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HRT Cuts CVD by 50%, Latest 'Unique' Data Show

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October 12, 2012 (Hvidovre, Denmark) — Hormone-replacement therapy (HRT) in postmenopausal women with a mean age of 50 significantly reduced the risk of the combined end point of mortality, MI, or heart failure in a new randomized Danish study published online October 9, 2012 in *BMJ* [1]. The participants, who used HRT for more than 10 years, were not at significantly increased risk of breast cancer or stroke either, report **Dr Louise Schierbeck** (Hvidovre Hospital, Denmark) and colleagues.

"This is the longest randomized trial with hard end points, and we found a 50% reduction in cardiovascular end points for the women who took HRT, and there was no increased risk of cancer," Schierbeck told **heart*wire*** . The women were also followed for a further six years after discontinuation of randomized treatment, she noted.

Schierbeck says the findings, in 1000 women, confirm the "timing hypothesis." In 2002, primary results from the Women's Health Initiative (WHI) showed no cardiovascular benefit from HRT--something that had been suggested by numerous observational trials--and even an indication there may be harm; this led to the widespread abandonment of this therapy. But subsequent analyses of WHI, and data from other studies, have suggested that the time at which HRT is first prescribed is key. The women in this Danish study were 13 years younger, on average, than the women in WHI (mean age 63 years). "It doesn't make much sense to start treating women 13 years after menopause

for menopausal symptoms. It's important to initiate the treatment at menopause and not many years later," she observes.

Asked to comment on the new findings, **Dr Howard N Hodis** (UCLA) told **heart*wire*** , "Until this came out there had been no trial to directly study the estrogen cardioprotective hypothesis. This is unique, because it is the only study to have looked at women, a priori, randomized basically at the time of or just a little beyond menopause. And that's a really important point that I think some of the detractors have glossed over. The women averaged 50 years old, just like the women that we treat who come in close to the menopause and say, 'I want hormones,' because they are having symptoms. So scientifically, this is a very important trial."

Ob/gyn **Dr James Liu** (Case Western Reserve University School of Medicine, Cleveland, OH) said: "This paper adds to the evolving data on HRT for newly menopausal women in the under-age-60 category. The study conclusions are worth noting and are statistically significant and congruent with older observational studies such as the **Nurses' Health Study** and the subgroup-stratified analyses of the WHI cohort from 50 to 60. Thus, there are two randomized trials that have congruent data." Among the "surprising points," says Liu, are no increase in breast cancer risk for the 16 years of follow-up and the fact that stroke risk was not increased.

Hodis also addressed criticisms that the new Danish trial is too small to yield any meaningful results. "Although the sample size is small, there are 16 years and 20 000 women-years of follow-up." Schierbeck concurs. "We had a very long study, so there are 10 000 person-years of randomized treatment, and we do have a significant outcome in 1000 women, so it's clinically relevant."

Greater-Than-50% Reduction in CV Events Without Increasing Cancer Risk

The 1006 healthy women aged 45 to 58 who were recently postmenopausal or had perimenopausal symptoms were participants in the Danish Osteoporosis Prevention Study and were randomized to receive HRT (n=502) or no treatment (control, n=504).

The primary end point was a composite of death, hospitalization for heart failure, and MI. Secondary end points were the individual components of the primary end point and admission to the hospital for stroke. Safety end points included death or a diagnosis of breast cancer or other cancer grouped together and admission to the hospital for pulmonary embolism or deep venous thrombosis (DVT).

The women in the treated group with an intact uterus received 2-mg synthetic 17-{:beta:}-estradiol for 12 days, 2 mg 17-{:beta:}-estradiol plus 1 mg **norethindrone acetate** for 10 days, and 1 mg 17-{:beta:}-estradiol for six days (Trisekvens, Novo Nordisk, Denmark). In women who had undergone

hysterectomy, first-line treatment was 2 mg 17-{:beta:}-estradiol a day (Estrofem, Novo Nordisk, Denmark). Other treatment modalities were offered to those who experienced side effects or insufficient relief of symptoms.

The planned duration of the study was 20 years. However, as the WHI data--which came out in 2002 around the time of the 10-year visit--indicated that use of HRT might result in more harm than benefit, the participants were advised to stop treatment. But they were followed for death, cardiovascular disease, and cancer for up to 16 years.

After 10 years of intervention, there was a 52% reduction in the primary composite end point of death, MI, or heart failure, and this was not associated with an increase in any cancer. Schierbeck said numbers were too small to draw any meaningful conclusions on venous thromboembolism (VTE), although she acknowledges that HRT is known to increase the risk of VTE but pointed out, "This is a less serious event than a CV event."

After 16 years, the reduction in the primary composite outcome was still present and still not associated with an increase in any cancer, something both Schierbeck and Hodis say is "reassuring," particularly in terms of breast cancer.

