
CARDIOVASCULOPROTECTIVE EFFECTS OF ESTROGEN AND ITS USE AS HORMONAL REPLACEMENT THERAPY

Didik Supriyadi Kusumo Budoyo¹, Hemi Sinorita²

Universitas Gajah Mada, Yogyakarta, Indonesia

kusumobudoyo95@gmail.com¹, hemisinorita@yahoo.com²

ABSTRACT

Epidemiologic studies have shown that the incidence of cardiovascular disease is closely related to gender. This is because endogenous estrogens have broad effects on the circulatory system, leading to the hypothesis that estrogens are cardiovascular protective, underlying their use as hormone replacement therapy (HRT) to reduce the incidence of cardiovascular disease. However, large prospective clinical trials (HERS and WHI) do not support this. This review aims to better understand the cardiovascularprotective effects of estrogen and answer the question of whether estrogen can be used as hormonal replacement therapy in post-menopausal women to prevent cardiovascular events by incorporating data from the most recent prospective clinical trial, the KEEPS study. HERS and WHI reported no reduction in cardiovascular events in postmenopausal women using HRT, even showing an increased risk of thromboembolism. This study was criticized because participants had been menopausal for 12 years, so the KEEPS study was conducted with participants within three years of menopause, with the result that there was no significant reduction in the progression of atherosclerosis between the HRT group and the placebo group. The KEEPS study states that HRT is safe, and no thromboembolic events were found. Although endogenous estrogen has cardiovascular protective effects, estrogen hormone therapy cannot reduce cardiovascular events in postmenopausal women despite metabolic improvements and beneficial effects such as improvement of postmenopausal-related symptoms, maintaining bone density, and improving sexual function.

Keywords: Cardiovasculoprotective Effects, Estrogen, Menopausal, Hormonal Replacement Therapy, WHI, KEEPS study.

Corresponding Author: Didik Supriyadi Kusumo Budoyo

E-mail: kusumobudoyo95@gmail.com



INTRODUCTION

Cardiovascular disease is the leading cause of death in both women and men in the USA, accounting for >20%. Each year, an estimated 390,000 women experience myocardial infarction and acute coronary syndrome that is either new or recurrent (Pagidipati & Peterson, 2016). Based on the Global Burden of Disease and the Institute for Health Metric and Evaluation (IHME) 2014-2019, heart disease is the highest cause of death in Indonesia, at 14.4%. Basic Health Research (Riskesdas) data from 2013 and 2018 also showed increased heart disease, from 0.5% in 2013 to 1.5% in 2018 (Tarmizi, 2022).

The incidence of cardiovascular disease is closely related to gender. Pre-menopausal women have a lower incidence of hypertension, atherosclerosis, myocardial dysfunction, ventricular hypertrophy, heart failure, and myocardial ischemia than men of the same age. However, this condition gradually decreases after menopause, and the risk of cardiovascular disease will increase even higher in women than men of the same age (Du et al., 2021). Epidemiological studies show that women before menopause can be said to be "protected" from the incidence of cardiovascular

disease compared to men. The incidence is lower in women than men at the same age and will only be equal in men ten years later (Iorga et al., 2017).

Acute coronary syndrome (ACS) includes three clinical conditions: STEMI (ST-segment elevation myocardial infarction) refers to complete coronary artery thrombosis and myocardial necrosis; NSTEMI (non-ST-segment elevation myocardial infarction) refers to partial coronary artery thrombosis and myocardial necrosis; while UAP (unstable angina pectoris) refers to partial coronary artery thrombosis but no myocardial necrosis. Among patients with ACS, women have a lower incidence of STEMI and NSTEMI, but UAP is more common than men. Analysis of the GUSTO IIb trial showed that STEMI was significantly lower in women than men (27.2% vs 37.0%; $P < 0.001$) (Pagidipati & Peterson, 2016).

The pathophysiology of ACS also differs based on gender. Plaque erosion is the most common cause of ACS in women, whereas plaque rupture is more common in men. Plaque erosion seen on vascular imaging is almost 1/3 of the cases in women with ACS, with no visible lesions identified on angiography. Conversely, plaque rupture is more easily detected on angiography. Spontaneous coronary artery dissection (SCAD), a rare cause of ACS, can be said to occur only in women. A prospective cohort study of SCAD patients stated that more than 90% occurred in women, 25.7% with STEMI, and 74.3% with NSTEMI (Costello & Younis, 2020).

Considering conventional risk factors, the main difference in these events is the level of Estrogen (Pathak et al., 2017). Women are thought to be protected from cardiovascular disease, especially ACS, due to endogenous Estrogen, which has far-reaching effects on the circulatory system (Costello & Younis, 2020).

