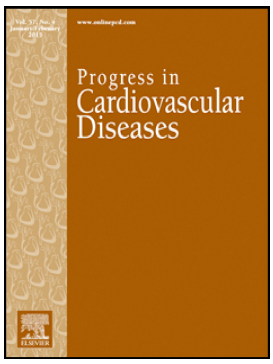

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Estrogen and Cardiovascular Disease

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Abstract

A large body of scientific research accumulated over the past twenty years documents the cardiovascular (CV) benefits of estradiol (E2) and progesterone (P4) in reproductive aged women. In contrast, accelerated development of CV disease (CVD) occurs in the absence of ovarian produced E2 and P4. Hormone replacement therapy (HRT) with E2 and P4 has been shown to cause no harm to younger menopausal women. This robust scientific data supports a reconsideration of the prescriptive use of E2 and P4 as preventative therapeutics for the reduction of CVD, even without additional large-scale studies of the magnitude of the Women's Health Initiative (WHI). With the current expanded understanding of the critical modulatory role played by E2 on a multitude of systems and enzymes impacting CVD onset, initiation of HRT shortly after cessation of ovarian function, known as the "Timing Hypothesis", should be considered to delay CVD in recently postmenopausal women.

Keywords: estrogen, women, hormone replacement therapy, cardiovascular disease, menopause

Abbreviations:

CEE – Conjugated Equine Estrogens

CHD – Coronary Heart Disease

CIMT - Carotid Intima Media Thickness

CV – Cardiovascular

CVD – Cardiovascular Disease

E2 – Estradiol

ER – Estrogen Receptor

ESRRs – Estrogen-related Receptors

GPERS – G-protein Coupled Estrogen Receptors

HF – Heart Failure

HRT – Hormone Replacement Therapy

IMT – Intima Media Thickness

LDL – Low Density Lipoprotein

MI – Myocardial Infarction

MPA - Medroxyprogesterone Acetate

P4 – Progesterone

PM – Postmenopausal

QoL – Quality of Life

VTE – Venous Thromboembolic

WHI - Women's Health Initiative

Introduction

Despite the high incidence of cardiovascular (CV) complications experienced by a large proportion of the aging female population, major CV societies do not currently support estradiol (E2) and progesterone (P4) use for the prevention or treatment of CV disease (CVD). There is, however, a large body of research confirming that a) loss of ovarian production of E2 and P4 is associated with detrimental vascular and myocardial changes[1] and b) postmenopausal (PM) use of human bioidentical transdermal E2, as a patch or gel, and of oral P4, is safe (Figure 1).[2]

Prior to the Women's Health Initiative (WHI), the results of which were published over twenty years ago, HRT was promoted by physicians, but support for HRT plummeted after the WHI results were publicized widely. Fortunately, its conclusions were reassessed and the data is now recognized as showing significant benefits to women in their 50's.[3] Additionally, it is now more widely recognized that the results of the WHI cannot be applied to hormone formulations other than those used – oral conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA).[3-5] An additional problem with the WHI was its inclusion of a preponderance of study subjects who were many years postmenopausal, including many with pre-existing medical conditions. [6-8] Despite current understandings of the flaws of the WHI and the robust data on the many important functions of E2 supporting CV health, little interest exists for the prescriptive use of safer hormonal formulations and delivery modalities for use as preventative medicine in cardiology. And the "Timing Hypothesis (initiation of HRT is beneficial only when begun within 10 years of last menstrual period)," though now

widely acknowledged, has only resulted in the half-hearted acceptance of short term, low dose HRT solely for the amelioration of hot flashes and night sweats.[9]

In the years since the WHI, a small number of randomized, prospective, placebo-controlled trials were conducted, and the results published. Each study adhered to the prevailing opinion that the smallest possible dose of estrogen was best. Fortunately, different forms of estrogen and progestins from those used in the WHI were included in subsequent studies, but transdermal E2 and oral micronized progesterone were not consistently the forms of hormones used. It is generally recognized now that those are the preferred forms of the hormones to be used for HRT.[10] The use of various types of hormones and delivery modalities, the smaller numbers of study subjects, the shorter duration of the studies, as well as of dosing regimens used which resulted in low serum levels of E2, may all have contributed to the study outcomes that have not demonstrated CV benefits with the use of HRT.[11] Although not clearly showing large CV benefits, the data from the major subsequent studies - the Kronos Early Estrogen Prevention Study (KEEPS) and Early Versus Late Intervention Trial with Estradiol (ELITE) studies, both showed no harm from HRT, with improvement in quality of life (QoL), and of vascular benefits for younger, recently PM women in the ELITE data, which similar to the WHI, was supportive of the "Timing Hypothesis." [12, 13]

