Title

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Journal

Diabetes Care, 26(10)

ISSN

1066-9442

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Publication Date

2003-10-01

DOI

10.2337/diacare.26.10.2810

Peer reviewed

Estrogen Therapy and Risk of Cardiovascular Events Among Women With Type 2 Diabetes

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OBJECTIVE — To evaluate the association between estrogen therapy and cardiovascular disease risk among women with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A retrospective, case-cohort study was conducted among 6,017 women aged 45–80 years with type 2 diabetes from 1 January 1986 to 31 December 1992 at the Group Health Cooperative in Washington state. Cardiovascular outcomes, including nonfatal myocardial infarction (n = 215), coronary revascularization (n = 253), and cardiovascular deaths (n = 229), were ascertained through 31 December 1998. Use of estrogen and progestin was derived from automated pharmacy records and modeled as a time-dependent variable. Median follow-up was 6.8 years. Multivariable-adjusted relative risk (RR) and 95% CI were calculated using Cox proportional hazard models for case-cohort analyses.

RESULTS — Current use of estrogen with (RR 0.43, 95% CI 0.22–0.85) or without (0.48, 0.30–0.78) progestin was associated with a decreased risk of cardiovascular events compared with never having used estrogen. Risk of cardiovascular events associated with a first episode of estrogen use (with or without progestin) of <25 months' duration (1.12, 0.49–2.54), first episode of use ≥25 months' duration (0.32, 0.06–1.70), and current use that was not the first episode of use (0.42, 0.42–0.67) indicated that recent initiation was not associated with an increase or decrease in risk.

CONCLUSIONS — These results show an association of estrogen therapy, with or without progestin, with decreased risk of cardiovascular events among women with type 2 diabetes. This association should be further investigated in large randomized, controlled trials.

Diabetes Care 26:2810–2816, 2003

Type 2 diabetes dramatically increases risk of cardiovascular disease in women (1). Observational studies have found that estrogen therapy with or without progestin is associated with reduced risk of coronary events (2,3). However, randomized, controlled trials have reported that estrogen therapy with progestin is associated with an increase in coronary events and stroke (4) and is not associated with a reduction in cardiovascular events in women with preexisting coronary disease (5). Taken together, these results have dramatically shifted our thinking about the benefits and risks of estrogen plus progestin therapy. How the balance of risks and benefits influences outcomes in women with diabetes remains uncertain. Two observational studies have reported a decrease in risk of myocardial infarction associated with current use of estrogen plus progestin among women with diabetes (6,7), whereas a third study has reported an increased risk (8). The purpose of this case-cohort study was to determine the association between postmenopausal estrogen therapy and fatal and nonfatal cardiovascular disease among women with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The study was conducted at the Group Health Cooperative (GHC) in Washington state. In 1995, the GHC served ~40,000 women aged 45–80 years. The GHC Institutional Review Board approved the study.

Case-cohort studies combine the advantages of cohort studies (multiple outcomes and time-dependent covariates) and case-control analyses (fewer subjects) and are more efficient than cohort studies (9). A subset of the cohort is randomly selected and covariate information is collected on this random sample and on all cases outside the random sample (Fig. 1).

To establish the analytic sample, we identified all women aged 45–80 years who were likely to have prevalent or incident type 2 diabetes between 1 January 1986 and 31 December 1992 using the following criteria: two fasting glucose measurements ≥140 mg/dl, two nonfasting glucose measurements ≥200 mg/dl, or one of each; HbA_{1c} >7.5% (3 SDs > GHC mean); prescription for insulin or oral diabetic agents; or hospitalization because of diabetes without ketoacidosis. From this cohort, we selected an age-stratified random sample (subcohort)

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Received for publication 6 March 2003 and accepted in revised form 18 May 2003.

K.M.N. has received grant support from Pfizer. A.Z.L. has received grants from Pfizer and Merck and has received honoraria from Proctor and Gamble.

Abbreviations: CDS, Chronic Disease Score; GHC, Group Health Cooperative; PEPI, Postmenopausal Estrogen/Progestin Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 2947.

