Women's Ischemia Syndrome Evaluation (WISE) Extension Protocol

ABSTRACT

This project will extend the follow-up of the Women's Ischemia Syndrome Evaluation (WISE) patients for a minimum of 5 years and will be carried out jointly with the applications "Altered Renin Angiotensin System as a Mechanism for Coronary Microvascular Dysfunction in Women" (C. Pepine PI) and "Immunologic Basis For Coronary Disease in Women" (S.Reis PI). The WISE contract began in September 1996 as a 4-center study to 1) optimize symptom evaluation and diagnostic testing for ischemic heart disease in women; 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. An extensive contemporary database has been assembled on 936 women referred for coronary angiography because of suspected ischemia. Data include demographic, clinical, symptomatic, functional, and psychosocial variables. Coronary angiography and ventriculography data, brachial artery reactivity testing, ECG monitoring, and blood determinations are all assessed by core laboratories. Site-specific innovative technologies have been used to develop potential markers of myocardial ischemia. We seek to **1)** Determine the incremental long-term prognostic value of novel testing developed in WISE: **2)** Develop sex-specific incremental outcome models to evaluate the prognostic value of female reproductive variables; **3)** Assess the incremental cost effectiveness and resource efficiency of the WISE innovative testing techniques as compared with traditional tests; **4)** Continue ongoing analyses and ancillary projects, collaborate with other WISE investigators RO1's submitted in this cluster, and maintain a WISE database and infrastructure to facilitate further investigations into the mechanisms underlying ischemia syndromes in women. To address these aims, a longer follow-up is necessary. Follow-up will consist of annual telephone contacts by experienced site coordinators. WISE will continue to use the well-established methods to implement study coordination, data management, quality control, statistical analyses, and manuscript preparation. Cox regression models will be used to analysies events with demographics risk factors, diagnostic testing and reproductive factors considered as explanatory variables. A hybrid decision model will be used that compares resource use patterns and sums cost estimates. The results of these studies will enhance our understanding of both the significance and pathophysiology of ischemic heart disease in women and serve as a foundation for diagnostic and therapeutic clinical trials aimed at reducing disease-related morbidity and mortality.

A. SPECIFIC AIMS

Prior reports demonstrate that more than one-half of women presenting with signs and/or symptoms of ischemic heart disease have no significant coronary artery disease at coronary angiography. Conversely, when women develop significant coronary artery disease they have a greater disease severity and disability compared to men. The majority of women in both groups have persistent symptom-related disability and continue to consume large amounts of health care resources and costs, in part because the pathophysiology of ischemic heart disease in women is poorly understood and specific diagnostic and treatment strategies are underdeveloped.

Previous findings from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study have demonstrated that it is feasible to apply multiple new and innovative diagnostic techniques in a cohort of women presenting with clinical findings suggestive of ischemic heart disease. Using a common protocol and core laboratory, pilot phase findings have confirmed that over half of women referred to coronary angiography do not have significant coronary artery disease. Full-scale WISE findings have confirmed: 1) the presence of metabolic myocardial ischemia, detected by ^{31}P magnetic resonance spectroscopy, in women without significant coronary artery disease; 2) evidence that microvascular dysfunction is potentially responsible for myocardial ischemia and related clinical adverse outcomes in women with and without significant coronary artery disease. Because chronic inflammation of the vessel wall is a hallmark of atherosclerosis, we hypothesize that common inflammatory mechanisms modulated by reproductive hormones along with the renin-angiotensin system may be involved in this microvascular dysfunction.

The specific aims for the WISE extension are as follows:

AIM 1: Determine the incremental long-term prognostic value of novel testing developed in WISE.

AIM 2: Develop sex-specific incremental outcome models to evaluate the prognostic value of female reproductive variables.

AIM 3: Assess the incremental cost effectiveness and resource efficiency of the WISE innovative testing techniques as compared with traditional tests.

