Coronary Heart Disease Mortality and Hormone Therapy Before and After the Women’s Health Initiative

Pauliina Tuomikoski, MD, PhD, Heli Lyytinen, MD, PhD, Pasi Korhonen, PhD, Fabian Hoti, PhD, Pia Vattulainen, MSc, Mika Gissler, Olavi Ylikorkala, MD, PhD, and Tomi S. Mikkola, MD, PhD

OBJECTIVE: To assess whether coronary heart disease mortality in Finnish hormone therapy (HT) users differed before and after 2002 when the Women’s Health Initiative study was published.

METHODS: The risks of coronary heart disease death in HT users in relation to the age-matched background population were compared between the pre–(1995–2001) and post–(2002–2009) Women’s Health Initiative eras. We used a nationwide register on HT (ie, estradiol with or without progestin) reimbursement and linked them to causes of death in 290,272 women aged 40 years or older.

RESULTS: Exposure to HT for 1 year or less was accompanied by a 29% reduction (0.71; 0.63–0.80; three per 10,000 fewer deaths) and an exposure of 1–8 years with a 43% reduction (0.57; 0.48–0.66; three per 10,000 fewer deaths) in the risk of coronary heart disease death in the pre–Women’s Health Initiative era. In the post–Women’s Health Initiative era, HT use of 1 year or less was associated with an 18% reduction (0.82; 0.76–1.00; one per 10,000 fewer deaths) and an exposure of 1–8 years with a 54% reduction (0.46; 0.32–0.64; two per 10,000 fewer deaths) in coronary heart disease mortality. Discontinuation of HT was associated with an increased risk of cardiac death of 42% (1.42; 1.17–1.71; seven per 10,000 extra deaths) in the pre–Women’s Health Initiative era and 31% (1.31; 0.92–1.82; two per 10,000 extra deaths) in the post–Women’s Health Initiative era during the first posttreatment year. This risk increase vanished in further follow-up during both eras.

CONCLUSION: Changes in HT use after the Women’s Health Initiative failed to affect coronary heart disease mortality of HT users in this nationwide study.

From the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, the National Institute for Health and Welfare, and the Folkhälsan Research Center, Helsinki, and the EPID Research Oy, Espoo, Finland; and the Nordic School of Public Health, Gothenburg, Sweden.

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Corresponding author: Tomi S. Mikkola, MD, PhD, Associate Professor, Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, PO Box 140, 00029 HUS, Helsinki, Finland; e-mail: tomi.mikkola@hus.fi.

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Dr. Korhonen, Dr. Hoti, and Ms. Vattulainen work for EPID Research. EPID Research is a company that performs financially supported studies for several pharmaceutical companies. The other authors did not report any potential conflicts of interest.

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The identification and classification of HT used were based on the trade names of the commercial products, which either contained estradiol alone or in combination with sequential or continuous progestin (estradiol–progestin therapy). Some women formed individual regimens by combining estradiol with individual progestin courses at 1- to 3-month intervals; they were considered as users of estradiol–progestin therapy. Exposure days to a given type of HT (estradiol-only, sequential or continuous estradiol–progestin therapy, oral or transdermal) were counted up for each woman regardless of the order these exposures accumulated. Separate subgroup analyses were carried out for each subtype of HT regimen, but the final study groups were divided into estradiol-only or estradiol–progestin therapy users, both including oral and transdermal regimens. Women with conjugated equine estrogen use (n=1,305) were included into estradiol-only use and women with tibolone (available from 2,000 onward) (n=30,255) were included into the estradiol–progestin therapy group. Because a systemic estradiol always results in higher elevations in the circulating levels of estrogens than a vaginal regimen may, the possible use of vaginal estrogens in addition to systemic HT was not considered as a confounding factor.

In Finland, all deaths are recorded in the Causes of Death Register. Reporting to this register is mandatory, and diagnoses are imported from death certificates signed by physicians. Entering of the data were double-checked by medical experts at the regional level and at Statistics Finland. It is noteworthy that if the cause of coronary heart disease death is not fully verified by clinical history or premortem findings from specific examinations (eg, electrocardiograms, laboratory), an autopsy is advocated; this occurs in approximately 31% of all deaths.17 Thus, the register is accurate concerning coronary heart disease death.18 From this nationwide register, we identified all deaths resulting from coronary heart disease (International Classification of Diseases, 9th Revision: 410–414 in 1995 and International Classification of Diseases, 10th Revision: I20–I25 since 1996) in women aged 40 years or older during 1995–2009.

