HRT
or Hormonal Treatments?

Controversies…
Contradictions…
in 2003

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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

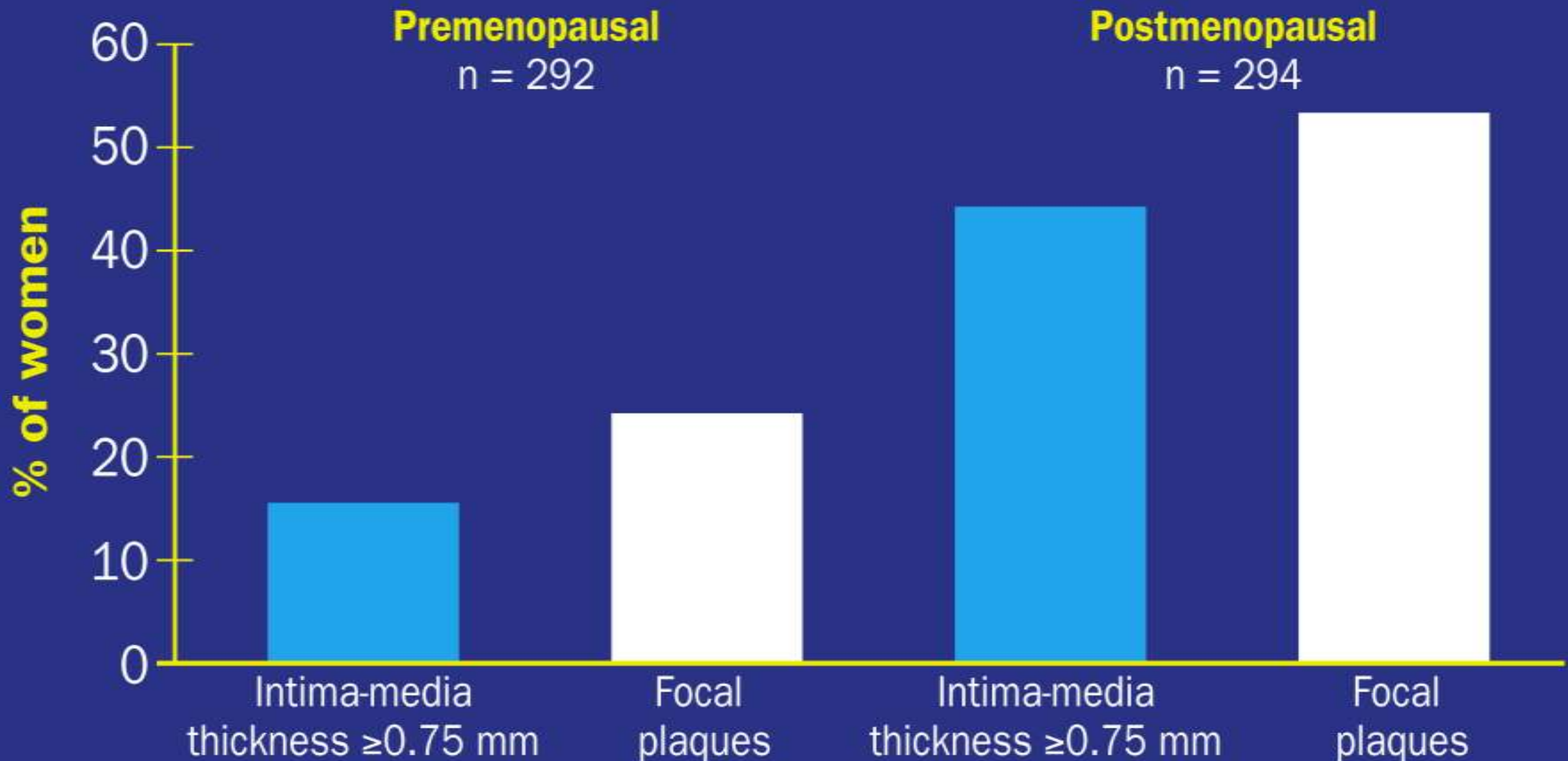
Brinton LA, Schairer C. N Engl J Med.1997;336:1769-1775

“HRT started at age 55 for 10 years can prolong life”.

