

Is Diabetes Mellitus a Heart Disease Equivalent in Women?

Results From an International Study of Postmenopausal Women in the Raloxifene Use for the Heart (RUTH) Trial

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Background—Several studies have concluded that diabetes mellitus and heart disease carry similar risk for future cardiovascular disease (CVD). Most of these studies were too small to quantify independent risks specific to women. The purpose of this study was to determine whether diabetes mellitus is a coronary heart disease (CHD) risk equivalent for prediction of future CHD and CVD events in women.

Methods and Results—The Raloxifene Use for the Heart (RUTH) trial was an international, multicenter, double-blind, randomized, placebo-controlled trial of raloxifene and CVD outcomes in 10 101 postmenopausal women selected for high CHD risk. Of these, 3672 had a history of diabetes mellitus without known CHD, and 3265 had a history of CHD without known diabetes mellitus. Cox proportional hazard models were used to compare cardiovascular outcomes in these 2 groups. Mean age at baseline was 67.5 years; median follow-up was 5.6 years. There were 725 deaths, including 450 cardiovascular deaths. In age-adjusted analyses, diabetic women had an increased risk of all-cause mortality compared with women with CHD. Although the overall risk of CHD and CVD was lower in diabetic women compared with women with CHD, the risk of fatal CHD, fatal CVD, and all-cause mortality was similar (hazard ratio [95% confidence interval]: 0.85 [0.65–1.12], 0.99 [0.78–1.25], and 1.18 [0.98–1.42], respectively, after adjusting for age, lifestyle factors, CHD risk factors, statin use, and treatment assignment).

Conclusions—In the RUTH trial, diabetes mellitus was a CHD risk equivalent in women for fatal, but not nonfatal, CHD and CVD.

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Key Words: diabetes mellitus ■ heart diseases ■ randomized trial ■ risk factors ■ women

In 1998, Haffner et al¹ reported that adults from Finland who had type 2 diabetes mellitus were at the same risk for future myocardial infarction (MI) as adults with prior MI.¹ The study, which reported the 7-year incidence of MI, was relatively small (n=2332) and did not evaluate men and women separately. Sex-specific results reported in an 18-year follow-up of that cohort suggested a higher mortality risk for diabetes mellitus than for coronary heart disease (CHD) in women, but there were few women with previous MI, and confidence intervals were wide.² Since the original Haffner publication, many studies³⁻¹⁶ and at least 2 systematic reviews^{17,18} have directly compared CHD (or cardiovascular disease [CVD]) outcomes in people with diabetes mellitus but without CHD, with outcomes in people with CHD without diabetes mellitus; most of these studies concluded that diabetes mellitus was a heart disease risk equivalent for

the prediction of future CHD. Not all were prospective; some defined diabetes mellitus or CHD by self-report only; and few had fasting glucose tests to permit the exclusion of unrecognized diabetes mellitus among those with heart disease. Only a subset of the studies reported sex-specific or women-only associations,^{2,3,7,10-15} and all but 2 studies based their sex-specific estimates on population sizes of <1000 women.

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The Raloxifene Use for the Heart (RUTH) trial compared CVD outcomes in 10 101 postmenopausal women (mean age, 67.5 years), who were randomly assigned to 60 mg/d of raloxifene (a selective estrogen receptor modulator) or placebo. After a median of 5.6 years, raloxifene offered no protection against cardiovascular or CHD events. The eligibility criteria for RUTH required that women be at high risk for heart disease.

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People and institutions participating in the RUTH trial are listed in the online-only Data Supplement Appendix.

The online-only Data Supplement is available at <http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.112.966986/-/DC1>. Correspondence to Lori B. Daniels, MD, MAS, Division of Cardiology, University of California, San Diego, Mail Code 7411, 9444 Medical Center Dr, La Jolla, CA 92037-7411. E-mail lbDaniels@ucsd.edu

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WHAT IS KNOWN

- The risk of death from coronary heart disease (CHD) among people with diabetes mellitus without prior myocardial infarction, as compared with nondiabetic individuals with prior myocardial infarction, is similar.

WHAT THE STUDY ADDS

- This article extends the results to the group of high-risk women, who are generally underrepresented in prior trials.
- Diabetic women without prior CHD are at higher risk of fatal cardiovascular disease but lower risk of nonfatal CHD and cardiovascular events compared with nondiabetic women with CHD.
- Diabetes mellitus is associated with an excess mortality risk in women.
- The risk of congestive heart failure was similar among diabetic women without CHD and nondiabetic women with CHD.

