Review article

Back to the future: Hormone replacement therapy as part of a prevention strategy for women at the onset of menopause

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ABSTRACT

In the late 1980s, several observational studies and meta-analyses suggested that hormone replacement therapy (HRT) was beneficial for prevention of osteoporosis, coronary heart disease, dementia and decreased all-cause mortality. In 1992, the American College of Physicians recommended HRT for prevention of coronary disease. In the late 1990s and early 2000s, several randomized trials in older women suggested coronary harm and that the risks, including breast cancer, outweighed any benefit. HRT stopped being prescribed at that time, even for women who had severe symptoms of menopause. Subsequently, reanalyzes of the randomized trial data, using age stratification, as well as newer studies, and meta-analyses have been consistent in showing that younger women, 50–59 years or within 10 years of menopause, have decreased coronary disease and all-cause mortality; and did not have the perceived risks including breast cancer. These newer findings are consistent with the older observational data. It has also been reported that many women who abruptly stopped HRT had more risks, including more osteoporotic fractures. The current data confirm a "timing" hypothesis for benefits and risks of HRT, showing that younger have many benefits and few risks, particularly if therapy is predominantly focused on the estrogen component. We discuss these findings and put into perspective the potential risks of treatment, and suggest that we may have come full circle regarding the use of HRT. In so doing we propose that HRT should be considered as part of a general prevention strategy for women at the onset of menopause.

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1. Introduction

In the late 1980s, several observational studies and meta-analyses suggested that hormone replacement therapy (HRT) for women after menopause was beneficial for prevention of osteoporosis, coronary heart disease (CHD), and dementia and decreased all-cause mortality [1–5]. Indeed it was a recommendation of the American College of Physicians to advocate the use of HRT as a prevention strategy in 1992 [6]. In the late 1990s and early 2000s, several randomized trials in mostly older women in which HRT was initiated 10 or more years after menopause suggested coronary harm and risks outweighed benefit [7–9]. Almost immediately after the initial publication of data from the hormone trial of the Women's Health Initiative (WHI) [9], HRT stopped being prescribed, even for women who had severe symptoms of menopause. Subsequently, reanalyzes of the older randomized trial data, using age stratification, as well as newer studies and meta-analyses have been consistent in showing that when initiated in younger women, 50–59 years or within 10 years of menopause onset, HRT decreases CHD and all-cause mortality; and did not have the perceived risks including breast cancer. These newer findings in younger women with initiation of HRT within 10 years of menopause are consistent with the older observational studies of younger women who initiated HRT at the time of menopause.

In public health, prevention strategies have been instituted with the expectation that it would be beneficial over time and reduce human suffering and mortality. Most aging-related diseases in women occur on average about 10 years after the onset of menopause [10]. Thus, an important opportunity is afforded by

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potentially intervening with preventative strategies at the onset of menopause. The coronary benefit in younger women using HRT, the reduced all-cause mortality and other benefits in terms of reduction in menopausal symptoms, osteoporosis prevention, prevention of new onset diabetes mellitus and improved quality of life; as well as the demonstration of cost effectiveness and the lack of effectiveness of other prevention strategies for younger healthy women make a compelling argument for the use of HRT for prevention. We propose here that use of HRT, and specifically the use of estrogen, should be part of a strategy for prevention of chronic diseases after menopause, and not restricted only for the treatment of moderate to severe hot flushes.

2. What was known about estrogen in women after menopause?

As introduced above, many observational studies showed a benefit of HRT for several endpoints. A meta-analysis and pooled analysis showing a coronary benefit of 0.65 (0.59–0.72) and a projected increase in longevity among users [5] led the American College of Physicians to publish guidelines in 1992 [6]. This statement suggested that "all women, regardless of race, should consider preventive hormone therapy" and that "women who have coronary heart disease or who are at increased risk for CHD are likely to benefit from hormone therapy" [6]. For many, the data on the cardioprotective effects of estrogen were so strong that there was serious concern over the potential attenuating effects of added progestogens; accordingly an International Consensus Meeting was convened in 1988 [11]. It was thought that even minor attenuation of the beneficial effects of estrogen would translate into less "lives being saved from ischemic heart disease " [11]. Although there was not clarity about the various mechanisms of potential cardioprotection by estrogen and attenuation of benefit with added progestogen, it was concluded that while progestogens were necessary in women with a uterus, different progestogens and regimens should be considered. This will be discussed in more detail below, but this conclusion is quite similar to the view today, almost 30 years later.

3. Randomized trials of HRT

Despite strong observational data, it was deemed important to carry out randomized trials to assess the purported coronary benefits of HRT in postmenopausal women. In the 1990's several secondary prevention trials were begun [7–9]. Just as WHI was beginning, reports from these trials, studying the effects of estrogen/progestogen *versus* placebo in women with established CHD showed no overall benefit with a complex pattern of "early harm" (more coronary events within first year of initiation) followed by a statistically significant reduction of coronary events with continued intervention [7].

