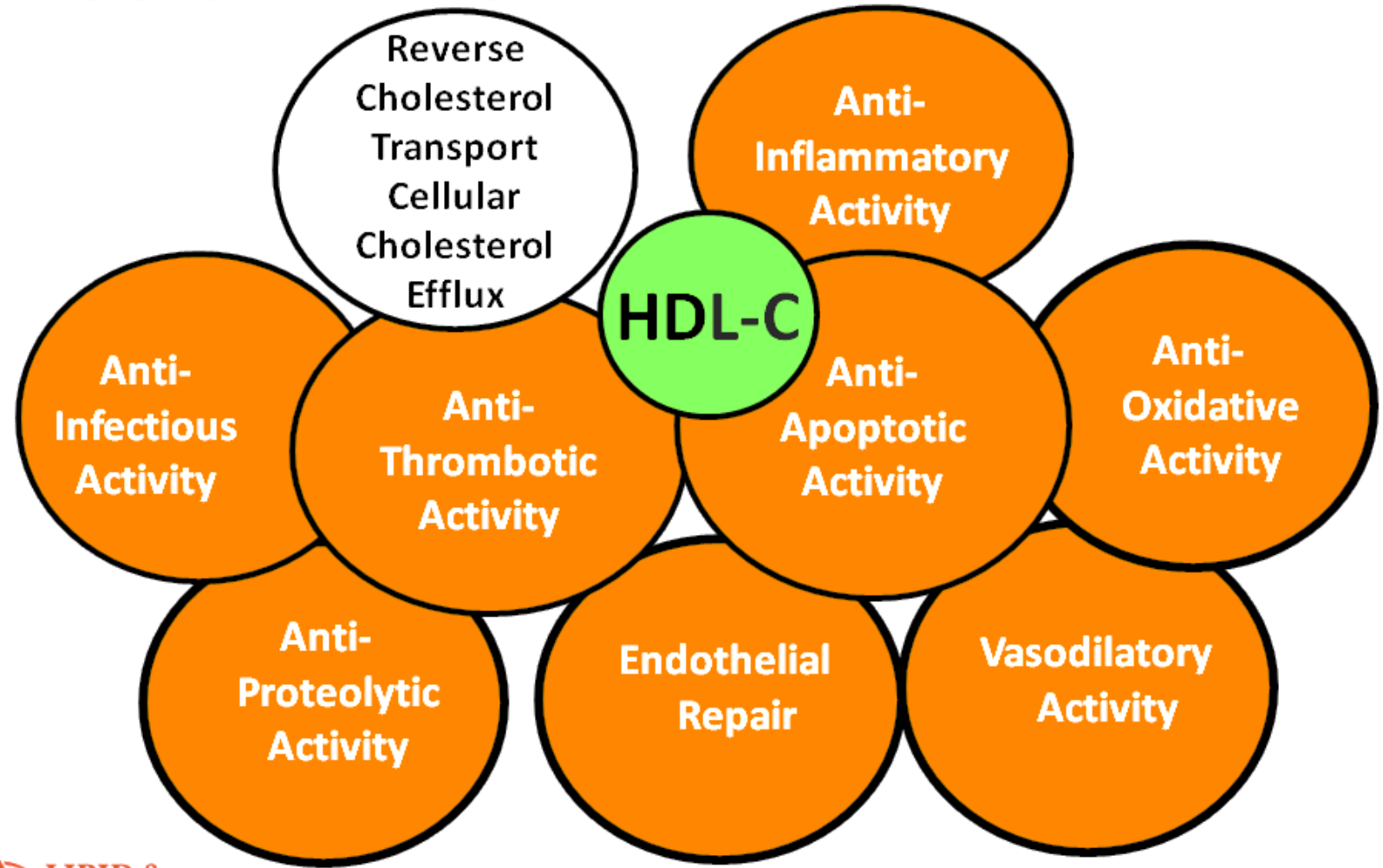
Vera Bittner Am J Cardiol 2002;90

PROTECTIVE EFFECT OF HIGH HDL LEVELS ON CARDIOVASCULAR DISEASES

modified from Brunner et al, 1987



Anti-Atherogenic and Vasculoprotective Actions of HDL-C



Increased Risk of major cardiovascular events with Increased Triglyceride Concentrations in Men and Women

Table 1. Risk increase associated with increasing triglyceride levels.

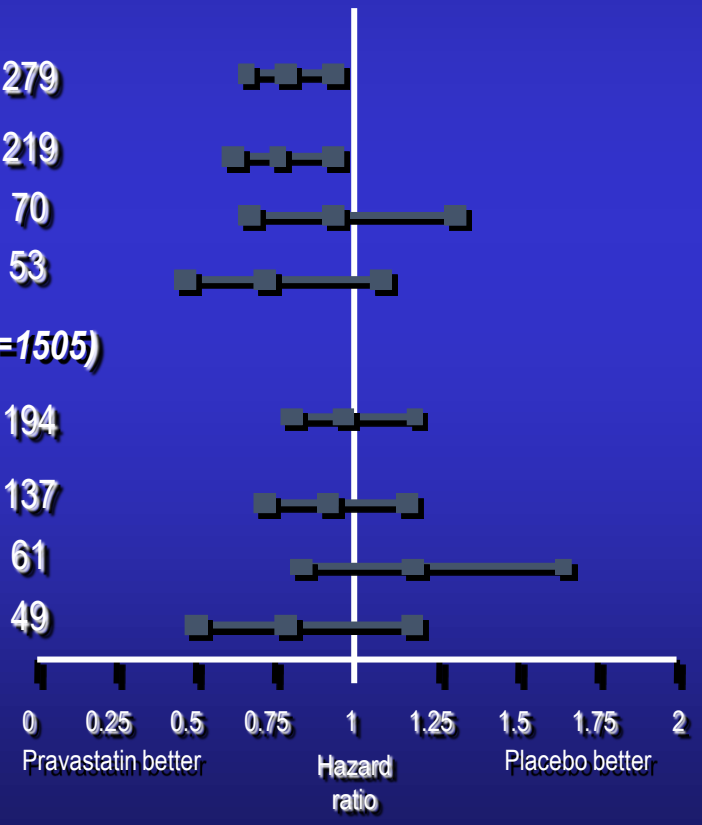
Men	
Triglyceride level increase	**% risk increase**
from 100 mg/dL to 200 mg/dL	36%
from 100 mg/dL to 300 mg/dL	72%
from 100 mg/dL to 400 mg/dL	108%
Women	
Triglyceride level increase	**% risk increase**
from 100 mg/dL to 200 mg/dL	85%
from 100 mg/dL to 300 mg/dL	170%
from 100 mg/dL to 400 mg/dL	255%

Extrapolation based on 32% (men) and 76% (women) increase in univariate risk per 89 mg/dL increase in triglyceride level.

Adapted from: Austin MA, Hokanson JE, Edwards KL. Am J Cardiol. 1998;81:7B-12B.

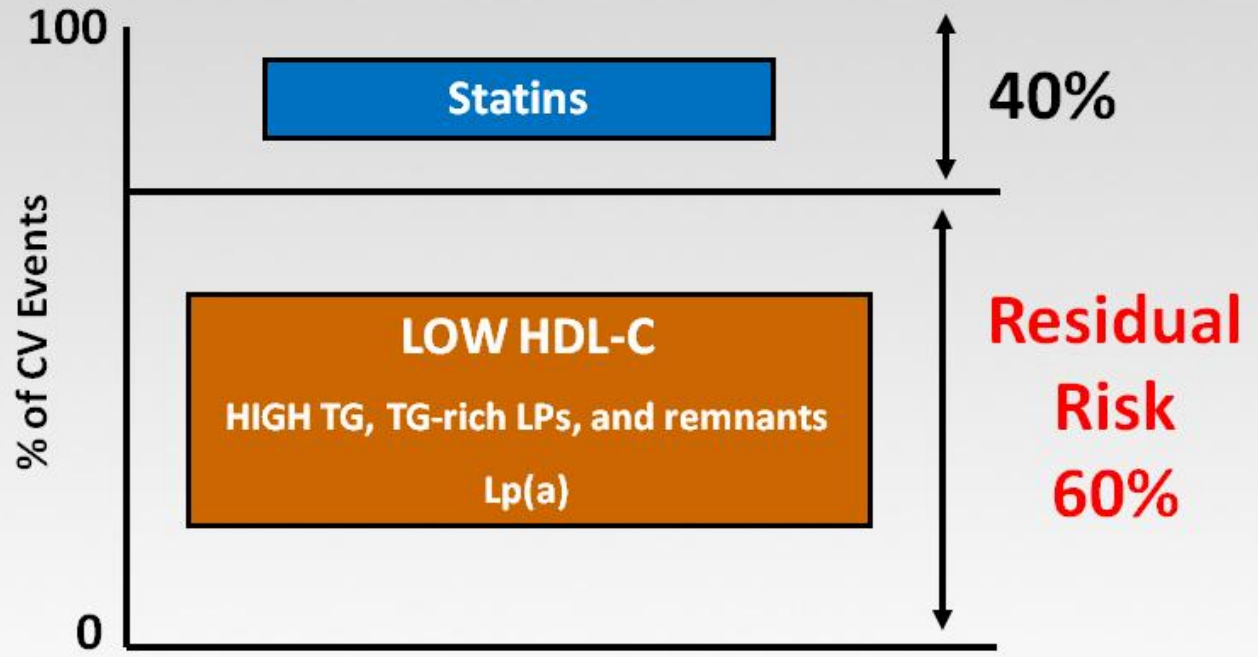
PROSPER – Cardiovascular end-points according to gender

	Pravastatin	Placebo
	(n=1396)	*(n=1408)*
Men		
Cardiac death, non fatal MI, Stroke	222	279
Cardiac death, non-fatal MI	167	219
Stroke fatal, non fatal	65	70
TIA	38	53
Women	*(n=1495)*	*(n=1505)*
Cardiac death, non fatal MI, Stroke	186	194
Cardiac death, non-fatal MI	125	137
Stroke fatal, non fatal	70	61
TIA	39	49



PROSPER Study Group. Lancet. 2002; 360:1623-30.

