ORIGINAL INVESTIGATION

Risk of Recurrent Coronary Events in Relation to Use and Recent Initiation of Postmenopausal Hormone Therapy

Susan R. Heckbert, MD, PhD; Robert C. Kaplan, PhD; Noel S. Weiss, MD, DrPH; Bruce M. Psaty, MD, PhD; Danyu Lin, PhD; Curt D. Furberg, MD, PhD; Jacqueline R. Starr, MPH; Gail D. Anderson, PhD; Andrea Z. LaCroix, PhD

Background: The finding from the Heart and Estrogen/Progestin Replacement Study (HERS) of increased coronary risk restricted to the first year after starting postmenopausal hormone therapy raises new questions about the role of hormone therapy in women with coronary heart disease. We assessed the risk of recurrent myocardial infarction or coronary heart disease death associated with the use and recent initiation of hormone therapy in women who survived a first myocardial infarction.

Methods: The setting for this population-based inception cohort study was Group Health Cooperative, a health maintenance organization. We studied 981 postmenopausal women who survived to hospital discharge after their first myocardial infarction between July 1, 1986, and December 31, 1996. We obtained information on hormone use from the Group Health Cooperative computerized pharmacy database and identified recurrent coronary events by medical record review.

Results: During median follow-up of 3.5 years, there were 186 recurrent coronary events. There was no difference in the risk of recurrent coronary events between current users of hormone therapy and other women (adjusted relative hazard [RH], 0.96; 95% confidence interval [CI], 0.62-1.50). Relative to the risk in women not currently using hormones, there was a suggestion of increased risk during the first 60 days after starting hormone therapy (RH, 2.16; 95% CI, 0.94-4.95) and reduced risk with current hormone use for longer than 1 year (RH, 0.76; 95% CI, 0.42-1.36).

Conclusion: These results are consistent with the findings from the HERS, suggesting a transitory increase in coronary risk after starting hormone therapy in women with established coronary heart disease and a decreased risk thereafter.

Arch Intern Med. 2001;161:1709-1713

From the Departments of Epidemiology (Drs Heckbert, Weiss, Psaty, and LaCroix and Ms Starr), Pharmacy (Drs Heckbert and Anderson), Medicine (Dr Psaty), Health Services (Dr Psaty), and Biostatistics (Dr Lin), Cardiovascular Health Research Unit, University of Washington, Seattle; the Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY (Dr Kaplan); the Department of Public Health Sciences, Wake Forest University, Winston-Salem, NC (Dr Furberg); and the Center for Health Studies, Group Health Cooperative, Seattle (Dr LaCroix).

IN POSTMENOPAUSAL women with established coronary heart disease (CHD), results of several observational studies[1,2] have suggested that hormone therapy is associated with a decreased risk of recurrent CHD events. Therefore, the results of the Heart and Estrogen/Progestin Replacement Study (HERS) randomized trial,[3] published in 1998, were unexpected: compared with placebo, there was no reduction in CHD events in recipients of a combined continuous estrogen and progestin regimen for an average of 4.1 years (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.81-1.22). Furthermore, the HERS[4] actually observed an increased risk of CHD events in hormone recipients during the first year of the trial (RH, 1.52; 95% CI, 1.01-2.29) and in particular during the first 4 months (RH, 2.29), although there was decreased risk in years 4 and 5 (RH, 0.75; 95% CI, 0.50-1.13).

We used data from a population-based inception cohort study of women who survived to hospital discharge after their first myocardial infarction (MI) to examine the risk of recurrent CHD associated with postmenopausal hormone therapy. Detailed information from a computerized pharmacy database on the type and timing of hormone use permitted us to assess the CHD risk present during different periods after starting hormone therapy and the risk associated with various formulations and regimens.

RESULTS

There were 981 postmenopausal women hospitalized for a first MI between July 1, 1986, and December 31, 1996, who survived to hospital discharge. Average age was 67.8 years, and average duration of enrollment in GHC at the time of the first MI was 17.1 years. Follow-up records were complete for 92% of women; only 8% of women had disenrolled from GHC before the end of follow-up.