The follow-up started from the first purchase of HT (at its earliest on January 1, 1995) and ended on December 31, 2009, or at death resulting from coronary heart disease, and the woman-years followed up were calculated for various types of HT

MATERIALS AND METHODS

In Finland, postmenopausal HT is available only by a doctor’s prescription, and part of the price of the HT (42–50% during the study period, currently 35%) is reimbursed by national health insurance. All Finnish HT users have been entered into the national reimbursement register since 1994. In Finland, systemic oral or transdermal estrogen regimens contain almost exclusively (99.6%) estradiol in contrast to conjugated equine estrogen regimens, which are dominant in the United States. According to the uniform national guidelines for optimal use of HT, hysterectomized women are allowed to use estradiol-only regimens, whereas nonhysterectomized women also use, in addition to estradiol, a progestin either for 10–14 days with 1- to 3-month intervals (sequential estradiol–progestin regimen) or everyday (continuous estradiol–progestin regimen) for endometrial protection.

For this study, we included all women who had started systemic HT use at 40 years of age or older. Women who were younger than 40 years (n=63,189) or had used only progestin regimens (n=47,492) or solely vaginal estrogens (n=195,756) were excluded. Because we could not know exactly whether the first HT purchase in the opening year, 1994, was really the first one for a given woman, we included only those who bought the first systemic HT in 1995 or later up to 2009 (new HT starters).

Hormone therapy regimens can be bought only for 3 months use at a time. Thus, women continuing HT use went to the pharmacy repeatedly, and respective HT purchases were entered into the register. The cumulative days of estradiol exposures were calculated based on the type of HT regimen (a single oral or gel dose=1-day exposure; a patch=3–4 days or 1-week exposure, based on the regimen type). The identification and classification of HT used were based on the trade names of the commercial products, which either contained estradiol alone or in combination with sequential or continuous progestin (estradiol–progestin therapy). Some women formed individual regimens by combining estradiol with individual progestin courses at 1- to 3-month intervals; they were considered as users of estradiol–progestin therapy. Exposure days to a given type of HT (estradiol-only, sequential or continuous estradiol–progestin therapy, oral or transdermal) were counted up for each woman regardless of the order these exposures accumulated. Separate subgroup analyses were carried out for each subtype of HT regimen, but the final study groups were divided into estradiol-only or estradiol–progestin therapy users, both including oral and transdermal regimens. Women with conjugated equine estrogen use (n=1,305) were included into estradiol-only use and women with tibolone (available from 2,000 onward) (n=30,255) were included into the estradiol–progestin therapy group. Because a systemic estradiol always results in higher elevations in the circulating levels of estrogens than a vaginal regimen may, the possible use of vaginal estrogens in addition to systemic HT was not considered as a confounding factor.

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The follow-up started from the first purchase of HT (at its earliest on January 1, 1995) and ended on December 31, 2009, or at death resulting from coronary heart disease, and the woman-years followed up were calculated for various types of HT

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use. The number of coronary heart disease deaths in HT users was compared with the expected number of deaths resulting from coronary heart disease in the age- and year-matched background population (also including HT users) by a standardized mortality ratio with 95% confidence intervals following the Poisson model. The statistical significance of the trend of the standardized mortality ratios difference between the pre- and post-Women’s Health Initiative eras was evaluated based on Poisson probability distribution.

The Women’s Health Initiative study published in 2002 brought along drastic changes in Finnish prescription practice (see “Results”), and therefore we delineated the pre-Women’s Health Initiative era as 1995–2001 and the post-Women’s Health Initiative era as 2002–2009. We chose a follow-up time of 1 year or less to identify the possible immediate procoagulatory effect of HT, which could lead to an increased risk of cardiac death. Moreover, the follow-up time could maximally be 8 years in the post-Women’s Health Initiative series, and thus, we classified the exposure times to HT as 1 year or less and greater than 1–8 years. The same follow-up periods were also used for the follow-up times since the discontinuation of HT. A summary of the study populations divided into the pre- and post-Women’s Health Initiative periods is presented in Figure 1.

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RESULTS

There were a total of 290,272 HT users with an average exposure time of 4.0±3.4 (mean±standard deviation) years during the entire study period of 1995–2009. Among women with exposure to HT greater than 1 year, the mean (±standard deviation) exposure time to HT was 5.2±3.1 years. The number of annual new HT starters decreased and those who discontinued HT use increased consistently during the entire study period of 15 years (Fig. 2). These lines crossed at 2002, which was selected as a cutoff year between the pre- and post-Women’s Health Initiative years. The prevalence of HT use was 21% in 2001 and fell down to 13% in 2009.

In the pre-Women’s Health Initiative era, a significantly higher (P<.005) proportion of the new starters (11.6%) were older than 60 years old as compared with 5.4% in the post-Women’s Health Initiative era. The types of HT preparations in the pre- and post-Women’s Health Initiative eras were comparable, although the transdermal estradiol regimen had become slightly more popular during the post-Women’s Health Initiative era (27.0% compared with 22.9%). Furthermore, the proportion of regimens containing medroxyprogesterone acetate also decreased.

