Chapter 3: Results

Results by Key Question

QUESTION 1

1. Are there accurate non-invasive approaches to evaluating suspected coronary disease in women? (3 subtopics, labeled 1.01-1.03)

Specifically, what are the summary estimates of sensitivity, specificity, and positive and negative likelihood ratios (using angiographic diagnosis of coronary artery disease as the gold standard) for the following tests, calculated separately for women, for men, and for women restricted to major ethnic groups (Caucasian, African-American, Hispanic, Asian):

1.01 exercise tolerance testing, with and without perfusion imaging (thallium)
1.02 exercise echocardiogram (ECHO)
1.03 coronary artery calcification score

1.01 Exercise testing

G.1. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999;83(5):660-6.[19]

This is a systematic review of the English language literature published from 1966 to 1995 that provided separate estimates of the accuracy of exercise EKG and exercise thallium using planar or tomographic imaging for diagnosis of coronary atherosclerosis in women. Mean weighted estimates of accuracy are given below.

	N Studies	N Women	Sensitivity	Specificity	Likelihood Ratio+	Likelihood Ratio-
Exercise EKG	19	3,721	.61	.70	2.3	0.55
Exercise thallium	5	842	.78	.64	2.9	0.36

These non-invasive tests appear to be only moderately accurate for diagnosis of CHD in women. Exercise thallium appears to be more sensitive but less specific than exercise EKG, resulting in similar likelihood ratios.

From the ten studies that provided data on men, Kwok et al. also calculated the accuracy of exercise EKG in men and found a mean weighted sensitivity of 0.70 and specificity of 0.77, suggesting that exercise EKG is somewhat more accurate in men than in women. A prior meta-analysis,[20] using similar selection criteria, identified 147 studies including 24,074 participants, most of whom were men, and calculated a mean weighted sensitivity and specificity for exercise EKG of 0.68 and 0.77, very similar to that calculated by Kwok, et al. These studies would suggest that the positive likelihood ratio for an abnormal exercise EKG in men is about 3, somewhat higher than the summary estimate of 2.3 reported from the Kwok et al. meta-analysis in women.

Kwok et al. did not calculate a summary estimate for the accuracy of exercise thallium in men, because only two studies included in their meta-analysis included men. A prior meta-analysis using similar inclusion criteria, that identified 56 studies with 6,038 mostly male participants, found a mean weighted sensitivity of exercise thallium of 0.85 and sensitivity of 0.85.[21] Based on these findings, the positive likelihood ratio for an abnormal exercise thallium test in men is 5.7, substantially higher than the summary estimate of 2.9 reported from the Kwok et al. meta-analysis in women.

G.2. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA 1998;280(10):913-20.[22]

The systematic review by Fleischmann et al. reviewed the accuracy of exercise single photon emission computed tomography (SPECT) and exercise echocardiography (see 1.02). The authors searched Medline for English language articles published from 1990 to 1997. The main results are given below (likelihood ratios were calculated from the summary weighted sensitivity and specificity). The sensitivity was high, but the specificity of exercise SPECT was low, resulting in a low positive likelihood ratio.

	N Studies	N Subjects	% Women	Sensitivity	Specificity	Likelihood Ratio+	Likelihood Ratio-
Exercise SPECT	27	3237	30	.87	.64	1.9	0.20

Unfortunately, the analysis does not provide separate estimates of the accuracy of these tests among women. Multivariate analyses suggested that fewer men (more women) in a study was associated with lower accuracy for exercise SPECT.

F.3. Iskandrian AE, Heo J, Nallamothu N. Detection of coronary artery disease in women with use of stress single-photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol 1997;4:329-35.[23]

This cross-sectional study provides data on the accuracy of exercise single-photon emission computed tomography (SPECT) imaging with thallium-201 in 727 men (87 percent with CHD) and 266 women (81 percent with CHD). The definition of an abnormal exercise test was not provided. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

Exercise thallium SPECT	N	Sensitivity	Specificity	Likelihood Ratio+*	Likelihood Ratio-*
Women	266	.72	.69	2.3	.41
Men	727	.92	.70	3.1	.11

*calculated from sensitivity and specificity

The sensitivity of exercise thallium SPECT imaging was lower in women than in men, while the specificity was similar. This resulted in both a lower positive likelihood ratio and a lower negative likelihood ratio for women than for men.

This study was rated fair quality because not all persons who underwent the stress tests had coronary angiography and the manuscript does not state that the angiographers were blinded to the results of the stress tests.

F.4. Miller TD, Roger VL, Milavetz JJ, Hopfenspirger MR, Milavetz DL, Hodge DO, et al. Assessment of the exercise electrocardiogram in women versus men using tomogrphic myocardial perfusion imaging as the reference standard. Am J Cardiol 2001;87:868-73.[24]

This cross-sectional study provides data on the accuracy of exercise EKG testing in 838 men (75 percent with CHD) and 205 women (60 percent with CHD). Patients exercised according to the Bruce or Naughton protocol to severe fatigue, moderate angina or $\geq$2 mm ST depression. An abnormal exercise test was defined as $\geq$1mm horizontal or down-sloping ST depression. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

Exercise EKG	N	Sensitivity	Specificity	Likelihood Ratio+*	Likelihood Ratio-*
Women	205	.53	.69	1.7	.68
Men	838	.63	.74	2.4	.50

*calculated from sensitivity and specificity

The sensitivity of exercise EKG was lower in women than in men, while the specificity was similar. This resulted in a lower positive likelihood ratio for women than for men.

This study was rated fair quality because not all persons who underwent the stress tests had coronary angiography and the manuscript does not state that the angiographers were blinded to the results of the stress tests.

Summary

The accuracy of exercise EKG and exercise thallium (with either conventional or SPECT imaging) for the diagnosis of CHD is lower in women than in men. The accuracy of these tests in women appears to be low due to both poor sensitivity and specificity with positive likelihood ratios ranging from 2 to 3 and negative likelihood ratios of .35 to .70.

1.02 Exercise echocardiogram

G.1. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA 1998;280(10):913-20.[22]

Summary estimates of the accuracy of exercise echocardiogram *in men and women* from the systematic review by Fleischmann et al. (also described in section 1.01) are given below.

	N Studies	N Subjects	% Women	Sensitivity	Specificity	Likelihood Ratio+	Likelihood Ratio-
Exercise ECHO	24	2637	31	.85	.77	3.7	0.19

Unfortunately, the analysis does not provide separate estimates of the accuracy of these tests among women. Multivariate analyses suggested that the average proportion of men in the study did not affect the summary accuracy estimates for exercise echocardiogram.

G.2. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999;83(5):660-6.[19]

Summary estimates of the accuracy of exercise echocardiogram *in women* from the systematic review by Kwok et al. (also described in section 1.01) are given below.

	N Studies	N Women	Sensitivity	Specificity	Likelihood Ratio+	Likelihood Ratio-
Exercise ECHO	3	296	.86	.79	4.29	0.18

Summary

The accuracy of exercise echocardiogram in women appears to be better than either exercise EKG or exercise thallium, but this finding is based on limited data (3 studies including only 296 women). Estimates of the accuracy of exercise echocardiogram among both men and women from the systematic review by Fleischmann et al.[22] are very similar to the estimates among women from the systematic review by Kwok et al.[19] and Fleischmann et al.[22] found no evidence of lower accuracy of exercise echocardiogram in studies that included a higher proportion of women.

1.03 Coronary artery calcification score

G.1. Detrano R, Hsiai T, Wang S, Puentes G, Fallovollita J, Shields P, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 1996;27:285-90.[25]

This cross-sectional study provides data on the accuracy of measures of coronary calcification in 280 symptomatic men and 211 symptomatic women. All participants underwent computed tomographic measures of coronary calcium (method for computing score and range not given) and coronary angiography. Abnormal coronary calcium was defined as a coronary calcium score >0 or <100. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

Calicum score >0	Sensitivity	Specificity	Likelihood Ratio+*	Likelihood Ratio-*
Women				
>55 years old	.98	.31	1.4	.06
≤55 years old	.93	.46	1.7	.15
Men				
>55 years old	.97	.13	1.1	.03
≤55 years old	.92	.30	1.3	.27
Calicum score >100				
Women				
>55 years old	.77	.65	2.2	.35
≤55 years old	.60	.88	5.0	.45
Men				
>55 years old	.86	.51	1.8	.27
≤55 years old	.49	.73	1.8	.70

*calculated from sensitivity and specificity

The overall accuracy of computed tomographic calcium score >0 was low in both men and women. Given the high sensitivity and low negative likelihood ratio of no calcium on computed tomography, a negative test might be useful to rule out CHD in both women and men. The accuracy of a calcium score greater than 100 appears to be low in both men and women. The positive likelihood ratio of a high calcium score in women under 55 appears to be higher than in any other group of men or women, but this probably occurred by chance or due to multiple comparisons.

G.2. Budoff MJ, Shokooh S, Shavelle RM, Kim HT, French WJ. Electron beam tomography and angiography: sex differences. Am Heart J 2002;143:877-82.[26]

This cross-sectional study provides data on the accuracy of measures of coronary calcification in 733 symptomatic men (70 percent with CHD) and 387 women (41 percent with CHD). All participants underwent computed tomographic measures of coronary calcium (method for computing score and range not given) and coronary angiography. Abnormal coronary calcium was defined as a coronary calcium score >0. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

	Sensitivity	Specificity	Likelihood Ratio+*	Likelihood Ratio-*
Women	.96	.57	2.2	.09
Men	.96	.46	1.8	.07

*calculated from sensitivity and specificity

The overall accuracy of computed tomographic calcium score is low in both men and women. Among women, 64 percent had a coronary calcium score of 0 compared to 44 percent of men. Given the high sensitivity and low negative likelihood ratio of a calcium score of 0, a negative test might be useful to rule out CHD in women.

Summary

The overall accuracy of computed tomographic calcium score is low in both men and women. For a calcium score of 0, the sensitivity is high and the negative likelihood ratio is low. Thus, a calcium score of 0 might be useful to rule out CHD in both women and men.

Overall Summary and Recommendations for Question 1

The accuracy of exercise EKG and exercise thallium for the diagnosis of coronary atherosclerosis in women appears to be low with positive likelihood ratios of 2 to 3 and negative likelihood ratios of .35 to .70. The accuracy of exercise echocardiogram appears to be higher than exercise EKG or exercise thallium imaging with a positive likelihood ratio of 4 and a negative likelihood ratio of .2. Based on the review of Fleischmann et al.,[22] exercise echocardiogram also seems to be superior to exercise SPECT.

Two good-quality studies[25, 26] of the accuracy of computed tomographic measures of coronary calcium suggest that a score of 0 has a high sensitivity and low negative likelihood ratio for angiographic coronary disease. Thus, while this test has a low positive likelihood ratio, it might be useful for ruling out disease in both men and women.

While we found two good quality systematic reviews, each is limited. The review by Kwok et al.[19] included only studies published until 1995 using exercise EKG or exercise thallium with planar imaging and the review by Fleischmann, et al.[22] did not estimate the accuracy of noninvasive tests separately for women. Importantly, the systematic reviews do not address the accuracy of current myocardial perfusion imaging technology using thallium and/or technetium agents with SPECT or gated SPECT imaging in women. A

systematic review of the accuracy of current myocardial perfusion imaging for the diagnosis of CHD in women is feasible and could contribute important clinical information.