Median duration of follow-up after the first MI was 3.5 years (range, 1 day to 9.9 years), and total follow-up was 3599

PATIENTS AND METHODS

SETTING

The setting was Group Health Cooperative (GHC), a health maintenance organization in western Washington State with more than 400 000 members.

STUDY DESIGN

We identified all female GHC enrollees aged 30 to 79 years who were diagnosed as having a first nonfatal MI between July 1, 1986, and December 31, 1996, from the computerized discharge abstracts for the 2 GHC hospitals, the bills for out-of-plan services provided by non-GHC physicians and health care facilities, and Washington State death records. Women with a first MI between July 1, 1986, and December 31, 1991, were included in a previous study[5] about the risk of reinfarction and mortality in relation to use of postmenopausal estrogen after the first MI. The present study includes an additional 522 women whose first MI events occurred after December 31, 1991, as well as additional follow-up of the earlier cohort.

For identification of women with a first MI, research assistants were trained to recognize hospitalized events that clearly were not MIs and events that clearly were MIs by review of medical records. Borderline or questionable events were reviewed by physicians (S.R.H. and B.M.P.) without knowledge of patients' use of hormone therapy. We used these methods in previous studies.[6,7] In a masked validation study,[6] the completeness of case ascertainment was 95%, and 97% of eligible cases met standard criteria for definite or probable MI according to cardiac enzyme determinations, electrocardiographic findings, and the presence of chest pain.[8]

We excluded women (1) who were enrolled in the health maintenance organization for less than 1 year or who had fewer than 4 visits before their first MI; (2) who were not postmenopausal at the time of the first MI; (3) whose first MI was a complication of a procedure or surgery; (4) who died before discharge from the hospital after the first MI; or (5) for whom no information was available in the medical record after the first MI. Menopause was defined as the cessation of ovarian function due to natural menopause or bilateral oophorectomy before natural menopause. A notation in the medical record of the cessation of menses, or, in women with a hysterectomy, symptoms of menopause, were used to establish the date of menopause. Women older than 55 years for whom menopausal status at the date of the first MI was not clear from the medical record were assumed to be postmenopausal. Women younger than 55 years whose menopausal status at the date of the first MI could not be determined were excluded; only 0.3% of otherwise eligible women were excluded for this reason.

DATA COLLECTION

Data collection included review of the available inpatient medical records for the first MI hospitalization and review of the entire GHC ambulatory medical record for the period before the first MI and the period after the first MI up to a predetermined date during 1996-1998. Trained research assistants reviewed these medical records to determine eligibility and to collect information about CHD risk factors such as smoking status, weight, serum cholesterol level, and hysterectomy status and medical conditions such as hypertension, diabetes mellitus, and congestive heart failure. Hypertension and diabetes mellitus were defined as pharmacologically treated disease present at the time of the first MI. Congestive heart failure was defined as probable

person-years. Overall, women used hormones during 686 person-years of follow-up (19%). Of the 2913 person-years with no hormone therapy, 52% was contributed by women younger than 70 years and 48% by women aged 70 years or older (**Table 1**). By contrast, during 686 person-years with hormone therapy, 75% of the time was contributed by women younger than 70 years and 25% by women aged 70 years or older. Compared with time without hormone therapy, a larger proportion of follow-up time with hormone therapy was contributed by women who were younger; were free of hypertension, diabetes mellitus, and congestive heart failure; and had lower body mass index and total serum cholesterol level at the time of the first MI (Table 1).

Among the 981 women, there were a total of 186 recurrent MI events or CHD deaths during follow-up (51.7 per 1000 per year). There were 149 recurrent MIs (118 nonfatal and 31 fatal) and 37 other CHD deaths. During time without hormone therapy there were 161 coronary events (55.3 per 1000 per year) and during time taking hormones there were 25 events (36.5 per 1000 per year).

