The Association of Angina Pectoris with Heart Disease Mortality Among Men and Women by Diabetes Status: The Rancho Bernardo Study

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Abstract

Objective: To study the sex-specific association of angina pectoris with mortality in community-dwelling older adults with and without diabetes.

Methods: Baseline prevalence of angina was evaluated in 822 men and 1184 postmenopausal women aged 50–89 years at the 1984–1987 Rancho Bernardo Study clinic visit, when an oral glucose tolerance test (OGTT) and the Rose angina questionnaire were administered. All-cause and coronary heart disease (CHD) mortality were assessed after an average follow-up period of 13.2 years. Sex-specific Cox proportional hazard models were used to examine the independent association of angina with mortality by glucose tolerance category.

Results: At baseline, average age was 71 years for both sexes; 61 men (7.4%) and 142 women (12.0%) had angina. Overall, 129 men (15.9%) and 130 women (11.0%) had type 2 diabetes; 228 men (27.7%) and 357 women (30.2%) had impaired glucose tolerance (IGT). During follow-up, 485 men (59%) and 557 women (47%) died, of whom 103 men (21.2%) and 104 women (18.7%) had fatal CHD. Women with diabetes and angina had a 3–4-fold greater risk of dying from CHD than women with diabetes but without angina, independent of covariates. Women with angina and IGT had twice the risk of CHD mortality compared with women with IGT but without angina. A smaller increased risk of fatal CHD in men was not statistically significant.

Conclusions: Angina was associated with an increased risk of dying from CHD among women, especially among those who also had IGT or diabetes.

Introduction

Cᴏʀᴏɴᴀʀʏ ʜᴇᴀʀᴛ ᴅɪsᴇᴀsᴇ (CHD) is the leading cause of death in both men and women in the United States, accounting for approximately one in every five deaths.[1] Diabetes mellitus is an established risk factor for cardiac morbidity and mortality, independently increasing the risk of fatal CHD 2–3-fold, with a higher odds of death in women than men.[1–3] In a meta-analysis comparing angina by Rose questionnaire in 74 cohorts, angina pectoris was almost always more common in women than men,[4] although its prognostic implications in women are less clear.

The association between angina and CHD mortality has been studied in populations, such as that of Framingham, which reported that angina was less predictive of future coronary events in women than in men,[5–7] a finding confirmed elsewhere.[8–10] Many studies used small clinic-based or hospital-based samples with short follow-up periods or did not examine the interaction between sex and diabetes status on long-term outcomes of angina.[7,9,11–15] Additionally, many of these studies captured diabetes by self-report or a history of fasting plasma glucose levels alone, potentially missing many undiagnosed cases. One recent registry study in Finland reported that, compared with women in the general population, women with chronic, stable angina had increased cardiac mortality and nonfatal myocardial infarctions (MI), which was particularly high in women with both diabetes and angina.[16] To our knowledge, however, no other population-based studies report the long-term mortality risk in people who have both angina and diabetes, and there are no published population-based studies of this comorbidity and cardiovascular outcome in the United States.

The purpose of this study was to examine the influence of diabetes status on the mortality risk associated with angina,

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independent of other cardiovascular risk factors, in a population-based sample of older, community-dwelling men and women.

Materials and Methods

Study population

The Rancho Bernardo Study enrolled 82% of a geographically defined, middle-class, mainly Caucasian adult community in Southern California between 1972 and 1974.[17–19] Participants have been followed ever since by annual mailed questionnaires and periodic clinic visits. In 1984–1987, 82% of all surviving community-dwelling participants aged ≥ 40 attended a follow-up visit ($n = 2479$). After excluding 105 people who exceeded the age range of 50–89 years, 21 premenopausal women, 7 participants with type 1 diabetes, 20 who could not be classified by diabetes status, and 320 with history of MI, ischemic resting electrocardiographic (ECG) abnormalities, or coronary artery bypass graft (CABG) surgery, there remained 2006 participants (822 men and 1184 postmenopausal women) who are the focus of this report. The study protocol was approved by the Human Subjects Protections Program of the University of California, San Diego; all participants gave written informed consent before participation.