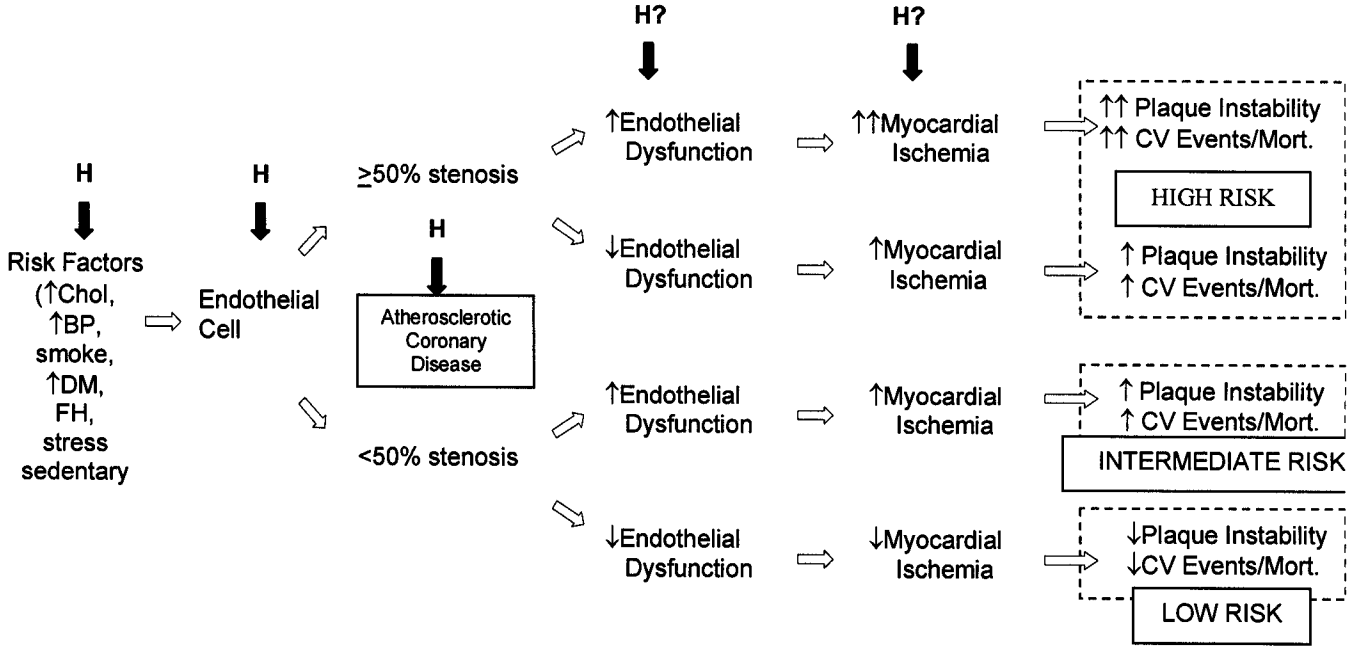
AIM 4: Continue ongoing analyses and ancillary projects.

- Collaborate with other WISE investigators RO1's submitted in this cluster
- Support ongoing WISE ancillary trials, testing the impact of (1) HRT, and (2) ACE therapy.
- Complete WISE gender-specific analyses and manuscripts.
- Maintain a WISE database and infrastructure to facilitate further investigations into the mechanisms underlying ischemia syndromes in women.

B. BACKGROUND AND SIGNIFICANCE

The primary hypothesis to be tested in this specific R01 is that the presence of myocardial ischemia mediated by endothelial dysfunction increases prognostic risk, in both obstructive and nonobstructive coronary disease, and that ischemia is modulated by female hormonal factors that influence endothelial dysfunction (Figure 1). Endothelial dysfunction is defined here as the disordered response of arteries (macrovascular dysfunction) and arterioles (microvascular dysfunction) to physiologic stimuli (flow, exercise or mental stress, acetylcholine). To test these hypotheses, the WISE women will be classified into three groups: 1) women <u>with</u> angiographic evidence of significant coronary disease defined as any epicardial coronary artery stenosis ≥50% with and without evidence of microvascular dysfunction, 2) women <u>without</u> significant coronary disease but evidence of microvascular dysfunction, and 3) women <u>without</u> significant coronary disease and no evidence of microvascular dysfunction. These three groups will be compared with regard to prognosis, pathophysiology and costs.

Figure 1. WISE Extension Hypotheses



H = reproductive hormones, Chol = cholesterol, BP = blood pressure, DM = diabetes mellitus, FH = family history of premature coronary disease, CV = cardiovascular

C. RESEARCH DESIGN AND METHODS

a. Follow-Up Methods. Follow-up information is obtained predominantly by telephone interview. All WISE women who completed a baseline evaluation and have not withdrawn consent will be followed annually for an additional five years (range of total follow-up will be 6-9 years with mean of 7.5 years). We will use the same methodology in order to test the original WISE hypotheses and evaluate the additional aims outlined in the current application. Contacting patients annually rather than less frequently minimizes reporting bias and assures a continued relationship with the patient.