Many observational studies have consistently shown safety and health benefits of menopausal hormone use.[14] A pervasive fear of HRT remains, and many patients and their physicians refrain from using HRT, and when utilized, the prevalent use is for symptom reduction and not as part of a strategy for achieving healthy longevity and CV

optimization, with most users choosing the smallest possible doses of E2 for the shortest possible time, and avoidance of cyclical P4 dosing.[15]

This review acknowledges that there are no large, prospective, placebo-controlled clinical trials utilizing physiologic and rhythmic dosing of human bioidentical hormones, designed to evaluate CVD outcomes. But as mortality and morbidity among women from CVD events remains high, practicing CVD specialists should consider the safe use of HRT, prescribing physiological doses of transdermal E2 and oral P4, as a modality to maintain a healthy, highly functional CV system for the promotion of healthy longevity. This article provides the framework to utilize human, bioidentical HRT as an integral component of preventive cardiology, including a general protocol for the prescriptive use of HRT for women (Table 1).

Overview of HRT Studies in PM Women

Many reviews of HRT studies in PM women have been published and generally conclude that more placebo-controlled prospective double-blinded trials are needed.[16] Such studies are not likely to happen soon because E2 and P4 are available as generic drugs, thus pharmaceutical companies are not incentivized to do large randomized trials.[17] Historically, over 50 observational studies have shown CVD benefits, documenting lowered incidence of atherosclerosis and CVD events.[18] These positive observational findings stimulated an interest and new studies were planned, such as the WHI, to assess HRT use for primary CVD prevention. The WHI utilized oral CEE combined with MPA. In women over age 60, the study outcomes involving CVD events were unfavorable. However, reanalysis of the WHI data revealed that when the

hormones were prescribed within 10 years PM, coronary heart disease (CHD) risk was reduced by 12% in the women on combined CEE and MPA, and by 52% in those taking only the CEE. All-cause mortality was lowered in both groups by 30%. Reanalysis of the breast cancer risk showed lowered risk in the CEE-only treated women and a higher risk only in those women receiving MPA + CEE therapy.[19]

A smaller randomized, double-blind, placebo-controlled trial done during the same time as WHI did not use CEE, but instead used 17 beta E2 (the dominant estrogen produced by human ovaries) orally at a dose of 1 mg/day, unopposed by any progestational agent. The study included 222 PM women aged 45 or older without preexisting CVD and with a low-density lipoprotein (LDL) cholesterol of at least 130 mg/dl. The rate of change in intima media thickness (IMT) of the right distal common carotid artery wall was followed for 2 years, using ultrasound imaging. The study found that the average rate of progression of subclinical atherosclerosis was lower in those taking the unopposed E2 than in the group given a placebo.[20] Additionally, the women on E2 had lowered fasting glucose, insulin and HgbA1C, with improved insulin sensitivity compared with the placebo group.

Another study begun at the time of the WHI was the Danish Osteoporosis Prevention Study, which was a large open-label study of women 45-56 years given triphasic E2 and the progestin norethisterone acetate, 2 mg E2 orally, or no hormones. The women given hormones had significantly reduced risk of all-cause mortality, heart failure (HF), and myocardial infarction (MI), with no added risk of cancer, venous thromboembolic (VTE) events, or stroke. The study demonstrated over a 50% reduction

in the risk of a CVD event in the women receiving HRT, compared to those without HRT.[14]

