ESHRE meeting, Edinburgh 6-7 October, 2008

HRT: promotion or prevention for cardiovascular disease?

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CASE REPORT

52-year old women
myocardial infarction, normal angio,
weight 50 kg, length 158 cm
discharged from CCU Nov 2007 with
aspirin, betablockade, statins (40 mg simva), nitrates
HRT discontinued (used since age 40, premature menopause)
Follow up 4 weeks:
heavy climacteric symptoms, sleepdisorders
sleeping pills, reduced dose simva
Follow up 8 weeks:
more sleeping pills, unchanged dose simva
Tel call to nurse: no QoL, depressed, suicide thoughts

Referred to Karin after 12 weeks-what did I do?

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ESC, Munchen,
August 31, 2008, abstract 191

”Cessation of hormone replacement therapy after acute MI increases risk of sudden death and recurrent myocardial infarction during the first 90 days after cessation”

Bretler DM , Hansen PR et al, Copenhagen,Dk

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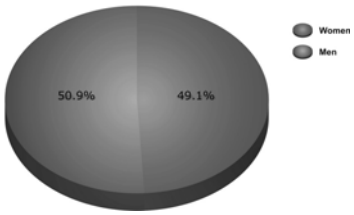
WHO-Women's Health Agenda:
Focusing on maternal **and** child health **only**

– **The Millennium Development Goals WHO:**

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

Cardiovascular disease & other chronic diseases are excluded

Global cardiovascular **deaths:**
Almost as many women as men die of CVD



Source: Based on the latest WHO estimations of 17.5 million total CVD deaths and 8.6 million female CVD deaths

The burden of disease in Europe

– CVD represents 51.9% of total deaths in the Euro region*
– It represents 42% of deaths in the European Union**
– CVD is the main cause of the disease burden in Europe (23% of all the disease burden)***
– CVD mortality, incidence and case fatality are falling in most Northern, Southern and Western European countries, but either not falling as fast or rising in Central and Eastern European countries*****
– 2,763,865 female CVD deaths*****
– The number of disability-adjusted life years lost due to CVD is 15 million for the women of the Europe region******

Sources:
**** The World Health Report 2002 –reducing risks, promoting healthy life, WHO 2002***
*****, ***, **** European Heart Network Statistical Data http://www.ehnheart.org/***
******** WHO country profile, aggregated country data, http://www.who.int/chp/countries/en/index.html***
********* Data for EURO, World Health Report 2001. mental health, new understanding, new hope, WHO 2001***

Differences in admission rates and outcomes between men and women presenting to emergency departments with coronary syndromes

Padma Kaul PhD, Wei-Ching Chang PhD, Cynthia M. Westerhout MSc, Michelle M. Graham MD, Paul W. Armstrong MD

54000 patients, 40% women

Interpretation: Women presenting to the emergency department with coronary syndromes are less likely than men to be admitted to an acute care hospital and to receive coronary revascularization procedures. These differences do not translate into worse outcomes for women in terms of 1-year mortality.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/177/10/1193/DC1

CMAJ 2007;177(10):1193-9

Non modifiable **CVD risk factors**

- **Age**
- **Gender**
- **Genes**
- **Co-morbidities**

Top modifiable **CVD risk factors**

- **Smoking**
- **Dietary intake**
- **Overweight and obesity**
- **High blood pressure**
- **Alcohol use**
- **Lack of physical activity**
- **High blood cholesterol**

Riskfactors for myocardial infarction in men and women: Insights from the Interheart Study

Anand, S. S. et al. Eur Heart J 2008 29:932-940;

27.098 pts from 52 countries, 6787 women

Proposed hormone related cardiovascular riskfactors

Polycystic ovarian syndrome
Premature menopause

Preclampsia
Complications at birth
Gestational diabetes
Gestational hypertension

Tako-tsubo Syndrome (Broken Heart Syndrome
Left ventricular ballooning Stress induced cardiomyopathy)

Postmenopausal women!

Japan 1990
USA 2004
Europe 2006
Australia 2006
("Neurohumoral features of myocardial stunning due to sudden emotional stress"
Wittstein I et al N Engl J Med, 352:539-548, Febr 10, 2005)

WHI studies (Designed 1991-2)

- Postmenopausal women ranging in age from 50 to 79 years were enrolled into either a clinical trial (CT) that would eventually include 68,132 women (mean age 63 years), or an observational study (OS) that would involve 93,676 women. The WHI Extension Study is following up 115,400 participants from each of the original WHI study components until 2010.

- The randomised CT evaluated three distinct interventions:
- 1] a low-fat eating pattern (n=48,835)
- 2] hormone replacement therapy (HRT)
- CEE 0.625mg for hysterectomised women (n=10,739),
- CEE 0.625mg and MPA 2.5mg for women with a uterus (n=16,608),
- 3] calcium and vitamin D supplementation (n=36,282).

