The Economic Burden of Angina in Women With Suspected Ischemic Heart Disease

Results From the National Institutes of Health–National Heart, Lung, and Blood Institute–Sponsored Women's Ischemia Syndrome Evaluation

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Background—Coronary angiography is one of the most frequently performed procedures in women; however, nonobstructive (ie, <50% stenosis) coronary artery disease (CAD) is frequently reported. Few data exist regarding the type and intensity of resource consumption in women with chest pain after coronary angiography.

Methods and Results—A total of 883 women referred for coronary angiography were prospectively enrolled in the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE). Cardiovascular prognosis and cost data were collected. Direct (hospitalizations, office visits, procedures, and drug utilization) and indirect (out-of-pocket, lost productivity, and travel) costs were estimated through 5 years of follow-up. Among 883 women, 62%, 17%, 11%, and 10% had nonobstructive and 1-vessel, 2-vessel, and 3-vessel CAD, respectively. Five-year cardiovascular death or myocardial infarction rates ranged from 4% to 38% for women with nonobstructive to 3-vessel CAD ($P<0.0001$). Five-year rates of hospitalization for chest pain occurred in 20% of women with nonobstructive CAD, increasing to 38% to 55% for women with 1-vessel to 3-vessel CAD ($P<0.0001$). The volume of repeat catheterizations or angina hospitalizations was 1.8-fold higher in women with nonobstructive versus 1-vessel CAD after 1 year of follow-up ($P<0.0001$). Drug treatment was highest for those with nonobstructive or 1-vessel CAD ($P<0.0001$). The proportion of costs for anti-ischemic therapy was higher for women with nonobstructive CAD (15% versus 12% for 1-vessel to 3-vessel CAD; $P=0.001$). For women with nonobstructive CAD, average lifetime cost estimates were $767 288 (95% CI, $708 480 to $826 097) and ranged from $1 001 493 to $1 051 302 for women with 1-vessel to 3-vessel CAD ($P=0.0003$).

Conclusions—Symptom-driven care is costly even for women with nonobstructive CAD. Our lifetime estimates for costs of cardiovascular care identify a significant subset of women who are unaccounted for within current estimates of the economic burden of coronary heart disease. **(*Circulation*. 2006;114:894-904.)**

Key Words: coronary disease ■ angina ■ women ■ angiography ■ cost-benefit analysis ■ prognosis

Diagnostic cardiac catheterization ranks as the sixth most commonly performed healthcare procedure utilized in more than one-half million women, with total charges exceeding $4 billion.[1,2] Although healthcare costs for coronary heart disease are $368.4 billion, this estimate does not address the economic burden of cardiac symptoms or costs specific to women. Preliminary evidence suggests that men and women do not consume healthcare resources in the same manner.[2–6] Differential referral and resource intensity patterns may limit the relevance of global cardiovascular cost estimates for female subsets of the population.[2–10]

Clinical Perspective p 904

A characteristic of female cohorts referred to coronary angiography is a lower prevalence of obstructive coronary artery disease (CAD) compared with male cohorts.[11] It has

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been suggested that health conditions may be detected earlier in women because of more frequent use of physician services.[12] The lower rate of obstructive CAD in women supports this theory.[13] However, an important caveat relates to symptom burden, and a recent report notes that pain is a more prominent factor driving healthcare costs and disability for women than men.[14] Few data exist regarding the type and intensity of resource consumption in women with chest pain.[15,16] Thus, the aim of the present study was to examine cardiovascular outcomes and costs in 883 women presenting for evaluation of chest pain or other equivalent symptoms suggestive of myocardial ischemia referred for coronary angiography.

Methods

Inclusion Criteria

Women prospectively enrolled in the National Institutes of Health–National Heart, Lung, and Blood Institute (NIH-NHLBI)–sponsored Women's Ischemia Syndrome Evaluation (WISE) study were clinically referred for coronary angiography.[11,17,18] Study procedures and follow-up methods were approved by each center's institutional review board.

Baseline Evaluation

Detailed demographics, clinical history, and socioeconomic descriptors were collected at baseline (Table 1). Type, frequency, location, nitroglycerin use, and precipitating factors for symptoms were reported. Self-reported life satisfaction and functional disability (Duke Activity Status Index [DASI] score in metabolic equivalents [METs] $\leq$4.7 defined functional disability) data were collected.[19,20] Stress ischemia before angiographic referral was documented. Physical examinations were performed. Obesity was defined as body mass index $\geq$30 kg/m^2.

Angiography Core Laboratory

The core laboratory (blinded to historical data) evaluated site-performed angiograms to determine CAD extent by the number of vessels with $\geq$50% stenosis.[21]

Outcome Data

Resource consumption data were collected at 6 weeks and yearly by means of a scripted interview.[22] During the interview, information regarding the occurrence of outpatient procedures, hospitalizations, and clinic visits to physician extenders, generalists, and specialists was collected. This data collection tool was validated previously.[22] Death certificates were reviewed blindly to determine causality. Cardiac hospitalizations were confirmed by review of medical records. Drug use, including hormone replacement, antihypertensive, anti-ischemic, lipid-lowering, diabetic, antianxiolytic, and antidepressive medications, was recorded. Source documentation was not obtained for drugs or office visits.

Cost Accounting Methods

Preliminary reports on WISE cost methods have been published.[23,24] Costs were summed with the use of standard approaches for economic analysis.[25–31] We used a hybrid cost model (including hospital-specific and published costs as inputs) for cases in which patient bills were not available. In this model, we used extensive prior published reports on procedural and hospital costs as well as cost estimates from national and regional average procedural and hospital charges (adjusted by state-specific cost-charge ratios).[8,9,13,22,32] Published costs for diagnostic[13,16,22] and invasive procedures[2,9,22] and hospitalization data[2,8,22] were applied in sensitivity analyses.