QUESTION 2

2. Are there effective treatments for women with coronary heart disease? (15 subtopics labeled 2.01-2.12 with secondary and primary prevention considered separately where appropriate)

Specifically, what are the summary estimates of the relative risk or risk reduction for mortality or CHD events for the following potential treatments, calculated separately for women and for women restricted to major ethnic groups (Caucasian, African-American, Hispanic, Asian):

2.01 aspirin
- a. secondary prevention
- b. primary prevention

2.02 beta-blockers
- a. secondary prevention
- b. primary prevention

2.03 angiotensin converting enzyme (ACE) inhibitors
- a. secondary prevention
- b. primary prevention

2.04 calcium channel blockers
2.05 nitrates
2.06 heparin, including low molecular weight heparin
2.07 IIb/IIIa drugs
2.08 thrombolysis
2.09 ticlopidine
2.10 clopidogrel
2.11 angioplasty or stenting (PTCA)
2.12 coronary bypass surgery (CABG)

2.01a Aspirin: secondary prevention

G.1. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994;308(6921):81-106.[27]

The Antiplatelet Trialists' Collaboration provides a systematic review of 145 randomized controlled trials published prior to 1990. Trial selection required that participants were randomized to aspirin and/or dipyridamole or sulphinpyrazone for at least one-month.

The primary outcome was defined as vascular events, including non-fatal MI, nonfatal stroke, and vascular death.

While the systematic review included both primary and secondary prevention trials, gender stratified results for vascular events are only available for high-risk women, defined as those with unstable angina, acute myocardial infarction, prior MI, stroke, transient ischemic attack, or other high risk conditions.

	Men (N=39,417)			Women (N=9,962; 20%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Vascular events	.78	NA	<.0001	.81	NA	<.0001

There was a similar 20 percent reduction in risk of vascular events among both men and women. Compared to high dose therapy (500 – 1500 mg daily), low and intermediate doses of aspirin (< 160 mg/day and 160 –325 mg) were slightly more beneficial, but the 95 percent confidence intervals overlap. In the entire high-risk population (approximately 50,000 individuals), there was no evidence that aspirin increased the risk of non-vascular death or fatal stroke. Evidence on the risks associated with aspirin therapy was not provided separately for women.

G.2. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2(8607):349-60.[28]

The Second International Study of Infarct Survival (ISIS-2) was a randomized trial of the effect of low-dose aspirin and streptokinase on cardiovascular outcomes following acute myocardial infarction. Between 1985 and 1987, 17,187 hospitalized patients in 16 countries were randomized to receive either one hour of intravenous streptokinase or identical placebo. Participants were also randomized to aspirin (162.5 mg daily) or identical placebo (2x2 factorial design); thus, there were four treatment groups: streptokinase alone, aspirin alone, both, or neither. Randomization occurred within 24-hours after the onset of symptoms of an acute MI. The main outcome was vascular death (cardiac, cerebral, hemorrhagic and other vascular deaths) during 5 weeks of follow-up.

	All Participants (N=17,187)			Women (N=3,945; 23%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Vascular death	.77	.70-.85	<.00001	.83	NA*	NA

*figure demonstrates that the 95 percent confidence interval does not cross 1.0.

There appeared to be about a 20 percent reduction in risk of vascular events in women that was similar to the benefit observed in all participants. There were no statistically significant differences in the odds ratios for vascular death among men and women. For both genders combined, the risks of major bleeding and hemorrhagic stroke were not increased with aspirin use. There was a small excess risk of minor bleeding (0.6 percent).

2.01b Aspirin: primary prevention

G.1. de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet 2001;357(9250):89-95.[29]

The Primary Prevention Project was a randomized trial of the effect of low-dose aspirin (100 mg/day) on cardiovascular risk (nonfatal MI, nonfatal stroke and cardiovascular death). All participants were over age 50 years and had at least one major cardiovascular risk factor (hypertension, hypercholesterolemia, diabetes, obesity, family history of premature MI or age ≥ 65 years). The trial was prematurely concluded after 3.6 years due to new information from other studies on the benefits of aspirin therapy, primarily in men.

	All Participants (N=3,012 men; 2,583 women)		
Outcome	RR	95% CI	p-value
Cardiovascular death	.56	.31-.99	NA
Combined endpoint*	.71	.48-1.04	NA
MI	.69	.38-1.23	NA

*cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

The results included in the report were not stratified by gender, but the authors state that the direction and size of the effects were similar in men and women. None of the findings were statistically significant, likely due to early termination of the trial. Participants in the aspirin group were more likely to report major bleeding (1.1 percent vs. 0.3 percent; $p < .001$).

G.2. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351(9118):1755-62.[30]
G.3. Kjeldsen SE, Kolloch RE, Leonetti G, Mallion JM, Zanchetti A, Elmfeldt D, et al. Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid. The HOT study. Hypertension Optimal Treatment. J Hypertens 2000;18(5):629-42.[31]

The Hypertension Optimal Treatment (HOT) trial was a randomized trial among 18,790 persons with hypertension (8,883 women) aged 50-80 years, who were randomized to 75 mg/day of aspirin or placebo and followed for 3.8 years. The main outcome was major cardiovascular events (fatal and nonfatal stroke, MI and all other cardiovascular deaths).

	All Participants (N=18,790)			Women (N=8,883; 47%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	.93	.79-1.09	.36	1.12	.86-1.47	.41
Cardiovascular events	.85	.73-.99	.03	.81	.63-1.04	.10
MI	.64	.49-.85	.0002	.81	.49-1.31	.38

There was a 15 percent reduction in risk of cardiovascular events and a 35 percent reduction in risk of MI in all participants. Risk of death was reduced 7 percent, but this finding was not statistically significant. Among women, mortality was not decreased. Risk of cardiovascular events and of MI was reduced about 20 percent, but these findings were not statistically significant. The risk of fatal bleeding was not increased by aspirin therapy in men or women, but the risk of non-fatal major bleeding was increased in both genders (RR in men 1.6, p-value .01; RR in women 2.1, p-value .006).

G.4. Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Speizer FE, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. JAMA 1991;266(4):521-7.[32]

The Nurses Health Study is a prospective cohort study of risk factors for various diseases. Between 1980 and 1986, 87,678 women aged 34 to 65 years were followed prospectively to determine the association between aspirin therapy (assumed dose 325 mg) and the risk of a cardiovascular event. The primary outcomes were nonfatal MI and CHD death.

The multivariate adjusted relative risks (RR) for cardiovascular events among women taking various numbers of aspirin per week compared to nonusers are as follows:

	Number of Aspirin per Week		
	1-6	7-14	>15
Outcome	RR (95% CI)	RR (95% CI)	RR (95% CI)
Mortality	.86 (.72-1.03)	1.14 (.89-1.47)	.97 (.76-1.23)
Nonfatal MI and CHD Death	.75 (.58-.99)	1.20 (.84-1.69)	.89 (.63-1.27)
Stroke	.99 (.71-1.36)	.83 (.49-1.42)	1.20 (.79-1.83)

Low-dose aspirin (1 to 6 aspirin/week) reduced risk of CHD events about 25 percent and mortality about 15 percent, but higher doses were not associated with benefit and there was no reduction in risk of stroke.

Summary and Recommendations

For secondary prevention, there is good evidence from a systematic review of randomized trials[27] that aspirin therapy reduces risk of cardiovascular events about 20 percent in women with coronary disease or women at high risk for CHD and that the reduction in risk appears to be similar in men and women. This result is supported by the findings of one clinical trial that included a large number of women[28] and found about a 20 percent reduction in risk of cardiovascular events among women admitted to the hospital for suspected MI. However, the systematic review[27] searched the literature only up to 1990, and the authors did not provide detailed information on dose, duration of treatment, subgroups of women (those with prior acute MI, distant MI, unstable angina, etc), specific outcomes in women (MI, stroke, cardiac death, etc) or on the effect of aspirin in low-risk women (primary prevention). The clinical trial[28] provides evidence only for women admitted to the hospital with suspected MI. A more detailed and current systematic review of the data in women is feasible and might provide clinically important information.

Evidence that aspirin is beneficial for primary prevention of cardiovascular disease among women is weak. The systematic review by the Antiplatelet Trialists' Collaboration[27] identified multiple small trials that included about 20,000 persons at "low risk" for vascular events for whom aspirin would be considered primary preventive therapy. However, no information on the number of women in the low risk group or the effect of aspirin in low-risk women was provided. Evidence from the Hypertension Optimal Treatment trial[31] among men and women with hypertension suggests that risk for cardiovascular events was reduced about 20 percent in women taking aspirin but total mortality was not reduced. A second large randomized trial included over 2,500 women,[29] but the results were not stratified by gender and the trial was stopped prematurely providing inadequate power. A large, well-conducted prospective cohort study among women[32] found that aspirin therapy reduced risk of CHD events about 25 percent, but the findings of this study are susceptible to bias due to the observational design. Definitive evidence may be available from the Women's Health Study, a clinical trial that is currently on-going among 40,000 postmenopausal women randomized to 100 mg daily of aspirin versus placebo.

A systematic review of aspirin for primary prevention could provide important evidence, assuming that data stratified by gender could be obtained from earlier small trials, the Primary Prevention Project[29] and the Hypertension Optimal Treatment trial.[31] However, a systematic review should likely await the results of the on-going Women's Health Study, a randomized trial of aspirin therapy among women that may be definitive.

2.02a Beta-blockers: secondary prevention

Outpatient Treatment in Patients with Congestive Heart Failure (CHF)

F.1. Leizorovicz A, Lechat P, Cucherat M, Bugnard F. Bisoprolol for the treatment of chronic heart failure: a meta-analysis on individual data of two placebo-controlled studies--CIBIS and CIBIS II. Cardiac Insufficiency Bisoprolol Study. Am Heart J 2002;143(2):301-7.[33]

This systematic review summarized the results of two randomized controlled trials of the effect of beta-blockers on risk for mortality in persons with CHF. All participants in the Cardiac Insufficiency Bisoprolol Study (CIBIS) and CIBIS II had symptomatic heart failure (New York Heart Association class III or IV) and ejection fraction of less than 40 percent. Participants were randomized to receive up to 10 mg of bisoprolol or identical placebo. The primary outcome was mortality during a mean follow-up of 1.9 years (CIBIS) and 1.3 years (CIBIS II).

	All Participants (N=3,288)			Women (N=627; 19%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	.71	.60-.83	.00003	.62	.40-.97	NA

There was a 30 percent reduction in risk of death among all participants assigned to beta-blockers compared to those assigned to placebo and a similar reduction in risk of death among women.

This study was rated fair quality because there was no systematic review of the literature and inclusion and exclusion criteria were not described.

F.2. Ghali JK, Pina IL, Gottlieb SS, Deedwania PC, Wikstrand JC. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). Circulation 2002;105(13):1585-91.[34]

The Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF) was a randomized trial that assessed the effect of metoprolol on CHF mortality. Participants had New York Heart Association class II-IV heart failure with ejection fraction 40 percent or lower and all received diuretics and ACE inhibitors. Participants were randomized to controlled release/extended release metoprolol (12.5 mg or 25 mg daily) or identical placebo. The primary outcome was mortality during a mean follow-up of one year.

	Men (N=3,093)			Women (N=898; 22%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	.66	.53-.81	.0001	.93	NA*	NS
Mortality or hospitalization	.82	.73-.92	.001	.79	NA	.04

Women appeared to have a smaller reduction in mortality associated with beta-blocker treatment compared to men, but a similar reduction in mortality or hospitalization.

This manuscript also presents a systematic review of data from 3 large randomized trials of beta-blocker therapy for CHF: MERIT-HF (described above in F.2), CIBIS II (described in F.1) and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS). COPERNICUS randomized 2,289 participants with symptomatic heart failure and an ejection fraction of less than 25 percent to carvedilol or placebo. Carvedilol dose was titrated from 3.125 mg to 25 mg twice daily and placebo was similarly titrated. Most participants were also taking diuretics, digoxin and angiotensin converting enzyme inhibitors. The average length of follow-up was 10.4 months.

	Men (N=7,044)			Women (N=1,883)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	.66	.58-.75	NA	.69	.51-.93	NA

In these three trials, there was a statistically significant 30 percent reduction in the risk of mortality associated with beta-blocker treatment in both men and women with CHF. Although the types of beta-blockers used differed in the three trials, there was little evidence of an effect on outcome.

This manuscript was rated fair quality because there was no systematic review of the literature, inclusion and exclusion criteria were not defined and the statistical methods were inadequately described.

