HEART DISEASE IS THE LEADING cause of death and illness for American women. Each year, about 250,000 American women die of coronary heart disease, the main form of heart disease. And nearly 90,000 die each year of stroke.

Heart disease is also the leading cause of death for men, but men and women differ in how and when heart disease develops. Typically, heart disease develops about 10 years later in women than in men.

The reason for this may be tied to women’s production of the hormone estrogen. When women go through menopause, their ovaries essentially stop making estrogen and their risk of heart disease rises dramatically. Eventually, it nearly equals that of men.

What Is Hormone Replacement Therapy?

Menopause denotes the completion of a full year without a period, including any bleeding, even spotting. It usually happens between the ages of 45 and 54.

Menopause can occur naturally or as the result of surgery. The procedure, called a hysterectomy, removes the uterus and sometimes the ovaries and fallopian tubes as well. Although a woman no longer has periods after a hysterectomy, she does not go through menopause unless both ovaries are removed—otherwise, menopause still occurs naturally.

Whether menopause occurs naturally or surgically, many women experience symptoms as their body adjusts to the fall in estrogen. The most common symptoms are hot flashes and flushes, sweats, and sleep disturbances. Other changes occur that may produce no recognized symptoms, such as an increased rate of bone loss that may result in osteoporosis. The osteoporosis may, in turn, lead to bone fractures usually after age 70. These symptoms may interfere with a woman’s regular activities. To relieve the symptoms, doctors may prescribe “hormone replacement therapy” (HRT). Today, this term is used to describe treatment with either estrogen alone or with estrogen and another hormone called progestin. The two hormones help regulate a woman’s menstrual cycle and progestin is added to prevent the overgrowth (or hyperplasia) of cells in the lining of the uterus.

Hormone therapy goes by various names, depending on the hormones used. “Estrogen replacement therapy” refers to treatment that uses only estrogen. “Combined progestin/estrogen replacement therapy” (PERT) is the use of both hormones.

Replacement therapies can be taken in several ways, including orally or through a patch on the skin. The hormones may be taken daily or on only certain days of the month.

New Possibilities for HRT

Women can greatly reduce their chance of developing heart disease by following certain behaviors—eating low-saturated fat, low-cholesterol foods; not smoking; being physically active; and keeping a healthy weight.

But, if estrogen helps protect women against heart disease, then it might offer...
another valuable preventive measure for many women past menopause. Through the years, evidence has accumulated suggesting that estrogen acts on some of the factors that define a woman’s risk of heart disease. These factors are listed in Box B.

For instance, estrogen seems to affect the levels in the blood of two important lipoproteins—high-density lipoprotein (HDL) and low-density lipoprotein (LDL). High-density lipoprotein helps remove cholesterol from the blood and is called the “good” cholesterol. Low-density lipoprotein carries most of the cholesterol and fat through blood vessels, where it can build up. LDL is called the “bad” cholesterol.

Both HDL and LDL are important risk factors for heart disease. For women, a low level of HDL appears to be the better predictor of heart disease risk—for men, a high LDL appears to be the better predictor. Estrogen seems to increase HDL and decrease LDL.

But it was thought that in addition to its benefits, estrogen use also posed risks—such as increasing both blood pressure and the chance of cancer of the endometrium, the lining of the uterus. The increased risk of endometrial cancer associated with estrogen-only therapy seems to be eliminated when estrogen is given with progestin. However, it was not known whether combined therapy might negate estrogen’s beneficial effects on heart disease risk factors and bone loss.

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**Box B: YOUR HEART DISEASE RISK PROFILE**

Certain factors can increase your chance of developing heart disease. These are called “risk factors.” The more risk factors you have, the more likely you are to develop heart disease—and the risk multiplies with each additional risk factor. So it is important to have as few risk factors as possible.

Some risk factors are beyond your control; others can be modified to reduce your heart disease risk. You can reduce your risk by adopting a healthier lifestyle—and, as a bonus, you’ll look and feel better too.

In choosing a hormone therapy, you and your doctor should talk over your heart disease risk profile.