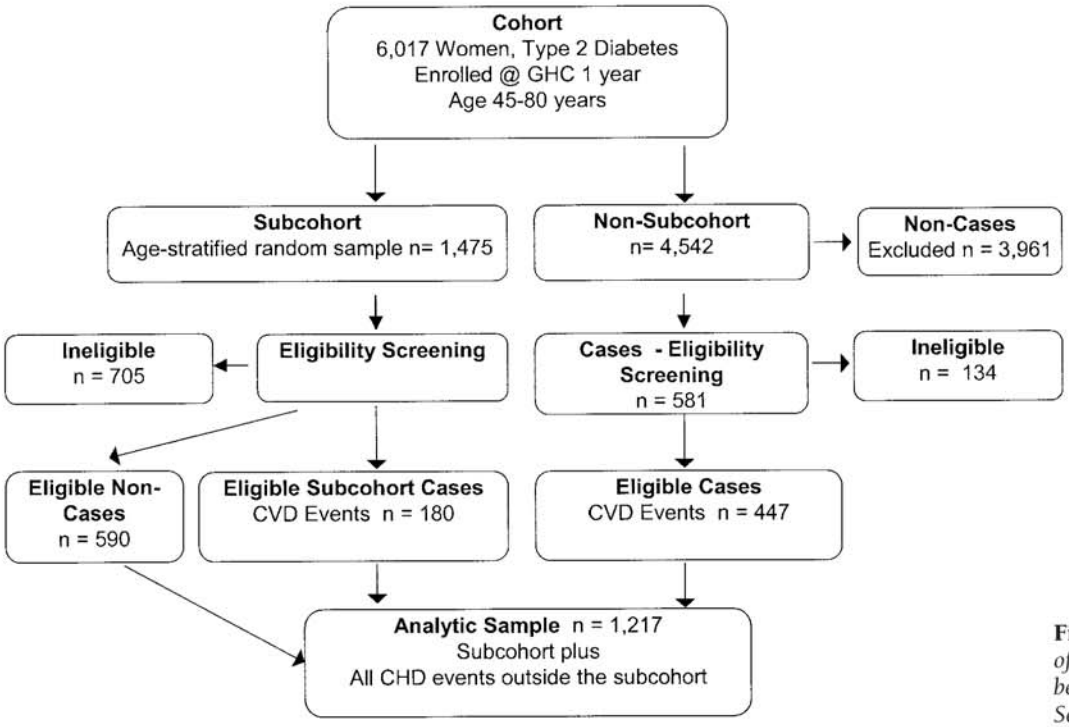

Figure 1—*Selection and screening of the analytic sample, study of diabetes and estrogen therapy (GHC, Seattle, WA).*

(Fig. 2). The sampling fractions, determined from the age distribution of deaths among GHC women with diabetes, were as follows: 45–49 years, 0.054%; 50–54 years, 0.091%; 55–59 years, 0.107%; 60–64 years, 0.113%; 65–69 years, 0.315%; 70–74 years, 0.467%; and 75–80 years, 0.543%. We identified all cohort women who had nonfatal myocardial infarction, coronary revascularization, or fatal cardiovascular disease between cohort entry and 30 September 1998. The subcohort plus all women with cardiovascular events comprised the analytic sample.

Inclusion criteria were *1*) type 2 diabetes confirmed at medical record review; *2*) age 45–80 years; *3*) GHC member ≥1 year; *4*) peri- or postmenopause; and *5*) absence of history of renal failure, contraindications to estrogen, and severe chronic diseases or diseases likely to result in death within 1 year of cohort entry.

Perimenopause was defined as amenorrhea for 6–12 months, menopause symptoms before 56 years of age in hysterectomized women without bilateral oophorectomy, or age <55 years with menopause symptoms and/or taking estrogen. Postmenopause was defined as amenorrhea for >12 months, a physician statement that the woman was menopausal, bilateral oophorectomy, or age >55 years.

