My enrollment by Serge at 2016 IMS congress in PRAHA

The title he gave me:

The evidence base for HRT: what can we believe?

Suggested readings:

Belief or TRUST?

The Changing Face of Clinical Trials
The evidence base for HRT: what can we believe?

OR

WHI = HOW to CAUSE HARM by DISTORTING GOOD SCIENCE!

According to the personal opinion of LANGER, our « internal spy » as one of the WHI investigators

Marc L’Hermite, CHU Brugmann, ULB

BMS 8-10-16 - Praha IMS 2016 congress
A COLLECTIVE HYSTERIA

Based on a NON-SIGNIFICANT and UNADJUSTED RR of 1.26 (1.00-1.59) for breast cancer

Seven endpoints imply to use as significance threshold 0.007 instead of 0.05 (= NO significance except thromboembolic risk)

Time magazine (july 2002)
An additional risk between 1/1,000 and 1/10,000 is a **RARE** event

These letters (+ other points) introduced **BIAS**, mostly in the **CEE+MPA** arm. Together with a high rate of **unblinding**, it led some authors to conclude that the E/P arm became **OBSERVATIONAL**

*(Shapiro et al, J Fam Plan Reprod Health Care 2011, 37:165-72).*
The apparent increase in BC in CEE+MPA is due to:

An unexplained lower rate in placebo women who had previously used HRT (NOT an increased rate in CEE+MPA women)!
Relative risks lower than 2 (and even more when < 1.5) bear little significance and make it impossible to discriminate among bias, confounding and causation!

But we had to suffer for more than a decade of US-imported INTELLECTUAL TERRORISM and patients stopped, refused or were denied to use HRT despite suffering of invalidating vasomotor symptoms!
The WHI trial was intentionally NOT designed to study outcomes in recently menopausal women. But it was NOT acknowledged = ABUSIVE GENERALIZATION

The most important contribution of WHI to science: Evidence a TIMING-EFFECT resulting from age-related differences in the pathophysiology of atheromatous plaque

Clarkson, 2002

HRT

MHT WHI
GLOBAL MORTALITY is REDUCED by 28% in patients < 60 yrs under MHT

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Randomized Trials</th>
<th>Treatment Deaths/n</th>
<th>Control Deaths/n</th>
<th>Relative Risk Random (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angerer 2000</td>
<td>1/215</td>
<td>0/106</td>
<td>1.2 (0.09, 3.892)</td>
<td></td>
</tr>
<tr>
<td>Arrehrech 2002</td>
<td>1/108</td>
<td>0/53</td>
<td>1.2 (0.10, 3.924)</td>
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<tr>
<td>Giske 2002</td>
<td>1/123</td>
<td>0/43</td>
<td>0.86 (0.07, 2.811)</td>
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<tr>
<td>Gudozzi 1999</td>
<td>32/62</td>
<td>41/68</td>
<td>0.86 (0.63, 1.16)</td>
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</tr>
<tr>
<td>Hall 1994</td>
<td>3/37</td>
<td>3/16</td>
<td>0.46 (0.11, 1.81)</td>
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<tr>
<td>Hall 1998</td>
<td>0/40</td>
<td>1/20</td>
<td>0.21 (0.01, 2.64)</td>
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<tr>
<td>Komulainen 1999</td>
<td>1/115</td>
<td>2/115</td>
<td>0.63 (0.07, 4.07)</td>
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<tr>
<td>Kyllonen 1998</td>
<td>1/52</td>
<td>0/26</td>
<td>1.24 (0.10, 3.998)</td>
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<tr>
<td>Lindsay 1976</td>
<td>1/63</td>
<td>1/37</td>
<td>0.91 (0.1, 8.49)</td>
<td></td>
</tr>
<tr>
<td>MacDonald 1994</td>
<td>1/22</td>
<td>1/22</td>
<td>1.00 (0.11, 8.95)</td>
<td></td>
</tr>
<tr>
<td>Mijatovic 1998</td>
<td>0/13</td>
<td>1/13</td>
<td>0.42 (0.01, 4.77)</td>
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<tr>
<td>Mosekilde 2000</td>
<td>4/502</td>
<td>9/504</td>
<td>0.49 (0.15, 1.38)</td>
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<tr>
<td>Nachtigall 1979</td>
<td>3/84</td>
<td>7/84</td>
<td>0.48 (0.13, 1.50)</td>
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<tr>
<td>PEPI 1995</td>
<td>3/701</td>
<td>0/174</td>
<td>1.32 (0.17, 39.44)</td>
<td></td>
</tr>
<tr>
<td>Perez-Jaritz 1996</td>
<td>0/26</td>
<td>1/52</td>
<td>0.81 (0.03, 10.08)</td>
<td></td>
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<tr>
<td>Ravn 1999</td>
<td>0/110</td>
<td>1/109</td>
<td>0.41 (0.01, 5.23)</td>
<td></td>
</tr>
<tr>
<td>WHI 2002</td>
<td>1/303</td>
<td>0/103</td>
<td>0.83 (0.06, 25.96)</td>
<td></td>
</tr>
<tr>
<td>WHI 2004</td>
<td>34/1637</td>
<td>48/1673</td>
<td>0.71 (0.52, 0.96)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>156/8889</td>
<td>211/7594</td>
<td>0.73 (0.47, 1.12)</td>
<td></td>
</tr>
</tbody>
</table>