The major risk factors for heart disease are as follows:

**Risk factors beyond your control—**
- Being age 55 or older
- Having a family history of early heart disease (this means having a mother or sister who has been diagnosed with heart disease before age 65, or a father or brother diagnosed before age 55)

**Risk factors under your control—**
- Cigarette smoking
- High blood cholesterol
- High blood pressure
- Diabetes (high blood sugar)
- Obesity
- Physical inactivity

Additional factors to consider—
- If you drink alcohol, do so in moderation
  While not a direct heart disease risk factor, drinking too much increases your risk of high blood pressure, which then increases your chance of heart disease. The Dietary Guidelines for Americans recommend that, for overall health, women have no more than one drink a day. A drink would be 1.5 ounces of 80-proof whiskey, 5 ounces of wine, or 12 ounces of beer (regular or light).
- Limit salt and sodium intake
  Sodium too is not a direct heart disease risk factor but increases the risk of high blood pressure. Salt is one form of sodium, so you need to watch your use of both. This includes whatever is added during cooking and at the table. Experts advise a total daily salt intake of no more than 6 grams, which equals about 2,400 milligrams of sodium.
The PEPI Study

To learn more about estrogen’s possible benefits and risks, the National Heart, Lung, and Blood Institute (NHLBI) and other units of the National Institutes of Health started a major clinical trial in 1987—the "Postmenopausal Estrogen/Progestin Interventions Trial," called PEPI.

PEPI’s other sponsors are the National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute on Aging.

PEPI was conducted at seven clinical centers across the United States. It followed 875 women, ages 45-64, for 3 years. All were healthy and postmenopausal, and about a third had had a hysterectomy. Participants included a variety of races but were predominantly white.

The women were closely monitored and had such tests as a yearly physical examination, mammogram, and, for those with a uterus, an endometrial biopsy.

The main goal was to see what effects different hormone regimens would have on some key risk factors for heart disease. The study also collected other information, including the regimens’ effects on quality of life, bone mass, and the risk of endometrial changes that might progress into cancer.

The four hormone regimens tested were:

- Estrogen alone, taken daily
- Estrogen taken daily and a synthetic progestin (medroxyprogesterone acetate), taken 12 days a month
- Estrogen and synthetic progestin taken daily
- Estrogen taken daily plus a natural progesterone (micronized progesterone), taken 12 days a month

The effects of these regimens were compared with those of a placebo, a substance that looks like the real drug but has no biologic effect.

The trial also compared for the first time the effects of cyclic and continuous use of progestin. Cyclic use means taking a medication for only some days of each month, while continuous use means taking the drug daily throughout the month. A main reason for the comparison was to see if continuous use produced less bleeding.

First Results—Heart Disease Risk Factors

A huge amount of information was collected in PEPI. Thus, the results will take time to be fully analyzed. But, because of their importance to women and their doctors, the findings are being released as they become available.

The first results, reported here, cover PEPI’s findings on changes in heart disease risk factors and on hormone safety.

For heart disease risk factors, key results are:

- Estrogen-only therapy raises the level of good HDL cholesterol. (This finding had been previously reported in short-term studies and can now be expanded to long-term effects.)

Box C: HORMONE THERAPY WITH ESTROGEN DOES NOT:

- Increase blood pressure
- Put women with high blood pressure at even greater risk of heart disease
- Cause weight gain

- Estrogen taken daily plus a natural progesterone (micronized progesterone), taken 12 days a month

The effects of these regimens were compared with those of a placebo, a substance that looks like the real drug but has no biologic effect.

• The combined estrogen-progestin therapies also increased HDL levels, although less than estrogen alone. At the same time, the addition of progestin produced the desired effect of reducing the increased risk of overgrowth of the lining of the uterus (endometrial hyperplasia) associated with estrogen-only therapy. The natural micronized progesterone produced a higher HDL level than the synthetic form.

• All of the hormone regimens decreased the level of the “bad” LDL cholesterol about equally well.

• Blood pressure was not increased by any of the hormone regimens.

• Fibrinogen levels were decreased by all of the hormones, which is thought to be a desirable change. Fibrinogen allows clots to form more readily, which increases the risk of heart disease and stroke.

• Insulin levels were not significantly affected by any of the hormone regimens. While fasting blood glucose seemed to be reduced by all of the regimens, the blood glucose 2 hours after eating seemed to be elevated by varying degrees. The importance of these changes is unclear, but they are of interest because of their relationship to carbohydrate metabolism and potentially to diabetes, which would in turn affect the risk of heart disease. These altered glucose levels need further evaluation.

• All of the hormone regimens caused a rise in triglyceride levels. These are fatty substances carried through the blood to tissues, where they are stored for use as energy. Their link to heart disease risk is not clear.

