Study shows increased risk of cardiac, stroke death in first year after stopping hormone therapy

Risk elevation markedly higher in women aged younger than 60 years when discontinuing HT


Summary. Current guidelines recommend that hormone therapy (HT) should be used only in recently menopausal women for moderate to severe vasomotor symptoms (VMS) for the shortest possible time. Based on the findings from recent clinical trials and on the guidelines, an increasing number of women choose or are recommended to discontinue HT. It is not clear how the acute withdrawal of HT affects cardiovascular risk.

Estrogen has direct cardiovascular effects, including rapid effects on vasodilation and blood pressure, not only through fluctuations in circulating estrogen levels during the menstrual cycle but also during estrogen supplementation. An increased risk of cardiovascular events has been shown in secondary prevention trials with HT initiation.

To find whether there is risk of cardiac or stroke death after the discontinuation of HT, a group of Finnish researchers followed 332,202 women who discontinued postmenopausal HT between 1994 and 2009, with almost 2 million years of follow-up, from the discontinuation date to death from a cardiac cause (n=3,177) or stroke (n=1,952) or until the end of 2009. The number of deaths, gathered from the National Cause of Death Register, were compared with the expected number of deaths in the age-standardized background population. Mean HT exposure was 6.2±6.0 (SD) years; mean follow-up after discontinuation was 5.5±3.8 (SD) years. Subanalysis compared HT stoppers with HT users.

Within the first posttreatment year, the risk of cardiac death was significantly elevated (standardized mortality ratio [SMR], 1.26; 95% confidence interval [CI], 1.16-1.37; P<.05), whereas follow-up after 1 year showed risk reduction (SMR, 0.75; 95% CI, 0.72-0.78). The risk of stroke death in the first posttreatment year was increased (SMR, 1.63; 95% CI, 1.47-1.79; P<.05), but follow-up after 1 year showed reduced risk (SMR, 0.89; 95% CI, 0.85-0.94). The cardiac (SMR, 2.30; 95% CI, 2.12-2.50) and stroke (SMR, 2.52; 95% CI, 2.28-2.77) death risk elevations were even higher when compared with HT users.
Similar risk pattern was detected when the women were stratified by age at HT initiation or discontinuation. Cardiac mortality risk was elevated in women who discontinued HT when aged younger than 60 years, but not in women aged 60 years and older (SMR, 1.94; 95% CI, 1.51-2.48).

Researchers say that the findings question the safety of annual discontinuation to evaluate whether a woman could manage without HT and that studies comparing the cardiovascular safety of immediate versus tapered HT discontinuation are needed.

**Comment.** The newest findings by Mikkola and colleagues are the largest (a nationwide study conducted over 15 years with 2 million follow-up years) and most solid data to date confirming that cardiovascular mortality, both coronary heart disease and stroke mortality, significantly increase after stopping hormone therapy (HT). These data are derived from a National Death Registry mandated for all deaths in Finland and in which 30% of causes of death are confirmed by autopsy. As a consequence of stopping HT, several studies showing increases in health hazards that have substantial mortality outcomes such as hip fractures are confirmed by these newest findings.  

Importantly, these newest findings add the final dimension to understanding the beneficial effect of HT on mortality in postmenopausal women who initiate HT in early postmenopause and/or when aged younger than 60 years. In fact, these newest findings show that the greatest harm to women who stop HT is to those women who initiated or stopped HT when aged younger than 60 years whether they used HT short term (<5 years) or long term (≥5 years). Even more revealing is the finding that compared with those who continued to use HT, women who stopped HT had increased cardiovascular mortality in the first year of stopping and continued beyond the first year of stopping, indicating both a short-term and long-term adverse effect of stopping HT on mortality.

The lines of published evidence confirms that HT reduces cardiovascular mortality more than any other primary prevention therapy in use today: 1) Starting HT within 10 years of menopause and/or when aged younger than 60 years reduces mortality; 2) Avoiding HT results in excess mortality; and, 3) Stopping HT is associated with cardiac and stroke mortality.

In the first line of evidence, observational studies consistently show that women who select HT have reduced mortality relative to women who do not use HT. Consistent with these long-term observational studies have been randomized trials in which women who are aged younger than 60 years and/or less than 10 years since menopause (similar to the observational populations) when randomized to HT versus placebo showed a reduction in total mortality. In a meta-analysis of 30 randomized controlled trials with 119,118 women-years of follow-up, a significant 39% reduction in total mortality (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.30-0.95) was shown in women who were on average aged 54 years when randomized to HT relative to placebo.