The unadjusted risk of recurrent MI or CHD death associated with hormone use was 0.69 (95% CI, 0.45-1.05) (**Table 2**, model 1). Subsequent models in Table 2 show the effect of adjustment for subject characteristics on the risk estimate. In sequential Cox regression models, the association between hormone use and recurrent coronary events was progressively attenuated by adjustment for age, calendar year of the first MI, and diabetes mellitus. With adjustment for age, year, and diabetes mellitus (model 4), there was no difference in the risk of recurrent coronary events during time with hormone therapy compared with time with no hormone therapy (RH, 0.96; 95% CI, 0.62-1.50). Further adjustment for congestive heart failure before or at the time of the first MI, aspirin use, or β-adrenergic blocking agent use at discharge from the hospital after the MI changed the risk estimate in only trivial ways (models 5-7). Further adjustment with other variables, including duration of enrollment at GHC, body mass index or weight before the first MI, serum cholesterol level, serum creatinine level, hypertension, smoking status, educational attainment, and hysterectomy status, also had trivial effects on the RH.

Table 3 summarizes the risk of recurrent coronary events according to the recency of starting hormone therapy during the post-MI period compared with the risk among women who were not using hormones. Within 60 days after starting hormone therapy, the rate

or definite disease based on the notes of the primary care physician and consultants and on the results of diagnostic tests for the period before the first MI or during hospitalization for the first MI. Information on first recurrent MI or death during post-MI follow-up was obtained from the ambulatory medical record, available inpatient medical records, and the results of a match between Washington State death records and GHC enrollment records.

MEDICATION USE

The GHC computerized pharmacy database was used to assess use of hormones and other medications. Since 1976, the GHC pharmacy database has included a record for all prescriptions dispensed to GHC enrollees. Each pharmacy record includes a patient identifier, drug type and dose, date and quantity dispensed, and dosing instructions. Although several health care plans in GHC include small to modest copayments for drugs, interview data from this population indicate that 96% of individuals with a history of MI fill all of their prescriptions at GHC pharmacies.[6]

Hormone therapy was defined as the use of unopposed oral estrogen or oral estrogen plus progestin. The estrogen formulations most commonly used for postmenopausal hormone therapy during the study were conjugated and esterified estrogens. The number of days that an estrogen prescription would last was calculated as follows: [number of pills dispensed/(pills per day prescribed × assumed compliance of 80%)] × [(number of days in a month)/(days per month that estrogen was to be taken)]. In the analysis, we allowed hormone use to vary over time during post-MI follow-up as women started and stopped hormone therapy. Starting hormone therapy during follow-up included not only new starting, defined as the use of estrogen with no evidence of previous use in the pharmacy database, but also restarting estrogen use 60 days or more after the supply of estrogen pills from the previous prescription was calculated to have run out. For women who were taking hormones at the time of the first MI but were not discharged from the hospital taking hormones and whose first follow-up clinic notes did not indicate hormone use, we defined starting hormone therapy as restarting estrogen use 60 days or more after hospital discharge. In a sensitivity analysis, we repeated the analysis and defined restarting hormone therapy as a lapse of 90 days or more after the supply of estrogen was calculated to have run out.

STATISTICAL ANALYSIS

Follow-up time started the date of discharge from the hospital after the first MI and extended until the date of first recurrent MI or CHD death or the date of censoring. Individuals were censored at the date of death from causes other than CHD, the date of disenrollment from GHC, or the end of assigned follow-up. The Cox proportional hazards model with a time-dependent estrogen exposure variable was used to model the association of hormone use with the risk of recurrent MI or CHD death after adjustment for potential confounding factors.[9]

To investigate the association of CHD risk with time since starting hormone therapy, follow-up time was divided into 4 mutually exclusive categories: (1) no hormone therapy (referent category), which included follow-up time of women who never used hormones after MI and that of women who had not yet started hormone therapy or had stopped using hormones during the post-MI period; (2) within 60 days of starting hormone therapy; (3) greater than 60 to 365 days after starting hormone therapy and still using hormones; and (4) greater than 365 days after starting hormone therapy and still using hormones.