As a consequence, at baseline, 3674 women (36%) had established CHD without diabetes mellitus and 3265 (32%) had established diabetes mellitus without CHD; an additional 1342 women (13%) had both diabetes mellitus and heart disease at baseline. This large cohort of women with a confirmed diagnosis of CHD or diabetes mellitus provided a unique opportunity to examine whether diabetes mellitus is a CHD equivalent in a large, well-characterized cohort of postmenopausal women for whom CHD outcomes were validated by medical records. We also examined CVD outcomes and all-cause mortality.

Methods

RUTH was an international, multicenter, randomized, double-blind, placebo-controlled trial. A detailed description of the design and study population has been published.^{19,20} The 2 primary objectives were to determine whether treatment with raloxifene reduces the incidence of (1) coronary events (coronary death, nonfatal [including silent] MI, and hospitalized acute coronary syndrome other than MI), and (2) invasive breast cancer. In this article, we consider only the cardiovascular outcomes.

The protocol was approved by the ethics review board at each investigative site. All women gave written informed consent for participation in accordance with the principles of the Declaration of Helsinki.

Study Population

The RUTH study comprised 10 101 postmenopausal women, recruited between June 1998 and August 2000, who were randomized at 177 sites in 26 countries. Eligible women were 55 years or older, were at least 1 year postmenopausal, and had established CHD or were at increased risk for CHD.¹⁹ Participants were required to have a cardiovascular risk score of ≥ 4 using the following point system¹⁹: established CHD (4 points if within the past 3 years, otherwise 2 points); lower extremity arterial disease (4 points); age ≥ 70 years (2 points); diabetes mellitus (3 points); current cigarette smoking (1 point); hypertension (1 point); or hyperlipidemia (1 point).

Exclusion criteria were an MI within 3 months of randomization or percutaneous coronary intervention within 6 months of

randomization; a history of cancer or venous thromboembolism; life expectancy < 5 years; unexplained uterine bleeding within 6 months of randomization; class III or IV heart failure; chronic liver or renal disease; use of oral or transdermal estrogens within 6 months; or current use of other sex hormones or selective estrogen receptor modulators.

The study protocol has been previously described.¹⁹ Briefly, eligible women were randomly assigned to raloxifene 60 mg/d orally (EVISTA, Eli Lilly and Company, Indianapolis, IN) or placebo identical in appearance. At each biannual visit or telephone contact, adherence to study medication, adverse events, and outcomes were ascertained. ECGs were performed at baseline, years 2 and 4, and the final visit. Fasting plasma glucose, hemoglobin A_{1c}, and serum lipids were measured at baseline and at follow-up visits. The present study is a post hoc analysis of a subset of the clinical trial population, which included women with diabetes mellitus but without known CHD, plus women with established CHD but no diabetes mellitus.

Diagnosis of Diabetes Mellitus and of Established CHD

Diagnosis of diabetes mellitus required that participants have a fasting plasma glucose level > 140 mg/dL at baseline or be taking physician-prescribed diabetes mellitus medication. Established CHD required a physician's prior written diagnosis of MI, a clinical history of angina or angina-like symptoms associated with $> 50\%$ narrowing of at least 1 major coronary artery at angiography, or a documented coronary revascularization procedure.¹⁹

Outcomes

Cardiovascular outcomes (coronary events, stroke, congestive heart failure, and death) were adjudicated by committees comprising experts blinded to treatment assignment who were not employees of the sponsor. A sponsor designee, blinded to treatment assignment, adjudicated the secondary outcome of myocardial revascularization and hospitalizations.

