In July 9, 2002, investigators in charge of the Women’s Health Initiative, the largest, most ambitious examination of menopausal women, abruptly stopped one arm of the study three years ahead of schedule. They and the National Institutes of Health, which provided funding, also took the unusual step of releasing preliminary trial results to the public. At the time, two out of five menopausal women in the United States were receiving hormone therapy, largely to protect them from cardiovascular disease. But the results of the WHI study’s randomized clinical trial demonstrated that the routinely prescribed combination of two hormones, estrogen and progesterin, was actually making many women more susceptible to heart attack, stroke, breast cancer and blood clots. That day, when reporters asked Isaac Schiff, chief of the Vincent OB/GYN Service at the Massachusetts General Hospital and editor of the journal Menopause, what women should do in light of the findings, his advice was clear: “If you’re taking hormone therapy to protect your heart, get off the drugs now.”

Millions of women did, including those whose primary motivation was to relieve the distressing symptoms—from hot flashes and night sweats to reduced libido—that afflict four out of five women entering menopause. Within a year, U.S. prescriptions of Prempro, the combination drug tested in the WHI trial, had plummeted 52%, and researchers in Australia, Britain and New Zealand had canceled a major hormone therapy trial that was about to begin.

That sudden shift was only the latest and most dramatic change in the prevailing attitude toward hormone therapy. Several times during its 80-year history, physicians and their patients have alternately embraced and rejected this approach to supplementing the ovaries’ production of estrogen, which falls off drastically at menopause. “In the early 1970s, estrogen was considered the fountain of youth, but by the middle of that decade, it had been identified as a cause of endometrial cancer,” says Schiff. “Then we added progesterin to estrogen because it protected against endometrial cancer, and hormone therapy was terrific again. Through the 1980s and ’90s, people thought it would prevent all sorts of diseases, including colon cancer, even though there was a suspicion it might cause breast cancer. Finally, the WHI threw cold water on hormone therapy. I’m not aware of any other medications for which advice has swung back and forth so strongly and so often.”

Once again, scientists are sharply divided over whether—and to what degree—hormone therapy should be rehabilitated. In the seven years since the WHI dropped its bombshell, the study’s results have been endlessly analyzed, with detractors wondering how a single randomized controlled clinical trial, even one as mammoth as this, could have negated dozens of observational and epidemiological studies that showed estrogen reduced women’s heart disease risk by as much as 50%. “A misunderstanding of the WHI results has turned off so many women and their physicians from hormone therapy,” laments Frederick Naftolin, director of reproductive biology research and co-director of menopause medicine at New York
University School of Medicine. “And there may be a price to pay. Women may die prematurely from heart disease and suffer unnecessarily from fractures or diabetes because they or their doctors didn’t want to consider estrogen.”

Naftolin and other estrogen researchers have become interested in a “timing hypothesis”: that if hormones are prescribed promptly at menopause, they’ll have the beneficial effect the WHI study seemed to disprove. These scientists fault the WHI for enrolling women who were many years past menopause—a demographic that didn’t match the newly menopausal participants in previous observational studies that had shown a positive cardiac effect from hormone therapy. “The women in the earlier research took hormone therapy when they started experiencing symptoms of menopause,” says S. Mitchell Harman, director and president of Kronos Longevity Research Institute, a sponsor of one of two new randomized controlled trials testing the timing hypothesis. “In the U.S., that’s at age 51, on average. But the women in WHI had an average age of 63—12 years past the onset of menopause—when they started taking these drugs.”

Other scientists consider the WHI findings definitive and use lipid-lowering statins to curb women’s cardiovascular risks and bisphosphonates to slow the development of osteoporosis, another condition that accelerates after menopause. But additional research and further shifts in the advice for women seem almost inevitable. “With evolution of the data since WHI, it is clear that hormone therapy still hasn’t been given the scientific justice it deserves,” says Howard N. Hodis, director of the atherosclerosis research unit at the University of Southern California.