Median (25th, 75th percentile) hospitalization (ie, for chest pain, myocardial infarction [MI], heart failure) and procedural (ie, coronary angiography, revascularization, stress cardiac imaging) costs were obtained from published reports.[2,8,9,11,13,16,22–28,32] We performed numerous sensitivity analyses using a range of costs for procedures and hospitalizations. Drug costs were derived from the 2003 Red Book.[33] Cost data are presented with 95% confidence intervals (CIs) or standard error estimates. Sensitivity analyses did not affect the results presented in this report, revealing a pattern of cost estimates and statistical significance similar to that reported.

We totaled 5-year and annual costs for cardiovascular hospitalizations, coronary revascularization and angiography, outpatient testing, and visits to generalists, specialists, nurse practitioners/physician's assistants, or community clinics. Summed 5-year costs were considered a measure of direct CAD costs.

Each patient's out-of-pocket expenses (ie, indirect costs) were also collected. Indirect cost data were estimated for hours lost from work for healthcare, estimated reduced productivity hours, transportation costs, and out-of-pocket costs for drugs, medical devices (eg, glucometer), and alternative therapies (eg, vitamins). Patient self-reported income was used to estimate indirect costs for lost productivity. Smoking costs were estimated by the number of packs consumed per day.

Costs were discounted with the use of a 5% annual rate, corrected for inflation by the US medical service sector estimate (city average) of the consumer price index (for urban wage earners and clerical workers).[34]

Statistical Analysis

Descriptive statistics were compared with the use of χ^2 or ANOVA statistics. Costs were compared for women by CAD extent with the use of ANOVA or general linear modeling (GLM) techniques. Because of the skewness of cost data, the log of costs was used in parametric models. Explanatory variance (or r^2) was calculated. Nonparametric statistics were also used, resulting in probability values similar to those obtained by linear techniques.

Time to death or MI was estimated with the use of Cox proportional hazards models. The proportional hazards assumption was evaluated visually and through regression diagnostics and examination of residuals. Overall and annual rates of events and hospitalizations and rates of typical angina and DASI were calculated.[11] Clinical site ($P>0.20$) was not included in the model.

Life expectancy was estimated with the use of data from the National Vital Statistics Report (2002;50:6), adjusted for time to observed death. Disability-adjusted life expectancy was calculated on the basis of methods of the World Health Organization,[35] with disability defined for those disabled or with a DASI $\leq$4.7 METs.

Lifetime costs were estimated with the use of a multivariate linear regression model that calculated a predictive equation on the basis of 5-year costs through estimated disability-adjusted life expectancy. Variables included in the prediction model were those significantly associated with clinical worsening including age, ethnicity, cardiac risk factors, symptoms, CAD extent, and socioeconomic factors. We compared predicted lifetime costs to 5-year costs to examine deviation from observed data. Use of this linear prediction model revealed a moderately strong correlation of the observed 5-year cost data over time ($r=0.58$, $P<0.0001$). We also devised a decision-analytic Markov model including 4 hypothetical cohorts of women (ie, nonobstructive and 1-vessel to 3-vessel CAD) undergoing coronary angiography to examine concordance between the linear regression results with the Markov model base cases of women aged 55, 60, and 65 years (TreeAge Pro, Treeage Software, Inc, Williamston, Mass). During each cycle, women could remain free of cardiovascular events including death or MI. These results were based on our Cox models and were used to estimate disease progression. For the Markov processes, we used age-dependent transition probabilities for life expectancy. The Markov results were similar in the magnitude and direction of cost estimates from our linear regression model.

To assess the plausible randomness and uncertainty around our regression model, multiple imputation methods were applied (AMOS, version 6.0, and SPSS, version 14.0, both SPSS Inc, Chicago, Ill). Estimated values were imputed by drawing at random

TABLE 1. Past Medical History, Clinical Characteristics, and Socioeconomic Descriptors Classified by CAD Extent

	Nonobstructive CAD (n=547)	1-Vessel CAD (n=148)	2-Vessel CAD (n=93)	3-Vessel CAD (n=95)	*P*
Age, mean±SD, y	56±11	61±12	62±11	65±11	<0.0001
Postmenopause	71%	80%	83%	84%	0.003
Hypertension	54%	64%	70%	72%	<0.0001
Diabetes	16%	33%	40%	47%	<0.0001
Obesity (body mass index ≥30)	46%	48%	34%	37%	0.05
Smoking history	51%	60%	55%	55%	0.195
Hyperlipidemia	46%	65%	73%	72%	<0.0001
Positive stress test	50%	36%	47%	41%	0.022
History of mitral valve prolapse	18%	7%	8%	2%	<0.0001
Depression requiring treatment	27%	21%	19%	17%	0.052
Hysterectomy	58%	50%	45%	44%	0.012
Polycystic ovary syndrome	8%	4%	2%	2%	0.031
Socioeconomic descriptors					
Race					0.24
Black, non-Hispanic	17%	24%	18%	14%	
Hispanic	0.4%	1%	0%	1%	
White, non-Hispanic	83%	74%	81%	82%	
Retired	25%	41%	39%	51%	<0.0001
Full-time employment	20%	21%	27%	10%	<0.0001
Income					0.004
<$20 000	32%	39%	37%	35%	
$20 000–$34 999	19%	21%	26%	33%	
$35 000–$49 999	20%	14%	16%	16%	
$50 000–$99 000	15%	10%	11%	11%	
≥$100 000	5%	6%	1%	1%	
Health insurance					<0.0001
Medicare	23%	38%	39%	57%	
Medicaid, CHAMPUS, Public	10%	13%	3%	10%	
Private	61%	48%	51%	31%	
None/self-pay	6%	2%	2%	2%	
Prescription drug coverage	42%	31%	32%	16%	<0.0001
Job classification					
Manager, professional specialty	28%	31%	25%	21%	0.38
Technical, sales, administrative support	22%	19%	23%	10%	0.033
Service worker	27%	27%	31%	41%	0.050
Laborer	6%	5%	3%	6%	0.79
Homemaker	25%	25%	30%	34%	0.29

