Chapter 2: Methodology

Identification of Evidence

Data Sources

We searched MEDLINE®, the Cochrane Database and DARE from 1985 through July 2001. We also reviewed the bibliographies of articles fitting our inclusion criteria and asked our expert Technical Expert Advisory Board and Peer Reviewers (Appendix A) to notify us of articles that provide evidence to address the key questions. Articles outside of the above date parameters were included if recommended by our advisors or reviewers.

Search Terms

We developed search terms to identify the outcome variable (i.e., mortality and coronary disease events), the predictors (defined by the individual key questions), and the study design (systematic reviews, Appendix B). We defined coronary disease events as nonfatal myocardial infarction and CHD death. We conducted a separate search for evidence regarding each predictor using the specific search terms listed in Appendix B. Each search used the same search terms for the outcome variable and for systematic review.

For each topic, we searched the databases above for evidence from systematic reviews. To identify evidence regarding the accuracy of diagnostic tests for CHD in women (questions 1.01-1.03), we additionally reviewed large cross-sectional studies. To identify evidence regarding the efficacy of treatments for CHD in women (questions 2.01-2.12), we also sought large randomized clinical trials that provided data on outcomes in women. To identify evidence regarding the strength of the association of traditional risk factors and CHD in women (questions 3.01-3.12), we also sought large prospective cohort studies with multivariate adjustment for potential confounders. To identify evidence regarding the utilization of accurate tests, effective treatments, and risk factor modifications in women compared to men (question 4.0); we also reviewed large prospective cohort and cross-sectional studies with multivariate adjustment for potential confounders. To identify evidence regarding the prognostic value of troponins, creatine kinase myocardial bands, and myoglobin (questions 5.01-5.03); we also sought large prospective cohort studies with multivariate adjustment for potential confounders.

Inclusion Criteria

To be categorized as an article that provides evidence regarding a key question, the article had to address the predictor variable (as defined by the key questions and search terms listed in Appendix B) and the outcome of CHD events or mortality (with the exception of angiographic evidence of atherosclerosis for question 1) and contain data to address the question specifically in women.

Article Identification

An initial search using the terms listed in Appendix B identified articles that potentially provided evidence regarding the key questions. One UCSF-Stanford EPC physician investigator reviewed the titles and excluded those that clearly did not provide data on humans or clearly did not address the key question.

The abstracts of all remaining articles were reviewed independently by two UCSF-Stanford EPC physician investigators, who classified each article using the codes listed below. The two abstractors discussed each abstract and decided by consensus on the code that was entered into the database.

PV – the article clearly does not address the correct predictor variable (as defined by the key question)
OV - the article clearly does not address the correct outcome variable (CHD events or mortality, or for question 1, angiographic evidence of coronary atherosclerosis)
NSR – the article is a review that is clearly not systematic
NH - the article clearly does not include data on humans
NW – the article clearly does not include data on women
E – the article may contain evidence regarding the key question in women

All articles coded E were retrieved and the full text was reviewed independently by two UCSF-Stanford EPC physician investigators using a standardized abstraction form (Appendix C). If the article did not address the key question, did not include data to answer the question in women, or was a review that was not systematic, it was eliminated from further consideration. Articles that addressed a key question in women *and* were a systematic review, large prospective cohort or cross-sectional study with multivariate analysis, or a large randomized trial were classified as eligible for review. Large cohort studies, cross-sectional studies, and randomized trials were those that included 1000 or more participants.

Quality Assessment

We considered any article that addressed a key question in women *and* were a systematic review, large prospective cohort or cross-sectional study with multivariate analysis, or large randomized trial to be *fair quality.*

To be categorized as *good quality*, articles were required to meet the following additional parameters:

Systematic Reviews (questions 4-8 on the abstraction sheet in Appendix C)

- information source appropriate
- information source adequately searched
- inclusion/exclusion criteria clear and appropriate
- data abstraction performed by at least 2 independent reviewers

- principal measures of effect and the methods of combining results appropriate

Randomized Trials (questions 4-8 on the abstraction sheet in Appendix C)
- intervention randomized
- control group received placebo
- participants and research staff blinded to the intervention
- inclusion/exclusion criteria clear and appropriate
- more than 75 percent complete follow-up

