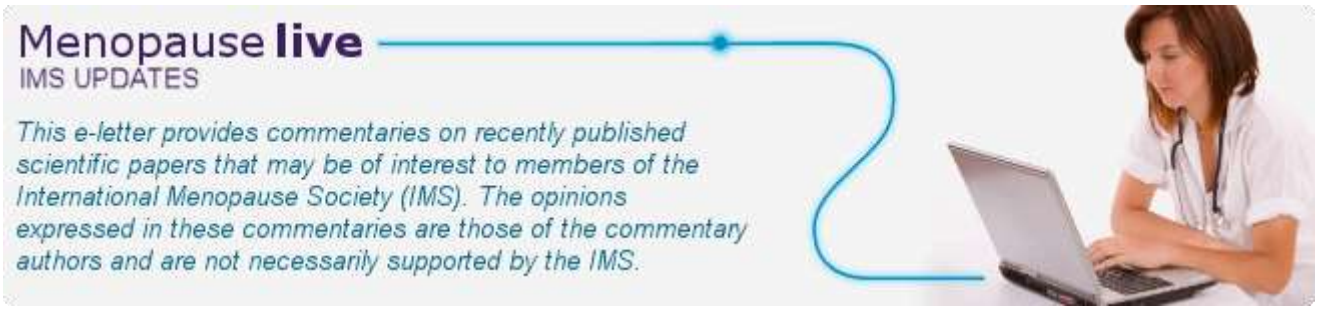


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## Cardiac and stroke death after withdrawal of hormone therapy

To determine whether there is a risk of cardiovascular death upon withdrawal of hormone therapy (HT), Mikkola and colleagues used the Finnish National Death Registry (including 30% autopsy data) to conduct a nation-wide population study of 332,202 women who discontinued menopausal HT analyzed over 15 years with 2 million years of follow-up [1]. From 1994 to 2009, there were 3177 cardiac deaths and 1952 stroke deaths; mean HT exposure was 6.2 ± 6.0 years and mean follow-up after HT withdrawal was 5.5 ± 3.8 years. Comparing the actual death rates in the background population, the standardized mortality ratio (SMR) within the first year of HT withdrawal was elevated for cardiac and stroke death; SMR = 1.27 (95% CI 1.17–1.37) and SMR = 1.63 (95% CI 1.47–1.79), respectively. When compared to women who continued to use HT, the risk of discontinuing HT was even greater and elevated in women within as well as beyond the first year of withdrawal for both cardiac and stroke death; SMR = 2.30 (95% CI 2.12–2.50) and SMR = 2.52 (95% CI 2.28–2.77), respectively within the first year of HT withdrawal, and SMR = 1.26 (95% CI 1.21–.31) and SMR = 1.25 (95% CI 1.19–1.31), respectively beyond the first year of HT withdrawal. A similar risk pattern was shown when women were stratified by age at HT initiation or discontinuation. In women who discontinued HT at < 60 years, but not in women aged ≥ 60 years, cardiac mortality risk was elevated, SMR = 1.94 (95% CI 1.51–2.48) as was risk of stroke death, SMR = 2.87 (95% CI 2.29–3.55).

**Comment**

These newest findings by Mikkola and colleragues are the largest and most robust data to date confirming that both cardiac and stroke mortality are potentially increased after discontinuing HT [1]. Although these data were derived from an observational study, rates of fatal cardiac and stroke events were unlikely influenced by biases. The data from Mikkola and colleagues are consistent with studies showing increased health hazards after stopping HT that have substantial mortality such as hip fractures [2].

In addition to the recent Mikkola study, data from at least three randomized, controlled trials addressing the issue of HT withdrawal and post-trial follow-up are available [3-5]. In the Women's Health Initiative estrogen + progestin (WHI E+P) post-trial follow-up, mortality was increased within 3 years of cessation of the trial in women assigned to E+P relative to those assigned to placebo (HR = 1.15; 95% CI 0.95–1.39) [3]. Importantly, women originally assigned to E+P and at least 80% compliant had significantly increased mortality in post-trial follow-up (HR = 1.53; 95% CI 1.04–2.24)

relative to those women assigned to placebo. After cessation of the WHI-E+P trial, 95% of the women who were actively taking E+P at trial termination stopped HT.