For the present analyses, the primary outcomes were fatal or nonfatal CHD, fatal or nonfatal CVD, congestive heart failure, and all-cause mortality. Primary outcomes criteria have been previously described.¹⁹ Briefly, CHD was defined as fatal or nonfatal MI, myocardial revascularization, or hospitalization for acute coronary syndrome (other than MI). MI was diagnosed if at least one of the following was present: (1) ischemic symptoms and abnormal cardiac enzymes, with or without new equivocal ECG changes; (2) new pathological Q wave, with or without ischemic symptoms or abnormal cardiac enzymes; or (3) new pathological Q waves or markedly abnormal cardiac enzymes following invasive coronary procedures. Coronary death was defined as death resulting from acute MI, sudden or unwitnessed death, heart failure, or death related to a coronary artery procedure. Myocardial revascularization, defined as either coronary artery bypass surgery or catheter-based coronary revascularization, was documented by a procedure report. Hospitalized acute coronary syndrome was defined as hospitalization for or development during hospitalization of cardiac symptoms with new ST-T changes on ECG or abnormal cardiac enzymes or troponin levels. CVD was defined as death resulting from cardiovascular causes (death resulting from coronary causes and death resulting from noncoronary cardiovascular causes such as cerebrovascular, venous thromboembolic, atherosclerotic noncoronary vascular disease, and other cardiovascular causes), nonfatal CHD, or congestive heart failure. Stroke was defined as the rapid onset of a persistent neurological deficit lasting > 24 hours, in most cases supported by findings on imaging studies. The cause of death was assigned based on available clinical information, death certificate, or autopsy.

Statistical Analyses

Comparisons of baseline characteristics between groups were performed using *F* tests from ANOVA models for continuous variables and Pearson χ^2 tests for categorical variables. Primary analyses used time-to-event methods based on the intention-to-treat principle. Women not experiencing an event were censored at the last date

when study information was collected or date of death. Age-adjusted Kaplan-Meier estimates of cumulative incidence of events were constructed for both groups and compared using log-rank tests. Hazard ratios (HRs) with 95% confidence intervals were determined from Cox proportional hazards regression models, and the groups were compared using likelihood ratio tests from the Cox models. Models were adjusted for (1) age and randomized treatment group; (2) model 1 plus lifestyle factors, which included current smoking (defined at baseline as having smoked an average of ≥ 10 cigarettes per day during the last 6 months, yes/no), alcohol use (none versus < 1 drink per week versus ≥ 1 drink per week), vigorous activity (not on a regular basis versus once per week versus twice per week versus ≥ 3 times per week), and prior estrogen therapy (yes/no); and (3) model 2 plus cardiovascular risk factors, which included systolic blood pressure, waist circumference, high-density lipoprotein level, low-density lipoprotein level, and triglyceride level as continuous variables. All covariates in the Cox proportional hazards models were from baseline (time-invariant). All analyses were prespecified. Reported *P* values are 2-sided. Statistical analyses were performed using SAS software version 8.2 or higher (SAS Institute, Cary, NC).

Study Management

The executive committee developed the protocol in collaboration with the sponsor. An independent data and safety monitoring board with independent statistical support performed interim analyses of safety and efficacy. For the current study, the data were analyzed by the sponsor according to the methods described above. The concept for this article was developed by the first and last authors, who had unrestricted request-based access to data, which were retained by the sponsor. All authors were involved in interpreting the data and drafting the article.

Results

Overall RUTH Study

Raloxifene had no significant effect on the risk of the combined coronary end point (coronary death, nonfatal MI, or hospitalized acute coronary syndrome; HR [95% confidence interval], 0.95 [0.84–1.07]), nor did it have any effect on all-cause mortality (HR, 0.92 [0.82–1.03]) or stroke (HR, 1.10 [0.92–1.32]), although raloxifene was associated with an increased risk of fatal stroke (n=98 overall; HR, 1.49 [1.00–2.24]).²¹ In addition, raloxifene did not significantly affect the risk of CHD in women with baseline CHD (HR, 0.97 [0.83–1.12]) or with baseline diabetes mellitus (HR, 0.89 [0.76–1.06]).²² Although there were differences in the baseline distribution of risk factors between those with diabetes mellitus but no CHD and those with CHD but no diabetes mellitus, the distribution of CHD risk factors within these diagnoses did not differ by treatment assignment. As previously published, women assigned to raloxifene had greater increases in high-density lipoprotein cholesterol, body mass index, and weight and greater reductions in low-density lipoprotein cholesterol and fibrinogen levels.²² No significant differences were observed between treatment groups for systolic or diastolic blood pressure.

