The Women's Ischemia Syndrome Evaluation (WISE) Study: protocol design, methodology and feasibility report

C. Noel Bairey Merz, Sheryl F. Kelsey, Carl J. Pepine, Nathaniel Reichek, Steven E. Reis, William J. Rogers, Barry L. Sharaf, George Sopko, for the WISE Study Group

This information is current as of October 14, 2007

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://content.onlinejacc.org/cgi/content/full/33/6/1453

The Women's Ischemia Syndrome Evaluation (WISE) Study: Protocol Design, Methodology and Feasibility Report

C. Noel Bairey Merz, MD, FACC,*† Sheryl F. Kelsey, PHD,‡ Carl J. Pepine, MD, FACC,§
Nathaniel Reichek, MD, FACC,‖ Steven E. Reis, MD, FACC,¶ William J. Rogers, MD, FACC,#
Barry L. Sharaf, MD, FACC,** George Sopko, MD,†† for the WISE Study Group

*Los Angeles, California; Pittsburgh, Pennsylvania; Gainesville, Florida; Birmingham, Alabama;
Providence, Rhode Island, and Bethesda, Maryland*

OBJECTIVES	The Women's Ischemia Syndrome Evaluation (WISE) is a National Heart, Lung and Blood Institute–sponsored, four-center study designed to: 1) optimize symptom evaluation and diagnostic testing for ischemic heart disease; 2) explore mechanisms for symptoms and myocardial ischemia in the absence of epicardial coronary artery stenoses, and 3) evaluate the influence of reproductive hormones on symptoms and diagnostic test response.
BACKGROUND	Accurate diagnosis of ischemic heart disease in women is a major challenge to physicians, and the role reproductive hormones play in this diagnostic uncertainty is unexplored. Moreover, the significance and pathophysiology of ischemia in the absence of significant epicardial coronary stenoses is unknown.
METHODS	The WISE common core data include demographic and clinical data, symptom and psychosocial variables, coronary angiographic and ventriculographic data, brachial artery reactivity testing, resting/ambulatory electrocardiographic monitoring and a variety of blood determinations. Site-specific complementary methods include physiologic and functional cardiovascular assessments of myocardial perfusion and metabolism, ventriculography, endothelial vascular function and coronary angiography. Women are followed for at least 1 year to assess clinical events and symptom status.
RESULTS	In Phase I (1996–1997), a pilot phase, 256 women were studied. These data indicate that the WISE protocol is safe and feasible for identifying symptomatic women with and without significant epicardial coronary artery stenoses.
CONCLUSIONS	The WISE study will define contemporary diagnostic testing to evaluate women with suspected ischemic heart disease. Phase II (1997–1999) is ongoing and will study an additional 680 women, for a total WISE enrollment of 936 women. Phase III (2000) will include patient follow-up, data analysis and a National Institutes of Health WISE workshop. (J Am Coll Cardiol 1999;33:1453–61) © 1999 by the American College of Cardiology

Each year in the U.S., nearly 250,000 women die of ischemic heart disease, and roughly 100,000 deaths occur before the average life expectancy, making it the leading killer of women (1). Although recent data demonstrate that rates of cardiac catheterization and diagnosis of nonfatal ischemic heart disease have doubled among women in the last decade (2), ischemic heart disease in women is still identified less often (3,4) and at a more advanced stage (5), and treated less aggressively (4,6) compared with that in men. Women with ischemic heart disease also have a worse prognosis compared with their male counterparts (7,8), suggesting that gender-related differences in disease detection and treatment may influence prognosis.

Abbreviations and Acronyms	
ECG	= electrocardiogram/electrocardiographic
MRI	= magnetic resonance imaging
SPECT	= single photon emission computed tomography
WISE	= Women's Ischemia Syndrome Evaluation

Accurate and timely diagnosis of ischemic heart disease in women is a major challenge to physicians. At least three problematic areas exist:

Symptom recognition: Women have a higher frequency of chest pain than men, yet have a lower prevalence of epicardial coronary artery stenoses (9). Chest pain/discomfort characteristic for angina is a less specific marker for ischemic heart disease in women compared with that in men (10). Gender-specific ischemic heart disease symptom tools are not available.

Diagnostic testing: Electrocardiographic (ECG) abnormalities, including rest- and exercise-induced changes indicative of ischemic heart disease, are believed to be more often "falsely positive" in women than in men (11). Myocardial perfusion (3), hemodynamic and ventriculographic response (12) to exercise is more commonly abnormal among women, without evidence of epicardial coronary artery stenoses, compared with that among men. Prognosis in women with symptoms and abnormal diagnostic tests but no coronary stenoses is largely unknown. Existing diagnostic testing modalities for both epicardial coronary artery disease and microvascular dysfunction are suboptimal in women.

Reproductive hormonal status: Diagnostic testing for ischemic heart disease in women demonstrates higher levels of test variability compared with that in men (13). Cycling reproductive hormones may account for this variability. Effects of fluctuating estrogen levels on vascular smooth muscle and coronary artery vasomotion have been postulated as explanations for why women have a higher frequency of chest pain and more frequent false positive stress test results in the absence of epicardial coronary artery disease compared with men. Experimental data show that estrogen affects coronary artery vasomotor function (14). The role reproductive hormones play in symptom manifestation and ischemic heart disease diagnostic testing is largely unknown.

