Original Article

Ten-Year Mortality in the WISE Study (Women's Ischemia Syndrome Evaluation)

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Background—The WISE study (Women's Ischemia Syndrome Evaluation) was a prospective cohort study of 936 clinically stable symptomatic women who underwent coronary angiography to evaluate symptoms and signs of ischemia. Long-term mortality data for such women are limited.

Methods and Results—Obstructive coronary artery disease (CAD) was defined as ≥50% stenosis on angiography by core laboratory. We conducted a National Death Index search to assess the mortality of women who were alive at their final WISE contact date. Death certificates were obtained. All deaths were adjudicated as cardiovascular or noncardiovascular by a panel of WISE cardiologists masked to angiographic data. Multivariate Cox proportional hazards regression was used to identify significant independent predictors of mortality. At baseline, mean age was 58±12 years; 176 (19%) were non-white, primarily black; 25% had a history of diabetes mellitus, 59% hypertension, 55% dyslipidemia, and 59% had a body mass index ≥30. During a median follow-up of 9.5 years (range, 0.2–11.5 years), a total of 184 (20%) died. Of these, 115 (62%) were cardiovascular deaths; 31% of all cardiovascular deaths occurred in women without obstructive CAD (<50% stenosis). Independent predictors of mortality were obstructive CAD, age, baseline systolic blood pressure, history of diabetes mellitus, history of smoking, elevated triglycerides, and estimated glomerular filtration rate.

Conclusions—Among women referred for coronary angiography for signs and symptoms of ischemia, 1 in 5 died from predominantly cardiac pathogeneses within 9 years of angiographic evaluation. A majority of the factors contributing to the risk of death seem to be modifiable by existing therapies. Of note, 1 in 3 of the deaths in this cohort occurred in women without obstructive CAD, a condition often considered benign and without guideline-recommended treatments. Clinical trials are needed to provide treatment guidance for the group without obstructive CAD. (***Circ Cardiovasc Qual Outcomes*****. 2017;10:e003863. DOI: 10.1161/CIRCOUTCOMES.116.003863.)**

Key Words: acute coronary syndrome ■ coronary artery disease ■ ischemia ■ mortality ■ women

About 190 000 American women die each year from cardiovascular disease, predominately ischemic heart disease (IHD) and related conditions, and current projections indicate that this statistic will dramatically increase with our aging population.[1] In fact, since 1984, more women have died annually from IHD than men.[2] Notably, IHD is the leading killer of women at all ages, with annual mortality rates greater than all forms of cancers combined.[3]

Clear sex differences in presentation, pathophysiology, and management underscore the need for an increased understanding of IHD in women. For instance, pathology reports demonstrate a higher frequency of coronary plaque erosion and distal embolization as pathogenic in younger women as compared with plaque rupture in men.[4–6] A review of data from randomized acute coronary syndrome clinical trials suggest a higher 30-day mortality rate after acute coronary syndrome in women versus men, 9.6% versus 5.3% (odds ratio, 1.91; 95% confidence interval [CI], 1.83–2.00).[7] Furthermore, women who are symptomatic more often have persistent and refractory chest pain requiring more hospitalizations compared with men, accompanied by lower ratings of general well-being, and limitations in activities of daily living.[8,9] Interestingly, these adverse outcomes are experienced by women despite possessing lower syntax scores than males. A variety of reports document that across all ages and diagnoses, more than half of women with clinically stable symptoms presenting to coronary angiography do not have obstructive coronary artery disease (CAD),[10] for which evidence-based guidelines do not exist. Moreover, sex-related variability in medical care may contribute to a higher case fatality rate for IHD in women.[11] In women, IHD is relatively more expensive to treat than it is in men; resource consumption in females is characterized by

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WHAT IS KNOWN

- Women and men differ in the presentation and pathophysiology of ischemic heart disease.
- Ischemic heart disease is a leading cause of death among women and presents a treatment challenge for clinicians because of the lack of evidence-based management.

WHAT THE STUDY ADDS

- This study enumerates a 20% rate of mortality within 10 years among women referred for coronary angiography for signs and symptoms of ischemia.
- This study demonstrates the elevated risk of all-cause mortality among women with signs and symptoms of ischemia but without obstructive coronary artery disease (13%) as compared with a nationally representative cohort of American women of approximately the same age during the same period (2.8%).
- This study provides evidence that most of the predictors of mortality are risk factors that can be modified by current therapies supporting the development of clinical trials in women symptomatic of ischemic heart disease even in the absence of obstructive coronary artery disease.

more frequent angina diagnosis, more office visits, more avoidable hospitalizations, higher myocardial infarction mortality, and higher rates of heart failure hospitalization.[12–14] Clinicians face a difficult challenge in women with IHD because of their greater symptom burden, functional disability, higher prevalence of nonobstructive CAD, and greater adverse outcomes as compared with men in the setting of a scarcity of information for evidence-based management.