Potential cases of myocardial infarction and coronary revascularization (coronary artery bypass, angioplasty/stent, thrombolysis) and cardiovascular deaths were identified from *1*) computerized outpatient and inpatient ICD-9-CM codes (myocardial infarction 410) and Current Procedural Terminology (CPT) codes (operations on vessels of the heart 30.0–36.3); *2*) the same codes from GHC billing databases from non-GHC hospitals; and *3*) GHC death files constructed from Washington State death certificates (ischemic heart disease 410–414, ventricular fibrillation or flutter 427.4, cardiac arrest 427.5, congestive heart failure 428, cardiovascular disease unspecified 429.2).

Medical record reviews verified type 2 diabetes, confirmed eligibility and outcomes, and ascertained medical history and demographic characteristics. Use of estrogen and progestin was identified from outpatient and computerized records; an earlier survey established that 96.7% of GHC women aged 50–80 years filled their prescriptions at the GHC (10). Both sources were used to establish hormone use as current, past, or never at the start of follow-up. Pharmacy records were the sole source of information on drug use during follow-up. We included oral estrogens and progestins and estrogen patches in these analyses.

The first date when incident or prevalent diabetes was identified between 1 January 1986 and 31 December 1992 marked the start of follow-up (reference date). All serum glucose measurements for the year before the reference date were averaged to yield a mean value for each woman. The last laboratory measurements before the reference date for blood urea nitrogen and serum creatinine and the averaged serum glucose values were divided into quintiles, based on the values for all eligible subcohort women. Total cholesterol was classified using cut points from the National Cholesterol Education Program (11). Use of insulin and sulfonylurea were ascertained from the pharmacy database.

The Chronic Disease Score (CDS), a validated case mix adjustor, is calculated using 6 months of pharmacy data for prescriptions for chronic conditions (12). The CDS for each 6-month interval of follow-up (January through June and July through December) was included as a time-dependent variable in all analyses, using the most recent complete 6-month interval preceding the risk set date.

Data analysis

A case-cohort analysis was used (13,14). All subcohort women plus all women from the cohort with cardiovascular events were included. The relationship of estrogen use to potential confounding

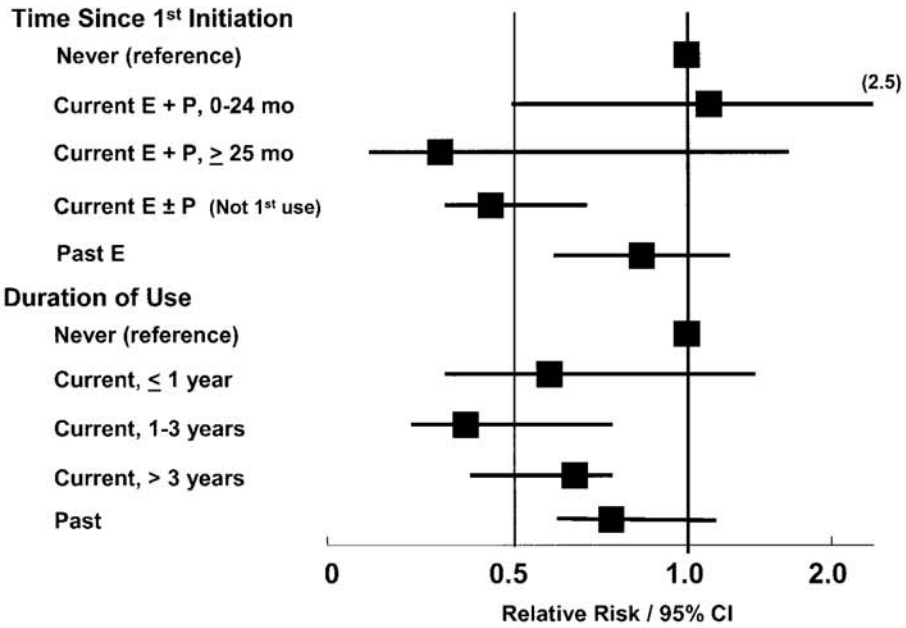

Figure 2—*RRs of cardiovascular disease events among women with type 2 diabetes, by recency of initiation and cumulative duration of estrogen therapy (GHC, Seattle, WA) adjusted for age, year, CDS, diabetes duration, cardiovascular disease, ulcer, smoking, and insulin. E, estrogen; P, progestin.*

variables was assessed using categorical analysis methods, χ^2 tests, and ANOVA. All other analyses entailed modeling the hazard rate, i.e., the risk of a cardiovascular event, using proportional hazards models (15). Subcohort members were included in all relevant risk sets from cohort entry until death or censoring. Cases outside the subcohort were only included in the risk set at the time of their event.

