

# HRT *or* Hormonal Treatments?

Controversies...

Contradictions...

in 2003

by *Manuel Neves-e-Castro, M.D.*

*Vice-President of the European Menopause  
and Andropause Society (EMAS)*

# Hormonal Treatments...

- . the **cardiovascular** risk/benefit
- . the **cancer** risk

White woman's risk of death between the ages of 50 and 94 are:

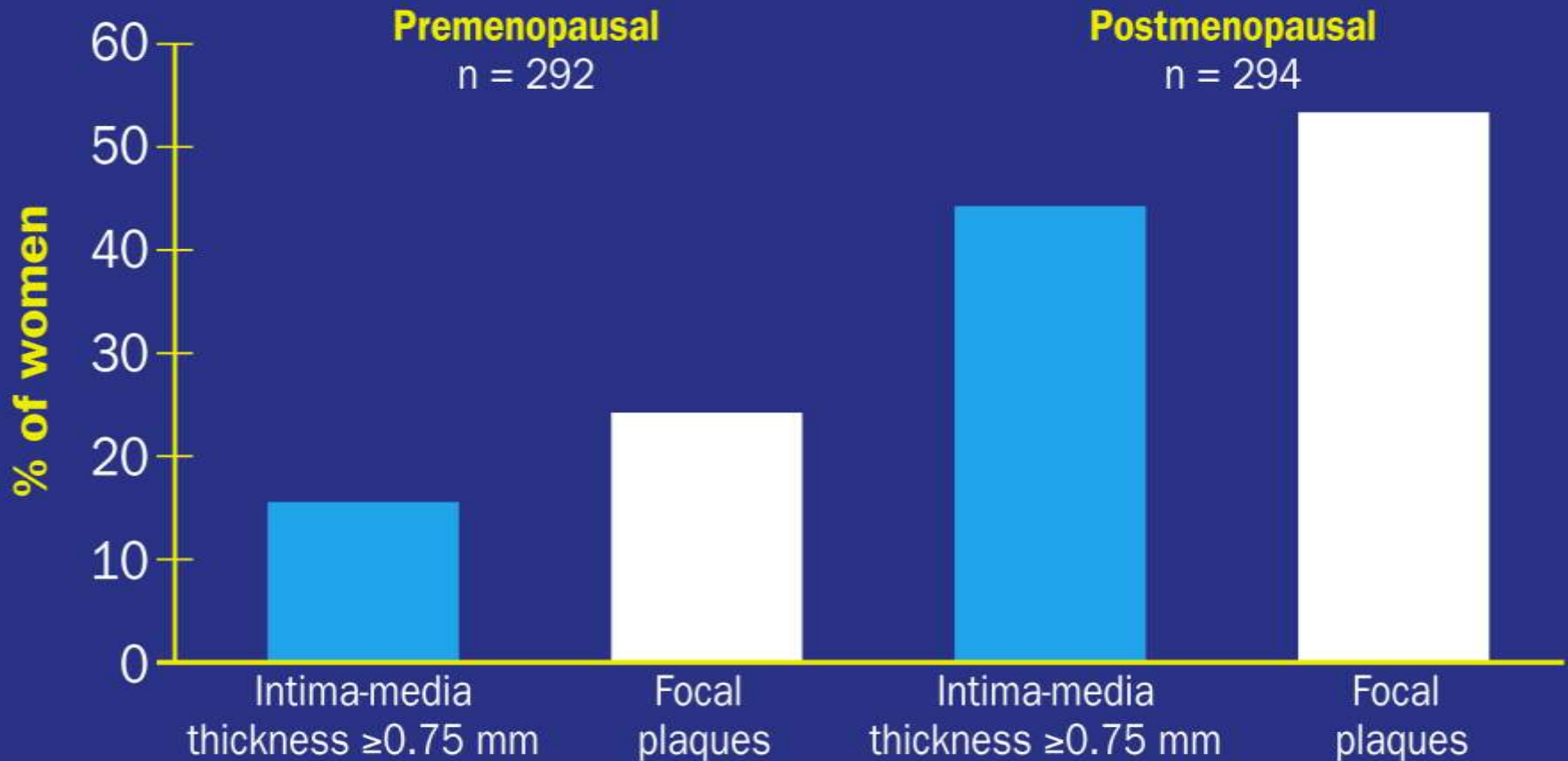
31.0% from heart disease

2.8% from breast cancer

2.8% from hip fracture

*Brinton LA, Schairer C. N Engl J Med. 1997;336:1769-1775*

# Evidence for CVD as a Continuum Associated With Estrogen Loss



# EPAT: The Estrogen in the Prevention of Atherosclerosis Trial

222 Women with LDL > 130; 1 mg E<sub>2</sub> or Placebo

After two years, Carotid Intima-Media Thickness:

Placebo: Significant Increase

Estrogen: Decrease



The Nurse's Health Study  
investigation of primary prevention  
indicates that “**hormone therapy**  
**may be associated with coronary**  
**benefits”**.

# Epidemiological studies

- How were they performed?

# Epidemiological studies

- How were they performed?
- What similarities do they have with our clinical practice?
- How to interpret them?



# The “*language*” of the results

- **Absolute Risk**
- **Relative Risk ( Risk Hazard )**
- **Number Needed to Treat ( NNT )**
- **Number Needed to Harm ( NNH )**
- **Events per woman / year (w/y)**

**Do not confuse...**

*Relative Risk*

with

*Absolute Risk!*

# Effect on the risk of breast cancer

## **WHI** Nonsignificant increased risk

**RR** 1.26 (CI 1.00-1.59); **26%** increased risk

**AR** 0.38% vs 0.30% (ie, **38** vs **30** events annually per 10.000 women)

## **HERS** Nonsignificant increased risk

**RR** 1.27 (CI 0.84-1.94); **27%** increased risk

**AR** 0.59% vs 0.47% (ie, **59** vs **47** events annually per 10.000 women)

# The published studies

- . **HERS 1 and 2**