CHAMPUS indicates Civilian Health and Medical Program of the Uniformed Services; administrative support, secretarial or administrative support work. Women may check >1 occupation (≈5% of cases).

from their conditional distribution on the basis of observed data. We used a multiple Bayesian imputation model to create multiple imputed data sets (ie, 5). For this analysis, standard errors of the estimate were calculated as $\sqrt{[(1-1/m)/B+W]}$, where m is the number of replicates, B is the variance of the imputations, and W is the average of the estimated variances. All lifetime cost estimates were presented with the use of standard error of the estimate.

A multivariable logistic regression equation was developed to examine predictors of the top quartile costs (≥$861 477). Candidate variables included risk factors, angina, DASI, ethnicity, and socioeconomic factors. The final model revealed an adequate model fit (Hosmer-Lemeshow $P=0.72$).

Finally, univariate and multivariate linear regression models were devised to identify significant estimators of cost. Linear techniques were used to calculate average higher or lower costs for a given variable (eg, >$100 000 added to lifetime costs).

A post hoc analysis revealed sufficient statistical power to detect differences in costs between nonobstructive versus obstructive CAD subsets ($\beta \geq 0.80$, $\alpha=0.05$) (Sample Power, version 2.0, Chicago, Ill).

TABLE 2. Angina and Other Symptoms and Self-Reported Quality of Life Classified by CAD Extent

	Nonobstructive CAD (n=547)	1-Vessel CAD (n=148)	2-Vessel CAD (n=93)	3-Vessel CAD (n=95)	*P*
Symptom description					
Unstable angina	30%	41%	37%	51%	<0.0001
Accelerating pain frequency	14%	21%	44%	58%	<0.0001
Rest angina	64%	61%	19%	31%	0.001
Left arm pain	35%	43%	29%	18%	0.012
Stress-related pain	53%	62%	60%	63%	0.152
Nitroglycerin use	41%	49%	47%	60%	0.085
Dyspnea	62%	56%	50%	43%	0.002
Heart failure symptoms	6%	13%	9%	19%	0.001
Esophageal reflux	48%	49%	39%	40%	0.19
Migraine headache	29%	25%	10%	11%	<0.0001
Typical angina	31%	40%	35%	35%	0.28
Menopausal symptoms	68%	62%	58%	51%	0.01
Perceived emotional stress	60%	64%	57%	54%	0.046
Quality of life					
Fair to poor general health	37%	42%	39%	44%	0.24
Functional capacity					
Able to perform self-care tasks	93%	87%	90%	91%	0.052
Able to walk indoors	87%	81%	87%	84%	0.162
Walk 1–2 blocks	63%	49%	55%	57%	0.039
Climb 1 flight of stairs	31%	19%	23%	29%	0.036
Run a short distance	16%	10%	5%	10%	0.001
Light housework*	86%	80%	82%	84%	0.47
Moderate housework*	54%	47%	46%	39%	0.024
Heavy housework*	30%	22%	17%	19%	<0.0001
Yard work	32%	24%	16%	20%	<0.0001
Sexual relations	54%	39%	44%	31%	<0.0001
Participate in recreational sports†	24%	17%	7%	7%	<0.0001
DASI (in METs)	6.3±4	4.9±4	4.6±3	4.6±4	<0.0001
≤4.7 METs	47%	56%	58%	66%	<0.0001

*Light housework: eg, dust, wash dishes; moderate housework: eg, vacuum, sweep floors; heavy housework: eg, scrub floors, move furniture.

†Recreational sports (eg, golf, bowling).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Data Including Past Medical History, Symptom Characteristics, and Socioeconomic Descriptors

Of the 883 women, those with obstructive CAD were older ($P<0.0001$), were more often postmenopausal ($P=0.003$), and had a greater prevalence of cardiac risk factors. Women with nonobstructive CAD were more often obese ($P=0.05$), with prior hysterectomy ($P=0.012$), polycystic ovary syndrome ($P=0.031$), and a positive stress test ($P=0.022$) (Tables 1 and 2).

Obstructive CAD was more often reported in women with accelerating ($P<0.0001$) or unstable chest pain symptoms ($P<0.0001$) or heart failure symptoms ($P=0.001$). Patients with nonobstructive CAD more often reported rest angina ($P=0.001$), left arm pain ($P=0.012$), and shortness of breath on presentation ($P=0.002$). Typical angina, however, was similar, with nearly 30% of women having exertional symptoms responsive to rest or nitroglycerin ($P=0.77$). Nearly half of women with nonobstructive CAD had DASI ≤4.7 METs versus 56% to 66% of women with 1-vessel to 3-vessel CAD ($P<0.0001$).

According to the socioeconomic descriptors, women working in service jobs more often had 2-vessel to 3-vessel CAD ($P=0.05$). Significant differences also existed by household income ($P=0.004$), health insurance ($P<0.0001$), and prescription drug coverage ($P<0.0001$).