Fig. 1. Summary of the study populations. Exposure years addresses the duration of hormone therapy (HT) use. Follow-up years comprise all years since the first purchase of HT (at its earliest on January 1, 1995) and ends on December 31, 2009, or at death.

from 19.9% in the pre–Women’s Health Initiative era to 9.9% in the post–Women’s Health Initiative era. The use of HT was accompanied by significant reductions in coronary heart disease mortality compared with the background population during both study eras (Table 1). Exposure to HT 1 year or less was accompanied by a 29% reduction and an exposure of 1–8 years with a 43% reduction in the risk of coronary heart disease death in the pre–Women’s Health Initiative era. In the post–Women’s Health Initiative era, HT use of was associated with a 54% (0.46; 0.32–0.64) reduction in coronary heart disease mortality (Table 1). The reduction of the coronary heart disease death risk was not related to the type of HT (estradiol-only, sequential or continuous estradiol–progestin therapy) or on the age when she had used HT (Table 2). No difference was seen between the study eras.

Because there appeared a larger benefit with HT use during the post–Women’s Health Initiative era (Tables 1 and 2), we carried out trend tests. We did not detect significant differences between the pre– and post–Women’s Health Initiative coronary heart disease death risks. We also analyzed the data stratified by age younger than 60 years and 60 years or older at the initiation of HT (Table 3). There were no significant differences in the risk of death resulting from coronary heart disease between the pre– and post–Women’s Health Initiative eras. However, in HT exposure greater than 1–8 years during the post–Women’s Health Initiative era, a significant protective effect against cardiac death.

Table 1. Effects of Various Types of Hormone Therapy on Coronary Heart Disease Mortality if Initiated in the Pre– and Post–Women’s Health Initiative Eras

<table>
<thead>
<tr>
<th>Type of Hormone Therapy</th>
<th>Exposure</th>
<th>Pre–Women’s Health Initiative Era</th>
<th>Post–Women’s Health Initiative Era</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed Deaths</td>
<td>Expected Deaths</td>
<td>Standardized Mortality Ratio (95% CI)</td>
</tr>
<tr>
<td>Any HT</td>
<td>1 y or less</td>
<td>251</td>
<td>354</td>
</tr>
<tr>
<td></td>
<td>Longer than</td>
<td>139</td>
<td>246</td>
</tr>
<tr>
<td></td>
<td>1–8 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol-only</td>
<td>1 y or less</td>
<td>163</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>Greater than</td>
<td>59</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>1–8 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol–progestin</td>
<td>1 y or less</td>
<td>128</td>
<td>184</td>
</tr>
<tr>
<td>therapy</td>
<td>Greater than</td>
<td>76</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>1–8 y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HT, hormone therapy.
was detected only in women younger than 60 years of age (Table 3).

The discontinuation of HT with any duration was accompanied by a 42% increase in coronary heart disease death risk in the pre–Women’s Health Initiative and 31% increase in the post–Women’s Health Initiative era within the first posttreatment year; the risk elevation vanished with more prolonged follow-up (Table 4) nor was this elevation in any relation to the type of HT discontinued.

No difference was seen between the study eras.

DISCUSSION

Our study shows how the Women’s Health Initiative study modified the Finnish HT-prescribing policy. The decline in the use of HT and particularly medroxyprogesterone acetate reflects the effects of the WHI study, because the failure of a combination of conjugated equine estrogens and medroxyprogesterone acetate in primary11 or secondary prevention10 of coronary heart disease has often been attributed to the possible adverse vascular effects of medroxyprogesterone acetate.19 We expected to find a higher coronary heart disease death risk in HT users during the pre–Women’s Health Initiative era. Instead, the use of HT was accompanied by significant reductions in the risk of death resulting from coronary heart disease. Indeed, the healthy woman bias is probably the primary reason for the significant HT use-associated falls in the coronary heart disease risks in

Table 2. Risk of Death Resulting From Coronary Heart Disease in Women With 1 Year or Less or More Than 1–8 Years of Exposure to Hormone Therapy in Different Age Groups Classified Into the Pre– and Post–Women’s Health Initiative Eras

<table>
<thead>
<tr>
<th>Age Group (y)</th>
<th>Pre–Women’s Health Initiative Era</th>
<th>Post–Women’s Health Initiative Era</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed Deaths</td>
<td>Expected Deaths</td>
</tr>
<tr>
<td>Exposure to HT 1 y or less</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>50–59</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>60–69</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>70–79</td>
<td>104</td>
<td>128</td>
</tr>
<tr>
<td>80 or older</td>
<td>80</td>
<td>115</td>
</tr>
</tbody>
</table>

CI, confidence interval; HT, hormone therapy.

