Postmenopausal hormone therapy for cardiovascular health: the evolving data

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ABSTRACT

Postmenopausal (PM) hormone therapy (HT) was extremely popular for years as a treatment for many conditions, including cardiovascular (CV) disease (CVD) prevention. The adverse results from the Women's Health Initiative (WHI) ended the widespread prescriptive use of HT for nearly 20 years. The WHI findings have been broadly and unfairly applied to all hormone formulations, including modern treatments using human-identical hormones. Although CV health is indisputably linked to oestrogen status, HT involving any combination of hormones currently is not recommended for primary or secondary prevention of CVD. In the wake of more positive results from recent studies and re-evaluation of the WHI, HT has re-emerged as an issue for specialists in CVD to discuss with their patients. Rigorous scientific analysis is needed to explain the paradox of cardioprotection conferred by endogenous ovarian hormones with apparent cardiotoxicity inflicted by HT. This review will cover the origins of HT, hormone terminology and function, and key studies that contribute to our current understanding. Based on evolving evidence, if HT is to be used, we propose it be initiated immediately after cessation of ovarian hormone production and dosed as transdermal oestradiol combined with cyclic dosing of human-identical progesterone (P4).

INTRODUCTION

Cardiovascular (CV) disease (CVD) is the primary cause of death in postmenopausal (PM) women. Prior to menopause, women's hearts enjoy a 'female advantage,' conferred in part by ovarian hormones. After menopause, this protection dissipates and by 65 years of age CVD incidence equalises between the sexes (figure 1).

Hormonal treatments gained in popularity for CVD prevention following initial success in treating hot flashes and vaginal dryness. By 2001, approximately 15 million American women used hormone therapy (HT), predominantly as a proprietary blend of conjugated equine oestrogens (CEE) derived from pregnant mare urine—hence, the trade name Premarin. Medroxyprogesterone acetate (MPA), a synthetic progestin, was commonly paired with CEE.

After early observational studies yielded favourable results, HT for CV health became generally endorsed. Two studies, the Women's Health Initiative (WHI) and Heart and Estrogen/Progestin Replacement Study (HERS), were designed to evaluate CEE/MPA in primary and secondary prevention of CVD, respectively. Both concluded that HT is not cardioprotective. Re-evaluations of WHI subgroups led to the Timing Hypothesis,[1] positing that the negative findings of the WHI and HERS derived from the older age of study participants and long duration between cessation of ovarian function and HT initiation. The Timing Hypothesis could explain the discrepancy between positive findings of observational studies versus the negative outcome of the WHI, reigniting interest in HT. The Kronos Early Estrogen Study (KEEPS)[2] and the Early versus Late Intervention Trial (ELITE)[3] tested the Timing Hypothesis, showing general safety, improved quality of life, and potential CV benefits.

Although various medical societies have modified HT position statements, permitting an individualised approach, major CV societies continue to recommend against HT for primary or secondary CVD prevention. This article combines evidence from influential studies with recent scientific data to re-evaluate the current position of major CV societies and presents our proposal for greater utilisation of HT in early PM women. Observational, randomised controlled and animal studies document HT safety and benefits. WHI re-analysis reveals it was underpowered to confirm cardioprotection in newly menopausal women beginning HT.[4] The importance of a personalised, individual approach to PM care should be acknowledged, considering specific risks for CVD, osteoporosis, dementia, mood disorders and breast cancer. While recognising the need for more hormone trials, given the known detrimental effects of menopause on CV health and quality of life, coupled with the recent reassuring safety data of appropriately prescribed HT, we suggest that a new approach to menopausal medicine be considered: incorporate discussions with recently menopausal women on the risks and benefits of HT, in addition to implementation of the standard CVD risk reduction approaches.

EARLY STUDIES: HT ASSOCIATED WITH CVD BENEFITS

Initial HT studies of symptomatic, young PM women revealed positive results. In the 1980s, the Nurses' Health Study, Lipid Research Clinics Follow-up Study, Leisure World Study and Kaiser Permanente studies all concluded that HT provided CV benefits. The Nurses' Health Study 10-year prospective follow-up report concluded that oestrogen reduced coronary heart disease (CHD) and CVD mortality.[5] Of 15 other prospective studies, 14 found decreased CVD risks.[6]

In 1991, a Food and Drug Administration Advisory Committee approved HT for PM CHD risk reduction. In 1992, a meta-analysis concluded that PM hormones decreased fatal CVD by 33%,[7] and the American College of Physicians recommended offering HT to high-risk PM women to prevent CVD,[8] a position widely adopted. Foreshadowing