Treatment of CV Disease: Current Status



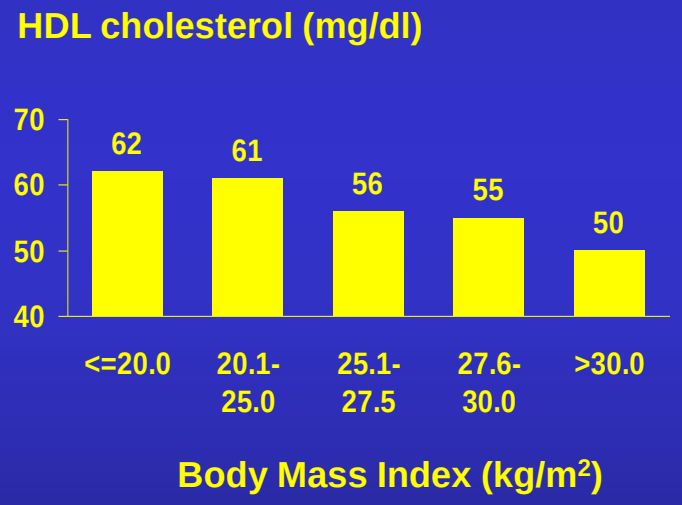
Lp(a) = lipoprotein a; LPs = lipoproteins, TG = triglyceride

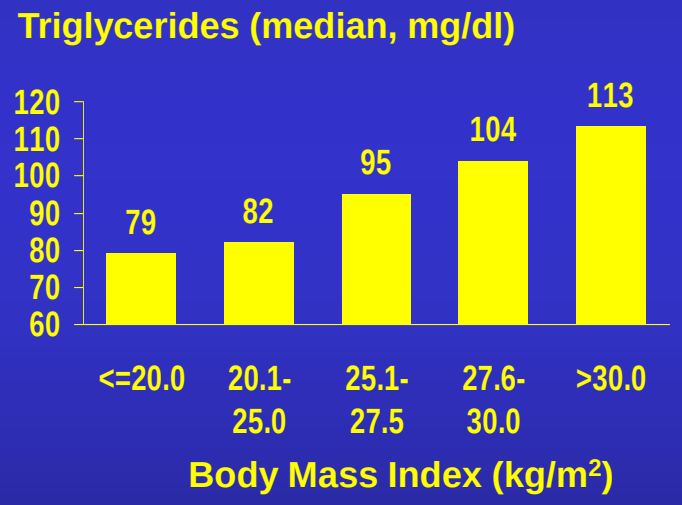
LIPID & METABOLIC

theheart.org from WebMD

Medscape EDUCATION

PROCAM (Münster Heart Study): HDL Cholesterol and Triglycerides According to Body Mass Index in Women Aged 40-65 Years (n=3.019)





Recommended “ lifestyle advice”

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

5.5 Dietary supplements and functional foods for the treatment of dyslipidaemias

Innovative nutritional strategies to improve dyslipidaemias have been developed. They are based on either changing some ‘risky’ dietary components or encouraging the consumption of specifically targeted ‘healthy’ functional foods and/or dietary supplements; these so-called nutraceuticals can be used either as alternatives or in addition to lipid-lowering drugs.[181] Nutritional evaluation of func-

2016 ESC/EAS Guidelines Atherosclerosis 253 (2016)

Berberine

It is a natural alkaloid extracted from the bark of ***Berberis aristata,*** a plant (a spiny shrub) which grows in Tibet and Himalaya regions.

Berberine traditional use comprehends antimicrobial activity for infective diarrhea, urinary infections and local treatment for wound and ulcers.

In order to reduce cholesterolemia, another important mechanism should be addressed: the **re-uptake of LDL by the liver LDL receptors**

Kong W et al. Nat Med. 2004; 10:1344-1351

Combination of Nutraceuticals

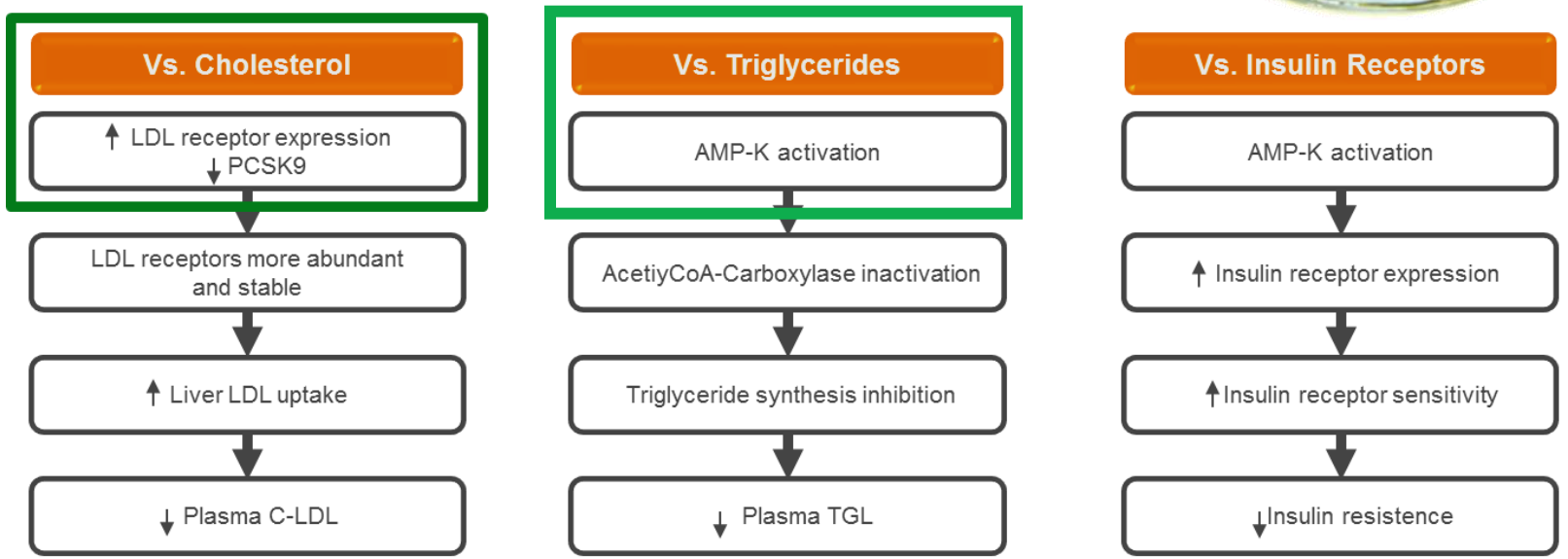
Nutraceutical = nutrition + pharmaceutical

Nutraceutical can be defined as a “food” or a part of food that provides medical or health benefits, including the prevention and/or treatment of a disease

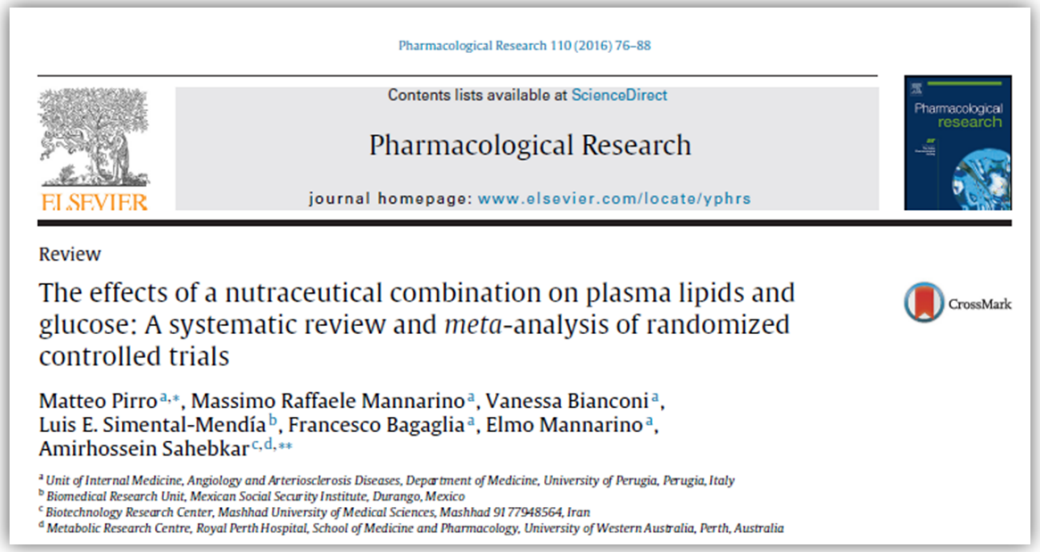
A pool of nutraceuticals combining, in a single formulation (Armolipid Plus), natural ingredients in sub-pharmacological dosage for:

- The control of blood lipids:
  - Red yeast rice 200 mg
  - Berberine 500 mg
  - Policosanol 10 mg
- Homocysteine levels
  - Folic acid 0,2 mg
- And oxidative stress
  - Astaxanthin 0.5 mg
  - Coenzyme Q10 2 mg

Berberine –pharmacological effects-



Kong W et al Nat Med 2004; 10:1344-1351/Brusq JM et al Lipid Res 2006; 47: 1281-1288/Kong W Metabolism Clinical & Experimental 2009; 58: 109-119



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journal homepage: www.elsevier.com/locate/yphrs

Review

The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and *meta*-analysis of randomized controlled trials

Matteo Pirro[a,*], Massimo Raffaele Mannarino[a], Vanessa Bianconi[a], Luis E. Simental-Mendía[b], Francesco Bagaglia[a], Elmo Mannarino[a], Amirhossein Sahebkar[c,d,**]

[a] Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy
[b] Biomedical Research Unit, Mexican Social Security Institute, Durango, Mexico
[c] Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad 91 77948564, Iran
[d] Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

- The literature was searched on PubMed and SCOPUS database from inception to February 10, 2016.
- 14 trials met the eligibility criteria for lipid analysis.
- In this publication **net changes in measurements** (change scores) of 14 randomized clinical trials (**1670 subjects treated with AP**) were calculated and a significant change in the lipid profile ($p<0.001$) was obtained.