Procedures

Participants were seen in the Rancho Bernardo Study clinic by trained nurses and interviewers between 7:00 and 11:00 AM after a requested 12–16-hour fast. Fasting blood was drawn from the antecubital vein for measurement of fasting plasma glucose, lipids, and lipoproteins. An oral glucose tolerance test (OGTT) (75 g load) was administered, and blood was collected 2 hours later for assessment of postchallenge glucose. Blood pressure was measured in fasting subjects according to the Hypertension Detection and Follow-up Program protocol using a standard mercury sphygmomanometer after the participant had been seated quietly for at least 5 minutes[20] and was calculated as the mean value of two measurements taken at least 1 minute apart. Categorical hypertension was defined as average systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of hypertensive medication.

Height, weight, hip girth, and waist girth were measured in the clinic with participants wearing light clothing and no shoes. Body mass index (BMI) calculated as weight (kilograms) divided by height (meters)^2, waist-to-hip ratio (WHR) calculated as waist circumference at the bending point divided by maximum hip circumference (centimeters/centimeters), and waist circumference alone were used as estimates of central adiposity. Current medication use was verified by prescriptions, pills, or containers brought to the clinic for this purpose.

Standard questionnaires were used to obtain personal and family history of diabetes mellitus, history of cigarette smoking (never/past/current), current physical activity (exercise ≥ 3 times/week, yes/no), and alcohol intake (number of drinks of beer, wine, and hard liquor consumed in the past week, converted to grams of alcohol). Angina was based on responses to a modified Rose angina questionnaire,[21] which asks: *Have you ever had any pain or discomfort in your chest? Do you get this pain or discomfort when you walk uphill or hurry?*

Do you get it when you walk at an ordinary pace on the level? What do you do if you get it while you are walking? If you stand still, what happens to it? (If relieved), how soon? Did you see a doctor because of this pain or discomfort? (If yes), what did the doctor say it was?

According to the Rose questionnaire protocol, a diagnosis of angina required pain that occurred while walking uphill or hurrying, was relieved in ≤ 10 minutes after exertion, and was located in any level of the sternum or in the left anterior chest and left arm. Classification was further graded as grade 1 if the pain was evoked while walking at an ordinary pace on the level; otherwise, angina classification was grade 2. For this study, angina pectoris was defined as meeting the Rose questionnaire criteria for angina (grade 1 or 2), self-reported physician diagnosis, or use of angina medication.

Total cholesterol and triglyceride levels were measured by enzymatic techniques using a ABA-200 biochromatic analyzer (Abbott Labortories, Irving, TX). High-density lipoprotein cholesterol (HDL-C) level was measured after precipitation of the other lipoproteins with heparin and manganese chloride. Determination of plasma glucose was performed in a research laboratory using a glucose oxidase method.

Type 2 diabetes and impaired glucose tolerance (IGT) were defined using the 1999 World Health Organization (WHO) criteria, where a diagnosis of type 2 diabetes requires a fasting plasma glucose level (FPG) ≥ 126 mg/dL or a 2-hour post-challenge glucose level (PCG) ≥ 200 mg/dL or a history of type 2 diabetes diagnosed by a physician or treatment with an oral hypoglycemic agent or insulin.[22] A diagnosis of IGT requires an FPG 110–<126 mg/dL and PCG<200, or FPG<110 and PCG 140–<200, without a prior diagnosis or treatment of diabetes. All others were classified as having normal glucose tolerance.

Classification of MI and ischemic resting ECG abnormalities for baseline exclusion were based on history, physician diagnosis, or ECG criteria. ECG changes were subcategorized into ECG coronary probable (major Q or QS wave [Minnesota Code 1.1, 1.2] and complete left bundle branch block [LBBB] [Minnesota Code 7.1.1]) and ECG coronary possible (small Q or QS wave [Minnesota Code 1.3], ST depression [Minnesota Code 4.1–4.3], and flattened or T waves [Minnesota Code 5.1–5.3]). This algorithm is based on Whitehall criteria as applied in the WHO Multinational Study of Diabetes and Vascular Disease.[23] Participants were followed through 2004 for vital status, with death certificates obtained for decedents. A certified nosologist coded underlying cause of death using the *International Classification of Diseases*, Ninth Revision (ICD-9).