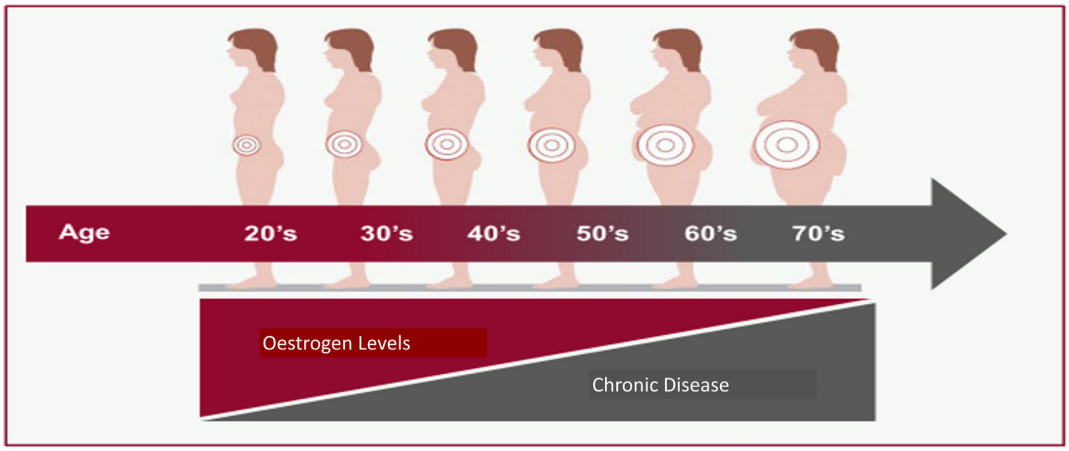

Figure 1 Age-dependent shift in oestrogen levels. Levels of oestrogen decline with age and result in increased visceral fat, higher rates of insulin resistance and an increase in cardiovascular disease.

future findings, in 1995 the Postmenopausal Estrogen/Progestin Interventions clinical trial found that MPA, but not human-identical progesterone (P4), negated CEE benefits by reducing the high-density cholesterol levels.[9]

HERS AND WHI: THE DEMISE OF HT

In the 1990s, two prospective placebo-controlled double-blind studies were launched—HERS to evaluate secondary prevention, and the WHI to focus on primary CVD prevention.[10] HERS included PM women aged 44–79 years (average 67 years) with documented pre-existing CVD. Daily oral CEE 0.625 mg with MPA 2.5 mg was given for approximately 4 years. Thromboembolic events and gallbladder disease increased, with no reduction of CHD events despite some positive lipid changes. Consequently, HT was not recommended for secondary prevention of CHD.[11]

WHI used the same HT combination as HERS–CEE+MPA. In a separate WHI arm, hysterectomised women received only CEE 0.625 mg/day. The subjects, aged 50–79 years (average age 63), were recruited as healthy PM women. WHI concluded of the CEE+MPA arm, 'Overall health risks exceeded benefits from use of combined oestrogen plus progestin … among healthy PM US women …'[12] but detailed analysis reveals 78% of subjects had pre-existing illness, including overweight, obesity, hypertension, diabetes mellitus (DM) and hypercholesterolaemia, disqualifying results as applicable to young healthy PM women.[13]

The CEE-only arm continued, but prematurely ended when harms outweighed benefits. As with HERS, CEE+MPA group experienced elevated venous thromboembolic events (VTE).[w1] WHI concluded HT did not prevent CVD death, non-fatal myocardial infarction (MI), angina or coronary revascularisation.[12] A 2015 Cochrane analysis of WHI results reported six additional strokes, eight additional cases of VTE and four additional cases of pulmonary embolism per 10 000 treated women.[14]

WHI and HERS had similarities in design. Both studied CEE and MPA (WHI also had a CEE-only arm) in predominantly older women, many with documented CVD and/or significant risk factors. Consequently, HERS and WHI produced comparable results—increased incidence of VTE disease and CVD events in year 1, with tapering risks thereafter.[15] Although applicable only to the cohort studied and hormone products used, the findings were broadly generalised to PM women of all ages and stages of menopause, and to all hormonal products, resulting in a general abandonment of HT.[16]

Recent research provides a more nuanced interpretation based on age, pre-existing conditions, and time in menopause. Reanalysed WHI data show no adverse events in women aged 50–54 years. Participants under 60 in the CEE-only arm, experienced lower risk of CHD events[17] and benefited per the WHI Coronary Artery Calcification Study, with lower mean coronary artery calcium (CAC) scores compared with placebo group, concluding 'Among women 50–59 years old at enrollment, … calcified-plaque burden in … coronary arteries after trial completion was lower in women assigned to oestrogen than those assigned to placebo'.[18]

Updated interpretations of HERS and WHI acknowledge HT initiated later in menopause offers no CVD benefit, noting MPA's harmful effects, and HT's possible CVD benefits with early initiation.[19] The Timing Hypothesis was born—oestrogen can delay or prevent atherosclerosis and complications in newly menopausal women but is harmful or shows no benefit in older PM women with significant atherosclerotic disease and vulnerable plaques.[20]

STUDIES SUPPORT THE TIMING HYPOTHESIS

The Timing Hypothesis is supported by animal and human studies.[21] When given immediately following ovariectomy, oestradiol (E2) produces anti-inflammatory and cardioprotective effects.[22] However, following prolonged E2 deficiency, its anti-inflammatory effects are abolished. E2 treatment had opposing effects on intima/media ratios in aged (+75%) versus young (−40%) rats. Ovariectomised, aged rats lost the anti-inflammatory and vascular protective responses to exogenous E2 observed in younger, recently ovariectomised animals.[23]

In the Danish study, an open-label, randomised controlled trial, 1006 recently menopausal healthy women received E2 and P4 for 11 years. Compared with controls, HT users had significantly reduced all-cause mortality, heart failure and MI, with no added risk of cancer, VTE or stroke.[24] A recent long-term follow-up WHI study showed reduced breast cancer incidence in CEE-only arm and higher breast cancer incidence in CEE+MPA arm, but without increased mortality.[25]