The Women's Ischemia Syndrome Evaluation (WISE) is a National Heart, Lung and Blood Institute–sponsored, four-center study designed to address ischemic heart disease recognition and diagnosis. The primary objectives of the WISE are: 1) to improve diagnostic testing for ischemic heart disease in women, including symptom evaluation

Table 1. Women's Ischemia Syndrome Evaluation Common Core Protocol

Testing and Data Collection	Core Lab
Demographic data	Coordinating Center
Symptom characterization	Coordinating Center
Psychosocial characterization	Coordinating Center
Fasting blood sugar	Coordinating Center
Fasting TC, TG, HDL-C, LDL-C	Cedars-Sinai Medical Center
Lipid peroxidation	University of Pittsburgh
Blood hormone levels	Cedars-Sinai Medical Center
Phytoestrogen levels	Cedars-Sinai Medical Center
Homocysteine levels	University of Pittsburgh
Genetic analysis	University of Pittsburgh
Left ventriculography	Rhode Island Hospital
Coronary angiography	Rhode Island Hospital
Resting ECG	University of Pittsburgh
Exercise ECG	St. Louis University, St. Louis
Ambulatory ECG	University of Florida, Gainesville
Brachial artery reactivity testing	University of Pittsburgh
MR spectroscopy	University of Alabama at Birmingham

ECG = electrocardiography; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; MR = magnetic resonance; TC = total cholesterol; TG = triglycerides.

tools, risk assessment algorithms and noninvasive imaging techniques; 2) to study pathophysiologic mechanisms and prognosis in women with chest pain and abnormal diagnostic testing for myocardial ischemia in the absence of epicardial coronary artery stenoses, and 3) to evaluate the influence of cyclical hormones, menopausal status and reproductive hormone levels on symptoms and diagnostic testing results.

METHODS

The WISE study design brings together a variety of expertise (Appendix) to assess different but complementary innovative diagnostic tests in four clinical sites. A common core protocol used by all four sites is itemized in Table 1. Individual site protocols include complementary physiologic and functional cardiovascular assessments (Table 2). The study protocols were each approved by the site institutional review boards. All women are followed for at least one year to assess clinical events and symptom status.

The study is organized into three phases. Phase I (1996–1997) was a pilot phase and enrolled 256 women. Data from the common core protocol as well as individual site protocols for this phase have been examined and protocol revisions were made before proceeding to Phase II. Phase II (1997–1999) is studying an additional 680 women, with a total WISE enrollment of 936 women. Phase III (2000) will

Table 2. Women's Ischemia Syndrome Evaluation Site-Specific Methodologies

	AGH	UAB	FLA	PGH
Echocardiography				
Dobutamine stress	X		X	
Exercise stress			X	
Magnetic resonance imaging				
CA	X			
Perfusion		X		
Spectroscopy	(X)	X	(X)	(X)
Nuclear scintigraphy				
Dipyridamole stress ^{99m}Tc sestamibi		X		
Positron emission tomography				
Intravenous adenosine				X
Mental stress				X
Brachial artery reactivity	X	X	X	X
Provocative coronary angiography				
Intracoronary acetylcholine			X	
Doppler coronary flow reserve				
Intracoronary adenosine	X		X	X
Mental stress				X
Intravenous adenosine				X
Intracoronary nitroglycerin				X

(X) = implemented in Phase II. AGH = Allegheny General Hospital; CA = coronary angiography; FLA = University of Florida, Gainesville; PGH = University of Pittsburgh Medical Center; UAB = University of Alabama at Birmingham.

Figure 1. Women's Ischemia Syndrome Evaluation common core testing flow diagram. CV = cardiovascular; ECG = electrocardiography; LV = left ventricular; MR = magnetic resonance; P = phosphorus.

include patient follow-up, data analysis and a National Institutes of Health WISE workshop.

Study Recruitment and Inclusion/Exclusion Criteria

Women are eligible for participation if they are older than 18 years of age and are undergoing a clinically indicated coronary angiogram as part of their regular medical care for chest pain symptoms or suspected myocardial ischemia. Major exclusion criteria include comorbidity which compromises one-year follow-up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association class IV congestive heart failure, recent myocardial infarction, significant valvular or congenital heart disease and a language barrier to questionnaire testing. Women with recent coronary angioplasty or coronary bypass surgery or who undergo these procedures after angiography but before their WISE testing are also excluded.

Common Core Protocol

All participants have data collected uniformly for a Common Core Protocol, as outlined in Figure 1. To characterize symptoms, WISE compares a questionnaire of known diagnostic v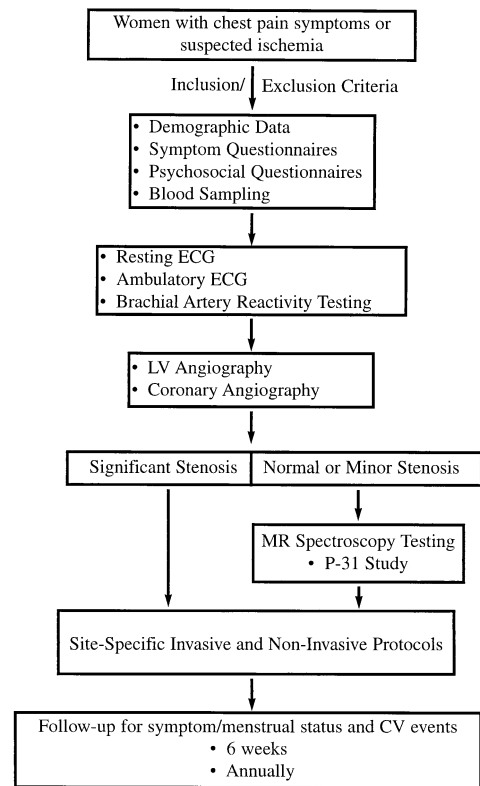alidity in women (15) to a new symptom questionnaire specifically developed for women (Hodgson and Berry, personal communication, August 1996). Questions regarding initial response to symptoms and health seeking behavior are included. Symptoms provoked during testing procedures are assessed using a uniform tool. Psychosocial assessment includes indicators of hostility/cynicism (16), typical depression (17), panic (18), avoidance (19), autonomic perception (20), reward dependence (21), trait anxiety (22), social support (23) and quality of life.