Women's Ischemia Syndrome Evaluation

The WISE study (Women's Ischemia Syndrome Evaluation) was a multicenter prospective study of a cohort of clinically stable women referred for coronary angiography to evaluate symptoms and signs suggestive of ischemia. The major aims of WISE were to improve diagnostic testing for IHD and to explore female-specific IHD pathophysiology.[15] Initiated in September 1996, recruitment of 936 women was completed in March 2000, and women were followed by site personnel through March 2006. A National Death Index (NDI) search was initiated to assess cardiovascular mortality data through December 2007 with the goal of enhancing the precision of mortality estimates and more clearly defining prognostic factors for long-term mortality in women with ischemia (regardless of whether they demonstrated evidence of obstructive coronary disease).

The goal of this analysis was to determine all-cause and cardiac mortality among WISE women up to 10 years after their index coronary angiography. We also sought to evaluate demographics, coronary risk factors, extent of obstructive CAD, hormonal status, psychosocial, and baseline diagnostic testing as predictors of long-term mortality.

Methods

Current Database of WISE Women

Currently, a large comprehensive database exists with information on these women. Systematic collection of serum samples for WISE core laboratory assays was added to the baseline protocol several months after initiation of recruitment; laboratory variables therefore are not complete for all women. The original WISE met recruitment goals on time and enrolled ≈20% minority women. Retention was excellent with only 3% withdrawals each of the first 3 years and lower rates in subsequent years. A coordinating center at the University of Pittsburgh was responsible for data management, statistical analysis, and study communication.

Definition of Baseline Variables

Menopausal status was adjudicated by the WISE hormone committee who reviewed the reproductive status questionnaire administered at baseline and the results of blood hormone assays.[16] Angina was assessed at baseline through a series of detailed questions that assessed the location of pain, whether it was provoked by stress or exertion, and whether it was relieved by rest or nitroglycerin. Lipid and fasting blood sugar levels and insulin resistance were ascertained by analysis of serum; low-density lipoprotein values were calculated from measured levels of total cholesterol, high-density lipoprotein, and triglycerides. Medical and treatment histories, demographics, and the Duke Activity Status Inventory were recorded by study coordinators at baseline through standardized questions. Study coordinators collected data on height, weight, waist circumference, pulse, and blood pressure through physical examination at baseline. Hypertension was defined by one of the following: a systolic blood pressure ≥140 mm Hg or diastolic blood pressure >90 mm Hg, or a self-reported history of hypertension.

Quantitative Angiographic Assessment of CAD

All coronary angiograms obtained at enrollment were analyzed quantitatively and qualitatively at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI) by investigators masked to all other WISE data. The presence of obstructive CAD was defined as ≥50% diameter stenosis in ≥1 major epicardial coronary artery. Minimal CAD was defined as ≥20% but <50% stenosis, and no CAD as <20% stenosis. An angiographic CAD severity index was calculated based on stenosis severity weighted by proximal lesion. Interobserver variability for this laboratory was 0.196 mm with a 6.3% coefficient of variation.[17]

Angiographic core laboratory assessments were completed for all but 1 woman whose angiogram was of poor quality; her data were excluded from current analyses. Institutional review board approval was obtained from the participating sites (University of Alabama at Birmingham, University of Florida at Gainesville, University of Pittsburgh Medical Center, and Allegheny General Hospital in Pittsburgh). Written informed consent for baseline and follow-up testing was obtained from all participants before enrollment.

NDI Search

The National Death Index Plus was used to obtain cause of death along with vital status. Clinical sites received a spreadsheet from the WISE Coordinating Center with WISE ID, date of birth, and status for surviving participants and prepared each record as specified at the website https://www.cdc.gov/nchs/data/ndi/ndi_users_guide.pdf. Each clinical site downloaded the NDI application from the website, and all coordinators emailed an unsigned application form to the NDI. NDI emailed an assigned NDI number. A final, signed NDI application was express mailed to the National Center for Health Statistics.

Two of the original WISE sites were in Pittsburgh, PA, one in Birmingham, AL, and one in Gainesville, FL. Florida had additional requirements over and above other states. The coordinator at the University of Florida contacted the NDI staff to receive confidentiality forms for use of National Death Index Plus at the coordinating

center by WISE ID without names and social security numbers to maintain confidentiality.

