

# The Discrepancy between Observational Studies and Randomized Trials of Menopausal Hormone Therapy: Did Expectations Shape Experience?

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Differences between observational and randomized studies of the effects of menopausal hormone therapy (HT) on coronary heart disease (CHD) have been attributed to the fact that women who choose to use HT tend to be healthier than those who do not. Although this bias should affect all clinical outcomes with modifiable risk factors, estimates for stroke and pulmonary embolism were unaffected. The authors sought possible explanations for this isolated discrepancy in CHD findings.

Unlike the randomized Women's Health Initiative (WHI) trial, the observational Nurses' Health Study (NHS) did not try to detect silent myocardial infarctions. Many women present with atypical ischemic symptoms. Hormone therapy users who believe that HT reduces CHD risks might not interpret ischemic symptoms as related to CHD, might not seek medical attention, and might present differently to their physicians, all of which could lead to more unrecognized myocardial infarctions among HT users in the

NHS. In addition, persons completing death certificates and NHS physicians interpreting death certificates were not blinded to the use of HT. If persons assigning cause of death knew the patient had used HT and believed that HT prevented CHD, they might have been more likely to assign a condition other than CHD as the cause of death. If HT users were 20% less likely to have their infarctions recognized and their deaths attributed to CHD, a true increase in CHD due to HT use would appear to be a reduction in CHD. Combining these reporting biases with socioeconomic differences between users and nonusers could explain discrepancies. Beliefs held by patients, clinicians, and investigators might have affected the ascertainment of CHD outcomes in observational studies.

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Although many observational studies have found that postmenopausal hormone therapy (HT) reduced the risk for coronary heart disease (CHD) (1–3), recent randomized trials have challenged this “truth.” When a randomized study of HT (4) reported an increased risk for recurrent CHD among HT users, the discrepancy was interpreted as evidence that “experimentation trumps observation” (5). The conclusions of dozens of observational studies were attributed to a consistent bias because consistent biases are expected to yield consistent results (5).

The choice by healthier women to use HT—the “healthy-user effect”—was proposed as the principal explanation (6–8). Women who choose to use HT have better cardiovascular risk profiles and are more educated than women who do not choose to use HT (9–11). Although many observational studies were adjusted for several potential confounders, not all differences between users and nonusers could be measured, nor could adjustment be complete.

Few studies adjusted for socioeconomic status, an important predictor of morbidity and mortality (12). Studies that corrected for socioeconomic status reported a higher relative risk for CHD events compared with that reported in studies that did not correct for socioeconomic status (relative risk, 0.97 vs. 0.71) (13). Even studies that corrected for socioeconomic status, however, continued to find that current HT use prevented CHD death (relative risk, 0.62) and had no effect on incident CHD, suggesting that differences in socioeconomic status among HT users only partially account for discrepant CHD findings.

Other related biases have been described. Hormone therapy users adhere to treatment regimens more often

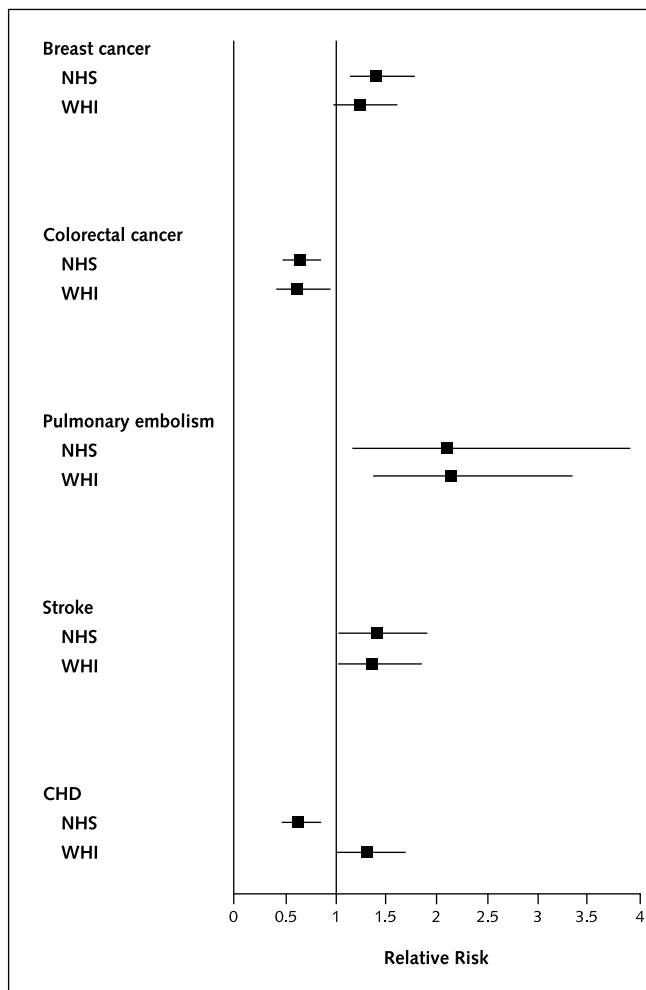
than nonusers, and adherent patients have a lower risk for CHD than nonadherent patients (14, 15). Hormone therapy users have more frequent contact with physicians than nonusers, which may lead to better clinical outcomes.