Statistical analysis

HDL-C and triglyceride levels were not normally distributed and were log-transformed for analyses. Comparisons of age, measures of obesity (i.e., BMI, WHR, waist circumference), lipid levels, and other characteristics by angina status and sex used two-sample independent t tests for continuous variables and chi-square analyses for categorical variables. Age-adjusted comparisons of obesity and lipids by angina status within men and women were performed with analysis of covariance (ANCOVA). The association of angina with CHD and all-cause mortality was examined with sex-specific Cox proportional hazards regression models. All models met the proportional hazards assumption and were assessed by

visualization of log-log plots. The varying impact of angina on mortality risk by sex and diabetes status was verified using an interaction term (i.e., gender×diabetes status) in the regression models. These interactions were significant ($p < 0.0001$), therefore, hazard ratios (HR) stratified by sex and diabetes status are presented. To avoid collinearity, BMI, waist circumference, and WHR were tested in individual regression models. Only WHR is presented; models using BMI or waist circumference yielded similar results. To assess confounding, 10% change in the beta-estimate approach was used. Confounding effects were assessed individually with age and WHR for all covariates of interest in the general proportional hazards model.

All tests except for the Cox proportional hazards regression models were two-tailed, with $p < 0.05$ indicating statistical significance. The Cox models were conducted using a one-tailed analysis based on the assumption that having angina pectoris would not decrease the risk of CHD mortality. Data were analyzed using SAS version 9.1 (SAS Institute Inc, Cary, NC) and Intercooled STATA 9 (StataCorp LP, College Station, TX).

Results

At the 1984–1987 clinic visit, there were 2006 participants aged 50–89 (mean 70.9 ± 9.7 years for men, 70.5 ± 9.1 years for women). A total of 61 men (7.4%) and 142 (12.0%) women had angina at baseline. By 2004, after an average follow-up of 13.2 years, 59% of men (485) and 47% of women (557) had died; of these, 21.2% of the deaths in men (103) and 18.7% of the deaths in women (104) were attributed to CHD. Among the 61 men with angina, a total of 7 of 33 (21.1%) with normal glucose, 2 of 18 (11.1%) with IGT, and 4 of 10 (40.0%) with diabetes died of CHD during follow-up; among the 761 men without angina, 52 of 432 (12.0%) with normal glucose, 18 of 210 (8.6%) with IGT, and 20 of 119 (16.8%) with diabetes died of CHD. Among the 142 women with angina, 9 of 66 (13.6%) with normal glucose, 9 of 54 (16.7%) with IGT, and 7 of 22 (31.8%) with diabetes died of CHD; among the 1042 women without angina, 39 of 631 (6.2%) with normal glucose, 31 of 303 (10.2%) with IGT, and 9 of 108 (8.3%) with diabetes died of CHD.

At baseline, women had lower BMI, WHR, waist circumference ($p < 0.0001$) and higher HDL-C levels ($p < 0.0001$) and were more likely to have IGT but less likely to have type 2 diabetes ($p = 0.008$) than men (Table 1). Women were also less likely to exercise three or more times per week, reported lower rates of having ever smoked and daily alcohol consumption and less formal education ($p < 0.01$). Approximately 30% of women reported current estrogen use.

Table 2 presents sex-specific comparisons of covariates in participants with and without angina. Men with angina were significantly older, had lower HDL-C levels, and were less likely to consume ≥3 alcoholic drinks/day than men without angina ($p < 0.05$). Women with angina were significantly older, had greater waist circumferences, higher triglycerides,

TABLE 1. BASELINE CHARACTERISTICS AMONG 822 MEN AND 1184 WOMEN AGED 50–89:
THE RANCHO BERNARDO STUDY, 1984–1987

Characteristic	Men (n = 822)	Women (n = 1184)	p value[a]
Age (years)[b]	70.9 ± 9.7	70.5 ± 9.1	0.61
BMI (kg/m^2)[b]	25.9 ± 3.3	24.2 ± 3.8	<0.0001
Waist/hip ratio (cm/cm)[b]	0.9 ± 0.05	0.8 ± 0.06	<0.0001
Waist circumference (cm)[b]	94.1 ± 9.0	78.7 ± 9.7	<0.0001
Triglycerides (mg/dL)[c]	99.0 (69.0–148.0)	99.0 (69.0–142.0)	0.54
HDL-C (mg/dL)[c]	52.0 (44.0–62.0)	67.0 (56.0–80.0)	<0.0001
Hypertension[d]			
Yes	219 (26.6)	349 (29.5)	0.17
Diabetes[d]			0.008
Normal	465 (56.6)	697 (58.9)	
Impaired glucose tolerance	228 (27.7)	357 (30.2)	
Type 2 diabetes	129 (15.7)	130 (11.0)	
Exercise (≥3 times/week)[d]			
Yes	698 (84.9)	933 (78.8)	0.0006
Smoking status[d]			
Current smoker	88 (10.7)	171 (14.4)	<0.0001
Alcohol consumption (daily average)[d]			<0.0001
None	234 (28.5)	498 (42.1)	
1–30 g/day (1–2 drinks)	449 (54.6)	595 (50.3)	
≥30 g/day (≥3 drinks)	139 (16.9)	91 (7.7)	
Education[d]			
College graduate	426 (52.0)	304 (25.9)	<0.0001
Estrogen Use[d]			
Current	—	1139 (29.8)	—