WHI was a series of large randomized controlled clinical trials conducted mainly in older women more than 10 years from menopause, and an observational study, one aim of which was to investigate whether or not HRT could help prevent major chronic diseases in postmenopausal women. The primary outcome of the HRT studies was CHD end-points, with other clinical outcomes as secondary events, including breast cancer, which was also designated as the primary adverse event; it is important to recognize that breast cancer was a-priori defined as a secondary outcome. The preliminary results from the study with regard to combined estrogen-progestogen HRT were published in a blaze of publicity in 2002 [12]. It was claimed that HRT use increased the risk of CHD events, stroke, pulmonary embolism and breast cancer, and therefore the treatment was not safe. This had a huge global impact,

with a significant decrease in the use of HRT world-wide. There has been much criticism about the results and interpretation of the findings in WHI and this discussion is beyond the scope of this review. The original results changed several time in terms of point estimates and confidence intervals, as reviewed by us previously [13]. In the most recent 13 year follow up of data from WHI, the early reported findings have been mainly negated. Indeed as will be reviewed below, the findings in younger women were extremely beneficial with decreases in coronary disease, all-cause mortality as well as cancer rates with very limited and rare side effects [14].

4. Aftermath of WHI: fractures, CV events, mortality

The large fall in use of HRT has had profound clinical consequences for postmenopausal women whose health and well-being has suffered. The reluctance of health care professionals to prescribe HRT has denied many women adequate and effective relief from menopausal symptoms and has impaired their quality of life. In addition, there are data showing that stopping HRT may result in increased CHD, stroke and all-cause mortality [15]. Of equal and well-documented concern is the substantial increase in hip fractures that has been seen due to HRT discontinuation following the WHI 2002 publication [16,17]; this burden is likely to grow. What will be the impact of the reduction in HRT use on cardiovascular disease (CVD)? It is too early to tell as yet, but it is likely that widespread avoidance of HRT use may have a serious negative impact (see below). The WHI had reported a reduction in CHD and in mortality in women initiating estrogen alone before age 60 years compared with those initiating placebo. When the excess mortality seen in this placebo group was related to similar women in the entire US population, it was estimated that during the 10 years following the WHI 2002 publication, avoidance of HRT would result in the premature deaths of anywhere between 19,000 and 92,000 women [18].

It was claimed that a fall in breast cancer incidence in the US was accompanied by the decline in HRT use following WHI 2002 [19]. But this was not borne out worldwide and in most cases the decreases in breast cancer incidence actually preceded the decline in HRT use [20].

5. Why the initial reports from WHI and the other secondary prevention trials were different from the observational data

Although the beneficial effects found in the earlier observational studies was hypothesized to be due to inherent biases of observational data such as a "healthy user effect", adjustments to the data have not negated these findings. A major difference between observational studies and randomized clinical trials of HRT is the age at initiation of therapy; observational studies included women who chose to start HRT around the time of menopause mainly for symptomatic relief, whereas the average age of women in WHI was 15 or more years older. Thus many women in WHI were outside the "window of opportunity", greater than age 60 years or more than 10 years post menopause. The areas that differ between the observational data and the randomized trials carried out in older women are the effects on CHD, and on cognitive decline and dementia. It is likely that these two disease processes are age dependent and also are affected by time from menopause onset.

The absent or diminished arterial response to estrogen in older *versus* younger women may be accounted for by several mechanisms. Loss of ERα, its methylation and interference by higher levels of 27-OH cholesterol with aging are all possible explanations for the lack of response in older atherosclerotic arteries [21–23]. The age effect may also be critically dependent on dose at initiation. Higher

doses of estrogen may have deleterious rather than beneficial effects on some cardiovascular processes such as coagulation activation [24] and vascular remodelling [25]. The "early harm" observed in the secondary prevention trials may be due to an increase in matrix metalloproteinases with oral estrogen leading to the breakdown of the fibrous cap in atheromatous arterial plaque, causing plaque instability and possible rupture and thrombosis [26].

6. Coronary heart disease and all-cause mortality

Mortality rates in women have risen in 44% of U.S. counties since 2002 along with the concomitant reduction in use of HRT, in contrast, mortality rates have risen in only 3% of counties for men [27]. While it is unclear if this increase in mortality has anything to do with HRT, over the last decade, data have accumulated to indicate the relative effectiveness of HT as a prevention strategy for CHD in postmenopausal women [28]. At the same time, no other primary prevention strategy, other than life style management, has been found to be beneficial [10] (see below).

Specifically, the data show that in primary prevention, HRT reduces CHD and all-cause mortality in women who initiate HRT before age 60 years and/or within 10 years-since-menopause. These data are consistent across observational studies, randomized controlled trials (RCTs) and meta-analyses (Table 1). Although there has been some reservation raised with these data in that some of the analyses were from sub-studies (for example the age stratified studies from WHI), the data are extremely consistent, with similar point estimates as noted in all categories of studies.

On the other hand, when initiated in women older than 60 years and/or more than 10 years-since-menopause, HRT appears to have a null effect on CHD and even a possible adverse CHD effect in some of the women who are distant from the onset of menopause. In addition, there are clear sex differences across almost every aspect of CVD including diagnostics, therapeutics and preventive therapies [28].

Consistent data across observational studies, clinical trials and meta-analyses show that when initiated in healthy young postmenopausal women, HRT reduces all-cause mortality (Table 1). In a recent nation-wide population study in Finland using data from a National Death Registry, use of estradiol products (oral and transdermal) with and without progestogen was associated with significantly lower all-cause mortality (12—38% reduction) [29], coronary heart disease mortality (17—70% reduction) [29,30] and stroke mortality (1—55% reduction) [29,31]. Results from this population study also showed that the beneficial effects are evident across all progestational agents studied [29]. In addition, all-cause mortality and CHD mortality were positively related to duration of use of HRT [29]. Using data from this Finnish National Death Registry, it was also recently shown that use of postmenopausal vaginal estradiol among 195,756 users (followed for 1.4 million women years) was associated with a 36% statistically significant reduction in both CHD and stroke mortality. The risk reduction for both CHD and stroke mortality was shown across all age groups, with the greatest reduction of 57% among women aged 50—59 years [32].