The hormone estrogen is one of several chemicals secreted by a woman’s endocrine glands, principally the ovaries, starting in puberty. Because estrogen is essential to readying the body for pregnancy, its production falls off when ovulation stops. But it also has a profound effect on other parts of a woman’s body, from the heart and the brain to the blood vessels, the liver, the urinary tract and the digestive system. It keeps skin smooth, apparently by increasing its thickness and water content, and promotes cell growth that keeps bones strong and breasts firm.

All those benefits cease when a woman’s ovaries virtually end the output of estrogen. “The transformation, within a few years, of a formerly pleasant, energetic woman into a dull-minded but sharp-tongued caricature of her former self is one of the saddest of human spectacles,” wrote gynecologist Robert Wilson in his book, *Feminine Forever*.
Robert Wilson in his 1966 bestseller, *Feminine Forever*. Today those ideas might be couched in more politic terms, but no one questions the profound nature of the changes.

The solution that Wilson and many others advocated was to restore what nature had taken away. Supplementing estrogen, they said, could help women keep the outward appearance of youth and bestow a range of other benefits. Beginning in the late 1970s, studies seemed to confirm that hormone therapy prevents the rapid bone loss that women experience after menopause. What’s more, by bestowing women with favorable cholesterol profiles—with ample high-density lipoprotein and minimal levels of low-density lipoprotein—estrogen also appeared to halt, or at least to slow, the atherosclerosis that clogs coronary arteries and causes heart attacks.

Dozens of observational and retrospective studies, looking for a link between health outcomes and hormone therapy, have shown that women who took estrogen had significantly fewer heart attacks and bone fractures than did nonusers. The largest, most persuasive of these, the Nurses’ Health Study, began in 1976 with nearly 122,000 nurses between the ages of 30 and 55, and continues today.

There’s a problem with such studies, however. Observational research, which measures outcomes but does not control the parameters of the experiment, considers only those who’ve chosen to follow a particular regimen—in this case, hormone therapy—and that group may differ from the population at large. For example, when the Nurses’ Health Study started, physicians and patients already knew that young women who smoked and took birth control pills were having heart attacks and strokes. The culprit seemed to be the Pill’s high dose of estrogen, and so nurses who smoked or who otherwise were not in peak health may not have wanted to risk taking estrogen to alleviate symptoms of menopause. Doctors, too, may have offered hormone therapy only to their healthiest patients. Those tendencies could have biased results, showing a reduction in heart attacks for those receiving the therapy in part because women taking the drugs were predisposed by lifestyle or genetics not to get heart disease in the first place.

The only way to obtain objective, conclusive proof that hormone therapy helped protect against heart attacks and stroke was through a large clinical trial that randomly assigned women to hormone therapy or a placebo treatment and then tracked participants until they actually developed disease. In 1991, when the WHI was getting started, hormone therapy was associated with a slightly increased risk...
of breast cancer and blood clots. With the hormone therapy arm of the trial, the National Institutes of Health hoped to determine definitively whether the treatment’s presumed benefits—preventing heart disease, osteoporosis and colorectal cancer—were sufficient to outweigh the potential harm. WHI investigators recruited 27,000 women ages 50 through 79 to be studied during what was to be a 12-year trial.

Meanwhile, drugmaker Wyeth was impatient to get its estrogen-plus-progestin drug Prempro approved to prevent heart disease, and it funded its own smaller, quicker study. Beginning in 1993, the Heart and Estrogen/Progestin Replacement Study (HERS) enrolled 2,763 participants, all of whom had heart disease—the women must have had a heart attack, angioplasty, cardiac surgery or catheterization. Wyeth reasoned that if HERS proved that estrogen plus progestin prevented additional cardiac events, Prempro could be used by all menopausal women to safeguard their cardiovascular health.

But in 1998, after the end of the four-year trial, HERS investigators published findings that Prempro-taking participants, whose average age was 67, had a 50% increase in the risk of heart attack and related deaths during the first year of the trial, though women who made it past the first year did benefit from a reduced risk of cardiac events.