- **in total cholesterol −26.15 mg/dL**
- **in LDL-cholesterol −23.85 mg/dL**
- **in triglycerides −13.83 mg/dL**
- **in HDL-cholesterol +2.53 mg/dL,**

→ **-0.7 mmol/L**
→ **-0.6 mmol/L**

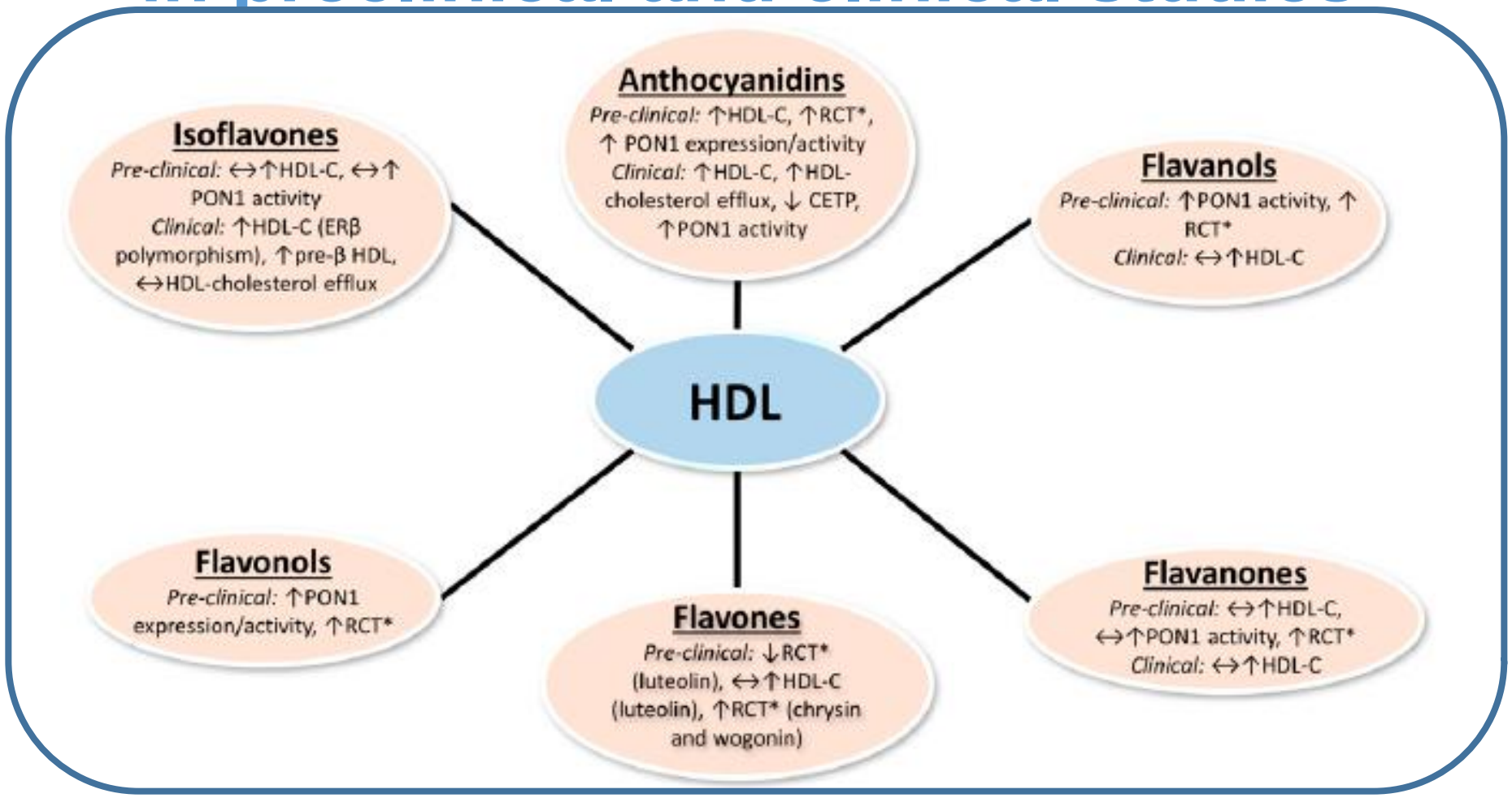
$p < 0.001$

39 mg/dl = 1 mmol/L

1mmol/L = 89 mg/dl

These effects are related to the Armolipid Plus efficacy.
Lifestyle change and low-fat diet may improve the lipid lowering effect

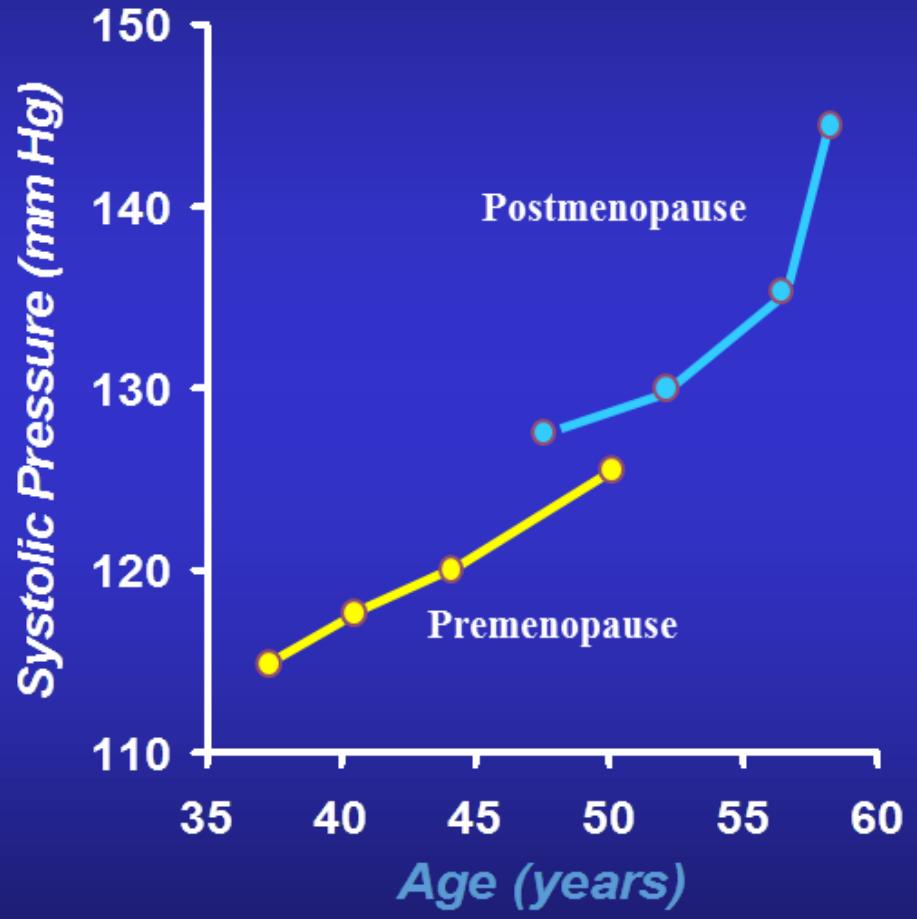
Reported effects of dietary flavonoids on RCT, HDL metabolism, and HDL function in preclinical and clinical studies