KEEPS, a randomised, double-blind, placebo-controlled trial, studied CV health impact of two formulations of HT on recently menopausal, healthy women; 727 participants were prescreened for subclinical coronary atherosclerosis via CAC score. All were younger than 53 years with generally healthy CV parameters and natural menopause within 6 months to 3 years. Serial carotid

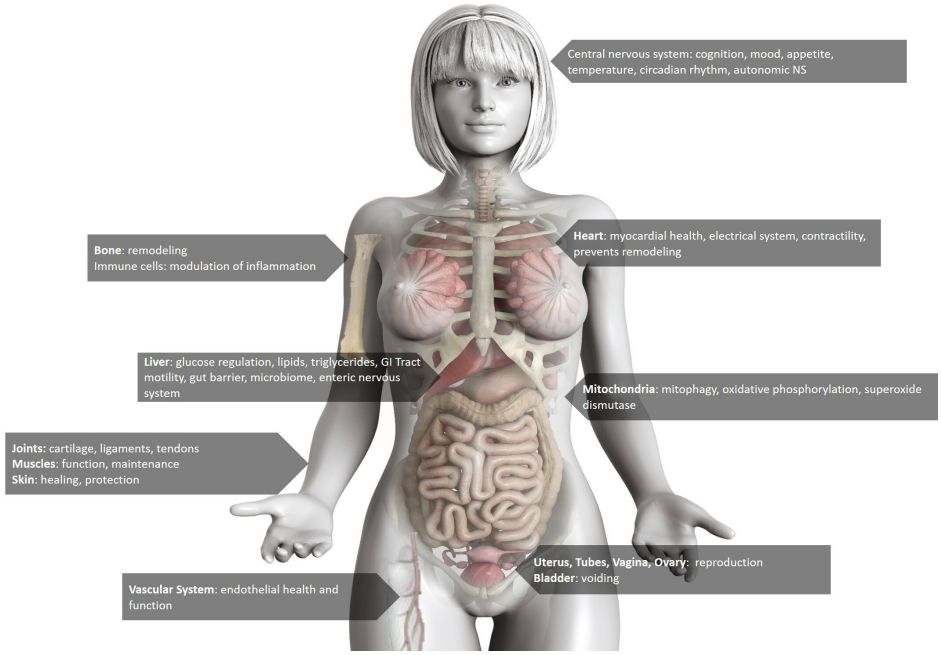

Figure 2 Oestrogen receptors: located throughout the female body. E2 is important for health and function. E2 has three types of receptors distributed throughout the body—alpha, beta and G-protein-coupled oestrogen receptors (GPERs). Through its receptors, E2 modulates the immune system, promotes metabolic homeostasis and sustains cardiovascular health. GI, gastrointestinal; NS, nervous system.

artery intima-media thickness (CIMT) measurements were monitored for HT effects on progression of atherosclerosis. Two regimens used low hormone doses—daily oral 0.45 mg CEE or 50 μg E2 patch, with 200 mg oral micronised progesterone 12 days each month. Matched control groups received placebo.[26] After 4 years, neither hormone regimen affected CIMT; CAC measurements showed no adverse findings; CVD markers and blood pressure showed mixed results—somewhat favourable effects or none. The KEEPS study concluded hormone regimens are safe and can improve quality of life, but no CVD benefits were realised.[2] A possible explanation for the unimpressive KEEPS results was its potentially subtherapeutic oestrogen dose. The average serum level of participants using the E2 patch was only 40 pg/mL, minimally above menopausal levels. Many maintained severely menopausal levels, as low as 9–11 pg/mL. Such E2 levels would not be expected to improve CV health.[2]

ELITE, double-blind and placebo-controlled, evaluated the differential effect of HT on slowing progression of subclinical atherosclerosis according to time-since-menopause. The women subjects, without clinical evidence of CVD or DM, were randomised based on time-since-menopause onset into two groups: <6 years since menopause onset vs 10 or more years since menopause, all given placebo or 1 mg oral oestradiol daily. Women retaining a uterus received 10 days a month of