Other placebo-controlled double-blind prospective studies on HRT in PM women, done in the following years, showed no harm with improved QoL, and vascular benefits in the younger women. The KEEPS study included younger, recently menopausal women under 53 years. Two matched groups were created. The treated group was given a low dose of estrogen, either an E2 patch of .05 mg/day, or CEE 0.45 mg/day, along with oral micronized P4 200 mg given for 12 days of each month. Although no vascular benefits were demonstrated after 4 years, the investigators concluded that the HRT led to an improved QoL without harm.[21] When the blood levels of E2 in the treated group were measured, they were found to be low, generally below 50 pg/ml.[11]

Another important study, ELITE, had 2 arms, 1 evaluating women near menopause (<6 years, mean age 55.4 years) and another consisting of women who became menopausal ≥10 years prior to study enrollment (mean age 63.6 years). The treated groups received 1 mg oral E2 daily and those women with a uterus also received 10 days per month of 45 mg of vaginal micronized P4 gel. The carotid intima media thickness (CIMT) was measured every 6 months, up to 6 years. The rate of CIMT progression was significantly reduced in the younger group receiving HRT compared with the placebo users. The older treated female group did not show any vascular benefits or harms. The conclusion was consistent with the “Timing Hypothesis” – hormones were beneficial to health when prescribed to women within 10 years PM and under 60 years of age, whereas HRT in older women did not show benefits.[13]

The many observational studies that have been reported since the termination of the WHI in 2002 repeatedly demonstrated the safety of transdermal E2 and P4 in PM women. Yet, the use of HRT for any purpose other than suppression of night sweats and hot flashes has not increased and HRT is still generally not recommended by guidelines.[22, 23]

HRT in PM Women for Prevention of CVD Revisited

Re-evaluations and reviews of HRT for PM women have been published, but many simply evaluated the status of women many years after they discontinued HRT, consider almost exclusively WHI data, or are meta-analyses of published HRT studies which are heavily weighted with WHI results so that these meta-analyses reflect WHI study findings.[23] Guidelines for the prescriptive use of HRT for PM women focus on data derived entirely or predominantly from the WHI, the results of which should not be applied to alternative hormones and regimes.[24] Data derived from the use of static dosing of CEE and MPA cannot be assumed applicable to the use of other hormone products or dosing regimens.[25]

An understanding of the myriad effects of E2 and P4 throughout the female body is essential if one is to appreciate fully their potential CV benefits.[26, 27] In a reproductive aged woman, E2 and P4 have synergistic effects systemically, a consequence of both their levels and rhythms.[28] There is a complex interplay involving the up and down regulation of estrogen and P4 receptors, as well as the receptors of other hormones. Additionally, there are genes that are up-regulated as well by the peaks and troughs of

the hormones, including tumor suppressor genes.[29] It is beyond the scope of this paper to detail all the myriad effects that occur throughout the body of a woman during a normal menstrual cycle, a consequence of the varying levels of ovarian hormones,[30, 31] but some fundamentals are requisite if one is to appreciate the potential for widespread beneficial CV effects of HRT when prescribed with optimal forms, dosages, and schedules (Table 2).

To fully appreciate the issues involving HRT, one first needs to understand that "estrogen" is a family of hormones, and within an adult human female there are 3 estrogens. These estrogens are designated by the letter E and a number, as well as a name. The estrogen made by ovaries is estradiol, E2, which is converted interchangeably as needed into E1, estrone. E3, estriol, is also made in the female from E2, as needed, and is also the dominant estrogen produced by the placenta during pregnancy. E3 cannot be converted back to E2 or E1. All 3 of these estrogens are essential for optimal health, and the healthy body of a reproductive-aged woman will produce E2 appropriately to create a normal menstrual cycle and convert the E2 into the other two estrogens as needed by circumstances. Each of these estrogens binds differently to the varying estrogen receptors of the body, and differing amounts of the various types of receptors exist in multiple sites and organs of the body. E1 predominantly binds to the alpha receptors. E3 binds predominantly to beta receptors. Only E2 binds in a balanced manner to all estrogen receptors, as needed, including G-protein coupled estrogen receptors (GPERS) located on the cell membranes.[32, 33] GPER1 knockout mice had increased cardiac oxidative stress and injury and increased expression of oxidative stress-related genes.[34] Studies show that estrogens via GPER

modulate function in the nervous, immune, musculoskeletal, and CV systems, adipocytes, liver, pancreas, and kidney.[35] Nuclear estrogen receptor (ER) alpha provides a protective effect in the heart, liver, pancreas, skeletal muscle, and white and brown adipose tissue, whereas its membrane receptors regulate various endothelial/vascular effects of E2 (Figure 2).[36, 37]