- If eligible, women could choose to enroll in one, two, or all three of the randomized trial components.

Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy

The Women's Health Initiative Randomized Controlled Trial

Estrogen Therapy and Coronary-Artery Calcification

JoAnn E. Manson, M.D., Dr.P.H. et al for the WHI and WHI-CACS Investigators

N Engl J Med 2007,
356:2591-2602 June 21, 2007 Number 25

Million Women Study:OS

- 1,084,110 women surveyed 1996-2000
- 75- 83% women invited to have mammogram accept
- 71% screened women surveyed
- 66 centres
- Baseline questionnaire for HRT use
- Follow up 2.6 years
- Outcomes include: breast cancer, endometrial cancer, ovarian cancer, gallbladder disease

Million Women Study Collaborators 2002, 1999
Banks et al 2002, NHSBSP Statistics

HRT February 2008 BMS consensus statement http://www.thebms.org.uk

Benefits	Risks	Uncertainties
Menopausal symptoms	Breast cancer	**Cardiovascular disease**
Osteoporosis	VTE	**Dementia/ Alzheimers**
Colorectal cancer	Gall bladder disease	**Ovarian cancer**
		Quality of life

HRT and VTE (WHI)

- Combined HRT VT risk increased (HR 2.06; 95% CI, 1.57-2.70).
- Risk increases with age
- Risk increases in overweight and obese women
- Factor V Leiden enhanced the hormone-associated risk of thrombosis 6.69-fold
- Other genetic variants (prothrombin 20210A, methylenetetrahydrofolate reductase C677T, factor XIII Val34Leu, PAI-1 4G/5G, and factor V HR2) did not modify the association of hormone therapy with venous thrombosis.
- Estrogen alone An early increased VT risk is associated with use of estrogen, especially within the first 2 years, but this risk increase is less than that for estrogen plus progestin (HR 1.32; 95% CI, 0.99-1.75). There were no significant interactions between estrogen use and age, body mass index, or most other VT risk factors.

Coronary heart disease per 10,000 women per year

- Combined HRT
  - The excess absolute risk at
  - 50-59 + 5
  - 60-69 +1
  - 70-79 + 23
- Oestrogen alone
  - The reduced absolute risk at
  - 50-59 - 10
  - 60-69 years -5
  - with an excess risk at 70-79 + 4

Years since menopause and starting HRT

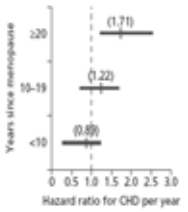


Figure 7.1 Influence of time since menopause on the effect of hormone replacement therapy on coronary heart disease. Adapted from Manson (2003)

Coronary heart disease per 10,000 women per year WHI combining both arms

- Absolute risk at
  - 50-59 -2
  - 60-69 -1
  - 70-79 + 19

Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465-77.

Randomized controlled trials of HRT secondary prevention for coronary heart disease

CEE=conjugated equine estrogens. MPA=medroxyprogesterone acetate.

Study	HRT	Route	Relative risk, mi (95% conf interval)	N
HERS (Hulley, 1998)	CEE/MPA	Oral	0.99 (0.8 to 1.22)	2769
PHASE (Clarke, 2002)	17 β - oestradiol	Patch	1.29 (0.84 to 1.95)	255
WEST (Viscoli, 2001)	17 β - oestradiol	Oral	1.1 (0.6 to 1.9)	664
ESPRIT (Cherry, 2002)	Oestradiol valerate	Oral	0.99 (0.7 to 1.41)	1017

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Stroke cases per 10,000 women per year.

- Combined HRT
  - Excess absolute risk at 50-59 + 4
  - 60-69 + 9
  - 70-79 + 13
- Oestrogen alone HRT
  - Excess absolute risk at 50-59 0
  - 60-69 +19
  - 70-79 +14

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Stroke cases per 10,000 women per year WHI combined trials.

- **Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12-1.56).**
- **Risk did not vary significantly by age or time since menopause.**

Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465-77.

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Premature menopause

- **POF increases risk CVD, osteoporosis, dementia, cognitive decline, parkinsonism**
- **Need HRT/estrogen until average age of menopause ie 52**
- **This does not increase breast cancer risk compared to that found in normally menstruating women**
- **Advice unchanged by WHI and MWS since both undertaken in women aged 50 and over**
- **CSM Dec 2003**

- **Ewertz et al. Br J Cancer 2005; 92:1293-7.**
- **Rocca et al. Neurology. 2007; 69:1074-83.**
- **Rocca WA et al. Neurology. 2008; 70:200-9.**

- **Jones GL, Ledger W, Mitchell C. Suspected premature menopause. *BMJ* 2008;336:833. (12 April.)**
- **Lewars MD.Premature menopause: Article's recommendation of HRT is highly questionable. BMJ. 2008 May 10;336(7652):1033-4.**
  'it seems irresponsible for Jones et al to recommend combined hormone replacement therapy for 15 years or more'
- **Rees MC.Premature menopause: Hormone replacement therapy is indeed indicated. BMJ. 2008 May 24;336(7654):1148.**

Endothelial dysfunction in resistance arteries after menopause

Karolina Kublickiene et al J Clin Endocrin Metabolism 4 March 2008

Isolated resistance arteries in subcutaneous biopsies from 55 postmenopausal women before and after 3 m estradiol (E2), medroxyprogesteroneacetate (MPA), E2 + MPA or placebo.
In addition, isolated human endothelial cells were studied.