Selection biases should affect all clinical outcomes; the healthy-user effect should especially affect clinical outcomes with important modifiable risk factors. The magnitude of the effect is expected to be proportional to the extent to which lifestyle factors affect risk. However, risk estimates from the observational Nurses' Health Study (NHS) (2, 16) were concordant with those from the randomized Women's Health Initiative (WHI) trial (17, 18) on all major clinical outcomes except CHD (Figure 1). Coronary heart disease and stroke share the same modifiable risk factors (19–21), and pulmonary embolism is closely associated with atherosclerosis (22). Therefore, any biases that select women at lower risk for CHD should also select women at lower risk for stroke and pulmonary embolism, although to varying degrees.

Differences in the diagnostic criteria for CHD in the NHS and the WHI trial could result in an isolated discrepancy in CHD end points. Diagnostic (or reporting) bias would occur if the diagnosis or classification of an outcome were influenced by knowledge of the patient's exposure status (23–25).

The WHI trial and the NHS defined CHD as the combined end point of nonfatal myocardial infarction and CHD death. However, their definitions of these end points differed substantially in ways that could have introduced bias (26, 27) (Appendix Table, available at [www.annals.org](http://www.annals.org)).

**Figure 1. Pairwise comparison of the relative risk for various neoplastic and vascular clinical outcomes associated with menopausal hormone therapy use reported in the Nurses' Health Study (NHS) and the Women's Health Initiative (WHI) trial.**



### NONFATAL MYOCARDIAL INFARCTION

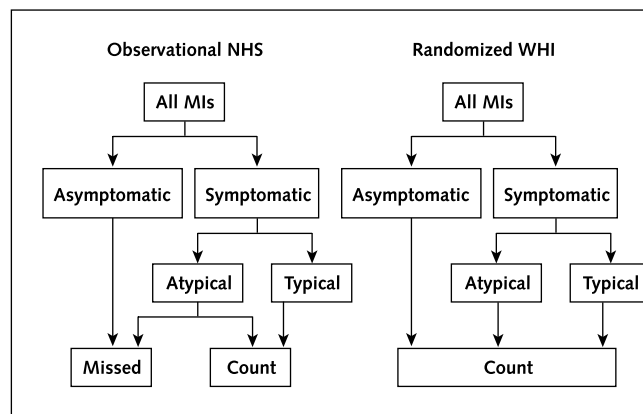
Approximately one third of myocardial infarctions among women are unrecognized (or “silent”) and are detected only by routine electrocardiography (28–30). About half of affected patients have no symptoms; the remainder have atypical symptoms. The WHI trial included silent infarctions. The NHS did not. Excluding silent infarctions could affect the comparative risk for nonfatal CHD if HT use influenced ascertainment of silent infarctions (Figure 2). Because they often present with atypical ischemic symptoms (31–33), women who believed that HT reduced the risks for CHD might be less likely to interpret ischemic symptoms as related to CHD, might not seek medical attention, and might present differently to their physicians, leading to more unrecognized infarctions among HT users. Because mortality rates after silent and recognized in-

farctions are similar (28, 30, 34), excluding silent infarctions should not substantially affect the risk for CHD death. However, exclusion of unrecognized infarctions could lead to systematic undercounting of nonfatal CHD events, which account for more than 75% of CHD events. No analyses have explored the prevalence of silent infarctions according to HT use. However, the higher rate of silent events among women has been attributed to the belief that CHD is uncommon among women (35, 36). The only observational study to conclude that HT substantially and significantly increased incident CHD risk, the Framingham Study (37), included silent infarctions in the count of CHD events.