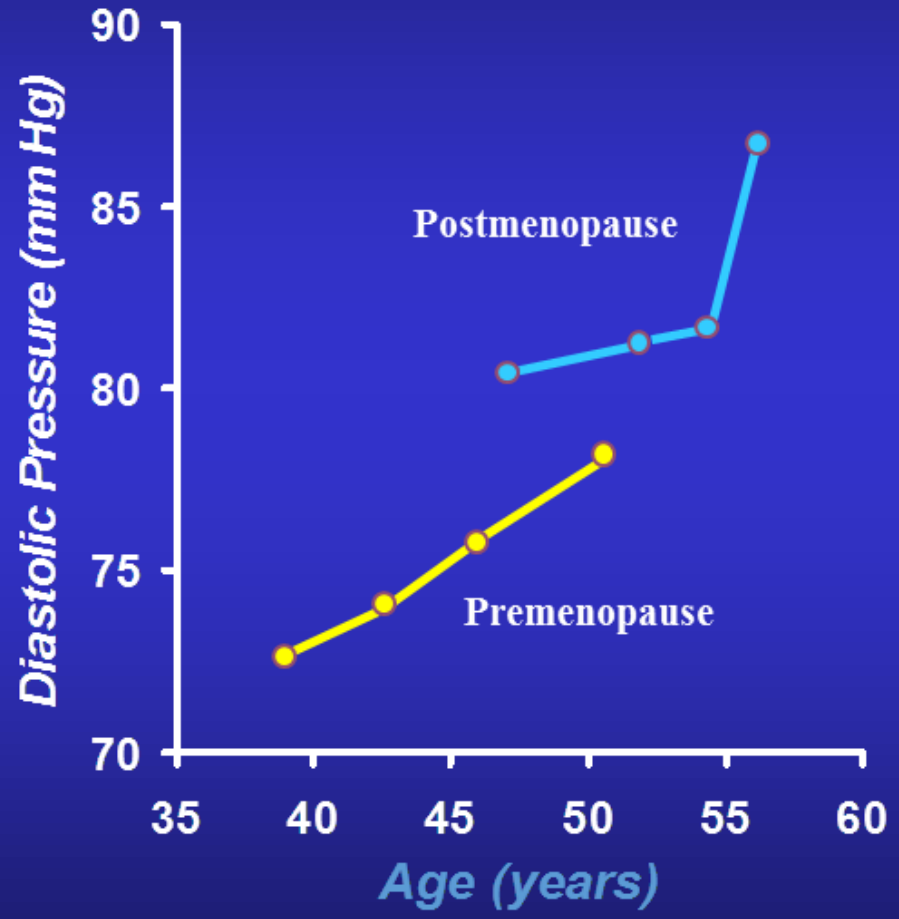


Courtney L Millar et al.Adv Nutr 2017;8:226–39

Menopause and CV risks:
Hypertension
Hot flashes
Vascular reactivity

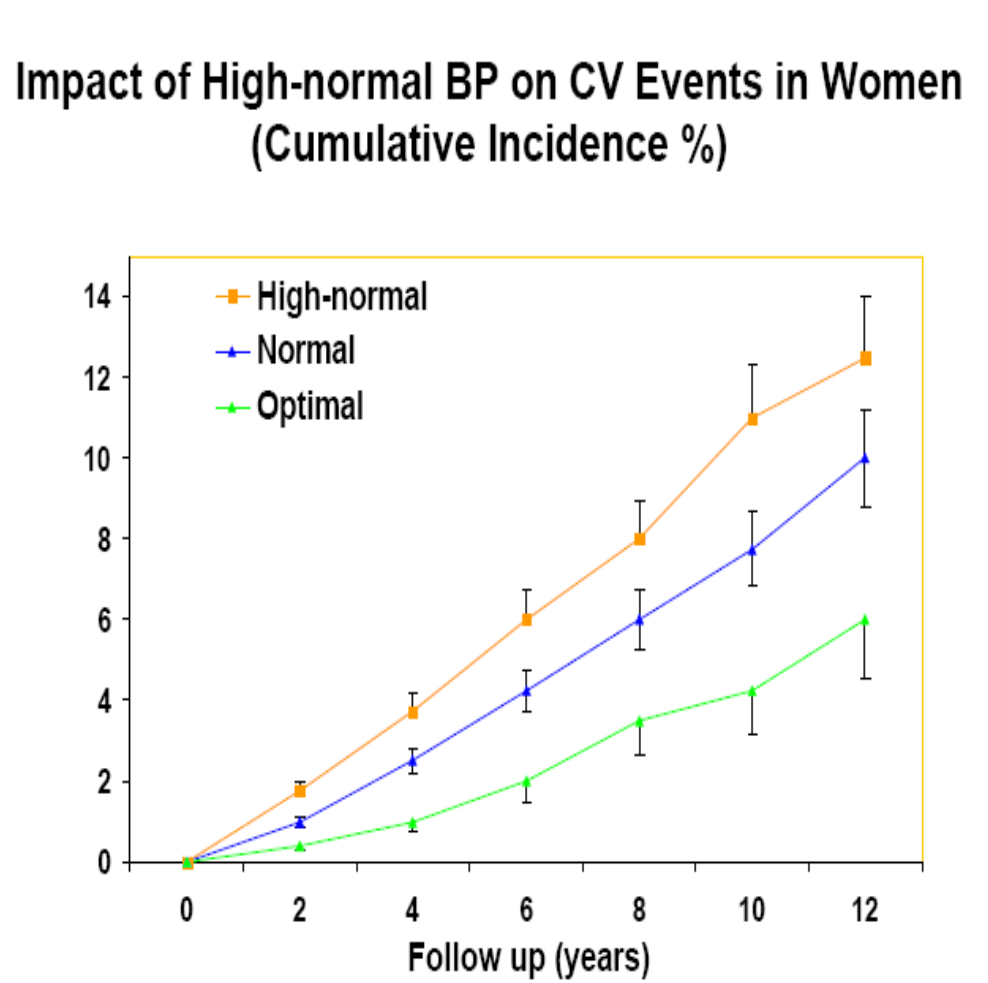
The Influence of Menopause on Blood Pressure





Staessen JA, et al. *J Hum Hypertens.* 1998;12:587-92.

Impact of High-Normal Blood Pressure on the Risk of CVD



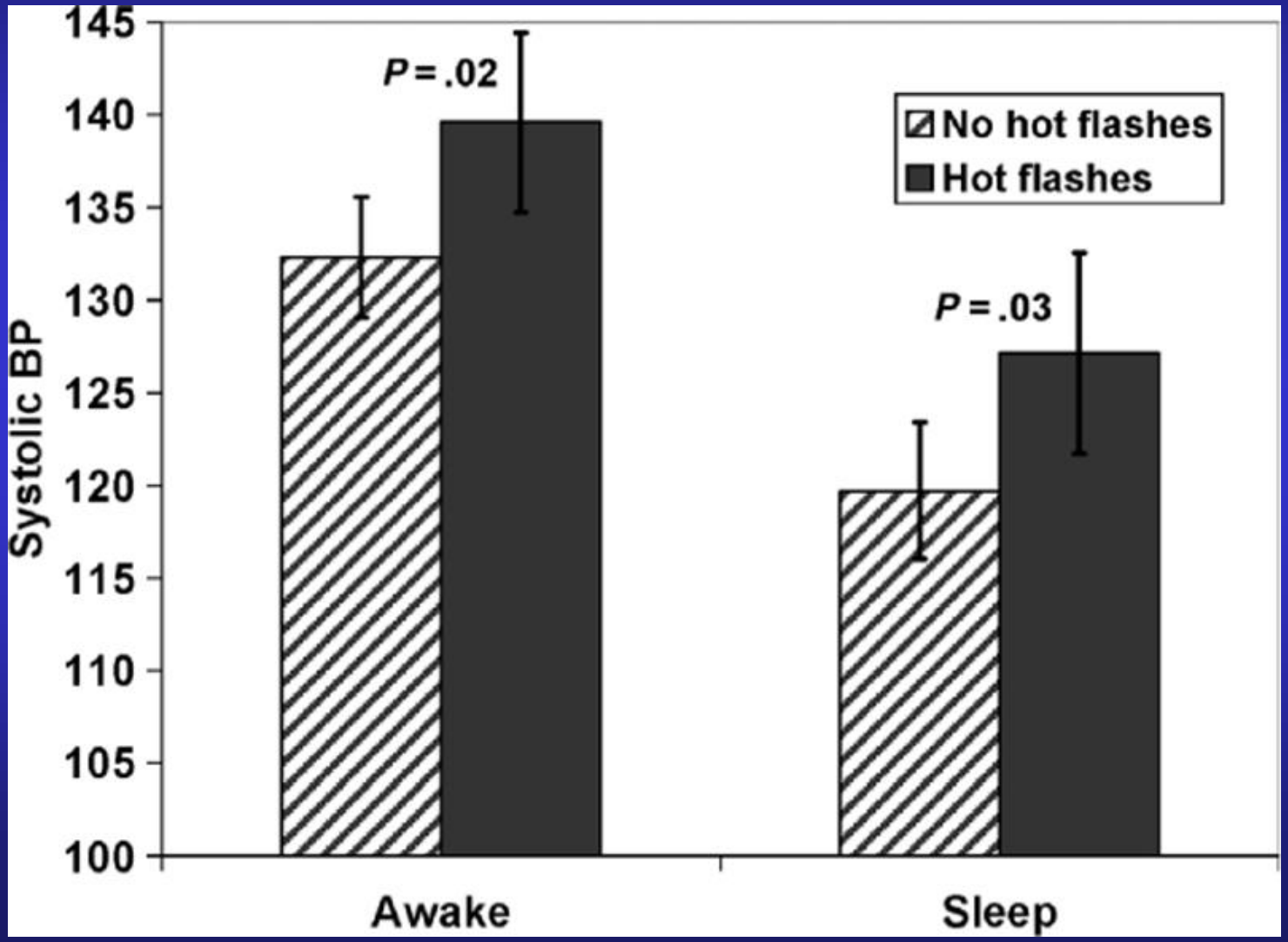
Definitions and Classification of Blood Pressure Levels

European Society of Hypertension – European Society of Cardiology (2003)

Category	*Systolic (mmHg)*	*Diastolic (mmHg)*
Optimal	**<120**	**<80**
Normal	**120–129**	**80–84**
High normal	**130–139**	**85–89**
Grade 1 hypertension (mild)	**140–159**	**90–99**
Grade 2 hypertension (moderate)	**160–179**	**100–109**
Grade 3 hypertension (severe)	**>180**	**>110**
Isolated systolic hypertension	**>140**	**90**

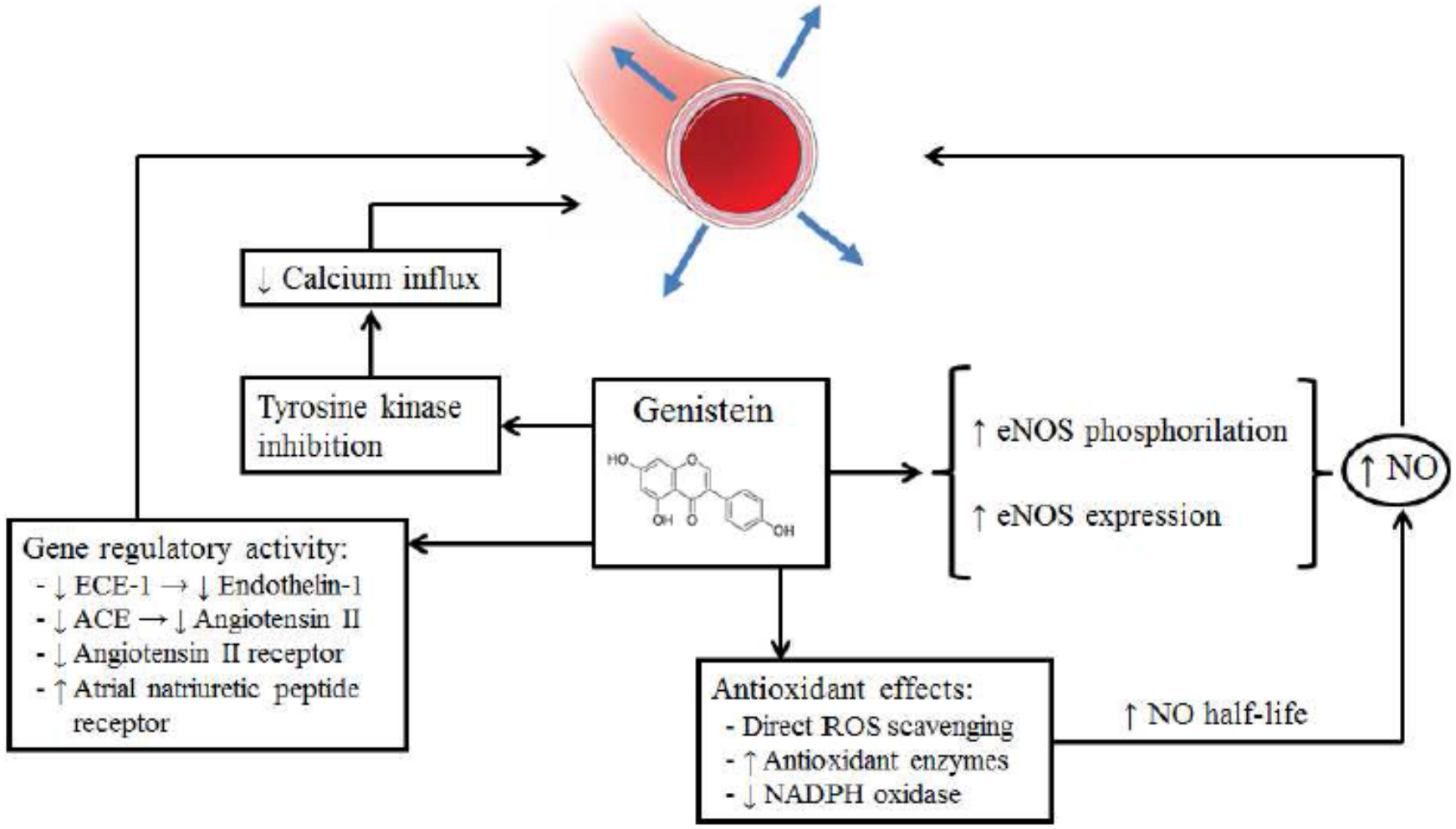
Journal of Hypertension 2003, Vol 21 No 6