Diabetes Mellitus Without CHD Versus CHD Without Diabetes Mellitus

Overall, 6939 women with a mean age of 67.0 ± 6.5 years were evaluated for the present analyses. Table 1 shows the baseline characteristics of subjects with diabetes mellitus but no CHD (n=3265) compared with those with CHD but no diabetes mellitus (n=3674). Women with diabetes mellitus were younger and had a higher prevalence of metabolic syndrome

Table 1. Baseline Characteristics of Diabetic Subjects Without CHD vs Nondiabetic Subjects With CHD

Characteristic	Diabetic No CHD (n=3265)	Not Diabetic With CHD (n=3674)	<i>P</i>
Demographics			
Age, y	66.1 \pm 6.5	67.8 \pm 6.5	<0.001
Ethnicity, %			<0.001
White	77.8	89.4	
Afro-Caribbean	1.8	1.0	
Asian	7.5	4.8	
Hispanic	8.5	1.4	
Other	4.5	3.4	
History and lifestyle			
History of HTN, %	82	68	<0.001
Treatment for HTN, %	81	66	<0.001
Cigarette smoking, %	10	13	<0.001
Second-hand smoke exposure, %	29	24	<0.001
Alcohol ≥ 1 per week, %	11	23	<0.001
Vigorous activity ≥ 3 per week, %	16	23	<0.001
Years postmenopausal	18	20	<0.001
Hysterectomy, %	23	22	0.39
Previous use of ERT, %	16	24	<0.001
Mean years of ERT	3	4	0.03
Coronary heart disease history, %			
Prior myocardial infarction	0	59	N/A
Prior coronary bypass surgery	0	32	N/A
Prior coronary angioplasty	0	34	N/A
Prior angina	0	65	N/A
Measurements			
Heart rate, bpm	74 \pm 10	68 \pm 11	<0.001
Systolic BP, mm Hg	147 \pm 19	143 \pm 20	<0.001
Diastolic BP, mm Hg	83 \pm 10	81 \pm 10	<0.001
Waist circumference, cm	98 \pm 13	91 \pm 12	<0.001
Body mass index, kg/m ²	30.3 \pm 5.6	27.7 \pm 4.5	<0.001
Laboratories			
Fasting plasma glucose, mg/dL	180 \pm 71	103 \pm 16	<0.001
Hemoglobin A _{1c}	8.3 \pm 1.7	6.2 \pm 0.5	<0.001
Total cholesterol, mg/dL	219 \pm 42	213 \pm 44	<0.001
HDL cholesterol, mg/dL	51 \pm 14	53 \pm 14	<0.001
LDL cholesterol, mg/dL	119 \pm 35	119 \pm 37	0.45
Triglycerides, mg/dL	175 \pm 127	141 \pm 89	<0.001
Medications, %			
Aspirin	28	82	<0.001
Lipid-lowering drug	32	69	<0.001
Statin	23	65	<0.001
β -blocker	27	66	<0.001
ACE inhibitor	51	35	<0.001

ACE indicates angiotensin-converting enzyme; BP, blood pressure; ERT, estrogen replacement therapy; HDL, high-density lipoprotein; HTN, hypertension; and LDL, low-density lipoprotein.

and its components than women with known CHD, although these differences are likely due, in part, to the study inclusion criteria. They were also less likely to smoke (but more likely to have secondhand smoke exposure), consume alcohol at least once per week, perform vigorous activity at least 3 times per week, take aspirin, take lipid-lowering medications, take β -blockers, or have a history of postmenopausal hormone therapy, but they were more likely to be taking angiotensin-converting enzyme inhibitors and diuretics and were more likely to report ethnicity other than white.

During a median follow-up period of 5.6 years (range, 0.01–7.1 years), there were 450 cardiovascular deaths (6.5%), including 226 CHD deaths. As shown in Table 2, diabetic women without a history of CHD were less likely to have nonfatal MI or hospitalization for acute coronary syndrome, but they did have a higher incidence of all-cause mortality compared with nondiabetic women with a history of CHD. The incidence of cardiovascular death, coronary death, and congestive heart failure was similar in the 2 groups.

The Figure shows age-adjusted Kaplan-Meier estimates of the incidence of all-cause mortality, CVD, CVD death, CHD, and CHD death. Diabetic women without CHD had a higher risk of all-cause death compared with women with CHD but no diabetes mellitus. Although diabetic women without a history of CHD were less likely to experience CHD and CVD events overall compared with nondiabetic women with known CHD, the likelihood of dying of CHD or CVD was similar.

In Cox proportional hazards analysis modeling for covariates, a similar pattern was seen (Table 2). In analyses adjusted for age and treatment assignment (model 1), diabetic women without CHD had an increased risk of all-cause mortality and of cardiovascular death compared with women with CHD but no diabetes mellitus and a similar risk of coronary death, although their risk of nonfatal CVD and CHD events was lower. After further adjusting for lifestyle factors and statin use (model 2) and for cardiovascular risk factors (model 3), diabetic women without CHD still had a

similar risk of all-cause, cardiovascular, and CHD death compared with nondiabetic women with CHD but a lower risk of nonfatal cardiovascular events.