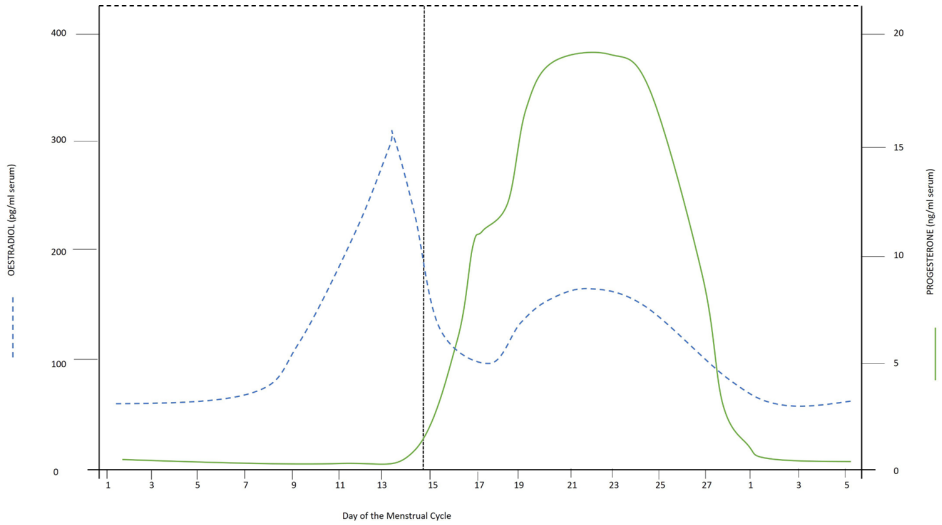

Figure 3 The Rhythms of Oestradiol and Progesterone: Oestradiol is not fixed at a static low level in a healthy reproductive-aged woman, but fluctuates in a rhythmic fashion, with varying serum levels throughout the menstrual cycle. During much of the cycle the level exceeds 100 pg/mL and is generally at least 50 pg/mL. Beneficial effects of hormones relate to physiological serum levels. The 'most efficacious dose' rather than the 'lowest dose' is the goal.

Table 1 Recommendations for hormone therapy

Absorption of E2 from any of the commercial products is variable Levels should be monitored at least annually				
Proposed regimen: transdermal E2 patch	**Proposed regimen: E2 gel product for use on arm/ thigh**	**Proposed regimen: micronised oral P4**	**Conventional regimen: oral E2**	**Conventional regimen: oral CEE**
Apply to abdominal skin twice weekly (every 3.5 days) ► Rotate application site ► Strive for serum E2 level near 100 pg/mL—always above 50 pg/mL ► First month prescribe a 0.05 mg patch ► Check serum E2 level after 1–2 months and increase to 0.075 or 0.1 mg patch, based on E2 level ► Follow serum E2 levels until goal is achieved, then recheck level at least annually. This also applies to gel and patch delivery systems ► Dosing is individualised to patient's goals and symptoms **Benefits of transdermal E2**: enters blood as E2 and no increased risk of thromboembolism	Month 1: apply one pump to arm each morning ► Check serum E2 level second month and increase to two pumps in AM, one per arm, as indicated by E2 level and symptoms ► Strive for serum E2 level close to 100 pg/mL but always above 50 pg/mL E2 gel product use on thigh ► Month 1: apply contents of pack to anterior thigh each morning ► Start with 1 mg dose ► Check serum E2 level second month and modify dose as indicated by E2 level and symptoms ► Strive for serum E2 level close to 100 pg/mL, always above 50 pg/mL. Dosing is individualised to patient's goals and symptoms	200 mg P4 at bedtime for first 14 days of the month If symptomatic and still having some menses, take P4 at bedtime for the 14 days preceding the expected onset of monthly menstruation Cyclic P4 is recommended for all patients, both with and without a uterus Benefits of cyclic 4 vs static P4: cyclic P4 may lower CVD risk; static P4 may increase it	Regimen 1: take 1–2 mg E2 each morning. Adjust dosage based on symptoms. Regimen 2: take 1 mg E2 twice daily—each morning and evening. Adjust dosage based on symptoms. **Why not recommended:** conversion to oestrone by liver and increased risk for thromboembolism	Regimen: dose options of CEE are 0.3 mg, 0.45 mg, 0.625 mg or 1.25 mg (most common dose 0.625), adjusting dosage based on symptoms. **Why not recommended:** conversion of CEE to oestrone and increased risk for thromboembolism Additional commercial product: combination of CEE +bazedoxifene **Why not recommended:** conversion of CEE to oestrone and lack of human-identical P4, which has recognised health benefits

Transdermal E2+oral micronised P4 for primary CVD prevention and overall quality of life and health.

vaginal micronised progesterone gel 4% (45 mg). Primary trial end point was progression of CIMT, measured every 6 months, up to 6 years. The rate of CIMT progression was significantly reduced in the young-aged HT group (average 3.5 years since menopause onset, mean age 55.4 years) versus placebo users. However, those 10+ years since menopause onset (average 14.3