The estrogens present in CEE, used in the WHI and many other studies, are a blend of conjugated estrogens from the urine of pregnant horses (Premarin is an acronym for pregnant mare's urine). CEE enters the blood of the women who take them as equine (native to horses) estrogens.[38] This unique blend of orally administered estrogens increases the risk of blood clotting in women compared with women not taking them or using transdermal E2.[39] As E1 binds predominantly just to the alpha receptor, the effects on the CV system and on other organ systems differ from those of transdermal E2 and of endogenous E2.[40, 41] Conclusions drawn from the use of CEE cannot be applied to the use of transdermal E2, as they are distinctly different hormonal products.

Oral E2 was the estrogen used in some studies. Unlike transdermal E2, which enters the bloodstream unaltered, E2 taken orally is converted to E1 by the liver and enters the bloodstream in this form. E1 increases blood clotting two-fold compared with transdermal E2, which does not increase clotting risk.[42]

MPA is distinctly different from human bioidentical P4, and there is a significant body of research showing the myriad differences, clarifying the benefits of P4 on many organ systems, including the neurological systems and the CV system. MPA, unlike P4,

is detrimental to the health of neurons, lowering antioxidant defense, blocking clearance of lipid peroxides, and abolishing E2-induced mitochondrial respiration in cultures of glia and hippocampal neurons, leading to a decline in glycolytic and oxidative phosphorylation protein and activity. Many other differences exist between P4 and MPA. P4 lowers the rise in intracellular calcium levels due to glutamate exposure, among a wide range of neuroprotective effects not replicated by MPA. MPA also negates many of the beneficial effects of E2 on coronary arteries, blunting vascular dilatation, increasing progression of atherosclerosis, facilitating LDL uptake into plaque, increasing thrombotic potential in plaque, and increasing insulin resistance and hyperglycemia.[43, 44] Essentially, combining transdermal E2 with P4 enhances estrogen's protective effects against coronary vasospasm, which is eliminated when MPA replaces P4.[45]

The WHI conclusions were widely generalized to human bioidentical hormone products and physiological regimens; however, E2 and P4 are different molecules differentially impacting PM women. Though well intentioned, the few subsequent trials were unable to demonstrate the potential benefits of transdermal E2 and oral P4 regimens. The KEEPS trial incorporated CEE in one trial arm, and utilized transdermal E2 patches in the other, but at too low of a dose to consistently raise serum E2 levels above 50pg/ml.[11] The ELITE trial incorporated a small dose of oral E2, not transdermal E2.[46] Interest in human bioidentical hormones has now largely waned[47] and women must deal with the effects of hormone deprivation either in silence or with procedures and non-hormonal pharmaceuticals used to ameliorate the effects of loss of E2 and P4. Proactive preventive care using human bioidentical hormones, initiated in early PM, to reduce or prevent the negative sequela of menopause, including CVD, is not currently

recommended, but should be discussed as an option with appropriately selected candidates.[48]

Effects of E2 in Females

Although there are no long-term prospective studies on the use of human bioidentical hormones in menopausal women, there is an abundance of research into the effects of E2 and P4 and the consequences to the CV system in their absence.[49] When taken in totality, the evidence clearly shows that these hormones confer benefits to global female health and specifically to the heart and vascular structures. A look at hormones during pregnancy helps one recognize why E2 and P4 receptors are found throughout the female body.