Blood determinations include follicle-stimulating hormone, luteinizing hormone, progesterone, estradiol, bioavailable estradiol, estrone, phytoestrogens, fasting blood glucose, lipids, homocysteine, lipid peroxidation and deoxyribonucleic acid analysis.

Coronary angiography as assessed by a core laboratory includes quantification of epicardial coronary artery size, quantification of left ventricular ejection fraction and qualitative and quantitative assessment as to the presence, severity and complexity of epicardial coronary artery stenoses, using a previously published coronary severity score (24). The following definitions are used for coronary artery group categorization: normal/minimal disease = <20% stenosis; mild = 20% to 49% stenosis; significant = ≥50% stenosis in any one major epicardial coronary artery. Resting ECGs are interpreted by a core laboratory, using

gender-specific interpretative criteria for left ventricular hypertrophy (25). Data are also being collected, when available, from routine clinical stress testing, including nuclear perfusion imaging, performed before WISE enrollment.

Ambulatory ECG monitoring is performed for 24 to 48 h according to previously described methods (26), using an all-digital recording system (27,28) with electronic transfer of the data to a core laboratory for analysis and interpretation. Brachial artery reactivity testing for both endothelium-dependent and endothelium-independent vasomotion is performed using standard techniques (29), with data analysis by a core laboratory.

Follow-up

Women's Ischemia Syndrome Evaluation participants are contacted at six weeks and then annually to assess symptom status, menstrual status and occurrence of cardiovascular events, including death, nonfatal myocardial infarction, coronary angioplasty, coronary bypass surgery, cardiac transplantation and hospitalization for unstable angina.

Specific Protocols

The testing protocol methods are organized below according to the three main WISE study goals. When testing is performed at more than one site, a uniform protocol is used. Interpretation of all studies is performed by masked observers for both qualitative and quantitative analysis.

Goal: to improve diagnostic testing for ischemic heart disease in women. The innovative diagnostic tests selected for the WISE represent the best technologic advances in ischemic heart disease detection currently available. An emphasis was placed on selection of techniques which might obviate difficulties relevant to women, such as breast imaging artifact (magnetic resonance imaging [MRI]-coronary angiography, MRI perfusion imaging and sestamibi single photon emission computed tomography [SPECT] perfusion imaging), as well as techniques commonly available currently (dobutamine stress echocardiography and exercise stress testing).

MAGNETIC RESONANCE IMAGING CORONARY ANGIOGRAPHY IMAGING. Magnetic resonance imaging coronary angiography depicts both anatomic features and flow effects of epicardial coronary artery stenoses using a 1.5-T Siemens Vision (Schaumberg, Illinois) with echo-planar capability. The patient is supine in a phased array thoracic coil for approximately 40 min, with the need for breath-holding eliminated. Depending on cardiac cycle length, 5 to 11 views per cycle are obtained. Tomographic slice thickness is 2 mm and stacks of 16 to 24 images are taken at a time, which can be viewed as obtained or put into a three-dimensional volume in any orientation desired for qualitative analysis. Image quantitation is performed with compound and curved plane reslicing and three-dimensional projection images.

MAGNETIC RESONANCE IMAGING PERFUSION IMAGING. Magnetic resonance imaging myocardial perfusion imaging is performed using "first pass" gadolinium–diethylenetriaminepenta-acetic acid and a 1.5-T Philips ACS Gyroscan system (Best, The Netherlands). Cardiac scout images (two- and four-chamber views) are acquired in two orthogonal planes and dynamic imaging is initiated just before the bolus of gadolinium and continues for 64 heartbeats. The BRISK (30) and interpolated keyhole (31) imaging sequences developed by one of the sites (University of Alabama at Birmingham) allow up to three or four near-simultaneous short-axis images to be acquired during each cardiac cycle. Imaging of left ventricular function is also performed. Qualitative defects by MRI are determined by describing regional signal intensity with that of the region containing the highest signal intensity in predefined regions. Quantitative analysis uses plots of MR signal intensity versus location about the circumference of the short-axis image.

SESTAMIBI SPECT IMAGING. Sestamibi SPECT myocardial imaging is performed at baseline and during dipyridamole infusion. Myocardial perfusion images are obtained on a 64×64 matrix using a single-head Siemens Orbitor SPECT camera (Schaumberg, Illinois) with a high resolution parallel-hole collimator for sestamibi imaging. Imaging is performed every 5° for 40 s over a 180° arc. Rest and dipyridamole images with sestamibi are obtained 1 h after injection. Qualitative and quantitative analyses are performed, the latter using gender-specific normal limits.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY. After acquisition of baseline images in standard views, dobutamine stress echocardiography is performed using published methodology (32). Image analysis includes calculation of a wall motion score index, which is the total score divided by the number of segments visualized and scored.

EXERCISE STRESS ECG. After standard 12-lead ECG recordings and blood pressure measurements at rest, the Asymptomatic Cardiac Ischemia Pilot treadmill exercise protocol is performed, since it provides continuous "ramp-like" increases in work, using previously published methods (26). Reports of symptoms, including chest pain or discomfort, are carefully elicited and recorded along with level of perceived exertion using the Borg scale (33).

Goal: to study pathophysiologic mechanisms for ischemia in the absence of epicardial coronary artery stenoses. Testing protocols were designed to determine the prevalence of this syndrome in women with normal or mild stenoses using a reference standard test for ischemia (MR spectroscopy) and to explore the pathophysiologic mechanisms involved (microvascular coronary flow reserve and endothelial function testing).