### CHD DEATH

Deciding whether a death, especially a sudden death, resulted from CHD can be subjective. Approximately 70% of CHD deaths occur suddenly outside the hospital, and only half are associated with previous angina or infarction (38). Because cardiac arrest is the common final pathway to death from other diseases, many death certificates list CHD as a cause of death. Whether CHD was listed as the primary cause of death in the NHS, however, was at the discretion of the study investigators who used medical records and interviews with family members to ascertain the most plausible cause of death. Inferring cause of death often involves subjective reasoning and the discretion of the physician preparing the death certificate. If the physician, the family member interviewed, or the investigator interpreting the death certificate were aware that a patient used HT and believed that HT decreased the risk for CHD, ascertainment of CHD death among HT users could be biased.

**Figure 2. Effect of excluding silent myocardial infarction.**



The differences in nonfatal cardiac events between the observational Nurses' Health Study (NHS) and the randomized Women's Health Initiative (WHI) trial are shown. Unlike the WHI trial, the NHS excluded silent (unrecognized) myocardial infarctions (MIs) from its definition of coronary heart disease, thereby missing all MIs that were asymptomatic or that presented with atypical symptoms not attributed to cardiac ischemia at the time.

Although both the NHS and the WHI trial reported that their investigators were blinded to participants' HT use, the protocol for observational studies makes true blinding nearly impossible. The NHS reports that "in no case was the cause listed on the death certificate used as the sole criterion for coronary death" and "for all deaths possibly attributable to cardiovascular causes, we requested permission . . . to review the medical records" (16). Most records were reviewed by 2 senior investigators, and references to HT exposure status were not expunged before medical record review. Physicians who prepared death certificates were not blinded to patients' HT use.

In contrast, investigators and physicians who prepared death certificates in the WHI trial were truly blinded because the medical records did not contain patients' treatment assignments. Although 40% of women assigned to HT (to manage vaginal bleeding) in the WHI trial were unblinded to gynecologists, the gynecologists were not typically involved in preparing death certificates. Because ascertaining the cause of death often requires subjectively interpreting medical records and death certificates, any implicit bias of the reviewer or the physician preparing the death certificate could lead to a spurious protective effect of HT.

### MATHEMATICAL MODELING

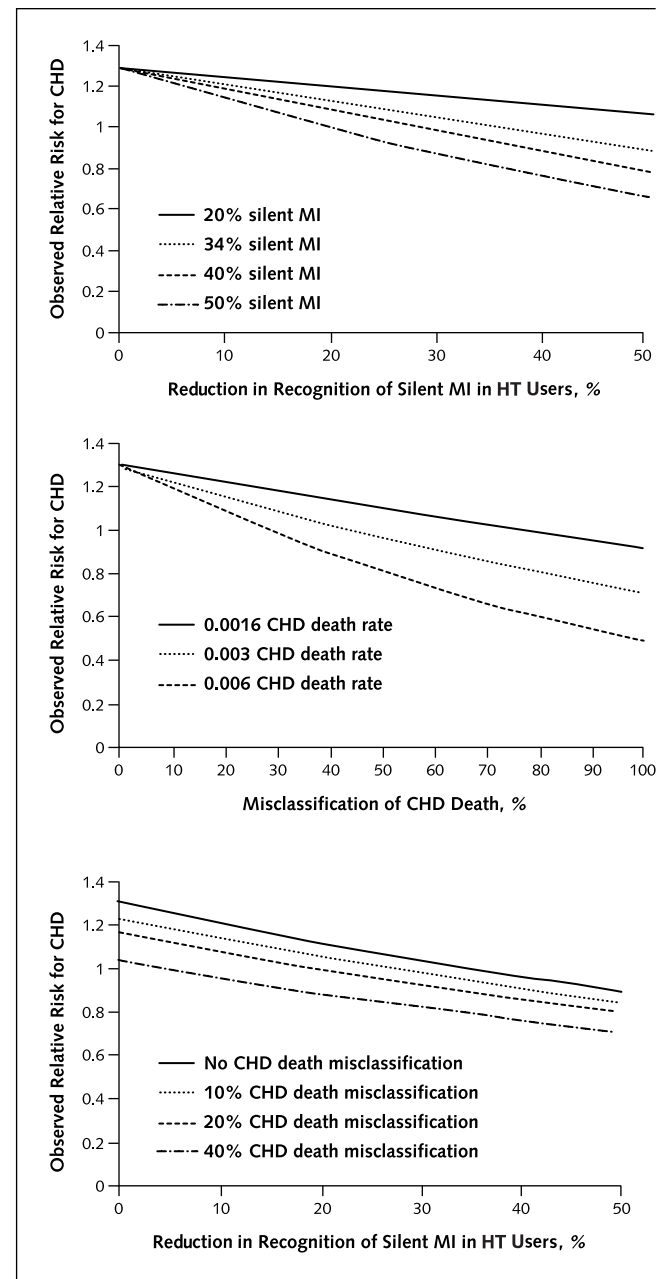
We developed a mathematical model to simulate the effect of excluding silent infarctions and misclassifying CHD deaths on the observed risk for CHD. Using standard spreadsheet software (Microsoft Excel, Microsoft, Inc., Redmond, Washington), we simulated 2 cohorts of women (1 cohort using HT, the other cohort not using HT) and counted CHD events with and without the hypothesized biases. The proportion of unrecognized nonfatal infarctions was varied from the base rate of 34% according to HT use. Proportional deviations from this base rate were applied to both HT users and nonusers. Only recognized infarctions were counted in the observational study simulation, whereas both recognized and silent events were counted in the randomized study.