Continued patient follow-up will be performed by current WISE investigators and WISE staff according to the previously established protocol, with additional questions related to continued medical resource use for the preceding year, such as outpatient visits, length of stay for hospital visits, as well as the Patient Economic Questionnaire (PEQ) that has been used in previous studies (Weintraub 1999). A Manual of Operations and Procedures will formally document and define all data being collected as well as follow-up contact procedures and strategies. The names of treating physicians and clinical centers will also be collected in order that we can contact them for relevant documentation, test results, and new angiographic results where available. Site coordinators will continue to complete these follow-up forms annually and send them to the Coordinating Center (CC) for data entry. After logical edits have been performed, site coordinators will work with the CC staff to resolve errors.

When the nurse coordinator learns from the telephone interview that a WISE woman has experienced an event, including MI, PTCA or CABG, the coordinator will contact the hospital where the woman was treated to verify the dates and diagnosis of MI or that the procedures occurred. For MI, the coordinator will verify that at least two of three circumstances are noted – symptoms, elevated cardiac enzymes, and/or ECG changes. These criteria are detailed below. When it is learned that a WISE woman has died, we will obtain a death certificate; further, the physician treating at the time of death and family members will be interviewed to determine the circumstances of death. The goal is to differentiate cardiac from non-cardiac deaths and further subdivide the cardiac event into sudden death, MI, congestive heart failure, or other.

b. Retention of Study Population. At each contact, the women will be reminded of the importance of continued annual contacts over the years and asked to provide any new contacts or names of primary care physicians. A key to successful follow-up is the valuable relationship established between coordinators and patients. Such relationships assure continued patient interest and cooperation. If a patient is unable to complete a follow-up interview, either due to illness or temporary absence, coordinators will contact close family members, listed back-up contacts, and/or primary care physicians. In order to maximize patient cooperation, the CC will conduct a training session for all nurse coordinators at the initiation of the extension. The coordinators will meet in conjunction with the first Steering Committee meeting to review the new data collection form and discuss follow-up strategies. Allowing them to renew their acquaintance at a central meeting and sharing information is a key factor in the project's success. Since many of the study withdrawals occurred during the WISE pilot phase, it is expected that our present follow-up success rate will be maintained over the ensuing years.

c. Ascertainment of Endpoints. As per WISE protocol, at each follow-up contact, patients provide information on their continuing symptoms, medical history and treatments. Specifically, information will be collected on changes in angina status and symptomology; types and doses of medications and number of adjustments in anti-anginal regime; change in risk factors, reproductive status, physical activity level and quality of life; number of visits to health-care provider for evaluation of chest pain; cardiac hospitalization; PTCA or CABG, or other cardiac procedure; and complications from any of these procedures. We will examine mortality and a

number of composite endpoints: 1)death, 2)death and MI, 3)death, MI, and cardiovascular hospitalization, 4)death, MI, cardiovascular hospitalization, revascularization and 5)death, MI, cardiovascular hospitalization, revascularization, continuing symptoms

Mortality: The frequency of death is expected to be small in this low-risk population. However, when a patient is identified as deceased, all information on the circumstances surrounding death, including best estimate of cause of death, are documented. Deaths will be classified as cardiac or non-cardiac related. Cardiac transplantation and resuscitation from documented ventricular fibrillation/tachycardia will be considered equivalent to cardiac death.

Myocardial Infarction: Myocardial infarction will be classified as (1) new pathologic Q waves (worsening by two grade, according to the Minnesota code) (Prineas 1982, Rautaharju 1991); or (2) non Q-wave MI, in the setting of diagnostic elevation of cardiac enzymes (CK > 2 upper limit normal (ULN) and abnormal CK-MB or total CK>ULN and CI-MB > 2 ULN; CK-MB takes precedence over CK. Within 24 hours after coronary revascularization: CK-MB > 3 ULN for PTCA and > 100 units for CABG). Development of new LBBB and abnormal CK-MB (as defined above) qualifies as an MI event. Silent MI is defined as development of major Q-wave worsening by Novacode in the absence of chest pain and enzyme changes, detected during a routine ECG. Non Q-wave MI is defined as the presence of abnormal cardiac enzymes (as defined above) and either (i) chest pain $\geq$ minutes or (ii) worsening ST or T wave items but absent diagnostic Q-wave criteria.