Successful reproduction requires an optimally functioning CV system due to the significant physiological changes of pregnancy. Inadequate hemodynamic adaptations that do not ensure the increased fetal and maternal metabolic demands are met, result in increased maternal and fetal mortality and morbidity. Inadequate uteroplacental circulation can result in preeclampsia and intrauterine growth restriction or fetal demise. Additionally, pregnancy is a significant “stress test” for the mother, and when pregnancy occurs in a metabolically unhealthy woman, the risk is significant, underlying the statistics that CVD is the leading cause of maternal mortality in North America. Published descriptions of the specifics of the hemodynamic changes of pregnancy make clear the reasons for there being a large role played by female hormones on the CV system to optimize function.[50, 51] Loss of these vital hormones with menopause results in deleterious effects.[52]

Mitochondria are essential for optimal cardiometabolic health, which can only be achieved in an estrogenized female body.[53] E2 plays a vital role via ER alpha to increase sirtuin transcription.[54, 55] SIRT3 in mitochondria reduces reactive oxygen species by deacetylation of manganese superoxide dismutase, also leading to a sequence of events required for the transcription of antioxidant factors and manganese superoxide dismutase.[56] Additional benefits accrue to the CV system from estrogen-related receptors (ESRRs), receptors requiring the presence of estrogen but utilizing a ligand that is not estrogen. ESRRs significantly influence metabolic functions and mitochondria (Figure 3).[57]

E2 is involved in a multitude of functions and reactions that have a great impact on CV status, both directly and indirectly. E2 has a significant role in regulating cholesterol production, modulation of hepatic LDL receptors, enabling high-density lipoprotein function, and protecting against its oxidation.[58] E2 is instrumental in optimizing arterial health[59] through the actions of endothelial nitric oxide synthase,[60] modulating the renin angiotensin aldosterone system,[61] regulating peptides such as endothelin-1 and thrombin,[62] as well as enzymes such as prostacyclin cyclooxygenase and prostacyclin synthase.[63] E2 helps to maintain a healthy gut microbiome and an intact gut epithelial barrier and is important for appetite regulation and energy production via modulation of adipokines such as leptin and adiponectin.[64] E2 plays a significant role in keeping the master clock in the hypothalamus regulated to prevent its drifting and the development of circadian rhythm dysfunction,[65] which is associated with metabolic dysfunction. E2 plays a key role in balancing the autonomic nervous system and its neurotransmitters,[66] which impact cardiac electrical conduction and function. The

global heart rate variability of postmenopausal women may increase after E2 therapy. Even E2 metabolites such as 2 methoxy estradiol have key roles,[67] with unique receptors for essential energy production in the myocardium (Table 3 and Table 4).

Conclusions

Although there is a deficiency of prospective, placebo-controlled studies on the use of human bioidentical HRT in PM women, this should not dissuade general clinicians and specialists in CVD from recommending HRT at least to the majority of their young, recently PM women patients, for maintaining ideal long-term CV health. The robust safety data of the KEEPS and ELITE trials, as well as many observational studies, combined with the limited but definitive vascular benefits as shown in the ELITE study, and in many rodent and primate studies, in conjunction with the abundance of basic scientific data outlining the mechanisms by which E2 protects CV structures, justifies the recommendation to provide young PM women with physiologic, rhythmic HRT. The goal is to replicate the hormonal levels and rhythms of a healthy reproductive aged woman. A proactive, rather than a reactive, approach to CV wellbeing is the desired therapeutic strategy. With prevention of CVD as a top priority, HRT is a safe and potentially highly beneficial therapeutic modality for appropriately selected women. Large-scale studies using better HRT preparations, would be ideal, but these are not likely to be on the horizon anytime soon. Therefore, clinicians should consider the preponderance of evidence already available for recently PM women, based on the Timing Hypothesis, and at the same time weigh the potential benefits vs risks of HRT for other PM women, using the superior, safer HRT preparations currently available.

