Harnessing Hormonal Signaling for Cardioprotection

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Cardiovascular disease is the leading cause of death in women in the Western world and is predominant among the elderly. A large body of evidence suggests that hormonal signaling plays a critical role in the regulation of cardioprotective mechanisms, as premenopausal women are at significantly lower risk of heart disease compared with men, but the risk greatly increases with the onset of menopause. This association indicates that estrogen may protect the heart from cardiovascular disease. Whereas a number of analyses of the effects of hormone replacement therapy (HRT) on postmenopausal women supported the idea that estrogen is a cardioprotective factor, the findings of the more recent Women's Health Initiative (WHI) study suggested that HRT may actually increase the risk of cardiovascular events. These conflicting reports have left both patients and clinicians reluctant to continue using current HRT regimes. The WHI findings do not, however, negate the epidemiological link between menopause and increased cardiovascular risk. Hence, the identification of the specific actions of estrogen that promote cardioprotective pathways without enhancing deleterious vascular mechanisms may provide novel estrogen-based alternatives to current HRT strategies.

In this Review, we outline the known actions of estrogen on the cardiovascular system, focusing on cardioprotective mechanisms that may be targeted for the development of new therapeutic approaches.

Introduction

Menopause (http://sageke.sciencemag.org/cgi/content/full/sageke;2002/10/ns3) is the stage of life when female reproductive activity declines as a result of the significantly decreased production of the two major reproductive hormones: estrogen and progesterone. In addition to the cessation of the menstrual cycle, menopause is associated with a range of physiological changes, including (i) progressive bone loss (osteoporosis), (ii) vasomotor dysfunction (often manifested as hot flashes), and, perhaps most important, (iii) an increased susceptibility to cardiovascular disease (CVD).

Hormone replacement therapy and cardiovascular disease risk

For more than three decades, hormone replacement therapy (HRT, http://sageke.sciencemag.org/cgi/content/full/2003/38/nf18) was considered an effective treatment for postmenopausal symptoms and the prevention of CVD. HRT typically consists of the administration of estrogen, in the form of 17β-estradiol or conjugated equine estrogen (CEE), alone or in combination with a progestin (a synthetic hormone with progesterone-like activity) to replace the hormones that are no longer produced endogenously by the ovaries. The rationale for using HRT was based, in part, on the fact that CVD is relatively rare in premenopausal women, but its incidence after menopause rises significantly, approaching proportions similar to those seen in men (1). In addition, women undergoing premature menopause who do not use HRT are at increased risk of CVD compared with premenopausal women of the same age (2). Thus, hormonal signaling was thought to be a major factor in cardioprotection (2–4).

A number of observational studies supported this hypothesis, including the Nurses Health Study, which demonstrated that after menopause, women receiving estrogen either alone or in combination with progesterin experienced significantly fewer cardiovascular events over a period of approximately 20 years than those who did not use HRT (5, 6). In addition, studies such as the Postmenopausal Estrogen Progestin Interventions (PEPI) trial concluded that the use of combined therapy after menopause reduced circulating concentrations of cholesterol, low-density lipoprotein (LDL), lipoprotein(a), and fibrinogen, which are all risk factors for CVD (7).

Recent findings from large-scale clinical trials, including the Hormone Estrogen/progestin Replacement Study (HERS) and the Women’s Health Initiative (WHI) study, however, have cast doubt on the role of estrogen-mediated pathways in cardioprotection. In the HERS trial, women with a history of cardiovascular disease (CVD) were selected to test the efficacy of HRT in preventing further cardiovascular events (8). In the WHI study, on the other hand, the participants were, for the most part, women with no preexisting clinical signs of CVD (9). Both trials found that HRT consisting of a combined treatment of estrogen plus progestin resulted in an increased risk of heart attack (albeit during the first year of HRT alone) and stroke in postmenopausal women. In addition, the WHI trial found a greater number of cases of breast cancer among trial participants (10, 11), which exceeded the boundary of risk. On the basis of this increased incidence of breast cancer and a global index of risk (an increased number of coronary events, stroke, and pulmonary embolism) that exceeded benefits, the estrogen plus progestin arm of the WHI trial was prematurely halted. Notably, women in the WHI study who received HRT consisting of estrogen alone showed neither greater risk of cardiovascular events nor any benefit. However, as with women on the combined regime, women using estrogen alone had an increased risk of venous thromboembolism than those taking a placebo (12).
Caveats and confusion