“If you didn’t have a heart attack in the first year, then hormone therapy began to be preventive,” says the MGH’s Schiff. Overall, however, averaging the results for women of all ages with existing heart disease, combination hormone therapy didn’t prevent subsequent cardiac problems. Nevertheless, a post-HERS survey of U.S. and European menopause experts revealed that many physicians dismissed those results. Though the poll didn’t ask why the doctors refused to change their views, their attitudes seemed to reflect the depth of a belief in the heart-health benefits seen in the Nurses’ Health Study and other observational research.

But the WHI results, announced four years later, reinforced the message that those benefits were illusory. When investigators halted the estrogen-plus-progestin arm of the study in 2002—an estrogen-only part of the trial continued until 2004—they were motivated by starkly negative findings. Though there were benefits, including a 44% dip in colorectal cancer risk and the chance of hip fracture dropping by a third, women on combination hormone therapy increased their risk of breast cancer by 24%, heart disease by 20%, stroke by 31% and blood clots by 106%. (The numbers of women represented by those percentages were small: 8 additional cases of breast cancer per 10,000 women each year, 6 more cases of coronary heart disease, 7 more strokes, 18 more cases of blood clots, 7 fewer colorectal cancers and 5 fewer hip fractures.) The estrogen-only WHI trial was also stopped ahead of schedule because estrogen seemed to confer no cardiac benefits and increased the risk of stroke by 39%, though one part of the estrogen-only trial population—women in their fifties and sixties—did have a lower risk of heart disease than those taking a placebo.

Regardless, the Food and Drug Administration responded with a package warning on both Prempro and Premarin (estrogen), stating they increased risk of cardiovascular disease. For the FDA and for thousands of doctors and millions of patients who thereafter shunned hormone therapy, the case seemed closed. It’s primarily the timing hypothesis that has
opened it again, and that idea largely hinges on an understanding of what happens to women's arteries after menopause.

As women age, most begin to develop atherosclerosis, characterized by calcified plaques in arteries and a thickening of the artery walls. Some researchers think the reason the WHI showed an increased risk of heart disease in women taking hormone therapy is that some already had atherosclerosis. “A fundamental principle of biology is that age matters,” says Hugh Taylor, director of the Division of Reproductive Endocrinology and Infertility at Yale University School of Medicine. “If we give hormone therapy to newly menopausal women whose coronary arteries are still in good shape, estrogen has a greater positive impact than if we wait until women are older and at higher risk of already having atherosclerosis. Intervening before a tissue is damaged is a lot more effective than doing so afterward.”

The timing hypothesis acknowledges estrogen's dual nature. In premenopausal women with healthy blood vessels, estrogen maintains a favorable balance of good and bad cholesterol to keep fatty deposits from building up on artery walls. The body's endogenous estrogen also keeps blood vessels relaxed and dilated to accommodate a strong blood flow. Moreover, it helps regulate insulin to prevent diabetes, which can also lead to heart attacks.

But once menopause really takes hold and the ovaries dramatically reduce estrogen production, cholesterol starts accumulating on artery walls until it traps plaques composed of cells that become calcified. The artery walls grow thick and rigid, restricting blood flow, and starting hormone therapy at that point may be what gets some women into trouble. Supplemental estrogen, with or without progestin, may stimulate inflammation in the arteries, which can cause a plaque to become unstable and rupture, spewing debris. The clot that forms around that debris—perhaps helped by estrogen's clotting factors—can block the vessel, causing a heart attack or stroke. The rupture of plaques probably happens soon after a woman starts hormone therapy, which may be why both the HERS and WHI studies showed sharp increases in heart attacks for women in the studies' first year.

After the WHI ended, some of the study's investigators used CT scans to assess the degree of atherosclerosis in estrogen-only study participants aged 50 to 59. Those women had 20% to 40% less coronary-artery calcification than did women in the study's control group—and the improvement was as much as 60% for those who were scrupulous about taking the medication during the trial.