The clinical site coordinators received the NDI designations and resolved questions as to the exact identity of the women whose vital statuses were queried. The process of submitting the NDI application and resolving questions about the women's identities lasted ≈ 1 year. Then each clinical site sent mortality information to the coordinating center by WISE ID so that the name and social security number were not given to the coordinating center. The data center and each clinical site received institutional review board approval for the project.

Dates of death were ascertained. Causes of death were reported by NDI, and this information was used to update previously known deaths for women for whom we did not have a cause. We assumed that women who were not reported as deceased in the NDI were alive as of December 31, 2007.

Classification of deaths as cardiovascular versus noncardiovascular was adjudicated by an Events Committee masked to identifying information obtained on the death certificates and, in the case of deaths discovered during the WISE study follow-up period, masked to physicians or family members' account of the circumstances surrounding the death. The adjudication protocol specified that strokes, venous thrombosis, pulmonary hemorrhage/bleeding vasculitis, renal disease associated with hypertensive heart, and sudden death without any additional information were classified as cardiovascular deaths. Ischemic bowel and unspecified renal failure were classified as noncardiovascular deaths.

Statistical Analyses

Ten-year Kaplan–Meier estimated mortality rates are presented by dichotomous baseline risk factors (Table 1). For continuous risk factors, established guidelines were used to divide these measures into normal versus abnormal values. Where such guidelines were not available, a median split was used to examine relationships.

Kaplan–Meier survival curves were used to plot 10-year mortality rates and cardiac mortality rates. Rates by CAD severity subgroups were examined. Overall and individual differences between subgroups were evaluated using the log-rank statistic. We considered both all-cause and cardiac mortality as the outcomes of interest. Using standard Cox proportional hazards regression techniques, we modeled univariate (Table 2) and multivariate (Tables 3 and 4) risk models. For these models, all continuous risk factors were entered as continuous variables. Variables that were highly skewed were log transformed.

A combination of forward and backward selection procedures was used to aid in determining the best model of independent predictors. This was followed by forcing potential confounders into the models and determining their effect on the relationship of interest. The likelihood ratio test was used to compare the incremental goodness of fit of nested models.

Fitted models were evaluated for departures from the proportional hazard assumptions by using diagnostic residual analyses, including plotting Schoenfeld residuals against time, and were found to meet assumptions. All tests were 2 sided, and $P \leq 0.05$ was considered statistically significant. All analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

Results

Recruitment was completed in March 2000. At the time of final follow-up, 96 women were known to have died over a median of 6.0 (mean 5.3) years of follow-up. The NDI search led to the discovery of an additional 88 deaths over a median of 9.5 (mean 8.9) years, with a range of 0.2 to 11.5 years. In all, 184 of the women enrolled had died. The all-cause mortality rate was 20%, and the cardiac mortality rate was 12% (Figure 1). The differences in all-cause mortality rates by clinical site (range, 14%–23%; χ^2 P=0.10) and cardiac mortality rates

Table 1. All Cause 10-Year Mortality and Cardiac Cause Mortality Rates by Baseline Factors

Kaplan–Meier Estimate Rates				
	All-Cause Mortality		CV Mortality	
Risk Factor	Mortality %	*P* Value*	Mortality %	*P* Value*
≥50% stenosis	36.4	<0.0001	24.6	<0.0001
50% stenosis	12.7		7.5	
Age ≥ 58 y, MD	29.7	<0.0001	20.9	<0.0001
Age <58 y, MD	14.9		7.7	
Post-menopausal	24.9	0.0001	16.4	0.0004
Not post-menopausal	12.7		6.6	
Education <HS	32.4	0.0004	22.9	0.0001
No education ≥HS	19.2		11.4	
Non-white race	29.5	0.023	21.0	0.004
White race	20.5		12.5	
Hx diabetes mellitus	38.5	<0.0001	29.6	<0.0001
No Hx diabetes mellitus	16.7		8.9	
Hx hypertension	28.4	<0.0001	19.4	<0.0001
No Hx hypertension	13.0		6.6	
HTN risk†	27.1	<0.0001	18.6	<0.0001
No HTN risk†	11.4		4.8	
Ever smoker	25.2	0.018	15.7	0.13
Never smoker	18.7		12.3	
Current smoker	25.4	0.41	13.5	0.89
No current smoker	21.3		14.2	
Insulin resistant	37.6	<0.0001	24.5	<0.0001
Not insulin resistant	18.2		10.9	
Ever HRT use	18.7	0.032	10.3	0.008
Never HRT use	24.8		17.0	
BMI ≥30	21.5	0.70	15.4	0.60
BMI <30	22.2		12.6	
Typical angina	18.5	0.36	12.5	0.84
No typical angina	22.6		13.2	
Waist ≥33 inches	23.9	0.14	15.5	0.12
Waist <33 inches	18.4		9.9	
Pulse pressure >58, MD	26.3	0.004	18.3	0.001
Pulse pressure ≤58, MD	18.1		10.0	
LDL ≥120 mg/dL	15.0	0.22	9.3	0.38
LDL <120 mg/dL	20.7		12.2	
HDL <50 mg/dL	23.8	0.19	14.3	0.37
HDL ≥50 mg/dL	19.0		11.5	
Triglycerides ≥126 mg/dL, MD	25.6	0.004	15.9	0.007
Triglycerides <126 mg/dL, MD	15.9		9.4	