Variations in study design, including differences in treatment regimens, end-point evaluation criteria, and populations studied, make it difficult to interpret the apparently contradictory findings of the observational studies and clinical trials. The Nurses Study, for example, has been suggested to consist mostly of “healthy users” who, by virtue of their lifestyles, may be less susceptible to CVD. The HERS and WHI trials recruited women whose average age was 63 and who therefore would have begun HRT a fairly long period after the onset of menopause, typically about 10 years later. Critics of the studies have argued that hormonal therapies may show a more pronounced positive effect on CVD prevention when administered closer to the time of menopause. Indeed, analysis of the global index of risk for women aged 50 to 59 in the estrogen-only arm of the WHI trial suggested that they responded favorably to estrogen therapy (12). In the combined estrogen plus progestin arm of the trial, women who were less than 10 years from the onset of menopause had a low hazard ratio for CVD, whereas those who began combined therapy 10 or more years after menopause had a significantly increased hazard ratio (13). Similarly, the Estrogen in the Prevention of Atherosclerosis (EPAT) trial demonstrated that younger postmenopausal women using unopposed estrogen (e.g., estrogen-based HRT that was not supplemented with progestin) had a slower rate of progression of atherosclerosis—the hardening of arteries due to lipid deposition and fibrosis—than women receiving a placebo (14).

Secondary prevention trials that examined the effects of HRT in postmenopausal women with coronary heart disease—such as the Estrogen Replacement on Progression of Coronary Artery Atherosclerosis (ERA) study, the Women’s Angiographic Vitamin and Estrogen (WAVE) study, and the Papworth HRT and Atherosclerosis Study (PHASE) (15–17)—further support the notion that delayed therapy cannot treat preexisting CVD, because no beneficial effects of HRT in reducing CVD were observed in these studies. Of these trials, only the ERA study specified that the onset of menopause in selected participants had occurred more than 5 years prior to the start of the trial. Thus, it is difficult to ascertain from these studies whether delaying HRT until after menopause plays a significant role in the progression of CVD. In addition, although the WHI trial aimed to recruit women with no signs of CVD, given the mean age of participants, it is likely that many had subclinical CVD. These conditions would have manifested themselves within the trial period regardless of treatment regime, as it is known that CVD risk increases with age and longer time from the onset of menopause.

Given these caveats, and the plethora of experimental data demonstrating that estrogen has proangiogenic and vasculoprotective effects, a beneficial role for estrogen on postmenopausal vascular function should not be dismissed prematurely. Indeed, it may be that the wide range of target tissues and downstream actions of estrogen prevent its effectiveness in blocking CVD in older women, suggesting that approaches that target estrogen’s positive effects on the cardiac vasculature may be beneficial and may circumvent the generation of unwanted secondary complications. However, regardless of the true extent of estrogen’s beneficial and deleterious effects, the use of HRT for treatment of postmenopausal symptoms and prevention of CVD has decreased considerably since the outcomes of the WHI trial were published and is unlikely to recover in the near future (18). Given this reality, it is important to identify the signaling pathways that specifically mediate the beneficial actions of estrogen on vascular function. This knowledge would provide novel targeted approaches for preventing CVD while avoiding the increased risks of stroke, cancer, and other pathologies, and thus provide patients with viable alternatives to current estrogen replacement strategies. In this Review, we outline some of the known mechanisms that may be targeted to promote the beneficial actions of estrogen, as well as alternatives to estrogen that may regulate similar vasculoprotective functions.

Estrogen’s Actions on the Vascular System

A comprehensive description of the cellular actions of estrogen that elicits its myriad effects on the vasculature is beyond the scope of this Review, and a number of excellent reviews may be consulted for more detail (19–21). However, a basic description of estrogen function is necessary to explain the hormone’s effects on the heart and vascular system. Briefly, estrogen, in the form of 17β-estradiol or estrone, diffuses through cell membranes to reach one of the two estrogen receptors (ERs), ERα or ERβ, located in the nucleus of the cell. Here, the receptors dimerize as either homo- or heterodimers and bind to estrogen response elements (EREs) located in the promoter regions of a wide range of genes, including those encoding for receptors, oncoproteins, growth factors, and other transcription factors (22). The binding of ERs along with cofactor complexes to these EREs acts to modulate gene transcription (21) (Fig. 1).