Results After 10 Years of Intervention in Danish Osteoporosis Prevention Study

End point	HRT group (n=502), n	Control group (n=504), n	Hazard ratio	95% CI	p
Primary[a]	16	33	0.48	0.26–0.87	0.015
Mortality	15	26	0.57	0.30–1.08	0.084
Cancer	36	39	0.92	0.58–1.45	0.71
Breast cancer	10	17	0.58	0.27–1.27	0.17
DVT	2	1	2.01	0.18–22.16	--[b]
Stroke	11	14	0.77	0.35–1.70	0.70

a. Composite end point of death, MI, or heart failure

b. Numbers too low to calculate p

Emotion Has Overtaken the Evidence in Discussions About HRT

Hodis says emotion has long overtaken reason in the HRT debate. "We have had observational studies for the past 50 years in this field, at least 40 of them, and they are all consistent--and you just don't see that in medicine--across two very important outcomes: they reduced cardiovascular disease and they reduced mortality" in women around the time of menopause, he asserts. "But when WHI was conducted, it was done in women who were 12 years or more past menopause. These are two completely different populations of women.

"In all of the emotions after WHI, that 'hormones are killing women'--which is absolutely ridiculous--nobody sat back and said, 'Where is the evidence to support that?' The guidance that unfortunately came out of the results of WHI was 'lowest dose for shortest period of time possible.' Now what we have is a well-conducted, 10-year randomized trial that clearly shows that short-term usage of these products is not going to derive maximum benefits for women."

And other "important" data have come out recently in support of HRT, he notes, including the KEEPS study, reported just last week. "This was the largest trial ever done to assess mood, and it showed positive effects in terms of anxiety, depression, and tension, and no adverse effects."

Schierbeck says: "It is a shame that so many women are anxious about HRT, because it's so important for life quality around the time of menopause." She agrees the current mantra seems to be that if a woman wants to use HRT to "go with the lowest dose for the shortest time," but she hopes that this study will have a major impact and influence international societies working on new guidelines.

Asked what she thinks the optimal duration of HRT should be, she said: "I don't think we can set a time limit on it. At least for 10 years, we didn't find any serious side effects."

Hodis says he does not believe there will be a seismic shift in recommendations, because doctors and women have lived in fear of HRT for so long, but "people will look at this and say we can feel comfortable going longer with therapy." Personally, he says, "I'm neither a proponent nor an opponent of HRT: I use these products in women, with or without symptoms, who want to be put on them, with caveats--for example, not if they have had blood clots. They do have risks, but they are so low, and certainly no higher than many other drugs we use."

Where Next? HRT and Chronic Disease Prevention

Hodis also believes there is a role for HRT in chronic disease prevention. "The data strongly indicate that hormones are an excellent prevention for chronic diseases, including bone fractures and heart disease." And although the reduction in deaths in the Danish study was not significant, Hodis says the totality of evidence points to HRT adding "almost two years" to the life of a

woman, with the additional benefit that hormones "are cost-effective, coming in at around $2300 per quality-adjusted life-year [QALY]. There's nothing else in women that does that. Statins do not extend life and they cost $50 000 $100 000 per QALY."

But not everyone agrees. KEEPS and WHI trialist **Dr JoAnn E Manson** (Brigham and Women's Hospital, Boston, MA) maintained last week that HRT should be used only for the treatment of menopausal symptoms.

"We certainly would not say at this point in time to initiate hormone therapy for the express purpose of trying to prevent heart disease or cognitive decline; the evidence is not to that point," she said in an interview. "But for women who have menopausal symptoms and who are considering HRT to reduce their symptoms and improve their quality of life related to these symptoms, there were many favorable effects seen of taking HRT for four years."

Differences in Doses of Hormones, Medication Schedules

Liu says there are also some limitations to the Danish study that are pointed out by the authors, but others that are not. The latter include the fact that the medication used was lower dose than the 0.625-mg conjugated equine estrogen traditionally used [in the US] and in the WHI, although "there are some who may state that the 2-mg estradiol dose is similar," he observes. And the **progestin** used is different.

In addition, the type of dosing is different: "The Danish study used cycle estrogen and progestin in a 28-day dose-pack form, and the pattern of estrogen-progestin administration is somewhat unique in that the last six days used a lower estradiol dose of 1 mg. Thus, the estrogen exposure is not uniform across the 28 days. This dose is also different from women with hysterectomy who received 2-mg estradiol continuously. This contrasts with WHI, which used continuous combined estrogen/progestin daily for those women with a uterus."

And the data end points for the Danish study--due to its small size--are combined for women on estrogen alone (due to hysterectomy) and cyclic estrogen-progestin. "This analyses is different from the WHI approach, where there were two separate studies (those with a uterus were in a separate study from those with a hysterectomy) with larger cohort sizes."

But on a more positive note, he points out: "Follow-up in the Danish study is longer than the WHI on a trial and posttrial surveillance basis."

Schierbeck reports no conflicts of interest; disclosures for the coauthors are listed in the paper. Hodis and Manson report no conflicts of interest.