Theoretically and in pre-clinical studies, estrogen replacement therapy is a logical intervention to reduce cardiovascular events in post-menopausal women, but the results of large-scale clinical trials such as HERS and WHI do not support this, even suggesting an increased risk of thromboembolism. The KEEPS study, which was conducted to overcome the design flaws of the WHI, has also received results. Whether the results are the same as the previous two clinical trials will be discussed in this review.

Based on the above, this review aims to understand the cardiovasculoprotective effects of Estrogen better and answer the question of whether Estrogen can be used as hormonal replacement therapy in postmenopausal women in order to prevent cardiovascular events.

METHOD

The method used was a literature review, conducted in January 2023 at the Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Dr. Sardjito Central General Hospital/Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Yogyakarta, Indonesia. It is based on data sources from offline and online references related to the topic to gather information regarding the cardio-vascular protective effects of Estrogen, its mechanism of action, and its possible use as hormone replacement therapy to reduce cardiovascular events in postmenopausal women.

RESULTS AND DISCUSSION

Estrogen and Estrogen Receptors

Estrogen is a fat-soluble steroid hormone that plays an important role in the development and physiology of various organs such as the mammary, uterus, bone, and cardiovascular systems. There are three types of Estrogen in humans, namely estrone (E1), 17 β -estradiol (E2), and estriol (E3). Among the three, E2 has the strongest biological activity (Du et al., 2021). Estradiol, also known as 17 β -estradiol or Estrogen (E2), is the most abundant type and is considered a female hormone. E2 is synthesized and secreted primarily by the ovaries in pre-menopausal women but is also produced by fat tissue, brain, bone, vascular endothelial, and aortic smooth muscle cells. Gonadal E2 acts broadly as an endocrine for distant tissues. In contrast, extra-gonadal E2 acts locally as a paracrine or intracrine in the tissue where it is synthesized (Iorga et al., 2017). Extra-gonadal E2 production plays an important role and is the sole source of endogenous E2 in pre-pubertal, postmenopausal women and men, acting as both endocrine and paracrine/intracrine to maintain tissue-specific functions (Du et al., 2021), (Iorga et al., 2017).

Almost 90% of estradiol in pre-menopausal women is produced by the ovaries; the precursor androstenedione is metabolized to estrone and then to estradiol. The conversion is mediated by aromatase (an enzyme from cytochrome P450); the process also occurs in extra-gonadal tissues such as the brain, fat, muscle, bone, and mammary glands (Morselli et al., 2017). Gonadal estrogen production of ovarian follicles (see Figure 1) is carried out by granulosa cells and theca cells under the influence of the synergistic effects of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Theca cells, under the influence of LH, will utilize LDL-cholesterol (LDL-C) as a precursor for synthesizing androstenedione and testosterone, which will diffuse to granulosa cells through the basement membrane. Aromatase activity in granulosa cells under FSH will convert androstenedione to estrone and testosterone to estradiol (Du et al., 2021), (Ko & Jung, 2021). The process is known as the two-cell-two gonadotropin theory of estrogen synthesis (Du et al., 2021).

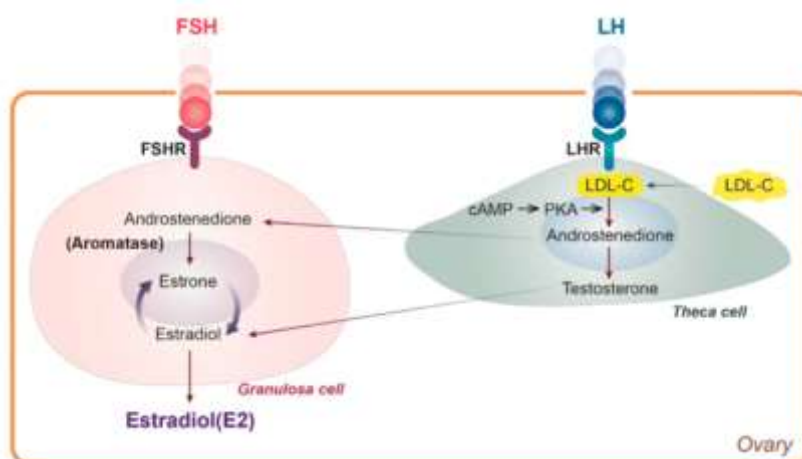


Figure 1. Synthesis of estradiol in the ovary (Ko & Jung, 2021)

The cellular effects of Estrogen are mediated by two estrogen receptors (ER): the classic nuclear estrogen receptor (nER) and the membrane estrogen receptor (mER). There are two types of nER, ER α and ER β . Further research found that some target cells can react quickly to Estrogen without going through estrogen receptors. So, in addition to the slow-acting classical nER, fast-acting

membrane receptors were found, namely G protein-coupled estrogen receptors (GPERs), which include G protein-coupled receptor 30 (GPR30) and ER-X (Du et al., 2021).