• None of the hormone regimens caused a significant weight gain.

For hormone safety, a key result is:

• Women with a uterus who took only estrogen had a higher risk of changes to the uterus lining. A third of these women developed serious abnormal cell growth of the endometrium. These hyperplasias can become cancerous but, if caught early, are treatable.

PEPI did not last long enough to study the effect of hormone therapy on the risk of breast cancer.

What Do PEPI’s Results Mean for You?

These results give women and their doctors guidelines to use in considering postmenopausal hormone therapy.

The results show that hormone therapy can benefit heart disease risk factors. They also emphasize that the choice of a hormone regimen must be based on many factors, including a woman’s heart disease risk profile.

Box D: TALKING WITH YOUR DOCTOR

Women need to be involved in their health care. Talk to your doctor about whether you should take a postmenopausal hormone therapy. Ask questions and express your concerns. For example:

• Should I take hormones? Why?
• How could hormone therapy improve my heart disease risk factor profile?
• At what age should I begin?
• What is the best regimen for me? Why?
• How long should I stay on the therapy?
• If breast cancer has occurred in my family, should I consider HRT?
• If I have had breast cancer, should I consider HRT?
• What followup tests will I need? How often will I need to have each test?

Your risk profile may change over time—review your health status with your doctor regularly.
Women need to be involved in decisions about their health care. Box D offers some questions women can discuss with their doctor or other health care provider.

In deciding whether to use a postmenopausal hormone regimen, women should consider these guidelines:

- Postmenopausal women who have not had a hysterectomy should consider taking a combination therapy that uses estrogen and progestin. If a woman with a uterus takes estrogen alone, she should have a yearly endometrial biopsy because of the risk of serious hyperplasias—this is vital for good health.

- Postmenopausal women who have had a hysterectomy should consider taking estrogen alone. These women are at no risk of endometrial changes, since they no longer have a uterus.

Will You Need Followup Tests?

Every woman should watch her health and this means taking a preventive approach.

For instance, women should be alert for side effects from any treatment, including hormone therapy. Women should discuss any side effect with their doctor.

If a woman has a uterus and takes estrogen-only therapy, she should have a yearly endometrial biopsy.

Finally, all women should know their cholesterol numbers—those for total, HDL, and LDL. If these numbers are known and are all right, then the levels can be remeasured within 5 years.

If women do not know these numbers, then they should have their total, HDL, and LDL cholesterol levels measured before starting a hormone regimen. If the decision to use replacement therapy is related to an expected improvement in HDL and LDL levels, then having this information at the outset gives “baseline measures” against which later tests can be compared. The response to hormone replacement can be measured in 6 or 12 months, or as advised by the doctor. If the levels are acceptable at that time, then they can be measured again once every 5 years. Those with high LDL cholesterol will have to take further steps to lower it.

What Lies Ahead?

PEPI is expected to release more findings in the future on endometrial and bone mass changes, and the effects of hormone therapies on quality of life.

Although data from PEPI will address a number of important issues, they will not answer all of the questions about the effects of replacement therapies. For instance, remaining questions include: How long should hormone therapy be taken? What’s the best age for a woman to start a hormone regimen? Do hormones actually reduce heart attacks and strokes?

Uncertainties also remain about the effects of hormone replacement therapies on breast cancer risk. So far, studies have reported conflicting findings. Most have reported a modest or no increased risk. However, others have reported significant increased risk in long-term hormone replacement users. Additional research is needed to more accurately assess whether there is an increased breast cancer risk and, if so, how to weigh this risk with the benefits related to hormone replacement use. Evidence currently available suggests that there is a small increased risk of breast cancer in hormone replacement users but that, for most women, the benefits of therapy probably outweigh the risks. Studies now under way include a large clinical trial and should eventually provide a basis for the development of more definitive guidelines.
Researchers at the National Institutes of Health and elsewhere are studying these and other questions about the effects of hormone replacement therapies.

For More Information

But, though questions remain, women need not wait to reduce their risk of heart disease. NHLBI has information to help women improve their risk profile. Materials cover such topics as heart-healthy eating plans and ways to become physically active.

Box E offers some easy ways to learn more. Or, contact:

NHLBI Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Phone: (301) 251-1222

The reward will be a healthier heart!