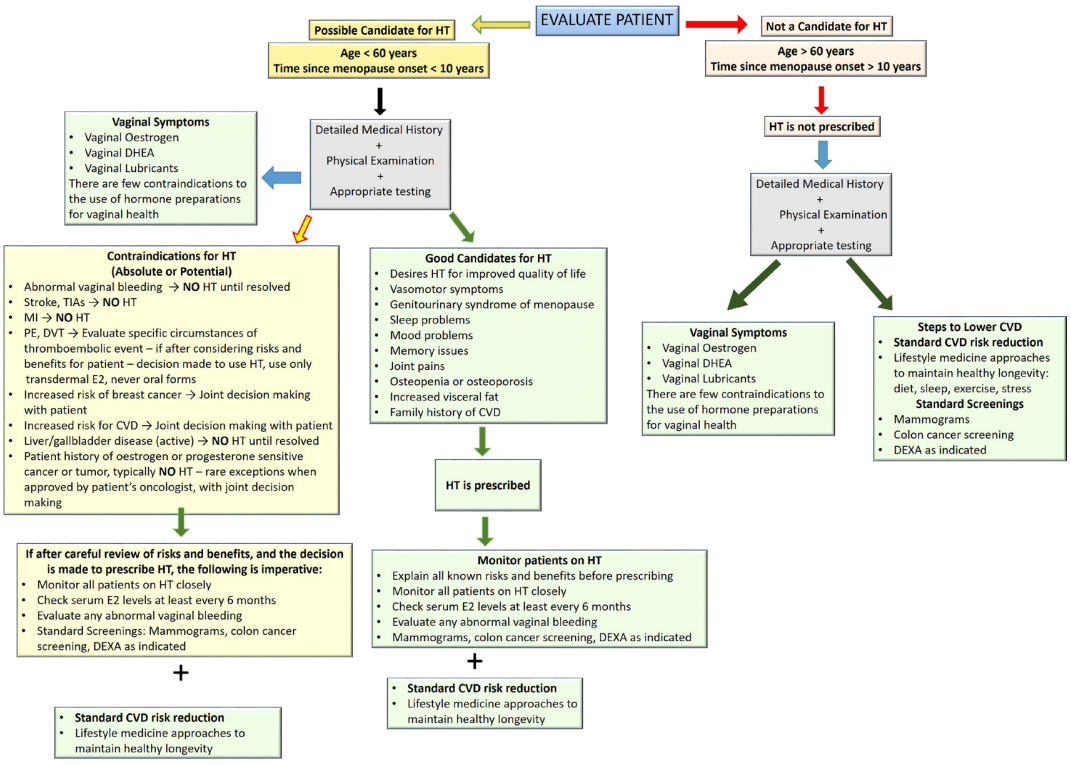

Figure 4 Individualised decision making for the prescriptive use of HT. The decision to prescribe HT to menopausal women must be undertaken only after careful consideration of each woman's unique set of risk factors and of the potential health benefits and contribution to quality of life derived from HT. All HT discussions should include joint decision making. Standard CV risk reduction measures should always be included in the care of PM and perimenopausal women. CV, cardiovascular; CVD, cardiovascular disease; DEXA, dual energy X-ray absorptiometry; DHEA, dehydroepiandrosterone; DVT, deep vein thrombosis; HT, hormone therapy; MI, myocardial infarction; PE, pulmonary embolism; PM, postmenopausal; TIA, transient ischaemic attack.

years since menopause onset, mean age 63.6 years) showed no benefits.[27] The ELITE results supported the Timing Hypothesis—only hormones initiated close to menopause onset reduced CVD progression, late initiation of HT did not.

UNDERSTANDING HORMONES FOR MENOPAUSAL CV HEALTH

Understanding the pros and cons of various HT options facilitates optimal HT use. CEE versus E2 and MPA versus P4 have very different molecular structures and safety-efficacy profiles, producing different physiological effects. E2—the physiological hormone—provides safety benefits compared with CEE. CEE undergoes a first pass through the liver, increasing thrombotic risk[w2] and hepatic transformation to oestrone (E1), providing predominantly E1, rather than the preferred E2.

Oestrogens comprise a class of hormones. Human female oestrogens include E1, E2 and oestriol (E3), each with varied receptor binding capabilities/affinities, and biologically active metabolites. E2 is the dominant oestrogen of reproductive-aged women; E1 dominates during menopause, and E3 dominates in pregnancy. Oestrogen receptors (ER) are ER alpha, ER beta and G-protein-coupled oestrogen receptor (GPER), a membrane receptor. ERs interact in complex ways, have varying functions[w3] and are located throughout the female body (figure 2). E2 is a non-selective ER agonist, binds to all ER receptors, maintains vascular health, reduces oxidative stress and prevents oxidation of low-density lipoproteins.[28] E2 diminishes vascular inflammation, the driver of CVD. Physiological levels of E2 maintain the functionality of endothelial nitric oxide synthase, promoting vascular endothelial health, while E2 deficiency results in oxidative stress and endothelial damage.[29] E2 metabolites also confer CV benefits; 2-methoxyoestradiol induces favourable CV effects, including blocking abnormal cardiac remodelling and downregulating angiotensin-1 receptors.[30]

CEE and E2 produce overlapping CV benefits, but CEE also produces uniquely negative effects not seen with transdermal E2. CEE comprises at least 10 unique oestrogens, several androgens, progestins and other substances with unclear vascular and procoagulatory effects. Oral CEE and oral E2 create a hormonal profile never naturally found in human females.[31] Oral CEE and oral E2 enter the serum predominantly as E1, not E2. E1 preferentially binds to ER alpha, creating an imbalance of receptor binding within the CV system. E2 levels minimally rise with CEE, but to subnormal levels. CEE's oestrogen profile produces unpredictable and potentially negative effects on oestrogen signalling pathways (figure 3).[32]

Progestins are a class of hormones including human-identical P4, and MPA. HERS and WHI used MPA, which unlike P4, is both an agonist and antagonist to P4 receptors, uniquely binding to androgenic and glucocorticoid receptors.[33] MPA abolishes beneficial oestrogen effects on vascular function, alters lipids and triggers coronary artery vasospasm.[34] CEE+MPA induce higher rates of blood clots compared with CEE, while P4 confers CV benefits, inhibiting atherosclerotic plaque formation and downregulating ERs.[35]

A large meta-analysis further validates the use of HT to support cardiometabolic health, documenting a 30% reduced incidence of DM versus placebo.[36] Additionally, HT is associated with lower all-cause mortality. A Cochrane Systematic Review stated, 'Those who started hormone therapy less than 10 years after the menopause had lower mortality'.[14] A WHI review of all-cause mortality and HT use concurred and documented an HR of 0.69 for women aged 50–59 years.[37] Data also suggest long-term safety of HT,[38] while abrupt discontinuation may predispose to potentially fatal CHD events.[39] Of note, oral contraceptives contain ethinyl oestradiol and various progestins, are thrombophilic[w4] and predispose to hypertension.[40] Oral contraceptives are not recommended as HT in PM women and must be used cautiously, with individualised risk management, during the menopausal transition.