Calendar time was the time axis. Age was controlled by including in each risk set only women whose age was within 2 years of the age of the case. Subjects were censored at nonfatal cardiovascular outcome, death, GHC disenrollment, or the end of the study, whichever came first.

Estrogen was coded as current unopposed estrogen, current estrogen with progestin, or past estrogen with or without progestin and was modeled as a time-dependent variable. For each prescription, we calculated a runout date based on the number of pills or patches dispensed. If the prescription was not refilled within 180 days after the runout date (lapse in use) the subject was coded as a past user until another prescription was filled. In this way, estrogen use was divided into episodes of use. To evaluate recency of initiation, we combined estrogen with and without progestin and classified use as follows: first episode of use (no lapses) with duration of 0–24 months or ≥25 months; current but not first use (at least one lapse); past use; or never used. To evaluate duration of use, the total number of estrogen pills dispensed was calculated. Cumulative duration of use was coded as never, <1 year, 1–3 years, >3 years, past use, or never used, assuming 1 day of use per pill. This method underestimates total duration for sequential regimens and, as such, is a conservative estimate. Recency and duration were modeled as time-dependent variables.

RESULTS — We screened for eligibility in the medical records of 1,475 subcohort women and 581 women with cardiovascular outcomes who were not in the subcohort. A total of 1,217 (59.5%) women were eligible: 770 subcohort members (180 cardiovascular outcomes) and 447 nonsubcohort women with cardiovascular outcomes (Fig. 1). The number and proportion of outcomes were as follows: incident myocardial infarction 193 (30.8%); recurrent myocardial infarction 22 (3.5%); angioplasty/stent 78 (12.4%); thrombolysis 18 (2.9%); coronary artery bypass 157 (25%); and cardiovascular death 229 (36.5%). Some outcomes were concurrent; therefore, the proportions exceed 100%. Reasons for ineligibility included no diabetes (15.4%); type 1 diabetes (4.8%); chronic diseases including dementia, lung disease, renal disease, and impending death (26.2%); history of breast, ovarian, or endometrial cancer (18.7%); current cancer (7.8%); history of clotting disorders or thromboembolism (7.0%); premenopause or undetermined menopause status (7.1%); incomplete medical records (7.6%); and other (5.4%). The median follow-up was 6.8 years (range 1 month to 12.8 years).

For descriptive purposes, we used data from throughout the follow-up period to categorize estrogen use as never, past (used only before follow-up), unopposed estrogen at any time during follow-up, and estrogen plus progestin at any time during follow-up; women who used both unopposed estrogen and estrogen with progestin were classified as using estrogen with progestin (Table 1). Women with cardiovascular events had a longer duration of diabetes, were more likely to be using insulin or sulfonylureas, had higher random glucose levels, and were more likely to smoke. The duration of diabetes at the start of follow-up was <1 year for ~40% of the subcohort women. Among women with cardiovascular events, 23.6% had a duration of diabetes of ≥11 years, compared with 16.1% in the subcohort. Compared with never users, estrogen users were younger, were more likely to be married, and had lower systolic blood pressure, less use of insulin and sulfonylureas, lower blood urea nitrogen and creatinine levels, and lower random glucose values.

After adjusting for age and the CDS, use of both current, unopposed estrogen (relative risk [RR] 0.52, 95% CI 0.34–0.79) and estrogen with progestin (0.49, 0.27–0.91) were associated with a reduced risk of cardiovascular outcomes compared with women who never used estrogen (Table 2). These risk estimates changed little after adjustment for baseline diabetes complications (angina, cardiovascular diseases, cardiovascular surgical procedures, congestive heart failure, and lower extremity amputation), baseline indicators of diabetes severity (duration of diabetes, insulin use, and sulfonylurea use), and other risk factors (hypertension and smoking). In multivariate models that included the CDS, duration of diabetes, insulin use, history of myocardial infarction, peripheral vascular disease, stroke, revascularization (coronary artery bypass, coronary angioplasty, ca-