(*Continued*)

Table 1. Continued

Kaplan–Meier Estimate Rates				
	All-Cause Mortality		CV Mortality	
Risk Factor	Mortality %	*P* Value*	Mortality %	*P* Value *
Total cholesterol ≥190 mg/dL, MD	17.7	0.048	10.5	0.09
Total cholesterol <190 mg/dL, MD	24.0		15.0	
TG/HDL ≥3	29.5	<0.0001	18.2	0.0002
TG/HDL <3	15.2		9.0	
FBS >100 mg/dL	29.8	<0.0001	19.3	<0.0001
FBS ≤100 mg/dL	15.5		9.3	
Insulin ≥8, MD	27.1	0.12	16.9	0.07
Insulin <8, MD	20.6		10.9	
Hemoglobin <12 g/dL	25.6	0.045	19.0	0.018
Hemoglobin ≥12 g/dL	20.4		12.4	
HOMA >2.5	30.0	0.023	19.2	0.029
HOMA ≤2.5	21.2		12.5	
DASI <16, MD	26.5	0.002	18.7	0.0001
DASI ≥16, MD	17.3		8.6	
eGFR <90‡	30.9	<0.0001	21.8	<0.0001
eGFR ≥90‡	14.6		7.3	

Typical angina defined as meeting all 3 criteria: substernal location, responding to physical exertion or stress, and relieved by rest or nitroglycerin. BMI indicates body mass index; CV, cardiovascular; DASI, functional capacity estimated by the Duke Activity Status Index; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high-density lipoprotein; HOMA, insulin estimated using the homeostasis model assessment formula; HRT, hormone replacement therapy; HS, high school; HTN, hypertension; Hx, history; LDL, low-density lipoprotein; MD, median split used where known splits were not available; and TG, triglycerides.

**P* values by log-rank statistics.

†If SBP >140 or DBP >90 or self-reported history of hypertension.

‡Estimated glomerular filtration rate—calculated by the Cockcroft–Gault formula.

by clinical site (range, 9%–14%; χ^2 P=0.33) were not found to be statistically significant.

Of the 184 deaths, 103 cases (56%) were adjudicated on the basis of death certificates only; 40 cases (22%) were adjudicated on the basis of hospital, police, or next of kin reports in addition to death certificates; 22 cases (12%) were adjudicated on the basis of hospital or police reports but no death certificate; and 18 cases (10%) were adjudicated on the basis of next of kin reports only. One woman lacked information on cause of death.

Among the 935 women with available data, the mean age at baseline was 58±12 years; 176 (19%) were non-white, primarily black; 25% had a history of diabetes mellitus, 59% had hypertension, 55% had dyslipidemia, and 59% had a body mass index ≥30.

Table 1 presents both the total mortality and cardiac mortality rates by subgroups of risk factors measured at baseline. The derived relationships between risk factors