Treatment in the Setting of Acute MI

F.3. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trials in post infarction patients. The Beta-Blocker Pooling Project Research Group. Eur Heart J 1988;9(1):8-16.[35]

The Beta-Blocker Pooling Project is a systematic review that included double-blinded, placebo-controlled trials with 200 or more participants who were randomized to beta-blockers within 1 to 45 days after acute MI and followed for at least one year. Nine eligible trials were identified. Beta-blockers differed by trial, and drug doses were within the range for treatment of angina or hypertension. All trials were published by the end of 1983.

	All Participants (N=13,679)			Women (N=2,281; 17%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.76	.66-.87	<.0001	.81	NA	.17

Treatment with beta-blockers after MI reduced risk of death by about 25 percent in all participants. The risk reduction was similar in women, but the findings were not statistically significant, likely due to the small number of women included. The test for homogeneity of outcomes indicated that the results of the trials were not consistent (p = .05), possibly due to differences in the beta-blockers studied.

This systematic review was categorized as fair quality based on the lack of information regarding the methods used, including inclusion criteria, search strategy and data abstraction.

F.4. Olsson G, Wikstrand J, Warnold I, Manger Cats V, McBoyle D, Herlitz J, et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. Eur Heart J 1992;13(1):28-32.[36]

This is a systematic review that includes outcomes from five large double-blind, placebo controlled randomized trials to assess the effect of treatment with metoprolol on mortality after MI. Randomization occurred 1 to 14 days after MI, with follow-up between 3 months and 3 years.

	All Participants (N=5,474)			Women (N=1,121; 20%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.81	NA	.04	.77	NA	NA

Mortality was reduced about 20 percent in all participants. The reduction in mortality was similar among women, but the finding was not statistically significant, likely due to the small number of women included. The ORs were not significantly different in men and women.

This systematic review was categorized as fair quality based on the lack of information regarding the methods used, including inclusion criteria, search strategy and data abstraction.

2.02b Beta-blockers: primary prevention

No systematic reviews or randomized trial that addressed the value of beta-blockers for primary prevention of CHD in women were identified.

Summary and Recommendations

Two small meta-analyses[33] that included data from 4 large randomized trials found that treatment with beta-blockers reduced the risk of mortality by about 30 percent in both men and women with heart failure. There have been approximately 20 randomized trials of the effect of beta-blockers in persons with CHF. Many of these included a small proportion of women, but did not report results specific to women. Since 1996 there have been approximately eleven other systematic reviews of the effect of treatment with beta-blockers in persons with CHF; however, none has presented data specific to women. A systematic review of the CHF literature is feasible and could provide a more accurate estimate of the effect on mortality, assess other outcomes such as hospitalizations and adverse effects, and evaluate outcomes in subgroups of women, such as those with severe CHF.

Based on evidence from two systematic reviews,[35, 36] treatment with beta-blockers shortly after MI in women appears to decrease mortality 20 to 25 percent. However, neither of these reviews was good quality. Both are over 10 years old and provide no data on long-term beta-blocker treatment after MI. It would be useful to update these systematic reviews using currently accepted methodologic standards.

No data addressed the value of beta-blockers for primary prevention of CHD in women.

2.03a Angiotensin converting enzyme (ACE) inhibitors: secondary prevention

Outpatient Treatment in Patients with Congestive Heart Failure (CHF)

G.1. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273(18):1450-6.[37]

The Collaborative Group on ACE Inhibitor Trials is a systematic review of findings from 32 trials (1985-1994) evaluating the effect of angiotensin-converting enzyme (ACE) inhibitors on CHD mortality. All study participants had New York Heart Association class II or greater CHF. The minimum length of follow-up was eight weeks. Twelve trials followed participants for greater than three months.

	Men (N=5,399)			Women (N=1,587; 23%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.76	.65-.88	NA	.79	.59-1.06	NA
Combined endpoint*	.63	.55-.73	NA	.78	.59-1.04	NA

*mortality or hospitalization for CHF

Risk for mortality was reduced about 20 percent in both men and women and risk for mortality or hospitalization was reduced about 30 to 40 percent. However, the results in women were not statistically significant, likely due to the small sample size. The analyses were primarily based on trials with the ACE inhibitor enalapril, although studies with captopril, lisinopril, quinapril, and ramipril were also represented in this review.

G.2. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355(9215):1575-81.[38]

The ACE-inhibitor Myocardial Infarction Collaborative Group provides a systematic review of randomized trials with 1,000 or more participants with left ventricular dysfunction or heart failure after acute myocardial infarction. The five trials included in the pooled analyses are Survival and Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE), Tandolapril in Patients with Reduced Left-ventricular Function after Acute Myocardial Infarction (TRACE), Studies of Left Ventricular Dysfunction (SOLVD) treatment and SOLVD prevention. The trial outcomes were mortality, readmission for CHF, and reinfarction.

	Men (N=10,367)			Women (N=2,396; 19%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.79	.72-.87	NA	.85	.71-1.02	NA
Combined endpoint*	.71	.65-.77	NA	.79	.67-.93	NA

*mortality, readmission for CHF or MI

Risk for mortality was reduced about 20 percent in both men and women. The estimate in men was highly statistically significant, while the estimate in women was only borderline significant, likely due to the smaller sample size. Women also had a statistically significant 20 percent reduction in risk of the combined endpoint.

Outpatient Treatment in Persons at High Risk for Coronary Events

G.3. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342(3):145-53.[39]

G.4. Dagenais GR, Yusuf S, Bourassa MG, Yi Q, Bosch J, Lonn EM, et al. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study. Circulation 2001;104(5):522-6.[40]

G.5. Lonn E, Roccafort R, Yi Q, Dagenais G, Sleight P, et al. Effect of long-term therapy with ramipril in high-risk women. J Am Coll Cardiol 2002;40:693.[41]

All three of these manuscripts are based on findings from the Heart Outcomes Prevention Evaluation (HOPE) trial, a randomized trial to evaluate the effects of ramipril 10 mg/day and vitamin E on cardiovascular outcomes (2x2 factorial design). The first manuscript (Yusuf, et al.) focuses on the main findings, the second (Dagenais et al.) on findings in subgroups at high risk and the third (Lonn et al.) on the results in women. All participants were older than age 55 years, and had vascular disease or diabetes plus one other cardiovascular risk factor, but not congestive heart failure. The trial was terminated after 4.5 years of follow-up due to a beneficial effect of ramipril on CHD outcomes.

	All Participants (N=9,297)			Women (N=2,480; 27%)		
Outcomes	RR	95% CI	p-value	RR	95% CI	p-value
Combined endpoint*	.78	.70-.86	<.001	.77	.62-.96	<.05
MI	.80	.70-.90	<.001	.89	.69-1.17	NA

*cardiovascular mortality, MI, or stroke

Risk for the combined endpoint of cardiovascular mortality, MI or stroke was statistically significantly reduced about 20 percent in all participants and in women. Risk for MI was also about 20 percent lower in all participants and 10 percent lower in women. This finding in women was not statistically significant, likely due to the smaller sample size and lower rate of MI in women (9.4 percent among women in the placebo group vs. 13.2 percent among men).

Inpatient Treatment in the Setting of Probable Acute MI

G.6. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998;97(22):2202-12.[42]

The ACE Inhibitor Myocardial Infarction Collaborative Group analysis provides a systematic review of four randomized trials (Cooperative New Scandinavian Enalapril Survival Study (Consensus-II), Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3), Second International Study of Infarct Survival (ISIS-4), Chinese Cardiac Study (CCS-1)) in which ACE inhibitor treatment was initiated within 36 hours after onset of symptoms of MI. The primary outcome was mortality after 30 days of therapy. All of the trials were conducted between 1990 and 1995. The four included trials studied the ACE inhibitors captopril, enalapril, and lisinopril.

	All Participants (N= 98,496)			Women (N=24,834; 25%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality at 30-days	.93	.89-.98	NA	.95	NA*	NA

*Figure demonstrates that the 95 percent CI overlaps 1.0.

There was a statistically significant but small (7%) reduction in risk of 30-day mortality among all participants. The reduction in risk among women was similar, but not statistically significant, likely due to the smaller number of women studied. Two known side effects of ACE inhibitors, persistent hypotension and renal dysfunction, were also evaluated by gender.

	Men (N=73,637)			Women (N=24,826; 25%)		
Outcome	OR	99% CI	p-value	OR	99% CI	p-value
Hypotension	2.11	1.99-2.23	NA	1.97	1.80-2.15	NA
Renal Dysfunction	2.11	1.73-2.57	NA	1.57	1.14-2.17	NA

Risk for hypotension and for renal dysfunction was increased about 2-fold in both men and women.

Randomized trials not included in the systematic reviews

F.7. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet 1994;343(8906):1115-22.[43]

Between 1991 and 1993, the GISSI-3 randomized trial enrolled 19,394 patients from 200 Italian hospitals. Participants were randomized to lisinopril, nitrates, or open control (2x2 factorial design) within 24-hours after the onset of symptoms of acute MI. Participants assigned to lisinopril received an initial 5 mg dose, which was titrated to 10 mg daily for 6 weeks. The primary outcomes were assessed after 6 weeks and 6 months of follow-up. The short-term results were included in the systematic review described above. This manuscript presents the 6-month findings.

	All Participants (N=19,318)			Women (N=4,276; 22%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.95	NA	NA	.89	NA	NA
Combined endpoint*	.92	.86-.99	NA	.87	.76-1.00	.05

* mortality and clinical CHF

At 6 months, there was no reduction in risk of mortality among all participants or in women. There was a statistically significant 10 percent reduction in risk of mortality and clinical CHF among all participants and among women. Among all participants, persistent hypotension and renal dysfunction were significantly more likely to occur on ACE inhibitor therapy compared to controls (OR for hypotension = 2.48: 95 percent CI , 2.09 – 2.93; OR for renal dysfunction = 2.15; 95 percent CI, 1.58 – 2.92).

This study was given a fair quality rating based on the lack of a placebo control group.

2.03b Angiotensin converting enzyme (ACE) inhibitors: primary prevention

No systematic review or randomized trial that addressed the value of ACE inhibitors for primary prevention of CHD in women was identified.

Summary and Recommendations

Among women with documented CHF, two good systematic reviews[37, 38] suggest that outpatient treatment with ACE inhibitors reduces the risk of mortality 15 to 20 percent.

Results of the HOPE trial[39-41] suggest that outpatient treatment of women with cardiovascular disease or with multiple risk factors results in about a 20 percent reduction in risk of cardiovascular events.

Based on the results of 4 large randomized trials, treatment with ACE inhibitors within 36 hours of acute MI is probably associated with about a 7 percent reduction in risk of mortality in the 30 days after MI, but this small benefit is associated with about a 2-fold increased risk of both hypotension and renal dysfunction.

New systematic reviews of these topics are feasible, but unlikely to provide additional information on use of ACE inhibitors in women.

No data addressed the value of ACE inhibitors for primary prevention of CHD in women.

2.04 Calcium channel blockers

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.

2.05 Nitrates

Inpatient Treatment for Probable Acute MI

F.1. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet 1994;343(8906):1115-22.[43]

Between 1991 and 1993, 19,394 patients (4,191 women) from 200 Italian hospitals were enrolled in the GISSI-3 randomized trial. Participants were randomized to lisinopril or nitrates or open control (2x2 factorial design) within 24 hours of the onset of acute MI symptoms. Participants assigned to nitrates received an intravenous infusion (glyceryl trinitrates) for 24 hours, followed by a transdermal patch (10 mg daily) or isosorbide

mononitrate (50 mg daily). Tolerance to the drug was minimized by removal of the transdermal patch for 10 hours each day. The primary outcomes measured after 6 weeks of therapy included all cause mortality and development of clinical CHF.

	All Participants (N=19,394)			Women (N=4,191; 22%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.94	.84-1.05	.28	.86	NA	NA
Mortality and CHF	.94	.87-1.02	.12	.87	.75-1.01	NA

Among all participants, treatment with nitrates did not result in lower risk for mortality or mortality and CHF. Among women, there appeared to be a trend to reduced risk, but differences in the outcomes between women and all participants are small, suggesting that the effect of treatment with nitrates in women is no different from the overall effect. Women assigned to nitrates were not at a significantly increased risk for persistent hypotension (OR = 1.07; 95% CI, .95 – 1.20).