of recurrent coronary events was 121.2 per 1000 per year. Relative to women not using hormones, the adjusted RH was 2.16 (95% CI, 0.94-4.95). After this initial period, the adjusted RH declined to 0.92 (95% CI, 0.40-2.12) among women 60 to 365 days after starting hormone therapy and to 0.76 (95% CI, 0.42-1.36) among women more than 365 days after starting hormone therapy. There was evidence for a trend of declining risk over time since starting hormone therapy among users ($P = .05$ for trend). The rate of recurrent events during the first year after starting hormone therapy was 57.9 per 1000 per year and the adjusted RH was 1.30 (95% CI, 0.71-2.37). Using the time intervals reported in the HERS, the adjusted RHs were 2.03, 0.75, and 0.85 for 0 to 4 months, greater than 4 months to 4 years, and greater than 4 years after starting hormone therapy, respectively. Use of a 90-day cutoff time to define restarting of hormone therapy produced similar results.

For 5 of 6 women with a recurrent CHD event within the first 60 days after starting hormone therapy, this was the first use of hormones recorded in the pharmacy database. The sixth woman had last used hormones more than 5 years before her first MI, and the recurrent CHD event occurred in association with restarting hormone therapy after the MI. None of the women with CHD events occurring within the first 60 days after starting hormone therapy were taking hormones at the time of the first MI.

Unopposed estrogen was used 67% of the total time with oral hormone therapy during follow-up, and estrogen plus progestin was used 33% of the time. The progestin used was medroxyprogesterone acetate for virtually all of the time with combined estrogen and progestin therapy. There was little difference between the unadjusted rate of recurrent coronary events during use of unopposed estrogen (17 events; 36.8 per 1000 per year) and use of estrogen plus progestin (8 events; 35.8 per 1000 per year). The age-adjusted RH for use of estrogen plus progestin compared with unopposed estrogen was 0.96 (95% CI, 0.41-2.25). The most commonly used formulation of oral estrogen was esterified estrogen, used 70% of the time with oral hormone therapy. Conjugated estrogen was used 28% of the time, and other estrogens were used 2% of the time. The unadjusted rate of recurrent coronary events was similar during time using esterified estrogen (15 events; 31.3 per 1000 per year) and time using conjugated estrogen (8 events; 41.8 per 1000 per year). The age-adjusted RH for conjugated estrogen use compared with esterified estrogen use was 1.35 (95% CI, 0.55-3.30).

COMMENT

In this observational study of women who survived to hospital discharge after a first MI, there was no overall difference in the adjusted risk of recurrent coronary events between current users and current nonusers of hormones (adjusted RH, 0.96; 95% CI, 0.62-1.50). Relative to the risk in women not currently using hormones, there was a suggestion of increased risk during the first 60 days after starting or restarting hormone use (adjusted RH, 2.16; 95% CI, 0.94-4.95) and reduced risk with current hormone use longer than 1 year (adjusted RH, 0.76; 95% CI, 0.42-1.36).

The strengths of this study include the use of a population-based inception cohort of women with a first MI, the validation of diagnoses for the first MI and for recurrent CHD events, and the use of a pharmacy database to assess the timing of starting and discontinuing estrogen use. In addition, we were able to assess the risk associated with various formulations and regimens of oral hormone therapy.

A main limitation of this study was the small number of recurrent events during hormone therapy, particularly shortly after starting hormone therapy. In analyses that examined the recency of starting hormone therapy, our ability to adjust for confounding factors was also limited because of the small number of events involved. As with all observational studies[10] of hormone therapy, patients and their physicians self-selected hormone therapy and the timing of its use, and this self-selection might have introduced bias. Detailed information on medical comorbidity was uniformly available and allowed us to adjust for characteristics known to be associated with use of hormones and recurrent events. Nonetheless, there might have been unknown or unmeasured confounding factors associated with the use and timing of hormone therapy.