The effect of misclassifying CHD deaths was modeled by altering the percentage of deaths that are misclassified as CHD deaths according to HT use. Differences in socioeconomic status were modeled by comparing the summary relative risk for CHD among current HT users in studies that adjusted for socioeconomic status with that for studies that did not adjust for socioeconomic status (relative risk, 0.97 vs. 0.71) (13). Thus, we assumed that unadjusted differences in socioeconomic status decrease the observed relative risk by  $1 - (0.71/0.97)$ , or 27%.

### Effect of Excluding Silent Infarctions

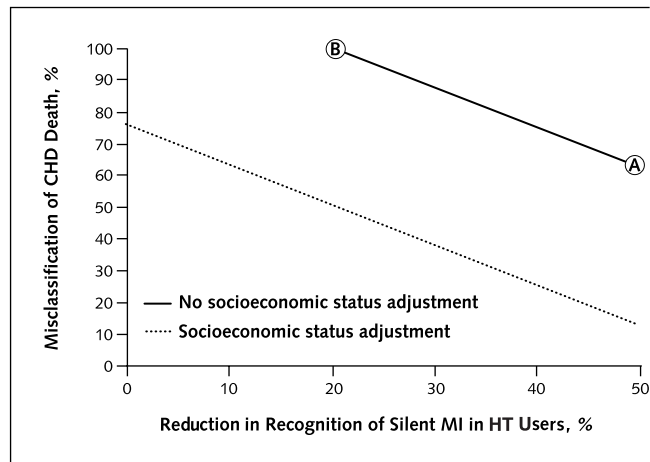
If the likelihood of recognizing an infarction is 50% lower among HT users, the observed relative risk decreases from 1.29 to 0.89. The greater the proportion of silent nonfatal infarctions, the greater the decrease in the observed relative risk (Figure 3, top).

Figure 3. Sensitivity analyses on the effect of misclassifying silent myocardial infarctions (MIs) and coronary heart disease (CHD) deaths on the observed relative risk for CHD.



The top panel shows the effect of excluding silent MIs on the observed relative risk for CHD, according to the percentage reduction in recognition of silent events between hormone therapy users and nonusers and the prevalence of silent events. The middle panel shows the effect of misclassifying a variable proportion of CHD deaths on the observed relative risk for CHD, according to the underlying CHD death rate, which was varied from 0.0016 to 0.006 during the 5.2-year simulation. The bottom panel shows the combined effect of excluding silent infarctions and misclassifying CHD deaths on the observed relative risk for CHD. The difference in the percentage of infarctions that are recognized according to hormone therapy use varied (assuming that 34% of infarctions are silent), as did the percentage of misclassified CHD deaths.