This study was given a fair quality rating based on the lack of a placebo control group.

G.2. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet 1995;345(8951):669-85.[44]

Between 1991 and 1993, 58,050 patients were enrolled in the ISIS-4 randomized trial within 24 hours of the onset of symptoms of an acute MI. Treatment interventions included oral captopril, oral mononitrates, and IV magnesium sulfate (2x2x2 factorial design). Participants were assigned to one month of oral controlled-release mononitrate therapy (30 mg initial dose titrated to 60 mg daily) or placebo. Total mortality was assessed after 5 weeks of therapy.

	All Participants (N=58,050)			Women* (N=14,990; 26%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.97	.91-1.03	NS	.90	NA	NS

*RR and 95 percent CIs for the main outcome stratified by gender are presented only in a figure and are thus estimated for women.

Nitrate therapy did not reduce risk for mortality among all patients or among women. Differences in the outcomes in all participants compared to women are small, suggesting that the effect of treatment with nitrates in women is no different from the overall effect.

Participants receiving mononitrate therapy were at increased risk for profound hypotension, requiring termination of study treatment (8.1 percent for treatment versus 6.7 percent for placebo; p < .0001).

F.3. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction: the GISSI-3 trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. J Am Coll Cardiol 1996;27(2):337-44.[45]

This follow-up report from the GISSI-3 randomized trial[43] indicates that there were no additional benefits associated with nitrate therapy in all participants or in women after six months of follow-up.

	All Participants (N=19,394)			Women (N=4,191; 22%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.98	NA	NA	.90	NA	NA
Mortality and CHF	.97	.90-1.04	.39	.92	.80-1.05	.22

This study was given a fair quality rating based on the lack of a placebo control group.

Summary and Recommendations

Good evidence from two randomized trials suggests that mortality in women is not reduced after MI by early treatment with nitrates. Further systematic review of the literature related to this question is unlikely to provide clinically useful information.

2.06 Heparin

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.

2.07. Glycoprotein IIb/IIIa Drugs

To Reduce Risk of Coronary Events in Patients Undergoing Percutaneous Coronary Intervention

F.1. Cho L, Topol EJ, Balog C, Foody JM, Booth JE, Cabot C, et al. Clinical benefit of glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC, EPILOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications. Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. J Am Coll Cardiol 2000;36(2):381-6.[46]

In this systematic review, results from three trials, Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG), Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) were pooled to assess the effect of treatment with abciximab on CHD outcomes. Between 1994 and 1998, 1,701 women and 4,824 men were randomized to abciximab or placebo. All participants were undergoing elective or urgent percutaneous coronary intervention. The maximum duration of treatment with abciximab was 12 hours. All participants received aspirin and heparin (either weight-adjusted standard dose or low dose heparin). The primary endpoint was a composite of death, MI and urgent revascularization at 6 weeks and 6 months. The main results are listed below:

	Men (N=4,824)			Women (N=1,771; 37%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality, 1 year	.70	NA	.06	.62	NA	.03
Combined endpoint*						
6 weeks	.51	NA	.001	.51	NA	.001
6 months	.59	NA	<.001	.62	NA	.01

*death, MI and urgent revascularization

Mortality was about 40 percent in women who received IIb/IIIa inhibitors compared to those who received placebo. Risk for coronary events was reduced about 50 percent six weeks after treatment and about 40 percent six months after treatment. There were no statistical differences in the RRs for men and women.

The incidence of major bleeding was not higher in women or men treated with abciximab compared to those treated with placebo.

Our reviewers classified this systematic review as fair because it lacked information regarding inclusion criteria, search strategy, and data abstraction.

To Reduce Risk of Coronary Events in Persons with Acute Coronary Syndromes

G.2. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359(9302):189-98.[47]

This systematic review included all randomized trials that: 1) included persons admitted to the hospital with acute coronary syndromes but without persistent ST elevation on EKG; 2) compared a glycoprotein IIb/IIIa inhibitor with placebo or control; 3) recommended against early coronary revascularization during study drug infusion and 4) enrolled at least 1000 patients. Six trials were identified that fit the inclusion criteria (PRISM, PRISM-PLUS, PARAGON-A, PARAGON-B, PURSUIT, GUSTO-IV ACS)

and individual patient data were obtained from each. The six trials enrolled 31,402 participants (10,991 women) from 41 countries and used 4 different glycoprotein IIb/IIIa inhibitors. In all trials, glycoprotein IIb/IIIa inhibitors were started within 12 to 24 hours of onset of symptoms and continued for 48 to 120 hours. In most of the trials, all participants were treated with aspirin and standard dose heparin. Outcomes at 30 days are given below:

	Men (N=20,388)			Women (N=11,013; 35%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.83	.71-.96	NA	1.08	.89-1.33	NA
Death or MI	.81	.75-.89	NA	1.15	1.01-1.30	NA
Major bleeding	1.6	1.3-2.0	NA	2.2	1.6-2.9	NA

Among treated men, mortality was reduced 17 percent and death or MI 19 percent at 30 days. Among women, risk for death or MI was increased 15 percent. Risk for major bleeding was increased about 2-fold in both genders. The difference in ORs for mortality and death or MI between men and women was highly statistically significant. There were multiple differences between men and women participants at baseline: on average, women were older, more likely to have diabetes, heart failure and ST depression on admission, less likely to have elevated CKMB concentrations and less likely to have had coronary revascularization or MI. However, sex differences in the effect of glycoprotein IIb/IIIa inhibitors remained after adjusting for these baseline differences. There was no interaction with level of CKMB, but both men and women with elevated baseline troponins (measured on only 34 percent of men and 37 percent of women) appeared to benefit from treatment with glycoprotein IIb/IIIa inhibitors while those without elevated troponins did not.

	Participants with elevated troponins (T or I $\geq$ 1 µg/L)					
	Men (N=7,002)			Women (N=4,057; 37%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.75	.55-1.04	NA	.80	.53-1.21	NA
Death or MI	.82	.65-1.03	NA	.93	.68-1.28	NA

Glycoprotein IIb/IIIa inhibitors increased major bleeding complications, and this increased risk appeared to be higher in women than in men. There was no increased risk for intracranial hemorrhage or stroke.

PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome events in a Global Organization Network; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression using Integrilin Therapy; GUSTO-IV ACS = Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes

Summary and Recommendations

A fair-quality, relatively recent systematic review[46] that included data from 3 large randomized trials of the effect of glycoprotein IIb/IIIa inhibitors in women undergoing percutaneous coronary interventions found a 40 to 50 percent reduction in risk of death, MI and urgent revascularization at 6 weeks to 6 months, and a 40 percent reduction in mortality at one year. There appears to be no difference in the effect of these drugs in men and women who are undergoing percutaneous coronary intervention.

Among women admitted to the hospital for acute coronary syndromes, the effect of glycoprotein IIb/IIIa inhibitor treatment is not clear. A good quality, recent systematic review[47] that included data from 6 large randomized trials of the effect of glycoprotein IIb/IIIa inhibitors in women admitted to the hospital with acute coronary syndromes found that women did not benefit from treatment. The risk of mortality or MI was statistically significantly increased by 15 percent at 30 days of follow-up and there was a highly statistically significant interaction between gender and the effect of glycoprotein IIb/IIIa inhibitors. In a subset of about 1/3 of both men and women in whom troponins were elevated, treatment appeared to reduce risk of mortality about 20 to 25 percent in both men and women. However, these findings are not statistically significant, are based on subset analyses in women with elevated troponins, and there does not appear to be a similar benefit in women with elevated CPKs.

New systematic reviews of these topics are feasible, but are unlikely to add important clinical information.

2.08 Thrombolysis

Thrombolysis compared to placebo or control

G.1. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet 1994;343(8893):311-22.[48]

This systematic review includes pooled data from nine trials including 58,600 patients (13,855 women) hospitalized for suspected myocardial infarction or unstable angina. The trials included in this analysis were published between 1986 and 1993. Participants were randomized to receive fibrininolytic therapy with streptokinase, anistreplase, tissue plasminogen activator or urokinase versus open control or placebo. In most trials participants received both aspirin and heparin. The primary outcome was mortality during the first 35 days after treatment.

	All Participants (N=58,600)			Women (N=13,855; 24%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality						
day 1	1.26	1.13-1.38	NA	1.13	NA	NA
day 35	.82	. 77-.87	NA	.88	NA*	NA
Stroke, day 35	1.5	NA	NA	1.6	NA	NA
Major bleed, day 35	2.75	NA	NA	2.8	NA	NA

* figure shows that 95 percent CI did not cross 1.0

In both women and men, thrombolysis was associated with excess mortality on the first day of treatment, but a statistically significant 20 percent reduction in risk of mortality by 35 days after treatment. There were no statistically significant differences between the risk reductions observed for women and men. Because the absolute risk of mortality was higher for women than for men (5.5 percent vs. 3.2 percent in the control group on the first day of treatment and 16.0 percent vs. 10.1 percent by 35 days after treatment), the absolute risk during the first day was higher in women (7 vs. 1 per 1000) and the absolute benefit by 35 days greater than in men (27 vs. 20 per 1000). Mortality may have been higher in women than in men because the women were older and were more likely to have experienced a delay in treatment, both major risk factors for mortality.

The overall risks of stroke and major bleeding were increased similarly in both men and women and were highest during the first day of therapy.

Thrombolysis compared to PTCA for acute MI

F.2. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, et al. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. Am J Cardiol 1995;75(15):987-92.[49]

The Primary Angioplasty in Myocardial Infarction (PAMI) trial was a randomized trial to compare CHD outcomes in participants with acute MI randomized to tissue plasminogen activator (100 mg) and subsequent conservative therapy or immediate PTCA. Between 1990 and 1992, 395 participants (107 women) were enrolled within 12 hours of onset of anginal symptoms. The primary outcome was in-hospital mortality and acute MI. Major findings comparing immediate PTCA to thrombolysis are as follows:

	Men (N=288)			Women (N=107; 27%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
In-hospital						
mortality	.60	NA	.46	.29	NA	.07
MI	.36	NA	.06	.57	NA	.64

Mortality and risk of MI were lower among both men and women with symptoms of acute MI treated with immediate PTCA compared to those treated with tissue plasminogen activator. However, none of the outcomes were statistically significant, probably because the trial was too small.

No strokes occurred among either men or women in the PTCA group, while 2.8 percent of men and 5.3 percent of women experienced a stroke in the tissue plasminogen activator group. All of the strokes in women were hemorrhagic. Among patients assigned to tissue plasminogen activator, mortality in women was higher than in men (14.0 vs. 4 percent); there was no difference in mortality rates among women and men assigned to PTCA. At baseline, women were, on average, 8 years older than men and more likely to have diabetes, hypertension, history of CHF and had a longer interval of time between onset of symptoms and randomization. After multivariate adjustment for these risk factors, gender was no longer predictive of mortality with tissue plasminogen activator ($p = .25$).

This trial was rated fair quality because it was not blinded.

Summary and Recommendations

A systematic review of 9 large randomized trials[48] demonstrates that thrombolysis reduces the risk of 5-week mortality in women and men hospitalized with suspected acute MI about 15 percent. Thrombolysis resulted in about a 50 percent increased risk of stroke and a nearly 3-fold increased risk of major bleeding in both men and women.

One small trial suggested that PTCA may be more effective than thrombolysis for reducing in-hospital mortality in women and much less likely to cause hemorrhagic stroke,[49] but none of the relative risk estimates were statistically significant.
The systematic review is somewhat out of date. An updated review might be useful by providing more complete estimates for the effects of thrombolysis in women, but is unlikely to alter the major findings.

2.09 Ticlopidine

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.