Cardiovascular Prognosis

Rates of major adverse cardiac events were higher for women with 1-vessel to 3-vessel CAD including all-cause ($P<0.0001$) or cardiovascular death ($P<0.0001$), MI

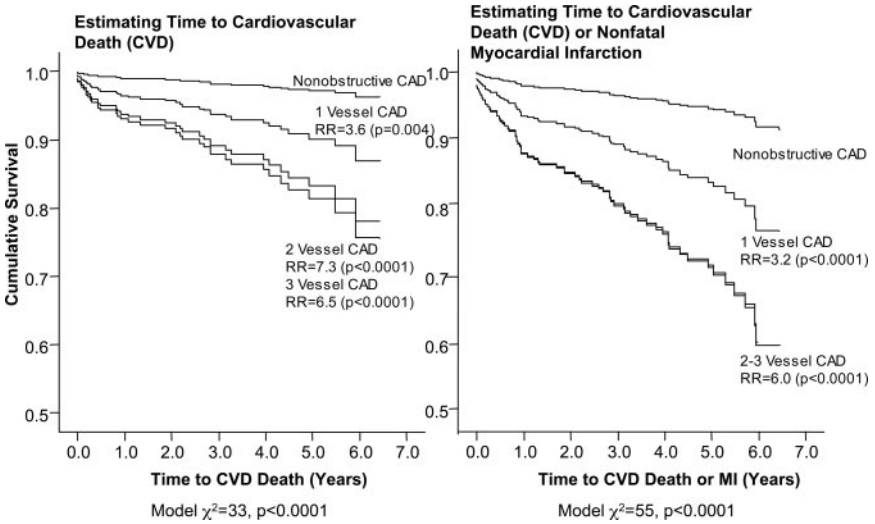


Figure 1. Cumulative cardiovascular death (left) and death or MI (right) for women with nonobstructive and 1- to 3-vessel CAD. For estimating cardiovascular death (left), relative risk (RR) ratios ranged from 3.6 to 7.3 for 1-vessel to 3-vessel CAD ($P<0.0001$). For death or MI (right), the RR ratios ranged from 3.2 to 6.0 for 1-vessel to 3-vessel CAD ($P<0.0001$).

($P=0.026$), and the combined end point of death or MI ($P<0.0001$) (Figure 1). Five-year cardiovascular death or MI rates ranged from 4% to 38% for women with nonobstructive to 3-vessel CAD (Figure 1; $P<0.0001$), rates that remained significant when we controlled for cardiac risk factors, angina, and body mass index.

Five-year rates of hospitalization for chest pain occurred in 1 of every 5 women with nonobstructive CAD (Figure 2). By comparison, 55% to 38% of women with 1-vessel to 3-vessel CAD were hospitalized for chest pain symptoms ($P<0.0001$).

Five-Year Follow-up Rates of Functional Disability and Typical Angina

Despite a similar frequency of typical angina at 5 years of follow-up ($P=0.68$), nearly half of women with nonobstructive CAD reported functional disability compared with 57% to 70% of women with 1-vessel to 3-vessel CAD (Figure 3; $P=0.037$).

Rates of repeat angiography ranged from 13.2% to 26.3% for women with nonobstructive to 3-vessel CAD (Table 3; $P<0.0001$). Within the first year of follow-up, higher rates of repeat angiography were reported for women with 1-vessel to 3-vessel CAD versus those with nonobstructive CAD ($P<0.0001$). After year 1, repeat angiography or angina hospitalization was 1.8-fold higher in women with nonobstructive CAD versus those with 1-vessel CAD ($P<0.0001$). Of women with nonobstructive CAD, only 4.8% and 1.5% underwent follow-up percutaneous coronary intervention and coronary bypass surgery ($P<0.0001$). By comparison, coro-

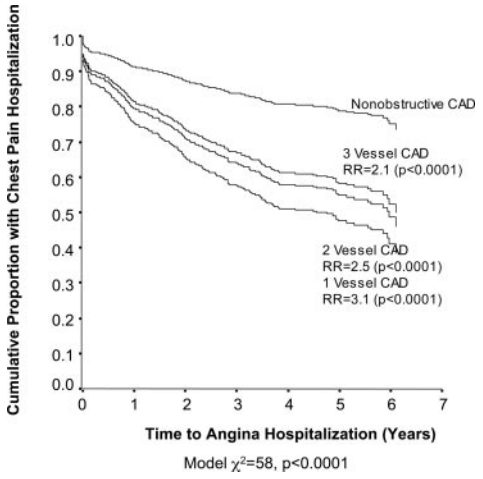


Figure 2. Cumulative unadjusted chest pain hospitalization rates for women with nonobstructive and 1-vessel to 3-vessel CAD (n=226 hospitalizations). RR indicates relative risk.