In addition to its nuclear actions, estrogen can elicit more rapid responses through pathways that do not require gene transcription (also referred to as nongenomic pathways) but involve the binding of estrogen ligands to ERα and ERβ localized at the cell surface. This binding triggers the activation of protein kinases—enzymes that trigger the phosphorylation of cellular proteins—including mitogen-activated protein kinases, growth factor tyrosine kinases (such as epidermal growth factor receptor), and phosphatidylinositol 3-kinase [associated with both AKT (http://sageke.sciencemag.org/cgi/content/full/2004/8/pe8) signaling, an important regulator of cell survival mechanisms, and the activation of endothelial nitric oxide synthase (eNOS), a mediator of nitric oxide (NO, http://sageke.sciencemag.org/cgi/content/full/2005/21/re4), which is a primary regulator of vascular tone] (23–26). These signaling pathways may also regulate gene transcription through the downstream actions of the kinases, for example. In general, the actions of estrogen that require responses within seconds or minutes, such as vasodilation via NO signaling, act through the more rapid nongenomic pathways, whereas changes that occur over longer periods of time, for example those involving changes in lipid levels or that protect against the progression of atherosclerosis, use the slower genomic pathways that involve transcriptional modification.

Beneficial effects of estrogen on the cardiovascular system

ERα and ERβ are encoded by different genes and exhibit different, but often complementary, patterns of expression. Studies that have examined the functions of these two receptors in vitro and in vivo help explain some of the known actions of estrogen on the cardiovascular system. In the heart, cardiac myocytes express both ER isoforms. Estrogen signaling is thought to be involved in cardiac remodeling after myocardial infarction and in protecting myocytes from apoptosis (http://sageke.sciencemag.org/cgi/content/full/2001/1/oa4#SEC8) (27, 28). Transgenic mouse models have revealed that a lack of ERs in cardiomyocytes results in the dysregulation of NO synthesis and an increase in the number of cardiac L-type calcium channels, which, in turn, increases the duration of ventricular action potentials and thus induces cardiac ar-
Atherosclerosis (atherosclerotic plaques) can inhibit the oxidation of LDL, a process that can lead to the narrowing of vessels due to the aberrant proliferation of vascular smooth muscle cells (55, 56). This latter mechanism is thought to depend on both ERs, because transgenic animals in which both genes encoding ERα and ERβ are knocked out, or antagonists to both receptors are used, estrogen treatment no longer inhibits smooth muscle proliferation of protection against atherosclerosis. Indeed, ERα protein expression is decreased in coronary arteries displaying atherosclerotic lesions (51), and this decrease may correlate with the increase in ERα gene methylation observed in clinical samples of coronary atherosclerotic plaques compared with healthy arteries (52). Furthermore, Post et al. have observed an increase in ERα gene methylation in cardiac tissue with increasing age (52).

The actions of estrogen on smooth muscle cells are also important for vasculoprotection. Estrogen attenuates smooth muscle cell proliferation both in vivo and in vitro (53, 54) and, after vascular injury, estrogen signaling inhibits neointima formation, the narrowing of vessels due to the aberrant proliferation of vascular smooth muscle cells (55, 56). This latter mechanism is thought to depend on both ERs, because transgenic animals lacking only one of the two genes do not display changes in estrogen response to carotid artery injury, suggesting the existence of compensatory mechanisms mediated by the remaining receptor. Indeed, when the genes encoding both ERα and ERβ are knocked out, or antagonists to both receptors are used, estrogen treatment no longer inhibits smooth muscle proliferation and neointima formation (57–59). Together, these studies therefore support a role for estrogen in protecting against the development of atherosclerosis.

A number of observational trials suggest that the potential cardioprotective actions of estrogen may depend on the degree of preexisting CVD at the time of therapy. For example, the ERA
clinical trial reported that women with preexisting atherosclerosis received no benefit from estrogen replacement therapy (15). Moreover, animal experiments comparing the effects of estrogen between healthy macaque monkeys and those that had received an atherogenic diet for two years before estrogen treatment demonstrated that the beneficial, antiatherosclerotic effects of estrogen were only evident in the healthiest animals (38). Thus, whereas estrogen may protect against the development of atherosclerosis, it does not appear to ameliorate existing CVD.

