Variation in Recovery
Role of Gender on Outcomes of Young AMI Patients (VIRGO)
Study Design

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Background—Among individuals with ischemic heart disease, young women with an acute myocardial infarction (AMI) represent an extreme phenotype associated with an excess mortality risk. Although women younger than 55 years of age account for less than 5% of hospitalized AMI events, almost 16 000 deaths are reported annually in this group, making heart disease a leading killer of young women. Despite a higher risk of mortality compared with similarly aged men, young women have been the subject of few studies. Methods and Results—Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) is a large, observational study of the presentation, treatment, and outcomes of young women and men with AMI. VIRGO will enroll 2000 women, 18 to 55 years of age, with AMI and a comparison cohort of 1000 men with AMI from more than 100 participating hospitals. The aims of the study are to determine sex differences in the distribution and prognostic importance of biological, demographic, clinical, and psychosocial risk factors; to determine whether there are sex differences in the quality of care received by young AMI patients; and to determine how these factors contribute to sex differences in outcomes (including mortality, hospitalization, and health status). Blood serum and DNA for consenting participants will be stored for future studies. Conclusions—VIRGO will seek to identify novel and prognostic factors that contribute to outcomes in this young AMI population. Results from the study will be used to develop clinically useful risk-stratification models for young AMI patients, explain sex differences in outcomes, and identify targets for intervention. (Circ Cardiovasc Qual Outcomes. 2010;3:684-693.)

Key Words: risk factors ■ sex ■ outcomes ■ quality of care ■ young

Young women with acute myocardial infarction (AMI) are a relatively large yet understudied population. Almost 16 000 US women 55 years or younger die from coronary heart disease (CHD) each year, ranking it among the leading causes of death in this group.1 Importantly, registries and cohort studies that have published data on young women have identified an excess mortality risk after AMI compared with similarly aged men.2,3 Moreover, this excess risk appears to be sustained; among young women who initially survive an AMI, their subsequent mortality risk is about 50% higher than men 2 years after AMI.4 Although recent evidence suggests a narrowing of the mortality gap after AMI between younger women and men, rates still remain higher for younger women.5 Unfortunately, these studies provide limited information about the presentation and natural history of AMI in young women, risk-factor profiles, treatment patterns, and nonmortality outcomes (including subsequent...
symptoms, function, and quality of life), nor have they been able to identify potential causes for this excess risk. The higher risk may be due to a higher prevalence of various traditional and emerging risk factors in this group compared with men, the greater potency of select risk factors, poorer quality of care, or some combination of these variables. Understanding the underlying causes of the adverse prognosis in young women and men is essential for developing interventions and strategies to improve their care and outcomes.

Conceptualization of the VIRGO Study Design and Selection of Research Domains

The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study is the first national, prospective, observational study of young AMI patients and has a planned enrollment of 2000 women and 1000 men. The specific aims of the study are:

1. To characterize sex differences after hospitalization for AMI in a broad range of outcomes including mortality, all-cause readmission, rehospitalization for cardiovascular causes, and adverse health status;
2. To evaluate the role of demographic, clinical, metabolic, biochemical, genetic, psychosocial, and lifestyle factors on outcomes for young women and men with AMI and to examine whether sex-based variation in these factors is associated with variation in outcomes;
3. To compare the clinical treatment of young men and women who present to the hospital with AMI and determine whether differences in the quality of care may be associated with differences in outcomes;
4. To describe the relationship of female-specific factors including genetic variants, sex hormones, reproductive history, prior use of estrogens, and menstrual cycle history with disease outcomes for women;
5. To develop comprehensive prognostic scores to stratify risk in this young population and identify predictors of early (within 1 month of discharge) and longer-term (1 year) outcomes;
6. To create a blood and DNA repository as a resource for future studies; and
7. To partner with the American Heart Association, the American College of Cardiology, and other national organizations to disseminate findings from the VIRGO Study to improve the prevention, care, and outcomes for young patients with AMI.

The VIRGO study will examine a spectrum of patient and clinical factors, from genetic and biological factors to psychosocial, lifestyle, demographic, and medical care factors that may influence disease trajectories and outcomes in young patients with AMI (Figure 1). The specific research domains were selected on the basis of available evidence from studies of young women as well as literature that has identified sex differences in the presentation, care, and outcomes for older patients with AMI.