All variables had <1% missing except estrogen use in women (3.8%).
[a]For comparisons between men and women (independent t and chi-square tests). Log-transformed values used for independent t tests for triglycerides and HDL variables.
[b]Mean ± SD.
[c]Median (25%–75%).
[d]n (%).
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation.

TABLE 2. AGE AND AGE-ADJUSTED BASELINE CHARACTERISTICS AMONG 822 MEN AND 1184 WOMEN AGED 50–89
BY ANGINA STATUS: THE RANCHO BERNARDO STUDY, 1984–1987

	Men			Women		
	Angina			Angina		
	Yes n = 61	No n = 761	p value[a]	Yes n = 142	No n = 1042	p value[a]
Age (years)	74.5 ± 8.7	70.4 ± 9.8	0.002	73.0 ± 8.8	70.2 ± 9.1	0.0004
BMI (kg/m²)	25.8 ± 0.4	25.9 ± 0.1	0.75	24.8 ± 0.3	24.1 ± 0.1	0.06
Waist/hip ratio (cm/cm)	0.91 ± 0.007	0.92 ± 0.002	0.75	0.80 ± 0.005	0.80 ± 0.0001	0.33
Waist circumference (cm)	93.1 ± 1.2	94.2 ± 0.3	0.36	80.3 ± 0.8	78.4 ± 0.3	0.03
Triglycerides (mg/dL)	102.2 ± 1.0	103.9 ± 1.1	0.82	97.9 ± 1.0	123.7 ± 1.0	<0.0001
HDL-C (mg/dL)	48.2 ± 1.0	52.4 ± 1.0	0.02	61.2 ± 1.0	67.2 ± 1.0	0.0002
Hypertension (present)	20.9%	26.8%	0.35	39.5%	27.1%	0.002
Diabetes (present)	13.6%	15.0%	0.69	13.2%	9.8%	0.19
Exercise (≥3 times/week)	83.5%	85.0%	0.77	77.9%	79.0%	0.82
Smoking status (current)	7.1%	10.0%	0.38	10.3%	14.1%	0.25
Alcohol consumption (≥3 drinks/day)	5.2%	17.6%	0.01	9.4%	7.4%	0.46
Education (college graduate)	40.5%	52.9%	0.07	26.2%	25.8%	0.88
Estrogen (current)	—	—	—	40.4%	39.8%	0.99

Data are expressed as age-adjusted mean ± SE or %.

[a]For comparisons between angina and no angina (independent t and chi-square tests). Log transformed values used for ANCOVA for triglycerides and HDL-C variables and transformed back for adjusted means.

SE, standard error; ANCOVA, analysis of covariance.

lower HDL-C levels, and higher rates of hypertension than women without angina ($p < 0.05$). Angina was associated with a nonsignificantly lower risk of all-cause mortality for both sexes before stratification by diabetes status (data not shown).

Sex-specific, multivariate hazard models comparing the time to CHD mortality stratified by angina and diabetes status are shown in Table 3. Each risk factor variable was found to confound the estimate in at least one strata. Therefore, HRs are presented for three models: an age-adjusted model, an age and biological risk factors model, and a fully adjusted model with age as well as biological and behavioral risk factors. In the age-adjusted analysis (model 1), women with diabetes who also had angina had a 3.87 times greater risk of dying from CHD compared with women without angina ($p = 0.01$). Among women who had normal glucose or IGT, women

with angina had a 2-fold greater risk of CHD mortality compared with women without angina (normal glucose: HR 1.99, $p = 0.03$; IGT: HR = 1.98, $p = 0.04$). Model 2 shows that after adjustment for age, WHR, hypertension, triglycerides, and HDL-C levels, there was also a significantly increased risk of CHD mortality in women with angina and IGT (HR = 2.10, $p = 0.03$) or type 2 diabetes (HR = 3.01, $p = 0.03$). Adjustment for all biological and behavioral risk factors yielded similar results (Table 3). No significant association was observed between angina and CHD mortality among men after adjustment for covariates and stratification by glycemic status.