In another recent prospective observational study, the Combined Cohorts of Menopausal Women − Studies of Register Based Health Outcomes in Relation to Hormonal Drugs (COMPREHEND), individual HRT use data was collected on menopausal women from 5 population-based Swedish cohort studies (n = 74,352) and CHD diagnoses and causes of death were obtained from a National Patient Register and Cause of Death Register. During a maximum 22.7 years (13.4 years average) follow-up, initiation of HRT within 5 years of menopause was associated with a decreased risk of incident CHD relative to non-users of HRT, whereas women who

Table 1
Coronary heart disease and all-cause mortality reported from randomized trials, observational studies and meta-analyses among women aged <60 years or <10 years-since-menopause when HT is initiated.

Studies	Age; time-since-menopause	Therapy	Coronary heart disease	All-cause mortality
			% Reduction (risk ratio; 95% confidence interval)	% Reduction (risk ratio; 95% confidence interval)
DOPS, 10 year [37]	50 yr; 7 mo-s-m	E2+NETA sequential	↓ 52% (0.48; 0.27—0.89)	↓ 43% (0.57; 0.30—1.08)
DOPS, 16 year [37]		and E2 alone	↓ 39% (0.61; 0.39—0.94)	↓ 34% (0.66; 0.41—1.08)
WHI-E, 11-year [14]	<60 yr	CE alone	↓ 41% (0.59; 0.38—0.90)	↓ 27% (0.73; 0.53—1.00)
WHI-E, 13-year [14]	<10 yr-s-m	CE alone	↓ 50% (0.50; 0.22—1.18)	↓ 36% (0.64; 0.33—1.25)
WHI-E + P, 13-year [14]	<10 yr-s-m	CE + MPA continuous	↓ 10% (0.90; 0.56—1.45)	↓ 21% (0.79; 0.52—1.21)
WHI-E, 13-year [14]	<60 yr	CE alone	↓ 35% (0.65; 0.44—0.96)	↓ 22% (0.78; 0.59—1.03)
WHI-E + P, 13-year [14]	<60 yr	CE + MPA continuous	↑ 27% (1.27; 0.93—1.27)	↓ 12% (0.88; 0.70—1.11)
WHI-E [39]	<10 yr-s-m	CE alone	↓ 52% (0.48; 0.20—1.17)	↓ 35% (0.65; 0.33—1.29)
WHI-E + P [38]	<10 yr-s-m	CE + MPA continuous	↓ 12% (0.88; 0.54—1.43)	↓ 19% (0.81; 0.52—1.24)
WHI-E/E + P [38]	<10 yr-s-m	CE and CE + MPA	↓ 24% (0.76; 0.50—1.16)	↓ 24% (0.76; 0.53—1.09)
WHI-E [38]	<60 yr	CE alone	↓ 37% (0.63; 0.36—1.09)	↓ 29% (0.71; 0.46—1.11)
WHI-E + P [38]	<60 yr	CE + MPA continuous	↑ 29% (1.29; 0.79—2.12)	↓ 31% (0.69; 0.44—1.07)
WHI-E/E + P [38]	<60 yr	CE and CE + MPA	↓ 7% (0.93; 0.65—1.33)	↓ 30% (0.70; 0.51—0.96)
Meta-analysis [41]	<60 yr <10 yr-s-m	HT	↓ 32% (0.68; 0.48—0.96)	
Meta-analysis [42]	54 yrs	HT		↓ 39% (0.61; 0.39—0.95)
Bayesian meta-analysis [44]	55 yrs	HT		↓ 27% (0.73; 0.52—0.96)
Cochrane meta-analysis [43]	<10 yr-s-m	HT	↓ 48% (0.52; 0.29—0.96)	↓ 30% (0.70; 0.52—0.95)
Observational studies [34,35]	30-55 yr <5 yr-s-m	HT	↓ 30—50%	↓ 20—60%

E,estrogen alone; E + p,estrogen + progestogen; Yr,years old; mo-s-m,months-since-menopause; yr-s-m,years-since-menopause; E2, estradiol; NETA,norethisterone acetate; CE,conjugated estrogens; MPA,medroxyprogesterone acetate; EAA,estrogen agonist/antagonist; HT,hormone therapy.

initiated HRT more than 5 years after menopause had similar incident CHD as to non-users of HRT [33].

These recently reported studies as well as previous observational studies, including the WHI observational studies, consistently show a reduction in CHD and all-cause mortality in women who use HRT [34,35]. Observational studies (primarily composed of women who began HRT around the time of menopause) consistently support the benefits of systemic HRT in reducing the risk of CHD and all-cause mortality [28,34,35]. The characteristics of women participating in observational studies are markedly different from those of many women enrolled in RCTs designed to evaluate the cardiovascular and chronic disease effects of HRT [28,36] as discussed previously.