Genetics and Biology

Twin and family-based studies of CHD have shown that heredity plays an important role in heart disease for young women. These patients represent a unique phenotype that is probably enriched by a greater prevalence of high-risk genetic profiles than similarly aged men or older women. A study of 21,004 Swedish twins found that premature death from CHD of a female identical twin conferred a 15-fold relative hazard for death from CHD in her cotwin (95% confidence interval, 7.1 to 31.9) after adjustment for other known CHD risk factors as compared with a relative hazard of 8.1 for men. Several early candidate gene studies indicated that genetic polymorphisms may be associated with AMI and ischemic heart disease risk in postmenopausal women but not in men; the impact on risk in premenopausal women has not been investigated. More recently, genome-wide association studies (GWAS) have implicated multiple polymorphisms in the occurrence of premature myocardial infarction, yet their specific impact on risk in young women remains unclear given that young women (especially minority women) were underrepresented in the clinical populations studied. Although a recent analysis involving the Women’s Genome Health Project revealed that the major risk variant in

Figure 1. VIRGO Study Overview.
the 9p21.3 region (rs10757274) does not add substantial incremental value to existing AMI risk prediction models based on traditional cardiac risk factors, it is possible that an allelic risk score based on a multigene panel of GWAS-identified genetic risk variants may have a different impact in young women versus young men with AMI. In addition, little is known for any clinical population of AMI survivors regarding the prognostic value of newly discovered genetic risk factors after the initial event.

Studies suggest that the pathophysiology of disease in young women may be distinct from that of men and older women. Young women with sudden cardiac death are more likely to have coronary plaque erosion, whereas plaque rupture is more common in men and in older women. The prognostic importance of various inflammatory biomarkers, lipid and metabolic measures, and other biomarkers in explaining the excess risk has not been examined in any large study of young AMI patients. Coronary risk factors such as diabetes, heart failure, and previous stroke have been shown to be more common in younger women with MI than men. Sex hormones may play an important role in risk among premenopausal women because younger women may be at greater risk of MI during the menstrual or follicular phase of their ovarian cycle, during which their estradiol blood levels are the lowest; however, these studies have been based on small populations and have not associated these factors with aspects of recovery or outcomes, nor have they been able to adjust for other potentially confounding factors present in younger women. The VIRGO study will be one of the first to examine the relationship of sex hormones, reproductive history, prior use of estrogens, and menstrual cycle history and phase with aspects of recovery and outcomes in a cohort of young premenopausal and perimenopausal women with AMI.

Sociodemographic and Psychosocial Factors

Results from studies of older populations suggest that sociodemographic and psychosocial factors play an important prognostic role for women with AMI. Studies in older women suggest that low socioeconomic class, low educational attainment, and double work loads of employment and family are strong risk factors for post-AMI adverse outcomes. Furthermore, older women with AMI are more likely to be on sick or disability leave, less likely to return to work, and less likely to adhere to cardiac rehabilitation programs than men; however, comparable studies have not been conducted in younger AMI populations. Studies also suggest that depression, marital stress, and lack of social support are important and more powerful risk factors for post-AMI adverse outcomes in older women than in older men. Depressive symptoms are more common among young women hospitalized with AMI, but the role of depression, marital stress, and social support on recovery have not been adequately investigated in young patients with AMI. AMI has also been shown to interfere with sexual relationships and functioning, which can exacerbate depression, marital stress, and impede full post-MI recovery. More is known about the sexual effects of AMI and sexual dysfunction as a precursor to AMI in men than women.

Clinical Risk Factors and Medical History

The prevalence and prognostic importance of traditional and emerging risk factors may differ by sex for young patients with AMI. Studies conducted in older populations suggest that certain risk factors such as smoking, diabetes, glucose intolerance, elevated cholesterol, and left ventricular hypertrophy are more prevalent and associated with greater mortality risk in women than men with CHD. The AMI risk associated with diabetes is particularly important for minority women for whom the prevalence of type II diabetes is 2 to 4 times that of white women. Obstructive sleep apnea and sleeping disorders are associated with cardiac events and are relatively common among patients with coronary artery disease, but little is known about these associations for women and young AMI patients.

