The Effect of Oral 17β-estradiol on Various Cardiovascular Atherosclerotic Indices in Postmenopausal Women: Does Chemical Structure Make a Difference?

Britany C. Rowan
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The Effect of Oral 17β-estradiol on Various Cardiovascular Atherosclerotic Indices in Postmenopausal Women: Does Chemical Structure Make a Difference?

Abstract

Background: Estrogen has, in the past, been widely recognized as an endogenous hormone that aids in the prevention of cardiovascular disease in postmenopausal women. However, conjugated equine estrogen with or without sequentially administered medroxyprogesterone, was demonstrated to provide no benefit in the prevention of cardiovascular disease and may in fact, aid in the progression of atherosclerotic disease in women on this type of hormone replacement therapy. More randomized controlled trials have been conducted recently to examine the effect of oral 17β-estradiol as opposed to conjugated equine estrogen, on the progression of atherosclerotic disease in postmenopausal women.

Objective: To determine whether oral 17β-estradiol with or without sequentially administered progestogen therapy has an effect on the progression and/or prevention of cardiovascular disease in postmenopausal women.

Study Design: Systematic review of the available medical literature.

Methods: An exhaustive systematic review of the medical literature was conducted using, MEDLINE, EBSCOhost, and EBMR Multifile using the keywords “estrogen replacement therapy” and “cardiovascular diseases.” Trials were only included in this review if published after 2001 and if the trial was randomized and controlled. Studies were rated using the Jadad criteria, and only studies with a Jadad score of 3 or higher were included in this review.

Results: Overall it was found that in three studies atherosclerotic risk was decreased in women on HRT, in three studies atherosclerotic risk was increased in women on HRT, and one study indicated no slowing in progression of atherosclerosis but decreased risk for cardiovascular disease by improving lipid profiles. It is important to note that all of the studies examined in this systematic review demonstrated a decrease in cardiovascular risk in patients taking HRT when the endpoint measured was a serum biochemical marker. The studies that demonstrated an increased risk for cardiovascular disease in women taking HRT measured endpoints including percent coronary or carotid artery stenosis.

Conclusion: Estrogen replacement therapy using 17β-estradiol appears to reduce multiple biochemical endpoints for cardiovascular disease risk including improving lipid profiles and decreasing inflammation. However, 17β-estradiol does not have a positive effect on the progression of atherosclerosis in the carotid or coronary arteries. Therefore, 17β-estradiol may reduce cardiovascular disease risk but evidence does not suggest that this improvement in lipid profiles and inflammation actually affects atherosclerosis progression.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/147
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Keywords
Estrogen replacement therapy, conjugated equine estrogen, 17?-estradiol, medroxyprogesterone, progestin

Subject Categories
Medicine and Health Sciences

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The Effect of Oral 17β-estradiol on Various Cardiovascular Atherosclerotic Indices in Postmenopausal Women: Does Chemical Structure Make a Difference?

Brittany C. Rowan, PA-S

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University
Hillsboro, OR

For the Masters of Science Degree, August 2009

Faculty Advisor: Anya Hill, PA-C
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Brittany Rowan is a proud native of Texas and graduated with a Bachelor of Science degree in molecular and cell biology from Texas A&M University in 2003. After completion of her undergraduate studies, she married her wonderful husband Chris who is on active duty with the United States Navy, and moved with him to Washington State. There, she completed prerequisites for entry into a physician assistant program, worked as a medical assistant at Whidbey Island Internal Medicine in Coupeville, Washington, and volunteered as an ultrasound technician and peer counselor at the Pregnancy Care Clinic in Oak Harbor, Washington. She was accepted into Pacific University’s School of Physician Assistant Studies in 2007. Brittany plans to return to Whidbey Island upon graduation to practice medicine. Brittany and Chris have two dogs, a wonderful and supportive extended family, and enjoy running, snow skiing, road biking, and participating as members of the worship team at their church.
Abstract

Background: Estrogen has, in the past, been widely recognized as an endogenous hormone that aids in the prevention of cardiovascular disease in postmenopausal women. However, conjugated equine estrogen with or without sequentially administered medroxyprogesterone, was demonstrated to provide no benefit in the prevention of cardiovascular disease and may in fact, aid in the progression of atherosclerotic disease in women on this type of hormone replacement therapy. More randomized controlled trials have been conducted recently to examine the effect of oral 17β-estradiol as opposed to conjugated equine estrogen, on the progression of atherosclerotic disease in postmenopausal women.