In this study, information on hormone use was restricted to that obtained using pharmacy data. Although this method ensures comparable and unbiased assessment of hormone use over time, it ignores hormone prescriptions that might have been filled at non-GHC pharmacies. Because 96% of individuals with a history of MI fill all of their prescriptions at GHC pharmacies,[6] few participants are likely to have filled hormone prescriptions outside of a GHC pharmacy. Finally, we made several as-

Table 1. Proportion of Post-MI Follow-up Time Without and With Hormone Therapy Contributed According to the Characteristics of 981 Women*

Characteristics at the Time of the First MI	Follow-up Time Contributed, %		
	Without Hormone Therapy† (2913 PY)	With Hormone Therapy (686 PY)	Total (3599 PY)
Age, y			
<70	52	75	56
≥70	48	25	44
Hypertension			
No	51	60	53
Yes	49	40	47
Diabetes mellitus			
No	81	91	83
Yes	19	9	17
Congestive heart failure			
No	75	80	76
Yes	25	20	24
Body mass index, kg/m^2			
<24	39	44	40
≥24	61	56	60
Total serum cholesterol level			
<240 mg/dL (<6.20 mmol/L)	34	48	37
≥240 mg/dL (≥6.20 mmol/L)	66	52	63

*MI indicates myocardial infarction; PY; person-years.
†Includes follow-up time for women who never used hormones and time not taking hormones for women who used hormones during part of follow-up.

Table 2. Effect of Adjustment for Patient Characteristics on the Association Between Hormone Therapy and Recurrent Myocardial Infarction or Coronary Heart Disease Death in 981 Women*

Model	Variables Included in Model	Relative Hazard (95% CI)
1	No adjustment	0.69 (0.45-1.05)
2	Age	0.74 (0.48-1.13)
3	Age, year	0.76 (0.49-1.18)
4	Age, year, DM	0.96 (0.62-1.50)
5	Age, year, DM, CHF	0.97 (0.62-1.51)
6	Age, year, DM, CHF, aspirin use	0.98 (0.63-1.54)
7	Age, year, DM, CHF, aspirin use, β-adrenergic blocking agent	0.98 (0.63-1.54)

*CI indicates confidence interval; year, calendar year of first myocardial infarction; DM, diabetes mellitus; and CHF, congestive heart failure.

Table 3. Risk of Recurrent MI or CHD Death Among 981 Women in Relation to Use of and Interval Since Starting Hormone Therapy*

Use of and Recency of Starting Hormone Therapy	Follow-up, Person-Years	Events, No.	Incidence (per 1000 per Year)	Relative Hazard (95% CI)	
				Unadjusted	Adjusted†
No hormone therapy‡	2913	161	55.3	1.00 (Referent)	1.00 (Referent)
Hormone therapy	686	25	36.5	0.69 (0.45-1.05)	0.96 (0.62-1.50)
0-60 d after starting therapy	50	6	121.2	1.69 (0.74-3.83)	2.16 (0.94-4.95)§
>60-365 d after starting therapy	158	6	38.0	0.72 (0.32-1.63)	0.92 (0.40-2.12)§
>365 d after starting therapy	480	13	27.1	0.52 (0.30-0.92)	0.76 (0.42-1.36)§

*MI indicates myocardial infarction; CHD, coronary heart disease; and CI, confidence interval.
†Adjusted for age, year of first MI, and diabetes mellitus.
‡Includes follow-up time for women who never used hormones and time without hormones for women who used hormones during part of follow-up.
§P=*.05 for trend.*

sumptions about compliance with hormone therapy and about how long estrogen prescriptions would last. Our sensitivity analyses indicate that the results were not affected by plausible changes in these assumptions or in the definition used for starting hormone therapy.

In contrast to an earlier observational study[2] in women with established CHD, the present study did not find a reduction in coronary events associated with postmenopausal hormone use after adjustment for confounding characteristics. As in studies[11] from the primary prevention setting and as previously reported from this study,[10] women who used hormones were younger and healthier than nonusers. Adjustment for these differences attenuated the protective association seen in the unadjusted analyses for the overall association of hormone use with recurrent coronary events in this study. We are unaware of previous studies comparing the risk of coronary events associated with use of esterified estrogen vs conjugated estrogen. As in previous studies[6,12] in the primary prevention setting, risks were similar for use of unopposed estrogen and estrogen plus progestin.