As such, randomized trials show a HRT-related reduction in CHD and all-cause mortality among women who are aged 60 years or less and/or within 10 years of menopause (consistent with the observational populations) when randomized to HRT *versus* placebo (Tables 1 and 2). These trial data are consistent with these outcomes from long-term observational studies (most participants in observational studies were younger than age 55 and within 2–3 years of menopause at the time HRT was initiated) [34,35]. The Danish Osteoporosis Prevention Study (DOPS) was the only prospective randomized trial specifically designed to study "hard endpoints" over a long period of time in healthy recently menopausal women. Women were on average 50 [45–58] years of age and 7 months postmenopausal when randomized [37]. DOPS had a prospective randomized open-label blinded end-point design. After 10 years of randomized treatment, the composite end point of all-cause mortality, hospitalization for myocardial infarction or heart failure was significantly reduced 52% (Hazard Ratio,HR = 0.48, 95% CI = 0.27–0.89) in the HRT group relative to the untreated group. After the trial ended, follow-up was extended for 6 years; after a total follow-up of 16 years, the composite end-point was significantly lower by 49% (HR = 0.61, 95% CI = 0.39–0.94) in the women originally randomized to HRT compared to women randomized to the untreated group [37].

When analyzed by age and time-since-menopause at initiation of HRT, the estrogen-only trial of the WHI [13,38,39] is in agreement with observational studies, suggesting that estrogen may reduce CHD risk (total myocardial infarction (MI), coronary revascularization and composite outcomes including MI and coronary death) when initiated in younger and more recently postmenopausal women without a uterus. These findings for estrogen, specifically conjugated equine estrogens (CEE), were even stronger with extended follow-up of the cohort, including 4 years and 6 year follow-up after stopping randomized estrogen. For 4 years of extended follow-up, women aged 50–59 years, the HR for CHD was 0.59 (95% CI, 0.38–0.90) and for total MI it was 0.54 (95% CI, 0.34–0.85); p for interaction by age = 0.05 and 0.007, respectively [49]. For 6 years of extended follow-up women aged 50–59 years, HR for CHD was 0.65 (95% CI, 0.44–0.96) and for total MI it was 0.60

(95% CI, 0.39–0.91; *p* for interaction by age = 0.12 and 0.007, respectively) [14].

The WHI trial of daily continuous combined CEE/medroxyprogesterone acetate (MPA) provided mixed results on CHD, none of which were statistically significant. When the data were analyzed by time-since-menopause at initiation of HRT, CEE/MPA therapy is in agreement with other trials and observational studies with a reduction in CHD in women within 10 years since menopause, compared to placebo (Table 1). However, when analyzed by age at initiation of CEE/MPA, CHD risk is elevated in women less than age 60, compared to placebo (Table 1). The CHD results from the latter subgroup of women analyzed by age when initiated on oral daily continuous combined CEE/MPA is not consistent with other randomized trials and observational studies, including the WHI observational study, and thus, it is the only outlier data. It is also inconsistent with meta-analyses (Table 1). In addition, these data are at odds using the same data from the same trial analyzed by time-since-menopause, rather than age, when HRT was initiated [13,38,40].

Combined data incorporating both the CEE and CEE/MPA trials of the WHI showed a statistical trend of an HRT effect relative to placebo on CHD by time-since-menopause, indicating that women who initiated HRT within 10 years of menopause were at a lower risk for CHD compared to placebo and those women who initiated HRT more than 10 years beyond menopause were at increased risk for CHD compared to placebo [38].

Meta-analysis of the cumulated data across 23 RCTs with 191,340 women-years of follow-up shows that in women who initiate HRT when younger than 60 years old or less than 10 years-since-menopause, the risk of CHD is statistically significantly 32% less than placebo [41]. In a meta-analysis of 30 RCTs with 119,118 women-years of follow-up, a significant 39% reduction in all-cause mortality (HR, 0.61; 95% CI, 0.30–0.95) was observed in women who were on average aged 54 years when randomized to HT relative to placebo [41]. The most recent Cochrane review reported a 48% reduction in CHD (RR, 0.52; 95% CI 0.29–0.96) and a 30% reduction in all-cause mortality (RR, 0.70; 95% CI 0.52–0.95) with HRT in women who initiate treatment when <60 years old or <10 years-since-menopause compared with placebo [43].

Mortality data from three large trials, the Women's Health Initiative (WHI) trials of CEE, CEE/MPA and the Danish Osteoporosis Prevention Study (DOPS), are consistent with observational studies and meta-analyses examining the effects of postmenopausal HT on all-cause mortality (Table 1). Both the WHI CEE/MPA trial (HR, 0.67; 95% CI, 0.43–1.04) and the WHI CEE trial (HR, 0.70; 95% CI, 0.46–1.09) showed a 30% reduction in all-cause mortality in women aged younger than 60 years and/or less than 10 years-since-menopause when randomized to HRT relative to placebo [38]. When the data from both WHI trials were combined, the reduction in mortality was significantly reduced by 30% (HR, 0.70; 95% CI, 0.51–0.96) in women randomized to HRT relative to placebo

Table 2
Lipid-lowering therapy, aspirin and angiotensin converting enzyme inhibitors in the primary prevention of coronary heart disease and all-cause mortality in women. Data are given as relative risks (95% confidence intervals).