“One excess breast cancer case is likely to occur per 5-6 averted cases of first myocardial infarction or hip fracture”.

Moerman CJ, Vanhout BA, BonneuxL, et al. J Intl Med 2000;248(2):143-150

Evidence for CVD as a Continuum Associated With Estrogen Loss



Sutton-Tyrrell et al. *Stroke*. 1998;29:1116.

EPAT: The Estrogen in the Prevention of Atherosclerosis Trial

222 Women with LDL > 130; 1 mg E_2 or Placebo

After two years, Carotid Intima-Media Thickness:

Placebo: Significant Increase

Estrogen: Decrease

Am Heart Assoc. 2000

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

Grodstein F, Manson JE, Colditz GA, et al. Ann Intern Med 2000;133:933-41

Epidemiological studies

- How were they performed?
- What similarities do they have with our clinical practice?
- How to interprete 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.

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As a mid-age woman:

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

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Thus,

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

Please remember:

Our main target is

<u>Mature Woman's</u>

<u>Health</u> and <u>Disease Prevention</u>

***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 .

<u>NOT the “Estrogen only” arm!</u>

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

The HOPE Study

"The lower dose (CEE 0.3 mg + MPA 1.5 mg) favorably affects the lipid profile, does not adversely affect carbohydrate metabolism, and maintains skeletal health".

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

National Registry of Myocardial Infarction

"HRT remained associated with improved survival"

OR = 0.65 (CI: 0.59- 0.72)

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".

Nussmeier NA et al.J Thorac Cardiovasc Surg 2002;24:1225-9

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)

	Women aged ~50–59 years	**Women aged ~60–69 years**
Excess incidence per 1000 HRT users, over 5-year period, for:		
Breast cancer	3·2	4·0
Stroke	1·2	4·0
Pulmonary embolism	1·6	4·0
*Total excess**	*~6 per 1000, ~1 in 170 users*	*~12 per 1000, ~1 in 80 users*
Reduction in incidence per 1000 HRT users, over 5-year period, for:		
Colorectal cancer	1·2	3·0
Fracture of neck of femur	0·5	2·5
*Total deficit**	*~1·7 per 1000, ~1 in 600 users*	*~5·5 per 1000, ~1 in 180 users*
Overall balance*	**Net excess:** *~4·3 per 1000, ~1 in 230 users*	**Net excess:** *~6·5 per 1000, ~1 in 150 users*

*Giving equal weight to each type of event.

WHI results calculated as

	NNT/1 year	NNH/1 year
CHD		1428
Stroke		1250
VTE		588
Breast Cancer		1250
Colon Cancer	1667	
Osteoporotic fractures (totals)	227	

Neves-e-Castro M (2003) "*WHI* menopause is in a *crisis*?" *Human Reproduction (submitted)*.

Nurses's Health Study

from 1980 to 1994 CHD ↓31%

↓ Smoking	**↓13%**
↑ Obesity	**↑ 8%**
↑ THS	**↓ 9%**
↑ 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.