MAGNETIC RESONANCE SPECTROSCOPIC STUDY. [31]Phosporus MR spectroscopy is a nonimaging direct biochemical
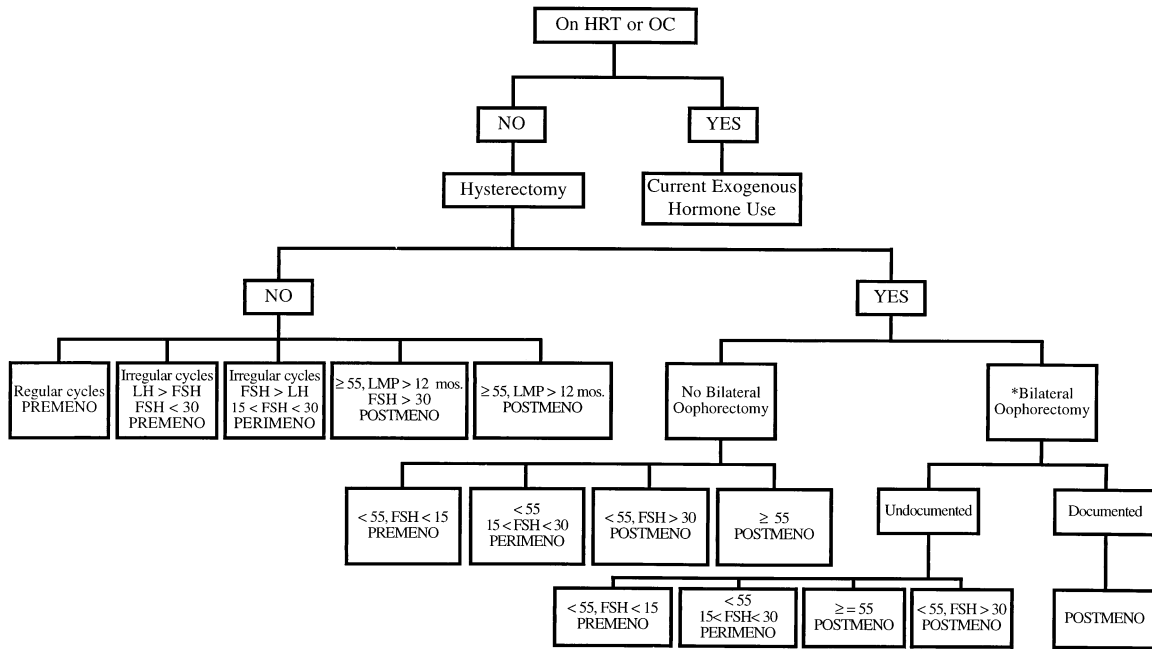
Figure 2. Women's Ischemia Syndrome Evaluation reproductive hormone status characterization diagram. FSH = follicle-stimulating hormone; HRT = hormone replacement therapy; LH = luteinizing hormone; LMP = last menstrual period; OC = oral contraceptives; PERIMENO = perimenopausal; POSTMENO = postmenopausal; PREMENO = premenopausal. *>3 months before study entry.

assessment of phosphocreatine, adenosine triphosphate and inorganic phosphate metabolites. The patient is placed supine in a Philips 1.5-T ACS MRI system (Best, The Netherlands), and the positioning of the ^{31}P surface coil over the heart is confirmed. After acquisition of a control spectrum at rest, the subject squeezes and holds a handgrip at 30% of maximum force for approximately 7 min, during which time a second spectrum is obtained. After the period of exercise, the subject is allowed to recover, another spectrum is collected and the study is complete. Spectral data are processed at a core laboratory using Philips software, and include phosphocreatine/adenosine triphosphate ratios and rate–pressure products during all phases as well as average dynamometer output for the exercise phase.

MICROVASCULAR CORONARY FLOW RESERVE. In women with normal or mild stenoses, the left anterior descending coronary artery is uniformly studied. When appropriate, the artery suspected as causing the abnormal diagnostic test response is studied. After administration of systemic heparin, a 0.014- to 0.018-in. (0.036 to 0.046 cm) Doppler-tipped guide wire is advanced into the target vessel, as previously described (14). After baseline recordings, adenosine (18 μg diluted in 2 ml saline followed by 5 ml saline flush) is hand-injected as a bolus via the coronary guiding catheter, and recordings are repeated. Time-averaged peak coronary blood flow velocity is assessed at baseline and after intracoronary adenosine and nitroglycerin (200 μg). One site (University of Pittsburgh) is also assessing this during a speech mental stress task and intravenous adenosine. A cineangiogram is performed immediately after measurement of coronary blood flow velocity. Quantitative coronary angiography is performed off-line to quantify epicardial coronary cross-sectional area 5.2 mm distal to the guide wire tip. Coronary flow reserve is computed as the ratio of post- to preadenosine average peak velocity (14). Volumetric blood flow calculations, using coronary lumen diameter measured from the angiograms, is also performed using previously reported techniques (34). The ratio of flow during each intervention (speech task, intracoronary and intravenous adenosine, intracoronary nitroglycerin) to baseline is used as a standard to define coronary vasomotion in the studied women.

CORONARY ARTERY ENDOTHELIAL FUNCTION. Two minutes after completion of maximum flow reserve (described above), repeat baseline recordings are made. The infusion catheter is primed with low dose (10^{-6M}) acetylcholine (0.036 μg/ml). Acetylcholine is then infused at a rate of 2 ml/min for 3 min. Three minutes after the beginning of the infusion, blood flow velocity, ECG and pressure recordings are obtained, and a left coronary cineangiogram is recorded using hand-injected low osmolar, nonionic contrast material. The same volumes of contrast material and the same optimal projection are used for each angiogram. High dose (10^{-4M}) acetylcholine (3.5 μg/ml) is then infused and after 3 min all recordings and an angiogram are repeated. Five minutes after this, coronary flow velocity and coronary angiography are obtained. Intracoronary nitroglycerin (150 μg) is given as a bolus from a glass syringe through the guide catheter. After 1 min, coronary angiography is performed. Nitroglycerin is given last as a direct acting

dilator to counteract any residual vasoconstrictive effects of acetylcholine and to assure a reference angiogram for analysis of maximal coronary lumen diameter at each coronary segment of interest.