Cardiovascular Hospitalization: For patients admitted to the hospital for cardiovascular reasons, documentation will be collected from the emergency room admission sheet, hospital discharge summary, admission and discharge ECG's. In addition to MI, reasons for hospitalization are classified as heart failure, vascular disease, stroke, and angina. We will also record any hospitalizations for "other" reasons (such as fractures and cancer).

Revascularization: Repeat revascularizations will be assessed through patient report and review of associated medical records and will include PTCA with and without stent placement or atherectomy, CABG (both open and closed chest), and alternative revascularization procedures (transmyocardial laser revascularization-TMR). Occurrence and dates of repeat angiograms are also recorded.

Ischemia or Chest Pain Symptoms. Detailed information on chest pain symptoms for the last 6 weeks, including severity and specific location, will be collected directly from the patient using both the traditional angina questionnaire (Diamond 1983) and the WISE female angina questionnaire (Bairey Merz 1998a).

d. Statistical Methods.

i. General Methods for Determination of Prognosis

Subgroups. The WISE testing protocol has identified three distinct subgroups of women: 1) women with significant ($\geq$ 50%) coronary disease with or without microvascular dysfunction; (2) women without significant coronary disease and evidence of microvascular dysfunction; and (3) women without significant coronary disease and no evidence of microvascular dysfunction (Figure 1). We hypothesize that women in Group 1 have the highest adverse outcome rates; women in group 2 have intermediate adverse outcome rates; and women in group 3 have the lowest adverse outcome rates.

Covariates. Adjustment will be key in our analytic strategies. Our ongoing investigation of the WISE cohort, together with findings from the literature, has provided us with insight into the predictive value of factors for atherosclerosis. One of the strongest predictors of cardiovascular disease is age; hence all analyses will control for age. Other strong predictors are diabetes and prior history of MI or revascularization procedures. These variables will be entered into survival analysis as time-constant covariates. **Secondary measures, including functional status,**

employment status, quality of life measures, chest pain assessment, and medication use will continue to be collected annually. Depending on the specified outcome, these measures will be entered into Cox proportional hazards regression analyses as time-dependent covariates. An important goal of WISE is to investigate the effect of sex-specific variables, including reproductive hormone and menopausal status, in mediating or incrementally adding to prognostic outcomes. Finally, the prognostic assessment of WISE women will include the role of traditional risk factors, laboratory measures, noninvasive tests, and interaction effects. Including these variables as fixed covariates in outcome models will provide information on the independence of the hypothesized main effects, mediation by additional factors, and possible interactions. For example, some effects may only be found in postmenopausal women. It is moreover expected that particular combinations of diagnostic tests may provide the greatest accuracy in estimating outcome.

Time-to-Event Analyses. The primary analytical tool will be survival analysis. Standard Kaplan-Meier survival curves and Cox proportional hazards regression techniques, as well as the logrank test that compares survival curves will be used to estimate outcome differences among various sub-groups. A Kaplan-Meier analysis is appropriate when examining event rates over an extended follow-up period and testing for univariate associations between survival time and quantitative covariates. The logrank test is commonly used to test the null hypothesis that the survival curves of two or more populations are identical. In Cox proportional hazards regression, cumulative rates will be modeled, both graphically and analytically, in order to identify the prognostic importance of ischemia and endothelial dysfunction, while controlling for time dependent and fixed covariates as well as their interactions.

ii. Statistical Analyses to Continue Ongoing Analyses

Analyses will continue to:

- Collaborate with other WISE projects including (1) assessment of the role of ACE and A-II activity and preclinical atherosclerosis as pathophysiological mechanisms for morbidity and mortality (Altered Renin Angiotensin System as a Mechanism for Coronary Microvascular Dysfunction in Women, Pepine PI) ; (2) evaluation of the role of hormones and inflammatory markers on vascular function (Immunologic Basis of Coronary Disease in Women, Reis PI).
- Support ongoing WISE ancillary trials. Currently, two ancillary trials are in progress. These are industry-supported, randomized, controlled, double-blind intervention trials testing the impact of (1) HRT, and (2) ACE therapy, on the outcomes of metabolic ischemia, endothelial dysfunction and morbidity in women without obstructive coronary disease.
- Complete gender-specific analyses and manuscripts. To date, the WISE study has established a reference algorithm for reproductive status determination, developed a chest pain tool specific for women, identified a mechanism whereby weight cycling increases cardiovascular risk for women and validated questionnaire measurement of physical activity level in women.
- Maintain a WISE database and infrastructure to facilitate further investigations into the mechanisms underlying ischemia. Preservation of the WISE infrastructure will allow this important database to be used to its fullest potential.