- . **WHI**
- . **Oxford Breast Cancer**

Interventions investigated...

**Only** *“hormone  
replacement therapy”!...*

**A menopausal woman is a  
mid-age woman**

*As a menopausal woman:*

She is hypoestrogenic and will suffer, at various levels, from its consequences.

*As a mid-age woman:*

She will suffer from the process of natural ageing, both from a biological and a psychological perspective.



*Thus,*

Studies based *ONLY* on the use  
of hormones do not reflect good  
clinical practice!...

**Please remember:**

**Our main target is**

**Mature Woman's**

**Health and Disease Prevention**

*by all means,*

**drug and non-drug related.**

The

**WHI**

The “**Estrogen plus Progestin**”  
arm of the *Women’s Health  
Initiative* randomised control  
trial was suspended .

**NOT the “Estrogen only” arm!**

*If Absolute Risks are plotted as percentages,*  
instead of the additional

**8** strokes

**7** heart attacks

**8** breast cancers *per 10.000 woman/year*

one would have, respectively

**0.08**

**0.07**

**0.08** *cases per 100 woman/year*

a figure that is easier to interpret

## WHI - Overall Risk and Benefit

- WHI "woman" mid sixties

  - risk of harm 2/1,000 women per year

  - 5 years of treatment net harm = 1/100

- Assume 10,000,000 users in US

  - 10,000 excess events/year

  - 100,000 excess events/5 years

*“THE WHI study authors took pains to emphasize that women should not be unduly alarmed. The increased risks in WHI applied to an entire population of women, not to increased risks for individual women – which were very small, less than a tenth of 1 percent per year”.*

(The American College of Obstetricians and Gynecologists, special Task Force on Hormone Replacement Therapy, July 2002).

