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In 2005, three years after the famous (and famously dubious) Women's Health Initiative study of the risks and benefits of hormone replacement therapy, clinical researchers at nine centers around the U.S. began a smaller but more focused study known as **KEEPS.** www.keepstudy.org It concentrated on a question the WHI left unanswered: Does HRT slow the progression of cardiovascular disease in post-menopausal women? The **results** were announced last week. They yielded some interesting and potentially valuable information. But what KEEPS didn't do was answer that central question. And that's a very big disappointment, given the buildup of expectations that surrounded its release at the annual meeting of the North American Menopause Society in Orlando, Florida.

UPDATE: A Danish study published by the British Medical Journal a few days after the KEEPS report found HRT cut heart disease by 50 percent without an increased cancer risk.
KEEPS stands for Kronos Early Estrogen Prevention Study. It was conducted over four years by the non-profit Kronos Longevity Research Institute. Here's how the institute's director, Dr. S. Mitchell Harman, summed up the key cardiovascular results: "[S]ome measures showed slight evidence that hormone therapy might be cardio-protective in this age group, although results were not definitive and would require additional study."
I was at the meeting, and I can't say I was especially surprised as I listened to the researchers describe their methods and results. Though I did find them somewhat ironic. The problem with the WHI study was that its 16,000 subjects were on average too old and too unhealthy to provide meaningful answers to women considering hormone replacement as they enter menopause. The problem with KEEPS was the opposite: its subjects were on the whole too young and too healthy, especially for a four-year study. The researchers should have either used a broader cross-section of subjects or made the study much longer to measure how hormone replacement affects measures of atherosclerosis.

The study's subjects were 727 women whose mean age was 52, who were within three years of the start of menopause, and who met fairly stringent standards of health. They were divided into three treatment groups. The first was given estrogen in the form of daily tablets of Premarin and Prometrium for the first 12 days of the month. The second was treated with Climara estradiol patches and cyclical Prometrium. The third group was given either a a placebo patch or pill and placebo Prometrium.

The researchers used two established methods of measuring atherosclerosis, the accumulation of plaque that thickens the walls of arteries and increases the risk of heart attack and stroke. One scans for coronary artery calcium (CAC); the other, known as CIMT, uses ultrasound to measure thickness of the inner two layers of the carotid artery wall. After four years, there was no difference between the two treatment groups and the placebo group, good or bad, on these measures of the progression of atherosclerosis.

The only finding in either direction was a "non-significant trend toward less accumulation of coronary artery calcium." One reason it was "non-significant" might have been that only a small percentage of the women admitted to the study had any coronary calcium to begin with. Some 85 percent of the participants had measurements of zero. For the 15 percent who had some degree of coronary calcium, both the estrogen and estradiol treatments showed a trend toward a reduction. It might have been a hint of something significant. To find out, the trial needed to be bigger and longer.

It's not that KEEPS was worthless. The news out of the announcement focused on the positives: That hormone replacement safely improves menopausal symptoms including hot flashes and night sweats, depression, diminished libido, and bone density. That's reassuring to women, and should help continue to reverse the decade-long misinterpretation of WHI data that led many physicians to advise against HRT. But it's hardly new information. Plenty of previous studies have established these benefits.

Yes, KEEPS adds to our base of knowledge of hormone replacement and cardiovascular disease. But it doesn't advance the science. It doesn't begin to answer the question that ultimately matters, the one it set out to resolve. That's a pretty dismal failure, given the number of research centers involved and the expectations they raised. And

my concern is that the agnostic results will discourage support for the kind of longer, bigger and better study that would prove (or disprove) the relationship between hormone replacement and cardiovascular disease. What researchers really need to do—what KEEPS should have done—is a study on the order of 5,000 subjects, with a broader range of age and baseline cardiovascular health, who are followed for 10 years. The KEEPS investigators are loudly calling for it, but given the scale and investment required, it seems unlikely. In that light, KEEPS might be more than disappointing. It might have done some real damage.