rotid endarterectomy, or lower extremity vascular bypass), congestive heart failure, smoking, and lower extremity ulcer, the RR for cardiovascular events associated with current estrogen was 0.48 (0.30–0.78) and the RR associated with current estrogen plus progestin was 0.43 (0.22–0.85). Past use of estrogen was not associated with a reduction in risk of cardiovascular events. Risk reductions were similar when the analyses were stratified by fatal versus nonfatal events and when women with a prior cardiovascular outcome were excluded from the analysis (data not shown).

We examined the impact of recency of initiation and duration of use using multivariate models. Compared with women who had never used estrogen, the RRs and 95% CIs for cardiovascular events associated with a first episode of estrogen use (with or without progestin) of <25 months' duration (1.12, 0.49–2.54), first episode of use of ≥25 months' duration (0.32, 0.06–1.70), and current use that was not the first continuous episode of use (0.42, 0.42–0.67) indicated that recent initiation was not associated with an increase or decrease in risk. The RRs for cardiovascular events associated with current estrogen, with or without progestin, with a cumulative duration of <1 year (0.64, 0.27–1.50), 1–3 years (0.34, 0.15–0.78), and >3 years (0.47, 0.29–0.77) indicated that current short-term use was not associated with an increase in risk.

CONCLUSIONS — In this retrospective longitudinal cohort study of women with type 2 diabetes, current postmenopausal use of estrogen was associated with a 52% reduction in cardiovascular events and current use of estrogen with progestin was associated with a 57% reduction in risk. We are aware of only three other studies examining this question to date. In an earlier case-control analysis among GHC women with pharmacologically treated diabetes, Kaplan et al. (7) found a nonsignificant 49% reduction in risk of first fatal or nonfatal myocardial infarction associated with current use of estrogen with progestin. Ferrara et al. (6) reported that in a cohort study of women with diabetes (types 1 and 2), current use of estrogen and use of estrogen with progestin were associated with modest decreases in the risk of acute myocardial infarction and with increased risk of recurrent myocardial infarction. This effect was limited to women with type 2 diabetes taking doses equivalent to 0.625 mg conjugated estrogen or less. In contrast, an observational study of Danish women reported that current use of estrogen with or without progestin increased the risk of ischemic heart disease and death in women with diabetes. However, the study included only 32 current estrogen users among 178 women with diabetes, and estrogen therapy was not modeled as a time-dependent variable (8). Our study was limited to women with type 2 diabetes, included women who were not on drug therapy, and included a broader range of cardiovascular outcomes. We completed detailed medical record reviews that allowed us to control for comorbid conditions and diabetes severity, whereas the study by Ferrara et al. (6) was based primarily on automated data. Nevertheless, our findings are similar.

The disparity between the benefit of postmenopausal estrogen plus progestin found in observational studies of incident (2,3,16) and recurrent (17–19) cardiovascular events, the lack of benefit (5) or increase in cardiovascular risk (4,20) found in randomized trials of estrogen plus progestin, and the increase in risk associated with recent initiation of estrogen plus progestin found in trials (4,5) and observational studies (21), compels us to interpret our results cautiously. However, there is some reason to believe that estrogen might offer protection in this vulnerable group. Estrogen therapy is associated with an increase in HDL and a decrease in LDL among women with diabetes (22–25). However, these same effects did not decrease mortality or cardiovascular disease events in the Heart and Estrogen/Progestin Replacement Study (HERS) trial (5) or the Women's Health Initiative (4), blunting optimism about the benefits associated with these intermediate end points.