Results of the fully adjusted models are shown in Figure 1. Having both angina and IGT or type 2 diabetes was associated with a greater risk of CHD mortality among women but not men.

TABLE 3. SEX-SPECIFIC MULTIVARIATE COX PROPORTIONAL HAZARDS FOR ANGINA AND CORONARY HEART DISEASE
MORTALITY BY GLUCOSE TOLERANCE CATEGORY: THE RANCHO BERNARDO STUDY, 1984–2004

	Normal glucose			Impaired glucose tolerance			Type 2 diabetes		
CHD mortality	HR	95% CI upper bound[a]	p value[a]	HR	95% CI upper bound[a]	p value[a]	HR	95% CI upper bound[a]	p value[a]
Men[b]									
Model 1	1.68	(3.27)	0.10	0.82	(2.82)	0.39	1.93	(4.83)	0.12
Model 2	2.21	(4.39)	0.03	1.00	(3.70)	0.50	1.63	(4.23)	0.20
Model 3	1.07	(4.01)	0.47	1.65	(4.42)	0.20	1.36	(3.27)	0.28
Women[b]									
Model 1	1.99	(3.67)	0.03	1.98	(3.71)	0.04	3.87	(9.34)	0.01
Model 2	1.64	(3.13)	0.10	2.10	(3.98)	0.03	3.01	(8.02)	0.03
Model 3	1.91	(3.83)	0.06	2.35	(4.59)	0.02	3.55	(11.18)	0.03

[a]Upper bound of 95% confidence interval (CI) and p values given for one-sided analysis.

[b]Model 1, adjusted for age only; model 2, model 1 + WHR, hypertension, triglycerides, HDL-C; model 3, model 2 + physical activity, current smoking, alcohol intake, education, and current estrogen (women).

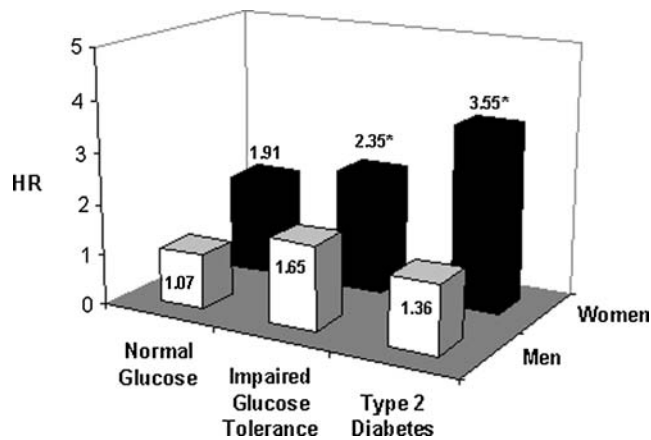CHD, coronary heart disease; HR, hazard ratio.

FIG. 1. Multivariate HRs for angina and CHD mortality by gender and diabetes status in 822 men and 1184 women aged 50–89: The Rancho Bernardo Study, 1984–2004. *$p < 0.05$. HR, hazard ratio.

Discussion

Although worldwide rates of CHD mortality in developed countries have declined by approximately 25% worldwide in the last three decades, CHD remains a significant public health issue.[1,24–31] The decline reflects a reduction in both the incidence of MI and case fatality rates. The prevalence of angina, estimated at 8.9 million American adults, is substantial and is expected to increase with the aging United States population,[1] causing a considerable clinical and economic burden associated with increased medical visits, medications, and expensive procedures.[32,33] Direct costs due to angina have been estimated to range from $8.8 billion for chronic angina to upwards of $75 billion for coronary artery disease.[34]

To our knowledge, this is the first long-term prospective study to evaluate the association between angina pectoris and CHD mortality by glycemic status and sex in the United States. In this cohort of community-dwelling older men and women, a significantly increased risk of fatal CHD was observed in women with both angina and IGT or diabetes, an association not observed in men. Angina was also marginally associated with long-term risk of CHD mortality in women with normal glucose tolerance ($p = 0.06$).