In addition to having vaso-protective functions, estrogen plays an important role in angiogenesis (http://sageke.sciencemag.org/cgi/content/full/2004/7/pe7), the growth of new blood vessels from existing blood vessels in response to vascular injury. Our group and others have demonstrated that the increased susceptibility to CVD with age is a result, in part, of the progressive dysregulation of angiogenic mechanisms that are essential to vascular maintenance and repair (60–62) [for a review, see (63)]. In vivo, estrogen is important for collateral vessel formation and microvascular remodeling, processes that are important to improving blood flow to ischemic tissue after vessel damage (64–66), and angiogenesis is impaired in ERα knockout mice (67). In vitro, estrogen increases proliferation, migration, tube formation, and survival of endothelial cells (68). Together, these data suggest that estrogen signaling may be essential to angiogenic repair mechanisms and that the proangiogenic actions of estrogen play a major role in the cardioprotection of premenopausal women.

Endothelial progenitor cell function
Recent evidence suggests that estrogen not only regulates local angiogenesis but also plays a role in postnatal vasogenic mechanisms through its actions on endothelial progenitor cells (EPCs; see Goldschmidt-Clermont Review at http://sageke.sciencemag.org/cgi/content/full/2003/45/re17 and Edelberg Perspective at http://sageke.sciencemag.org/cgi/content/full/2003/26/pe17). EPCs, which are largely derived from the bone marrow, make an important contribution to neovascularization after tissue injury, such as myocardial infarction or tissue ischemia (which occurs as a result of a low oxygen state) (61, 69–72). The mechanisms by which these cells are produced and then mobilized and recruited to sites of injury are not fully understood [for reviews, see (73, 74)].

Two studies have highlighted a novel role for estrogen in the generation of EPCs and their mobilization from the bone marrow into the systemic circulation. Estrogen treatment of ovariectomy-mized mice increases the number of EPCs (identified by the coexpression of the stem cell marker Sca-1 and the endothelial/EPC marker Flk-1) in the bone marrow and peripheral blood. The increase in EPCs is thought to be responsible for the improvement in re-endothelialization and diminished neointima formation in these mice following carotid artery injury (75, 76). The increased numbers of EPCs observed after estrogen treatment are, at least in part, due to increased cell survival, a result of the inhibition of caspase 8-dependent apoptotic pathways (75). Imanishi et al. have recently demonstrated that estrogen also inhibits EPC senescence in vitro and promotes proliferation of EPCs and their incorporation into forming vascular networks (77). These findings suggest that specifically targeting the actions of estrogen to the bone marrow, for example by developing selective estrogen receptor modulators (SERMs) that have estrogen agonist activity solely in the bone marrow cell population, may be a way to limit the effects of estrogen to a subset of cells that respond to vascular injury.

Negative actions of estrogen on the vasculature
Although the proangiogenic effects of estrogen may be beneficial in protecting against ischemic disease, the other side of the coin is that the progression of atheroma, the narrowing of blood vessels as a result of the accumulation of lipids, is also dependent on angiogenesis (78). It is therefore possible that whereas estrogen may be protective in preventing the onset of atherosclerosis, as described above, the angiogenic actions of estrogen may promote the growth of atherosclerotic lesions in individuals who begin HRT after developing atherosclerosis. Angiogenic pathways are also activated in tumors and are important in promoting neoplastic growth and metastases. Thus, the association between estrogen use, both as a contraceptive and as a form of HRT, and increased risk of breast cancer may be attributed, at least in part, to increased angiogenesis via local mechanisms and/or through the actions of EPCs (11, 79) (see also “Dangerous Liaisons” at http://sageke.sciencemag.org/cgi/content/full/2004/7/pe7).

In addition to increasing the risk of aberrant angiogenesis, estrogen signaling may confer other harmful effects on the cardiovascular system. Whereas estrogen treatment generally leads to lower concentrations of most inflammatory markers, expression of C-reactive protein (CRP), the concentration of which correlates closely with CVD risk, is notably up-regulated in women taking estrogen supplements (80). The full implications of this finding remain unknown, although evidence suggests that this effect of estrogen may be dependent on the route of administration, because no increase in CRP is seen in women using transdermal patches as the route of estrogen delivery (81). Estrogen also has well-documented prothrombotic effects—in other words, it induces mechanisms that promote the coagulation of blood and its subsequent adherence to the vessel wall, resulting in the formation of clots (10). Indeed, the incidence of stroke is higher among women taking high doses of estrogen or estrogen combined with progestin (6, 12). Lower doses of estrogen, however, appear to confer less risk of stroke (6). This difference may be related to the production of soluble adhesion molecules, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which promote coagulation and thrombosis and are regulated by estrogen in a time- and dose-dependent manner (82).