Postmenopausal estrogen may favorably affect glucose metabolism. This question has been examined in studies of women with and without diabetes, with inconsistent findings. In the Postmenopausal Estrogen/Progestin Trial (PEPI), conjugated equine estrogen with progestin decreased fasting glucose and insulin, whereas 2-h glucose and insulin in response to a glucose tolerance test were increased among women not taking insulin and with a fasting glucose level <7.77 mmol/l (26). In small trials of postmenopausal women with diabetes, estrogen has been associated with lower levels of HbA_{1c} (27,28), fasting glucose, and insulin (23); improved insulin sensitivity (27); and decreased hyperandrogenicity (23). In large observational cohort studies of women with diabetes, estrogen with or without progestin has been associated with lower HbA_{1c} concentrations (29,30) and lower fasting glucose levels (30). However, one small crossover study found no effects of either transdermal or oral estrogen on these parameters among women with type 2 diabetes (31). Population-based observational studies have found lower fasting glucose (32–34) and insulin levels (32), higher 2-h glucose levels (33), and higher 2-h insulin levels (32) in current estrogen users compared with nonusers, mirroring the PEPI findings. The totality of the evidence suggests that postmenopausal estrogen may have a favorable effect on glucose metabolism.

Our findings raise the hypothesis that the risk/benefit equation for postmenopausal estrogen therapy with or without progestin may differ for women with diabetes or those destined to develop it. We speculate that an explanation of long-term benefit could be improved glucose control, which thwarts or delays cardiovascular complications. This possibility should be explored to the extent possible in existing trials.

This is one of the first population-based studies to evaluate the effect of postmenopausal estrogen use among women with diabetes, a group at high risk for cardiovascular disease. Among the study strengths is our use of automated pharmacy records to carefully assess estrogen and progestin use and to model them as time-dependent variables. Access to and complete review of medical records and automated laboratory data allowed us to control for a wide range of cardiovascular and diabetes-related comorbidities. We were unable to control for HbA_{1c} because a large proportion of women had not undergone this test.

In summary, we found that estrogen therapy with or without progestin was associated with a decreased risk of cardiovascular events among women with type 2 diabetes. There are plausible biologic reasons to believe that estrogen may benefit women with diabetes, but our results may be due to healthy user bias or other biases beyond the reach of our data. These findings require confirmation in large random-

Table 1—*Baseline demographic and health characteristics of women who had cardiovascular events and of the study subcohort by use of estrogen therapy during follow-up* (women aged 45–80 years with type 2 diabetes; GHC, Seattle, WA)*

