Despite the clear-cut epidemiological evidence of protective effects of endogenous estrogens in premenopausal women,\(^1,2\) the results of randomized clinical trials using conjugated equine estrogens and medroxyprogesterone acetate instead of natural hormones have led to a paradigm shift in the usefulness of hormone treatment in postmenopausal women.\(^3,4\) One of the main criticisms in addition to the types of drugs chosen for treatment was the age of the patients. Indeed, in both WHI trial and HERS study, treatment of patients was initiated in women many years beyond menopause.\(^5\) In fact, the number of years since menopause was an independent indicator for nonfatal myocardial infarction or coronary artery disease.\(^6,7\) In this context, it appears of interest that heart disease may contribute to menopausal age and that menopausal age actually may be an indicator of cardiovascular risk.\(^8,7\)

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It was noted as early as 1952 that the natural endogenous estrogen 17\(^\beta\)-estradiol inhibits experimental atherosclerosis,\(^8\) and oral estrogens were even unsuccessfully evaluated to treat coronary artery disease in male patients.\(^9-11\) However, at the time little was known about the mechanisms by which sex steroid hormones affect vascular homeostasis and thrombogenesis. During the past 2 decades, considerable advances were made in the understanding of how natural estrogens act on the vasculature. 17\(^\beta\)-estradiol causes rapid and endothelium-independent dilation of coronary arteries of men and women,\(^12\) and chronic treatment with 17\(^\beta\)-estradiol inhibits experimental atherosclerosis in males and females.\(^13,14\) On the other hand, treatment with conjugated equine estrogens, which contain more than 30 different steroid compounds including testosterone and substances of still undefined vascular activity (Table), have shown less favorable effects,\(^2-4\) as has been reported for the synthetic progestin medroxyprogesterone acetate.\(^5\) With the identification of molecular targets of 17\(^\beta\)-estradiol and other estrogens it now appears that estrogen receptor \(\alpha\) represents the predominant target mediating the beneficial effects of 17\(^\beta\)-estradiol,\(^2,14,16\) although novel isoforms of estrogen receptor \(\beta\)\(^17\) and novel targets such as GPR30\(^18,19\) have been identified. It is still unclear to what extent aging itself in the presence of coronary artery disease has any effects on vascular signaling and responsiveness to natural estrogen in postmenopausal women (Figure).

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Sherwood et al present results of a double-blind, crossover randomized clinical study investigating the short-term effects of transdermally administered 17\(^\beta\)-estradiol alone or in combination with norethindrone acetate or placebo on flow-mediated endothelium-dependent dilation in women with documented coronary artery disease shortly and many after menopause. The authors studied more than 100 postmenopausal women and found that aging, but not the presence of coronary artery disease, was a determinant of the beneficial effects of hormone treatment. Interestingly, only the treatment with 17\(^\beta\)-estradiol but not the combination of 17\(^\beta\)-estradiol and norethindrone acetate had a positive effect on endothelium-dependent vasoreactivity in younger postmenopausal women, whereas in older postmenopausal women neither treatment was effective, regardless of the presence of coronary artery disease. Importantly, endothelium-dependent vasomotion was preserved in younger postmenopausal women despite the presence of coronary artery disease.

Why are these findings important? (1) A very rigid study design was used to address the questions reducing bias to a minimum; (2) This study is the first to systematically compare effects of hormone treatment in postmenopausal women in 2 defined age groups; (3) The data show that hormone replacement with a natural estrogen can improve peripheral arterial vascular function even in the presence of angiographically documented coronary artery disease. The results presented by Sherwood et al indicate that the beneficial effects of 17\(^\beta\)-estradiol on vascular function occur within hours, comparable to what has been shown in premenopausal women during different stages of the menstrual cycle.\(^20,21\) A question that remains is whether such short-term effects of hormone replacement therapy also affect function or structure of arteries other than the brachial artery, which in humans is less likely to develop atherosclerotic lesions than coronary or carotid arteries.\(^22\) At least in vitro studies suggest that short-term treatment with 17\(^\beta\)-estradiol also augments endo-
Constituents of Drug Treatments (So-Called “Conjugated Equine Estrogens”) Used in Large-Scale Prospective Hormone Replacement Trials (HERS, WHI) in Postmenopausal Women

<table>
<thead>
<tr>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
</tr>
<tr>
<td>Sodium-estrone sulfate</td>
</tr>
<tr>
<td>Sodium-equilinsulfate</td>
</tr>
<tr>
<td>Sodium-17α-dihydroequilinsulfate</td>
</tr>
<tr>
<td>Sodium-17β-estradiol sulfate</td>
</tr>
<tr>
<td>Sodium-17α-dihydroequilinsulfate</td>
</tr>
<tr>
<td>Sodium-17β-hydroequilinsulfate</td>
</tr>
<tr>
<td>Sodium-equileninsulfate</td>
</tr>
<tr>
<td>Sodium-17β-estradiol sulfate</td>
</tr>
<tr>
<td>Sodium-delta 8,9-dehydroestrosulfate</td>
</tr>
<tr>
<td>Progestins</td>
</tr>
<tr>
<td>5α-Pregnane-3β, 20β-diol</td>
</tr>
<tr>
<td>5α-Pregnane-3β, 16α, 20β-triol</td>
</tr>
<tr>
<td>5α-Preg-16-en-3β-ol-20-one</td>
</tr>
<tr>
<td>5α-Pregnane-3β-ol-20-one</td>
</tr>
<tr>
<td>Sodium-4-pregene-20-ol-3-one-sulfate</td>
</tr>
<tr>
<td>3β-Hydroxy-5(10), 7-estriadiene 17-one-3-sulfate</td>
</tr>
<tr>
<td>Androgens</td>
</tr>
<tr>
<td>5α-Androstane-3β, 17α-diol</td>
</tr>
<tr>
<td>5α-Androstane-3β, 16β-diol</td>
</tr>
<tr>
<td>5α-Androstane-3β, 16α-diol</td>
</tr>
<tr>
<td>5α-Androstane-3β-ol, 16-one</td>
</tr>
<tr>
<td>Other substances</td>
</tr>
<tr>
<td>5,7,9 (10) Estratriene-3β, 17β-diol</td>
</tr>
<tr>
<td>17α-Dihydr-0-delta 8,9-dehydroestrevone</td>
</tr>
<tr>
<td>17β-Dihydro-delta 8,9-dehydroestrevone</td>
</tr>
<tr>
<td>5,7,9,(10) Estratriene-3β-ol-17-one</td>
</tr>
<tr>
<td>2-Hydroxyestron</td>
</tr>
<tr>
<td>2-Methoxyestron</td>
</tr>
</tbody>
</table>