Clinical Presentation and Medical Care

Studies have shown that women are less likely than men to present with chest pain and more likely to have other symptoms such as nausea and vomiting during an AMI though little research has examined symptom presentation among young patients with AMI. Differences in presentation and referral may be the cause of longer time to diagnosis and delays (or omissions) in the administration of life-saving therapies such as aspirin, β-blockers, fibrinolytic therapy, and revascularization. Cardiac procedures are performed less often for women with AMI compared with men, but whether sex is independently associated with referral for an indicated procedure is largely unexplored in young populations with AMI. The few studies that have examined sex differences in outcomes after percutaneous coronary intervention procedures in younger patients indicate that young women have higher in-hospital mortality and vascular and bleeding complications than similarly aged men; however, little is known about the long-term outcomes for young patients who undergo these procedures.

Methods

Design Overview

VIRGO will recruit 2000 women and a comparison sample of 1000 men from a large, diverse, national network of hospitals over a 3-year enrollment period. Patients will be enrolled after admission for AMI. Data will be collected during the hospitalization, as well as at 1 and 12 months after hospital discharge. To avoid temporal changes in levels of specific biomarkers due to the acute AMI event, blood will be drawn at 1-month for markers of inflammation, lipids, metabolism, and sex hormones.

Site Network

A research network was established in collaboration with more than 100 U.S. and international hospitals. Hospitals were selected based on the following considerations: commitment to women’s heart health; presence of a committed and enthusiastic research team including a Site Coordinator and Principal Investigator; sufficient representation of women and/or minority patients; geographic location of hospitals across the country; prior experience with participating in a research study or registry; ability to identify potential subjects with AMI using daily screening of
patients with abnormal troponin or CK-MB levels; and feasibility of conducting the study in the hospital.

The VIRGO study is working collaboratively with investigators from Spain (IMJOVEN; plan to enroll 300 women, 150 men) and Australia (VIRGO-Australia; plan to enroll 90 women, 45 men) to develop an additional international cohort of young AMI patients using the instruments and study design from the parent VIRGO project. Replication of VIRGO in Spain and Australia will facilitate identification of cultural, environmental, health care, and health system–related differences in the diagnosis and outcomes for young women and men after AMI.

Study Population and Recruitment

Patients ages 18 to 55 years of age are screened for eligibility on the basis of the most recently adopted AMI criteria.55 To be eligible, participants must have a rise of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit within 24 hours of admission. In addition, there must be evidence of acute myocardial ischemia, including at least 1 of the following: symptoms of ischemia; ECG changes indicative of new ischemia (New ST-T changes; new or presumably new left bundle branch block (LBBB); Development of pathological Q waves); or other evidence of myocardial necrosis (imaging, pathology).

3. PRESENTATION: Must meet one of the following two criteria

- Patient was transferred here from another facility within 24h of original presentation

Exclusion Criteria

Patients are excluded if any of the following criteria were met:

- Previously enrolled in VIRGO
- Non-English/Spanish-speaking
- Inability to provide informed consent
- Inability to contact for follow-up (e.g., no access to phone, not planning on living in the country for next year)
- Acute MI due to chest trauma
- Currently a prisoner
- Other reason

Data Collection Overview

Data will be collected from patient interviews (at baseline, 1 month, and 12 months), physical assessments at baseline, review of the medical record, and the analysis of blood specimens. Enrolled participants will sign a consent form in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and institutional review board regulations. The coordinator at each site will perform the routine screening, enroll eligible participants, administer the baseline interview, collect height, weight, waist, and neck circumference measurements during the index hospitalization, and complete the medical record review. Screening data on all eligible patients will be collected for comparison of enrolled and nonenrolled patients. Blood will be obtained 4 to 6 weeks after hospital discharge for biomarker analyses and storage for future genetic studies. The 1- and 12-month interviews are administered by the Yale Follow-Up Center.
**Medical Record Abstraction**

Information on clinical variables, including cardiac and noncardiac history, vital signs and laboratory results, in-hospital complications, cardiac function testing, data from all procedures, discharge medications, and discharge disposition will be abstracted from the medical chart by the local site coordinator. All site coordinators receive standardized training and certification, and undergo routine assessment from the Yale Coordinating Center. A comprehensive data dictionary is provided to ensure standardization of abstracted data. Several test and procedure reports including the qualifying ECG, CT imaging report, cardiac catheterization, echocardiogram, stress test, and admission and discharge summaries are forwarded to the Yale Coordinating Center where an expert team of reviewers will abstract detailed clinical information.

**Participant Interviews**

Participants are interviewed in person during the index hospitalization by the local site coordinator. The 1-month and 12-month interviews are conducted by field staff from the Yale Follow-Up Center. For Spanish-speaking participants, the baseline, 1-month, and 12-month interviews are completed using linguistically valid translations. All site interviewers receive standardized training and certification and undergo routine assessment from the Yale Coordinating Center.