2.10 Clopidogrel

To Reduce Risk of Coronary Events in Persons with Acute Coronary Syndrome

G.1. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345(7):494-502.[50]

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study was a randomized trial to assess the effect of clopidogrel among persons with acute coronary syndromes (hospitalization for ischemic symptoms without ST-elevation). Between 1998 and 2000 12,562 patients (38 percent women) were randomized to clopidogrel (300mg loading dose, followed by 75mg/day) or placebo within 24-hours of the onset of acute coronary symptoms. Treatment continued for 3 to 12 months. All participants also received daily treatment with aspirin (75-325 mg). The primary outcome was death from cardiovascular causes, nonfatal MI, or stroke.

	All (N=12,562)			Women (N= 4,836; 38%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Primary Events*	.80	.72-.90	<.001	.89	.NA	NA**

*Death from cardiovascular causes, nonfatal MI, or stroke
**figure demonstrates that 95 percent CI crosses 1.0.

Among all participants, there was a highly statistically significant 20 percent reduction in risk of cardiovascular death, nonfatal MI or stroke among those assigned to clopidogrel. The reduction in risk was about 10 percent in women and was not statistically significant. The risk of a major bleeding was 38 percent higher for participants receiving clopidogrel (p = .001); however risks for life-threatening bleeding complications and hemorrhagic strokes were not increased.

To Reduce Risk of Coronary Events in Patients Undergoing Percutaneous Coronary Intervention

G.2. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358(9281):527-33.[51]

PCI-CURE is a randomized trial comparing the effect of extended treatment with clopidogrel among a subset of CURE participants who underwent percutaneous coronary intervention (PCI). All participants received open-label treatment with aspirin (75-325 mg/day) and were randomized to clopidogrel (300mg loading dose, followed by

75mg/day) or placebo within 24-hours of the onset of acute coronary symptoms. Those who underwent PCI had blinded study medication stopped and received 2-4 weeks of open label treatment after PCI with either clopidogrel or ticlopidine. They were then restarted on blinded study medication that continued for 3 to 12 months. Thus, the main comparison is between short-term treatment with clopidogrel or ticlopidine (2 to 4 weeks) after PCI compared to long-term treatment (3 to 12 months). The risk of death from cardiovascular causes, nonfatal MI, or stroke was assessed among 2,658 participants (30 percent women) who underwent PCI.

	All (N=2,658)			Women (N=804; 30%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Primary Event*	.70	.50-.97	.03	.77	.52-1.15	NA**

*Death from cardiovascular causes, nonfatal MI, or stroke
**figure demonstrates that 95 percent CI crosses 1.0.

In this subgroup analysis, risk for death from cardiovascular causes, nonfatal MI or stroke was statistically significantly reduced 30 percent among all participants. Among women, the risk reduction was about 20 percent and was not statistically significant. The risk of bleeding following PTCA was not increased by treatment with clopidogrel.

Summary and Recommendations

Results from the CURE trial [50] suggest that 2 to 4 weeks of treatment with clopidogrel among women with acute coronary syndromes probably reduces risk of cardiovascular events and death about 10 to 20 percent. This benefit was associated with about a 40 percent increased risk of major bleeding, but risks for life-threatening bleeding complications and hemorrhagic stroke were not increased. Prolonged treatment (3 to 12 months) with clopidogrel among women undergoing percutaneous coronary intervention[51] also appears to reduce risk of cardiovascular events and death about 20 to 30 percnet more than brief treatment (2 to 4 weeks). However, these estimates of benefit are based only on the results of one trial, the effects in women were uniformly lower than in men, and the results were not statistically significant. Treatment with clopidogrel among persons undergoing PCI was not associated with serious adverse side effects.

A systematic review of the effect of clopidogrel on CHD outcomes in women is not feasible given that only one major randomized trial has been published.

2.11 Percutaneous transluminal coronary angioplasty (PTCA) and stenting

Angioplasty compared to medical management in patients with CHD

F.1. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. Lancet 1997;350(9076):461-8.[52]

RITA-2 was a randomized trial to compare long-term CHD outcomes following PTCA to medical management in patients with CHD. Patients were required to have coronary disease that was suitable for either PTCA or medical management and a significant stenosis of at least one major coronary vessel that appeared technically amenable to PTCA. Participants were not required to have symptoms of angina. Between 1992 and 1996, 1,018 participants (183 women) were enrolled. The primary outcome was death plus nonfatal MI after an average of 2.7 years of follow-up. Major findings, comparing PTCA to medical management are presented below:

	All (N=1,018)			Women (N=183; 18%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	1.6	NA	.32	NA		
Death + nonfatal MI	1.9	1.08-3.41	.02	NA		
CABG	1.4	NA	NA	NA		

Among all patients, risk of death or nonfatal MI was 90 percent higher among those randomized to PTCA compared to those randomized to medical therapy. The authors state that there were no differences in the primary outcome by gender, but no quantitative estimates are given. Both men and women were less likely to experience grade 2 or worse angina (Canadian Cardiovascular Society) during the first six months following PTCA (in women: 22.8 percent PTCA versus 39.8 percent medical management, in men: 20.5 percent PTCA versus 31.4 percent medical management). However, these differences in prevalence of angina in the treatment groups were markedly attenuated over time such that there was no difference in prevalence of angina by 3 years of follow-up.

This trial was rated fair quality because it was not blinded.

Angioplasty compared to CABG for treatment of symptomatic multivessel coronary disease

G.2. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. Lancet 1995;346(8984):1179-84.[53]

The Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI) was an international randomized trial comparing CABG and PTCA for 1,054 patients with symptomatic multivessel coronary disease. Recruitment began in 1988 and continued for 53 months. The primary outcomes were angina (Canadian Cardiovascular Society class >1) and mortality after one year of follow-up. Major findings comparing PTCA to CABG are presented below:

	All (N=1,054)			Women (N=234; 22%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	1.42	.73-2.76	.30	NA	NA	NA
Nonfatal MI	1.42	.80-2.54	.23	NA	NA	NA
Angina	1.54	1.09-2.16	.01	3.12	1.4-6.5	.002
Revascularization	5.23	3.9-7.0	<.001	NA	NA	NA

For both genders combined there were no significant differences in risk of death or nonfatal MI between the CABG and PTCA groups. Overall, PTCA was associated with an increased risk for clinically significant angina and with a marked increased risk of undergoing another revascularization procedure within one year. Among women, the prevalence of angina after 1 year was 3-fold higher with PTCA compared to CABG. In contrast, men were about 50 percent more likely to experience angina after PTCA compared to CABG but this difference between men and women was not statistically significant (p for interaction = .052). Other risk estimates for women were not presented.

Angioplasty compared to thrombolysis for acute MI

F.3. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, et al. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. Am J Cardiol 1995;75(15):987-92.[49]

The Primary Angioplasty in Myocardial Infarction (PAMI) trial was a randomized trial to compare CHD outcomes in participants with acute MI randomized to tissue plasminogen activator (100 mg) and subsequent conservative therapy or immediate PTCA. Between 1990 and 1992, 395 participants (107 women) were enrolled within 12 hours of the onset of anginal symptoms. The primary outcome was in-hospital mortality and acute MI. Major findings comparing immediate PTCA to thrombolyis are as follows:

	Men (N=288)			Women (N=107; 27%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
In-hospital mortality	.60	NA	.46	.29	NA	.07
MI	.36	NA	.06	.57	NA	.64

Mortality and risk of MI were lower among both men and women with symptoms of acute MI treated with immediate PTCA compared to those treated with tissue plasminogen activator. However, none of the outcomes were statistically significant, probably because the trial was too small.

No strokes occurred among either men or women in the PTCA group, while 2.8 percent of men and 5.3 percent of women experienced a stroke in the tissue plasminogen activator group. All of the strokes in women were hemorrhagic. Among patients assigned to tissue plasminogen activator, mortality in women was higher than in men (14.0 vs. 4 percent); there was no difference in mortality rates among women and men assigned to PTCA. At baseline women were, on average, 8 years older than men and more likely to have diabetes, hypertension, history of CHF, and had a longer interval of time between onset of symptoms and randomization. After multivariate adjustment for these risk factors, gender was no longer predictive of mortality with tissue plasminogen activator (p = .25).

This trial was rated fair quality because it was not blinded.

Prospective Cohort Studies

We reviewed eight prospective cohort studies that assessed the association between PTCA and CHD outcomes. The findings from these studies indicate that women are at higher risk than men for in-hospital mortality following PTCA.[7, 54-58] Possible explanations for this observation include older age, more severe underlying disease and anatomical differences, such as smaller vessel size and decreased body surface area, which may predispose women to an increased risk of death in the post-procedure period.[58] Longer term clinical success rates following PTCA were also measured in several cohorts.[7, 55, 56, 59] In these studies, the main measure of clinical success was the probability of survival following PTCA (1 year to 10 years). Between 70 and 90 percent of all patients survived during this time interval. Survival rates did not differ by gender; however, women were as much as 78 percent more likely than men to experience symptoms of angina during long-term follow-up.[7]

G.4. Holmes DR, Jr., Holubkov R, Vlietstra RE, Kelsey SF, Reeder GS, Dorros G, et al. Comparison of complications during percutaneous transluminal coronary angioplasty from 1977 to 1981 and from 1985 to 1986: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. J Am Coll Cardiol 1988;12(5):1149-55.[54]

G.5. Kelsey SF, James M, Holubkov AL, Holubkov R, Cowley MJ, Detre KM. Results of percutaneous transluminal coronary angioplasty in women. 1985-1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry. Circulation 1993;87(3):720-7.[7]

G.6. Weintraub WS, Wenger NK, Kosinski AS, Douglas JS, Jr., Liberman HA, Morris DC, et al. Percutaneous transluminal coronary angioplasty in women compared with men. J Am Coll Cardiol 1994;24(1):81-90.[55]
G.7. Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann FJ, Schomig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. JAMA 2000;284(14):1799-805.[56]
F.8. Bell MR, Holmes DR, Jr., Berger PB, Garratt KN, Bailey KR, Gersh BJ. The changing in-hospital mortality of women undergoing percutaneous transluminal coronary angioplasty. JAMA 1993;269(16):2091-5.[57]
G.9. Ellis SG, Roubin GS, King SB, 3rd, Douglas JS, Jr., Shaw RE, Stertzer SH, et al. In-hospital cardiac mortality after acute closure after coronary angioplasty: analysis of risk factors from 8,207 procedures. J Am Coll Cardiol 1988;11(2):211-6.[58]
F.10. Shaw LJ, Miller DD, Romeis JC, Kargl D, Younis LT, Chaitman BR. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994;120(7):559-66.[14]
F.11. Bell MR, Grill DE, Garratt KN, Berger PB, Gersh BJ, Holmes DR, Jr. Long-term outcome of women compared with men after successful coronary angioplasty. Circulation 1995;91(12):2876-81.[59]

Coronary stenting

No studies were identified that provided data on the efficacy of coronary stenting to reduce risk of CHD events in women.

Summary and Recommendations

Evidence regarding the efficacy of PTCA to reduce the risk of CHD events in women is weak. For treatment of patients with symptomatic coronary artery disease who are suitable for PTCA or medical therapy, one small trial including only 183 women suggests that PTCA is more likely to result in death or nonfatal MI at 3 years than medical management, but no specific estimates were given for women.[52] PTCA did appear to be superior to medical management for relief of angina in the first 6 months, but there was no difference in symptoms after 3 years of follow-up.

One trial,[53] including only 234 women, suggested that CABG and PTCA have similar effects on risk for CHD events at one year after the procedure among women with symptomatic multivessel coronary disease. In women, PTCA was associated with 3-fold higher rates of angina at one year compared to CABG, but quantitative estimates among women for other outcomes were not given.[53]

For treatment of patients during acute MI, one small trial including only 107 women suggested that PTCA may be more effective than thrombolysis for reducing in-hospital mortality in women (70 percent reduction) than in men (40 percent reduction), and much less likely to cause hemorrhagic stroke,[49] but none of the relative risk estimates were statistically significant.