Figure and Table Legend

Figure 1

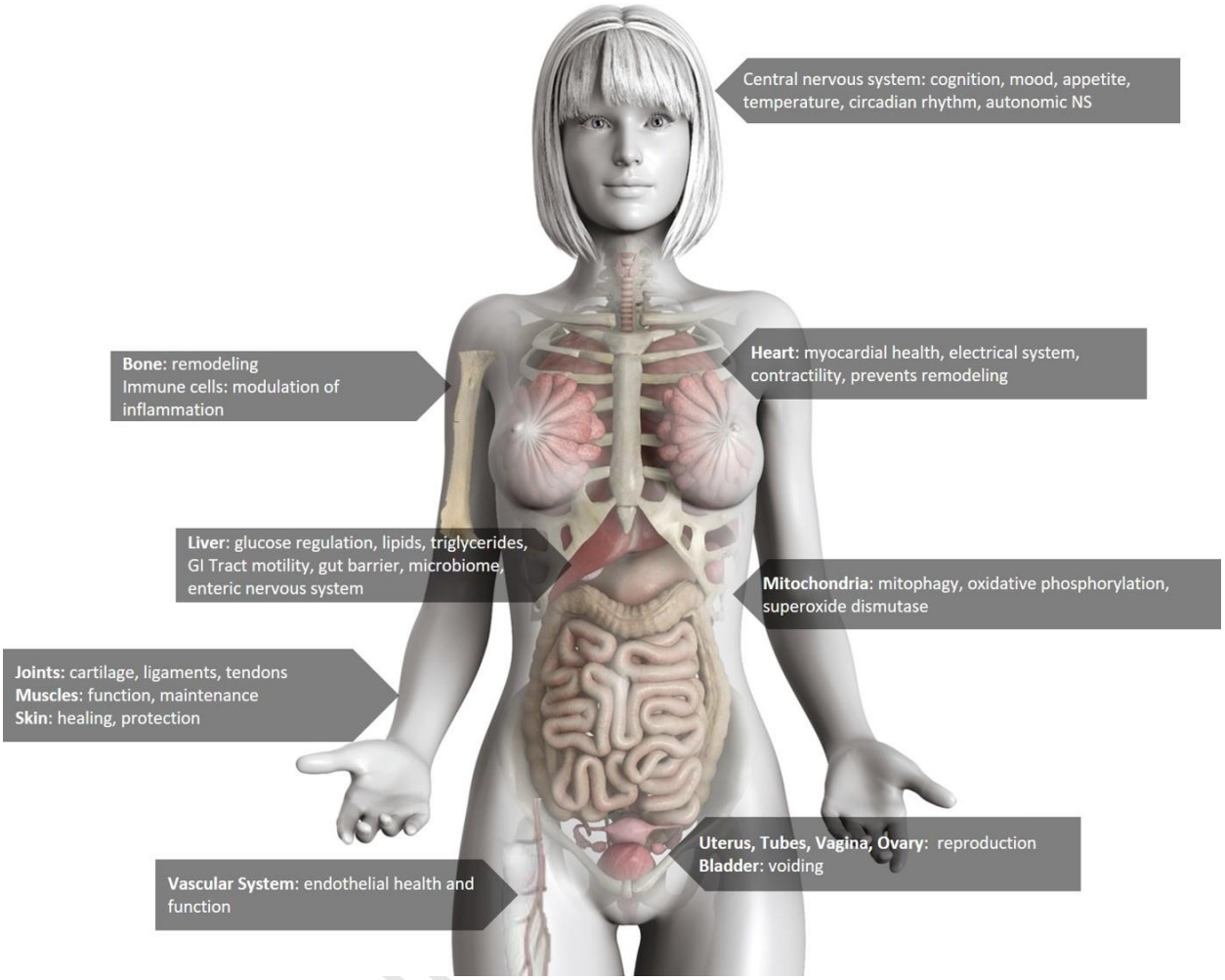
Central nervous system: cognition, mood, appetite, temperature, circadian rhythm, autonomic NS
Bone: remodeling
Immune cells: modulation of inflammation
Heart: myocardial health, electrical system, contractility, prevents remodeling
Liver: glucose regulation, lipids, triglycerides, GI Tract motility, gut barrier, microbiome, enteric nervous system
Mitochondria: mitophagy, oxidative phosphorylation, superoxide dismutase
Joints: cartilage, ligaments, tendons
Muscles: function, maintenance
Skin: healing, protection
Uterus, Tubes, Vagina, Ovary: reproduction
Bladder: voiding
Vascular System: endothelial health and function