**Figure 4. Three-way sensitivity analysis: combined effect of 2 reporting biases in an observational study (with and without adjustment for differences in socioeconomic status).**



Each line represents the combination of missing silent myocardial infarctions (MIs) and misclassified coronary heart disease (CHD) deaths needed to produce a reported event rate equivalent to the rate observed in the observational Nurses' Health Study (relative risk, 0.6), given that the actual event rates correspond to those in the randomized Women's Health Initiative trial. The solid line does not adjust for differences in socioeconomic status, while the dotted line does. At the extremes, without adjustment for socioeconomic status (*solid line*), if the percentage reduction in recognition of silent MIs according to hormone therapy use were 50%, 63% of CHD deaths have to be misclassified to bring the relative risk to 0.6 (A). On the other hand, if the percentage reduction in recognition of silent MIs were 20%, every CHD death (100%) would need to be misclassified (B). Combinations of missed and misclassified events falling above a line in the Nurses' Health Study would have an observed risk below 0.6; combinations falling below a line would have a risk more than 0.6.

### Effect of Misclassifying CHD Deaths

Misclassifying 50% of CHD deaths decreases the observed relative risk from 1.29 to 0.96 (Figure 3, middle). The greater the ratio of fatal to nonfatal CHD events, the greater the effect on the observed risk.

### Combined Effect

Both biases are probably present to some extent. Misclassifying 20% of CHD deaths and differentially recognizing 20% of nonfatal infarctions reverse the apparent direction of risk from 1.29 to 0.99 (Figure 3, bottom). These biases are synergistic. To change the relative risk for CHD among HT users from 1.29 to 0.6 (the risk observed in the NHS) (16), the required magnitude of each bias varies according to the magnitude of the other (Figure 4). If residual confounding by socioeconomic status is considered, smaller biases are necessary to change the direction of risk.

## DISCUSSION

### Time Trends

Studies conducted when patients, physicians, and investigators had no preconceived beliefs about the effects of HT should not have been affected by lack of blinding.

Testing this hypothesis, however, is impossible. The belief that HT is cardioprotective was so entrenched when the first NHS HT study was published in 1985 (39) that estrogen was administered to men to determine whether they could benefit (40, 41). The justification for that study, published in 1973, stated that "during the late 1940s and early 1950s, extensive evidence was accumulated . . . suggesting a possible protective effect of these hormones against atherosclerotic coronary disease" (40).

### Other Potential Explanations

#### Demographic Differences

If a purported cardioprotective effect of HT is greater among women without CHD risk factors, as suggested, (42) or among women who initiate HT at menopause, then the WHI trial's older population would be expected to demonstrate smaller cardioprotective effects of HT. Women in the WHI trial were older than women in the NHS (63 vs. 57 years of age, respectively) and started HT later in life. However, the WHI trial found no effect of age on the effect of HT on CHD. Similarly, the NHS found HT to have the same cardioprotective effect among women in their 50s or 60s and among women with and without CHD risk factors (2). Such analyses cannot completely rule out these effects. However, such effects would probably be small and would affect stroke as well as CHD.

#### Differences in Frequency of Data Collection

The periodic, every-2-year sampling of exposure status and outcomes in the NHS might explain some of the discrepant findings. Women enrolled in the NHS who initiated HT after survey completion, had a CHD event soon afterward, and then discontinued HT might have been recorded as "never users." This might underestimate the first-year CHD risk but should not spuriously reduce risk. In addition, the NHS reported that only a small percentage of patients recorded as "never users" had an event shortly after starting HT, making it unlikely that this substantially influenced the NHS results (43).

#### Differences in HT Formulations and Treatment Regimens

The findings of the WHI trial pertain only to a specific preparation of combined HT. The NHS, on the other hand, included different formulations, regimens, and doses. Different progestins differentially affect serum cholesterol levels, plasminogen activator inhibitor-1, and other coagulation factors that may affect CHD risk (44), but no data demonstrate that differences in treatment formulation, regimen, or dose differentially affect CHD clinical end points. Furthermore, such differences should affect stroke risk as well.

## CONCLUSIONS

Although randomized studies, such as the WHI trial, have greatly contributed to our current knowledge, obser-

vational studies, such as the NHS, have been valuable sources of information to guide clinical practice. Observational studies cost less, are more timely, and include a broader range of patients (45), which may make their results more generalizable.