POSITRON EMISSION TOMOGRAPHY IMAGING. Baseline myocardial perfusion is quantified in each of the three coronary artery distributions by $^{13}N-NH_3$–positron emission tomography imaging using standard techniques (35,36). Twenty millicuries of $^{13}N-NH_3$ is injected at rest, during a continuous infusion of intravenous adenosine (140 μg/kg/min), and during performance of a mental stress speech task. The speech task uses predetermined stress-provoking scenarios (37), and consists of a 2-min preparation period followed by a 3-min speech. The first several minutes of temporal data acquired as $^{13}N-NH_3$ is distributed in the blood and myocardium are analyzed by a previously validated two-compartment model to quantify myocardial blood flow (38,39).

Goal: to evaluate the influence of menopausal status and reproductive hormone levels on diagnostic testing results. This testing is designed to assess diagnostic test reproducibility in women, determine sources of variability, such as cyclical reproductive hormones, and investigate the influence of reproductive hormonal status and hormone therapy on diagnostic test response and symptomatic status.

HORMONAL STATUS DETERMINATION. The hormonal status determination developed for WISE uses both historical and single sampling blood hormonal characterization (Fig. 2). Premenopausal women also undergo menstrual cycle phase (follicular, luteal, menstrual) determination using estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone levels, at the time of WISE testing. Information regarding hormone therapy, including estrogenic, progestational and androgenic agents taken within 24 h of each WISE test are recorded.

REPRODUCIBILITY STUDIES. A randomly chosen 3% of the WISE participants are undergoing repeat dobutamine stress echocardiography, ECG exercise stress testing, ambulatory ECG monitoring, brachial artery reactivity testing, blood sampling and quality of life assessment within six months after the initial testing period in the absence of intercurrent cardiovascular event. Careful, repeat assessment of menstrual history, hormone therapy use and blood hormone levels are carried out.

Plan of Analysis

The planned WISE analyses based on the three main study goals are outlined.

Goal: to improve diagnostic testing for ischemic heart disease in women. Analyses will determine the sets of characteristics and test results (symptom characterization, diagnostic techniques, reproductive hormone status and level) that optimally predict presence or absence of signifi-

cant epicardial coronary artery stenoses, as well as outcomes (cardiac events and symptom status) during follow-up. Preliminary modeling for this has begun with data from patients entered into Phase I. This allows for assessment of necessity for transforming data, and assessment of stability of the models by comparing the model for Phase I with the model for Phase II, and provides focus for analyses to be performed when all data are available. Estimates of sensitivity, specificity and predictive accuracy from derived indexes will have 95% confidence intervals no wider than ±7%, based on a minimum clinically defined subgroup sample size of 200 for specific diagnostic tests. Due to the referral nature of this symptomatic population, selection bias(es) will be present which will probably influence conclusions regarding the various tests' diagnostic accuracy.

Goal: to study pathophysiologic mechanisms and prognosis of myocardial ischemia in the absence of epicardial coronary artery disease. Women with evidence of myocardial ischemia by ^{31}P MR spectroscopy in the absence of significant epicardial coronary artery stenoses will be compared with women without evidence of myocardial ischemia, as well as with women with significant epicardial coronary artery stenoses according to physiologic measures such as coronary flow reserve and endothelial function. Hormonal status, symptoms and psychosocial characteristics will also be compared to explore potential pathophysiologic mechanisms of myocardial ischemia in the absence of epicardial coronary artery stenoses. Prediction of cardiovascular events, as previously defined, during the 1- to 3-year follow-up will include comparison of those with and without significant epicardial coronary artery stenoses and/or myocardial ischemia. The estimated population of 200 participants with myocardial ischemia by MR spectroscopy is expected to have a relatively low annual event rate (<2%) compared with the approximately 300 participants with significant epicardial coronary artery disease with an estimated cumulative event rate of 20%. Since these rates are not likely to provide sufficient power to detect meaningful differences in prognosis by baseline assessment, an extension in the long-term follow-up of WISE participants is being planned.

Goal: to evaluate the influence of menopausal status and reproductive hormone levels on diagnostic testing results. Reproductive hormonal status (premenopausal, perimenopausal, postmenopausal and hormone replacement therapy) and serum hormone levels will be analyzed as to their influence on diagnostic test accuracy and reproducibility. Reproductive status and hormone levels will be analyzed as to their influence on symptoms, as well as measures of coronary flow, endothelial function and myocardial ischemia measured by ^{31}P MR spectroscopy. These measures will be compared among hormonal status groups using analysis of variance with factors of hormonal status and diagnostic test results. Diameter change will also be related directly to estrogen levels as well as to symptoms, the presence and