As expected, given the absence of any significant cardiovascular benefit of raloxifene in the overall study, a repeated analysis limited to participants assigned to the placebo group did not materially change these results (data not shown). In addition, results were similar when diabetes mellitus was alternately defined using fasting plasma glucose >125 mg/dL or using hemoglobin A_{1c} $\geq 6.5\%$.

Discussion

Haffner et al¹ found that the HR for death from CHD for diabetic subjects without prior MI as compared with nondiabetic subjects with prior MI was not significantly different from 1.0 (adjusted HR, 1.2; 95% confidence interval, 0.6–2.4). We found a similar result in this large cohort of high-risk women in fully adjusted models: the risk of CHD death (and of CVD death) was similar in women with diabetes mellitus and women with CHD at baseline. This is the largest prospective study and the first multinational study with validated diabetes mellitus and CVD diagnoses at baseline to report on cardiovascular risks from diabetes mellitus versus CHD in women and to adjust for multiple risk factors and medication use.

Diabetic women without CHD had a higher risk of all-cause mortality than women with CHD but no diabetes mellitus in age-adjusted analyses. Although this risk was somewhat attenuated after further adjusting for clinical covariates, the data strongly suggest that diabetes mellitus is associated with an excess mortality risk in women.

In fully adjusted analyses, diabetic women without CHD had a lower risk of nonfatal CHD and CVD events compared with nondiabetic women with CHD, but their risk of CHD mortality, CVD mortality, and all-cause mortality was similar. This may suggest that women with diabetes mellitus have a more severe or more delayed presentation of CHD and CVD.

Table 2. End Point Rates and Time-to-Event Analysis of End Points in Diabetic Subjects Without CHD vs Nondiabetic Subjects With CHD

End Point	Diabetic No CHD (n=3265), n (%)	Not Diabetic With CHD (n=3674), n (%)	P	Model 1 HR (95% CI)*		Model 2 HR (95% CI)*		Model 3 HR (95% CI)*	
				P	P	P	P		
All-cause mortality	382 (11.7)	343 (9.3)	0.001	1.48 (1.28–1.72)	<0.0001	1.17 (0.99–1.37)	0.06	1.18 (0.98–1.42)	0.08
Cardiovascular disease	443 (13.6)	767 (20.9)	<0.001	0.68 (0.60–0.76)	<0.0001	0.63 (0.55–0.72)	<0.0001	0.61 (0.53–0.71)	<0.0001
Cardiovascular death	227 (7.0)	223 (6.1)	0.14	1.36 (1.13–1.64)	0.001	1.02 (0.83–1.25)	0.87	0.99 (0.78–1.25)	0.92
Coronary heart disease	275 (8.4)	428 (11.6)	<0.001	0.79 (0.68–0.92)	0.003	0.66 (0.55–0.78)	<0.0001	0.61 (0.50–0.74)	<0.0001
Coronary death	158 (4.8)	168 (4.6)	0.60	1.22 (0.98–1.52)	0.07	0.90 (0.71–1.15)	0.41	0.85 (0.65–1.12)	0.25
Nonfatal MI	88 (2.7)	168 (4.6)	<0.001	0.65 (0.50–0.84)	0.001	0.52 (0.39–0.70)	<0.0001	0.49 (0.36–0.68)	<0.0001
Myocardial revascularization	177 (5.4)	448 (12.2)	<0.001	0.44 (0.37–0.53)	<0.0001	0.52 (0.43–0.63)	<0.0001	0.51 (0.41–0.64)	<0.0001
Hospitalized for ACS other than MI	64 (2.0)	153 (4.2)	<0.001	0.51 (0.38–0.68)	<0.0001	0.49 (0.35–0.67)	<0.0001	0.41 (0.28–0.59)	<0.0001
Congestive heart failure	221 (6.8)	226 (6.2)	0.30	1.30 (1.08–1.57)	0.006	1.05 (0.85–1.29)	0.67	1.03 (0.81–1.30)	0.81

ACS indicates acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; SBP, systolic blood pressure; and MI, myocardial infarction. Model 1: adjusted for age and treatment assignment; model 2: adjusted for model 1 covariates plus lifestyle factors (current smoking, alcohol use, vigorous activity, statin use, and prior estrogen therapy as categorical variables); model 3: adjusted for model 2 covariates plus traditional CHD risk factors (HDL, LDL, triglycerides, SBP, waist circumference as continuous variables).