Outcome	HRT[a]	Lipid-lowering therapy	Aspirin	ACE-inhibitors
Coronary heart disease	0.68 (0.48–0.96) [41]	0.89 (0.69–1.09) [58]	1.01 (0.84–1.21) [61]	1.00 (0.83–1.21) [64]
	0.52 (0.29–0.96) [43]	0.95 (0.78–1.16) [59]	0.91 (0.80–1.03) [62]	
		0.79 (0.56–1.13) [60]	0.88 (0.53–1.44) [63] [b]	
All-cause mortality	0.61 (0.39–0.95) [42]	0.95 (0.62–1.46) [58]	0.94 (0.74–1.19) [61]	0.92 (0.81–1.04) [65] [c]
	0.73 (0.52–0.96) [44]	0.96 (0.81–1.13) [59]	0.95 (0.85–1.06) [62]	
	0.70 (0.52–0.95) [43]	0.91 (0.76–1.08) [60]		

[a] Initiated in women aged <60 years and/or <10 years-since-menopause.
[b] Women with diabetes.
[c] Mortality from CHF.

[38]. In DOPS, women were on average aged 50 years and were 7 months postmenopausal when randomized [37]. After 10 years of randomization, women had a 43% (HR, 0.57; 95% CI, 0.30–1.08) reduction in all-cause mortality relative to a control group, with a persistent reduction in all-cause mortality of 34% (HR, 0.66; 95% CI, 0.41–1.08) after 16 years of total follow-up [37]. 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) relative to placebo in the women aged younger than 60 years who were originally randomized to CEE/MPA (median intervention of 5.6 years and 7.4 years of post-trial follow-up) and CEE (median intervention of 7.2 years and 5.8 years of post-trial follow-up), respectively [14]. The concern of excess mortality in women stopping use of estrogen is also supported by a recent observational study in Finland, showing that CHD and stroke mortalities are increased 1.25–2.3-fold after withdrawal of HT relative to women who continue HRT [15].

Convergence of evidence that HRT reduces all-cause mortality in recently menopausal women derives from a Bayesian meta-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) [44]. All-cause mortality was reduced 22% (HR, 0.78; 95% CI, 0.69–0.90) in HRT users compared to nonusers in the observational studies and reduced 27% (HR, 0.73; 95% CI, 0.52–0.96) in the RCTs. With observational studies and RCTs combined, all-cause mortality was reduced 28% (HR, 0.72; 95% CI, 0.62–0.82) [44].

7. Carotid artery intima-media thickness

Carotid artery intima-media thickness (CIMT) is a direct measurement of subclinical atherosclerosis that is predictive of future clinical cardiovascular events, CHD and stroke. Observational and case-control studies show that HRT was associated with a lower average level of CIMT compared to non-users [45–47]. In a randomized controlled trial of HRT in perimenopausal women, 2-year change in CIMT was reduced relative to placebo; however the confidence intervals were wide, indicating no significant group differences, possibly due to the small sample size [48]. In a subgroup analysis from a 3-year randomized controlled trial of statin therapy, postmenopausal women who self-selected HRT showed lower progression of CIMT than non-users [49]. In a 2-year randomized controlled trial specifically designed to test the effects of estradiol on the progression of subclinical atherosclerosis progression, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) showed that oral micronized estradiol relative to placebo significantly reduced the progression of CIMT in healthy postmenopausal women (average age, 61 years) [50]. In the Kronos Early Estrogen Prevention Study (KEEPS), low-dose oral and patch HRT relative to placebo had no significant effect on 4 year progression of CIMT in a selected healthy group of postmenopausal women (42–58 years old) who were randomized within 6–36 months of menopause onset [51]. CIMT is dose-responsive to estrogen, with CIMT progressively decreasing from low-dose to standard dose to high-dose HRT [52].

The Early *versus* Late intervention Trial with Estradiol (ELITE) was a RCT specifically designed to test the HRT timing hypothesis in relation to atherosclerosis progression in postmenopausal women [53]. After a median of 5 years of intervention, the effect of randomized estradiol, with or without vaginal progesterone, on CIMT progression differed between the early and late postmenopause strata ($p = 0.007$ for the interaction). Among women who were less than 6 years past menopause at the time of randomization, the mean CIMT increased by 0.0078 mm per year in the placebo group *versus* 0.0044 mm per year in the estradiol group ($p = 0.008$). Among women who were 10 or more years past menopause at the time of randomization, the rates of CIMT progression in the placebo and estradiol groups were similar (0.0088 and 0.0100 mm per year, respectively; $p = 0.29$) [53].

8. Coronary artery calcium

Even though coronary artery calcium is a late manifestation of atherosclerosis, some [54,55] but not all [56] observational studies suggest that long-term HRT is associated with less accumulation of coronary artery calcium. Coronary artery calcium is correlated with atheromatous plaque burden and future risk of clinical CHD events. In an ancillary substudy of younger women (<60 years) in the WHI CEE trial, after an average of 7 years of treatment, women who had been randomized to CEE had lower levels of coronary artery calcium than did those randomized to placebo [57]. Although the effect in older women was not evaluated, these findings suggest that CEE initiated by recently postmenopausal women may slow the development of calcified atherosclerotic plaque. Both the KEEPS and ELITE trials showed no effect of HT on coronary artery calcium [51,53].