Nonetheless, observational studies may have incorrectly estimated the association between HT and CHD by undercounting CHD events among HT users. Unblinded HT users may have been more likely to have the diagnosis of CHD missed; failure to identify silent infarctions and failure to blind those preparing or interpreting death certificates to the use of HT may have compounded the magnitude of the error. Differences in socioeconomic status between HT users and nonusers could also have contributed to spurious findings in observational studies that could not adjust fully for these differences. However, this effect may be small in the NHS, which consists entirely of registered nurses (46).

We presume that the NHS would have detected a 1.29 relative risk for CHD in HT users if the study had been free of any biases. When this relative risk is used as a baseline, a relatively small misclassification bias in the NHS (approximately 20%) could reduce the relative risk for CHD to 0.99 in HT users. Our main finding is that this bias in combination with others could explain a substantial portion of the discrepancy between the relative risk for CHD in those assigned to HT in the WHI and the relative risk observed in the NHS. These biases combined with postulated differences between HT users and nonusers in socioeconomic status and lifestyle habits provide a plausible explanation for the large difference in risk for CHD in the observational study and the randomized trial. Of course, proof of plausibility is not evidence, and it is important to remember that we have not presented evidence that the NHS underdiagnosed CHD.

These reporting biases should affect only outcomes for which there were widespread beliefs about the efficacy of HT and for which diagnostic criteria are relatively subjective or ascertained differently in randomized and observational studies. There were no widely held beliefs about the effect of HT on stroke, and the diagnostic criteria for pulmonary embolism and stroke were similar in both studies. Therefore, reporting biases should not affect these non-CHD outcomes.

No study has examined whether physicians or investigators are biased by their belief about HT efficacy when they assign a diagnosis of CHD death or whether patients' beliefs about the efficacy of HT affects women's decisions to seek care after atypical ischemic symptoms. However, studies have shown that patient expectations can influence clinical outcomes (47–50) and modify responses to drugs (51). Approximately 20% to 30% of women receiving placebo in randomized trials of HT reported substantial symptomatic relief (52–54). Patient beliefs about efficacy affect subjective outcomes, such as pain, although it has not been established that such expectations affect how

women interpret atypical chest pain. In addition, reporting bias may have been a factor in trials finding placebo to have powerful clinical effects. One analysis found that placebo affected unblinded subjective outcomes but not objective or binary outcomes (55). Whether patients' beliefs affect outcomes or investigators' beliefs affect the recording of these outcomes remains to be determined. The potential for these effects emphasizes the need for double-blinded protocols in randomized trials.

If persons assigning cause of death know that a patient used HT and believe that HT protects against CHD, they might be more likely to assign a condition other than CHD as the cause of death. There is evidence that inadequate blinding of investigators can affect reported outcomes. An empirical study of 33 meta-analyses found that randomized trials that did not conceal treatment allocation yielded substantially larger estimates of treatment effects (41% higher) than of studies that were double-blinded (56). The authors concluded that “inadequate concealment can lead to introduction of bias in many ways—sometimes as the result of deliberate subversions (usually well-intentioned), sometimes as the net result of subconscious actions” (56).

The potential for bias in the NHS raises questions about the validity of other unblinded observational studies involving CHD end points. Expectations about efficacy could lead to the appearance of efficacy in unblinded studies. Rather than “seeing is believing,” believing could become seeing. To avoid bias, investigators in observational studies should be blinded to exposure status whenever assessing CHD outcomes. The study protocol should seek clinically unrecognized CHD events and include them. Investigators should use objective CHD measures to ensure that ascertainment of CHD outcomes is not affected by beliefs held by patients, clinicians, and investigators.

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## APPENDIX

### Prevalence of Silent Myocardial Infarctions in Various Cohorts

The prevalence of silent infarctions in the NHS cohort is expected to be similar to other population-based studies of healthy women, in which rates range from 22% to 44% (57–62). Risk factors for silent myocardial infarction (hypertension, diabetes, advanced age, and female sex) (58) were similar between the NHS and the WHI trial. Silent myocardial infarction rates should also be affected by the intensity of surveillance, with lower rates expected in randomized trials with rigorous monitoring protocols.