Artery flow-mediated dilatation was augmented after treatment with E2 or E2+MPA,

whereas MPA or placebo had no effect.
Pressure-induced myogenic tone was reduced by E2 + MPA,while it was unchanged in the other groups.

Scanning microscopy showed that E2 improved endothelial cell morphology and decreased signs of endothelial apoptosis, but the addition of MPA impaired these events.

HRT
with estrogens or in combination with MPA may benefit function of resistance arteries

may preserve the morphological integrity of endothelial cells by

regulatory actions on the cytoskeleton

Human Reproduction Vol.22, No.6 pp. 1769–1777, 2007 doi:10.1093/humrep/dem011
Advance Access publication on March 8, 2007

Estrogen affects post-menopausal women differently than estrogen plus progestin replacement therapy

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BACKGROUND: In the Women's Health Initiative Randomized Controlled Trial (WHI RCT), estrogen-only treatment compared with combined estrogen–progestin treatment resulted in less coronary artery disease, no increase in breast cancer and no reduction in colorectal cancer. Since we previously reasonably replicated the combined estrogen–progestin WHI RCT using the UK General Practice Research Database (GPRD), estrogen-only treatment was investigated using a similar methodology. METHODS: This GPRD study simulated the estrogen-only WHI RCT of women who had undergone a hysterectomy except for randomization. The primary analysis examined 11 572 unexposed and 6890 Exposed women (aged 55–79) treated with conjugated equine estrogen and was compared with the combined estrogen–progestin GPRD study. RESULTS: At baseline, women with a hysterectomy exhibited more cardiovascular disease than those with an intact uterus. In the estrogen-only GPRD study, adjusted hazard ratios (HRs) were 0.50 (0.38–0.67) for myocardial infarction (MI), 1.13 (0.91–1.41) for breast cancer, and 1.18 (0.72–1.92) for colorectal cancer. Compared to the HRs in the estrogen–progestin GPRD study, the estrogen-only results are significantly lower for MI and breast cancer and higher for colon cancer, a pattern similar to the WHI RCT study comparisons. CONCLUSIONS: This study confirms that post-menopausal women in the overall population respond differently to estrogen-only treatment compared with estrogen–progestin treatment, due to different hormone regimens and/or increased cardiovascular disease in hysterectomized women.

Keywords: cohort studies/coronary heart disease/hormone replacement therapy/hysterectomy/menopause

Discussion

- **Differences between regimens (E v E+P)**
- **Timing**
- **Duration of use**
- **Should not be used for the first time in women over 60**
- **Premature menopause**
- **Dose: one size does not fit all**
- **Route: oral v transdermal**
- **Place and safety of alternative treatments:**

Conclusions

- **Women's heart health is not on the agenda**
  Women's health is too often focused exclusively on maternal and child care and does not include CVD prevention
- **Women are equal**
  Of 17.5 million deaths worldwide due to CVD, 8.6 million are in women*
- **Women are different**
  The presentation, progression and outcomes of CVD in women differ from those in men. Women with CVD are more likely to die or suffer disability from a re-attack or heart failure**
- **Women are under-represented**
  Women have been under-represented in CVD clinical trial design, enrolment and analysis. Much of what is known and understood about CVD is based upon research done in men. One of the biggest studies to date, the Research on Cardiovascular Disease in Women funded by the US Agency for Healthcare Research and Quality, found out that among 810 selected scientific articles on CVD, only 162 provided evidence for women***
- **Women are under-treated**
  Shortage of crucial clinical trial information on women leads to inappropriate diagnosis and treatment of women with CVD. Studies have shown that they are less likely to be prescribed aspirin in prevention of a second attack, less likely to receive sophisticated pacemaker models, less likely to be recommended for potentially life-saving cardiac surgery****
- **Hormonal status seldom taken into account in cardiology**
- **We don´t know what to do with the hormones**

Sources:
, **, *: latest WHO estimates; http://www.escardio.org/initiatives/WomenHeart/womenCVD.htm; Women and Heart Disease, AHRQ Publication No. 01-P01,US Agency for Healthcare Research and Quality, September 2001*
***** Ricciotti, H, MD. Heart Disease: Are men and women different? Beth Israel Deaconess Medical Center. Boston, March 2003*