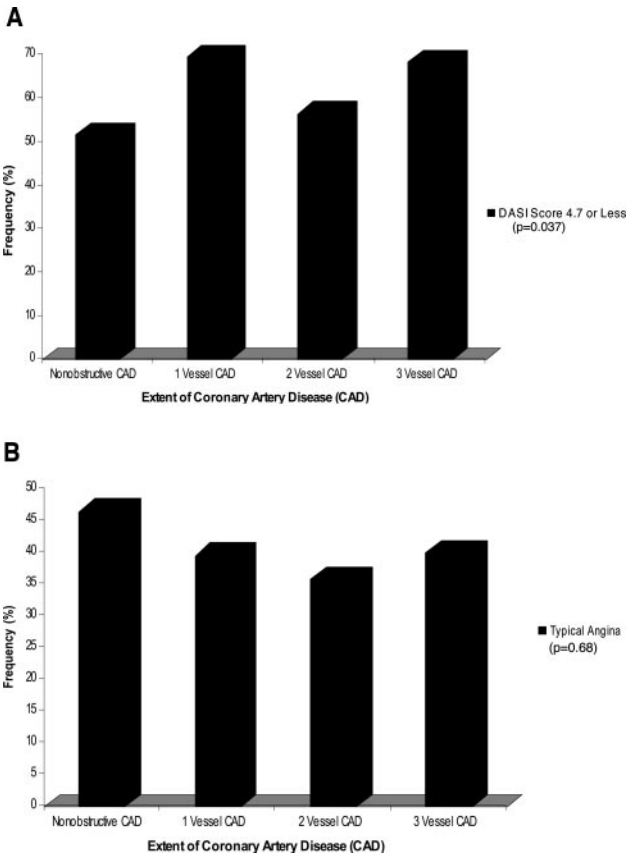


Figure 3. A, Five-year rates of functional disability (DASI ≤4.7 METs) for women with nonobstructive and 1- to 3-vessel CAD. B, Five-Year rates of typical angina for women with nonobstructive and 1-vessel to 3-vessel CAD.

TABLE 3. Cumulative Rates of Downstream Angiography and Coronary Revascularization Categorized by CAD Extent

	Nonobstructive CAD (n=547)	1-Vessel CAD (n=148)	2-Vessel CAD (n=93)	3-Vessel CAD (n=95)	*P*
Repeat angiography at years					
1	3.7%	14.2%	14.0%	15.8%	<0.0001
3	12.2%	28.4%	31.2%	22.1%	<0.0001
5	15.7%	37.2%	32.3%	26.3%	<0.0001
Percutaneous coronary intervention at years					
1	1.6%	7.4%	11.8%	7.4%	<0.0001
3	4.4%	15.6%	19.4%	17.0%	0.018
5	4.8%	18.3%	23.7%	20.3%	<0.001
Coronary bypass surgery at years					
1	0.9%	2.0%	5.4%	7.4%	<0.0001
3	1.5%	5.4%	8.6%	10.6%	0.054
5	1.5%	6.1%	9.7%	11.7%	0.114

nary bypass surgery rates were 6.1% to 11.7% for women with 1-vessel to 3-vessel CAD ($P<0.0001$). Percutaneous coronary intervention rates were 18.3%, 23.7%, and 20.3% for women with 1-vessel, 2-vessel, and 3-vessel CAD, respectively ($P<0.0001$).

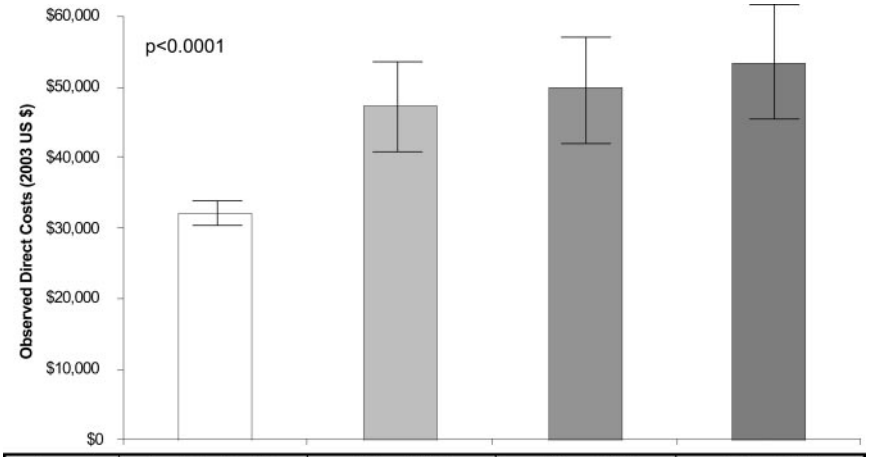
Five-Year Cardiovascular Costs

Cumulative costs were, on average, lower for women with nonobstructive CAD ($32 239; 95% CI, $29 496 to $34 982) and increased to $53 398 (95% CI, $43 854 to $62 942) for those with 3-vessel CAD (Figure 4; $P<0.0001$). Drug costs, including hypertension, diabetes, and lipid drug costs, represented 32.6% of total costs for women with nonobstructive CAD, which was a higher proportion than for women with 2-vessel to 3-vessel CAD ($P<0.0001$). Anti-ischemic drugs encumbered 14.8% of total costs for women with nonobstructive CAD versus 13.6% to 12.1% for women with 1-vessel to 3-vessel CAD ($P=0.004$). Women with typical angina had 10% to 100% higher costs at years 1 ($P=0.07$), 3 ($P=0.004$), and 5 ($P=0.005$) of follow-up. Figure 5 depicts cumulative costs of care for women with nonobstructive CAD versus those with 1-vessel to 3-vessel CAD ($P<0.0001$).

Although a greater percentage of outpatient visits or procedural costs was noted for women with 2-vessel to 3-vessel CAD, women with nonobstructive CAD had more frequent visits to internists (average per year=2.7 visits) and less frequent visits to cardiologists (0.3 visit per year; $P<0.0001$).

Yearly indirect costs ranged from $1830 to $2221 for women with nonobstructive and 1-vessel to 3-vessel CAD ($P=0.048$) (Figure 6; trend across CAD subsets $P=0.094$). For women with nonobstructive or 1-vessel CAD, the greater proportion of drug costs resulted in higher indirect costs due to increased copayment expenses.