For women of menopause age, this leaves open the question of whether to take hormone replacement in the absence of symptoms. Will it protect their arteries and reduce their risk of cardiovascular disease? And for how long should they take them? As with most questions related to age management, it comes down to what I call the N of 1 concept. In clinical research lingo, N signifies the number of subjects in a study. KEEPS, for instance, had an N of 727. (It would be written as N=727 in a scientific publication). But the only evidence that really matters to any one person is the kind that actually applies to them–which may or may not be the same that applies to those 727 subjects. Even a well-done study with persuasive evidence published by a respected journal might not necessarily apply to you if you are not like the average of the people in that study. Or it might apply to you, but not precisely in the way reported. Thus the N of 1 approach: An individual, evidence-based judgment, based on one's own biomarkers.
In the case of HRT and cardiovascular and cognitive health, women should have annual CIMT and computerized cognitive testing to measure the effect of what they are doing, whether they are taking hormone replacements or a wait-and-watch approach.

All things considered, the risk-to- benefit ratio favors hormone replacement for symptoms around menopause, probably for as long as you have them. Despite its disappointing findings on cardiovascular benefit, even the KEEPS study confirmed once again that the risk of adverse events from HRT are very small, far outweighed in almost all cases by the many proven quality-of-life benefits.

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Study Finds Estrogen Therapy Improves Depression and Anxiety in Recently Menopausal Women Without Adverse Cognitive Effects

Kronos Early Estrogen Prevention Study results to help clinicians assess HT risk-benefits

(PHOENIX, Ariz. - Oct. 3, 2012) - Kronos Longevity Research Institute (KLRI) today announced that a major finding of the Kronos Early Estrogen Prevention Study (KEEPS) indicates that hormone therapy (HT) improves symptoms of depression and anxiety in recently menopausal women, without adverse effects on cognition. The findings come as a result of a four-year randomized clinical trial involving nearly 730 menopausal women.
"The KEEPS was a complex study to address issues that are important to menopausal women and their caregivers," said KLRI Director and President S. Mitchell Harman, M.D., Ph.D. "These preliminary results are of major clinical significance, as they will help clinicians assess the overall risk-benefit profile for each woman wishing to receive hormone therapy for symptoms of menopause."

KEEPS was a four-year randomized, double-blinded, placebo-controlled clinical trial of low-dose oral or transdermal (skin patch) estrogen and cyclic monthly progesterone in 727 healthy women aged 42-59 (mean age, 52.7) who were within three years after menopause at randomization. The participants were randomized into the following three arms, along with cyclical micronized progesterone (Prometrium®):

- Oral conjugated equine estrogens (o-CEE) given as Premarin®, 0.45 mg/day (a lower dose than the 0.625 mg/d used in the Women's Health Initiative [WHI].
- Transdermal Estradiol (t-E2) given by Climara® patch, 50 µg/day
- Placebo

Of the original 727 women, 662 enrolled in the Cognitive and Affective ancillary study, funded by the National Institutes of Health (NIH). Demographic and health factors relevant to cardiovascular risk in the three treatment groups were comparable at baseline and none of the women had cognitive deficits, dementia, or mood disorders at enrollment.
The results of the cognitive study showed that menopausal hormone therapy, especially o-CEE, had beneficial effects on depression and anxiety. In contrast to the Women's Health Initiative Memory Study (WHIMS), which

found deleterious effects of HT on cognition in women 65 years and older, KEEPS found no adverse effects of HT on any test of cognition, including the 3MSE memory test, a test of global cognitive abilities used in WHIMS.
HT effect on mood:

- Responses on the Profile of Mood States (POMS) questionnaire showed significant improvement in symptoms of depression (p=0.03) and anxiety (p=0.02) for women assigned to receive o-CEE. Additionally, these women, showed a trend for improvement in anger/hostility (p=0.10).
- The Brief Patient Health Questionnaire (BPHQ) showed a trend toward benefit in the symptoms of depression in women taking o-CEE (p=0.09).