*HR is for comparison of diabetic subjects without CHD and subjects with a history of CHD but no diabetes mellitus (reference group).

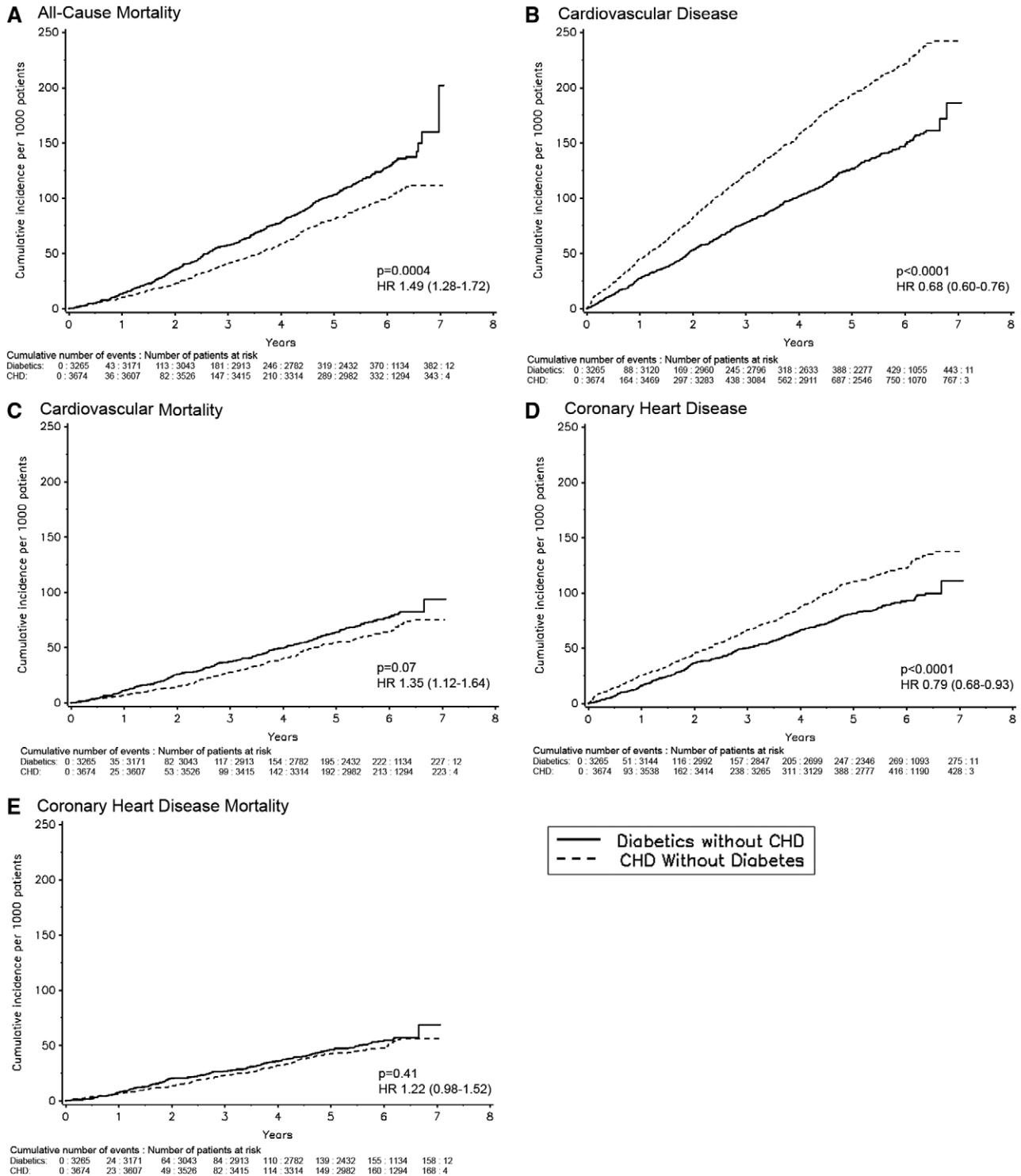


Figure. Age-adjusted estimates of cumulative incidence of events. *P* values are for log-rank test. Hazard ratios (HRs) (95% confidence intervals) are derived from Cox models and represent risk in diabetic subjects without coronary heart disease (CHD) compared with risk in CHD subjects without diabetes mellitus.