Hot flash correlates with high blood pressure



Menopause 2007; 14: 308-15

Potential protective effects of genistein in hypertension through promoting vasodilation and reducing vascular smooth muscle contraction.



Vasomotor menopausal symptoms are associated with increased risk of coronary heart disease

Menopause, Vol. 18, No. 2, 2011

Gerrie-Cor M. Gast, PhD,[1,2] Victor J.M. Pop, MD, PhD,[3] Göran N. Samsioe, MD, PhD,[2] Diederick E. Grobbee, MD, PhD,[1] Peter M. Nilsson, MD, PhD,[4] Jules J. Keyzer, PhD,[5] Colette J.M. Wijnands-van Gent, MD, PhD,[6] and Yvonne T. van der Schouw, PhD[1]

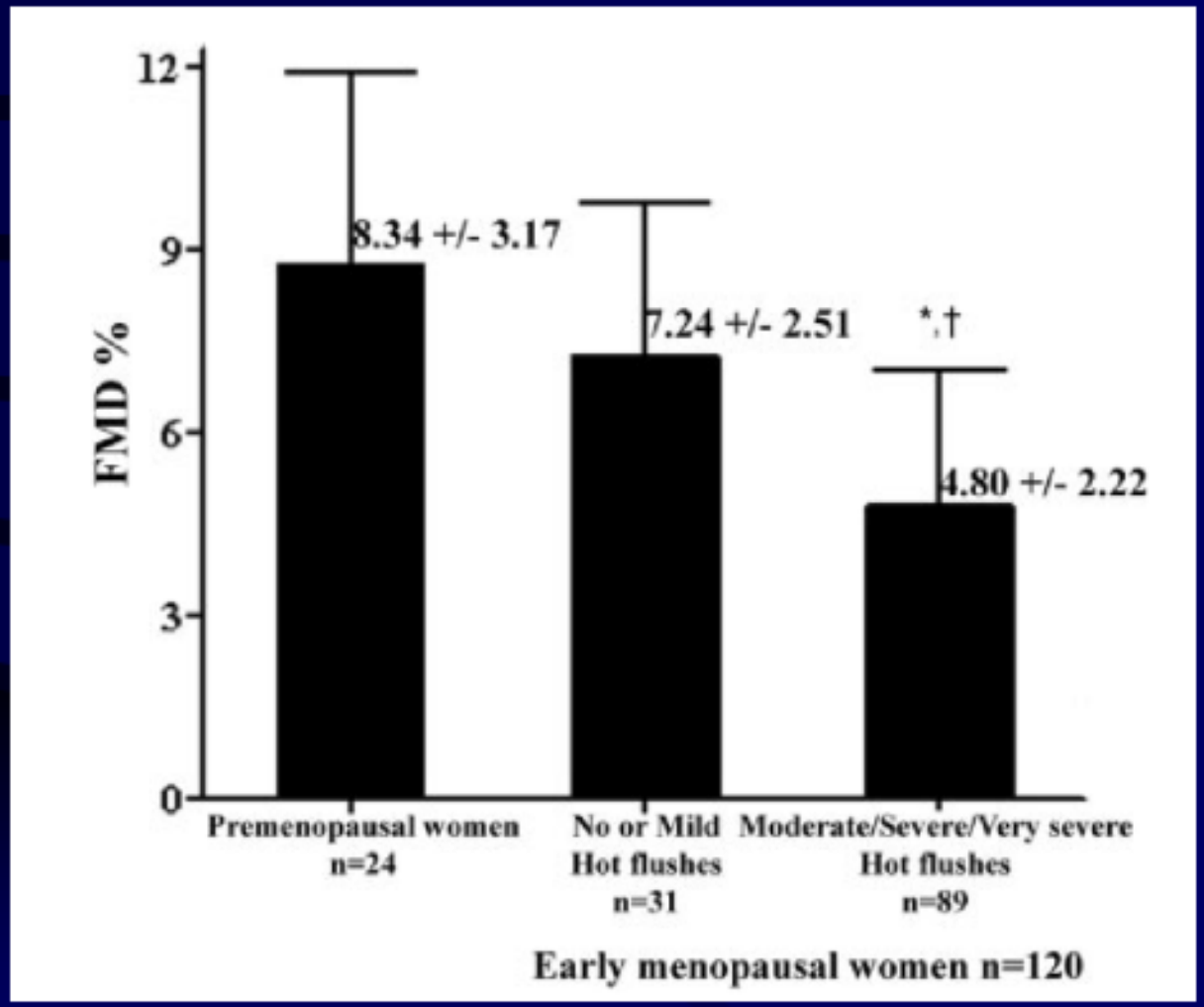
Hazard ratios (95% CIs) for vasomotor symptoms and coronary heart disease risk among the total study population

	Hot flushes	Night sweats
No. of cases	150	134
Model 1	1.11 (0.89-1.40)	1.39 (1.11-1.74)
Model 2	1.06 (0.84-1.35)	1.33 (1.05-1.69)
Model 3	1.01 (0.79-1.28)	1.25 (0.99-1.58)

Models were stratified by study center.
Model 1, adjusted for age (continuous); model 2, adjusted for education level (low, medium, high), smoking (never, past, current), physical activity (inactive, active), ovariectomy (yes, no), hormone therapy use (never, past, current), oral contraceptive use (never, past, current), and menopause status (premenopausal, postmenopausal, perimenopausal); model 3, model 2 with body mass index (continuous), systolic and diastolic blood pressure (continuous), and total cholesterol (continuous).

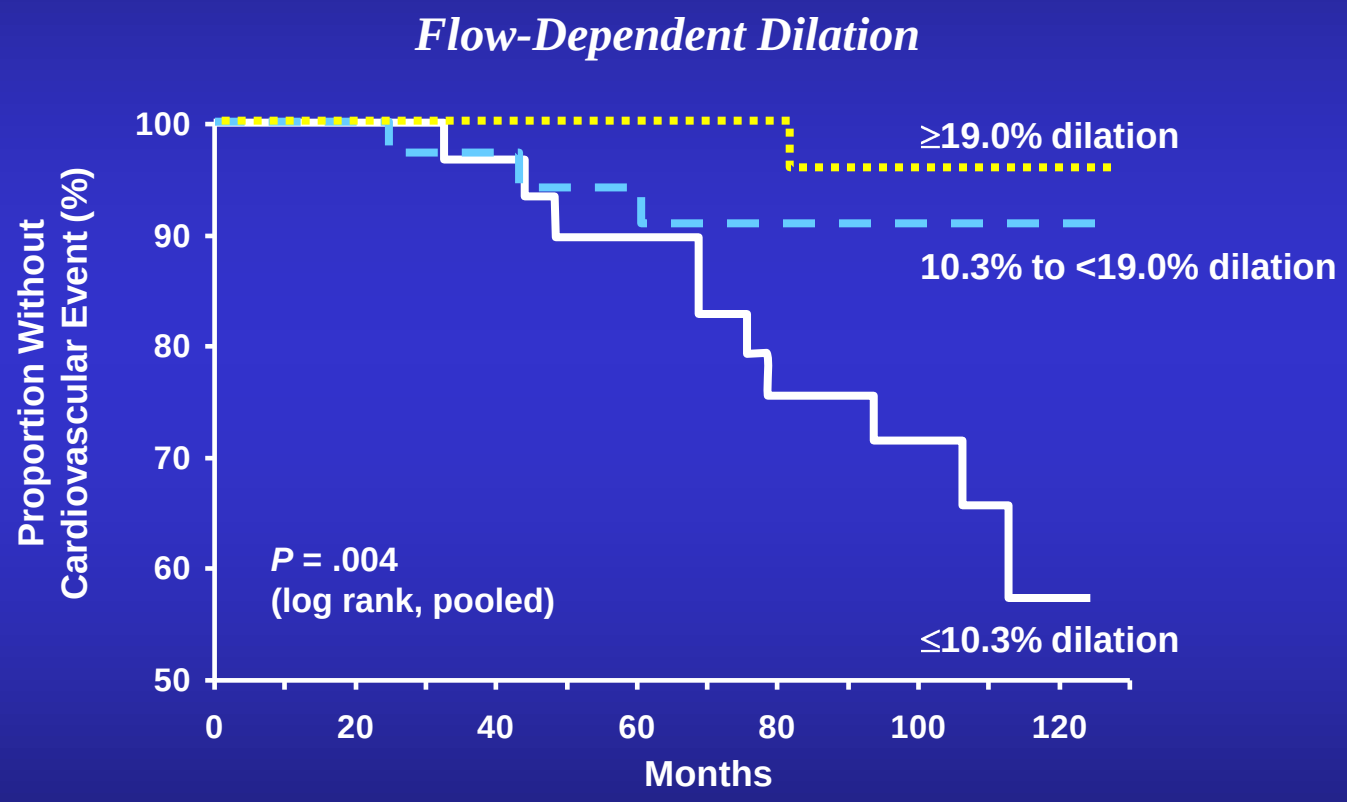
Conclusions: Women with menopausal symptoms of night sweats have a significantly moderately increased risk of CHD, which cannot be totally explained by the levels of CVD risk factors.