e. **Study Organization.** WISE investigators will continue to collaborate through the system organized during the contract period. The Steering Committee is chaired by C. Noel Bairey Merz (WISE study chair), with members Carl Pepine, Nathaniel Reichek, Steven Reis, William Rogers (clinical center investigators), Barry Sharaf (angiographic core lab director), Gerald Pohost (P31 core lab director), Sheryl Kelsey (CC director), and George Sopko (NHLBI). The Steering Committee has formed a number of individual working committees:

A Policy and Publications Committee, chaired by Carl J. Pepine, is responsible for approving topics for analysis, forming writing groups, and overseeing the timely submissions of abstracts, presentations, and publications. A P-31 Committee, co-chaired by Gerald Pohost and Nathaniel Reichek, determines guidelines for the new P-31 technology to diagnose ischemia, oversees patient responses, and recommends improvements in the P-31 protocol. A Hormone Committee, chaired by C. Noel Bairey Merz, is responsible for adjudicating WISE women's hormone status, particularly in cases where a woman's reproductive history and actual hormone assays produce contradictory evidence. An Angiography Committee, chaired by Barry Sharaf, assures that all angiography films are read in a uniform manner in order to eliminate possible inter-site variation

The Data and Safety Monitoring Board (DSMB) is an independent committee appointed by NHLBI to advise on scientific issues, review patient safety, and recommend future directions.

f. Data Management, Quality Control, and Computing. The WISE data management system is centralized in the CC. The CC is also an integral part of the data collection process at the clinical sites. At the initiation of WISE, the CC took an active part in protocol development, designed the data collection forms, and conducted a training session for the coordinators. WISE data can only be collected by persons certified by such training. Continued frequent communications with the clinical sites have fostered an interdependent, collaborative relationship between the CC and the study coordinators. This relationship will continue to be instrumental to the smooth operations of the follow-up phase. During the initiation of the extended follow-up, the CC will develop a Manual of Operations and conduct a training session for coordinators to discuss the various problems and solutions specific to follow-up. Additionally, **one person** from the CC will perform annual site visits to audit records, review protocol adherence, and solve potential problems.

The CC data management system is designed for optimal quality control by passing each data form through a routine system of visual inspections and computer verification. Data collection forms will continue to be completed and visually reviewed at each site and then mailed or faxed to the CC for further review, entry, and logical editing. The data manager logs the receipt of these forms and inspects them visually for their completeness. Incomplete or problematic forms are followed up by queries to the site coordinators. From these data, the CC generates monthly patient recruitment and protocol compliance reports in the form of time trend analyses across clinical sites. These reports help to quickly identify newly apparent or emerging problems and to provide feedback, guidance and possible remedial action to the clinical site personnel.

Data are then keyed into the PoP data entry system where they must pass a series of rigorous within-form logical edits. The PoP data entry and management system, developed at the Epidemiology Data Center, has been used successfully on dozens of clinical studies, including WISE, over the past 11 years. This software provides features such as double entry verification, real-time range checking, within-form logical editing and an automatic patient and form logging feature to track the progress of forms through the system. Data files now reside on a microcomputer dedicated to WISE data entry and management procedures. Data that have successfully passed all quality control measures are converted into SAS datasets and are made available to statisticians for analysis via the EDC Local Area Network (Novell). Follow-up data will be converted to new SAS datasets as well as merged with existing data into "patient history" files that contain each patient's cumulative history, including dates of events and status at each follow-up contact.

Some of the laboratory data submitted to CC arrives in the form of spreadsheets. To respond to quality control needs, the Epidemiology Data Center has developed a system of edits which these spreadsheets must pass before being converted into SAS datasets. Edits have been designed to check for ID matches, range checks, handling missing data, and logical consistency.

g. Security and Confidentiality of Data. Patient confidentiality is ensured through the use of alphanumeric codes to identify patient records. Data collection forms and computerized

records are identified by this ID code. Paper copies of data collection forms are maintained in locked filing cabinets.

The PoP system files and site data are backed up daily while full system archives are created monthly. Virus detection software is updated and executed routinely on all WISE related computers. All WISE data and analysis files are password protected on all computers to protect against unauthorized access and against inadvertent change.

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