Prospective Cohort Studies (questions 4-7 on the abstraction sheet in Appendix C)
- inclusion/exclusion criteria clear and appropriate
- more than 75 percent complete follow-up
- analysis includes multivariate adjustment for potential confounders
- outcome adjudicated blindly

Cross-sectional Studies
For Question 1: Non-invasive diagnostic tests (questions 7-8 on the abstraction sheet in Appendix C)):
- all women who underwent the non-invasive test also underwent angiography
- diagnosis of CAD on angiography made by investigators blinded to results of the non-invasive test

For Question 4: Utilization differences in women and men (questions 4-5 on the abstraction sheet in Appendix C)):
- inclusion/exclusion criteria clear and appropriate
- analysis includes multivariate adjustment for potential confounders

Our searches identified several articles that presented the pooled results of individual level data from multiple randomized trials or cohort studies. We treated these articles as fair quality systematic reviews. We did not rate the quality of cost-effectiveness analyses, decision analyses, evidence reports, or clinical practice guidelines.

Completeness

Determining whether evidence-based reports are complete and up-to-date is difficult. For example, if a good systematic review of randomized trials was completed in 1994 and no additional important randomized trial has been completed, the systematic review can be considered complete. However, if the results of several new trials have been published

and could alter the results of the systematic review, the review may be out-dated. Determination of completeness can only be definitively decided by a formal update of the systematic review.

Data Management and Archive

The titles and abstracts identified by each search were electronically transferred into separate EndNote[17] files identified by key question. The code assigned to each article after review of the abstract was entered in the EndNote file as a keyword. Using the EndNote keyword, articles can be classified by reason for exclusion. Lists of excluded articles categorized by reason for exclusion can be provided on request.

We also constructed a Microsoft Access[18] database that was used to enter data from the abstraction forms completed at review of the full text of articles. This database allows us to track and report the reasons for exclusion of each article for which the full text was reviewed, the type of study (systematic review, randomized trial, cohort, cross-sectional, cost-effectiveness or decision analysis, evidence report and clinical practice guideline), and the number or proportion of eligible articles that were judged good quality.

The full-text articles that were retrieved, along with the completed abstraction sheet and names of the two reviewers for each article are filed by key question in Dr. Grady's offices at the Women's Health Clinical Research Center at UCSF.

Results of Literature Searches

Our systematic reviews identified 6,403 articles that potentially addressed a key question (Figure 1). In addition, we reviewed articles that were recommended by our Technical Expert Advisory Group and Peer Reviewers (Appendix A) or were identified by review of the bibliographies of articles eligible for full text review. We searched the websites of large clinical trials and large cohort studies for additional publications. After review of the titles and abstracts of these articles, we eliminated 5,520 that did not address a key question, did not contain data on women or were a review that was not systematic Thus, we reviewed the full text of 810 articles (Appendix D). Of these, 648 did not address the key question, did not include data to answer the question in women, or were reviews that were not systematic, leaving 162 articles that provide evidence to address the key questions (Evidence Table 1).

The 162 articles that provided evidence in women are characterized with regard to study design and quality as follows:

	Total	Good Quality	Fair Quality
Systematic review	32	17	15
Randomized trial	25	17	8
Prospective cohort	66	59	7
Cross-sectional	39	25	14
Total	162	118	44

Good quality articles are denoted with the superscript "a" in Evidence Table 1. Our searches also identified 21 cost-effectiveness or decision analyses (Appendix E), 43 clinical practice guidelines (Appendix F) and nine evidence reports (Appendix G) which were not rated for quality or reviewed in detail.

Table 2 displays the key question number, the topic of the question, the total number of articles identified, the number of articles for which the full-text was reviewed, the number of articles that provide evidence regarding the key question in women and the number of good quality articles that provide evidence regarding the key question in women.

In total, we reviewed the full text of 272 systematic reviews and 55 randomized trials; only 32 systematic reviews and 25 randomized trials contained evidence on the key question in women. In general, most of authors of systematic reviews and randomized trials that we identified did not perform subgroup analyses in women or ethnic minorities, even though a substantial proportion of participants were women or minorities.