Estrogen receptors α (ER α) are found in the uterus, testes, ovaries, prostate, skeletal muscle, kidney, skin, and many more (Du et al., 2021). Animal studies have shown that this receptor has cardioprotective and vasculo-protective functions. These results are consistent with human data that decreased ER α is associated with an increased risk of atherosclerotic plaque, especially in pre-menopausal women (Morselli et al., 2017). ER β is found in the ovaries, colon, brain tissue, kidney, and male reproductive system (Du et al., 2021). This receptor has more metabolic effects, such as insulin resistance and glucose intolerance, by involving the activation of peroxisome proliferator-activated receptor γ (PPAR γ) in adipose tissue, it does not play a vasculoprotective role but can improve myocardial function after acute myocardial infarction (Morselli et al., 2017).

G protein-coupled receptor 30 (GPR30) is widely found in brain tissue, adrenal medulla, renal pelvis, and ovary. It is also widely found in the cardiovascular system, such as endothelial cells and cardiomyocytes. Meanwhile, ER-X expression is limited during the fetal development phase and rarely found in adulthood. GPR30 is cardioprotective (Du et al., 2021), (Morselli et al., 2017).

The classical pathway of estrogen action is through a genomic mechanism where Estrogen enters the nucleus and combines with the ER of the nucleus to form a dimer that will regulate gene expression and a series of further actions. While the non-genomic mechanism does not involve gene expression, Estrogen activates estrogen receptors in the membrane that will trigger further signal transduction (see Figure 2). Genomic mechanisms are slow-acting, taking hours to days to take effect, while non-genomic mechanisms are fast-acting, taking seconds to minutes to take effect (Lizcano & Guzman, 2014), (Du et al., 2021).

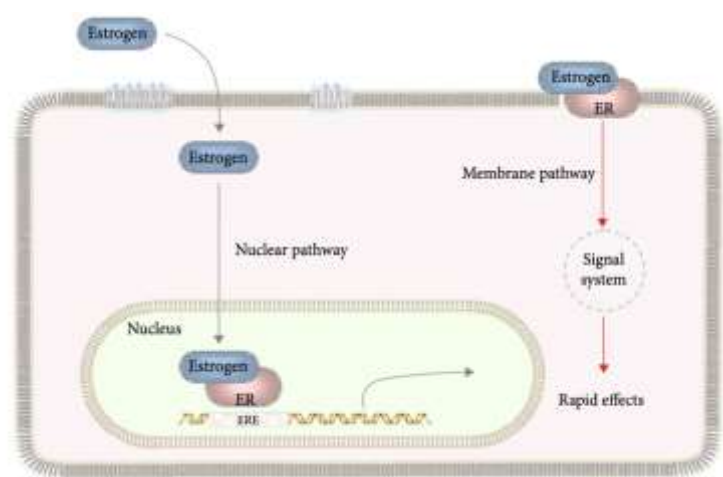


Figure 2. Genomic and non-genomic mechanisms of estrogen receptors (Du et al., 2021)

Cardiovascular Protective Effects of Estrogen

Estradiol (E2) works by binding to its receptors, namely traditional receptors (ER α and ER β), which work slowly because they must activate transcription genes in the nucleus (genomic pathway), and receptors (GPR30), which work faster because they do not pass through activation of transcription genes in the nucleus (non-genomic pathway). E2 binding to ER α and ER β (see Figure 3) can activate both genomic and non-genomic pathways. E2 binds to estrogen receptor (ER) in the genomic pathway, will form homo/hetero dimer formation, translocate to the nucleus, then bind to estrogen receptor element (ERE) or bind to transcription factors that regulate gene expression such

as eNOS (endothelial nitric oxide synthase) a potent vasodilator and VEGF (vascular endothelial growth factor) a pro-angiogenesis factor. E2 binds to the ER and GPR30 with the plasma membrane in the non-genomic pathway, activating MAPK/ERK/PI3K/cAMP, resulting in eNOS expression. E2 also binds to ER in the mitochondrial membrane, improving mitochondrial function by reducing the production of ROS (reactive oxygen species) and increasing cell survival (Iorga et al., 2017).