Extrapolation to lifetime costs revealed a heavy economic burden of symptoms and cardiovascular care for WISE women (Figure 7). For younger women, total cost was related to greater life expectancy and drug treatment costs. For



Cost Components	Nonobstructive CAD	1 Vessel CAD	2 Vessel CAD	3 Vessel CAD
Outpatient	6.7%	5.8%	14.3%	14.8%
Drug	32.6%	29.5%	27.0%	25.5%
Hospitalization	60.7%	64.7%	58.7%	59.7%

Figure 4. Observed 5-year cardiovascular costs of drug treatment, office visits, outpatient procedures, and hospitalization for women with nonobstructive and 1-vessel to 3-vessel CAD. The proportion of costs from outpatient procedures, drugs, and hospitalizations is reported in the table below the graph. Error bars are derived from sensitivity analyses.

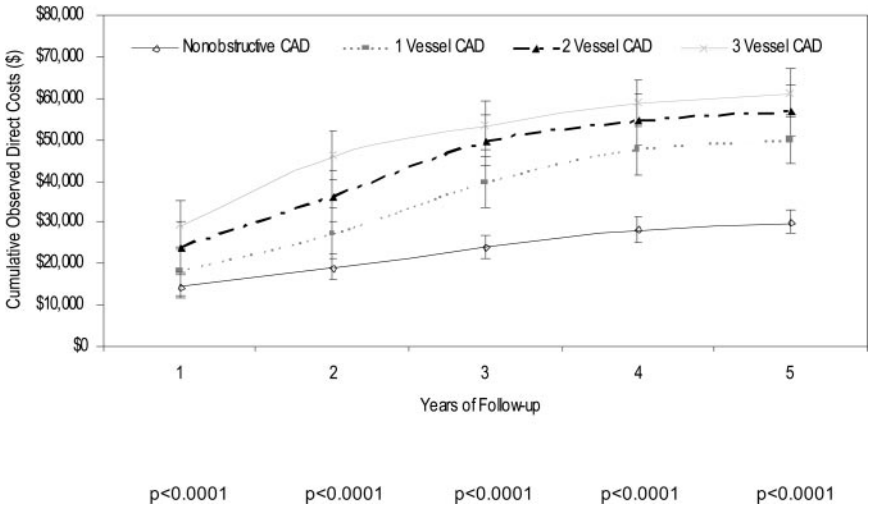


Figure 5. Cumulative 5-year costs of cardiovascular care for women with nonobstructive CAD and 1-vessel to 3-Vessel CAD. Error bars are standard error of the estimate.

women with nonobstructive CAD, average lifetime costs were $767 288 (95% CI, $708 480 to $826 097; $P=0.0003$). Of women with nonobstructive CAD, lower lifetime costs of care were reported for those with DASI scores ≥4.7 METs ($P=0.025$). Lifetime costs exceeded $1 million for women with 1-vessel to 3-vessel CAD (Figure 7; $P=0.0003$ for GLM model across CAD subsets).

Linear Regression Models Estimating Lifetime Costs

In our final multivariate model (Table 4; $P<0.0001$), positive predictors reflecting higher costs included CAD extent, diabetes, hyperlipidemia, managerial job, prior percutaneous coronary intervention, typical angina, nitroglycerin use, and accelerating angina. Pain relieved with rest was associated with $174 981 lower costs ($P=0.001$). Women with noninvasive ischemia also had lower costs ($P<0.0001$). Higher-income patients had lower lifetime costs ($597 775 versus $1 018 698 for high to low incomes; $P=0.008$). Women with lower self-perceived quality of life had higher lifetime costs ($P<0.0001$).

Discussion

Among women with signs and symptoms of myocardial ischemia undergoing coronary angiography, symptom-driven care is costly. Data from the WISE study reveal that the direct and indirect costs for cardiovascular disease consign a heavy economic burden, with 5-year costs in the range of $32 000 to $53 000 for women with nonobstructive to 3-vessel CAD. Similar estimates from the World Health Organization report costs for women with ≥3 cardiac risk factors at $38 059.[35,36] When this was projected to lifetime costs, in WISE, the total encumbrance increased dramatically and exceeded $1 million for women with obstructive CAD.

Our predictive estimates revealed that even women with nonobstructive CAD would be expected to consume nearly $750 000 of cardiovascular healthcare resources related to their burden of continuing symptoms and drug treatments throughout their projected lifespan. In fact, women with nonobstructive CAD consumed more of their total costs for anti-ischemic therapies compared with women with 1-vessel to 3-vessel CAD ($P=0.004$). These results are compelling given that nearly half of women undergoing clinically indicated coronary angiography have nonobstructive CAD.[11] These data underscore the importance of angina, in addition to obstructive disease burden, as a prominent factor driving near-term and lifetime costs of cardiovascular care for women.

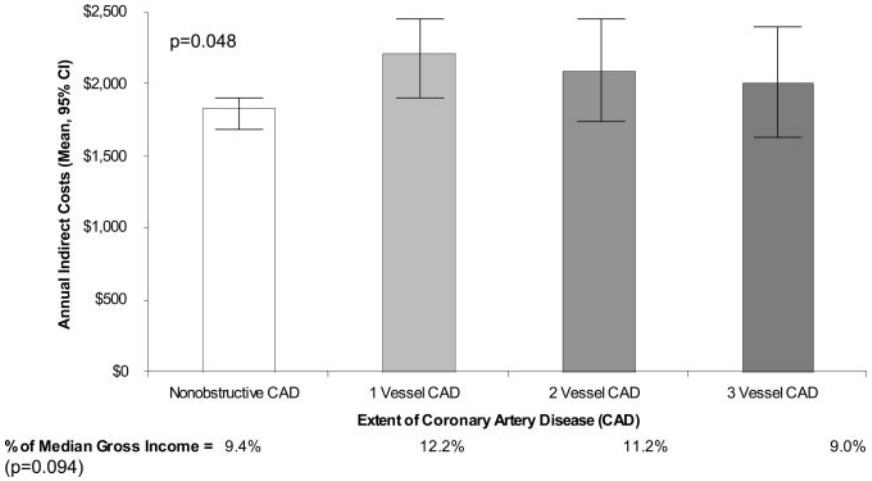


Figure 6. Annual indirect costs for women with nonobstructive and 1-vessel to 3-vessel CAD. Indirect costs include out-of-pocket expenses, home care costs, lost work, lost productivity, travel costs, medical equipment, vitamin and supplement costs, and copayment costs. Error bars are 95% CIs.