Mortality outcome data from three large trials, the Women’s Health Initiative (WHI) trials of HT and the Danish Osteoporosis Prevention Study (DOPS), are consistent with meta-analyses examining the effects of postmenopausal HT on mortality. Both the WHI-conjugated estrogens (CE) plus medroxyprogesterone acetate (MPA) trial (HR, 0.69; 95% CI, 0.44-1.07) and the WHI-CE alone trial (HR, 0.71; 95% CI, 0.46-1.11) showed a 30% reduction in total mortality in women aged younger than 60 years and/or less than 10 years since menopause when randomized to HT relative to placebo. When the data from both WHI trials were combined, the reduction in mortality was significantly reduced 30% (HR, 0.70; 95% CI, 0.51-0.96) in those women randomized to HT relative to placebo. In DOPS, women were on average aged 50 years and were 7 months postmenopausal when randomized. After 10 years of randomized HT, women had a
43% (HR, 0.57; 95% CI, 0.30-1.08) reduction in mortality relative to a control group, with a persistent reduction in mortality of 34% (HR, 0.66; 95% CI, 0.41-1.08) after 16 years of total follow-up. Similarly, after 13 years of cumulative follow-up in the WHI trials, reduction in total mortality was 12% (HR, 0.88; 95% CI, 0.70-1.11) and 22% (HR, 0.78; 95% CI, 0.59-1.03) in the women aged younger than 60 years who were originally randomized to CE plus MPA (median intervention of 5.6 years and 7.4 years of post-trial follow-up) and CE alone (median intervention of 7.2 years and 5.8 years of post-trial follow-up), respectively relative to placebo.5

Convergence of evidence that HT reduces total mortality derives from a Bayesian analysis of eight prospective observational studies (212,717 women followed for 2,935,495 woman-years over a range of 6-22 years) and 19 randomized, controlled trials (mean age of women, 54.5 years randomized for 1-6.8 years and followed for 83,043 woman-years).6 Total mortality was 22% (HR, 0.78; 95% CI, 0.69-0.90), significantly lower in HT users than nonusers in the observational studies and significantly reduced 27% (HR, 0.73; 95% CI, 0.52-0.96) in the randomized, controlled trials; with observational studies and randomized, controlled trials combined, total mortality was significantly reduced 28% (HR, 0.72; 95% CI, 0.62-0.82).

In the second line of evidence, it has been shown that avoiding estrogen therapy adversely affected mortality rates among hysterectomized women aged younger than 60 years. Applying a formula relating mortality in hysterectomized women assigned to placebo in the WHI and the entire population of comparable US women, it has been estimated that over a 10-year period since 2002, a minimum of 18,601 and a maximum of 91,610 postmenopausal women died prematurely because of ET avoidance.7 These analyses were based on the largest randomized, controlled trial data from WHI and are now confirmed by the largest and most complete population mortality data from Mikkola and associates.

In the third line of evidence from Mikkola and colleagues, the demonstration of stopping a therapy (namely HT) with resultant death is unheard of in the primary prevention of cardiovascular disease. The mechanism of such a link is unclear, but the rapidity of death after stopping HT suggests at least two well-understood nongenomic mechanisms. The first is immediate withdrawal of HT leading to decreased NO production, resulting in vasoconstrictive reactive arteries leading to cardiac and stroke death. The second is the rapid rise and continued exposure of the vascular system to activated inflammatory processes seen with menopause and normalized with HT. This inflammatory process has implications for acute events resulting from plaque rupture of underlying susceptible plaques and long-term induction of atherosclerosis through the activation of atherogenic inflammatory processes.

Avoiding or stopping HT with a resultant increase in mortality axiomatically stems from the long-standing and consistent findings that HT reduces mortality when initiated in women aged younger than 60 years and/or in close proximity to menopause. The inexplicable sex-specific rise in female mortality rates in 42.8% of US counties (vs male mortality that rose in only 3% of US counties over the same period of time), despite increasing healthcare expenditures, likely resulted from the precipitous drop in HT use in the United States after the first WHI report of 2002, as the three lines of evidence supporting mortality reduction with HT indicate.8

The evidence for a cardiovascular disease beneficial effect of HT initiated early after menopause is supported by the cumulated data.

Howard N. Hodis, MD
Harry J. Bauer and Dorothy Bauer Rawlins Professor of Cardiology
Professor of Medicine and Preventive Medicine
Professor of Molecular Pharmacology and Toxicology
Director, Atherosclerosis Research Unit
Division of Cardiovascular Medicine
Keck School of Medicine
University of Southern California, Los Angeles

Disclosure: Dr. Hodis reports no relevant conflicts of interest.

References