### Inclusion of Silent Myocardial Infarctions in Other Observational Studies

In addition to the Framingham Study (37), 3 other studies suggested a possible increased risk for incident CHD (63–65). Of these, 2 studies (63, 64) used study designs that included some but not all silent myocardial infarctions. This does not confirm that such differences in findings were due exclusively to

design, since other differences in study design may have accounted for their findings.

## Methods

The model assumes that the true relative risk for CHD among HT users is 1.29 (as reported in the WHI trial). The model explores the isolated and combined effect of 2 reporting biases on the observed relative risk for CHD in a simulated cohort of women. The model applies the same overall event rates for CHD as were observed in the WHI cohort during their follow-up period, with nonfatal MIs accounting for 76% of CHD outcomes (0.32% CHD deaths and 1.18% nonfatal infarctions over the 5.2 years of follow-up).

The model assumes, on the basis of data from the Framingham Study (28), that 34% of all nonfatal myocardial infarctions were silent (unrecognized) in the base case. The proportion of unrecognized nonfatal infarctions varied from this base rate according to HT use. Proportional deviations from this base rate (34%) were applied to HT users and nonusers. For example, a 10% bias would result in 10% more silent infarctions among HT users and 10% fewer silent infarctions among nonusers. Because the proposed bias should occur principally among “close calls” (that is, nonfatal myocardial infarctions that present with some, although atypical, symptoms), the proportional change in the recognition of silent myocardial infarctions is limited to the 50%

**Appendix Table. Comparison of the Definition of Coronary Heart Disease between the Nurses' Health Study and the Women's Health Initiative Trial\***

Variable	Nurses' Health Study: Major Coronary Disease (13)	Women's Health Initiative: Coronary Heart Disease
Nonfatal probable or definite myocardial infarction	+	+
Silent myocardial infarction	–	+
PTCA or angioplasty or thrombolysis	–†	–‡
CHD death	+	+
Sudden cardiac death	+	+
Ascertainment of nonfatal myocardial infarction	Nurses who reported a nonfatal infarction or stroke were asked for permission to review their medical records. Nonfatal myocardial infarctions were confirmed by hospital records if they met WHO criteria. Infarctions that required hospitalization and were corroborated by interview or letter but for which medical records were unobtainable were included as “probable.” Infarctions of indeterminate age discovered on routine examination were excluded.	The diagnosis of acute myocardial infarction was established according to an algorithm adapted from standardized criteria that included cardiac pain, cardiac enzyme and troponin levels, and electrocardiography readings.
Ascertainment of CHD death	For all deaths possibly attributable to cardiovascular causes, we requested permission from relatives (subject to state regulations) to review the medical records. Deaths were considered to be due to CHD if medical records or autopsy findings confirmed a fatal myocardial infarction. We also included CHD listed on the death certificate as the underlying cause without another more plausible cause if the nurse was known (from hospital records, family, or other sources) to have had CHD before death. In no case was the cause listed on the death certificate used as the only criterion for coronary death. Sudden death within 1 hour of the onset of symptoms in participants with no other plausible cause of death besides coronary disease was also included.	Coronary death was defined as death consistent with CHD as the underlying cause plus 1 or more of the following: preterminal hospitalization with myocardial infarction within 28 days of death, previous angina or myocardial infarction and no potentially fatal noncoronary disease, death resulting from a procedure related to coronary artery disease, or death certificate consistent with CHD as the underlying cause.

\* CHD = coronary heart disease; PTCA = percutaneous transluminal coronary angioplasty; WHO = World Health Organization; + = included as part of the definition of CHD; – = not included.

† These events were tracked separately but not included as major coronary disease.

‡ These events were tracked separately but not included as CHD.

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of silent myocardial infarctions that present with nonspecific symptoms. Silent events that present with no symptoms are not expected to be affected by the proposed bias because they would be missed in both the HT and non-HT cohorts.

For example, in a cohort of 100 000 women with the same event rates as the WHI trial and a relative risk of HT on CHD of 1.29, if 34% of myocardial infarctions are silent, 518 of the 1522 infarctions would be silent among HT users and 401 of 1180

infarctions would be silent among nonusers. If HT users are 20% more likely to have undetected infarctions, the number of silent events increases to 621 among HT users and decreases to 321 among nonusers. When the number of recognized events is adjusted accordingly, the observed relative risk of HT on nonfatal events changes from 1.29 to 1.05. These calculations do not consider the effect of CHD deaths.