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Conclusion: Estrogen replacement therapy using 17β-estradiol appears to reduce multiple biochemical endpoints for cardiovascular disease risk including improving lipid profiles and decreasing inflammation. However, 17β-estradiol does not have a positive effect on the progression of atherosclerosis in the carotid or coronary arteries. Therefore, 17β-estradiol may reduce cardiovascular disease risk but evidence does not suggest that this improvement in lipid profiles and inflammation actually affects atherosclerosis progression.

Keywords: Estrogen replacement therapy, conjugated equine estrogen, 17β-estradiol, medroxyprogesterone, progestin, progesterone, progestogen
Acknowledgements

To Chris, my wonderful husband. I wouldn’t be where I am today without your love and support. Thank you for always believing in me and encouraging me to reach farther. The end is worth it.

To my family: Thank you for every word of encouragement and prayer for perseverance. I can’t imagine being part of a more wonderful family.

To The Landolt family, my Portland family. I don’t know what I would do without you all.
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List of Abbreviations

WHI .............................................................................. Women’s Health Initiative
CEE ............................................................................... Conjugated equine estrogens
HRT ........................................................................... Hormone replacement therapy
FSH ............................................................................... Follicle stimulating hormone
LDL ........................................................................... Low density lipoprotein
SAC .................................................................................. Systemic arterial compliance
PWV ........................................................................... Pulse wave velocity
FMD ............................................................................... Flow mediated dilation
ADMA ............................................................................ Asymmetric dimethylarginine
MCP-1 ........................................................................... Monocyte chemoattractant protein-1
WELL-HART ................................................................. Women’s Estrogen-Progestin Lipid Lowering Atherosclerosis Regression Trial
ACOG ........................................................................... American Committee on Gynecologic Practice

List of Appendices

Appendix A .............................................................. Description of Jadad Score Criteria
The Effect of Oral 17β-estradiol on Various Cardiovascular Atherosclerotic Indices in Postmenopausal Women: Does Chemical Structure Make a Difference

Introduction

A great deal of research has been generated in recent years revolving around the issue of the safety and efficacy of hormone replacement therapy for postmenopausal women. One aspect of the issue that has been of intense debate, is whether hormone replacement therapy has an effect on either the prevention or progression of cardiovascular disease in postmenopausal women, and more specifically, whether this type of therapy has a deleterious effect on the cardiovascular health of women taking hormone replacement therapy. Prior to the publication of the findings of the landmark Women’s Health Initiative (WHI) study in 2002, it was widely believed and accepted that estrogen had a cardioprotective effect, though the mechanism by which estrogen produced this effect was not well understood. However, the findings of the WHI study demonstrated that women taking hormone replacement therapy using conjugated equine estrogen (CEE), with or without sequentially administered medroxyprogesterone for progesterone replacement, not only did not receive cardioprotection, but were possibly at an increased risk for atherosclerotic disease compared to the study participants taking placebo. Since 2002, many studies have been done to address the issue of whether the increased risk of atherosclerotic disease in patients taking hormone replacement therapy demonstrated by the WHI study, applies across the board to women of various ages and various stages of menopause. It is not clearly understood whether this risk factor can be extrapolated to women using various routes of estrogen administration including oral, transdermal, and vaginal administration, and whether, sequentially administered progestin or progesterone therapy decreases the potential cardioprotective benefit of estrogen. Another question that remains without a clear answer is whether using estrogen that is chemically and structurally identical to endogenously produced estrogen, 17β-estradiol, for hormone replacement therapy, has a similar effect on the prevention and/or progression...
of cardiovascular and atherosclerotic disease as CEE, which has a chemical structure that is not molecularly identical to naturally produced estrogen. The aim of this systematic review is to examine the available medical literature published since 2001 to determine the effect of oral 17β-estradiol in women using this type of hormone replacement therapy, with or without sequentially administered progestogen therapy, on various markers and indices of atherosclerotic disease.