9. Sex specificity of preventive therapies

Sex-specific meta-analyses that have carefully separated primary and secondary prevention trials and only included women in the analyses do not show a statistically significant reduction of CHD in primary prevention with lipid-lowering, including statin therapy in women [58–60]. Under both primary and secondary prevention, lipid-lowering therapy has a null effect on all-cause mortality in women [58–60]. A sex-specific effect is similarly seen for aspirin where primary prevention trials show no statistically significant reduction of CHD or all-cause mortality with aspirin therapy in women [61–63]. As with lipid-lowering therapy, the null effect of aspirin on CHD extends to high-risk women with diabetes without a history of CVD [63]. In addition, angiotensin converting enzyme (ACE) inhibitors have a null effect on CVD, all-cause mortality and mortality from heart failure in women in primary prevention [64,65]. Unlike women, CHD risk appears to be reduced by lipid-lowering therapy, aspirin and ACE inhibitors in men in primary prevention. However, all-cause mortality is unaffected [59–65]. A recent study suggesting a coronary benefit for rosuvastatin in women with intermediate risk studied only women over 65 years and there was no significant benefit in all-cause mortality or mortality from CVD in the male and female' combined groups [66] (Table 2).

10. Use of HRT in women at the onset of menopause

For young healthy women at the onset of menopause, the choice of prescribing some form of HRT is straight forward if she is symptomatic. This includes more than "hot flushes", and may involve body aches and pains, genitourinary symptoms, sleep disturbances, and depressive mood as well as other less precise symptoms which affect the quality of life after menopause. It has been established that use of HRT in women at the onset of menopause is cost-effective [67]. The median persistence of moderate to severe vasomotor symptoms has been found prospectively to last 7.4 years [68]. The prescription of HRT is also of added benefit in women with a higher risk of osteoporosis based on demographic details or a bone density test. A recent systematic review and meta-analysis confirmed that there was a substantial decrease in fracture risk with HRT, particularly in women <60 years: risk ratio 0.55

(0.44–0.68) [69]. In addition, the WHI showed that HRT significantly reduces bone fracture in unselected women not at high-risk for bone fracture [14].

In other women without a straight forward indication, careful assessment of risk factors for all diseases should be carried out and life style interventions instituted as appropriate [8]. In this setting we opine that there should also be a consideration of HRT. Robust and compelling data reviewed above suggest that apart from quality of life issues, prevention of coronary disease, osteoporosis and fracture risk, reduction in new onset diabetes mellitus and all-cause mortality occur; and there are no other therapies that are able to confer this prevention role. This commitment need not be for the long term, and should be reevaluated annually. Even 3–6 years of HRT has been shown to be of benefit in long term follow up studies [14,70,71]. However, regardless of duration of use, withdrawal of HRT will eventually result in bone loss and an increased potential for bone fracture. Although there need not be any predetermined duration of use, we may suggest that approximately 10 years of use may be considered.

## 11. What are the real risks of HRT in young healthy women?

If HT is to be considered more broadly for postmenopausal women, it is important to examine the real risks of such exposure. As noted above, the reported risks associated with HRT in the WHI trials were not statistically significant, with the exception of venous thrombosis and ischemic stroke in older women. In women <60 years of age and/or <10 years-since-menopause the only statistically significant risk with HRT in WHI was a rare risk of deep vein thrombosis (Fig. 1). Breast cancer risk with combined HRT for the duration of the trial was not significant elevated in women who had never been exposed previously. Even if we assume these risks were statistically significant, the absolute risks, which are in the range of 5–8 cases per 10,000 women per year, are considered "rare" according to the World Health Organization (<10/10,000). Note that

the risks may vary depending on the dose and regimen prescribed, and the venous thrombosis risk could be eliminated with non-oral therapy [72], as discussed below. It is clear that the risks associated with HRT are similar, or of less magnitude, to other medications routinely used for the prevention of CVD and other chronic conditions.

In that there are risks in everyday life, the true risks of HRT need to be compared to such exposures. According to the US National Safety Council, the annual risk of death in a motor vehicle is 1/6500; death from walking across the street 1/48,500; and getting murdered 1/10,000 to 1/16,500 [73]. The risk of some dietary supplements also may carry risks; calcium supplementation has been shown to increase the risk of myocardial infarction 2-fold [74] and calcium channel blockers increase the risk of breast cancer by 2-fold [75]. Even aggressive control of diabetes mellitus in a randomized trial has been suggested to significantly increase the risk of cardiovascular and all-cause mortality [76].