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**Box E: TAKING ACTION**

Every woman can reduce her risk of heart disease. The NHLBI has information to take you step by step on the path to better health:

- **Phone 1-800-575-WELL.** This NHLBI information line gives recorded messages about the prevention and control of high blood pressure and high blood cholesterol—two key heart disease risk factors. Callers can leave their name and address to receive more information about both conditions, as well as heart-healthy recipes.

- **Order The Healthy Heart Handbook for Women.** This publication, available from the Government Printing Office (GPO), is a workbook to help women reduce their risk of heart disease. It includes a sample walking program, a quit-smoking guide, and heart-healthy recipes. A copy costs $4.75, which includes postage and handling within the United States. Order forms are available through GPO. Write to: New Orders, Superintendent of Documents, P.O. Box 371954, Pittsburgh, PA 15250-7954. Give the publication’s title and number, which is S/N 017-043-00122-2.
Glossary

Atherosclerosis—The gradual build up of fatty substances in blood vessels, which become narrowed and less flexible, until blood does not flow easily through them or is completely blocked.

Cardiovascular disease—A disease of the heart or blood vessels. Cardiovascular diseases include heart disease, heart attack, stroke, and atherosclerosis.

Cholesterol—A waxy substance produced by the body and needed for many functions, such as helping to make cell membranes and some hormones.

Clinical trial—A scientific test that compares different treatments. It often uses a placebo for comparison and may be double-blind, which means that neither participants nor researchers and doctors know who is on what treatment.

Combined hormone therapy—When estrogen is taken with progestin.

Continuous hormone therapy—Taking hormones daily.

Coronary heart disease—A disease of the blood vessels of the heart that can cause heart attacks.

Cyclic hormone therapy—Taking hormones only on certain days.

Diabetes—High blood sugar, a serious disorder. The risk of death from heart disease is about three times higher for women with diabetes than for those without the condition. After age 45, about twice as many women as men develop diabetes. The condition can often be controlled or prevented with lifestyle changes, such as weight loss and physical activity.

Endometrial biopsy—Removal of some cells of the lining of the uterus for examination.

Endometrial hyperplasia—Abnormal growth of cells that line the uterus. If severe, it may develop into cancer.

Endometrium—Lining of the uterus.

Estrogen—Hormone produced by the ovaries until menopause and important in helping to regulate the menstrual cycle. It is now believed to help reduce the risk of heart disease.

Estrogen replacement therapy—Hormone replacement therapy that uses only estrogen.

HDL—High-density lipoprotein, often called the “good” cholesterol because it helps remove cholesterol from the blood.

HRT—Hormone replacement therapy in which estrogen is taken alone or with progestin.

Hypertension—High blood pressure, a condition in which blood pressure is at or above 140/90 mm Hg. It usually produces no symptoms but if not treated can result in serious health problems. It is a risk factor for heart disease and stroke.

Hysterectomy—Surgical removal of the uterus. A woman who has had her uterus removed but not her ovaries does not become menopausal until her ovaries stop producing hormones.

Lipids—Fatty substances, including cholesterol and triglycerides. Lipids are present in blood and tissues.

Mammogram—X ray of the breast, also called mammography.
Menopause—The end of menstruation, when
the ovaries stop producing estrogen,
progesterone, and other hormones. “Natural
menopause” applies to women who are usually
age 45-54 and who have gone 12 months
without a period, including no spotting;
“surgical menopause” refers to women who
have had both ovaries removed.

Micronized progesterone—A natural form of
the hormone progesterone.

PEPI—Postmenopausal Estrogen/Progestin
Interventions Trial, conducted at seven
American clinical centers. PEPI is the first
major clinical trial to examine the effects of
estrogen and progestin replacement therapies
on heart disease risk factors in postmenopausal
women.

Placebo—A substance that looks like a drug
but has no biological effect.

Postmenopausal—A woman who has gone
through menopause.

Progesterone/progestin—Two words often
used interchangeably. Progesterone is a
hormone produced by the ovaries until
menopause; it is important in controlling the
growth of cells lining the uterus. Progestin
is a synthetic form of progesterone.

Progestin—A synthetic form of progesterone.

Regimen—Schedule of medication.

Stroke—Damage to the brain resulting from
blockage of blood flow to the brain or from
hemorrhage (bleeding) of blood into the brain.

Triglyceride—A type of lipid carried through
the blood to tissues. Most of the body’s fat
tissue is in the form of triglycerides, stored for
use as energy.