# The HOPE Study

>2600 healthy, symptomatic, with intact uterus

**At 2 years:**

**“NO increase in venous thromboembolism was seen in the large group of relatively healthy postmenopausal women”.**

Thacker HL. The case for hormone replacement: New studies that should inform the debate. *Cleveland Clinic Journal of Medicine* 2002;69(9):670-678



# National Registry of Myocardial Infarction

“Women with MI who had used postmenopausal HRT had a **lower mortality rate:**

**7.4%** vs **16,2%** in nonusers”.

**Shipak MG** et al. Hormone Therapy and in-hospital survival after myocardial infarction in postmenopausal women. *Circulation* 2001;104:2300-2304

*Hormone replacement therapy is associated with improved survival in women undergoing coronary artery bypass grafting*

*(Review of 4259 records of consecutive patients aged 55 years or older)*

“Postmenopausal women undergoing coronary artery bypass had a **significantly improved in-hospital survival** if they had been receiving hormone replacement therapy”.

**Panel 2: Estimated change in incidence of major, potentially fatal conditions in 1000 healthy postmenopausal women from western countries using HRT over 5-year period, based on results from randomised trials (see appendix for methods)**

	<b>Women aged ~50-59 years</b>	<b>Women aged ~60-69 years</b>
<b>Excess incidence per 1000 HRT users, over 5-year period, for:</b>		
Breast cancer	3.2	4.0
Stroke	1.2	4.0
Pulmonary embolism	1.6	4.0
<b>Total excess*</b>	<b>~6 per 1000, ~1 in 170 users</b>	<b>~12 per 1000, ~1 in 80 users</b>
<b>Reduction in incidence per 1000 HRT users, over 5-year period, for:</b>		
Colorectal cancer	1.2	3.0
Fracture of neck of femur	0.5	2.5
<b>Total deficit*</b>	<b>~1.7 per 1000, ~1 in 600 users</b>	<b>~5.5 per 1000, ~1 in 180 users</b>
<b>Overall balance*</b>	<b>Net excess: ~4.3 per 1000, ~1 in 230 users</b>	<b>Net excess: ~6.5 per 1000, ~1 in 150 users</b>

\*Giving equal weight to each type of event.

“It appears that **half of the benefits** in the prevention of cardiovascular diseases **are not hormone related**”!

*Mosca L, Grundy SM, Judelson D, et al. Circulation  
1999;99:2480-4*

# Nurses's Health Study

*from 1980 to 1994 CHD ↓ 31%*

↓ Smoking	↓ 13%
↑ Obesity	↑ 8%
↑ <b>THS</b>	↓ <b>9%</b>
↑ Better nutrition	↓ 16%

Hu FB, Grodstein F et al. Trends in the Incidence of Coronary Heart Disease and Changes in Diet and Lifestyle in Women. *NEJM* 2000;343:530-537.

# **Lifestyle targets for all patients**

- . Stop smoking**
- . Make healthier food choices**
- . Aerobic exercise**
- . Moderate alcohol consumption**