For the FDA and for thousands of doctors and millions of patients, the case on hormone therapy seemed closed. It's primarily the timing hypothesis that has reopened it.
Two randomized controlled trials now under way are examining aspects of the timing hypothesis. The Kronos Early Estrogen Prevention Study (KEEPS) will track measures of coronary artery calcification and arterial wall thickness in 728 newly menopausal women to determine whether hormone therapy with estrogen and progestin prevents or reduces the progression of atherosclerosis. A second trial of 504 women, Early Versus Late Intervention Trial With Estradiol (ELITE), will test the timing hypothesis head-on by comparing the ways both estrogen-only and estrogen-plus-progestin therapy affect the progression of atherosclerosis in women who have recently stopped menstruating vs. women who have been in menopause 10 years or more. In addition, the trials will study different formulations of hormone therapy, including natural progesterone and estrogen (estradiol), lower and cyclical doses, and alternative routes of drug delivery, such as a transdermal patch and a vaginal progestin gel. Though opinions vary widely about whether dosage, delivery systems and hormone formulations may affect the results of hormone therapy, these trials’ investigators want to factor in as many variables as possible.

Both trials will also examine the effect of hormone therapy on quality of life, including mood and verbal and spatial ability. “Observational studies have shown that women who take supplemental estrogen have a lower incidence of Alzheimer’s disease,” says Yale’s Taylor, a KEEPS investigator. “The damage of Alzheimer’s is irreversible, and if you don’t intervene early with hormone therapy, you may lose the chance to preserve that cognitive function.”

Because the two trials are measuring the progression of atherosclerosis as a reliable predictor of cardiovascular disease rather than looking at the actual incidence of disease—which would require following participants for many years—their findings, to be released in 2010 (ELITE) and 2012 (KEEPS), won’t prove or disprove the timing hypothesis. But, says NYU’s Naftolin, who is also an investigator for KEEPS, “the trials will have sufficient power to make the point that either the WHI...”

The Cancer Question //

There’s little doubt that hormone therapy affects a woman’s risk of malignancies. But that’s where the clarity ends.

Even if new research restores hormone therapy’s reputation as a tool for fighting heart disease, there remains another reason many physicians are reluctant to recommend it: cancer. It’s a complex issue, says oncologist Rowan Chlebowski, a researcher at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and an investigator for the Women’s Health Initiative. “Combination therapy,” he notes, “increases the risk of breast cancer, but estrogen alone may decrease it; estrogen increases endometrial cancer, but combination therapy prevents it; and combination therapy reduces colon cancer, while estrogen has no effect.”

Breast cancer is what patients of Hugh Taylor, director of the Division of Reproductive Endocrinology and Infertility at Yale University School of Medicine, fear most. And though he feels comfortable reassuring women that supplemental estrogen by itself does not cause breast cancer, according to WHI findings, he can’t do the same for women taking estrogen with progestin.

Chlebowski points out that 20,000 fewer cases of breast cancer were detected the year following the release of the 2002 WHI findings and millions of women stopped taking combination hormone therapy. And the women taking estrogen plus progestin in the WHI trial had a 43% reduction in breast cancer risk soon after they stopped the therapy. So, he says, while a woman’s risk of breast cancer returns to normal within a year or two of ending combination hormone therapy, taking estrogen with progestin for longer than five years results in a persistent doubling of breast cancer risk. “I think the risk of breast cancer has been marginalized too much,” he says.

Marcia Stefanick, chair of the WHI steering committee and a professor of medicine, obstetrics and gynecology at Stanford University School of Medicine, agrees. “The problem I have with this drumroll to get hormone therapy back on the market is that the WHI showed that combination therapy offers no benefit for cardiovascular disease, and we have very clear evidence that it increases risk of breast cancer and stroke in women 50 and older,” she says. “We have enough data to suggest that we should discourage women from taking combined hormone therapy for more than two or three years.”
was correct and there is no cardioprotective effect of hormone therapy or that the WHI was wrong and hormone therapy does protect younger women.” If there does seem to be a protective effect, he adds, “we may convince the timing hypothesis needs to be looked at with a much larger trial.”