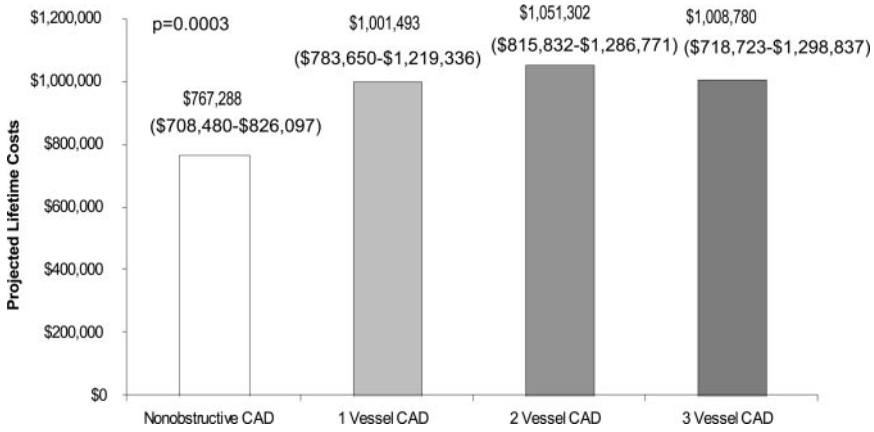


Figure 7. Estimated lifetime costs (including sensitivity analyses ranges) of drug treatment and hospitalization for cardiovascular disease for women with nonobstructive and 1-vessel to 3-vessel CAD.

Furthermore, women with nonobstructive CAD presenting with angina and frequently documented myocardial ischemia are often diagnosed with the cardiac syndrome X. Although this is the topic of much ongoing research, it is noteworthy that prior reports have uniformly noted that women with the cardiac syndrome X have excellent near-term cardiac survival compared with women with obstructive CAD.[18,23,37] Our current data are consistent with these reports, noting that women with nonobstructive CAD were at relatively low risk for cardiovascular death. However, when related morbidity is considered, including refractory chest pain symptoms requiring hospitalization, the women with nonobstructive CAD perhaps should be reclassified as being at intermediate risk compared with those with obstructive disease. The burden of persistent chest pain symptoms was often not accounted for in prior survival analyses. Our results note that 1 woman in 5 with nonobstructive CAD was hospitalized for chest pain during follow-up. In our cohort of women with nonobstructive CAD, 46% had typical angina at 5 years of follow-up, a rate similar to that of women with 1-vessel to 3-vessel CAD.

Underappreciated Economic Burden of Angina

Extrapolating current results to US prevalence rates for angina (≈4.1 million women) reveals that annual cardio-

TABLE 4. Multivariate Linear Regression Model Estimating Lifetime Cardiovascular Costs

	β Coefficient	SE	t	P
Constant	$369 184	$ 16 072	8.8	<0.0001
Socioeconomic factors				
Income	−$ 32 919	$ 16 700	−2.0	0.049
Disabled or unable to work	$172 198	$ 66 973	2.6	0.010
Managerial job	$151 773	$ 55 925	2.7	0.007
Quality of life				
Life satisfaction	−$ 19 372	$ 9769	−2.0	0.048
DASI (in METs)	−$ 9178	$ 6230	−1.5	0.14
CAD history				
Prior percutaneous coronary intervention	$178 894	$ 72 865	2.5	0.014
Abnormal stress test	−$155 402	$ 49 539	−3.1	0.002
Risk factors				
Age (per year)	−$ 28 841	$ 2298	−12.6	<0.0001
Diabetes	$302 363	$ 60 465	5.0	<0.0001
Hyperlipidemia	$176 518	$ 52 514	3.4	0.001
Symptom descriptors				
Stress-induced pain	$153 789	$ 53 833	2.9	0.004
Pain relieved with rest	−$174 981	$ 53 249	−3.3	0.001
Nitroglycerin use	$102 956	$ 56 907	1.8	0.071
Rest angina	$219 895	$ 75 452	2.9	0.004
Recent acceleration in angina	$447 039	$116 516	3.8	<0.0001
CAD extent (per vessel with ≥50% stenosis)	$127 148	$ 28 327	4.5	<0.0001

r^2=0.32, P<0.0001.

vascular costs would encumber a large proportion of current cardiovascular healthcare costs.[8] Previous estimates for women aged ≥45 years enumerate total costs for cardiovascular disease at $60.4 billion, far exceeding costs for osteoporosis and breast or gynecological cancers.[38] Estimates of costs for women undergoing coronary angiography have identified the societal burden of procedural costs that, on the basis of our results, would be 10% of the total costs at 5 years.[1] Thus, the addition of downstream costs is critical to estimating the total burden of cardiovascular disease for both women and men. In 2003, the American College of Cardiology reported that ≈6.8 million coronary angiograms were performed,[39] with "normal or <50% stenosis" being reported in nearly 20% of men and up to 60% of women.[40] Thus, cost estimates for the burden of heart disease, at $255 billion, would vastly underestimate direct and indirect costs of care for women and men with nonobstructive CAD presenting with angina requiring ongoing palliative care.[8] Data from the WISE study suggest that further classification of estimated costs should also include costs specific to chest pain syndromes, even in the absence of obstructive CAD.