“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

Lifestyle targets for all patients

. Stop smoking

. Make healthier food choices

. Aerobic exercise

. Moderate alcohol consumption

BMJ 2002;320:705-708

Menopausal hormonal treatments

are very good, *but*

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

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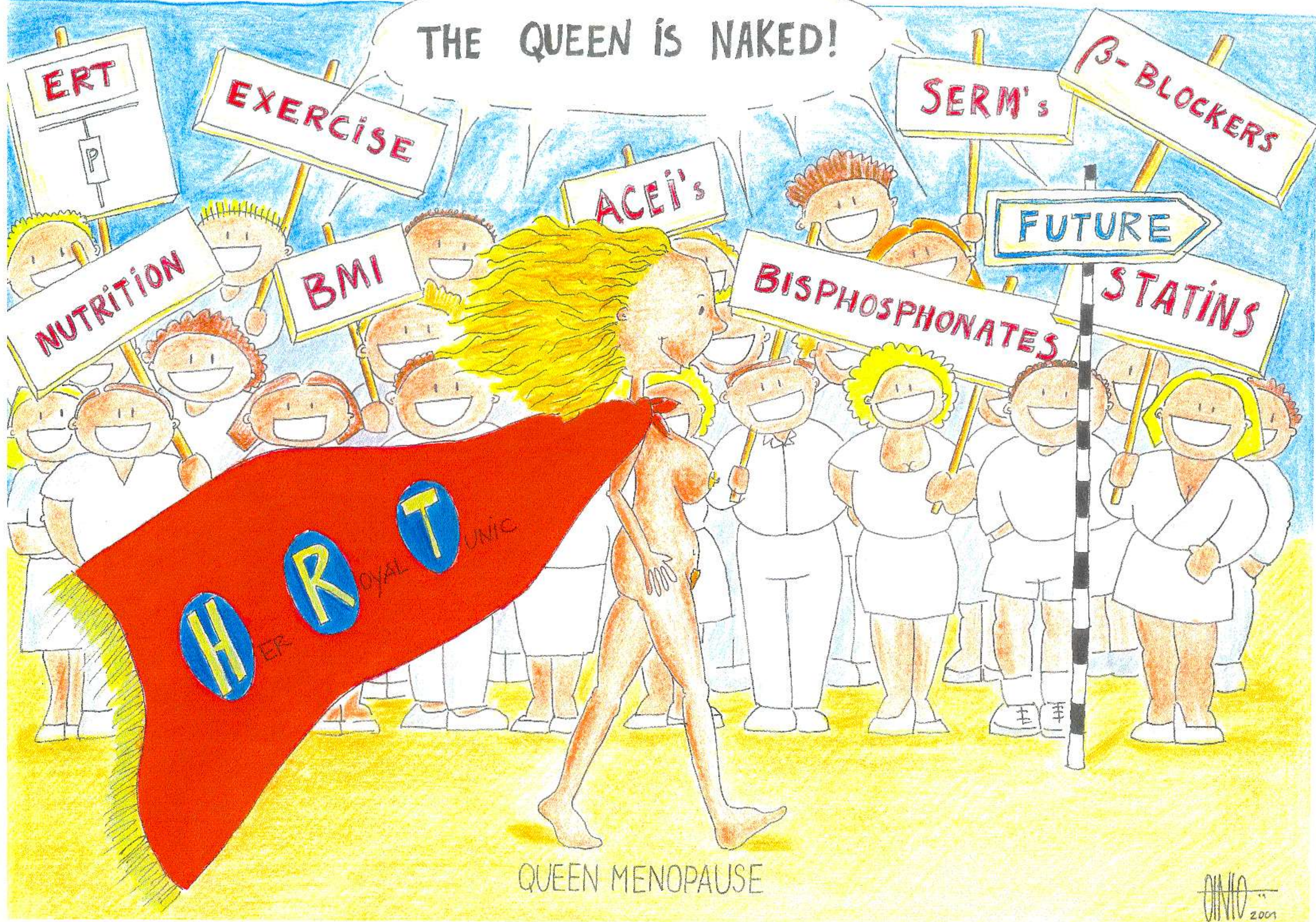

Neves-e-Castro M-Tthe Queen is naked-Maturitas 2001;38:235-7

“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.

A modern gynecologist must ...

know how to identify risk factors and to modify them in order to prevent diseases.

- “***If you are a clinician***, you must believe that you know what will help your patient; otherwise, you cannot counsel, you cannot prescribe”.
- “***If you are a scientist***, however, you must be uncertain – A scientist who no longer asks questions is a bad scientist…”

George Pickering “Physician and scientist”,Br Med J 1964;2:1615-9*(quoted by E Barrett-Connor.Keynote address.Menopause 2002;9(1):23-31)*

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 <u>benefit/risk</u> analysis *in comparison with other non-hormonal medications and strategies*.**

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The take-home message is (3):

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

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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...

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