The use of unopposed estrogen can also result in an increased risk of endometrial cancer, because of the proangiogenic actions of estrogen on the uterus. The hormone progesterone exerts important actions on the uterus during the reproductive years that promote implantation of a fertilized ovum. For postmenopausal therapy, estrogen is often supplemented with progestins, which abrogate the proangiogenic effects of estrogen on the uterus and thereby reduce the risk of endometrial cancer. However, this regimen can also be damaging, because progestin can also attenuate the beneficial effects of estrogen on inhibition of atherosclerosis (83).

It remains unclear whether progestins contribute to the putative increased risk of CVD when used as part of HRT. Because unopposed estrogen appeared to confer neither increased risk nor benefit to cardiovascular health in the WHI trial, but the combined use of CEE and progestin increased CVD risk, it was suggested that progestin may be the detrimental factor. The actions of progestins on vascular function are, however, unclear, because outcomes of different clinical trials have produced varied results (84, 85). As with estrogen, it appears that differences in the dose and form of progestin may account for the differential effects in both clinical and experimental studies. For example, whereas medroxyprogesterone may attenuate the beneficial effects of estrogen on thrombo-
sis, natural progesterone does not have this effect (86). The results of the HERS trial suggested that combined therapy increased the risk of thrombosis in women with preexisting CVD compared with those taking estrogen alone (10). In the WHI trial, however, the risk of stroke was comparable in women taking either unopposed estrogen or combined therapy (87, 12). It is thus possible that progestins may have limited effect on thrombosis in healthy women but exert prothrombotic actions in those with existing CVD.

Targeting Selective Actions of Estrogen

Given the drawbacks of current estrogen-based replacement therapies, it would be valuable to develop novel approaches to regulate the vasculoprotective and angiogenic effects of estrogen and thereby limit the extent of estrogen’s deleterious effects, such as the increased risk of thrombosis and tumor angiogenesis. Based on our knowledge of the downstream actions of estrogen signaling, pharmacological approaches that specifically promote the positive effects of estrogen in a cell- or tissue-specific manner may provide favorable substitutes to current HRT.

Selective estrogen receptor modulators and other compounds

SERMs are nonsteroidal molecules with both estrogen agonist and antagonist effects, depending on their site of action. Although these compounds are not structurally related to estradiol, they interact with ERs at the ligand-binding domain and recruit cofactors to produce their effects (88). The most well-studied among this group of compounds is tamoxifen, a drug that acts as an antagonist to estrogen in breast tissue and is therefore commonly used to treat breast cancer, particularly when it is in advanced stages (89). As far as cardiovascular health is concerned, tamoxifen appears to have multiple protective functions, including (i) lowering cholesterol levels, (ii) acting as an antiinflammatory and antioxidant agent, (iii) promoting endothelial function, and (iv) decreasing the extent of both atherosclerosis and myocardial infarction (reviewed in (90)). However, this drug also has drawbacks. In uterine tissues, tamoxifen has estrogen agonist properties and thus its use carries an increased risk of endometrial cancer (89). In addition, tamoxifen use is associated with an increased risk of stroke and pulmonary thromboembolism (91, 92). For these reasons, the benefits of tamoxifen therapy to cardiovascular health may be outweighed by the risks of cerebrovascular events, which are particularly prevalent among the postmenopausal population.

Raloxifene, another SERM, has similar actions to tamoxifen in breast tissue but is antiestrogenic in the uterus, and its use therefore limits the risk of endometrial cancer. Like tamoxifen, raloxifene also acts as an estrogen agonist in bone, thereby preventing or limiting the rate of osteoporosis (see also “The Plot Thickens on Thin Bones” at http://sageke.sciencemag.org/cgi/content/full/sageke:2002/44/ns8). Whereas clinical trials have demonstrated that raloxifene promotes thrombosis to the same extent as tamoxifen or standard HRT (93–95), animal studies have revealed that raloxifene has beneficial effects on endothelial function and LDL concentrations (96, 97). Similarly, clinical trials comparing raloxifene therapy to placebo in healthy postmenopausal women, over periods ranging from 6 months to 2 years, have demonstrated reductions in LDL and cholesterol concentrations. However, these studies did not find corresponding increases in HDL, triglycerides, or CRP concentrations (98–101). A more recent study, the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, has shown that raloxifene does not provide any cardiovascular benefit to postmenopausal women with low risk of CVD. However, in women with high risk, raloxifene treatment was associated with a 30% decrease in the incidence of CVD (102).