The specific domains of the data collection instruments are presented in the Table.26,56 – 67 Many of the selected instruments have been included in prior longitudinal studies of patients with AMI.68 Demographic information includes the patients’ address and contact information for follow-up purposes, race/ethnicity, country of origin, marital/relationship status, education level, living situation, employment, income, and monthly finances. Participants are asked about their usual source of health care, satisfaction with the care they receive, difficulty obtaining medical care, insurance coverage, the impact of medical costs on their finances, and beliefs about decision making in the health care setting.61

Clinical information includes the patients’ prodromal and presenting symptoms, medical history, acute symptoms, help-seeking experience, perceived risk, general health,56 cardiovascular functional status,57 sexual activity and function,63 and health-related quality of life.56 For women, information on their menstrual and reproductive history is obtained. Detailed information will be collected for both traditional and novel cardiovascular risk factors including family history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, smoking status, smoking environment, physical activity, alcohol consumption,59 substance abuse, weight change, and sleep disorders.60 Site coordinators will collect physical measurements including height, weight, and hip, waist, and neck circumference during the hospital interview.

Psychosocial variables include stress and major life events within the past year,62,63 social support,65 depression,64 prior depressive episodes and treatment, quality of sexual life, communication with a physician about sexuality or sexual problems,67 marital stress,26 and discrimination.66

Information on clinical management and treatment will be assessed during the index hospitalization as well as during follow-up interviews. Details related to pharmacological treatments (drugs, doses, and timing), invasive interventions (coronary angiography, percutaneous or surgical coronary revascularization), and noninvasive studies received by patients during hospitalization and at discharge will be recorded. Patients will be asked about their current medications, medication adherence, follow-up physician visits (all-cause and cardiac-related), and participation in cardiac rehabilitation programs during the 1- and 12-month interviews.

Study outcomes will be assessed during the follow-up interviews. The primary outcomes are mortality; hospitalization (all-cause and hospitalization for AMI, heart failure, arrhythmia, or angina); and health status as measured by the Seattle Angina Questionnaire57 and the Medical Outcomes Study Short-Form 12-Item Health Survey.56 Secondary outcomes will include the composite of mortality and hospitalization, components of the health status assessments, quality of care, depressive symptoms, outpatient physician visits, admissions at

### Table. VIRGO Study Domains

<table>
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CVD indicates cardiovascular disease; SF-12, Medical Outcomes Study Short-Form 12-Item Health Survey; SAG, Seattle Angina Questionnaire; EQ-5D, EuroQol Group 5-Dimension Self-Report Questionnaire; CAGE, CAGE Questionnaire; Berlin, Berlin Questionnaire; Deber-Kraetschmer, Deber-Kraetschmer Problem-Solving Decision-Making Scale; PSS, Perceived Stress Scale; Life Events, Stressful Life Events; PHQ-9, Patient Health Questionnaire 9-item depression scale; ESSI, Enhancing Recovery in Coronary Heart Disease (ENRICHD) Social Support Inventory; Stockholm, Stockholm Marital Stress Scale; and Everyday, Detroit Area Study Everyday Discrimination Scale.
nonacute care facilities (including home health care, skilled nursing facility, or rehabilitation hospital), and receipt of outpatient diagnostic tests and procedures.

**Blood Collection and Analysis**

Blood will be obtained 4 to 6 weeks after hospital discharge for biomarker analyses and storage for future genetic studies using 1 of the following strategies selected by the VIRGO participant: (1) return to the enrollment hospital for a blood draw arranged by the local site coordinator; (2) receive a blood collection kit by mail that can be brought to the participant’s local physician for a blood draw; or (3) for select locations, receive a visit from a home-health agency to perform an in-home blood draw. Enrolled participants will provide a separate informed consent for blood specimen and DNA storage. A study specific patient identification number will be used on all study materials and will not contain any patient identifying information.

Blood analyses are planned to include lipid profiles (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, Apolipoprotein AI, Lipoprotein(a), and Apolipoprotein B1), glucose, insulin, high-sensitivity C-reactive protein, total homocysteine levels, hemoglobin A1c, estradiol, bioavailable estradiol, estrone, progesterone, follicle-stimulating hormone, sex hormone–binding globulin, and luteinizing hormone.