HF and FMD



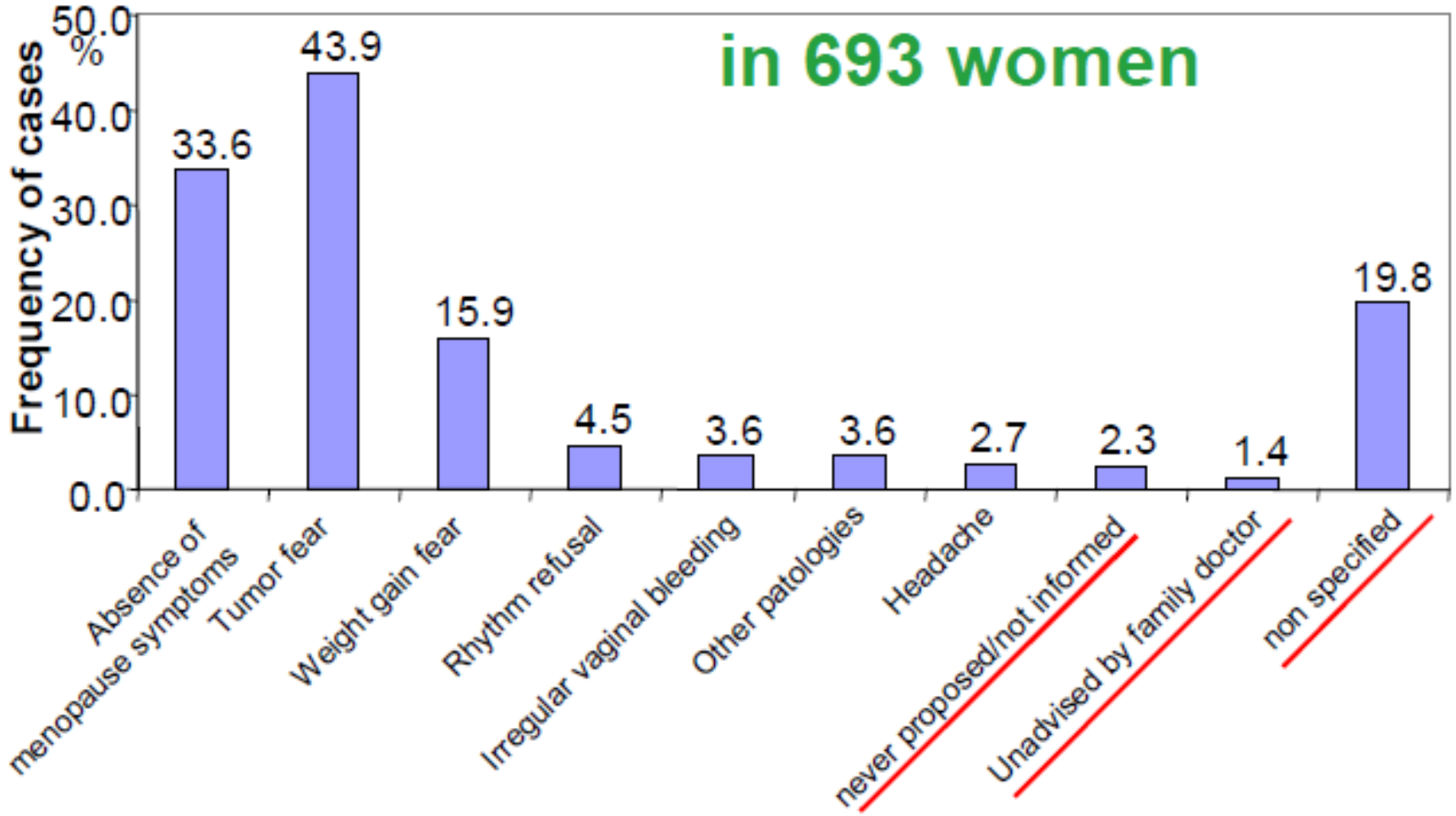
Bechlioulis A et al., JCEM 2010

Coronary Vasodilator Dysfunction Predicts Cardiovascular Events



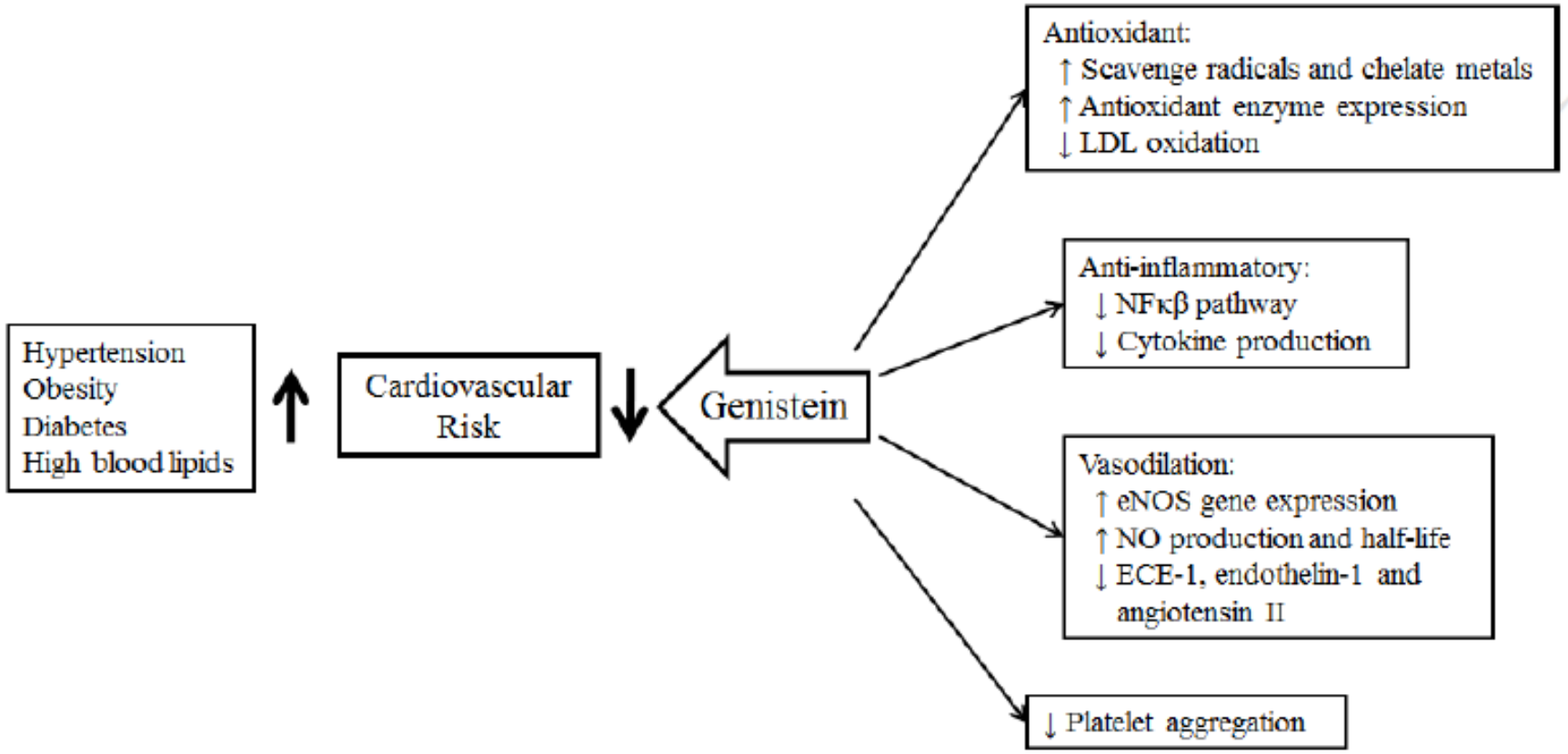
Schachinger V, et al. *Circulation.* 2000;101:1899-906.