A study in Finland using data from over 118,000 men and women identified as having "nitrate angina" or "test-positive angina," based on reimbursement for prescription nitrate medications or abnormal invasive tests, indicated that the overall prognosis of angina did not differ in women and men.[17] Increases in CHD mortality after a 4-year follow-up period were observed in both men and women with nitrate angina, although increases were higher among women with test-positive angina, and diabetes was strongly associated with cardiac events for either classification. However, this Finnish study reported the combined risk of fatal CHD and non-fatal MI and did not separately assess the impact of IGT, limiting comparison to the present study. Furthermore, angina and comorbid conditions were assessed via prescription reimbursements, which may not capture untreated or undiagnosed angina, hypertension, or diabetes. In contrast, in the Rancho Bernardo cohort, angina was assessed for all participants; diagnoses of hypertension, IGT, and diabetes were

based on clinical criteria and blood tests; and participants were followed over 20 years, significantly longer than participants in the Finnish study.

The physiological mechanisms underlying increased cardiac mortality risk of women with angina and diabetes remain unclear. Type 2 diabetes, an important predictor of CHD risk and prognosis in men and women, may have greater prognostic implications in women over other traditional CHD risk factors.[1,35] Women with diabetes have a substantially greater risk of CHD and CHD mortality than men.[35–37] In a meta-analysis of type 2 diabetes and fatal CHD from 37 studies of over 447,000 people, the summary relative risk for CHD mortality was 3.5 (95% CI 2.70-4.53) in women and 2.06 (95% CI 1.81-2.34) in men.[35]

It has been proposed that women with diabetes have a greater risk of cardiovascular abnormalities than do men with diabetes.[38–40] For example, women with diabetes have more hypertension and higher lipid levels than men with diabetes. Similar trends between men and women were also observed in the present study about angina. However, even after adjustment for hypertension, triglycerides, and HDL-C, women with angina and diabetes had a greater mortality risk than men.

Significant differences in the epidemiology, diagnosis, and treatment patterns of CHD between men and women may also explain the greater risk of CHD mortality associated with angina and diabetes in women. Women carry a greater risk factor burden for CHD and may experience different coronary disease manifestations from men, such as having more chest pain than a clearly defined event such as MI.[9,41] A 26-year follow-up from the Framingham study indicates that in women, angina pectoris was more frequently uncomplicated (80%), whereas angina in men often occurs after an infarction (66%).[6] The clinical presentation of angina between men and women also often differs, with women less likely to have typical angina but more likely to report more intense chest pain and more frequently having pain and other sensations in the neck and throat.[42] However, women are less likely to be referred for diagnostic or aggressive therapeutic procedures than men [43,44] when experiencing either acute or chronic coronary symptoms.[45–48] Moreover, women with diabetes or cardiovascular disease are less likely than men to receive aspirin, statins, or antihypertensive medications.[49–52]

Several potential limitations of this study were considered. The Rancho Bernardo cohort is predominantly white, educated, and middle class; thus, results may not apply to other ethnic and socioeconomic groups. Another limitation is the relatively small sample of participants, particularly men with angina. It is possible that many of the men with CHD excluded from the study sample may have been those with a history of angina as well, thus resulting in a smaller sample and limited power to observe a significant association. Of the 320 individuals excluded at baseline for CHD, more men were excluded than women (216 vs. 104, respectively, $p < 0.001$). Although this was expected because men have a higher risk of MI/CHD at an earlier age than women, this could explain the observed lack of an association in the study results for the men.

Men typically have higher rates of MI and coronary artery disease than women, although women have at least an equal prevalence of angina. This study suggests that the association between angina and CHD mortality is particularly high for

women in the presence of diabetes or IGT. Earlier studies have failed to identify an increased risk of coronary events after angina because they did not examine CHD mortality risk by glucose status. An association in women with IGT or diabetes may not be evident if the prevalence of IGT or diabetes is low in the population. Further long-term population-based studies are needed to confirm this association.

A recent study compared two populations of women, one with nonobstructive coronary artery disease and a community-based population of women who were asymptomatic with no history of heart disease. Although not exactly comparable with our study, the study by Gulati et al.[53] indicates more cardiovascular events in the population with signs and symptoms suggestive of ischemia compared with the asymptomatic population, further highlighting the significant adverse outcomes of CHD observed in women.

Results of this study support the clinical importance of taking into account the copresence of angina and diabetes in the care of women with either of these conditions. Women with symptoms of angina and diabetes should be evaluated for risk of subsequent coronary events, with treatment to control or reduce current risk factors for CHD considered.

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Disclosure Statement

The authors have no conflicts of interest to report.

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