Posterior Estimate from Trials Using Non-informative Prior Distribution

Observational Studies

- Bush 1987: 0.62 (0.47, 0.82)
- Cauley 1997: 0.63 (0.47, 0.82)
- Croqui 1988: 0.70 (0.53, 0.91)
- Folsom 1995: 0.74 (0.57, 0.98)
- Grodstein 1997: 0.66 (0.51, 0.88)
- Pagano-Hill 2006: 0.77 (0.58, 1.02)
- Petitti 1987: 0.75 (0.57, 0.99)

Posterior Estimate from Observational Studies Using Non-informative Prior Distribution

0.73 (0.52-0.96)

Observational studies

Essentially CEE + MPA!

Figure 2  Bayesian meta-analysis: effect of hormone therapy on mortality in younger postmenopausal women.
Only the women with accurately known age at HT initiation were included in the analysis (n = 310 305). The data are expressed as standardized mortality ratio with 95% confidence intervals. The vertical line at 1.0 denotes the risk in the age-matched background population. The observed and expected numbers of deaths are given for 5-year periods.

P < .05 for trend.

Similar for all-cause mortality (Mikkola et al Menopause 2005, 22: 976-83)

Published in: Hanna Savolainen-Peltonen; Pauliina Tuomikoski; Pasi Korhonen; Fabian Hoti; Pia Vattulainen; Mika Gissler; Olavi Ylikorkala; Tomi S. Mikkola; The Journal of Clinical Endocrinology & Metabolism 2016, 101, 2794-2801.

DOI: 10.1210/jc.2015-4149
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QUALY GAIN, « cost-effective » for 5, 15 as well as 30 years of MHT!

15 years MHT initiated at 50 or at 65 years

**Bayesian meta-analysis.**

Initial LOSS of QUALY during the first 9 years!

FIRST HARM from WHI:

DEPRIVATION of the best Tx of VSM symptoms = disturbed wellbeing and quality of life
UNINTENDED HARMS caused by WHI (2): from scaring into stopping HRT

- Increased HIP FRACTURES rate (RR= 1.55 – IC: 1.36-1.77) unselected population, at low-risk of osteoporosis

(Karim et al Menopause 2011, 18:1172-7)
UNINTENDED HARMS caused by WHI (3): scaring to avoid ERT

The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years

In the 1990s, estrogen therapy (ET) became the standard of treatment of the almost 600,000 women a year in the United States undergoing hysterectomy. Clinical studies had indicated ET was effective for treatment of menopausal symptoms and appeared to be bone protective and cardioprotective. More than 90% of hysterectomized women in their 50s used ET, with a continuance rate averaging 4 to 5 years.1–3

In July 2002, the Women’s Health Initiative (WHI) published the results of the Estrogen Plus Progesterin Trial and announced that the study was being terminated ahead of schedule because of adverse effects in the women receiving hormones compared with those receiving placebo.4 The media impact was immediate, widespread, and persistent.5 The objectives. We examined the effect of estrogen avoidance on mortality rates among hysterectomized women aged 50 to 59 years.

Methods. We derived a formula to relate the excess mortality among hysterectomized women aged 50 to 59 years assigned to placebo in the Women’s Health Initiative randomized controlled trial to the entire population of comparable women in the United States, incorporating the decline in estrogen use observed between 2002 and 2011.

Results. Over a 10-year span, starting in 2002, a minimum of 18,601 and as many as 91,610 postmenopausal women died prematurely because of the avoidance of estrogen therapy (ET).

Conclusions. ET in younger postmenopausal women is associated with a decisive reduction in all-cause mortality, but estrogen use in this population is low and continuing to fall. Our data indicate an associated annual mortality toll in the thousands of women aged 50 to 59 years. Informed discussion between these women and their health care providers about the effects of ET is a matter of considerable urgency. (Am J Public Health. 2013;103:1583–1588. doi:10.2105/AJPH.2013.301295)
UNINTENDED HARMS caused by WHI (4): after stopping HRT

Within the first post-treatment year:
- Increased Cardiac mortality & stroke death
- When discontinuation < 60 years

Using these exceptionally reliable Finnish Registers
Change in mortality from pre- to post-WHI era

Mostly IMPROVEMENT

Even As Mortality Fell In Most US Counties, Female Mortality Nonetheless Rose In 42.8 Percent Of Counties From 1992 To 2006

Unexplainable WORSENING of female (over male) mortality rates

Kindig, Health Affairs 2013, 32:451-8
After WHI, patients stopped, refused or were denied to use HRT despite invalidating vasomotor symptoms!