PROPOSED HORMONE PRESCRIPTION FOR CV HEALTH

Prescribing human-identical hormones for CVD primary prevention in menopause is not currently recommended by any CV society, but we believe it should now be considered and discussed, based on scientific data and human studies (table 1).[41–44 w4] All discussions concerning HT initiation should be individualised, reviewing each woman's risk for CVD, breast cancer, dementia, mood disorders and osteoporosis. Medically indicated standard CVD risk reduction must always be included (figure 4). Following these discussions, if it is determined that HT will be prescribed, waiting to reach the arbitrary definition of menopause '12 months following the last menstruation' is not necessary.

Numerous studies document beneficial cardiometabolic effects of endogenous E2 and P4 during the reproductive years, effects related to hormonal rhythms and serum levels. The concept of 'the smallest dose' solely derived from misapplied WHI results. We propose abandoning that approach, instead advocating for the 'most efficacious dose'. Animal models of atherosclerosis demonstrating that physiological oestrogen levels attenuate atherosclerosis lesion development in newly menopausal females support this modification.[45 46]

Ultimately, data may show that restoring physiological hormonal rhythms best optimise cardiometabolic health. Pending studies confirming that hypothesis, we advocate applying current knowledge of CV effects of hormonal levels to guide our proposed recommendations.

Physiological serum levels of E2 attenuate oxidative stress[47] and correlate with elevated glutathione and glutathione peroxidase activity.[48] Lower E2 is associated with reduced serum 25 OH vitamin D levels, impacting immune system regulation.[43] In one publication, PM women with higher levels of E2 had reduced CAC scores, independent of age and other CHD risk factors.[44]

The Danish Sex Hormone Register Study used the national registry to assess risk of MI with HT use, reviewing duration, doses, regimens and routes of administration. In all age groups, highest risk of MI occurred with continuous P4/oestrogen regimen, with no increased risk when cyclic combined therapy was used,[33] supporting the premise that cyclic P4 is superior for CV health than daily, continuous P4.

After considering the entirety of data concerning human-identical hormones and CV health, we recommend using continuous transdermal E2, as a gel, cream or patch, dosed to achieve a serum level of approximately 100 pg/mL (at least 50 pg/mL), to support CV and menopausal health—improving quality of life, mood disorders, sleep quality, bone health, hot flashes, night sweats and urogenital health (online supplemental figure 1).[46] Serum E2 levels should be measured to ensure proper dosing. We also recommend oral P4, dosed at 200 mg at bedtime for the first 14 days each month, approximating menstrual cycle rhythms. Vaginal bleeding may occur mid-month, following 2 weeks of P4 dosing, reflecting a physiological hormonal milieu with regular shedding of the endometrial lining. We recognise that not all women will prefer or do best on this regimen, therefore,

Table 2 Hormone replacement studies

Trial name	Study design	Result
Heart and Oestrogen/Progestin Replacement Study	*Design* Randomised, double-blind placebo controlled trial *Cohort* 2763 PM women with confirmed CAD average 66.7 years *Formulation* CEE 0.625 mg+MPA 2.5 mg daily	No protection for secondary protection of CVD
Women's Health Initiative (WHI): CEE+MPA ARM	*Design* Randomised, double-blind placebo controlled trial *Cohort* 16 608 PM women with uterus *Formulation* CEE 0.625 mg+MPA 2.5 mg daily	*Initial result conclusions*: increased risk for CHD and stroke *Counter interpretation*: design of study was underpowered to confirm impact on CVD prevention in newly menopausal women
WHI: CEE alone ARM	*Design* Randomised, double-blind placebo controlled trial *Cohort* 10 739 postmenopausal women without uterus *Formulation* CEE 0.625 mg daily	*Initial result conclusions*: no benefit for primary risk prevention for CHD plus an increased incidence of stroke *Counter interpretation*: reduced rates of MI in women aged <60 years at the start of the study
2017 Cochrane Collaboration Systemic Review	► The review included 23 randomised double-blind studies, involving 43 627 women ► About 30% of women from this review were 50–59 years of age ► Studied the effects of using HT for 1 year or more	► HT for primary or secondary prevention of CVD or for preservation of cognitive function was not indicated ► Analysis of these data of younger women showed that at the end of 2 years, only venous thromboembolism incidence increased, whereas no other risk was noted
The Danish Osteoporosis Prevention Study	*Design* Partly randomised study that included normal and healthy postmenopausal women. Study was stopped after average of 11 years *Cohort* 1006 healthy postmenopausal women *Formulation* Oral E2: 2 mg/day if no uterus Oral E2: 2 mg/day or 1 mg/day (various days)+oral norethisterone for 10 days if women had a uterus	► HT has beneficial effects on CAD ► HT initiated immediately following menopause (up to 7 months) significantly reduced mortality due to CAD ► HT reduced incidence of HF and MI ► No increase in thromboembolic events, strokes or cancer
The Kronos Early Estrogen Study	*Design* Randomised, double-blind placebo controlled multicentric trial *Cohort* 727 postmenopausal women with average age 50 years all of whom were within 3 years of menopause. Assessed the progression of CIMT and atherosclerosis by using US CIMT and CAC score *Formulation* CEE 0.45 mg/day+oral P4 200 mg for 12 days/month OR E2 patch 0.05 mg+oral P4 200 mg for 12 days/month	► HT had no statistical impact on CIMT or atherosclerosis ► HT was safe and can improve quality of life
Early versus Late Intervention Trial	*Design* Randomised double-blind placebo controlled trial *Cohort—two groups* <6 years postmenopause >10 years postmenopause Evaluated CIMT every 6 months for up to 6 years *Formulation* 1 mg oral E2+vaginal progesterone	► HT prescribed to the younger cohort showed less CIMT progression compared with matched placebo group; older cohort did not differ from matched placebo group ► Supports the Timing Hypothesis