In analyses of the risk associated with recently starting hormone therapy, like the HERS, we found evidence for an early increased risk of recurrent coronary events. In the HERS,[4] the greatest risk reported was associated with the first 4 months after starting hormone therapy (RH, 2.29), whereas in the present study, the greatest risk was during the first 2 months after starting hormone therapy (adjusted RH, 2.16). During the first year of follow-up with hormone therapy, the risk observed in the HERS (RH, 1.52; 95% CI, 1.01-2.29) was similar to the adjusted risk in the present study (adjusted RH, 1.30; 95% CI, 0.71-2.37). Early increased risk of coronary events was also reported in the Coronary Drug Project trial in men receiving high-dose conjugated estrogen,[13] in a pooled analysis of short-term clinical trial data,[14] and in our observational study of women without previous MI at GHC.[15] Moreover, participants in the Women's Health Initiative hormone clinical trial[16] were recently advised that compared with placebo, an early increase in coronary events was observed in hormone recipients in the first 2 years of the trial, with an apparent decline in risk subsequently. Several authors[3,17,18] have discussed possible mechanisms for an early increase in risk in this setting.

At present, the only clinical trial data available suggest no beneficial effect of hormone therapy in women with established CHD and the possibility of an early increase in risk after starting hormone therapy. Further information is needed about the mechanisms by which an early increase in risk might operate and the long-term effects of hormone therapy after MI.

Accepted for publication January 11, 2001.

This research was supported by grants HL53375, HL40628, and HL43201 from the National Heart, Lung, and Blood Institute, Bethesda, Md.

Corresponding author and reprints: Susan R. Heckbert, MD, PhD, Cardiovascular Health Research Unit, University of Washington, 1730 Minor Ave, Suite 1360, Seattle, WA 98101-1448 (e-mail: heckbert@u.washington.edu).

REFERENCES

1. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med.* 1992;117:1016-1037.
2. Sullivan JM, Vander-Zwaag R, Hughes JP, et al. Estrogen replacement and coronary artery disease: effect on survival in postmenopausal women. *Arch Intern Med.* 1990;150:2557-2562.
3. Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605-613.
4. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Final results of the HERS main trial. Available at: http://www.keeptrack.ucsf.edu/hers2/HERSfindat.htm. Accessed May 2, 2001.
5. Newton KM, LaCroix AZ, McKnight B, et al. Estrogen replacement therapy and prognosis after first myocardial infarction. *Am J Epidemiol.* 1997;145:269-277.
6. Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med.* 1994;154:1333-1339.
7. Heckbert SR, Weiss NS, Koepsell TD, et al. Duration of estrogen replacement therapy in relation to the risk of incident myocardial infarction in postmenopausal women. *Arch Intern Med.* 1997;157:1330-1336.
8. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol.* 1995;5:275-285.
9. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc.* 1972;34:187-220.
10. Heckbert SR, Kaplan RC, Starr JR, Psaty BM, Furberg CD, Anderson GD. Cardiovascular health and treatment after myocardial infarction: differences between users and non-users of hormone replacement therapy after myocardial infarction [abstract]. *Circulation.* 2000;101:725.
11. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol.* 1996;143:971-978.
12. Falkeborn M, Persson I, Adami HO, et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. *Br J Obstet Gynaecol.* 1992;99:821-828.
13. Wenger NK, Knatterud GL, Canner PL. Early risks of hormone therapy in patients with coronary heart disease [letter]. *JAMA.* 2000;284:41-43.
14. Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ.* 1997;315:149-153.
15. Heckbert SR, Weiss NS, Psaty BM. Hormone replacement therapy for secondary prevention of coronary heart disease [letter]. *JAMA.* 1999;281:794-797.
16. National Heart, Lung, and Blood Institute Women's Health Initiative. WHI HRT update: what you should know about hormones and cardiovascular health. Available at: http://www.nhlbi.nih.gov/whi/hrt-en.htm. Accessed June 26, 2000.
17. Barrett-Connor E, Stuenkel C. Hormones and heart disease in women: Heart and Estrogen/Progestin Replacement Study in perspective. *J Clin Endocrinol Metab.* 1999;84:1848-1853.
18. Herrington DM. The HERS trial results: paradigms lost? Heart and Estrogen/Progestin Replacement Study. *Ann Intern Med.* 1999;131:463-466.