

Questions Arising Since The HRT/WHI Newsletter (September, 2002)

How does the older age of participants in the WHI affect our interpretation of the results?

- Average age in the WHI was 63 years (healthy postmenopausal women; HRT not used for acute symptoms).
 - 5,522 subjects were in the lower, 50-59 year age subgroup.
 - The original WHI article (JAMA 2002;288: 21-333) included a preliminary sub-analysis stating:
 - ♦No noteworthy interactions with age, race/ethnicity, body mass index, prior hormone use, smoking status, blood pressure, diabetes, aspirin use, or statin use were found for the effect of estrogen plus progestin on CHD, stroke, or VTE.
 - ♦No interactions between estrogen plus progestin and age, race/ethnicity, family history, parity, age at first birth, body mass index, or Gail-model risk score were observed for invasive breast cancer.
- <http://jama.ama-assn.org/issues/v288n3/ffull/joc21036.html>

How does the 5 year WHI - Global Index (overall risk/benefit of evaluated clinical outcomes) vary with age?

Age	Estr+Prog 5 Year Global Index %	Placebo 5 Year Global Index %	NNH (Number needed to treat for one net harm)
50-59	4.78	4.16	161 (NS)
60-69	8.94	7.69	80
70-79	15.8	14.4	71 (NS)
ALL	8.82	7.69	88

NS=not statistically significant; study not powered to evaluate risks for subgroups.

Unpublished WHI Data; accessed from NIH, 15Nov02.

<http://www4.od.nih.gov/orwh/workshop2002.html>

<http://www4.od.nih.gov/orwh/htslides/stefanic2.ppt>

Clinical Outcomes (Annualized Percentage) by Randomization Assignment				
Global Index				
	Estrogen+Progestin	Placebo	Ratio	95% Nominal CI
Age				
50 - 59	142 (0.92%)	115 (0.80%)	1.16	(0.91, 1.48)
60 - 69	339 (1.72%)	271 (1.48%)	1.18	(1.00, 1.38)
70 - 79	270 (3.03%)	237 (2.76%)	1.10	(0.93, 1.32)

- For all age groups, risk (cardiovascular & breast cancer) exceeded benefit (colorectal cancer & fracture); however, since baseline risk is lower for younger women, the number needed to harm (NNH) would be correspondingly higher. This trend was seen in the WHI; confidence intervals lack statistical power for the sub-analysis. The Odds Ratio consistently suggested 5.2 year risks outweighed benefits for all age groups. (Quality of Life issues not evaluated.)

Is the risk of combination HRT small?

- It all depends! The **risk of breast cancer** expressed as **8 extra cases per 10,000 women per year** seems small to most people. However the **risk of any adverse event** (breast cancer, coronary heart disease, stroke, blood clots) **over 5.2 years** was \cong 1.5% or **one extra adverse event for every 66 women**. This number is not so small, and shows how perceived risk can vary depending on duration of therapy, and addition of multiple risks. The individual risk would vary depending on a patient's age and baseline risk factors. Individual assessment must weigh potential benefits with potential risks.

Isn't the WHI just one of many studies? Are there more studies coming?

- The WHI is a landmark study. Previous evidence that HRT had very positive effects on heart disease were based on observational trials such as the Nurses Health Study. There are few Level-1 (randomized, double blind placebo controlled) HRT outcome trials.
- The other major Level-1 trial that was in progress (**WISDOM**) has been halted due to the analysis of the WHI results. (BMJ:2002;325:987) It had hoped to evaluate combination HRT outcomes in >20,000 women over 10 years.
- The only large scale randomized controlled trials currently in progress are estrogen-only studies.
- Further sub-analysis and follow-up studies are planned for the WHI – combination HRT arm trial.
- There is a need for good outcome studies related to the many questions yet unanswered (e.g. regarding alternate hormonal regimens; HRT use in symptomatic menopausal women; early versus late initiation of HRT)
- For an interesting summary of questions remaining & **consensus versus lack of consensus**, see recent report in JAMA: <http://jama.ama-assn.org/issues/v288n19/ffull/jmn1120-2.html>

Where can I get a patient information sheet that summarizes HRT & the WHI for my patients?

- The Annals of Internal Medicine has a 1 page patient summary available at: <http://www.annals.org/issues/v137n10/fpdf/200211190-00004.pdf> (see sample – page 2)
Copies for non-profit educational use may be made as noted at bottom of page.