CAC, coronary artery calcium; CAD, coronary artery disease; CEE, conjugated equine oestrogens; CHD, coronary heart disease; CIMT, coronary intima media thickness; CVD, cardiovascular disease; HF, heart failure; HT, hormone replacement therapy; MI, myocardial infarction; US, ultrasound.

individualisation is recommended. Oral oestrogen regimens are included for completeness but are not recommended by us (table 2).

CONCLUSIONS

- Data support endogenous E2 and P4 as cardioprotective—numerous animal and observational studies reveal CV beneficial effects.
- Discordance of WHI/HERS and data on hormone benefits is likely explained by the (1) Timing Hypothesis, (2) negative CV effects of CEE+MPA, (3) pre-existing CVD and older age of women in WHI and HERS.
- Transdermal E2 with oral P4, begun early in menopause, appears to support long-term CV health.
- Recommendations for the 'lowest dose' of HT derived from the negative data on CEE and MPA. HERS and WHI data should not be applied to human-identical transdermal E2 and oral P4.
- E2 effects are dose related. Low E2 doses, resulting in serum levels near typical PM levels, are less likely to provide benefits compared with physiological dosing.
- Women have high rates of CVD after menopause. Human-identical hormones initiated early in menopause appear safe to be continued indefinitely, under close supervision,

Table 3 Most organisations and societies now recognise the safety and quality of life benefits of HT, but do not endorse HT for primary prevention of CVD

Acknowledges or endorses HT for:	Current article	USPSTF	ES	ACC	AACE	AHA	ACOG	NAMS	IMS	EMAS	UKNHS
Treatment of menopausal symptoms	√	√	√	√	√	√	√	√	√	√	√
HT has different potential risks and benefits based on age and time since menopause—the Timing Hypothesis	√		√	√	√		√	√	√	√	√
Transdermal E2 is safer than oral E2 or CEE concerning risk of thromboembolic events	√		√	√	√		√	√	√	√	√
Recommends an individualised approach to HT based on clinical factors and patient preference	√		√	√	√	√	√	√	√	√	√
HT may have beneficial effects in the primary prevention of CVD in appropriate menopausal women	✓								✓	✓	

We believe that available data support a new approach to the CV care of PM women.
AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACOG, American College of Obstetricians and Gynecologists; AHA, American Heart Association; CEE, conjugated equine oestrogen; CV, cardiovascular; CVD, cardiovascular disease; EMAS, European Menopause and Andropause Society; ES, Endocrine Society; HT, hormone therapy; IMS, International Menopause Society; NAMS, North American menopause Society; PM, postmenopausal; UKNHS, United Kingdom National Health Service; USPSTF, United States Preventive Services Taskforce.

offering PM women greater potential for long-term CV health and improved quality of life.

- Individualised decision-making is a key component of all HT conversations; standard CVD risk reduction must be included in all therapeutic plans.

OUR RECOMMENDATIONS AND PROPOSED FUTURE DIRECTIONS

Medical societies, including the American College of Cardiology (ACC),[49] American Heart Association and European Society of Cardiology, modified their HT positions, shifting to individualised approaches based on CVD risk assessment and patient-specific medical situations, recommending HT initiation within 10 years of menopause or prior to age 60 years. The United Kingdom National Health Service website states, '… recent evidence says … risks of HT are small and … usually outweighed by the benefits'. ACC acknowledges reduced risk with transdermal E2 over oral hormonal preparations. Recommendations for 'the lowest dose for the shortest time' remains, without an official HT recommendation for cardioprotection. We feel these recommendations should be reconsidered (table 3).

The North American Menopause Society states that data do not support routine discontinuation of HT at age 60–65 years, with continued use based on assessing quality of life, persistent vasomotor symptoms or desire to prevent bone loss and fracture. Women using hormones long-term would continue with appropriate surveillance measures.[38] We concur with this assessment, but go further.