Table 2. Factors Related to Long-Term All-Cause Mortality in WISE

Factors Univariate	Hazard Ratio (Unadj.)	95% CI	*P* Value (Unadj.)	*P* Value (Age-Adj.)
CAD predictors				
CAD (50% stenosis +)	3.52	2.59–4.78	<0.0001	<0.0001
CAD (70% stenosis +)	3.35	2.50–4.48	<0.0001	<0.0001
CAD severity score (log)	2.10	1.78–2.49	<0.0001	<0.0001
Demographics				
Age, y	1.05	1.03–1.06	<0.0001	…
Post-menopausal	2.45	1.57–3.82	<0.0001	0.73
HS education or more	0.58	0.42–0.80	0.001	0.038
White race	0.70	0.50–0.99	0.041	0.005
Body size				
Waist circumference, inches	1.02	1.00–1.04	0.06	0.052
BMI	0.98	0.96–1.01	0.20	0.70
Waist/hip ratio	3.64	1.04–12.80	0.044	0.12
Self-reported risk factors				
Hx diabetes mellitus	2.71	2.02–3.63	<0.0001	<0.0001
Family hx of CAD	0.80	0.59–1.08	0.15	0.36
Hx hypertension	2.42	1.72–3.40	<0.0001	<0.0001
Hx dyslipidemia	1.82	1.32–2.52	0.0003	0.003
Ever smoker	1.42	1.06–1.91	0.020	0.0009
High stress	0.76	0.55–1.05	0.10	0.58
Hemodynamic measures				
Heart rate, beats per minute	1.01	1.001–1.03	0.03	0.006
Systolic BP (per 10 U mm Hg)	1.12	1.06–1.20	0.0003	0.041
Pulse pressure (per 10 U mm Hg)	1.21	1.12–1.30	<0.0001	0.006
Mean arterial pressure (per 10 U mm Hg)	1.08	0.97–1.21	0.16	0.44
SBP >140 mm Hg or DBP >80 mm Hg (yes/no)	1.32	0.99–1.78	0.056	0.27
Laboratory values				
LDL, mg/dL	1.00	0.99–1.00	0.12	0.15
HDL, mg/dL	0.99	0.98–1.00	0.21	0.16
Triglycerides, mg/dL (log)	1.77	1.38–2.27	<0.0001	<0.0001
Fasting blood glucose (per 10 U mg/dL)	1.06	1.04–1.07	<0.0001	<0.0001
Insulin, μIU/mL	1.016	1.01–1.03	0.002	0.0008
Insulin resistant	2.40	1.67–3.45	<0.0001	<0.0001
Creatinine, mg/dL (log)	2.93	2.12–4.05	<0.0001	<0.0001
Hemoglobin, g/dL	0.85	0.76–0.94	0.002	0.006

(*Continued*)

Table 2. Continued

Factors Univariate	Hazard Ratio (Unadj.)	95% CI	*P* Value (Unadj.)	*P* Value (Age-Adj.)
HOMA	1.04	1.02–1.06	<0.0001	<0.0001
Triglycerides/HDL ratio	1.06	1.03–1.09	<0.0001	<0.0001
Ever HRT user	0.71	0.53–0.96	0.024	0.024
Current HRT user	0.65	0.47–0.90	0.009	0.017
Functional capacity (DASI)	0.97	0.96–0.98	<0.0001	<0.0001

One hundred and eighty-four deaths in 935 women (20%) during a mean follow-up of 8.9 years (median 9.5 y), ranging from 0.2 to 11.5 years.

Hazard ratios, 95% confidence intervals, and *P* values for univariate (unadj.) and *P* values for age-adjusted (age-adj.) Cox proportional hazards regression models predicting all-cause mortality are listed.

Not significant characteristics: BMI >30, typical angina, current smoking, diastolic BP, total cholesterol, non-HDL cholesterol.

BMI indicates body mass index; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; DASI, functional capacity estimated by the Duke Activity Status Index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, insulin resistance estimated using the homeostasis model assessment formula; HRT, hormone replacement therapy; HS, high school; Hx, history; LDL, low-density lipoprotein; SBP, systolic blood pressure; and WISE, Women's Ischemia Syndrome Evaluation.

and all-cause mortality were remarkably similar to those seen with cardiac mortality. Many baseline risk factors were predictive of mortality. For instance, women who presented with at least 1 coronary lesion of >50% stenosis, all-cause mortality was 36% compared with 13% for those without a lesion of this degree. The difference in cardiac mortality was more pronounced: women with a 50% stenosis or more demonstrated a 25% cardiac mortality rate compared with only 7% for their counterparts. Older and postmenopausal women had the highest mortality rates. In addition, higher rates were seen among minorities compared with white women and women with less than a high school education. Among the classic coronary risk factors, a history of smoking, hypertension, dyslipidemia, and

Table 3. Significant Independent Predictors of All-Cause Mortality in WISE

	n=759, 142 Events	
	HR (95% CI)	*P* Value
Obstructive CAD	2.13 (1.47–3.10)	<0.0001
Age	1.02 (1.002–1.03)	0.027
Hypertension*	1.65 (1.06–2.58)	0.027
Hx diabetes mellitus	2.02 (1.41–2.90)	0.0001
Hx smoking	1.97 (1.39–2.80)	0.0001
Triglycerides (log)	1.39 (1.05–1.83)	0.020
GFR (log)	0.42 (0.30–0.58)	<0.0001

CAD indicates coronary artery disease; CI, confidence interval; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HR, hazard ratio; HTN, hypertension; Hx, history; SBP, systolic blood pressure; and WISE, Women's Ischemia Syndrome Evaluation.

*Hypertension defined as SBP >140, DBP >90, or self-reported history of HTN.

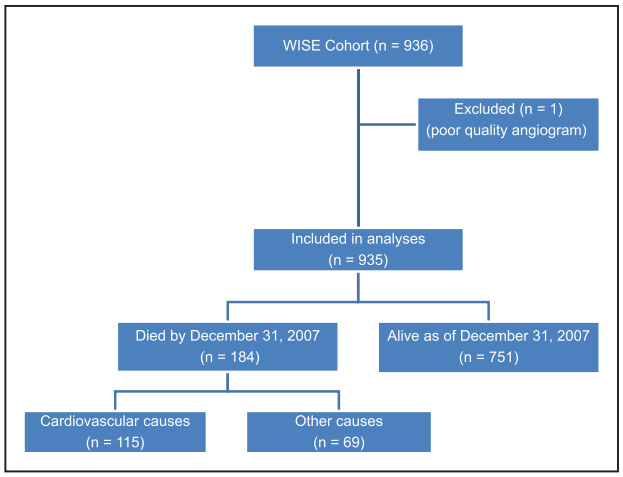

Figure 1. Vital status of the WISE (Women's Ischemia Syndrome Evaluation) cohort as of December 31, 2007.

diabetes mellitus were all associated with higher mortality rates. Of note, typical angina and measures of obesity, including waist circumference and body mass index, were not predictive of mortality.

Sixty-two of the 184 deaths (34%) occurred among women without obstructive CAD. Thirty-six of the 115 cardiovascular deaths (31%) occurred among women without obstructive CAD. Differential risks for all-cause and cardiac mortality by severity of CAD are shown in Figure 2. These angiographic severity categories show a strong gradient (P<0.0001). Ten-year all-cause mortality rates were 10%, 17%, and 35% in women with no CAD, minimal CAD, and obstructive CAD, respectively. The difference between the curves was statistically significant (P=0.008 for no versus minimal CAD; P<0.0001 for minimal versus obstructive CAD). Cardiac mortality rates were 6%, 11%, and 25%, respectively (P=0.009 for no versus minimal CAD and P<0.0001 for minimal versus obstructive CAD).

Univariate and age-adjusted Cox proportional hazards regression models predicting all-cause mortality are listed in Table 2 and further underscore the relationships between baseline risk factors and mortality noted in Table 1. Significant independent predictors of mortality are presented in the multivariate models listed in Tables 3 and 4. For all-cause mortality, these were obstructive CAD, older age, hypertension, history of diabetes mellitus, history of smoking, higher triglycerides, and lower glomerular filtration rate (Table 3).

Similar significant independent predictors were found for cardiac mortality, but use of hormone therapy was also found to be a protective factor (Table 4).

No other variables found in Table 2 to be significant univariate predictors entered these models as independent predictors. These include race, education, waist circumference, waist/hip ratio, typical angina, family history of CAD, high stress, other lipids, fasting blood sugar, anemia, insulin, and insulin resistance (homeostasis model assessment). These predictive risk models were robust to sample size variation as variables with missing values were forced into or removed from the models.

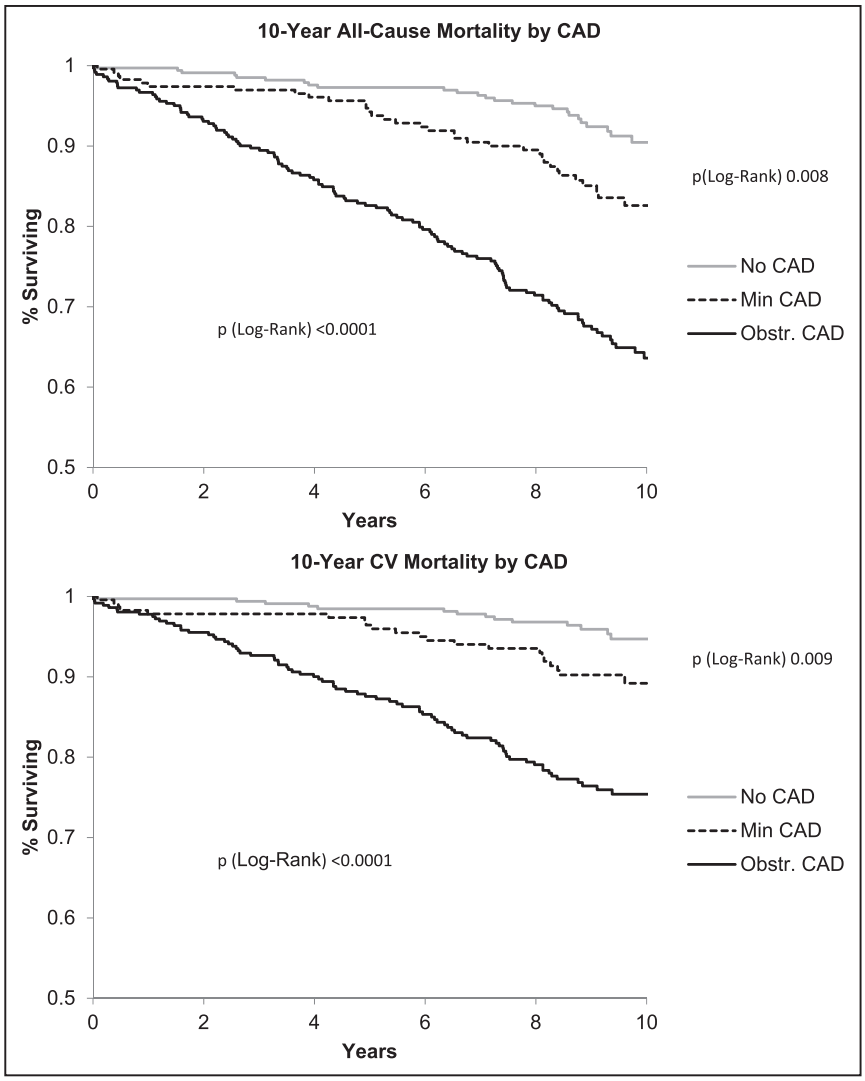

Figure 2. Ten-year all-cause and cardiovascular (CV) mortalities by coronary artery disease (CAD).

It should be noted that including other baseline medication use in our multivariate models (both all-cause and cardiac cause mortality) did not substantively change the models.

Table 4. Significant Independent Predictors of Cardiac Mortality in WISE

	n=748, 85 Events	
	HR (95% CI)	*P* Value
Obstructive CAD	1.71 (1.05–2.80)	0.032
Age	1.03 (1.01–1.05)	0.007
Hypertension*	1.96 (1.04–3.70)	0.038
Hx diabetes mellitus	2.60 (1.64–4.12)	<0.0001
Hx smoking	2.10 (1.34–3.30)	0.001
Triglycerides (log)	1.49 (1.04–2.14)	0.030
GFR (log)	0.43 (0.28–0.67)	0.0002
Ever HRT use	0.60 (0.39–0.94)	0.025

CAD indicates coronary artery disease; CI, confidence interval; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HR, hazard ratio; HRT, hormone replacement therapy; HTN, hypertension; Hx, history; SBP, systolic blood pressure; and WISE, Women's Ischemia Syndrome Evaluation.

*Hypertension defined as SBP >140, DBP >90, or self-reported history of HTN.

However, we did find recent statin use (hazard ratio [HR]=1.64, 95% CI: 1.16–2.33, *P*=0.005; HR=1.63, 95% CI: 1.04–2.58, *P*=0.04, respectively), recent digitalis use (HR=1.63; 95% CI: 1.001–2.66; *P*=0.05 all-cause mortality), and recent antiplatelet drug use (HR=2.85; 95% CI: 1.52–5.37; *P*=0.001 for cardiac mortality) at baseline to be predictive of mortality in these sensitivity analyses. We found recent vitamin C, E, or A use at baseline to be protective against both all-cause and cardiac mortality (HR=0.60, 95% CI: 0.39–0.90, *P*=0.02; HR=0.51, 95% CI: 0.29–0.90, *P*=0.02, respectively).

Discussion

The current WISE results document that women referred for coronary angiography to further evaluate signs and symptoms of ischemia have a 20% risk of all-cause mortality and 12% risk of cardiac mortality within 9.5 years after angiography. Using the NDI, we found that, during a median follow-up period of 9.5 years (range, 0.2–11.5 years), 184 (20%) of the women enrolled had died, including a cardiac mortality rate of 12%.

To put our 10-year Kaplan–Meier estimated mortality rates in perspective, we compared them to a study of 10-year mortality rates among a nationally representative cohort of

comparably aged American adults in the 1998 wave of the Health and Retirement Study. Observed during a similar time period (1998–2008), women aged 50 to 59 years at baseline scoring low on a mortality index demonstrated a 10-year Kaplan–Meier estimated mortality rate of 2.8%.[18] The WISE all-cause mortality rate among those with obstructive CAD (≥50% stenosis) at baseline was 36% and among those without obstructive CAD (<50% stenosis) at baseline was 13%. Notably, the latter rate is substantially higher than the currently proposed threshold for initiation of lipid-lowering therapy for primary prevention in the new American College of Cardiology/American Heart Association Guidelines of 7.5% combined death, nonfatal myocardial infarction, and nonfatal stroke.[19] Yet, these women were most often not treated[20,21]; clinical trials have not addressed this group, and evidence-based guidelines do not exist.

A majority of the variables predictive of mortality are those traditionally linked to CAD risk factors which can be successfully managed by existing therapies. This finding contributes to the growing body of literature suggesting that clinical review of conventional risk factors is one of the best tools for assessing the risk of cardiovascular events in women. The WISE 10-year mortality findings reinforce the conclusions of recent studies targeting hypertension and cholesterol control to actively reduce the risk of cardiovascular disease.[22–24] In addition, our results also corroborate prior reports that elevated serum triglyceride levels are an independent risk factor for CAD in women.[25–29]

These results call for more research and awareness of nonobstructive CAD and its consequences. Clinical trials are warranted, particularly in women, aimed at traditional risk factor modification in the population without obstructive CAD.

Our results indicate that body mass index was not associated with mortality in this population of women. These results are consistent with other published reports demonstrating nonlinear relationships between body mass index and mortality.[30–32] However, one should exercise caution when interpreting this result; excess weight is an established prerequisite of metabolic syndrome (which in turn has been shown to increase mortality). Simply stated, although the relationship between excess weight and mortality is equivocal, the relationship between excess weight and higher morbidity, such as metabolic syndrome, is definitive. Furthermore, our group has also shown that the presence of metabolic syndrome in patients with significant CAD amplifies its cardiovascular risk.[33,34]

Adding baseline medication use to the multivariate models did not substantively alter the effects of the other variables in the base models, suggesting that medication use is a proxy for measuring severity of illness.

With the advent of the new risk assessment algorithm by the American College of Cardiology/American Heart Association,[19] we considered whether the new risk stratification schema was a better fit for modeling the risk of mortality in the WISE population than our own models. Our study demonstrates that the new risk assessment tool does not adequately specify the risks in our population. Although the new risk score incorporates diabetes mellitus, lipids, and smoking status, we found fasting blood sugar, log triglycerides, and history of smoking remained independent predictors of all-cause mortality. This finding is not unexpected given that the new risk model was validated in a healthy population as compared with our cohort of women with a high prevalence of risk factors and demonstrated signs and symptoms of coronary ischemia.

Providing new insight, the 10-year cardiac mortality rate in this population was substantially higher than the currently proposed threshold for initiation of lipid-lowering therapy for primary prevention in the new American College of Cardiology/American Heart Association Guidelines.[19] Our findings, which corroborate the general consensus, document that in the absence of obstructive CAD on coronary angiography, women are most often provided reassurance rather than cardiovascular therapy.[35,36] The current data combined with lipid-lowering therapy guidelines[19] suggest that women with signs and symptoms of ischemia are an at-risk group that should be treated although clinical trials in this area are nonexistent.

The framing of nonobstructive CAD as being relatively benign could extend to a bias against making a diagnosis of cardiac death among women who had shown signs and symptoms of ischemia even in instances when no other definite cause of death is found.

Limitations

Several potential limitations are noteworthy. Although the WISE study was a prospective cohort design of consecutive cases enrolled at the 4 centers, all had referral networks for women with IHD symptoms. Thus, selection bias is always a concern. However, our adverse outcome findings for patients with nonobstructive coronary disease recently have been replicated in several large, population-based registries of all patients undergoing coronary angiography in a specific region and also extended to men.[36–38]

Although data were collected on baseline and follow-up medications, attrition of study participants over repeated follow-up contacts limited our ability to analyze in-depth medication use (or lack thereof) over the long term. Furthermore, we did not collect data on medication doses. Thus, it was not possible to formulate conclusions about medication associations with 10-year mortality. We found ever having used hormone replacement therapy to be associated with lower cardiac mortality (Table 4), but this variable had no significant association with all-cause mortality. Because we did not collect detailed data on historical regimens of hormone replacement therapy, our data do not permit an exploration of a possible pathophysiological pathway between hormone replacement therapy and lower cardiac death.

Conclusions and Implications

Longer-term and more detailed assessment of mortality in the original WISE cohort reveals an all-cause mortality rate of 20% and a cardiac mortality rate of 12% among the 936 women. Coronary artery stenosis >50%, age, racial minority status, less than a high school education, postmenopausal status, smoking, hypertension, dyslipidemia, and diabetes mellitus were all associated with higher mortality rates. A majority of the factors associated with increased risk of death can potentially be modified by current therapies. Providing new

insight, 1 in 3 of the deaths in this cohort occurred in women without obstructive CAD, a condition often considered benign and without guideline-recommend treatments. Clinical trials are needed to provide treatment guidance for women who lack obstructive CAD.

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Disclosures

None.

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