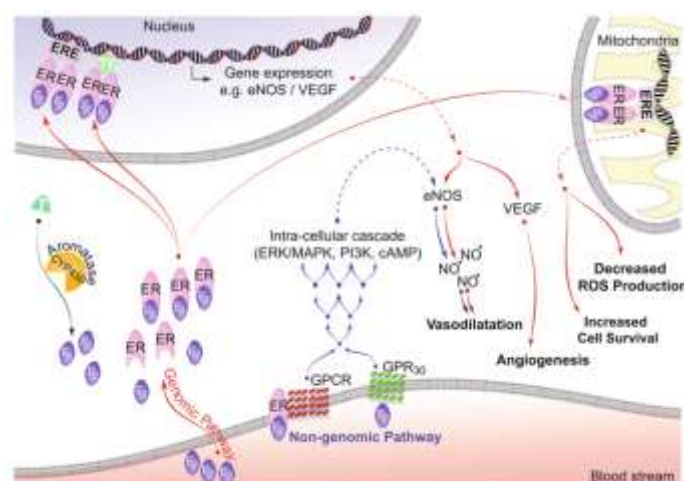


Figure 3. Genomic and non-genomic pathways (Iorga et al., 2017)

Genomic: red arrow, non-genomic: blue arrow. Also shown is the local biosynthesis of E2 through the conversion of T (testosterone) to E2 via the aromatase process of the CYP P450 enzyme

The cardioprotection and atheroprotection properties of estradiol can be seen in Figure 4. Estradiol inhibits angiotensin II (AGT II), resulting in PI3K activation and suppression of CaN (calcineurin) activity, resulting in an anti-hypertrophic effect. Estradiol protects cardiomyocytes by activating PI3K, PKB, and MAPK, preventing ROS formation and inhibiting apoptosis. Activation of sirtuin 1 (SIRT) by estradiol will inhibit AGT II from producing ROS. Estradiol suppresses the expression of microRNA-22 (miR-22) through ER α , which increases the transcription factor Sp1 in cardiomyocytes. Sp1 increases the expression of cardioprotective genes, such as the gene encoding cystathionine- γ -lyase (CTH), leading to increased levels of hydrogen sulfide (H₂S) so that cardiomyocyte protection against ROS increases. Cardiovascular protective effects also occur through GPER1 (GPR30) through PI3K dependent. Exposure to physiological concentrations of estradiol can reduce the pro-inflammatory activity of vascular endothelial cells by reducing the production of IL-6, IL-8, ICAM1, and VCAM1, which play a role in leukocyte recruitment, thus preventing the development of atherosclerosis. Estradiol also plays a role in stimulating endothelial repair during vascular injury through the genomic/non-genomic pathway by increasing eNOS activity, which is a vasodilator. Estradiol also plays a role in the lipoprotein profile by increasing the amount of HDL (high-density lipoprotein). HDL will stimulate the production of NO (nitric oxide) through scavenger receptor B type 1 (SRB1), which will activate eNOS, resulting in vasodilation (Morselli et al., 2017).

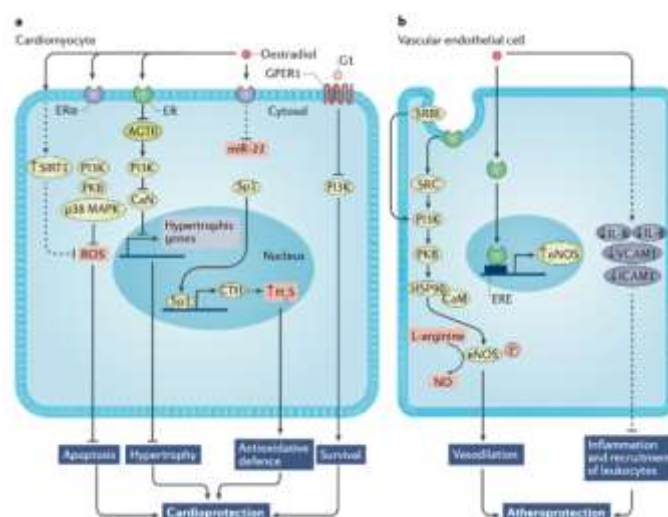


Figure 4. Mechanisms of cardioprotection and atheroprotection of estradiol (Morselli et al., 2017)

PI3K: phosphoinositide 3 kinase; PKB: protein kinase B; MAPK: mitogen-activated protein kinase; IL-6/8: interleukine-6/8; VCAM1: vascular cell adhesion molecule 1; ICAM1: intercellular adhesion molecule 1

A summary of the mechanism of Estrogen's protective effect on cardiovascular disease through suppression of fibrosis, stimulation of angiogenesis and vasodilation, improving mitochondrial function, and reducing oxidative stress can be illustrated in Figure 5.