**Menopausal hormonal treatments**

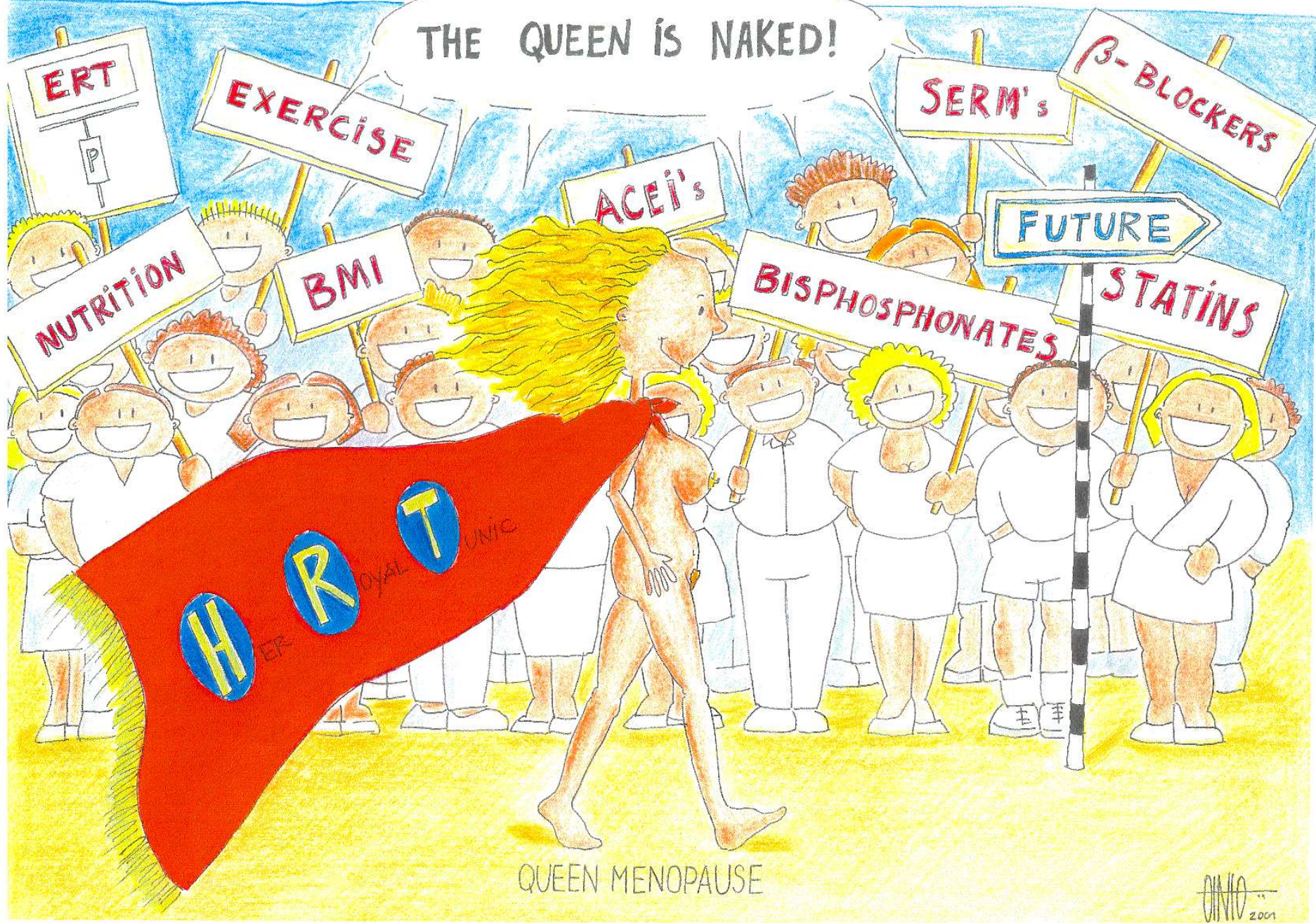
**are very good...**

**Menopausal hormonal treatments**

**are very good, *but***

**Treatments without hormones may also  
be very good for a woman's health.**





QUEEN MENOPAUSE

ONVO 2001

**“Our main goal, as attending physicians of postmenopausal women, is the maintenance of their health and the primary and secondary prevention of the diseases, which are more prevalent after age 50”.**

Neves-e-Castro M. When hormone replacement therapy is not possible. *The Management of the Menopause. The Millennium Review*, Parthenon 2000:91-102.

**The take-home message is (1):**

**Prescribe postmenopausal  
hormonal treatments  
when clinically indicated,  
if not contraindicated!**

# The take-home message is (2):

- The prescription of long-term hormonal treatments must depend always on a benefit/risk analysis *in comparison with other non-hormonal medications and strategies.*

# The take-home message is (3):

- No answers from ongoing clinical trials are indispensable to practice today a good Medicine

Preventing a woman from the  
benefits of a

**sound postmenopausal hormone  
therapy**

because of the fear of rare side  
effects

*does not seem to be satisfactory  
Medicine...*