**Materials and Methods**

A comprehensive search of the medical literature was conducted using various search modalities including MEDLINE, EBSCOhost, and EBMR Multifile and using the keywords “estrogen replacement therapy” and “cardiovascular diseases.” Inclusion criteria for this review were all English language randomized controlled trials published after 2001 which included perimenopausal and postmenopausal women and the use of only oral 17β-estradiol for hormone replacement therapy, be it with progestogen therapy or without. The studies included, followed women on estrogen using various types of progestogen therapy, mainly for protection against endometrial hyperplasia in women with intact uteri. Studies were also included in this review regardless of the method of confirming menopause in the study participants and regardless of the participants’ stage of menopause. The participants were included even if they had preexisting cardiovascular disease. Studies using various endpoints for cardiovascular or atherosclerotic disease were examined in this review, including any biochemical marker generally regarded to contribute to inflammatory or atherosclerotic cardiovascular disease. Other endpoints that are considered to be markers for cardiovascular disease, including average percent coronary artery stenosis and carotid intima-media thickness, were addressed in this review. Studies which examined transdermal or vaginal estrogen replacement were excluded from this review.
The studies were subsequently rated and assessed for quality using the Jadad criteria. (For a detailed description of the Jadad criteria please see Appendix A). The results of the remaining studies were then compiled and examined.

**Results**

A total of 7 articles which met all of the inclusion and exclusion criteria were examined in this review (See Tables 1 and 2). The average sample size was approximately 142, with the largest group studied consisting of 321 postmenopausal women, and the smallest group consisting of fifty one. The shortest study lasted twelve weeks, and the longest followed study participants for a median of 3.3 years. All studies included in this review were randomized, controlled trials. Three trials were double-blinded, one was observer-blinded, and in three, neither participants nor observers were blinded. All studies compared women on hormone replacement therapy (HRT) to participants on placebo pills, except one study, which compared HRT patients to patients not taking any pills. All study participants receiving therapy were given oral 17β-estradiol, however in four studies participants received 17β-estradiol as a dose of 1 mg daily and in three studies participants received 17β-estradiol 2 mg daily. Only one study examined study participants taking unopposed 17β-estradiol, and the remainder of the studies used 17β-estradiol replacement therapy with or without sequentially administered progestagen therapy, according to certain conditions individually outlined in each study. The overall average age of the women participants in all of the studies examined in this review is 58 years of age. However, the age of participants ranged from approximately 40 to 75 years of age. Each study used its own method for determining the definition of “postmenopausal.” These methods ranged from determining minimum follicle stimulating hormone (FSH) serum concentrations, maximum estradiol serum concentrations, or establishing a minimum length of time since the last menstrual period. Three of the seven studies, examined women with a clinically documented increased risk for cardiovascular disease and in two of the studies, participants concomitantly received lipid-lowering medications if low density
lipoprotein (LDL) levels matched a certain criterion outlined in the study for determining hyperlipidemia. The remaining four studies were of healthy women with no pre-existing cardiovascular disease. Accordingly, the use of 17β-estradiol as both primary and secondary prevention for cardiovascular and atherosclerotic disease was considered in this review. Since each study in this review included different endpoints, inclusion and exclusion criteria, and management of comorbid medical conditions in the study participants, each will be discussed individually with particular attention to similarities and differences.

Four studies examined 17β-estradiol replacement therapy in healthy women without pre-existing cardiovascular disease. Hodis, et al examined 222 postmenopausal women, 45 years of age or older with mean age of 62.2 years of age, for a length of two years, in the Estrogen in the Prevention of Atherosclerosis (EPAT) trial. This study received a Jadad score of 5. Postmenopausal status in this study was confirmed by the presence of a serum estradiol level of <20 pg/mL. The participants received unopposed 1 mg 17β-estradiol therapy daily. Women also received dietary counseling and hydroxymethylglutaryl coenzyme-A reductase inhibitors therapy if LDL cholesterol level exceeded 160 mg/dL. The primary trial endpoint was the rate of change of intima-media thickness in the right distal common carotid artery measured with B-mode ultrasound. However, other endpoints were also examined including lipid parameters, and laboratory indices of carbohydrate metabolism. Results demonstrated that subclinical atherosclerosis progressed more slowly in the group receiving HRT as opposed to the placebo group (P=0.046). Laboratory values assessed in this study showed a significant increase in triglyceride (P=0.006) and HDL (P<0.001) levels in the estradiol group compared with the placebo group, as opposed to a significant decrease in LDL (P=0.001), insulin (P=0.01), and hemoglobin A1C (0.007) levels in the estradiol versus control groups. Overall, atherosclerosis progressed more slowly in participants using HRT than those on placebo. Results of this study were also analyzed after stratifying participants to those receiving lipid lowering medications and those not
receiving lipid lowering medications, and the slowing of atherosclerosis progression was actually
greatest in those participants not receiving any lipid lowering medications (P=0.046).

Teede, et al\textsuperscript{8} also examined healthy women without preexisting cardiovascular disease in a
double-blinded randomized, placebo-controlled study that received a Jadad score of 5. The length of
this study was also two years, however, only fifty nine women were examined and fifteen of them
withdrew before completion of the study. Patients were treated for medical issues diagnosed during
the study; however neither the treatment type nor parameters were discussed in the study. The average
age of the participants was sixty one years of age, and all participants were at least two years post
menopause as determined by self-reporting. Therapy consisted of 2 mg 17\(\beta\)-estradiol daily plus
progestogen in the form of norethisterone 1 mg versus placebo. Endpoints measured included lipid
profiles and indices of arterial function including systemic arterial compliance (SAC), a measure of the
mechanical properties of the arteries, pulse wave velocity (PWV), a measure of arterial stiffness, and
endothelial function, including flow-mediated vasodilation (FMD). All parameters are well-
established positive risk factors for cardiovascular disease.\textsuperscript{8} Results of this study demonstrated no
statistically significant reduction in lipid parameters in the treatment versus placebo group except for a
statistically significant decrease in lipoprotein a (P=0.006) in the treatment group when compared to
placebo. However, this study was underpowered to detect differences in lipid profiles. No statistically
significant change in SAC, PWV, or FMD and therefore no positive effect on arterial compliance,
endothelial function, or cardiovascular risk were demonstrated by this study.

Thijis, et al\textsuperscript{9} studied sixty women without preexisting cardiovascular disease who were
postmenopausal, normotensive, and nonhysterectomized. The study design was prospective,
randomized, and placebo-controlled, but only partially blinded—observers were aware of study
medications. Therefore, this study only received a Jadad score of 3. All participants were between
forty five and sixty years of age with an average age of 52.2 years. All had been amenorrheic for at
least six months but for no more than five years and postmenopausal status was determined by
laboratory measurement of FSH of > 20 IU/L and serum estradiol < 150 pmol/L. Participants were treated for only twelve weeks with 2 mg micronized 17β-estradiol daily, unopposed or sequentially combined with progestogen therapy using either trimegestone 0.5 mg daily or dydrogesterone 10 mg daily versus placebo. Since activation of platelets is accompanied by antigenic changes on their surface,9 endpoint measurement was for three of these parameters of antigenic change indicating platelet activation including Von Willebrand factor receptor, P-selectin, and Glycoprotein 53. Factors that influence platelet activation are widely regarding as causing an increase for risk of cardiovascular events.9 This study demonstrated no statistically significant change in Von Willebrand factor among the three groups, however a statistically significant increase in P-selectin was detected among the unopposed 17β-estradiol as well as 17β-estradiol plus progestogen treatment groups (P=0.04 for both). An increase in glycoprotein 53 (P=0.04) was also noted in the 17β-estradiol plus progestogen group but not the unopposed estradiol treatment group. The results of this study suggest that 17β-estradiol therapy may increase the risk of cardiovascular events by increasing platelet activation.

The last study which examined women without preexisting cardiovascular disease was the study conducted by Post et al.10 Post et al studied the effect of HRT on asymmetric dimethylarginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase, thus a known risk factor for cardiovascular events. The study design was a randomized, placebo-controlled, prospective trial which received a Jadad score of 3. All study participants were between the ages of forty five and sixty, with an average age of 52.2 years. Sixty early postmenopausal, nonhysterectomized women were included. Participants must have been amenorrheic for six months to five years with a serum FSH level of > 20 IU/L and serum estradiol < 150 mL. Participants received 2 mg 17β-estradiol daily unopposed, or with either 10 mg dydrogesterone or 0.5 mg trimegestone daily for progestogen therapy. Results of this study, showed that 17β-estradiol in combination with progestogen therapy, significantly lowered ADMA levels more than unopposed estradiol therapy or placebo.
The remaining three studies all examined study participants with clinically established preexisting cardiovascular disease or cardiovascular risk factors. Angerer et al\textsuperscript{3} conducted a randomized, placebo-controlled, observer blinded trial of 321 postmenopausal women that received a Jadad score of 3. This comprised the largest cohort examined in this review. All participants were between the ages of forty and seventy, had undergone either surgical or natural menopause for one year or greater, and had serum FSH levels of greater than 40 IU/L. Inclusion criteria required that all participants have ultrasound documented increased intima-media thickness (IMT) in at least one segment of either carotid artery. Therapy consisted of 1 mg daily of 17β-estradiol continuously plus either 0.25 mg gestodene for daily for twelve days every month or daily for twelve days every third month—standard and low progestin groups respectively versus no HRT. Duration of the study was forty eight weeks, and endpoints measured were carotid IMT, total cholesterol, LDL cholesterol, serum fibrinogen, and serum FSH at 12, 22, and 48 weeks. Results of ultrasound analysis of carotid IMT actually increased in all groups, and the increase in both HRT groups was greater than the group with no HRT. However, the results were not statistically significant (P>0.2). Other outcome measures including LDL cholesterol and fibrinogen were statistically significantly reduced in both HRT treatment groups all with P values of < 0.001. Overall, this study demonstrated without statistical significance that, carotid IMT remained unchanged with HRT versus no HRT and that HRT did lower LDL cholesterol and fibrinogen levels, in both treatment groups.

Störk et al\textsuperscript{11} studied fifty one postmenopausal women who had experienced either natural or surgical menopause for more than one year and had serum FSH levels of > 40 IU/L in a prospective, randomized, placebo-controlled trial that received a Jadad score of 3. The average age of participants in this study was sixty years old. Therapy consisted of 1 mg 17β-estradiol daily plus 25 mcg gestodene for the last twelve days of either each month or every third month. To be included, all patients had exhibited >1.0 mm carotid IMT at some point of the carotid artery system. Participants were followed for one year. The endpoint measure was monocyte chemoattractant protein-1 (MCP-1), which is
considered a propagator of atherosclerosis. The results of this study demonstrated a 16.8% reduction in MCP-1 levels among HRT users as compared to placebo, indicating a possible anti-atherosclerotic effect among HRT users. Furthermore, this study concluded that in women stopping HRT, MCP-1 levels again rose while MCP-1 levels remained lowered in the group continuing HRT.

Finally, women with preexisting cardiovascular disease were studied by Hodis et al in the Women’s Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART). This randomized, double-blinded, placebo-controlled trial of 226 postmenopausal women with a mean age of 63.5 years, who were all younger than seventy five years of age, included only participants with a pre-existing coronary artery lesion. This study received a Jadad score of 5. Menopause was confirmed by a serum estradiol level of < 20 pg/mL, and treatment was with 17β-estradiol 1 mg daily either with or without 5 mg medroxyprogesterone acetate daily versus placebo. The primary outcome measure was percent change in coronary artery stenosis measured by coronary angiography. Women in this study were followed for a median of 3.3 years. The results of this study demonstrated no statistically significant difference among the unopposed estrogen, estrogen plus progestin, and control groups when comparing progression of coronary artery stenosis. However, interestingly, several other laboratory values were measured and participants in the estrogen and estrogen-progestin groups had a statistically significant increase in high density lipoprotein (HDL) laboratory values and decreases in cholesterol and LDL values as compared to placebo. Therefore, this study found that estrogen therapy created no change in coronary artery stenosis, however, it is important to note that an improvement in lipid profiles was demonstrated in the participants taking HRT.

Multiple endpoints for cardiovascular disease have been assessed in this systematic review. Overall it was found that in three studies atherosclerotic risk was decreased in women on HRT, in three studies atherosclerotic risk was increased in women on HRT, and one study indicated no slowing in progression of atherosclerosis but decreased risk for cardiovascular disease by improving lipid profiles.
Discussion

The primary goal of this review was to identify, based on the most current medical literature, whether the use of 17β-estradiol for HRT had an effect on various outcomes used to predict the progression of atherosclerotic and cardiovascular disease. The WHI study, a very large randomized placebo-controlled trial, demonstrated a possible deleterious effect with regard to the use of estrogen replacement therapy on cardiovascular disease. Though the landmark WHI study, taught us a great deal about the safe and effective use of estrogen replacement therapy, it is important to remember that the WHI study was not the final word on HRT. It was merely a starting point to identify a myriad of questions about HRT that remain without clear answers.

For example, in 2007, Rossouw et al\textsuperscript{12} examined hormone replacement therapy and its effect on cardiovascular disease in relation to the initiation of HRT and to the number of years since the onset of menopause. Rossouw et al found that women, who initiated HRT closer to the onset of menopause, had a decreased risk for cardiovascular disease when compared to women who initiated HRT further from the onset of menopause. Since participants in the WHI study ranged in age from fifty to seventy nine years old, initiating HRT in women closer to the onset of menopause could make a difference with regard to cardiovascular risk. In fact, in November, 2008, the American Committee on Gynecologic Practice (ACOG), issued a revised opinion on hormone therapy and heart disease and stated: “Hormone therapy use should be limited to the treatment of menopausal symptoms at the lowest effective dosage over the shortest duration possible and continued use should be reevaluated on a periodic basis.” This statement also recognized that, “women in early menopause who are in good cardiovascular health are at low risk of adverse cardiovascular outcomes and as such should be considered candidates for the use of [hormone replacement therapy].” The final outcome of the WHI study even suggested a decreased cardiovascular risk among the women included in the age group of fifty to fifty nine years old.\textsuperscript{13}
Another aspect of HRT that must be considered is route of administration. In the WHI trials, all hormones were administered orally. However, recent evidence has suggested that administering HRT transdermally may have a different effect on inflammatory markers, and may decrease cardiovascular risk when compared to oral HRT. It is hypothesized that this could be because of the fact that estrogen is extensively broken down in the liver via first pass metabolism and by administering HRT transdermally this effect may be attenuated. However, much more research is needed before a conclusive determination is researched.

This systematic review addressed another issue that must be taken into consideration when initiating HRT and that is the specific type of HRT that should be prescribed. In the WHI trials CEE and medroxyprogesterone acetate were used for HRT. Though CEE does produce beneficial effects of HRT such as reducing vasomotor symptoms, from a molecular, biochemical, and pharmacokinetic perspective, CEE introduces via breakdown products, types of estrogen such as equilin that are not naturally produced, and can lead to various inflammatory responses that are not created by biochemically identical 17β-estradiol. It is important to note that all of the studies examined in this systematic review demonstrated a decrease in cardiovascular risk in patients taking HRT when the endpoint measured was a serum biochemical marker. The studies that demonstrated an increased risk for cardiovascular disease in women taking HRT measured endpoints including percent coronary or carotid artery stenosis. This raises the question of whether HRT only improves biochemical profiles and does not have a positive effect on endothelial plaque formation, or if the mechanism by which estrogen produces a cardioprotective effect is much more complicated than just decreasing plaque formation in the arterial system. Though much more research remains to be done on this topic, it is important to note that the bioidentical form of estrogen could possibly be important especially to overall secondary effects of estrogen such as the reduction of inflammation and thus various risk factors for cardiovascular disease.
Though this review is limited by the fact that a countless number of confounding and modifying factors are present when studying a process such as cardiovascular disease progression in postmenopausal women, it does help to elucidate many of the topics that remain to be studied with regard to the overall and holistic health of postmenopausal women.

**Conclusion**

Based on the results of this literature review, evidence exists to support the fact that 17β-estradiol does in fact decrease biochemical markers for atherosclerotic disease including lipid and inflammatory markers in women using HRT. However, the use of 17β-estradiol does not positively affect the progression of atherosclerosis in carotid or coronary arteries. Therefore, 17β-estradiol may reduce cardiovascular disease risk but evidence does not suggest that this improvement in lipid profiles and inflammation actually affects atherosclerosis progression. The molecular mechanism by which estrogen produces cardioprotection is extremely complex and minimally understood, though research suggests that estrogen may act directly as a transcription factor and can produce long term and short term effects on vasculature and circulating mediators of cardiovascular disease.\(^4\) Many questions about the use of HRT in postmenopausal women remain and much research remains to be done including research to assess whether 17β-estradiol has a unique effect on cardiovascular risk when compared to other forms of HRT. Research on differential effects of starting HRT at multiple stages of menopause, on multiple routes of estrogen administration, as well as research on the usage of different molecular forms of estrogen should be conducted in the future to better establish the efficacy and, more importantly, safety of HRT for postmenopausal women.
References


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<td>17β-estradiol 2 mg/d + norethisterone 1 mg/d</td>
<td>2 years</td>
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<td>HRT increased platelet activation parameters</td>
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<td>Randomized, prospective, placebo controlled</td>
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<td>60 women, 45-60 years old</td>
<td>Amenorrheic 6 mo-5 yrs; FSH&gt;20 IU/L, estradiol&lt;150 pmol/L</td>
<td>Micronized 17β-estradiol 2 mg/d with or without trimegestone 0.5 mg/d or dydrogesterone 10 mg/d</td>
<td>12 weeks</td>
<td>ADMA level</td>
<td>HRT reduced ADMA levels with or without progestogen</td>
</tr>
</tbody>
</table>

**TABLE 1:** Comparison of trials examining 17β-estradiol for hormone replacement therapy in healthy postmenopausal women
<table>
<thead>
<tr>
<th>Author</th>
<th>Published</th>
<th>Study Type</th>
<th>Jadad Score</th>
<th>Method for determining cardiovascular disease</th>
<th>Patients/Population</th>
<th>Method for determining menopause</th>
<th>Intervention</th>
<th>Length of study</th>
<th>Endpoint measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angerer, P</td>
<td>2001</td>
<td>Randomized, placebo-controlled, observer blinded</td>
<td>3</td>
<td>Increased IMT in &gt;1 segment of carotid arteries</td>
<td>321 women, 40-70 years old</td>
<td>Natural or surgical menopause for ≥ 1 yr; FSH&gt;40 IU/L</td>
<td>17β-estradiol 1 mg/d + 0.25 mg gestodene for 12 d/mo or 12 d/every 3rd mo</td>
<td>48 weeks</td>
<td>Carotid IMT, chol, LDL, fibrinogen</td>
<td>HRT did not affect carotid IMT but did improve lipid profiles</td>
</tr>
<tr>
<td>Stö rk, S</td>
<td>2002</td>
<td>Randomized, prospective</td>
<td>3</td>
<td>&gt;1 mm IMT in carotid artery system</td>
<td>51 women, average age 60</td>
<td>Natural or surgical menopause for &gt; 1 yr FSH&gt;40 IU/L</td>
<td>17β-estradiol 1 mg/d + 0.25 mg gestodene for 12 d/mo or 12 d/every 3rd mo</td>
<td>1 year</td>
<td>MCP-1 level</td>
<td>HRT decreased MCP-1 levels</td>
</tr>
<tr>
<td>Hodis, H.N.</td>
<td>2003</td>
<td>Randomized, double-blinded, placebo controlled</td>
<td>5</td>
<td>At least one coronary artery lesion present</td>
<td>226 women, average age 63.5, must be &lt; 75 years old</td>
<td>Serum estradiol &lt; 20 pg/mL</td>
<td>17β-estradiol 1 mg/d with or without 5 mg medroxyprogesterone acetate/d</td>
<td>Median follow-up 3.3 years</td>
<td>Percent stenosis in coronary arteries measured by angiogram</td>
<td>HRT did not affect progression of coronary artery atherosclerosis</td>
</tr>
</tbody>
</table>

**TABLE 2**: Comparison of trials examining 17β-estradiol for hormone replacement therapy in postmenopausal women with pre-existing cardiovascular disease
## Appendix A

### Jadad Score Calculation

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study described as randomized (this includes words such as randomly random, and randomization)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the study described as double blinded?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was there a description of withdrawals and dropouts</td>
<td>0/1</td>
</tr>
<tr>
<td>Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)</td>
<td>0/-1</td>
</tr>
<tr>
<td>Deduct one point if the study was described as double blinded but the method of blinding was inappropriate (e.g., comparison of tablet vs injection with no double dummy)</td>
<td>0/-1</td>
</tr>
</tbody>
</table>