Table 3. Comparative Characteristics—WISE Phase I

Variable	Healthy Women, Framingham—Women (40) (n = 1,627)	Menopausal, PEPI (41) (n = 875)	Menopausal/CAD, HERS (42) (n = 2,762)	Suspected CAD, WISE—Phase I (n = 308)
Age (yr) (range)	49 (19–78)	56 (45–64)	67 (44–79)	59 (21–86)
Minority	0%	11%	11%	21%
>High school	NA	82%	32%	35%
HTN	22%	6%	58%	57%
DM	2%	0.5%	19%	23%
Smoke	30%	13%	13%	20%
BMI (kg/m²)	25 ± 5	26 ± 5	28	30 ± 6
SBP (mm Hg)	121 ± 18	115 ± 14	135 ± 14	138 ± 23
DBP (mm Hg)	77 ± 10	72 ± 8	73 ± 10	77 ± 13
FBS (mg/dl)	92 ± 21	97 ± 10	NA	118 ± 53
TC (mg/dl)	207 ± 43	224 ± 30	NA	200 ± 49
TG (mg/dl)	106 ± 123	104 ± 55	168 ± 64	153 ± 93
HDL-C (mg/dl)	59 ± 14	63 ± 16	50 ± 13	53 ± 13
LDL-C (mg/dl)	130 ± 38	140 ± 26	130 ± NA	116 ± 41
TC/HDL	4.0 ± 1.5	3.9 ± 0.1	4.7 ± 1.5	3.9 ± 1.3
Menopausal	NA	100%	100%	86%
HRT	NA	0%	24%*	38%

*Use >3 months before study screening.

BMI = body mass index; CAD = coronary artery disease; DBP = diastolic blood pressure; DM = diabetes mellitus (medication or FBS >140 mg/dl); FBS = fasting blood sugar; HDL-C = high density lipoprotein cholesterol; HERS = Heart and Estrogen/Progestin Replacement Study; HRT = hormone replacement therapy; HTN = hypertension (medication or SBP >140 mm Hg or DBP >95 mm Hg); LDL-C = low density lipoprotein cholesterol; NA = not available; PEPI = Postmenopausal Estrogen/Progestin Interventions; SBP = systolic blood pressure; Smoke = current smoking; TC = total cholesterol; TG = triglycerides; WISE = Women's Ischemia Syndrome Evaluation.

magnitude of myocardial perfusion abnormalities, coronary arterial microvascular and endothelial testing and hormonal status using scatterplots and regression analyses.

RESULTS

Characteristics of the pilot phase participants. A total of 1,979 women were screened, of whom 450 (23%) were eligible for study entry during the pilot phase between November 15, 1996 and July 16, 1997. The three most frequent exclusions were recent revascularization procedures (n = 257, 21%), contraindications to ischemia provocation (n = 254, 21%) and recent myocardial infarction (n = 154, 12%). Among the 249 (55%) enrolled women, 23 (9%) of subjects have been terminated from the study for reasons that included revascularization procedures after study entry but before WISE testing, contact with patient lost and patient found to be ineligible/refused testing. There were three deaths remote from the WISE protocol testing.

Characteristics for the initial 308 WISE participants are listed in Table 3. These women with suspected ischemic heart disease are compared with previously described populations of women, including healthy women from the Framingham Study (40), healthy postmenopausal women from the Postmenopausal Estrogen/Progestin Interventions study (41) and postmenopausal women with established ischemic heart disease from the Heart and Estrogen/Progestin Replacement Study (42). Table 3 documents that the WISE protocol identifies a group of women with a constellation of cardiac risk factors greater than that seen in both healthy women and women with established ischemic heart disease. Notably, minority recruitment is good at 21%.

Review of reproductive status demonstrates that 85% of the pilot phase WISE participants were postmenopausal, 3% were perimenopausal and 11% were premenopausal. Among these participants, 38% were current users of hormone replacement therapy. Among the postmenopausal women, 60% reported prior hysterectomy and among these women, 50% also reported bilateral salpingo-oophorectomy.

Characterization of the chest pain symptoms revealed that 35% reported typical angina, 60% reported atypical angina and 45% reported daily/almost daily symptoms. Ninety-one percent of the participants had a low functional capacity of <8 metabolic equivalents, measured by the Duke Activity Score Index (43). Comorbid conditions are frequent and included history of treatment for depression (26%), autoimmune disease (20%), weight cycling (>10 lbs [>4.54 kg] >3 times) (32%) and polycystic ovary disease (8%).

Coronary angiography results in the first 323 WISE participants revealed that 31% of the participants have significant coronary artery stenoses (≥50%) in any major coronary artery, 32% have mild stenoses (20% to 49%) and 37% have no (<20%) stenoses. The cumulative frequency distribution of the severity scores in the WISE participants is depicted in Figure 3, and demonstrates that 50% have a low severity score <10. The average left ventricular ejection fraction is 68% (range 23% to 86%), and the majority (87%) are greater than 50%.
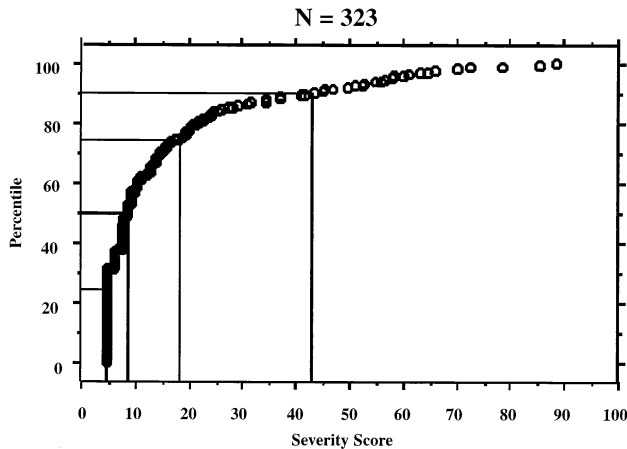
N = 323

Figure 3. Women's Ischemia Syndrome Evaluation cumulative frequency distribution of coronary artery severity scores.

DISCUSSION

Initial pilot phase data indicate that the WISE protocol is safe and feasible for identifying symptomatic women with and without significant epicardial coronary artery stenoses. Pilot data indicate that WISE participants have high frequency of coronary artery disease risk factors and experience symptoms that are limiting, despite often minimal epicardial coronary artery stenoses and preserved left ventricular function.