Of the articles that provide evidence to address one of the key questions in women, only 35 percent are systematic reviews or randomized trials. The remaining cohort and cross-sectional studies provide some evidence, but the study designs are susceptible to bias due to confounding.

Summary of Evidence

Hierarchy of Evidence and Completeness of Searches

We assumed that a systematic review of the literature provided the most evidence-based data to address a key question. Thus, we focused our searches by including terms to identify systematic reviews and are confident that we identified all systematic reviews published in English that provide data on any of the five key questions in women.

When systematic reviews were not available, we relied on the findings of individual large randomized trials to address key questions related to treatment (question 2.01-2.12) and risk factor modification (question 3.01b-3.08b). We reviewed articles that were recommended by our Technical Expert Advisory Board and Peer Reviewers (Appendix

A) or were identified by review of the bibliographies of articles eligible for full text review. We additionally searched the websites from large clinical trials for publications.

Key questions concerning the accuracy of non-invasive testing (1.01-1.03), the strength of CHD risk factors (3.01a-3.08a, 3.09-3.12), comparative utilization of diagnostic tests and treatments in men and women (4.0) and the prognostic value of biochemical markers (5.01-5.03) cannot be addressed by randomized trials. When systematic reviews were not available for these key questions, we relied on the findings of individual cohort or cross-sectional studies. We reviewed articles that were recommended by our Technical Expert Advisory Board and Peer Reviewers (Appendix A) or were identified by review of the bibliographies of articles eligible for full text review. We additionally searched the websites from large prospective cohort studies for publications.

For the question concerning utilization of tests and treatments (Question 4), we searched for systematic reviews. When these were not available, we relied on the findings of individual cohort or cross-sectional studies, which were identified during our database searches (Appendix B). We also consulted with our Technical Expert Advisory Board (Appendix A) to identify studies that our searches may have missed.

We tracked all decision and cost-effectiveness analyses (Appendix E), clinical practice guidelines (Appendix F) and evidence reports (Appendix G), that were identified by our searches and advisors, but we did not search specifically for these publication types and did not review these publications to determine if they address a key question in women or include evidence-based recommendations.

Summary of Studies

All good and fair quality studies are summarized. Each reference is preceded by either a "G", indicating a good quality study, or "F", indicating a fair quality study. The reasons that a study is rated only fair quality are stated at the end of each review.

If a randomized trial, prospective cohort study or cross-sectional study was summarized in a systematic review that was included in our analysis, we did not independently report the findings from the primary study.

For each systematic review and randomized trial, we describe the study design, participants, predictor and outcome variables, and the main findings. When possible, we present the findings as odds ratios (OR) or relative risks (RR) with 95 percent confidence intervals (CI) and p-values for all participants combined and for women separately. The general format for presenting the results is demonstrated in the following table:

	All Participants (N=x)			Women (N=x; y% women)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
CHD Event	x.x	x.x-y.y	.xx	x.x	x.x-y.y	.xx

We elected to present data for all participants rather than for men. If there is no evidence of an interaction by gender, the outcome estimate for all participants is the most precise and accurate estimate for all subgroups, including women. When there was evidence of an interaction by gender, or when the manuscript presented only data for men and women separately, we included estimates in the tables for men rather than for all participants.

All identified good and fair quality prospective cohort and cross-sectional studies are listed by key question. The number of cohort studies was large, multiple publications from the same cohort were identified, definitions of the predictor variable were not uniform (i.e., socioeconomic status defined as level of income, education, postal code, etc), duration of observation varied markedly, definition of the outcomes were not uniform and the quality of the studies was much more variable than for randomized trials. Given these problems, we did not describe each cohort study individually, but present a general summary of the overall findings of the cohort studies. For most of the key questions where the evidence comes entirely from cohort studies, the number and size of the studies identified allows us to make clear recommendations concerning the feasibility of conducting a systematic review. Decision analyses and cost-effectiveness analyses, evidence reports and clinical practice guidelines were not reviewed or summarized, but are listed in Appendices E, F and G.

Evidence by Ethnicity

We found very little evidence to address the five key questions in minority populations of women. Where this information is available, it is included in the description of each study and in the summaries of the evidence for each key question.

Abbreviations

The abbreviations and acronyms that were used throughout the review are listed in Appendix H.