Mistrust of FDA-approved drugs led patients and physicians towards custom-compounded bioidentical hormones, becoming in North America an unregulated industry in disguise, a business of billion(s)-dollar a year! (making FALSE claims and advertisements!).
From CHARYBDE to SCYLLA

WHI & TIME magazine having DEMONIZED HRT:

Patients & physicians were driven towards CUSTOM-COMPOUNDED BIOIDENTICAL HORMONES
UNINTENDED HARMS caused by WHI (5): a drive towards potentially harmful custom-compounded « bioidentical » hormones, instead of registered « natural » hormones

- Unspecific risks of custom-compounding:
  - contamination by pathogens: e.g. a large series of fungal meningitis, including > 26 deaths (USA)
  - other « contaminants »: mistakenly using, for weight reduction, a nephrotoxic and carcinogenic Chinese herb (BE)
  - ...

- Specific risk of CC sex hormones:
  imbalance between E2 and P4
  = excess of ENDOMETRIAL CANCERS

- But a major advantage when using non-oral estrogen:
  NO increase in thromboembolic and stroke risks
Control of the Message

Requests to conduct the full cohort analyses, stratified on hysterectomy status, with adjustment for covariates – as planned in the protocol – were refused by the WHI Publications Committee

... culminating with correspondence from the Chairman of the Publications Committee that

"the Principal Investigators ... have reached a consensus on interpretation of our data and prefer that our publications not be contradictory."
OPINION of LANGER (one WHI investigator)

But I fully agree

How good science became distorted and caused harm ...

The WHI reports ...

- Failed to:
  - properly identify the study goals and population characteristics
  - put the findings in context of existing knowledge
- Inappropriately generalized the findings:
  - to a key subgroup – newly menopausal women - that was not adequately represented
  - from specific medications to an entire class
- Favored publicity, fear and sensationalism over science
- Departed from protocol, focusing on unadjusted results and avoiding planned analyses with better statistical power
- Deliberately maintained “a consistent interpretation” to the point of refusing to consider analyses that could challenge it
WHI: conclusions, interpretations and recommendations

•Clearly a MESSAGE that was NOT evidence-based
•Because they favored publicity, fear and sensationalism over science
•More than a decade of errance and cheating
Did you imagine what would be the last messages of lead WHI investigators?

We have been MISINTERPRETED!

HT can be SAFELY used for VSM symptoms
A proof beyond reasonable doubt requires a much smaller P value. P<0.05 is only the MINIMUM required!
- Is it clinically meaningful? Examine the effect on both relative and absolute scales.
- Carefully inspect composite primary endpoints.
- Are findings consistent across all patient types?
- False findings can arise when analyzing multiple subgroups.
- Early stopping = often a newsworthy event. But this procedure tends to exaggerate the reported effects.
- Are there flaws in trial design or conduct? Caution with nonadherence and withdrawals.
- Any trial applies to the specific patients enrolled. Thus avoid unwarranted generalization.
Wouldn’t you conceive that it could be time for our society, the BMS, to engage in a crusade in Belgium in order to rehabilitate it in the mind of belgian regulatory authorities, belgian doctors (both specialists and home doctors), and to change guidelines from the CBIP-BCFI AND to inform correctly the LAY PRESS??

Oct 18 = WORLD MENOPAUSE DAY

CBIP: Centre Belge d’information pharmacothérapeutique
Statistics is the number one inexact science

Science is infallible but scientists often make mistakes

THANK YOU FOR YOUR ATTENTION

And what about the media??
Kaplan-Meier estimates of hot flush duration by menopausal stage and symptom onset

50% still symptomatic at 65 years and some even 24 after their final spontaneous menstruation

(Hunter – Bit J Obstet Gynaecol 2012, 119: 40-50)
Risk of death or admission to hospital due to heart failure or MI (primary endpoint) over 16-year follow-up, including 11 years of randomized treatment.

CARDIOPROTECTION of HRT started 11 years before is maintained for the 16 observation years.

DO NOT MIX UP/CONFUSE:

- **HRT INITIATION** after 60-70 years

  = a significant (?) CV risk, mainly if after 70 years

- **HRT CONTINUATION** after 60-70 years

  = the early gained cardioprotection does not vanish…there seems to be no additional gain but CV risk remains less than for HRT initiated at the same age!

**IMS**: there should be no arbitrary constraint to limit the length of HRT use.
Because some women aged 65 years and older may continue to need systemic hormone therapy for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years.