Figure 2

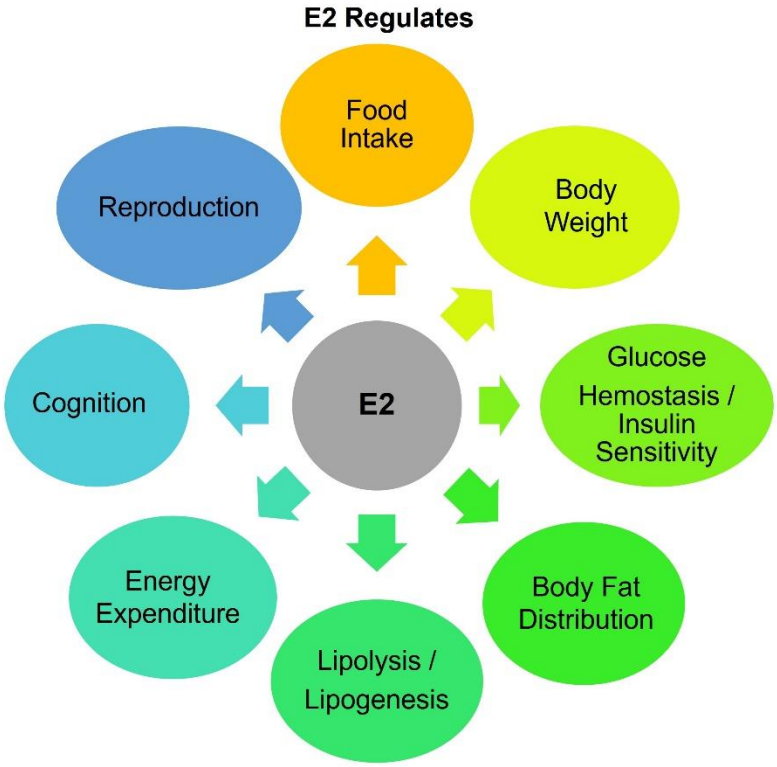

Figure 3

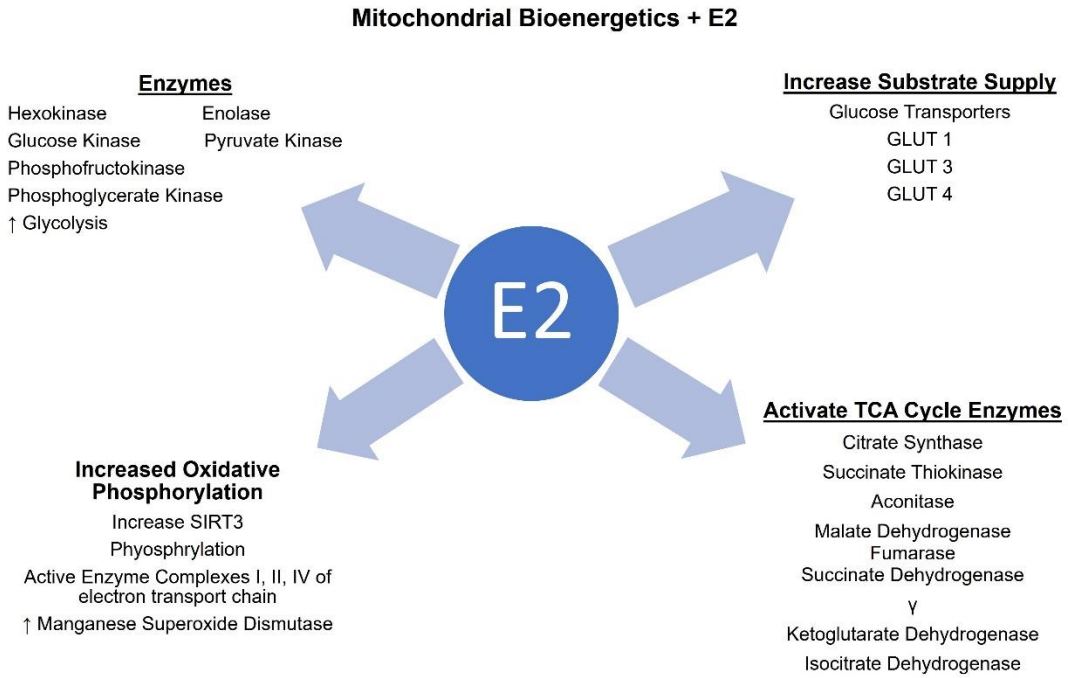

Table 1

TRIAL NAME	STUDY DESIGN	RESULT
Heart and Estrogen/Progestin Replacement Study (HERS)	**Design** Randomized, double-blind placebo controlled trial **Cohort** 2763 Postmenopausal women with confirmed CAD avg 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** Randomized, double-blind placebo controlled trial **Cohort** 16,608 postmenopausal 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
Women's Health Initiative (WHI): **CEE Alone ARM**	**Design** Randomized, 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 < 60 years at the start of the study
2017 Cochrane Collaboration Systemic Review	• The review included 23 randomized double-blind studies, involving 43,627 women • About 30% of women from this review were 50-59 years old • Studied the effects of using HRT for 1 year or more	• HRT 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 (DOPS)	**Design** Partly randomized study that included normal and healthy postmenopausal women. Study was stopped after average of 11 years. **Cohort** 1006 healthy postmenopausal women **Formulation**	• HRT has beneficial effects on CAD • HRT initiated immediately following menopause (up to 7 months) significantly reduced mortality due to CAD • HRT reduced incidence of HF and MI • No increase in thromboembolic events, strokes, or cancer

	Oral E2 – 2 mg/day if no uterus Oral E2 – 2 mg or 1mg per day (various days) + oral norethisterone for 10 days if women had a uterus	
The Kronos Early Estrogen Study (KEEPS)	**Design** Randomized, double-blind placebo controlled multi-centric trial **Cohort** 727 Postmenopausal women with avg 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	• HRT had no statistical impact on CIMT or atherosclerosis • HRT was safe and can improve quality of life
Early versus Late Intervention Trial (ELITE)	**Design** Randomized double-blind placebo controlled trial **Cohort – 2 Groups** < 6 years post-menopause > 10 years post-menopause Evaluated CIMT every 6 months for up to 6 years **Formulation** 1 mg oral E2 + vaginal Progesterone	• HRT 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 Estrogens; CIMT – CIMT - Carotid Intima Media Thickness; E2 – Estradiol; HF – Heart Failure; HRT – Hormone Replacement Therapy; MI – Myocardial Infarction