Kronos president Harman envisions a day in the near future when women are again encouraged to take hormone therapy as a preventive agent, as they were prior to the WHI. “If we can show that hormone therapy is cardioprotective, younger women at risk for heart disease may be advised to take it even if they don’t have severe menopausal symptoms, provided they aren’t also at high risk for breast cancer,” he says. “You have to consider that breast cancer kills about 4% of women and heart disease kills 10 times that many. If you have an intervention that increases the risk of breast cancer by 30%, which estrogen studies have shown, but decreases the risk of heart disease by 40%, which observational studies showed, that’s a pretty good tradeoff. Most women might be better off taking estrogen and having a mammogram each year than taking a chance of having a heart attack.”

But for many women, who worry more about breast cancer than heart disease, that’s not a comfortable exchange. Some proponents of hormone therapy are more cautious, recommending that, regardless of whether the timing hypothesis is proved, younger women take hormone therapy for no more than five years and only for relief of menopausal symptoms. “I believe that at present, hormone therapy should not be started or continued for the express purpose of trying to prevent cardiovascular disease in any woman,” says JoAnn Manson, chief of the Division of Preventive Medicine at Brigham and Women’s Hospital in Boston and a principal investigator of both WHI and KEEPS. “In order to get cardiovascular benefits, you’d probably have to take it for many years—long enough to increase your risk of breast cancer, especially with combination hormone therapy. And the same may apply to using estrogen to prevent osteoporosis. We need to know if lower doses and different formulations of hormone therapy, as we’re studying in KEEPS, confer a more favorable tradeoff.”

But the alternative treatments for heart disease and osteoporosis—statins and bisphosphonates, respectively—may have problems of their own. “After the WHI, everyone jumped to put women at risk of osteoporosis on bisphosphonates, thinking it was safer,” says USC’s Hodis, who is a principal investigator for ELITE. “But the drugs hadn’t been around long enough to collect much data, and now we find that some women taking bisphosphonates have bone loss in the jaw, which causes them to lose teeth, and atrial fibrillations, which can cause stroke or death in 10% of people. And since the drug stays in bone forever, the long-term risks, such as bone cancer, remain unknown.”

A final, definitive decision about whether hormone therapy is a safer way to fight heart disease and bone loss in older women won’t come from ELITE and KEEPS. Indeed, it may never come, as additional research inevitably brings new complications and exceptions to any therapeutic approach. But these latest studies could help physicians become more comfortable in identifying the women least likely to be harmed by hormone therapy. “I see women whose lives are destroyed when severe symptoms of menopause wreck careers and relationships,” says Yale’s Taylor. “If the new research lets us safely restore quality of life in at least some women who are having an awful menopause, that alone will be no small comfort.”

### DOSSIER

1. “Can Menopausal Hormone Therapy Prevent Coronary Heart Disease?” by Eliot A. Brinton, Howard N. Hodis, George R. Merriam, S. Mitchell Harman and Frederick Naftolin, Trends in Endocrinology & Metabolism, August 2008. The authors make the case for the timing hypothesis, citing meta-analyses of randomized trials that show cardioprotective effects of hormone therapy in women younger than 60.

2. Hot Flashes, Hormones, and Your Health: Breakthrough Findings to Help You Sail Through Menopause, by JoAnn E. Manson with Shari S. Bassuk (McGraw Hill, 2007). The consumer-oriented title belies a serious approach to the topic: Manson, a Women’s Health Initiative investigator, interprets the confounding results of the trial.

3. The Estrogen Elixir: A History of Hormone Replacement Therapy in America, by Elizabeth Siegel Watkins (The Johns Hopkins University Press, 2007). Watkins artfully tells the fascinating story of hormone therapy, which was influenced as much by science as it was by the rise of feminism and the medicalization of menopause.