HRT refusal/withdrawal reasons



Caputi AP et al. *Giorn. It. Ost. Gin. Vol. XXVIII - n. 5 (2006)*

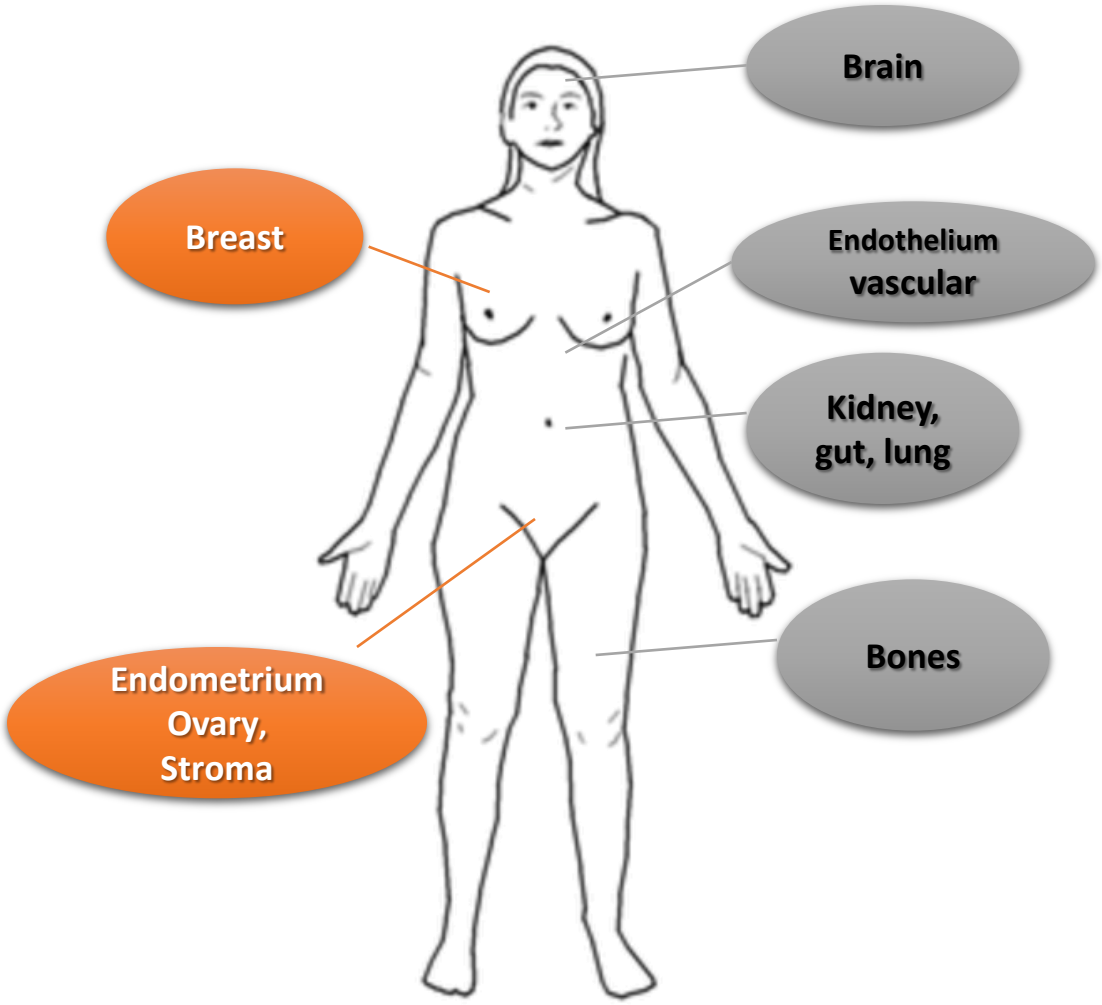
Protective role of genistein against cardiovascular disease



Soy Isoflavones : estrogenic selective activity

Estrogenic effectiveness	
Estradiol	100
Genistein	0,084
Equolo	0,061
Daidzein	0,013

Receptor Affinity		
	ERα	ERβ
Estradiol	100	100
Genistein	4	87
Daidzein	0,1	0,5



Murkies et al. Phytoestrogens – Journal of Clin. Endocr. Metab. 1998 2 (83) 297-303

Gruber et al .Production and action of estrogen N Engl J Med. 1998 5 (346)340-351

Dosage of Isoflavones

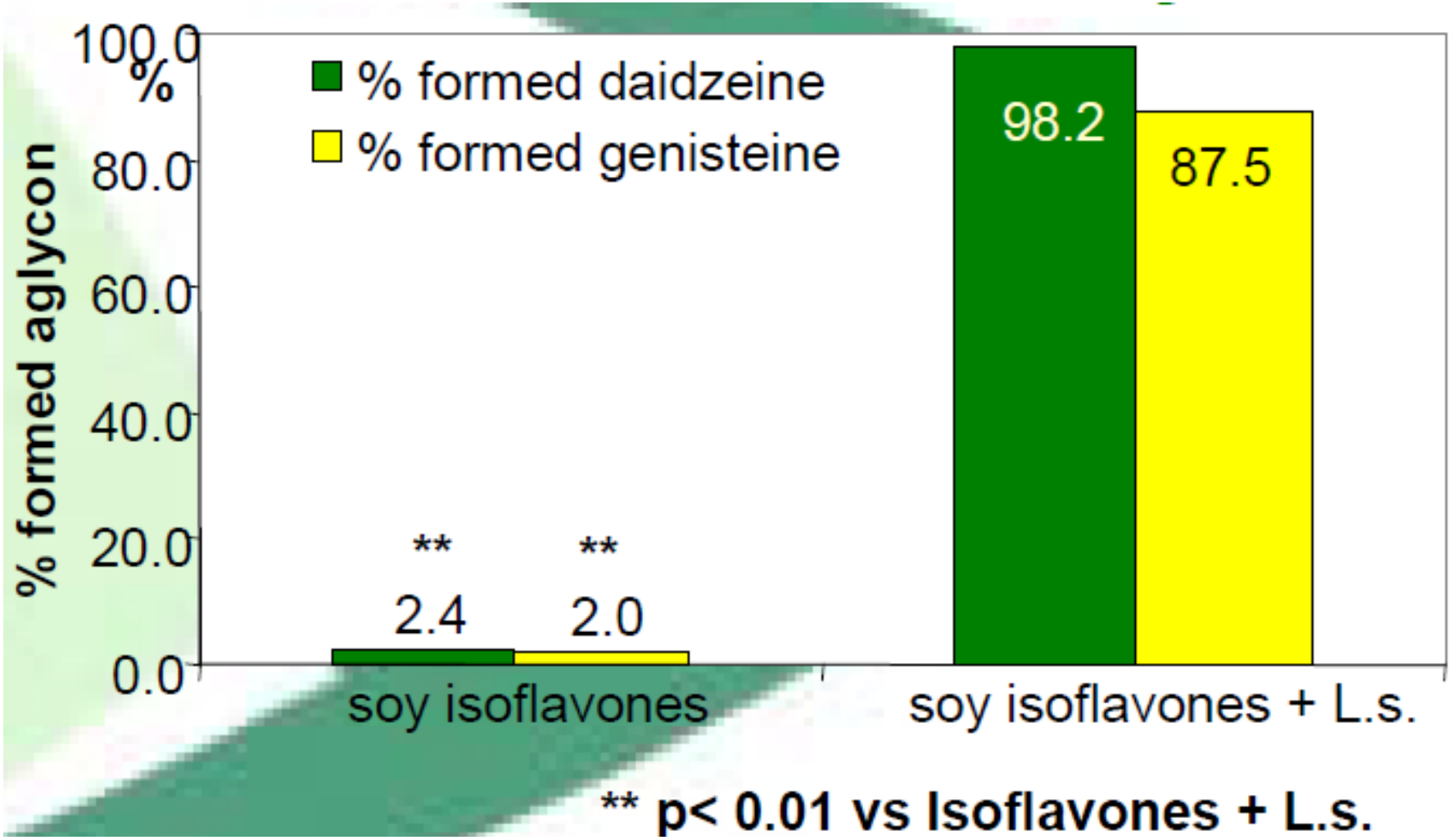
The dosage of I.s. essential to obtain a biologic effect is
50-90 mg / day.

The dosage of I.s. considered safe is lower then **2mg/kg** *of body weight [2].*

I.s. are in GRAS list (Granted as Safe) by FDA - USA.

[1]Messina, Womens Health, 2008 - [2]Barnes, Br J Nutr 2003

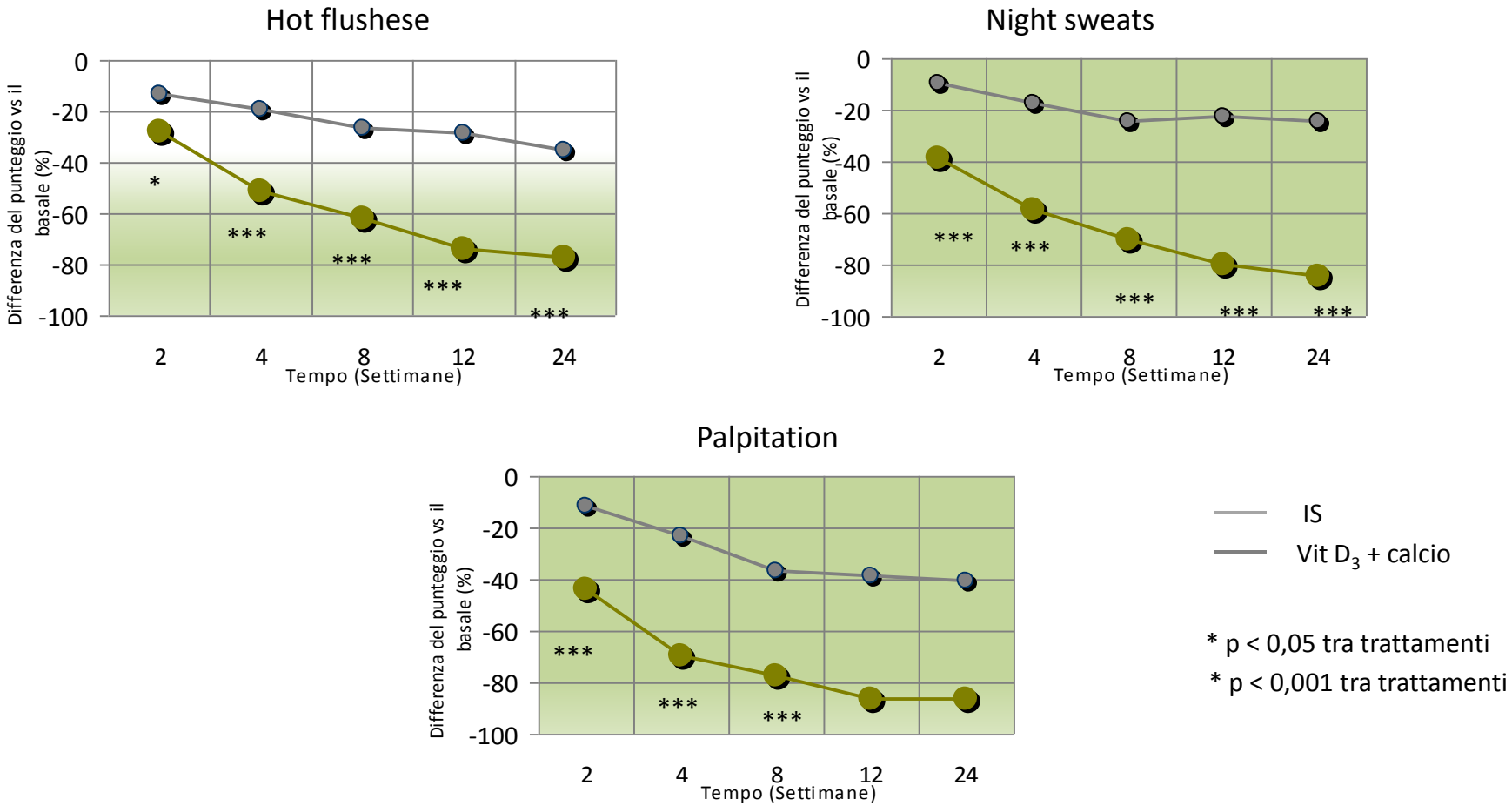
Conversion of isoflavones in active forms by *Lactobacillus sporogenes*.