Summary. Previous evidence suggests that gender-specific differences exist in ischemic heart disease symptoms, detection and management. The WISE study is: 1) defining new, comprehensive diagnostic strategies to evaluate women with suspected ischemic heart disease; 2) exploring the pathophysiology and significance of ischemia in the absence of epicardial coronary stenoses, and 3) evaluating the role of reproductive hormones on symptoms and diagnostic test response. Phase II of the WISE is in progress.

APPENDIX: WISE PARTICIPANTS

Clinical Sites and Investigators

Allegheny General Hospital - MCP Hahnemann School of Medicine, Pittsburgh: Nathaniel Reichek, MD (principal investigator [PI]), Christopher Kramer, MD (coinvestigator [CoI]), Douglas Schulman, MD (CoI), Sinda Dianzumba, MD (CoI), Walter Rogers, MS (CoI), Bryan C. Donohue, MD (CoI), James Joye, DO (CoI), Diane Vido (coordinator [C]), Diana Lynn Pakstis, RN(C)

University of Alabama at Birmingham, Birmingham: William J. Rogers, MD (PI), Gerald M. Pohost, MD (CoI), Alfred A. Bartolucci, PhD (CoI), Vera Bittner, MD (CoI), Joseph R. Logic, MD (CoI), Steven Buchthal, PhD (CoI), Carol E. Cornell, PhD (CoI), Jan A. Denhollander, PhD (CoI), Marc Doyle, PhD (CoI), Anthon R. Fuisz, MD (CoI), Edward T. Martin, MD (CoI), Thomas D.

Paine, MD (CoI), Michelle L. Robbin, MD (CoI), Lindsey Tauxe (CoI), Edward G. Walsh, PhD, MSPH (CoI), Kathy Clay, RN(C), William C. Gamble III, RN(C), Kathleen Armstrong, RN(C)

University of Florida, Gainesville: Carl J. Pepine, MD (PI), Jannet Lewis, MD (CoI), Lang Lin, MD (CoI), Eileen Handberg-Thurmond, PhD (CoI), Rick Kerensky, MD (CoI), Keith Stone, MD (CoI), Susan McGorray, PhD (CoI), Alix Baxter, MD (CoI), Alice Boyette (C)

University of Pittsburgh: Steven E. Reis, MD (PI), Katherine Detre, MD, DrPH (CoPI), Richard Holubkov, PhD (CoI), Flordeliza Villanueva, MD (CoI), Jane Owens, PhD (CoI), Karen Matthews, PhD (consultant), Janine Flory, PhD (CoI), A.J. Conrad Smith, MD (CoI), Daniel Edmundowicz, MD (CoI), David Townsend, PhD (CoI), Carolyn Meltzer, MD (CoI), Kathleen Zell, BSN (C), Cheryl Rickens, RN(C)

Coordinating Center—University of Pittsburgh: Sheryl F. Kelsey, PhD (PI), Katherine M. Detre, MD, DrPH (CoI), Richard Holubkov, PhD (CoI), Tanya Kenkre, MPH(C), Marian Olson, MS(C), B. Delia Johnson, PhD(C)

Core Angiography Laboratory—Rhode Island Hospital: Barry L. Sharaf, MD (PI), David O. Williams, MD (CoI), Nicholas Miele (C)

National Heart, Lung and Blood Institute Project Officers: George Sopko, MD, Paul Albert, PhD, Gail Pearson, MD, Donna Berkowitz (contract C), William Stevens (contract C), Doug Frye (contract C)

Study Chair—Cedars-Sinai Medical Center, Los Angeles: C. Noel Bairey Merz, MD (PI)

Data and Safety Monitoring Board: Bernard J. Gersh, MD (Chair), Robert O. Bonow, MD, Richard O. Cannon III, MD, Katherine Stoney, PhD, Madison Powers, PhD, JD, Erica Brittain, PhD

REFERENCES

1. Statistical Abstract of the United States. 112th ed. Washington (DC): U.S. Department of Commerce, Economics and Statistics Administration, Bureau of the Census, 1992.
2. DeStefano F, Merritt RK, Anda RF, et al. Trends in nonfatal coronary heart disease in the United States, 1980 through 1989. Arch Intern Med 1993;153:2489–94.
3. Tobin JN, Wassertheil-Smoller S, Wexler JP, et al. Sex bias in considering coronary bypass surgery. Ann Intern Med 1987;107:19–25.
4. Shaw LJ, Miller DD, Romeis JC, et al. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994;120:559–66.

5. Khan SS, Nessim S, Gray R, et al. Increased mortality of women in coronary artery bypass surgery: evidence for referral bias. Ann Intern Med 1990;112:561–7.

6. Krumholz HM, Douglas PS, Lauer MS, Pasternak RC. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? Ann Intern Med 1992;116:785–90.

7. Tofler GH, Stone PH, Muller JE, et al. Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. J Am Coll Cardiol 1987;9:473–82.

8. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1524 women after myocardial infarction: comparison with 4315 men. Circulation 1991;83:484–91.

9. The Principal Investigators of CASS and Their Associates. The National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS). Circulation 1981;63 Suppl 1:1–81.

10. Kennedy JW, Killip R, Fisher LD, et al. The clinical spectrum of coronary artery disease and its surgical and medical management, 1974–1979. The Coronary Artery Surgery Study. Circulation 1982;66 Suppl 3:16.

11. Barolsky SM, Gilbert CA, Farugui A, et al. Differences in electrocardiographic response to exercise of women and men: a non-Bayesian factor. Circulation 1979;60:1021–7.

12. Higgenbotham MB, Morris KG, Coleman E, Cobb FR. Sex related differences in the normal cardiac response to upright exercise. Circulation 1984;70:357–66.

13. Detrano R, Froelicher VF. Exercise testing: uses and limitations considering recent studies. Prog Cardiovasc Dis 1988;31:173–204.