Estimates are that one third to one half of lifetime expenditures are incurred during middle-age to senior years,[41,42] with women having higher elder-care costs.[41] On the basis of administrative claims data from 2002, lifetime hospitalization costs for women with known cardiovascular disease were $423 000 and $233 000 for diabetic women.[42] Women with CAD have 3.4-fold higher costs compared with women without cardiovascular disease. We noted that hospitalization costs for our symptomatic women were 1.5 times higher than those for asymptomatic women during follow-up. The inclusion of drug and indirect cost estimates resulted in higher cost estimates, with lifetime predictions in the range of $767 288 to >$1 000 000 for women with nonobstructive to 1-vessel to 3-vessel CAD.

Indirect Costs of Cardiovascular Disease

The American Heart Association estimates that lost productivity due to heart disease results in a total cost burden of $17 to $27 billion.[8] In our WISE women, indirect costs of care averaged $1830 to $2010 annually for women with nonobstructive to 3-vessel CAD ($P=0.048$). With nearly half of the WISE women having an annual household income of <$35 000 per year, indirect costs encumbered ≈10% of their financial resources ($P=0.094$). Out-of-pocket expenses for medical equipment, over-the-counter drugs and vitamins, and drug copayment expenditures accounted for the majority of indirect costs. Few of our women had full-time jobs, and only a minority had prescription drug coverage, leading to higher indirect costs. As based on population statistics, costs for cardiovascular drugs represent >10% of total drug expenditures.[43] For women with limited earnings, such as those in our WISE cohort, the low rate of prescription drug coverage would be expected to affect compliance and the available remaining financial resources for engaging in healthy lifestyle practices.

Burden of Extensive Cardiovascular Disease

Recently, international health organizations and others have focused on allocations of health resources for women.[44–48] Our results reveal that women with 2-vessel to 3-vessel CAD may be our most vulnerable female patients. In this cohort with 2-vessel to 3-vessel CAD, cardiovascular survival was lowest, with nearly 1 woman in 3 experiencing a major adverse event during follow-up. This burden of illness is dramatic given that nearly two thirds of the women with multivessel CAD earned <$35 000 per year. Prior evidence notes that reduced financial resources have been implicated as primary contributors to declining health status.[46] These results are consistent with data from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy trial, in which lower-income patients had greater healthcare needs.[49]

Study Limitations

WISE women included those clinically referred to coronary angiography, representing appropriate and potentially inappropriate referrals. This is an important limitation but reflects patterns similar to those in most angiographic laboratories. We also used hybrid cost models, relying on detailed resource data that may underestimate consumption levels as a result of patient recall. Our model estimates may be less reliable for women with nonobstructive CAD than for higher-risk women with multivessel CAD. A final limitation is that the WISE cohort represents selected women who have access to healthcare. Thus, the present results may have limited applicability to women without a regular source of healthcare.

Conclusions

Symptom-driven care for women is costly and accounts for the majority of cardiovascular care costs. On the basis of WISE estimates, the societal economic burden for CAD care for women with angina is expansive and could be responsible for a sizeable proportion of US healthcare costs. For women undergoing coronary angiography, a lack of identifiable obstructive CAD lesions does not portend a low risk for persistent and refractory symptoms precipitating high lifetime costs of care. The greater need for medical resources in this group with nonobstructive CAD is likely multifactorial, but the greater need for anti-ischemic therapies for control of anginal symptoms appears foremost for our WISE women.

Our estimates for lifetime costs increased dramatically to >$1 million for women with obstructive CAD. Those with the greatest healthcare needs included women with 2-vessel to 3-vessel CAD. These data reveal the complexity of care for women undergoing coronary angiography. We believe that enumerating the expected costs of care for women with nonobstructive and obstructive CAD is an important step toward identifying vulnerable subsets of women who require more resource-intensive cardiovascular care.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Every year, the American Heart Association provides an assessment of the economic costs of cardiovascular disease. Although precise estimates of cardiovascular healthcare costs are difficult to define, these estimates from the American Heart Association are a valuable source of information on the global burden of disease in this country. Current estimates of direct and indirect costs of care exclude the economic burden of disease for women, including a large proportion with nonobstructive coronary disease, thereby significantly underestimating costs attributable to chest pain symptoms. Our recent report from the National Institutes of Health–National Heart, Lung, and Blood Institute Women's Ischemic Syndrome Evaluation revealed that, on average, a woman with nonobstructive coronary disease, with frequent, persistent, and refractory chest pain symptoms, would consume estimated cardiovascular healthcare costs in excess of $750 000 over her lifetime. By comparison, women with obstructive disease would have lifetime costs of care of ≈$1 million. The most prominent factor in driving healthcare costs for women is their burden of angina, which requires ongoing anti-ischemic therapy as well as frequent hospitalizations for worsening symptoms. This pattern of more intensive care occurs in varying degrees for women with and without obstructive coronary artery disease. For the clinician, care should be taken to understand the ongoing healthcare needs of women with anginal symptoms. Furthermore, symptom-driven care is costly and for women with limited financial means can be devastating, consuming ≈10% of their annual income for out-of-pocket expenses. Our data underscore the importance of discerning the unique healthcare needs of female patients.