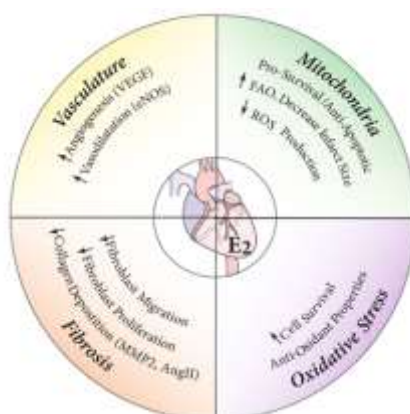


Figure 5. Summary of the mechanism of Estrogen's protective effect (Iorga et al., 2017)

FAO: fatty acid oxidation; MMP2: matrix metalloproteinase 2

Menopause and Cardiovascular Disease

Women are more protected against cardiovascular events than men. Overall, the differences in risk factors and outcomes of cardiovascular events between men and women lie in sex hormones and their receptors (Davezac et al., 2021). Clinically, the Framingham Heart Study first demonstrated the clinical presentation pattern of women in the 1980s, showing that women generally have more angina as the clinical presentation of ischemic heart disease and less often with acute myocardial infarction clinical presentation than men. In ACS, women more often present with unstable angina/NSTEMI than STEMI (Ketepe-Arachi & Sharma, 2017). Pathophysiology also shows differences in the mechanism of ACS. In women, mechanisms other than plaque rupture and thrombus formation are more common causes (see Figure 6), namely plaque erosion, coronary

vasospasm, spontaneous coronary artery dissection, and stress-related cardiomyopathy (Takotsubo cardiomyopathy). Prospect studies showed that women have smaller coronary lumens, fewer plaque ruptures, and less necrotic plaque, with less calcium content than men. Women are likelier to have plaque erosion without obvious plaque rupture (Pagidipati & Peterson, 2016).

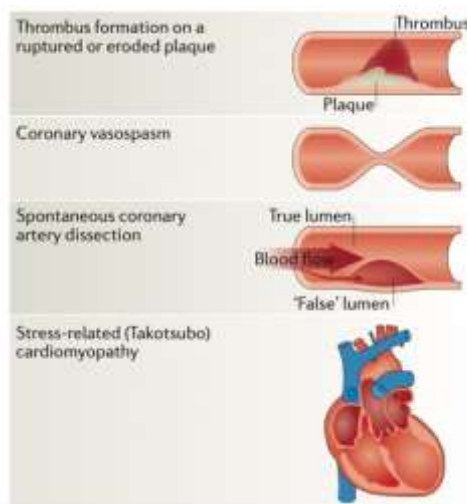


Figure 6. Differences in ACS pathophysiology based on gender (Pagidipati & Peterson, 2016)

Women are more likely to have coronary vasospasm, spontaneous coronary artery dissection, and stress-related cardiomyopathy.

Menopause is characterized by the permanent end of a woman's menstrual cycle, which occurs around the age of 49-52 years. Along with the depletion of ovarian follicles, the ovaries stop producing Estrogen so that estradiol (E2) levels, which normally range from 60-200 pg/ml, decrease to 20 pg/ml (Davezac et al., 2021) (Ko & Jung, 2021). Levels of 17b-estradiol (E2), the main Estrogen in circulation, decrease abruptly from the onset of menopause. As a result of this sudden decline, women lose their cardiovascular protective effect, and the risk of cardiovascular events is comparable to that of men (see Figure 7). The cardiovascular incidence of postmenopausal women is 4.3 times higher than that of pre-menopausal women (Davezac et al., 2021).

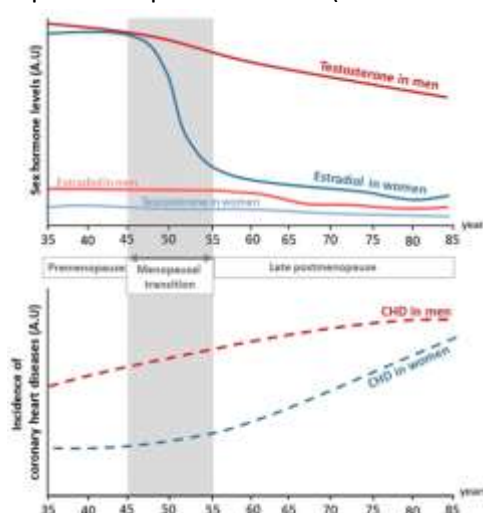


Figure 7. Evolution of sex hormone levels on coronary heart disease in women and men (Davezac et al., 2021)

Decreased estrogen levels in postmenopausal women are associated with an increased risk of cardiovascular events (Davezac et al., 2021). This is supported by research conducted (by Pathak et al., 2017), who reported that estrogen levels in older women with coronary heart disease decreased significantly compared to older women without coronary heart disease, with the more severe the coronary lesions, the lower the estrogen levels. Estrogen levels are also associated with lipid profiles and fibrinolysis status (Pathak et al., 2017).