Table 2

Some Peptides, Genes + Enzymes Modulated by E2		
Endothelial Nitric Oxide Synthase	Prostacyclin Cyclooxygenase	Prostacyclin Synthase
Renin	Angiotensin	Endothelin-1
Lipoprotein Lipase	Apolipoprotein	Leptin
PON1	LDL Receptor	Cytokines: IL1, IL6, IL4, IL10, TNF∝, IFNϐ
Cytokine Receptors	HMG-Co AR Activity	Super Oxide Dismutase
Genes of Innate & Adaptive Immune Cells	Glycolytic Enzymes	TCA Cycle Enzymes
Matrix Metalloproteinases	Vascular Endothelial Growth Factor	Brain Derived Growth Factor
Fibrinogen	Coagulation Factors	Proteins

Table 3

Cardiovascular Consequences of E2 Deficiency		
Pancreas Impaired Insulin Secretion	Muscle Impaired Glucose Uptake	Liver Increased Lipogenesis Accumulation of Triglycerides Increased VLDR Increased Gluconeogenesis Reduced Function LDL Receptors
Adipose Increased Inflammation Increased Lipolysis Increased Adipocyte Size Altered Production Adipokines	Arteries Increased Stiffness Increased Remodeling Hypertension Atherosclerosis Increased Calcification Increased Intima Thickening	Heart Increased Oxidative Stress Increased Fibroblast Proliferation & Migration Reduced Collagen Deposition Reduced Angiogenesis & Artery Vasodilation Increased Arrhythmia

Table 4

Absorption of E2 from any of the commercial products is variable. Levels should be monitored at least annually				
Transdermal E2 Patch	**E2 gel product for use on arm / thigh**	**Micronized Oral P4**	**Oral E2**	**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 individualized to patient's goals and symptoms **Benefits of transdermal E2**: Enters blood as E2 and no increased risk of thromboembolism	Month 1: Apply 1 pump to arm each morning • Check serum E2 level second month and increase to 2 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 individualized 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 estrone 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 estrone and increased risk for thromboembolism Additional commercial product: Combination of CEE + Bazedoxifene **Why not recommended:** Conversion of CEE to estrone and lack of human-identical P4, which has recognized health benefits

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