HT effect on memory:

- Self-reported ability to recall printed materials, as measured by the Memory Function Question (MFQ), showed a trend of better recall in women taking o-CEE, compared to placebo (p=0.12).
- Self-reported ability to recall past events measured with the MFQ showed a slight increase in memory complaints among women using transdermal estradiol (p=0.05). Similarly, on the same test, these women rated their memory changes as more serious compared to those on placebo (p=0.09).

For more information about the KEEPS study results, visit http://www.keepstudy.org

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Rationale for KEEPS The results of the WHI estrogen plus progestin trial, which was halted by the National Institutes of Health in July 2002, prompted a consortium of health researchers to study the risks and benefits of hormone therapy (HT) in a younger subset of women who recently entered menopause. Prior to the WHI, most data suggested HT was associated with a high degree of protection against coronary heart disease and a favorable benefit-risk ratio.

Rationale for the KEEPS Cognitive and Affective Study
The Women's Health Initiative Memory Study had found adverse effects of HT on the risk of cognitive decline and dementia in women 65 years and older, but had not assessed cognitive outcomes in women younger than 65. Observational studies in newly menopausal women had suggested the possibility of benefits of HT for memory and cognition. The Cognitive and Affective Study is an NIH-funded ancillary study of KEEPS that was coordinated by investigators based at the University of Wisconsin in Madison. It evaluated the potential effects of HT on cognition and mood by administering a comprehensive battery of cognitive tests at four time points: baseline, 18, 36 and 48 months. The data collection procedures were standardized and monitored regularly throughout the study. The cognitive battery included tests shown to be affected by HT and targeted the following domains: global cognition, memory (both verbal and visual), executive function, mood, quality of life, and memory complaints.

About the University of Wisconsin-Madison (UW-Madison)
The UW-Madison is a public, land-grant institution with world-class recognition in biomedical research, discoveries, education and outreach programs. It has a rich history of excellence in academics, including 17 Nobel Laureates and 33 Pulitzer Prize winners. The UW School of Medicine and Public Health sponsored the cognitive study and supports an extensive program in cognitive neuroscience research, including the NIA-funded Wisconsin Alzheimer's Disease Research Center (ADRC). The Wisconsin ADRC has acknowledged expertise in hormone therapy research and made significant contributions toward successful completion of the KEEPS Cognitive Study.

About Kronos Longevity Research Institute (KLRI)

KLRI is a not-for-profit 501(c)(3) organization that conducts state-of-the-art clinical translational research on the prevention of age-related diseases and ways to increase longevity. Translational research is the critical link between findings from the basic research laboratory and corresponding improvements in clinical care.

The core KEEPS was funded by the Phoenix-based KLRI which is supported by the not-for-profit Aurora Foundation and carried out at nine U.S. academic medical centers (see appendix). The Cognitive and Affective Study is National Institutes of Health funded ancillary study of KEEPS that was coordinated by investigators based at the University of Wisconsin in Madison, Wisc.

The nine KEEPS study centers

- Kronos Longevity Research Institute (the Sponsor) (Dr. Mitch Harman, PI)
- Albert Einstein College of Medicine/Montefiore Medical Center (New York City; Drs. Nanette Santoro and Genevieve Neal-Perry, PIs)
- Columbia University College of Physicians and Surgeons (New York City, Dr. Rogerio Lobo, PI)
- Harvard Medical School/Brigham and Women's Hospital (Boston, Dr. JoAnn Manson, PI)
- Mayo Clinic College of Medicine (Rochester, MN, Dr. Virginia, Miller, PI)
- University of California, San Francisco/Center for Reproductive Health (Dr. Marcelle Cedars, PI)
- University of Utah School of Medicine (Salt Lake City, Drs. Eliot Brinton and Paul Hopkins, PIs)
- University of Washington School of Medicine (Seattle, Dr. George Merriam, PI)
- Yale University School of Medicine (New Haven, CT, Dr. Hugh Taylor, PI)