For breast cancer risk, the regimen of CEE combined with MPA in WHI only increased the risk of breast cancer with prolonged exposure of approximately 6–7 years, and the risk during the period of the trial was limited only to women who used HRT prior to randomization [77]. For estrogen therapy alone, the risk of breast cancer was decreased as was total mortality and breast cancer mortality [78]; the risk of breast cancer was statistically significantly reduced in women who were 80% compliant with therapy [79]. In the Nurses' observational study, estrogen alone at a dose of CEE 0.625 mg given to women with a hysterectomy was not seen to increase the risk of breast cancer until after 20 years, and primarily in lean women in the subgroup analysis of current users *versus* non-users [80]. Endogenous risk factors such as increased breast density, increased waist/hip ratio and late first birth are all higher than the putative risk of breast cancer associated with combined estrogen/progestogen exposure [81]. Although, not confirmed by randomized trial data, observational studies suggest that the addition of natural progesterone to estrogen therapy does not increase the
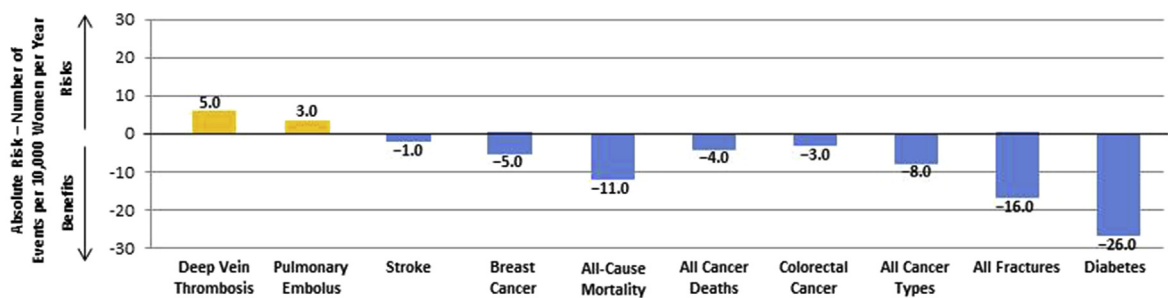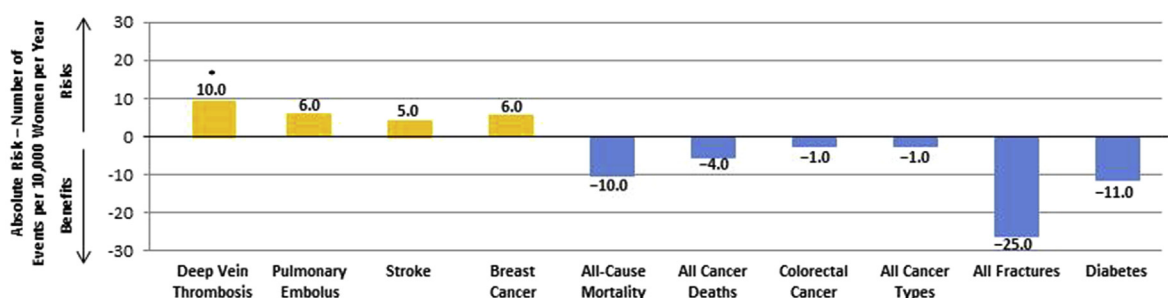

Fig. 1. **Absolute benefits and risks from the 13 year follow up study from the hormone trials of WHI: Conjugated Estrogens (CEE) alone trial and the trial with CEE combined with medroxyprogesterone acetate (MPA.)** Data on the initiation of HRT in women 50–59 years of age or < 10 years from the onset of menopause: number of events per 10,000 women per year.* The only statistically significant adverse outcome. Adapted from Manson JE et al. N Engl J Med 2016; 803–806 [86].
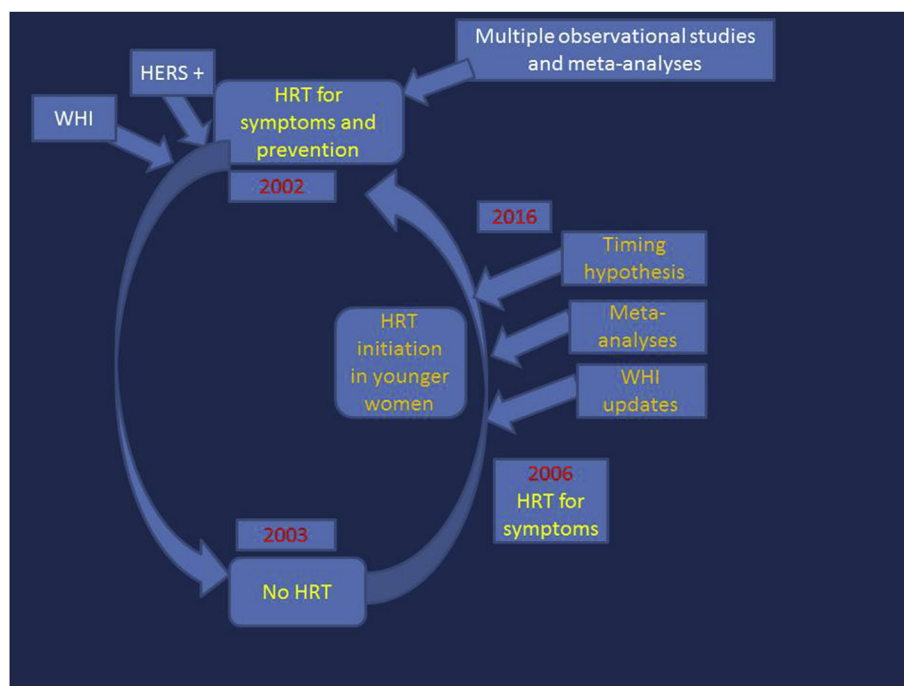
Fig. 2. Diagrammatic depiction asking the question as to whether we come full circle in the prescribing of HRT. HRT use prior to 2002, based on strong epidemiological data and meta-analyses, was for symptom control and prevention. HRT use essentially stopped soon thereafter. Some limited use for symptoms began again around 2006. The suggestion in the figure is that the use should be coming around full circle based on new data as depicted by the arrows.

risk of breast cancer as may occur with the addition of other progestogens [82]. However, other data do not indicate an increased risk of breast cancer with the addition of norethindrone acetate [29,37].