One potential explanation is that a significant portion of recurrent events in CHD patients could be the result of coronary artery restenosis, which may tend to be less lethal (recurrent angina rather than acute coronary syndrome).²³ Another possibility is that patients with a history of CHD are more vigilant and aware of the presenting symptoms of CVD and seek medical care more expeditiously, and their physicians may be

quicker to pursue revascularization in women with prior CHD. In contrast, individuals with diabetes mellitus are known to have more silent or unrecognized MI, leading to later presentation and higher mortality.^{24,25} Higher mortality after MI has been reported previously in individuals with diabetes mellitus.^{26,27} In addition, diabetes mellitus is associated with small vessel coronary artery disease,^{28,29} which may be less

amenable to complete revascularization and is a known predictor of worse outcomes.^{30,31}

The risk of congestive heart failure was also similar among diabetic women without CHD and nondiabetic women with CHD. Although CHD is a strong risk factor for development of heart failure, diabetes mellitus itself has long been recognized as a heart failure risk factor; many years ago, the Framingham Heart Study showed that the risk of heart failure was increased 2.4-fold in diabetic men and 5-fold in diabetic women independently of other comorbidities.³² More recently, diabetes mellitus has been recognized as an especially strong risk factor for development of heart failure with preserved ejection fraction, particularly in women.³³ Abnormalities of left ventricular diastolic function, including increased stiffness of the left ventricle and relaxation disturbances, have been observed in 27% to 70% of asymptomatic diabetic patients^{34,35} and may be due to fibrosis and increased left ventricular mass.³⁶ Our finding that diabetic women without prevalent CHD are at a risk level for development of congestive heart failure that is on par with the risk of nondiabetic women with known CHD is therefore both plausible and consistent with prior studies.

Strengths and Limitations

This study has several strengths. This very large study allows us to compare individual components of the CVD end point and to adjust for multiple covariates. In addition, fasting plasma glucose levels were obtained at baseline in all women, allowing a more accurate baseline classification of diabetes mellitus than diabetes mellitus history or medication use alone. The prospective adjudication of CVD outcomes also improves the strength of our findings. Another advantage is the inclusion of multiple ethnic groups and 26 countries. However, this also meant that there was divergent use of CVD medications based, in part, on regional economy, and this may modify the applicability of findings for individuals from any given country.

The major limitation is that during the study, statins were recommended for all individuals with diabetes mellitus by the American Diabetes Association, which likely reduced CVD risk but could have increased diabetes mellitus risk.^{37,38} In addition, although all RUTH women were selected to be in this randomized intervention trial based on their high CVD risk, participation in a clinical trial generally improves the prognosis, even in the placebo group (a common but incompletely understood observation).³⁹ Therefore, the results may not be applicable to women not participating in clinical trials or to women with lower CVD risk profiles. Indeed, previous studies have shown that people with diabetes mellitus are not all at equal risk of developing CVD, and lower risk subsets have been identified.⁴⁰ Misclassification of cause of death is a possible limitation that we attempted to minimize via use of a central adjudicating panel that reviewed all available clinical information. If anything, we would expect that deaths are more often misclassified as cardiovascular in subjects with known CHD than in subjects with diabetes mellitus but no CHD. Thus, our finding that diabetes mellitus was a CHD risk equivalent in women for fatal events seems robust. Finally, we did not have data on duration of either diabetes mellitus or CHD. Although risk scores in use today, including

the Framingham and the Reynolds Risk scores, treat diabetes mellitus as a dichotomous variable, in reality there is probably a spectrum of risk based on diabetes mellitus duration, its severity, and other factors.^{41,42} Our results, therefore, should be applied within the clinical context of an individual's overall risk profile.

Conclusions

The RUTH trial results support the hypothesis that diabetes mellitus is a CHD risk equivalent in women for fatal, but not nonfatal, coronary disease. In addition, diabetic women in the RUTH trial had risk levels similar to those in women with CHD for fatal CVD and all-cause mortality. We must continue to educate women who have diabetes mellitus and their physicians about their increased risk and to recommend CVD prevention medication and lifestyle modifications when appropriate.

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Is Diabetes Mellitus a Heart Disease Equivalent in Women?: Results From an International Study of Postmenopausal Women in the Raloxifene Use for the Heart (RUTH) Trial

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