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Whether hormone “replacement” therapy using 17β-estradiol from the results presented by Sherwood et al is the question whether hormone regulation by the estrogen receptor plays a role in the progression of atherosclerosis in the carotid or coronary arteries in postmenopausal women.28,29 In these studies, Hodis and coworkers investigated the effects of 17β-estradiol treatment on changes in intima-media thickness of the common carotid artery in postmenopausal women without evidence for ischemic heart disease and observed that treatment halted the progression of intimal thickening compared with placebo.28 Interestingly, the age of the patients was approximately 60 years. In the WELL-HART study the effects of chronic 17β-estradiol treatment in patients with documented advanced atherosclerosis as coronary artery disease over a period of 3.3 years were investigated.29 Patients were again older (mean age, 63.5 years) and on average 2 decades past menopause.29 Similar to the study presented by Sherwood et al reporting no effects on endothelium-dependent vasomotion in the brachial artery of older women, the WELL-HART study found no effect on established coronary atherosclerosis after 17β-estradiol treatment in older postmenopausal women.29 Interestingly, most recent studies suggest that hormone treatment may improve cardiovascular risk in younger postmenopausal women even when using conjugated equine estrogens.30,31

The data presented by Sherwood et al have important implications for cardiovascular medicine in general and the issue of hormone replacement therapy in particular. Based on the results of the randomized trials HERS and WHI using conjugated equine estrogens and medroxyprogesterone acetate as hormone therapy, guidelines on the use of postmenopausal hormone replacement therapy in patients with cardiovascular disease have been published by the National societies, including the American Heart Association. At a second look, it is not surprising that the use of drugs of unknown activities such as conjugated equine estrogens (Table) and medroxyprogesterone acetate, which is actually also used for chemotherapy, have resulted in adverse outcomes. Therefore, the question whether hormone “replacement” therapy with natural sex steroids may affect the course of atherosclerotic vascular disease cannot be currently answered (Figure). Future research should be directed not only toward deciphering the molecular mechanisms by which targets of estrogen regulate cardiovascular homeostasis, but also in the investigation of using natural steroids at lower doses, possibly using intermittent administration mimicking the menstrual cycle, long before the body has adjusted to the withdrawal of endogenous estrogens for many years.37 Prospective clinical trials are currently underway to address these issues, including the KEEPS study conducted by the Kronos Longevity Research Institute38 and the ELITE study performed at the University of California.39 Up to now, research indicates that using high-dosed regimens of sex steroids of unknown activity in postmenopausal women increases cardiovascular mortality, involving numerous mechanisms.40,41 The availability of clear-cut studies like the one by Sherwood et al will contribute to a more profound understanding of how natural estrogens modulate vascular function and atherogenesis (Figure). At the same time, it will be equally important to rigidly identify and treat known cardiovascular risk factors such as hyperlipidemia, hypertension, and obesity, which are independent predictors of coronary artery disease in women.42,43 Finally, information for patients about possibilities to improve cardiovascular health and prognosis such as simple changes in lifestyle including maintaining normal body weight, a healthy diet, and regular physical exercise should be intensely communicated.43
Cellular targets and possible mechanisms of effects of endogenous sex hormones and hormone therapy on the vascular wall during atherogenesis and aging. Activity of hormones is mediated by steroid receptors (ERα, ERβ1, ERβ2, ERβ3, ERβ4, ERβ5, GPR30, PR-A, PR-B, AR, and others) and receptor coactivators as well as enzymes (aromatase, COMT). Function of these targets and enzymes in the cardiovascular system has only in part been characterized. In the healthy vasculature, protective effects of endogenous estrogens include endothelium-dependent and -independent vasodilation, suppression of inflammatory response cascades and ROS formation, as well as inhibition of vascular smooth muscle cell (VSMC) proliferation. These mechanisms contribute to the inhibition of atherosclerotic vascular disease in premenopausal women and possibly also in men. As the development of atherosclerotic lesions progresses with age, the response to endogenous and also exogenous estrogens will also change. In fact, most of the effects of estrogens on the atherosclerotic vascular wall are unknown. The type of steroid used, duration, route of application (oral versus transdermal), mode of application (continuous versus intermittent), dose of hormone treatment, and the overall cardiovascular health of the patient including risk factors such as hypertension, high age, and obesity are determinants of therapeutic benefits. Artwork in part reproduced from Mendelsohn and Karas with permission from AAAS. AR indicates androgen receptor; COMT, catechol-O-methyltransferase; ER, estrogen receptor; LXR, liver X receptor; NO, nitric oxide; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; ROS, reactive oxygen species.

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Disclosures

None.

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Hormone Replacement Therapy and Atherosclerosis in Postmenopausal Women: Does Aging Limit Therapeutic Benefits?
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