Arcoraci V 2005

Soy Isoflavones

Improvement in severity of vasomotorial symptoms



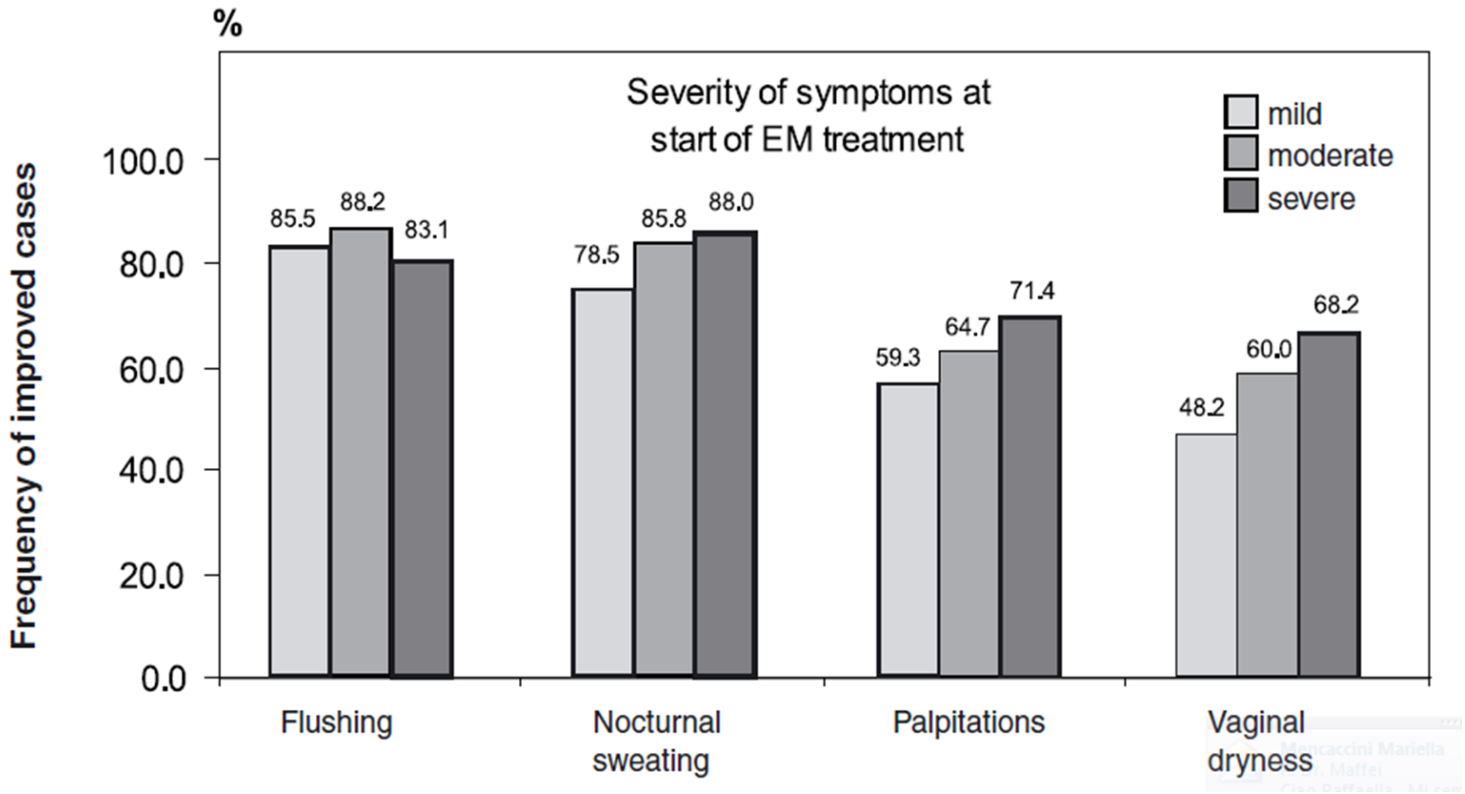
Mucci et al. Soy Isoflavones, Lactobacilli, Magnolia Bark extract, Vitamin D_3 and Calcium. Controlled clinical study in menopause. Minerva Ginecol. 2006 Aug; 58(4):323-34

Soy isoflavones, lactobacilli, vitamin D_3 and calcium. Observational study in menopause

A.P. CAPUTI, V. ARCORACI, C. BENVENUTI,
ESTRONET STUDY GROUP*

*181 gynaecologists collected a sample of 1398 menopause women of which 607 not treated, 327 on estrogens, and 464 on phytoestrogens. 392 women used a phytoestrogen named **Estromineral containing isoflavones** (genistine 30mg and daidzine 30mg) +Lactobacillus sporogenes +Ca +vit.D3. The mean treatment duration was 112.9 days.*

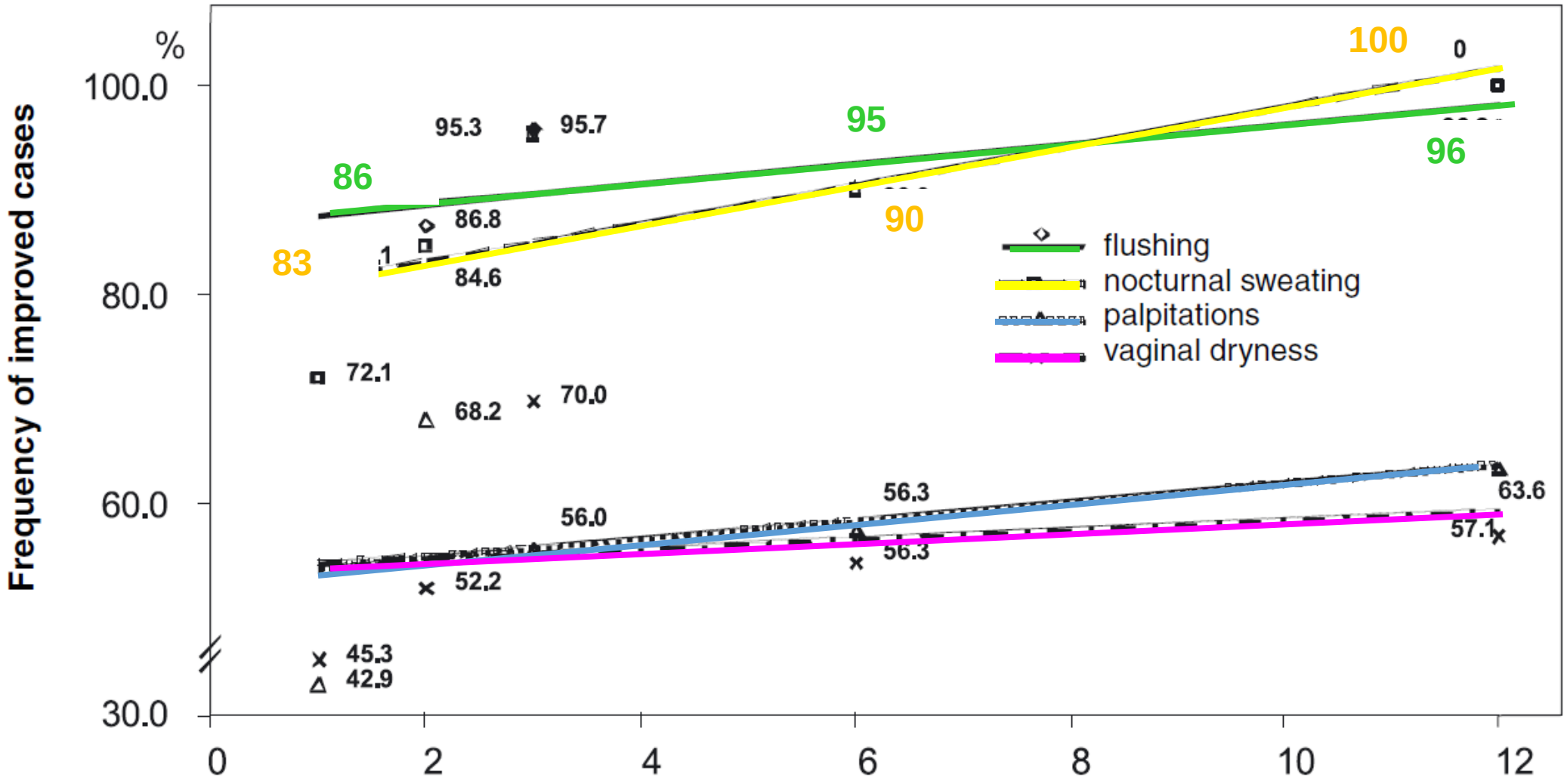
Concomitant therapies according to the stratification in menopause treatments



Clinical activity of EM related to symptom severity at baseline

Giorn. It. Ost. Gin. Vol. XXVIII - n. 5 (2006)

Clinical activity of EM related to duration of treatment



Giorn. It. Ost. Gin. Vol. XXVIII - n. 5 (2006)

Conclusion

- *Women treated (HRT or phytoestrogens) appear more controlled both before and during the treatment.*
- *In presence of concomitant clinical conditions, the natural approach with phytoestrogens are preferred.*
- *Phytoestrogens plus lactobacilli and mineral supplement show a satisfactory clinical activity, correlated to duration of treatment*

Dipinto di Ursula Ferrara