Estrogen Replacement Therapy

Pre-menopausal women have a lower risk of cardiovascular disease than men of the same age, but the incidence increases after menopause. As explained above, Estrogen has beneficial effects on the cardiovascular system. These beneficial effects and the lower incidence of cardiovascular disease in pre-menopausal women led to the hypothesis that Estrogen is cardioprotective, which underlies its use as hormonal replacement therapy (HRT) to reduce the incidence of cardiovascular disease (Murphy & Steenbergen, 2014).

Postmenopausal women show several features of metabolic syndrome as estrogen levels decline, such as dyslipidemia (hypertriglyceridemia, increased LDL and decreased HDL), insulin resistance, hypertension, increased central fat and decreased lean body mass as well as hypercoagulation and pro-inflammatory conditions (Modena, 2016).

Although HRT is a logical intervention given its many advantages based on pre-clinical studies, evidence based on clinical trials does not support the use of estrogen therapy for the prevention of cardiovascular disease (Manrique-Acevedo et al., 2020). Several observational studies have reported that postmenopausal women receiving HRT have lower cardiovascular events and cardiac mortality than those without HRT. However, prospective clinical trials with many participants have shown different results. The Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) reported no reduction in cardiovascular events in postmenopausal women with HRT. These studies suggest that HRT is associated with an increased risk of stroke, thromboembolism, and deep vein thrombosis (dos Santos et al., 2014). Although WHI and HERS reported that HRT showed improved lipid profiles and reduced type 2 DM, it did not improve cardiovascular outcomes (Murphy & Steenbergen, 2014).

Several hypotheses have been proposed to explain the WHI and HERS results as to why Estrogen does not protect postmenopausal women against cardiovascular events. One popular hypothesis is the "timing hypothesis," which states that the average age at HRT is around 63 years. The participants of the study were postmenopausal women who had already experienced estrogen deficiency several years before receiving HRT, giving rise to the suggestion that perhaps the administration of Estrogen immediately after menopause would be more beneficial. A re-analysis of the WHI data on this issue found that HRT administered immediately after menopause showed no beneficial effect on cardiovascular events and stroke (Murphy & Steenbergen, 2014).

The second explanation is age-related changes that result in a decreased protective effect of estrogen administration. Estrogen improves cardiovascular outcomes by activating eNOS. Tetrahydrobiopterin (BH4) is a co-factor of eNOS; a decrease in BH4 due to age will cause NOS uncoupling, resulting in decreased NO production and increased ROS. Giving Estrogen to activate NOS without BH4 will be more detrimental than cardioprotective (Murphy & Steenbergen, 2014).

The third explanation is that in postmenopausal women, there is an increase in 27-hydroxycholesterol, which will bind to estrogen receptors and is antagonistic to the increase in

estrogen-activated eNOS. Therefore, re-administering estrogen post-menopause will be antagonistic. The fourth explanation relates to age-related estrogen receptor levels/activity/proportion changes. The ER can undergo post-translational modifications that alter its activity, acetylation that affects transcriptional activity, or methylation associated with decreased ER levels. Thus, ER levels, activity, and composition change with age (Murphy & Steenbergen, 2014).

A Cochrane meta-analysis of 22 studies of postmenopausal women found an increased risk of coronary heart disease and stroke associated with combined HRT. The American College of Obstetricians and Gynecologists and the North American Menopause Society have started to reduce the routine use of estrogen hormonal therapy in postmenopausal women. The timing of HRT administration is still a matter of debate. Administration early in menopause may still have beneficial effects. Transdermal administration is still under promising research regarding less risk (Manrique-Acevedo et al., 2020).

The use of estradiol as a cardiovascular protective therapy is controversial, as is the use of oral contraceptives containing estradiol, which is associated with an increased risk of venous thrombosis and consequent myocardial infarction, stroke, and peripheral arterial disease. The WHI study showed that the estrogen component of HRT is associated with the risk of venous thrombosis. Canonico et al. reported the same. These studies suggest that estradiol is pro-thrombotic, although it is still controversial and not fully understood, by increasing pro-coagulant factors (factors VII, X, XII, and XIII) and decreasing anti-coagulant factors (protein S and anti-thrombin). Rosendaal et al. reported that estradiol supplementation as oral contraceptives or HRT increases the risk of thrombosis, especially in women with coagulation disorders. Progestins as oral contraceptives or HRT with third-generation progestogen content (desogestrel, gestodene) are associated with a higher risk of thrombosis compared to second-generation progestogen content such as levonorgestrel (Iorga et al., 2017).

The Kronos Early Estrogen Prevention Study (KEEPS) was initiated because the WHI results surprisingly did not support the observational study hypothesis that estrogen replacement therapy can reduce cardiovascular events. The WHI design was criticized for not being clinically practical, as most of the WHI participants, despite an average age of 63 years and 12 years of menopause, did not experience postmenopausal symptoms such as hot flashes and, therefore, did not seek treatment for these symptoms. The WHI included many participants who were at risk of cardiovascular events. KEEPS was designed to address this weakness by recruiting women within three years of menopause and excluding participants with known clinical or subclinical atherosclerosis. In a randomized, double-masked, placebo-controlled trial, 72,8 participants were given oral conjugated equine Estrogen (oCEE; 0.45 mg/day) or transdermal 17 β -estradiol (tE2; 50 mg/day), both with progesterone (200 mg/day for 12 days/month), or placebo pills and patches for four years (V M Miller et al., 2021).

The primary outcome of KEEPS was the change in carotid intima-medial thickness (CIMT) measured by B-mode ultrasound. There was no significant change in CIMT in all three groups (oCEE, tE2, and placebo). The secondary outcome is coronary artery calcification (CAC); there was also no significant difference (Virginia M Miller et al., 2019), (V M Miller et al., 2021). There were no venous thrombotic events but one myocardial infarction event in the tE2 (transdermal estrogen administration) group. However, the event occurred before the start of treatment (Virginia M Miller et al., 2019). There were no major adverse cardiovascular events or cognitive impairment events,

and there were no differences in the incidence of breast cancer among the three treatment groups (V M Miller et al., 2021). A summary of the KEEPS study results can be seen in Figure 8.

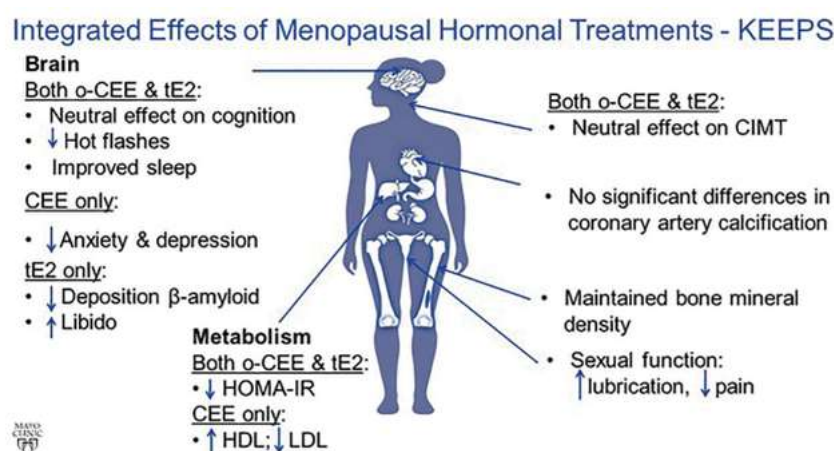


Figure 8. Summary of KEEPS study results (V M Miller et al., 2021)

KEEPS did not show a significant reduction in the progression of atherosclerosis measured by CIMT and CAC in participants with hormonal replacement therapy compared to placebo. However, there were improvements in metabolic factors in the hormonal replacement therapy group. In general, the KEEPS data assure the effectiveness and safety of oCEE (0.45 mg/day) or tE2 (50 mg/day) dosing, both accompanied by oral progesterone (200 mg/day for 12 days/month) for women considering using hormonal replacement therapy to reduce postmenopausal symptoms with the additional outcomes of improving sexual function and maintaining bone mass density (V M Miller et al., 2021).

CONCLUSION

Epidemiologic studies have shown that pre-menopausal women are more protected against cardiovascular disease than men. A comparison of women and men for the same cardiovascular event rate showed that women aged ten years later than men. This protective effect is related to sexual hormone (Estrogen) levels; the incidence and severity of cardiovascular disease increases in postmenopausal women, and the incidence of coronary heart disease also increases in women with oophorectomy compared to women with ovarian intake. Cardiovascular protective effects in reproductive women are believed to be related to estrogen levels and estrogen receptor expression. The mechanism of Estrogen's cardioprotective effect is through increased angiogenesis and vasodilation, as well as reducing ROS, oxidative stress, and fibrosis.