Whether PTCA is superior to medical management or CABG for management of CHD in women is very important and currently unanswered. However, there appears to be insufficient data to conduct a definitive systematic review of these questions.

2.12 Coronary artery bypass graft surgery

CABG surgery compared to medical therapy for treatment of symptomatic coronary disease

G.1. Davis KB, Chaitman B, Ryan T, Bittner V, Kennedy JW. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS registry study. Coronary Artery Surgery Study. J Am Coll Cardiol 1995;25(5):1000-9.[60]

This is a prospective cohort study based on the Coronary Artery Surgery Study Registry of men and women with operable symptomatic coronary disease who were treated with either medical therapy or CABG surgery at one of 15 medical centers in the US between 1974 and 1979. The main outcomes were 8 and 15-year survival, based on 6,018 men and 1,095 women who were initially managed medically, and 6,922 men and 1,291 women who were initially managed surgically. Operative mortality was 2.5 percent among men and 5.3 percent among women (P<.0001). Multivariate adjusted relative risks for 8-year survival comparing medical management to CABG surgery are given below:

	Men (N=12,940)			Women (N=2,386; 16%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
8-year survival						
single vessel disease	1.07	NA	<.05	1.05	NA	>.05
double vessel disease	1.17	NA	<.05	1.13	N A	<.05
triple vessel disease	1.41	NA	>.05	1.56	NA	<.05

At 8 years, both men and women with double or triple vessel CHD appear to have improved survival, with the largest benefit in those with triple vessel disease. At 15 years, there were no differences between survival rates for medical and surgical management in either men or women, but 75 percent of all of the men and 72 percent of the women had undergone CABG surgery at 15 years.

CABG surgery compared to angioplasty for treatment of symptomatic multivessel coronary disease

G.2. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. Lancet 1995;346(8984):1179-84.[53]

The Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI) was an international randomized trial comparing CABG surgery and PTCA for 1,054 patients with symptomatic multivessel coronary disease. Participant recruitment began in 1988 and continued for 53 months. The primary outcomes were angina (Canadian Cardiovascular Society class >1) and mortality after one year of follow-up. Major findings comparing PTCA to CABG surgery are presented below:

	All (N=1,054)			Women (N=234; 22%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	1.42	.73-2.76	.30	NA	NA	NA
Nonfatal MI	1.42	.80-2.54	.23	NA	NA	NA
Angina	1.54	1.09-2.16	.01	3.12	1.4-6.5	.002
Revascularization	5.23	3.9-7.0	<.001	NA	NA	NA

For both genders combined there were no significant differences in risk of death or nonfatal MI between the CABG surgery and PTCA groups. Overall, PTCA was associated with an increased risk for clinically significant angina and with a marked increased risk of undergoing another revascularization procedure within one year. Among women, the prevalence of angina after 1 year was 3-fold higher with PTCA compared to CABG surgery. In contrast, men were about 50 percent more likely to experience angina after PTCA compared to CABG surgery, but this difference between men and women in effect of the procedures on angina was not statistically significant (p for interaction = .052). Other risk estimates were for women were not presented.

G.3. Jacobs AK, Kelsey SF, Brooks MM, Faxon DP, Chaitman BR, Bittner V, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). Circulation 1998;98(13):1279-85.[61]

The Bypass Angioplasty Revascularization Investigation (BARI) was a randomized trial to assess the effect of CABG surgery compared to PTCA among 1,829 participants (489 women; 27 percent) with angina or myocardial ischemia and multivessel coronary disease amenable to both CABG surgery and PTCA. The average length of follow-up was 5 years.

Data from this article are difficult to interpret because only crude rates are presented. Relative risk estimates, confidence intervals and p-values were not provided. The authors note that the risk for in-hospital MI was significantly reduced among women who underwent PTCA compared to CABG surgery (4.8 vs. 9.8 percent; p=.03). In men, rates of in-hospital MI were also lower among those randomized to PTCA compared to CABG surgery (2.4 vs. 4.6 percent), but this comparison was presumably not statistically significant, as no p-value was given. No information on 5-year outcomes among women is presented.

Summary and Recommendations

Evidence regarding the efficacy of CABG surgery to reduce the risk of CHD events and death in women is limited. One large cohort study[60] suggests that despite a high perioperative mortality rate (5.3 percent), 8-year survival is improved in women with double or triple vessel coronary disease who undergo CABG surgery compared to initial medical management. By 15 years of observation, the majority of women (72 percent) had undergone CABG surgery and there was no difference in long-term survival among those initially treated surgically compared to those initially treated medically. The results of this study may be biased by differences in risk between patients who are chosen to undergo CABG surgery compared to those chosen to receive medical therapy.

Randomized trials to compare the effectiveness of CABG surgery and PTCA provide little evidence regarding the relative effectiveness of these procedures in women. The Coronary Angioplasty versus Bypass Revascularisation Investigation[53] suggests that neither revascularization procedure is superior with regard to mortality or CHD outcomes in women, but that CABG surgery is more effective than PTCA in relieving angina and is less likely to be followed by additional revascularization procedures.

Coronary artery bypass surgery is a major procedure that is associated with substantial perioperative morbidity, mortality and expense. It is not clear that a systematic review of the data regarding the efficacy of this procedure for preventing CHD events in women is feasible. However, this topic is very important given the potential benefits and risks of bypass surgery in women. Given this, we recommend that a systematic review be attempted. If data are inadequate to provide definitive answers, additional research should be conducted.

QUESTION 3

3. What are the risk factors for coronary heart disease in women, does modifying these risk factors result in reduced risk for coronary heart disease events, and what are the most effective methods for modifying these risk factors? (20 subtopics labeled 3.01-3.12 with subtopic as a risk factor for CHD or treatment/modification of a risk factor for CHD prevention considered separately where appropriate)

3.01 hypertension:
- a. as a risk factor
- b. treatment

3.02 diabetes
- a. as a risk factor
- b. treatment

3.03 hyperlipidemia (high LDL, triglycerides, Lp(a), low HDL)
- a. as a risk factor
- b. treatment

3.04 homocysteine
- a. as a risk factor
- b. treatment

3.05 C-reactive protein
- a. as a risk factor
- b. treatment

3.06 cigarette smoking
- a. as a risk factor
- b. smoking cessation

3.07 obesity
- a. as a risk factor
- b. weight reduction to reduce risk

3.08 inactivity
- a. as a risk factor
- b. exercise

3.09 age

3.10 age at menopause

3.11 ethnicity

3.12 socioeconomic status

3.01a Hypertension as a risk factor for CHD in women

We identified no systematic reviews that addressed the strength of hypertension as a risk factor for CHD outcomes in women.

Prospective Cohort Studies

Data from the Nurses' Health Study[62] and from the Framingham Heart Study[63] suggest a 2 to 3-fold increased risk of coronary heart disease events among women with hypertension, after adjustment for other CHD risk factors. However, the evidence from these two studies is not convincing. In the Nurses' Health Study,[62] hypertension was self-reported and blood pressure was not measured. The report from the Framingham Heart Study[63] provides no definition of hypertension and no confidence intervals or p-values for the reported risk estimates. Among women in the Copenhagen City Heart Study, [64], isolated systolic hypertension (SBP $\geq$ 160 mm Hg and DBP < 90 mm Hg) was not associated with an increased risk of MI (RR = 0.8; 95 % CI, 0.3 – 2.0), but women with diastolic hypertension (DBP > 90 mm Hg) were 1.7 times more likely than normotensive women to have a MI (95 % CI, 1.1 – 2.8). In the Walnut Creek Cohort, [65] the risk all-cause mortality (excluding accidental death) was 1.6 times higher among premenopausal women with high blood pressure compared to those without. The risk of all-cause mortality was not significantly higher among postmenopausal women with high blood pressure compared to those without.

G.l. Fiebach NH, Hebert PR, Stampfer MJ, Colditz GA, Willett WC, Rosner B, et al. A prospective study of high blood pressure and cardiovascular disease in women. Am J Epidemiol 1989;130(4):646-54.[62]
G.2. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA 1996;275(20):1571-6.[63]
F.3. Nielsen WB, Vestbo J, Jensen GB. Isolated systolic hypertension as a major risk factor for stroke and myocardial infarction and an unexploited source of cardiovascular prevention: a prospective population-based study. J Hum Hypertens 1995;9:175-80.[64]
F.4. Perlman JA, Wolf PH, Ray R, Lieberknecht G. Cardiovascular risk factors, premature heart disease, and all-cause mortality in a cohort of Northern California women. Am J Obstet Gynecol. 1988;158:1568-74.[65]

3.01b Treatment of hypertension to reduce risk of CHD events in women

Systematic Reviews

F.1. Gueyffier F, Boutitie F, Boissel JP, Pocock S, Coope J, Cutler J, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. Ann Intern Med 1997;126(10):761-7.[66]

This systematic review from the Individual Data Analysis of Antihypertensive intervention trials (INDANA) pooled data from seven large randomized trials that studied the effect of treatment for hypertension on CVD outcomes. All trials were conducted between 1972 and 1990. Only trials that enrolled both men and women were included. Results from only 7 of 15 published clinical trials were included in this review, but these 7 trials represent 97 percent of all participants in the 15 trials. Drug interventions included thiazide diuretics and/or beta-blockers. The primary outcomes were fatal and nonfatal cardiovascular events among hypertensive men and women aged 30 to 84 years.

	Men (N=19,975)			Women (N=20,802; 68%)		
Outcome	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Mortality	.88	.80-.97	.01	.91	.81-1.01	.09
Fatal CHD events	.83	.71-.97	.02	.92	.74-1.16	.48
Major CHD events	.82	.73-.92	<.001	.85	.72-1.01	.06

Among treated hypertensive men, there was a statistically significant 12 percent reduction in risk of mortality, a 17 percent reduction in risk of fatal CHD events, and an 18 percent reduction in risk of major coronary events. While none of the risk estimates in women were statistically significant, there were strong statistical trends suggesting that the patterns of risk reduction for mortality (9 percent reduction) and major coronary events (15 percent reduction) were similar to those in men. There was no evidence of an interaction between treatment effect and gender (p >.10).

This manuscript was given a fair quality rating because it did not describe the search or data abstraction methods.

G.2. Quan A, Kerlikowske K, Gueyffier F, Boissel JP. Efficacy of treating hypertension in women. J Gen Intern Med 1999;14(12):718-29.[67]
Quan A, Kerlikowske K, Gueyffier F, Boissel JP. Pharmacotherapy for hypertension in women of different races. Cochrane Database Syst Rev 2000(3):CD002146.[68]

This is a systematic review of the findings of 11 randomized trials that studied the effect of treatment for hypertension on risk for CVD events in women. Clinical trials were included if they met the following criteria: publication between 1966 and 1998, more than 100 women, hypertension was defined, the intervention was a drug, the control group received a placebo or standard care, and the outcomes included CVD events. CHD outcomes included all cause mortality, fatal CHD events and all CHD events (fatal and nonfatal). Interventions included diuretics, beta-blockers, calcium channel blockers, and clonidine. After adjustment for baseline risk factors, the findings were as follows.

	Women 30-54 years (N=8,565)			Women ≥ 55 years (N=17,604)		
Outcome	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Mortality	.92	.68-2.79	NA	.89	.77-1.02	NA
Fatal CHD	1.47	.78-4.76	NA	.84	.65-1.08	NA
CHD events*	.80	.56-2.86	NA	.82	.67-1.01	NA

*fatal and nonfatal events

None of the effects of treatment were statistically significant. However, there were strong trends to reduced risk of mortality, fatal CHD and CHD events in older women. Among younger women, the pattern of risk reduction for mortality and CHD events was similar to that among women 55 or older, but the confidence intervals were much wider. There was no statistical evidence of an interaction between treatment effect and age.