Existing data generally support that PM HT is safe and beneficial. Approximately 1.3 million American women enter menopause every year. Based on current knowledge, E2+P4 use should be discussed with appropriately selected women to treat symptoms, strengthen bones, improve quality of life and to preserve CV health through their PM years, augmenting standard CVD risk reduction measures.

Additional references can be found in online supplemental file 1.

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Estrone (Oestrone)

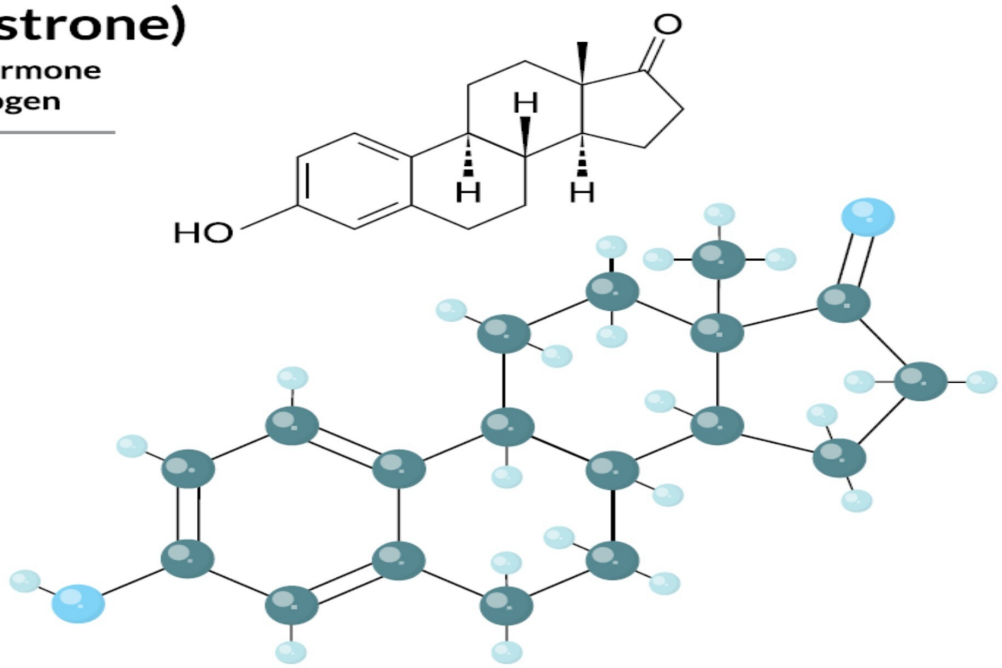
Minor Female Sex Hormone Steroid, a Weak Estrogen

VECTOR OBJECTS
EPS 10

Molecular Formula of Estrone:

$C_{18}H_{22}O_2$

Structural Formula of Estrone:



C Carbon
O Oxygen
H Hydrogen

Estrogen

Estradiol, Oestradiol

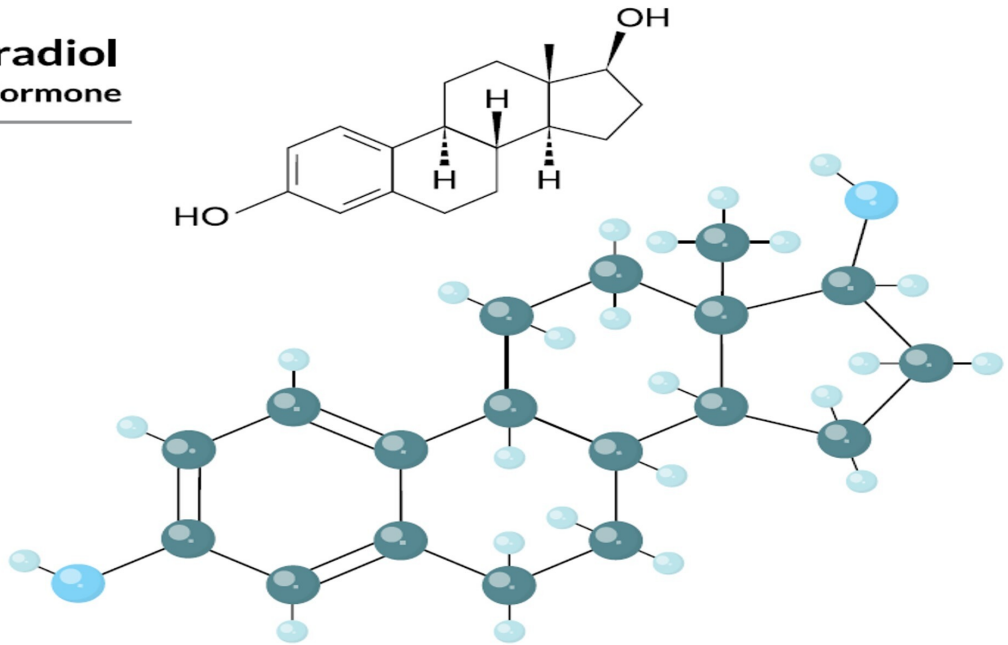
Female Steroid Sex Hormone

VECTOR OBJECTS
EPS 10

Molecular Formula of Estrogen/Estradiol/Oestradiol:

$C_{18}H_{24}O_2$

Structural Formula of Estrogen/Estradiol/Oestradiol:



C Carbon
O Oxygen
H Hydrogen