Although HRT is a logical intervention given its many advantages based on pre-clinical studies, evidence based on clinical trials does not support the use of estrogen therapy for the prevention of cardiovascular disease. HERS and WHI showed no reduction in cardiovascular events in postmenopausal women with hormonal replacement therapy, even suggesting an increased risk of stroke, thromboembolism, and deep vein thrombosis. One of the analyses of these events is the timing hypothesis, so the KEEPS study was initiated, which participated in women within three years of menopause onset. The KEEPS study stated no significant reduction in atherosclerosis progression between the hormonal replacement therapy group and placebo. HERS, WHI, and KEEPS showed metabolic improvement in the hormonal replacement therapy group. However, KEEPS differed from

HERS and WHI, which stated that there was an increased risk of thromboembolism, KEEPS stated that hormonal replacement therapy was safe, there was no risk of major cardiovascular events, and beneficial effects such as improving symptoms related to postmenopausal symptoms, maintaining bone density, and improving sexual function.

REFERENCES

- Costello, B. T., & Younis, G. A. (2020). Acute coronary syndrome in women: An overview. *Texas Heart Institute Journal*, 47(2), 128–129.
- Davezac, M., Buscato, M., Zahreddine, R., Lacolley, P., Henrion, D., Lenfant, F., Arnal, J.-F., & Fontaine, C. (2021). Estrogen receptor and vascular aging. *Frontiers in Aging*, 2, 727380.
- dos Santos, R. L., da Silva, F. B., Ribeiro Jr, R. F., & Stefanon, I. (2014). Sex hormones in the cardiovascular system. *Hormone Molecular Biology and Clinical Investigation*, 18(2), 89–103.
- Du, X., Liu, Y., Zhou, S., Zhou, E., & Wang, Y. (2021). Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. *Oxidative Medicine and Cellular Longevity*, 2021.
- Iorga, A., Cunningham, C. M., Moazeni, S., Ruffenach, G., Umar, S., & Eghbali, M. (2017). The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biology of Sex Differences*, 8, 1–16.
- Ketepe-Arachi, T., & Sharma, S. (2017). Cardiovascular disease in women: understanding symptoms and risk factors. *European Cardiology Review*, 12(1), 10.
- Ko, S.-H., & Jung, Y. (2021). Energy metabolism changes and dysregulated lipid metabolism in postmenopausal women. *Nutrients*, 13(12), 4556.
- Manrique-Acevedo, C., Chinnakotla, B., Padilla, J., Martinez-Lemus, L. A., & Gozal, D. (2020). Obesity and cardiovascular disease in women. *International Journal of Obesity*, 44(6), 1210–1226.
- Miller, V M, Taylor, H. S., Naftolin, F., Manson, J. E., Gleason, C. E., Brinton, E. A., Kling, J. M., Cedars, M. I., Dowling, N. M., & Kantarci, K. (2021). Lessons from KEEPS: the kronos early estrogen prevention study. *Climacteric*, 24(2), 139–145.
- Miller, Virginia M, Naftolin, F., Asthana, S., Black, D. M., Brinton, E. A., Budoff, M. J., Cedars, M. I., Dowling, N. M., Gleason, C. E., & Hodis, H. N. (2019). The Kronos early estrogen prevention study (KEEPS): what have we learned? *Menopause*, 26(9), 1071–1084.
- Modena, M. G. (2016). *“Estrogens and the Heart: Do they Help or Hurt?” How Estrogen impacts the Cardiovascular System*.
- Morselli, E., Santos, R. S., Criollo, A., Nelson, M. D., Palmer, B. F., & Clegg, D. J. (2017). The effects of oestrogens and their receptors on cardiometabolic health. *Nature Reviews Endocrinology*, 13(6), 352–364.
- Murphy, E., & Steenbergen, C. (2014). Estrogen regulation of protein expression and signaling pathways in the heart. *Biology of Sex Differences*, 5, 1–7.
- Pagidipati, N. J., & Peterson, E. D. (2016). Acute coronary syndromes in women and men. *Nature Reviews Cardiology*, 13(8), 471–480.
- Pathak, L. A., Shirodkar, S., Ruparelia, R., & Rajebahadur, J. (2017). Coronary artery disease in women. *Indian Heart Journal*, 69(4), 532–538.
- Tarmizi, S. N. (2022). *Penyakit Jantung Penyebab Utama Kematian, Kemenkes Perkuat Layanan Primer*. Sehatnegeriku.Kemkes.Go.Id. <https://sehatnegeriku.kemkes.go.id/baca/rilis-media/20220929/0541166/penyakit-jantung-penyebab-utama-kematian-kemenkes-perkuat-layanan-primer/>



© 2024 by the authors. Submitted for possible open-access publication under the terms and conditions of the Creative Commons Attribution (CC BY SA) license (<https://creativecommons.org/licenses/by-sa/4.0/>).