	White Women (N=22,963)			African-American Women (N=3,206)		
Outcome	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Mortality	.98	.85-1.13	NA	.59	.44-80	NA
Fatal CHD	.95	.73-1.23	NA	.71	.40-1.25	NA
CHD events	.88	.72-1.08	NA	.61	.42-.89	NA

Among white women, there was no evidence that treatment reduced risk. In contrast, treatment was associated with a 30 to 40 percent reduction in the risk of mortality and CHD events among African-American women. These risk reductions were statistically significant among African-American women, despite the relatively small number included in the trials. There was statistical evidence of interaction of the effects of treatment and race on total mortality (p =.003).

Randomized Trials Not Included in the Systematic Reviews

F.3. Wang J, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. The Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med 2000;160:211-20.[69]

Syst-China was a randomized trial to test the effect of treatment for isolated systolic hypertension on CVD outcomes. Between 1988 and 1991, 2,394 persons age 60 or older (36 percent women) with systolic blood pressures between 160 and 219 mm Hg, were randomized to active treatment (nitrendipine plus captopril, and/or hyrochlorothiazide) or placebo. The median follow-up time was 3 years.

	Men (N=1,541)			Women N=853)		
Outcome	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Mortality	.74	.50-1.09	.12	.34	.16-.72	.005

The treatment-by-sex interaction approached statistical significance (p = .06), indicating that the mortality benefit associated with treatment of isolated systolic hypertension may be greater in women than in men.

Summary and Recommendations

Hypertension as a Risk Factor for CHD in Women

Results of four large cohort studies[62-65] suggest that hypertension, especially diastolic hypertension, is associated with a 1.6 to 3-fold increased risk for coronary heart disease events in women. Substantial additional data regarding the association of high blood pressure and CHD outcomes in women could likely be obtained from the placebo groups followed in large clinical trials of treatment for hypertension. Based on these data, a systematic review and meta-analysis would likely be feasible. Summary estimates of the effect of blood pressure on CHD risk could be important in helping to identify the women who are most likely to benefit from therapy.

Treatment of Hypertension to Reduce Risk of CHD Events in Women

The best evidence regarding the effect of treatment of hypertension on risk for CHD events among women comes from two systematic reviews. The systematic review by the INDANA investigators[66] suggests that treatment of hypertension in women results in small reductions in risk of mortality (9 percent) and CHD events (15 percent), but the findings were not statistically significant. The systematic review by Quan et al.[67] found

strong statistical trends to reduced risk of mortality (11 percent), fatal CHD events (16 percent) and all CHD events (18 percent) among women over age 55 years, but not among younger women. These differences between younger and older women may be due to the small number of events that occurred in younger women. The systematic review by Quan et al.[67] also provides the only evidence regarding treatment of hypertension in women by race. Although relatively few black women were included in the trials, they experienced a statistically significant reduction in risk of mortality (41 percent) and of CHD events (39 percent). There was no evidence of benefit among white women, and there was statistical evidence that the effect of treatment on mortality differed in white and black women. The findings of the Syst-China trial[69] suggest that treatment of isolated systolic hypertension may reduce the risk of mortality by as much as 65 percent in elderly Chinese women. The reason for this difference in the effect of treatment of hypertension between races is not clear.

Repeating the two relatively recent systematic reviews is unlikely to add additional clinical information.

3.02a Diabetes as a risk factor for CHD in women

Systematic Reviews

F.1. Orchard TJ. The impact of gender and general risk factors on the occurrence of atherosclerotic vascular disease in non-insulin-dependent diabetes mellitus. Ann Med 1996;28(4):323-33.[70]

This is a systematic review of the results from 12 prospective cohort studies published between 1980 and 1993 that address the association between non-insulin dependent diabetes and CHD events in men and women. Diabetes was defined by glucose tolerance testing, medication use, or medical history. The main outcomes were CHD death and MI. Follow-up ranged from 2 to 30 years. The authors did not calculate summary estimates comparing risk for CHD death among diabetic and nondiabetic men and women. Instead, they calculated a summary relative risk comparing the risk for CHD events among women to that among men.

	RR	95% CI
CHD death		
Diabetics	1.47	1.09-1.99
Nondiabetics	2.52	1.91-3.34
MI		
Diabetics	1.75	1.23-2.49
Nondiabetics	1.92	1.36-2.79

The findings suggest that men diabetics and non-diabetics have a higher risk for CHD events than women. The increased risk associated with male sex is about 2 to 2.5-fold for nondiabetics, but only 1.5 to 2-fold for diabetics. The narrowing of the male disadvantage with respect to CHD risk suggests that diabetes is a stronger risk factor for CHD in women than in men. These findings are limited because the outcomes of the individual studies were not adjusted for other predictors of CHD events, and there was significant between-study heterogeneity of the findings.

This study was rated fair quality based on the lack of a systematic literature search.

G.2. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care 2000;23(7):962-8.[71]

This is a systematic review of 10 prospective cohort studies published between 1966 and 1999 evaluating the association between diabetes and CHD risk. The criteria for inclusion were prospective cohort studies that provided data on the risk of CHD events in both men and women with diabetes. Diabetes was diagnosed by self-report, physician diagnosis, treatment with insulin or oral hypoglycemic agents, or random or fasting glucose measures. The primary outcome was CHD mortality. Follow-up time ranged from 4 to 36 years.

	Men			Women		
	RR*	95% CI	p-value	RR*	95% CI	p-value
CHD death	1.85	1.47-2.33	NA	2.58	2.05-3.26	NA

*summary RR comparing risk for CHD death among diabetics to nondiabetics

These results suggest that risk for CHD death is increased 2.6-fold in diabetic women compared to nondiabetic women and 1.8-fold in diabetic men compared to nondiabetic men. While many of the individual studies provided outcomes adjusted for other predictors of CHD risk, the meta-analytic techniques used to calculate summary estimates included only unadjusted estimates.

Cohort Studies Not Included in the Systematic Reviews

We reviewed data from four cohort studies, including the Framingham Heart Study[72-74] and the Nurses Health Study.[75, 76] The findings suggest that diabetes is associated with a 1.5 to 3-fold increased risk of CHD events in women after adjustment for other risk factors. The relative risk of CHD events among women with diabetes appears to be almost twice that of men with diabetes.[72, 74] However, there is considerable variation in the levels of other CHD risk factors among men and women in these studies making evaluations of gender differences difficult.

G.3. Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. JAMA 1988;260(23):3456-60.[72]
G.4. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication, and risk of cardiovascular events. The Framingham Study. Diabetes 1989;38(4):504-9.[73]
G.5. Kannel WB, D'Agostino RB, Wilson PW, Belanger AJ, Gagnon DR. Diabetes, fibrinogen, and risk of cardiovascular disease: the Framingham experience. Am Heart J 1990;120(3):672-6.[74]
G.6. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 1991;151(6):1141-7.[75]
G.7. Donahue RP, Goldberg RJ, Chen Z, Gore JM, Alpert JS. The influence of sex and diabetes mellitus on survival following acute myocardial infarction: a community-wide perspective. J Clin Epidemiol 1993;46(3):245-52.[77]
G.8. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 2000;102(9):1014-9.[78]
G.9. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med 2001;161(14):1717-23.[76]

3.02b Treatment of diabetes to reduce risk of CHD events in women

There were no systematic reviews or randomized trials identified that addressed the effectiveness of treatment of diabetes to reduce risk of CHD events in women.

Summary and Recommendations

Diabetes as a Risk Factor for CHD in Women

The systematic review by Orchard et al.[70] suggests that the relative risk for CHD events is higher among women than among men diabetics, but does not provide an estimate of the summary relative risk in women. The systematic review by Lee et al.[71] reported that risk for CHD death was about 2.6-fold higher among women diabetics compared to non-diabetics. This increase in risk appears to be higher than that associated with diabetes in men (1.8-fold increased risk). One explanation for the higher risk among women than among men diabetics is that diabetes is, by mechanisms that are not clear, more harmful in women than in men. Alternatively, women diabetics may be more likely to have other CHD risk factors, or more severe CHD risk factors than men diabetics. The summary estimates calculated by Lee et al.[71] were based on unadjusted findings and do not address this issue. In addition, the systematic review by Lee et al.[71] does not include the results

from several studies that were analyzed in the earlier systematic review by Orchard et al.[70] It is feasible to update these systematic reviews and to calculate comparable, adjusted relative risk estimates in men and women diabetics. An adjusted analysis may provide clinically and scientifically important evidence to determine if diabetes has more harmful effects on CHD risk in women or is more likely to be associated with other risk factors in women.

Treatment of Diabetes to Reduce Risk of CHD Events in Women

There was no evidence regarding the efficacy of treatment of diabetes to reduce the risk of CHD events in women.

3.03.a Hyperlipidemia as a risk factor for CHD in women

Total, LDL- and HDL-cholesterol, and triglycerides

F.1. Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. Ann Epidemiol 1992;2(1-2):161-76.[79]

This systematic review includes the findings of 22 United States (US) and international cohort studies presented at a workshop at the National Heart Lung and Blood Institute in 1991. Inclusion criteria were measurement of serum cholesterol, follow-up for CHD events, explicit criteria for CHD outcomes and availability of results stratified by gender, age and ethnicity. The review includes 90,349 women, 891,882 men, and data stratified by ethnicity among approximately 348,600 men who were screened for the Multiple Risk Factor Intervention Trial (MRFIT) (316,000 white, 22,000 black, 6,600 Hispanic and 4,000 Asian men). Findings were summarized separately by gender, age at the time of lipid measurements (less than 65 years versus 65 years and older) and, where possible, ethnicity. The majority of the participants in these studies did not have CHD at the beginning of the study, but had either elevated cholesterol or other risk factors for CHD. Unadjusted relative risks for CHD mortality were summarized.

	Summary Relative Risk (95% CI)			
Sex and Age	Total Cholesterol*	LDL-C*	HDL-C*	Triglycerides*
Women				
<65 years	2.44†	3.27†	2.13†	1.98†
≥65 years	1.12	1.13	1.75†	1.39†
Men				
<65 years	1.73†	1.92†	2.31†	1.16†
≥65 years	1.32†	1.51†	1.09	1.24†

*RR compares those with total cholesterol <200 to ≥ 240 mg/dL; those with LDL-cholesterol <140 to ≥ 160 mg/dL , those with HDL-cholesterol ≥ 60mg/dL to < 50, and those with triglycerides < 100 mg/dL to ≥ 130 mg/dL.
† p<.05 for unadjusted comparisons

For women less than 65 years old, risk for CHD death increased with higher total cholesterol, LDL-C and triglycerides and with lower HDL-C. For women and men less than 65 years old, the increased relative risk associated with elevated total cholesterol, LDL-C and triglycerides was higher for women than for men, while the increased risk associated with low HDL-C was similar. Among older men, CHD mortality was increased with higher total cholesterol, LDL-C and triglycerides, but not with lower HDL-C. Among older women, only low HDL-C and high triglycerides were associated with increased risk.

No specific risk estimates were given for minority populations, but relative risks associated with elevated total cholesterol were said to be similar for white, black, Hispanic and Asian middle-aged and older men based on data from the MRFIT screenees.

This study was rated as fair because it did not provide information on how the cohorts included were identified or selected for inclusion. In addition, the summary estimates may be biased because the comparisons are not adjusted for potential confounding factors.

F.2. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, et al. Report of the Conference on Low Blood Cholesterol: Mortality Associations. Circulation 1992;86(3):1046-60.[80]

This systematic review includes the findings of 11 US and international cohort studies presented at a workshop at the National Heart Lung and Blood Institute in 1992. The purpose of this workshop was to investigate the association of low blood cholesterol and risk for non-cardiovascular death. Inclusion criteria were not stated. The review includes 124,814 women and 523,737 men, most of whom did not have CVD at the start of the studies. The main outcomes were death, CVD death, cancer death, and non-CVD, non-cancer death. When possible, adjusted outcomes from each individual cohort were used

to calculate the summary estimates. Results for the men included in the MRFIT screenees were presented separately because they constituted 67 percent of the population.