**Data Management**

We have developed data management procedures using web-based technology to ensure accurate and efficient data collection and analysis, confidentiality, and real-time, on-demand study monitoring reports. Screening and baseline interview data are entered by local site coordinators using an electronic data management system. Follow-up interviews are entered real-time into this system by Yale Follow-Up Center staff. The collection, shipping, and receipt of blood samples are tracked using this online technology. The system has been constructed specifically with the goal of managing multiple, simultaneous, and integrated information from multiple data entry sources. It is validated according to the Code of Federal Regulations and industry standards, and meets other federal standards including those of HIPAA.

**Analyses**

To address the primary objectives of the study, we will compare health outcomes, risk factors, treatment measures, genetic factors, and biomarkers between sex groups. We will report summary results for all collected baseline, treatment, and genetic/metabolic and outcome data by sex, both overall and by racial/ethnic and age subgroups. For each aim, we will use standard parametric and nonparametric techniques for observational data, including t tests, χ² tests, linear regression models, Wilcoxon rank sum tests, and ANOVA. Because patient characteristics, treatment, and outcomes may be correlated within study sites, analyses will account for the effect of clustering of patients within sites. To examine and adjust for differences between comparison groups, we will use linear, logistic, Cox proportional hazard, and Poisson models that either explicitly model intersite correlation or adjust estimated variances, accordingly; for models other than survival models we will primarily use hierarchical generalized linear models to account for correlation of measures within recruitment site. We will develop risk models to examine the differences between men and women and to stratify young women according to risk of adverse outcomes. For each model, we will identify a set of candidate variables based on clinical relevance and the relationship between the variables and the outcome using appropriate statistical techniques according to whether the dependent variable is time to event, other continuous, or binary.

**Sample Size Calculations**

Because survival differences by sex will be smaller and more difficult to detect than other primary outcomes, the sample size was determined by the number of patients needed to detect an absolute difference in 1-year mortality rates between women and men of 2%, assuming a 3% 1-year mortality rate for men. We estimated statistical power to detect the corresponding ratio of hazard rates, after accounting for enrollment rate and annual loss-to-follow-up. We assumed a uniform patient entry rate over the first 3 years, with a total 4-year study period and an annual dropout of 20%. Accounting for the effect of clustering on survival times is problematic; there is no natural or accepted way of partitioning the variance of the hazards A into within- and between-cluster components. To adjust our anticipated sample size for our sampling design, we considered the intrahospital correlation, denoted \( r \), suggested by Xie and Waksman. Using a conservatively inflated value of \( r = 0.05 \), we adjusted the effective sample size by the design effect of \( VIF = 1 + (m-1)r \), where \( m \) is the average number of subjects per hospital. Thus, with 2000 women and 1000 men we will have a power of 82% to detect a 1-year mortality hazard ratio of 1.68 of women relative to men. We anticipate higher prevalence rates for the other outcomes and will have adequate power to detect relative differences between groups.

**Strategies for Dissemination of Research**

We have developed collaborations with the American Heart Association Go Red for Women Movement, the American College of Cardiology, and the National Heart, Lung, and Blood Institute to facilitate the rapid dissemination of information from the study. Reports and publications will be targeted for enrolled participants and their families, participating VIRGO study centers, clinicians, the scientific community, and policymakers. A VIRGO website was developed (www.VIRGOSTudy.org) to provide current information about our progress fielding the study as well as to highlight current research topics about heart disease in young women and men.

**Summary**

Despite perceptions that young women are protected from heart disease, it is one of the leading causes of death in women 55 years and younger, accounting for more than 16 000 deaths annually in the United States. Young women with AMI represent an extreme phenotype of ischemic heart disease that is associated with an excess mortality risk. Even though more than a decade has passed since the publication of initial studies reporting an excess mortality risk for young women with heart disease, there is currently little information about the etiology of premature heart disease or factors that may contribute to this excess risk. The VIRGO study exemplifies outcomes research by combining the disciplines of biology, the social sciences, health services research, and clinical medicine to examine the spectrum of factors, ranging from genetics to bedside, that influence the experience of young AMI patients. The VIRGO study will be the first and most comprehensive study of young women and men with heart attacks to identify the key determinants of recovery and discover knowledge that will assist us in improving their care.

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VIRGO Investigators (Enrolling Participants as of July 15, 2010)

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See online-only Data Supplement for List of VIRGO Coordinators.

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Disclosures
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Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO)

Study Design


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