Importantly, whereas the HERS and WHI trials showed that treatment with estrogen plus progesterone significantly increased CVD risk within the first year of use, there was no single year during the 5-year MORE trial period in which increased risk of cardiovascular events occurred. Thus, raloxifene appears to be a viable alternative to current HRT for postmenopausal symptoms, at least for women with preexisting CVD risk. Because the subgroup of women studied in the MORE trial consisted of a small sample size (~700 participants), results from the much larger Raloxifene Use in the Heart (RUTH) trial (>10,000 participants) are required to confirm the safety and evaluate the cardioprotective efficacy of this SERM.

Recently, another source of compounds with estrogen-like properties have come under scrutiny as mediators of cardioprotection. The phytoestrogens are plant-derived compounds that are similar in structure and activity to estradiol. Unlike estrogen, which has a similar affinity for both ER isoforms, many phytoestrogens preferentially bind to ERβ (103). The most studied agents in this category, the isoflavones, are found predominantly in soy-based foods such as soybeans and tofu. The high levels of soy protein consumption in Asian countries have been linked to the relatively low incidence of breast and prostate cancer and CVD, as compared with the rates in Western countries. Indeed, the U.S. Food and Drug Administration now states that higher amounts of soy consumption as part of a balanced diet may decrease CVD risk (104). It is unclear how much of the beneficial cardiovascular effects attributed to soy consumption may be a result of associated differences in diet and exercise between Western and Asian populations. Indeed, a recent systematic analysis of data concerning the effects of phytoestrogens on vascular tone (as measured by the daily frequency of hot flushes) found that these compounds confer no added benefit compared with placebo (105). Nevertheless, as with estrogen, experimental studies suggest that isoflavones have favorable effects on lipoprotein levels, endothelial function, blood pressure, and oxidative stress (106). In addition, isoflavones specifically up-regulate expression of eNOS and the genes encoding the antioxidants manganese superoxide dismutase (http://sageke.sciencemag.org/cgi/genedata/sagekeGdbGene;146) and cytochrome c oxidase (107). Given the potential benefits of phytoestrogens in preventing CVD, this class of compounds may prove to be a safe and efficacious alternative to traditional HRT strategies. However, much more research is needed to support the use of phytoestrogens as viable alternatives to estrogen.

Promise for the Future

In light of results from the HERS and WHI studies, estrogen-based replacement therapy is being limited in dose and duration and used only for the treatment of severe postmenopausal symptoms. Thus, it is imperative to develop alternative strategies, for example those that harness the potent cardioprotective actions of premenopausal hormonal pathways (as illustrated in Fig. 1), so as to limit the dramatic increase in CVD that occurs in women after menopause.

The use of selected SERMs, including the plant-based phytoestrogens, may represent such an alternative, although long-term analyses are necessary to evaluate the safety of these compounds. Another possibility is to target specific downstream actions of estrogen. For example, selective up-regulation of estrogen within the EPC population may promote proangiogenic effects without enhancing prothrombotic pathways. However, here too more research is needed to determine the extent of estrogen signaling that takes place in bone marrow-derived cells. Finally, the modifi-
cation of existing estrogen-based treatments should not be ruled out as a feasible option to replace current strategies. It should be noted that the WHI trial studied only one form of HRT (CEE plus medroxyprogesterone) at a single dose and using only one route of administration (oral). Because not all conventional therapies can be considered equal in their risks, further analyses of other forms of estrogen-based therapy are essential. Indeed, the variation in estrogen dose that women receive as part of HRT (about 0.3 to 0.625 mg CEE or 0.25 to 0.5 mg 17β-estradiol, taken orally, or about 20 mg 17β-estradiol absorbed daily via a transdermal patch) likely explains, at least in part, the discrepancies in the conclusions of various clinical and observational trials investigating the effects of estrogen on CVD. Furthermore, although oral administration of HRT is the predominant choice among postmenopausal women, evidence suggests that transdermal routes may be associated with lower CVD risk.

At the moment, the conflicting data concerning the safety of estrogen-based HRT has created confusion and decreased public confidence in this treatment. It is clear that more research and analysis is needed to determine the safest and most effective forms of therapy for postmenopausal women. However, the promising findings that have been generated along multiple lines of investigation suggest that alternatives to standard approaches will be available in the near future.

References


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