14. Reis SE, Gloth ST, Blumenthal RS, et al. Ethinyl estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. Circulation 1994;89:52–60.

15. Diamond GA, Staniloff HM, Forrester JS, et al. Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. J Am Coll Cardiol 1983;1:444–55.

16. Cook WW, Medley DM. Proposed hostility and pharasaic virtue scales for the MMPI. J Appl Psychol 1954;38:414–8.

17. Beck AT, Ward CH, Mendelsohn M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.

18. Schmidt NB, Telch MJ. The role of safety information and fear of bodily sensations in moderating responses to a hyperventilation challenge. Behav Ther 1994;25:197–208.

19. Cloninger CR. A systematic method for clinical description and classification of personality variants. Arch Gen Psychiatry 1987;44:573–88.

20. Mandler G, Mandler J, Uviller E. Automatic feedback: the perception of autonomic activity. J Abnorm Soc Psychol 1958;56:367–73.

21. Freedland KE, Carney RM, Krone RJ, et al. Psychological factors in silent myocardial ischemia. Psychosom Med 1991;53:13–24.

22. Spielberger CD, Gorsuch RL, Lushene RD. Manual for the State-Trait Anxiety Inventory. Palo Alto (CA): Consulting Psychologists Press, 1970.

23. Cohen S, Doyle WJ, Skoner DP, et al. Social ties and susceptibility to the common cold. JAMA 1997;277:1940–4.

24. Sharaf BL, Williams DO, Miele NJ, et al. A detailed angiographic analysis in patients with ambulatory electrocardiographic ischemia: results from the Asymptomatic Cardiac Ischemia Pilot (ACIP) Study Angiographic Core Laboratory. J Am Coll Cardiol 1997;29:78–84.

25. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of left ventricular hypertrophy: test performance in relation to definition of hypertrophy and presence of obesity. J Am Coll Cardiol 1996;27:124–31.

26. Pepine CJ, Geller NL, Knatterud GL, et al. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study: design of a randomized clinical trial, baseline data and implications for a long-term outcome trial. J Am Coll Cardiol 1994;24:1–10.

27. Hill JA, Bertolet BD, Duran A, et al. An ambulatory ECG monitoring approach to the problems of ischemia-guided therapy. J Amb Monitor 1991;4:175–85.

28. Pepine CJ, Cohn PF, Deedwania PC, et al, for the ASIST Study Group. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. Circulation 1994;90:762–8.

29. Celermajer DS, Sorensen KE, Bull C, et al. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. J Am Coll Cardiol 1994;24:1468–74.

30. Doyle M, Walsh EG, Blackwell GG, Pohost GM. Block regional interpolation scheme for k-space (BRISK): A rapid cardiac imaging technique. Magn Reson Med 1995;33:163–70.

31. Walsh EG, Doyle M, Lawson MA, et al. Multislice first-pass myocardial perfusion imaging on a conventional clinical scanner. Magn Reson Med 1995;34:34–47.

32. Lewis J, Lin L, McGorray S, et al. Dobutamine stress echocardiography in women with chest pain: pilot phase data from the NHLBI Women's Ischemia Syndrome Evaluation (WISE). J Am Coll Cardiol 1999;33:1462–8.

33. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2-3:92–8.

34. Doucette JW, Corl D, Payne HM, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. Circulation 1992;85:1899–911.

35. Muller P, Czernin J, Choi Y, et al. Effect of exercise supplementation during adenosine infusion on hyperemic blood flow and flow reserve. Am Heart J 1994;128:52–60.

36. Krivokapich J, Smith JT, Huang S-C, et al. ^{13}N Ammonia myocardial imaging at rest and with exercise in normal volunteers. Quantification of absolute myocardial perfusion with dynamic positron emission tomography. Circulation 1989;80:1328–37.

37. Goldberg AD, Becker LC, Bonsall R, et al. Ischemic, hemodynamic, and neurohumoral responses to mental and exercise stress: experience from the Psychophysiological Investigations of Myocardial Ischemia Study (PIMI). Circulation 1996;94:2402–9.

38. Choi Y, Huang SC, Hawkins RA, et al. A simplified method for quantification of myocardial blood flow using nitrogen-13-ammonia and dynamic PET. Circulation 1989;80:1328–37.

39. Kuhle WG, Porenta G, Huang SC, et al. Quantification of regional myocardial blood flow using ^{13}N-ammonia and reoriented dynamic positron emission tomographic imaging. Circulation 1992;86:1004–17.

40. Lamon-Fava S, Wilson WF, Schaefer EJ. Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham Offspring Study. Arterioscler Thromb Vasc Biol 1996;16:1509–15.

41. The Writing Group for the PEPI Trial. Effects of estrogen and estrogen/progesting regimens on heart disease risk factors in postmenopausal women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1995;273:199–208.

42. Schrott HG, Bittner V, Bittinghoff E, et al. for the HERS Research Group. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: The Heart and Estrogen/Progestin Replacement Study (HERS). JAMA 1997;277:1281–6.

43. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). Am J Cardiol 1989;64:651–4.

The Women's Ischemia Syndrome Evaluation (WISE) Study: protocol design, methodology and feasibility report

C. Noel Bairey Merz, Sheryl F. Kelsey, Carl J. Pepine, Nathaniel Reichek, Steven E. Reis, William J. Rogers, Barry L. Sharaf, George Sopko, for the WISE Study Group

J. Am. Coll. Cardiol. 1999;33;1453-1461

This information is current as of October 14, 2007

Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/33/6/1453
References	This article cites 40 articles, 15 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/33/6/1453#BIBL
Citations	This article has been cited by 38 HighWire-hosted articles: http://content.onlinejacc.org/cgi/content/full/33/6/1453#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl