New evidence for cardiac benefit of postmenopausal hormone therapy

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ABSTRACT
Coronary artery disease (CAD) is still the most common killer of western women. Coronary arteries, expressing estrogen receptors, are a target for estrogen action. Prior to the Women’s Health Initiative (WHI) study, postmenopausal hormone therapy (HT) was widely advocated for primary prevention of CAD, but such use was criticized after the WHI publication. However, new data accumulated in the USA and in Europe indicate that the use of estradiol-based HT regimens does not endanger the heart, but rather, it significantly reduces the incidence of CAD events and mortality. This effect may be related to the presence of hot flushes before HT initiation, because they may indicate a greater responsiveness of the cardiovascular system to HT. To get maximal cardioprotective efficacy of HT, a woman should initiate HT as soon as symptoms occur, and preferably within the first 10 postmenopausal years. Recent guidelines for optimal use of HT recommend pauses of HT at 1–2-year intervals to see whether hot flushes and other symptoms still persist. However, new data question the safety of this policy, because acute withdrawals of estradiol from the circulation may predispose to potentially fatal CAD events. All these data support modernized guidelines for optimal HT use.

Introduction
Postmenopausal hormone therapy (HT) has been used for more than 80 years to alleviate menopausal symptoms. However, during the past couple of decades the health benefits and risks of HT have been under vigorous debate. The controversy has primarily focused on the possible impact of HT on the risk of coronary artery disease (CAD), since it remains the leading cause of morbidity and mortality among women in western populations. In the late 1990s, many dominant medical organizations advocated the use of HT for both primary and secondary prevention of CAD. This dogma was challenged, and basically reversed, after initial results from two placebo-controlled, randomized trials, the Heart and Estrogen-progesterin Replacement Study (HERS) and the Women’s Health Initiative (WHI), which disputed the use of conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA) in secondary or primary prevention of CAD, respectively. As a result, the same medical organizations which had praised the efficacy of HT in CAD prevention only a few years earlier now started warning against the cardiac hazards of HT. However, several sub-analyses of the WHI have revealed that the impact of HT on CAD risk depends on important confounders, such as age and/or sub-clinical CAD at the initiation of HT use. Diagnosis of sub-clinical CAD in routine clinical practice may be challenging, whereas CAD as a cause of death is usually accurately verified and, if not on a clinical basis, confirmed with autopsy. Thus, we review here the post-WHI data on the impact of HT primarily on CAD-caused mortality but also on non-fatal cardiac outcomes.

Coronary arteries as target for estrogen action
The effects of estrogen on coronary arteries have been extensively studied in in vitro, ex vivo and in vivo experimental studies, therefore here we only briefly allude to the various estrogen-mediated vascular mechanisms (Table 1). Estrogen receptors alpha and beta in coronary arteries and the heart are targets for estrogen-mediated action. In some instances estrogen effects are non-genomic, operating rapidly via membrane receptors. The direct cardiac effects of estrogen contribute to the dilation of coronary arteries and prevention of occlusive events within them. In addition, estrogen mediates a number of secondary changes in the vasculature that slow down the initiation and progression of atherosclerosis (Table 1). However, in the presence of atherosclerotic plaques, estrogen may up-regulate matrix metalloproteinase (MMP) expression in macrophages and stimulate thrombogenesis, promoting rupture of atherosclerotic plaques. This may lead to acute myocardial infarction and potentially to death. The effect of estrogen on MMPs and thrombogenesis is dose-dependent and thus, HT may only be harmful at high doses. All this gives further support for the epidemiological data that cardiac effects of HT depend markedly on the extent of pre-existing coronary atherosclerosis, which is closely related to the age of a woman.
Age at initiation of HT as a determinant for cardiac effects of the WHI trial

Several sub-analyses of the WHI study indicate that HT provides CAD protection against cardiac events if initiated close to menopause. Risk ratios of cardiac events were (HT vs. placebo) 0.89, 1.22, and 1.71 for women randomized at <10 years, 10–19 years, and 20 or more years past menopause, respectively\(^6\). These significant results were confirmed later in more detailed sub-analyses\(^6\). Also in the WHI trial, estrogen therapy was accompanied with reduced coronary artery calcium (CAC) content only in the 50–59-year age group\(^7\). Furthermore, in women with a favorable low density lipoprotein/high density lipoprotein cholesterol ratio (<2.5), HT led to a 40% lower risk for CAD incidents whereas, among women with a less favorable ratio, such therapy resulted in a 73% higher risk\(^16\). These findings also indicate that, in the WHI study, HT reduces the progression of atherosclerosis and accumulation of CAD in recently menopausal women.

Pre-WHI prescribing policy of HT caused no increased cardiac mortality risk

The WHI study rapidly changed guidelines world-wide for the optimal use of HT and, most importantly, it ended the use of HT for primary prevention of CAD. The overall use of HT also decreased markedly\(^7\), and HT initiation after 60 years of age almost disappeared\(^18\). Since cardiac death is the most reliable index for CAD, we compared CAD mortality in two Finnish HT user populations: during the more liberal HT prescribing policy before the WHI publication and after the WHI trial when HT was not recommended for primary or secondary prevention of CAD\(^18\). Although we expected to find a higher CAD death risk in HT users during the pre-WHI era, we eventually detected significant reductions in the CAD death risk in ever- and current HT users both during the pre- and post-WHI era, and these reductions did not differ significantly between the two study periods (Table 2). Thus, the prophylactic HT prescribing policy did not lead to an excess of CAD mortality in this population using estradiol-based HT, and most likely the situation was similar, e.g. in the Nurses’ Health Study population\(^19\). It is possible that even in the pre-WHI era the majority of the women initiated HT for the control of the typical menopausal symptoms, and their risk of CAD was reduced during the use of HT.

### Table 1. Biochemical mechanisms by which estrogen may exert cardioprotective effects in coronary arteries. The data have been collected from recent reviews\(^6,11,12,14\).

<table>
<thead>
<tr>
<th>Direct effects</th>
<th>Indirect effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cell growth</td>
<td>Total cholesterol, LDL, HDL</td>
</tr>
<tr>
<td>Smooth-muscle cell growth</td>
<td>Antioxidant effects: oxidation of LDL</td>
</tr>
<tr>
<td>Atherosclerotic plaque progression</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Nitric oxide production and release</td>
<td>Cardiomyocytes: ischemia/reperfusion injury, cardiac hypertrophy</td>
</tr>
<tr>
<td>Prostacyclin production and release</td>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Cytokine release</td>
<td>Inflammatory response</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein; HDL, high density lipoprotein.

### Table 2. Risk of death due to coronary heart disease in two populations treated with liberal (pre-WHI era; 1995–2001) and with more strict guidelines (post-WHI era, 2002–2006) for hormone therapy\(^16\).

<table>
<thead>
<tr>
<th>Duration of HT</th>
<th>Fewer deaths per 10 000 WYs</th>
<th>Pre-WHI era</th>
<th>Post-WHI era</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>0.71</td>
<td>0.63–0.80</td>
<td>0.82</td>
</tr>
<tr>
<td>1–8 years</td>
<td>0.57</td>
<td>0.48–0.66</td>
<td>0.46</td>
</tr>
</tbody>
</table>

### Cardiac benefits from HT in several post-WHI studies

New clinical trials and epidemiological studies suggest that HT reduces the incidence of CAD in recently menopausal women (Table 3)\(^10,21\). In a Danish multicenter trial with 1006 women and 10 years of intervention, the women randomized to HT experienced half the rates of myocardial infarctions, heart failure and death than women randomized to no treatment\(^22\). Although this study was primarily evaluating the effect of HT on the prevention of osteoporotic fractures, and has been criticized for its small number of women and open-label design, cardiac benefits of HT after a randomization at a mean of 7 months after the onset of menopause strongly support the timing hypothesis derived from the WHI, although this was not verified in all studies\(^23\). It is possible that surrogate markers of CAD, such as carotid artery intima media thickness (CIMT) or CAC are not always sensitive enough to reveal the timing phenomenon. However, in the Early versus Late Intervention Trial with Estradiol, 643 post-menopausal women free from cardiovascular disease, stratified according to time since menopause (<6 years vs. ≥10 years), were randomly assigned to receive either 17β-estradiol plus micronized progesterone vaginal gel or placebo over a median of 5 years\(^24\). As compared with placebo, estrogen treatment resulted in a significantly slower progression of CIMT, but only among women who initiated HT less than 6 years after menopause. This finding was estradiol-specific and not affected by the use of progesterone. This suggests that HT suppresses the development of atherosclerosis when initiated early after menopause, although the trial failed to show an effect on CAC progression.

Death being probably the most reliable marker of CAD, we compared this death risk in almost half a million estradiol-based HT users with that in an age-matched female background population\(^25\). The risk for CAD death in HT users was reduced in an exposure-dependent manner up to 54% (Table 3).

Furthermore, the younger the women were at the initiation of HT, the smaller was their CAD mortality risk\(^26\). Thus, 60 years of age at the initiation of HT is evidently not a threshold age, as suggested by the WHI sub-analyses\(^6\), but the sooner HT is initiated after the onset of menopause, the more protective it is against CAD\(^26\). In another study we compared recent myocardial infarction-caused mortality between HT users (ever or current) and non-users\(^27\). The attack-related death risk was 38% smaller in ever-HT users than in non-users, and this difference may contribute to a
reduced cardiac death risk in the overall HT user population\textsuperscript{25}.

**Progestin components do not determine the cardioprotection of estrogen**

The progestin component of HT, and particularly MPA, has often been blamed for the failure of HT in the prevention of CAD\textsuperscript{28}. All progestins act as antiestrogens, e.g. in uterine endometrium, and they might function analogously in coronary arteries. Various progestins used as part of HT show structure-specific differences in their capacity to bind to progestosterone and other steroid receptors\textsuperscript{39}. Thus, it is important to compare whether these progestins used as complements to estradiol modify differently the cardiac effects of estrogen. However, MPA, norethisterone acetate and a number of other progestins used with estradiol were accompanied with comparable reductions in cardiac death risk\textsuperscript{26}. Thus, our data may imply that MPA is unlikely to explain the lack of preventive efficacy of the CEE + MPA regimen in the secondary\textsuperscript{3} or primary\textsuperscript{4} prevention trials. Moreover, our data as well as some other new data\textsuperscript{34} suggest that the progestin component of HT does not antagonize the beneficial cardiovascular effects of estrogen.

**Estradiol vs. CEE in the cardiovascular system**

CEE, which are extracted from the urine of pregnant mares, contain various biologically active estrogen compounds, the primary being estrone but also equilin sulfate, which has estrogenic actions\textsuperscript{30}. In contrast, 17\(\beta\)estradiol is a ‘natural’ estrogen. The former was used in the HERS and WHI trials, whereas some post-WHI studies, also in the USA, have been conducted with estradiol\textsuperscript{24}. Estradiol has been used almost exclusively in Europe. Although there are no studies comparing head-to-head CEE and estradiol with CAD mortality as the primary end-point, CEE has been proved to be more prothrombotic than estradiol\textsuperscript{31}. This would indicate a higher CAD death rate in CEE users than estradiol users, especially if such a regimen has been initiated in elderly women who quite likely have atherosclerotic plaques in their coronary arteries. This speculation calls for caution in comparisons between clinical CAD outcomes obtained with CEE or estradiol.

**Oral vs. transdermal administration of estrogens and the cardiovascular system**

Compared to oral administration of estrogens, the transdermal route provides more constant blood levels of estrogen, and a close to physiological 1:1 ratio of estradiol:estrone\textsuperscript{12}. The transdermal route avoids the hepatic first-pass metabolism, resulting in fewer adverse effects on coagulation markers compared to oral estrogens\textsuperscript{33}. Both oral and transdermal estrogens appear to have equally beneficial effects on the nitric oxide synthase pathway, endothelial function, and reductions in circulating angiotensin-1-converting enzyme activity\textsuperscript{13}, but the transdermal route is devoid of increased risk of deep vein thromboembolism\textsuperscript{34}. If this phenomenon was also present in coronary arteries, the risk of CAD death would likely be smaller in women using transdermal rather than oral estrogen. Even though in the KEEPS trial oral CEE and transdermal estradiol did not differ in their effect on CIMT\textsuperscript{22}, head-to-head comparisons between oral and transdermal estradiol with CAD events as primary endpoints are needed. The use of local estradiol to alleviate vaginal atrophy leads to slight increases in circulating estradiol levels\textsuperscript{35}. Interestingly, this estradiol rise appears to benefit the heart; the risk of CAD death was significantly decreased in 330 000 women using vaginal estradiol\textsuperscript{36}. Thus, the low levels of non-oral estradiol appear to provide cardiac benefits, and perhaps particularly in elderly women.

**Hot flushes as a determinant for cardiac effects of postmenopausal HT**

Hot flushes derive from estrogen insufficiency-induced alternation in hypothalamic temperature control, but they are accompanied, primarily or secondarily, by drastic changes in sympathetic/parasympathetic nervous function\textsuperscript{37,38}. Hot flushes were mild or absent in the majority of women taking part in the WHI trial since the disappearance of disturbing hot flushes during the active regimen would have revealed the code of the study medication and, thus, 90% of potential study subjects were excluded for hot flushes\textsuperscript{39}. Therefore, HT

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**Table 3. Clinical and epidemiological studies published after the first WHI results (2002): the impact of hormone therapy on cardiovascular outcomes.**

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Number of participants</th>
<th>Study type</th>
<th>Type of HT</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lokkegaard et al. 2003\textsuperscript{25}, Denmark</td>
<td>13 084</td>
<td>Observational</td>
<td>E2; E2 + P</td>
<td>Ischemic heart disease</td>
<td>CHD death HR 0.84 (95% CI 0.74–0.94) for &lt;5 years of use; CHD death HR 0.79 (95% CI 0.36–1.73) for &lt;5 years of use; CHD death SMR 0.77 (95% CI 0.73–0.80) for HT &gt;10 years of use</td>
</tr>
<tr>
<td>Chilvers et al. 2003\textsuperscript{30}, UK</td>
<td>864</td>
<td>Observational</td>
<td>E; E + P</td>
<td>MI</td>
<td>MI OR 0.74 (95% CI 0.55–0.99)</td>
</tr>
<tr>
<td>Pentti et al. 2006 (OSTPRE)\textsuperscript{57}, Finland</td>
<td>11 667</td>
<td>Observational</td>
<td>E2; E2 + P</td>
<td>CHD death</td>
<td>CHD death HR 0.84 (95% CI 0.74–0.95)</td>
</tr>
<tr>
<td>Kim et al. 2006\textsuperscript{58}, UK</td>
<td>166 310</td>
<td>Observational</td>
<td>E; E + P</td>
<td>MI</td>
<td>MI OR 0.76 (95% CI 0.68–0.86)</td>
</tr>
<tr>
<td>Stram et al. 2011 (CTS)\textsuperscript{59}, USA</td>
<td>71 237</td>
<td>Observational</td>
<td>E; E + P</td>
<td>MI</td>
<td>MI OR 0.76 (95% CI 0.68–0.86)</td>
</tr>
<tr>
<td>Schierbeck et al. 2012 (DOPS)\textsuperscript{22}, Denmark</td>
<td>1006</td>
<td>RCT</td>
<td>E2; E2 + P</td>
<td>Death, HF or MI (composite)</td>
<td>Death, HF or MI (composite) HR 0.48 (95% CI 0.26–0.87) after 10 years</td>
</tr>
<tr>
<td>Mikkelø et al. 2015\textsuperscript{25}, Finland</td>
<td>489 105</td>
<td>Observational</td>
<td>E2; E2 + P</td>
<td>CHD death</td>
<td>CHD death SMR 0.77 (95% CI 0.73–0.80) for HT &gt;10 years of use</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; CI, confidence interval; CTS, California Teachers Study; DOPS, Danish Osteoporosis Prevention Study; E, any estrogen; E2, estradiol; HF, heart failure; HR, hazard ratio; HT, hormone therapy; MI, myocardial infarction; OR, odds ratio; OSTPRE, Osteoporosis Risk Factor and Prevention; P, progesterone; RCT, randomized controlled trial; SMR, standardized mortality ratio.
users in observational studies and randomized trials differ drastically in their pretreatment hot flush status. This limits a comparability of these data if hot flushes are a determinant for the effects of HT towards the cardiovascular system.

Menopausal hot flushes may be related to cardiovascular health before and during the use of HT. Hot flushes are accompanied with altered heart rate variation and increased blood pressure reactions\(^8,9\). The mechanisms of these actions of hot flushes are not fully understood, but it is possible that hot flushes become a determinant for cardiovascular health through effects on sympathetic/parasympathetic activity\(^9\). HT might be particularly beneficial to women with hot flushes by improving endothelial function\(^41\) or increasing insulin sensitivity\(^42\), both reducing the risk for CAD. Hot flushes may reflect potentially more reactive coronary arteries that respond favorably to exogenous estrogen\(^43\). This may also be in line with the timing hypothesis suggesting a beneficial vascular effect of HT in recently menopausal women, typically with hot flushes and healthy arteries, but not in older women without hot flushes but possibly with more calcified and less reactive arteries\(^14\).

**Discontinuation of HT and cardiac safety**

Current guidelines recommend that HT should be used for the shortest possible time, and an annual or biennial HT pause has become a routine practice to evaluate if a woman could manage without HT\(^45\). Long-term consequences of HT discontinuation have been assessed in several clinical trials\(^46,47\). In the WHI study, 3 years after HT cessation, the overall mortality was significantly increased in women originally assigned to CEE + progestin treatment relative to those who were assigned to placebo and who were at least 80% compliant with intervention\(^49\). In the HERS unblinded, post-trial, 2.7-year follow-up, women originally assigned to CEE had a 3.3-fold higher rate of ventricular arrhythmia requiring resuscitation compared with those women assigned to placebo\(^48\). A recent large-scale population study revealed that women who stopped estradiol-based HT relative to women who continued it had a 2.3-fold greater risk of CAD death within the first post-HT year\(^49\). Furthermore, these risk elevations were markedly higher in women who had been younger than 60 years at the initiation or discontinuation of HT use (Table 4). Although these epidemiological data do not prove a direct cause-and-effect relation, such may well be present in view of the rapid biological cardiac effects of estrogen. Acute withdrawal of vasodilatory estrogen, as in discontinuation of HT, may result in constriction of coronary arteries\(^50\) that could potentially cause fatal myocardial infarction. Furthermore, reoccurrence of vasomotor hot flushes after HT withdrawal is associated with increased sympathetic activity and palpitations\(^51,52\), and this could predispose some women to fatal arrhythmias\(^51,52\). Thus, regardless of the mechanism of action, these data\(^49\) strongly question the safety of the annual discontinuation practice to evaluate whether a woman could manage without HT. Furthermore, it is mandatory to compare the cardiac safety of abrupt or gradual discontinuation of HT in future studies.

**Table 4. The impact of age at HT initiation or discontinuation on cardiac death risk during the first year after discontinuation of HT as compared with age-matched background population\(^49\).**

<table>
<thead>
<tr>
<th>HT exposure</th>
<th>&lt;5 years SMR (95% CI)</th>
<th>&gt;5 years SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HT initiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>1.74 (1.37–2.19)</td>
<td>1.27 (1.14–1.41)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>1.12 (0.95–1.31)</td>
<td>1.30 (0.90–1.82)</td>
</tr>
<tr>
<td><strong>HT discontinuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>1.94 (1.51–2.48)</td>
<td>2.54 (1.84–3.44)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>1.11 (0.94–1.29)</td>
<td>1.19 (1.07–1.33)</td>
</tr>
</tbody>
</table>

**Conclusions**

New research data have accumulated after WHI, which uniformly witness for the efficacy of estradiol-based HT regimens in primary prevention of CAD. These data should be acknowledged in modernized guidelines for optimal use of HT, and HT could even be considered for primary prevention of CAD. However, the control of hot flushes should remain the primary indication for prescribing HT and, to achieve a concomitant cardiac benefit maximally, such use should be started soon after the onset of menopause. The longer HT is used, the larger is the cardiac benefit. The safety of annual or biennial pausing to test the persistence of hot flushes is potentially dangerous, because acute withdrawal of estrogen may predispose to cardiac events.

**Conflict of interest** T.M. has been a speaker and/or received consulting fees from Mylan and Novo Nordisk. H.S-P has been a speaker for Mylan and received funding for congress trips from Mylan and Finox Biotech. M.V. and O.Y. report no conflict of interest.

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**References**


16. Bray PF, Larson JC, LaCroix AZ, et al. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. *Am J Cardiol* 2006;101:1599–605