	Subcohort members					
Characteristics	Total	Never used	Used in the past	Estrogen	Estrogen and progestin	Cardiovascular events
n	770	351	233	103	83	247
Age at reference (mean years)†	68.9	69.5	70.4	66.3	65.0	66.1
White (%)	87.2	84.6	88.7	90.1	89.3	91.0
Married (%)‡	57.3	52.6	59.6	56.0	71.8	59.3
CDS (mean)†	2,366.4	2,286.1	2,560.5	2,513.9	1,976.2	2,604.1
Years enrolled at GHC (mean)†	10.5	8.8	12.2	10.2	13.7	10.1
Physician visits in past year (mean no.)	5.9	5.7	6.3	6.5	5.1	6.5
BMI (kg/m^2, mean)‡	30.2	30.5	29.6	31.4	29.0	30.7
Systolic blood pressure (mean)‡	147.5	148.1	149.5	143.4	144.6	149.0
Diastolic blood pressure (mean)	81.0	81.0	80.1	81.2	82.6	81.8
Insulin use in past 6 months (%)	11.3	13.7	9.9	8.7	8.4	18.5
Sulfonylurea use in past 6 months (%)	42.7	45.3	43.3	40.8	32.5	47.2
Age at menopause ≤50 years (%)	48.2	44.8	50.7	53.8	47.4	47.9
Hysterectomy (%)†	37.3	23.1	41.2	93.2	16.9	38.2
Oophorectomy (%)†	16.3	6.9	24.6	38.8	6.0	17.1
Total cholesterol >240 mg/dl (%)	50.1	47.6	55.1	42.4	54.7	60.9
Blood urea nitrogen quintiles (%)‡						
<13	16.4	14.7	14.2	21.2	23.2	18.9
13–14	17.0	15.3	16.4	23.2	18.3	15.7
15–17	25.0	22.2	28.8	22.2	29.3	22.1
18–21	20.8	23.7	20.8	17.2	13.4	21.5
≥22	20.8	24.0	19.9	16.2	15.9	21.8
Creatinine quintiles (%)						
≤0.8	27.2	26.8	26.7	31.0	25.6	32.6
0.9	18.4	17.3	18.7	14.0	28.0	19.6
1	17.2	18.2	15.6	18.0	17.1	14.1
1.1–1.2	21.0	20.5	22.7	22.0	17.1	18.1
≥1.3	16.2	17.3	16.4	15.0	12.2	15.6
Random glucose quintiles (mg/dl, %)§						
≤118	7.0	6.9	5.6	6.8	12.0	5.9
119–140	13.2	12.0	14.7	13.6	13.3	11.2
141–167	22.0	18.6	25.0	27.2	21.7	17.6
168–219	27.2	27.7	28.0	24.3	26.5	28.4
≥220	30.6	34.9	26.7	28.2	26.5	36.9
Prior history of (%)						
Myocardial infarction	6.0	6.8	6.9	4.9	1.2	12.1
High blood pressure	70.0	69.8	72.1	72.8	61.4	74.3
Angina pectoris‡	19.7	17.9	26.0	18.6	12.0	31.2
Congestive heart failure	9.0	7.7	10.8	10.7	7.2	12.1
Peripheral vascular disease	5.3	4.9	6.9	5.8	2.4	8.8
Stroke	5.1	4.9	7.3	4.9	0	6.2
Nephropathy	7.8	9.2	7.1	6.0	6.1	7.9
Neuropathy	12.9	12.3	13.8	11.7	14.5	15.8
Lower extremity amputation	0.9	1.1	0.4	1.0	1.2	0.8
Prior history of (%)						
Endarterectomy	0.9	0.9	0.9	1.0	1.2	1.9
Any CVD	30.1	26.8	39.8	28.4	19.3	44.9
Ulcer, gangrene, osteomyelitis	4.3	5.1	4.7	1.9	2.4	6.5
Current cigarette smoking (%)	13.4	13.3	12.6	10.1	19.5	21.0
Duration of diabetes (%)						
<1 year	39.9	37.8	41.1	37.2	48.6	29.4
1–5 years	29.5	32.2	23.3	37.2	25.0	29.9
6–10 years	14.6	14.8	17.8	11.7	8.3	17.1
11+ years	16.1	15.1	17.8	13.8	18.1	23.6

*Cardiovascular events include nonfatal and fatal cardiovascular disease among 180 subcohort members and 447 events not from the subcohort (subcohort and cardiovascular events are not mutually exclusive categories); †$P \leq 0.001$; ‡$P \leq 0.05$ (subcohort comparisons, χ^2 for categorical variables, ANOVA for continuous variables); §average of all glucose values recorded in the year prior to start of follow-up.

Table 2—*Risk for coronary heart disease associated with postmenopausal estrogen therapy with or without progestin, relative to that for never users, among women aged 45–80 years with type 2 diabetes (GHC, Seattle, WA)*

	Follow-up (person-years)	Cardiovascular events (*n*)	RR (95% CI)		
			Age stratified	Adjusted for CDS*	Multivariable model†
Never	10,233	306	1.0	1.0	1.0
Current estrogen	3,589	46	0.54 (0.36–0.82)	0.52 (0.34–0.79)	0.48 (0.30–0.78)
Current estrogen with progestin	1,508	18	0.51 (0.28–0.94)	0.49 (0.27–0.91)	0.43 (0.22–0.85)
Past estrogen with or without progestin	8,009	257	1.03 (0.81–1.30)	0.95 (0.75–1.22)	0.88 (0.65–1.19)

*Stratified by age (±2 years); †model includes age, CDS (modeled as a time-dependent variable), duration of diabetes, insulin use, history of myocardial infarction, angina, congestive heart failure, stroke, peripheral vascular disease, lower extremity amputation, lower extremity ulcer, revascularization (coronary artery bypass, coronary angioplasty, carotid endarterectomy, or lower extremity vascular bypass), and current smoker at start of follow-up.

ized, controlled trials before clinical implications can be derived from them.

Acknowledgments— This study was supported by National Health Lung and Blood Institute Grant HL-56675.

We would like to thank Kelly Ehrlich for outstanding assistance during the conduct of this study.

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