Apart from the risks of developing serious disease, there are practical concerns women have to consider regarding the use of HRT, particularly if they are considering a therapy when they are asymptomatic. These include breast tenderness, abdominal or pelvic bloating, vaginal bleeding, and some mood disturbances. These are very individual potential complaints which can usually be dealt with by changes in the HRT regimen to be discussed below. There is also the idiosyncratic reaction of increased blood pressure which appears in a small percentage of women and is related only to certain doses of oral estrogen. Women may also report weight gain, which is not supported by clinical studies [10,83], but may be a real concern on an individual basis.

More significant concerns are venous thrombosis risk and uterine cancer. Venous thrombosis which typically occurs early in the course of treatment may be 2-fold increased and is related to oral estrogen in moderate to higher doses [72]and is most likely due to an uncovered thrombophilic risk. This is similar to the occurrence in users of oral contraceptives. While this may be avoided by use of non-oral estrogens [72], particularly in more high-risk women such as those who are overweight, the absolute risk of this occurrence is rare and does not affect mortality [43]. Uterine cancer (well differentiated and early stage cancer) may occur if the progestogen regimen is not adequate for uterine protection, reinforcing the importance of careful monitoring and follow up of all women with a uterus.

In the final analysis even though risks are extremely rare and no greater than other commonly used medications and supplements, and somatic complaints may easily be dealt with by regimen changes, there is no escaping that for some women the overall "fear" of using hormones outweighs any potential benefits; the choice of using HT remains very much an individual one.

12. The choice of the HRT regimen may be critical

While there are no randomized trial data to guide specific prescriptions for HT, particularly with a goal of prevention, there are some general principals which may be employed. It is clear however that woman react differently in terms of treatment of symptoms and side effects, and flexible prescribing should always be considered. In general HT should be estrogen-based. That is, progestogen use should be minimized merely for endometrial protection in women with a uterus, and not used in hysterectomized women. There are attenuating effects of progestogens on coronary end-points and some evidence for an increase in the promotional effect on breast cancer. Furthermore, there are many women who do not feel well on progestogens and some who are relatively "intolerant." While this should still be regarded as the current situation, there have been several trials in Europe where the addition of progestogen (usually norethindrone) has not affected outcomes [29,37]. Alternatives to progestogen use, such as bazedoxifene/conjugated estrogens also offer an attractive alternative [84], although long term data are not available at present.

It has been thought that the type of estrogen is of critical importance; the predominance of data has been generated with CEE. However emerging data suggest that the use of estradiol may have similar efficacy. However, dose is likely to be important, notwithstanding a recent publication of a coronary benefit with vaginal estrogen [32]. The notion of using the lowest effective dose for the shortest period of time has fallen out of favor and may not be of benefit from a prevention perspective. Clearly, doses should be chosen to reflect symptoms and kept at a threshold of the equivalent of 1 mg of 17 β estradiol daily. Because individual responses vary widely, in some women the equivalent of 0.5 mg may be sufficient, but at present we have no data to support this. Clearly the bone protective effects are attenuated at lower doses.

Non oral estrogens have the benefit of not increasing the risks of thrombosis [72,85] and are well-suited for more high risk women

with other risk factors, particularly obesity. Until recently this recommendation could not be supported entirely in the absence of protective data in terms of mortality. Although the data are not extensive, it has recently been suggested that similar beneficial coronary outcomes have been found with non-oral estrogens [29].

We propose that we have almost come full circle in prescribing HRT for women. Before 2002, HRT was prescribed for symptoms and prevention, after 2002 virtually no HRT was being prescribed; and now with new data at hand, for younger women, HRT may be indicated for symptoms and prevention (Fig. 2.) While use of HRT for prevention is not in common practice, we suggest that this approach has merit. In the final analysis, only large and long term randomized trials in women treated with various types of HRT from the onset of menopause will be able to prove our assertion. Nevertheless the difficulty and costs involved with this endeavor seem to be prohibitive.

13. Conclusions

In the future, we are likely to have more data available, particularly in the area of personalized medicine, and pharmacogenomics. Thus a more personalized approach will be available to guide therapy, as well as the type of therapy and the particular regimen when choosing to use HRT.

Until then we can only rely on good clinical judgment and what data we have at hand. Based on the discussion above we put forth the notion that prevention of diseases after menopause should remain the primary focus of heath care providers. In this setting we would like to advance the notion of considering HRT, particularly an estrogen —based regimen, as part of this preventative strategy since HRT clearly reduces bone loss, bone fractures, new onset diabetes mellitus, CHD and all-cause mortality with rare, non-statistically significant risks particularly when initiated in women <60 years of age and/or <10 years-since-menopause.

Conflict of interest

Dr. Lobo has consulted for Pfizer, Teva and Allergan and conducts clinical trial work for TherapeuticsMD. Dr. Pickar was formerly an employee of Wyeth Research, and has received consultant fees from Wyeth/Pfizer, Besins Healthcare, Shionogi Inc, Metagenics, Radius Health and TherpeuticsMD, and has stock options with TherapeuticsMD. Dr Stevenson has received grants/research support and/or speakers fees from Abbott, Mylan and Pfizer; consulting fees from Abbott and Pfizer; and speaker's honoraria from Abbott, Bayer, Mylan, and Pfizer. Drs Mack and Hodis report no potential conflicts of interest.

Author contributions

All authors contributed significantly to the analysis, composition and writing of this manuscript.

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