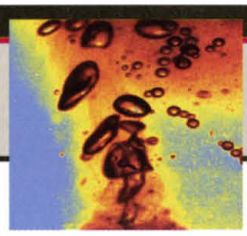
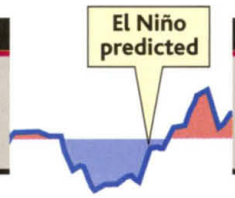


PAGE 496
Bubble fusion deemed unlikely




497
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EPIDEMIOLOGY

# Despite Safety Concerns, U.K. Hormone Study to Proceed

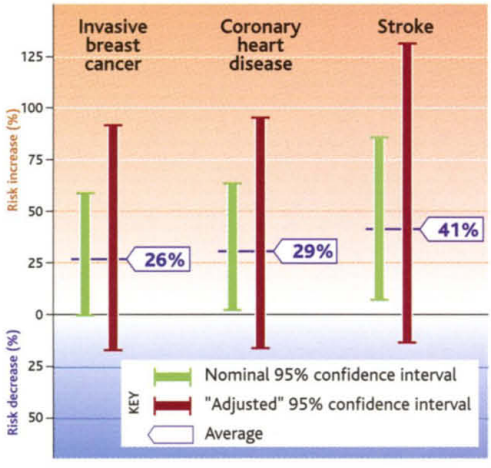
When a huge U.S. study of hormone drugs came to an abrupt standstill 2 weeks ago, women's health experts cast a curious glance across the Atlantic. Would leaders of an even bigger trial funded by the U.K. government and the Medical Research Council be shaken by the damning evidence of risk from the Women's Health Initiative (WHI)? Would they halt their study and advise participants to stop taking their pills? Not at all, is the surprising answer.

Meeting last week, an independent safety panel for the $32 million Women's International Study of long Duration Oestrogen after Menopause (WISDOM) unanimously concluded that WHI's evidence that hormone replacement therapy raises the risk of heart disease is not convincing. The trial's steering committee, equally skeptical, decided to forge ahead with WISDOM. The U.S. researchers "have not determined the size of the risks reliably," says the chair of the steering committee, Oxford epidemiologist Rory Collins. This split, according to many observers, reflects a difference between cultures as much as a disagreement over the science.

The British researchers argue that WHI's ambiguous results make WISDOM even more important. Proponents of hormone therapy also take heart in the prospect that WISDOM's fresh data might offset the recent findings. But the decision is drawing criticism from some U.S. researchers, who say the study puts women at unnecessary risk. "It may be good for science," says epidemiologist Curt Furberg of Wake Forest University in Winston-Salem, North Carolina, "but patients will pay the price." WHI director Jacques Rossouw calls the British misgivings about his study "bogus."

Both WHI and WISDOM were designed to test a combination of estrogen and progestin. These hormone substitutes are taken by millions of women to counter short-term menopausal symptoms such as hot flashes and insomnia, or to prevent age-related diseases over the long term, such as osteoporosis and heart attacks (*Science*, 19 July, p. 325). More than 16,000 U.S. women participated in WHI; WISDOM has enrolled 5000 British women so far but aims to recruit 17,000 more in the United Kingdom, Australia, and New Zealand.

The U.S. trial ended when an independent data and safety monitoring board (DSMB) concluded 31 May that the increased risk of breast cancer from hormones had crossed a previously set line. Typically, DSMBs study the accumulating data several times a year and recommend quick action if early results show that a drug is clearly effective—making it unethical to continue participants on placebo—or clearly harmful. Statistics can help clarify the choices, but "in the end, it's often a difficult decision," says statistician Janet Wittes, president of the Statistics Collaborative in Washington, D.C., and chair of the panel that has monitored WHI since 1997. In the case of WHI, the data failed to convince WISDOM's counterpart review panel, chaired by statistician Richard Gray of the University of Birmingham, U.K.




**Uncertainty.** The range of likely risk from hormone therapy is wider when the data are adjusted for multiple sampling.

The two teams look at risk differently. In their paper in the 17 July issue of the *Journal of the American Medical Association* (*JAMA*), the U.S. researchers present the average risks for each adverse outcome along with a "confidence interval"—a range of values between which the true value lies with 95% certainty. But the approach has a problem, says Gray: Analyzing data multiple times and testing for several outcomes increases the chances of getting a spurious result.

The WHI team also presented "adjusted confidence intervals," statistically corrected for multiple sampling, which show a different picture. For each of the three main adverse outcomes, the adjusted range includes the possibility of no increased risk at all or even a decreased risk (see graph). That leaves room for doubt about hormones' effect on heart disease, says Gray—especially because the increased risk conflicts with previous data. (His panel does not question the findings on stroke and breast cancer.)

To Rossouw, this is a quibble. He says the adjusted intervals were put in the *JAMA* paper mainly as a service to "aficionados," adding that most trial reports never even mention them. He thinks the WISDOM researchers are looking for "an excuse to dismiss the results. … They have their own trial to protect."

The rift highlights how ethical frameworks differ on opposite sides of the Atlantic, others say. Whereas U.S. DSMBs tend to emphasize individual patients' safety, "the Brits are much more comfortable proceeding with a trial in order to get statistically significant results," says Wittes. Collins points out, however, that stopping a trial early is not always the best way to protect patients. He recalls that several U.S. trials of AZT, the first AIDS drug, were cut short because it seemed to prolong life. But despite pressure to halt, a French-British collaborative study, called Concorde, continued and eventually showed that AZT alone had no overall effect on mortality.

What remains unclear in this technical debate is how women in the U.K., Australia, and New Zealand will respond. Will they want to enroll in WISDOM now that American participants have been advised to stop taking the pills? All current and future WISDOM participants will be told about the U.S. results, says Collins, and some might opt out. But it's possible that the dropouts will be offset by newly motivated recruits. In the past, some women were so convinced about the benefits of therapy that they refused to participate, he says. Some might now enroll in WISDOM to support a second look at that question.

—MARTIN ENSERINK

SOURCE: *JAMA*