Table 3. Risk of Death Resulting From Coronary Heart Disease in Women Younger Than 60 Years or 60 Years or Older at Hormone Therapy Initiation and With 1 Year or Less or More Than 1–8 Years of Exposure to Hormone Therapy

<table>
<thead>
<tr>
<th>Age Group (y)</th>
<th>Pre–Women’s Health Initiative Era</th>
<th>Post–Women’s Health Initiative Era</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed Deaths</td>
<td>Expected Deaths</td>
</tr>
<tr>
<td>HT exposure 1 y or less</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 60</td>
<td>33</td>
<td>58</td>
</tr>
<tr>
<td>60 or older</td>
<td>218</td>
<td>296</td>
</tr>
<tr>
<td>HT exposure longer than 1–8 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 60</td>
<td>46</td>
<td>85</td>
</tr>
<tr>
<td>60 or older</td>
<td>93</td>
<td>161</td>
</tr>
</tbody>
</table>

CI, confidence interval; HT, hormone therapy.
Coronary Mortality and Hormone Therapy of Any Duration

<table>
<thead>
<tr>
<th>Time Since Last HT (y)</th>
<th>Pre–Women’s Health Initiative Era</th>
<th>Post–Women’s Health Initiative Era</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed Deaths</td>
<td>Expected Deaths</td>
</tr>
<tr>
<td>1 or less</td>
<td>104</td>
<td>73</td>
</tr>
<tr>
<td>Greater than 1–8</td>
<td>175</td>
<td>186</td>
</tr>
</tbody>
</table>

HT, hormone therapy; CI, confidence interval.

Table 4. The Risk of Death Resulting From Coronary Heart Disease in Women Discontinuing Hormone Therapy of Any Duration

our study, like in many other open studies. However, estradiol-based HT regimens may have a better risk profile than conjugated equine estrogens, which were used in the Women’s Health Initiative, and therefore, the Women’s Health Initiative results may not be fully comparable to our Finnish population. Surprisingly, we did not detect any differences between the estradiol-only compared with estradiol–progestin therapy users, a finding that is in contrast with the Women’s Health Initiative data.

A subgroup analysis of the Women’s Health Initiative produced the timing or window hypothesis, which suggests that conjugated equine estrogens could reduce the risk of coronary heart disease in women younger than but not older than 60 years of age at HT initiation. The HT exposure of more than 1–8 years in our study in the post–Women’s Health Initiative era may support this hypothesis also in estradiol-based HT users. This indicates that estrogen is beneficial in healthy coronary arteries, but perhaps not in those affected by atherosclerotic plaques, likely to be present in arteries of elderly women. Our nonrandomized data may not justify any definitive clinical recommendations for the use of HT. However, post–Women’s Health Initiative use of estradiol-based HT appears to reduce the risk of cardiac death more effectively in recently postmenopausal women than in elderly women, and this is in line with the “window theory.”

The coronary heart disease death risk in HT users was increased only within the first year of HT discontinuation, but no increased risk was detected greater than 1–8 years after HT cessation. It is likely that the first post-HT treatment year collected deaths resulting from coronary heart disease, which were consequences of myocardial infarction experienced during HT exposure. Because roughly half of the women die within the first postinfarction year, they were accumulated in the first year post-HT follow-up. Second, in view of potential positive effects of estradiol on coronary arteries, an acute withdrawal of estradiol may have resulted in coronary occlusion and perhaps in myocardial infarction. Thus, intermittent estradiol-based HT use might not be wise with regard to cardiac event risk.

The limitations of our study include a lack of demographic and medical data for HT users such as smoking, hypertension, and diabetes. We do not know the primary indications for the initiation for HT; eg, how many women were prescribed with HT for coronary heart disease prevention. Neither do we know the status of hot flushes, which may bear an effect on the cardiac effect of HT. These biases were similarly present in both the pre- and post–Women’s Health Initiative eras. We compared HT users with an age-matched background population, also including HT users. Thus, the effects were slightly diluted in our study. A more common use of modern medical interventions such as angioplasty and preventive drugs has reduced the incidence of myocardial infarction, death, or both more during the post–Women’s Health Initiative era worldwide and also in Finland. Medical care is heavily subsidized in Finland. Thus, the reduced death rates were similarly present in HT users and in the background population and therefore caused no bias.

The strengths of our study include a reliable assessment of the exposure times for given HT regimens. Furthermore, as a result of only partial reimbursement, the HT medications bought are also likely to be used. Thus, we could avoid recall bias. The coronary heart disease deaths were also accurately recorded into the register. Although the coronary heart disease mortality has declined in Finnish women, they still are at a higher risk for coronary heart disease death than women in many other industrialized countries. Therefore, the possible Women’s Health Initiative-related effects on coronary heart disease death rate in HT users might become most easily detectable in this population.
REFERENCES