In the unblinded, post-trial, 2.7-year follow-up Heart and Estrogen/progestin Replacement Study (HERS) II, women originally assigned to E+P relative to placebo had a 3.3-fold higher rate of ventricular arrhythmia requiring resuscitation (HR = 3.30; 95% CI 1.08–10.1) [4]. During the first 6 months of post-trial follow-up of the Women's Estrogen for Stroke Trial (WEST), there were three fatal strokes and 18 non-fatal strokes among women originally randomized to estradiol therapy and one fatal stroke and eight non-fatal strokes among women assigned to placebo (HR = 2.3; 95% CI 1.1–5.0; $p = 0.03$) [5]. During the intervention phase of WEST, eight of the nine ischemic stroke deaths that occurred in the estradiol group occurred among the women who stopped estradiol therapy (personal communication, Philip M. Sarrel). These data are reflected within the compliance analysis of the trial that showed no significant difference between estradiol therapy and placebo on the outcomes of ischemic stroke or stroke death.

These newest findings by Mikkola and colleagues that discontinuing HT is associated with increased cardiac and stroke mortality are consistent with the large body of data showing that HT reduces mortality in postmenopausal women. In fact, the cumulative evidence that HT reduces mortality is the strongest and most robust of any primary prevention therapy currently in use and is supported by observational studies, randomized trial data in women initiating HT within 10 years of menopause and/or < 60 years of age and by data showing that avoidance of HT results in excess mortality.

Observational studies consistently show that, relative to women who do not use HT, those who use HT have reduced mortality [6]. Consistent with these long-term observational studies, randomized trials in which women < 60 years and/or < 10 years since menopause (similar to the observational populations) when randomized to HT versus placebo show 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 (HR 0.61; 95% CI 0.30–0.95) was shown in women who were on average aged 54 years when randomized to HT relative to placebo [7].

Mortality outcome data from the WHI and the Danish Osteoporosis Prevention Study (DOPS) are consistent with meta-analyses examining the effects of postmenopausal HT on mortality. Women < 60 years old and/or < 10 years since menopause when randomized to HT relative to placebo showed a 30% reduction in total mortality in both the WHI-E+P 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) [8]. The reduction in mortality was significantly reduced by 30% (HR 0.70; 95% CI 0.51–0.96) in those women randomized to HT relative to placebo when the data from both WHI trials were combined. Women were on average 50 years old and 7 months postmenopausal when randomized in DOPS [9]. After 10 years of randomized HT, women had a 43% (HR 0.57; 95% CI 0.30–1.08) reduction in mortality with a persistent reduction in mortality of 34% (HR 0.66; 95% CI 0.41–1.08) after 16 years of total follow-up [5]. Similarly, after 13 years of WHI cumulative trial follow-up, 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 < 60 years old 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 [10].

Convergence of evidence that HT reduces mortality derives from a Bayesian analysis of eight prospective observational studies (212,717 women followed for 2,935,495 women-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 women-years) [11]. Total mortality was 22% (HR 0.78; 95% CI

0.69–0.90), significantly lower in HT users than non-users in the observational studies and significantly reduced by 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 by 28% (HR 0.72; 95% CI 0.62–0.82).

In addition, it has been shown that avoiding estrogen therapy adversely affected mortality rates among hysterectomized women aged < 60 years. Applying a formula relating mortality in hysterectomized women assigned to placebo in the WHI and the entire population of comparable United States women, it has been estimated that, over a 10-year period since 2002, 18,601–91,610 postmenopausal women died prematurely because of estrogen therapy avoidance [12]. These analyses were based on the largest randomized controlled trial data from the WHI and confirmed by the largest and most complete population mortality data from Mikkola and colleagues.

The demonstration of stopping a therapy (namely HT) with resultant death is unique 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 non-genomic mechanisms. The first is immediate withdrawal of HT leading to decreased NO production, resulting in vasoconstrictive reactive arteries and cardiac arrhythmias, 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 < 60 years of age and/or in close proximity to menopause. The inexplicable sex-specific rise in female mortality rates in 42.8% of US counties after 2002 (vs. male mortality that rose in only 3% of US counties over the same period of time) despite increasing health-care expenditures may reflect the large numbers of women who discontinued or avoided initiation of HT following the first WHI report of 2002 as the robust evidence supports mortality reduction with HT [13].

In conclusion, these newest findings from Mikkola and colleagues add the final dimension to understanding the beneficial effect of HT on mortality in postmenopausal women who initiate HT in early postmenopause and/or < 60 years of age. In fact, these newest findings show that the greatest harm to women who stop HT are those women who initiated or stopped HT when < 60 years of age whether they used HT short-term (< 5 years) or long-term (≥ 5 years). Even more revealing is the finding that, compared to those who continued to use HT, women who discontinued HT had increased cardiovascular mortality in the first year of stopping and beyond, indicating both a short-term and long-term adverse effect of stopping HT on mortality [1].

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