Total Cholesterol (mg/dL)	Relative Risk*			
	All death	CVD death	Cancer death	Non-CVD, non-cancer
MEN				
<160	1.17†	1.04	1.18†	1.32†
160-199	1.00	1.00	1.00	1.00
200-239	1.00	1.16†	.95	0.89†
≥240	1.14†	1.48†	.95	0.87†
MRFIT MEN				
<160	1.17†	0.89	1.23†	1.48†
160-199	1.00	1.00	1.00	1.00
200-239	1.05†	1.31†	.95	0.87†
≥240	1.22†	1.86†	.91†	0.84†
WOMEN				
<160	1.10	0.96	1.05	1.41†
160-199	1.00	1.00	1.00	1.00
200-239	0.94	0.95	1.01	0.92
≥240	0.97	1.09	0.97	0.82†

*comparing total cholesterol of 160-199 mg/dL to the other categories and excluding deaths that occurred in the first 5 years of follow-up
†p-value less than .05

Among men, risk for death was increased 15 to 20 percent and risk for CVD death was increased 50 to 80 percent among those with total cholesterol ≥240 mg/dL. Among men with cholesterol <160 mg/dL, risk for cancer death was increased about 20 percent and risk for non-CVD, non-cancer death was increased 30 to 50 percent. There were no statistically significant associations between total cholesterol levels and any cause of death among women, except that risk for non-CVD, non-cancer death was increased among women with cholesterol levels <160mg/dL.

This study was rated as fair because it did not provide information on how the cohorts included were identified or selected for inclusion.

G.3. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3(2):213-9.[81]
G.4. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 1998;81(4A):7B-12B.[82]

These two manuscripts report the results of a systematic review of population-based international studies, published between 1965 and 1994, that assessed the correlation between triglyceride levels and risk for CVD (CVD death, CHD death, and MI). Inclusion criteria were prospective cohort design, population-based sampling, and a fasting triglyceride measurement. Seventeen studies provided data on men (N=46,413), with an average duration of follow-up of 8.4 years. Five studies provided data on women (N=10,864), with average duration of follow-up of 11.4 years. Six studies with men (N= 22,293) and two studies with women (N = 6,345) provided risk estimates adjusted for other potential confounders, including HDL-cholesterol level. Most participants in these studies did not have CVD at the start of the studies.

	Men (N=46,413/22,293)			Women (N=10,864; 19%/6,345; 22%)		
Outcome	OR*	95% CI	p-value	OR*	95% CI	p-value
CVD events						
unadjusted	1.32	1.26-1.39	NA	1.76	1.50-2.07	NA
adjusted	1.14	1.05-1.28	NA	1.37	1.13-1.66	NA

*per 1 mmol/L increase in triglyceride level

Risk of CVD events among men and women was correlated with triglyceride levels. The increased cardiovascular risk associated with elevated triglycerides appeared to be higher in women (about 40 percent increase in CVD risk per 1 mmol/L increase in triglyceride level) compared to men (about 15 percent increase per 1 mmol/L increase in triglyceride level).

Lipoprotein (a)

F.5. Craig WY, Neveux LM, Palomaki GE, Cleveland MM, Haddow JE. Lipoprotein(a) as a risk factor for ischemic heart disease: meat-analysis of prospective studies. Clin Chem 1998;44(11):2301-6.[83]

This is a systematic review of observational studies on the association between lipoprotein a (Lp(a)) and risk for CHD. The articles in this review were published between 1991 and 1997, and included persons without known CHD. The average length of follow-up was between 1 and 15 years. The outcomes were fatal and nonfatal CHD. The 12 cohort and nested case-control studies included in this review included 11,105 men. Three studies provided data on women (N = 547). The summary outcome was expressed as the ratio of Lp(a) level in mg/dL among cases and controls.

The overall association between Lp(a) and risk of ischemic heart disease was similar for males and females (case:control ratio = 1.42; 95% CI 1.21 – 1.63 in men, and case:control ratio = 1.32; 95% CI 1.19 – 1.45 in women). Adjustment for age, blood pressure, body mass index, smoking, and lipoprotein-related variables did not modify the significance of this relation. However, there was considerable between-study variability

in Lp(a) case:control ratios (p for heterogeneity < .001). Among women, the dose response relation between Lp(a) and ischemic heart disease was equivocal.

This study was rated fair quality because it did not describe the inclusion criteria or methods for independent data abstraction.

3.03b Treatment of hyperlipidemia to reduce risk of CHD events in women

F.1. Walsh JM, Grady D. Treatment of hyperlipidemia in women. JAMA 1995;274(14):1152-8.[84]

Primary and secondary prevention trials published between 1971 and 1994 were included in this systematic review of the effectiveness of interventions to lower cholesterol in women. The outcomes were total and CHD mortality. The authors identified three primary prevention trials and six secondary prevention trials. However, only two of the primary prevention trials, and three of the secondary prevention trials, included adequate data for inclusion in the meta-analyses. Interventions studied in the two primary prevention trials included low-saturated fat diet and colestipol. The interventions included in the three secondary prevention trials included clofibrate and simvastatin. Summary estimates of relative risks were calculated using standard meta-analytic methods.

	Primary Prevention (N=5,848)			Secondary Prevention (N=1,048)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	1.15	.90-1.46	NA	1.17	.70-1.96	NA
CHD Mortality	1.03	.62-1.70	NA	.36	.25-.52	NA

For primary prevention, there was no effect of treatment on CHD or total mortality. Given the small number of outcome events, there may have been inadequate power to detect differences. Also, two of the primary prevention trials were conducted in institutionalized populations that may not be representative of healthy women. For secondary prevention, there was a statistically significant 64 percent reduction in risk of CHD mortality among treated women, but no reduction in overall mortality.

This study was rated fair quality because it did not describe inclusion criteria or a blinded review of the findings.

F.2. Byington RP, Jukema JW, Salonen JT, Pitt B, Bruschke AV, Hoen H, et al. Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation 1995;92(9):2419-25.[85]

This is a systematic review of the data from four randomized, blinded, placebo controlled trials using pravastatin for reduction of cholesterol among persons with CHD and mildly to moderately elevated cholesterol. Outcomes were mortality and MI.

	All (N=1,891)			Women (N=67)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	.54	.25-1.09	.17	NA	NANA	
MI	.48	.20-.63	.001	NA	NA.04	

Only 4 MIs occurred among the women assigned to pravastatin and none in the placebo group. Thus, these 4 randomized trials of pravastatin provide no information on the effect of lipid-lowering in women.

This review was rated fair quality because it did not provide a clear description of search methods, inclusion criteria or methods for extracting data.

F.3. Buchwald H, Campos CT, Boen JR, Nguyen P, Williams SE, Lau J, et al. Gender-based mortality follow-up from the Program on the Surgical Control of the Hyperlipidemias (POSCH) and meta-analysis of lipid intervention trials. Women in POSCH and other lipid trials. Ann Surg 1996;224(4):486-98; discussion 498-500.[86]

This is a systematic review of lipid intervention trials. All trials were published between 1971 and 1994. Among the seven primary and secondary prevention trials included in the review, interventions were diet, clofibrate, colestipol, simvastatin, pravastatin, and ileal bypass surgery. Primary and secondary prevention trials were not analyzed separately.

	Men (N=11,173)			Women (N=7,077)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	.81	.67-.98	.03	.89	.60-1.32	.56

The findings suggested a 20 percent reduction in risk of mortality among men treated with cholesterol-lowering interventions, but no benefit in women.

The results from the Program On Surgical Control of the Hyperlipidemias (POSCH) were also presented in this report. Treatment with partial ileal bypass surgery in women did not reduce the risk of overall mortality, CHD mortality, or CHD events (CHD mortality or

nonfatal MI). In contrast, risk of CHD death and CHD death or nonfatal MI were significantly reduced among men in the surgical intervention group.

This review was rated fair quality because it did not provide a clear description of methods for searching or extracting data from identified studies.

G.4. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999;282(24):2340-6.[87]

This is a systematic review of five clinical trials published between 1966 and 1998 on the effect of statin therapy on CHD risk. The criteria for inclusion were: treatment with statin drugs or placebo, at least 4 years of follow-up and clinical disease or death as the primary endpoint. The review included three secondary prevention trials (4S, CARE, LIPID) and two primary prevention trials (WOSCOPS and AFCAPS/TEXCAPS). Standard meta-analytic methods were used to calculate the following summary estimates.

	All (N=30,817)			Women (N=3,916;13%)		
Outcome	RR	95% CI	p-value	RR	95% CI	p-value
Mortality	.79	.72-.86	NA	NA	NA	NA
Major CHD events	.69	.64-.74	<.001	.71	.58-.87	<.001

Results were not stratified by primary and secondary prevention. There was about a 30 percent reduction in risk of major CHD events in all participants and in women treated with statins. Risk for total mortality was decreased in men treated with statins, but no data regarding total mortality in women was provided, probably because the number of women studied was relatively small.

4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events trial; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; WOSCOPS = West of Scotland Coronary Prevention Study; AFCAPS/TEXCAPS = Air Force/Texas Coronary Artherosclerosis Prevention Study

Clinical Trials Not Included in the Systematic Reviews

G.5. Miettinen TA, Pyorala K, Olsson AG, Musliner TA, Cook TJ, Faergeman O, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 1997;96(12):4211-8.[88]

This manuscript provides additional data on women included in the Scandinavian Simvastatin Survival Study (4S). Main findings of the 4S were included in each of the three systematic reviews described above. 4S was a randomized trial that studied the effect of treatment with simvastatin on the risk of coronary events in persons with CHD. Between 1988 and 1989, 4,444 high-risk patients (827 women) from 94 clinical centers were randomized to simvastatin or placebo. All participants (age 35 – 70 years) had a

history of angina pectoris or myocardial infarction, and elevated serum cholesterol. The treatments were titrated between 10 mg and 40 mg, to achieve the goal LDL-cholesterol levels of 115-200 mg/dL. Outcomes were total mortality and major coronary events (coronary death, nonfatal definite or probable MI, silent MI or resuscitated cardiac arrest). The trial was stopped prematurely after a mean follow-up of 5.4 years, due to evidence of benefit with treatment.

	Men (N=3,617)			Women (N=827; 19%)		
Outcome	RR*	95% CI	p-value	RR*	95% CI	p-value
Mortality	.65	.53-.80	<.001	1.16	.68-1.99	.58
CHD death	.55	.43-.71	<.001	.86	.42-1.74	.67
Major CHD events	.66	.58-.75	<.001	.66	.48-.91	.01

Both men and women had a statistically significant 34 percent reduction in risk of major CHD events. However, men also had a statistically significant 35 to 45 percent reduction in risk of CHD death and total mortality. Similar benefits were not observed in women. The interaction between treatment and gender for the mortality outcome was not statistically significant. Overall, there was no difference between the treatment groups in other causes of death or side effects.

G.6. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,538 high-risk individuals: a randomized placebo controlled trial. Heart Protection Study Collaborative Group. Lancet 2002; 360:7-22.[89]

The MRC/BHF Heart Protection Study was a randomized trial to assess the effect of cholesterol-lowering on CHD outcomes. Between 1994 and 1997, 20,536 participants (5082 women) with known CHD, other occlusive arterial disease or diabetes were randomly assigned to simvastatin (40 mg daily) or identical placebo. The average length of follow-up was 5 years.

	All (N=20,536)			Women (N=5,082; 25%)		
Outcome	RR	95% CI	*P*-Value	RR	95% CI	*P*-Value
Mortality	.87	.81-.94	.0003			
Major vascular event*	.76	.72-.81	<.001	.81	NA	NA**

*Coronary death, nonfatal MI, stroke, coronary or non-coronary revascularization
**figure demonstrates that 95% CI does not cross 1.0.

The findings from this study indicate that, among men and women with known CHD or at high risk for CHD, treatment with simvastatin significantly lowers cardiovascular event rates by approximately 25 percent, regardless of pretreatment cholesterol levels. The risk of myopathy associated with treatment was about 0.01 percent.

Summary and Recommendations

Hyperlipidemia as a Risk Factor for CHD in Women

Evidence regarding the association of abnormal lipoprotein levels and CHD risk in women is inconclusive. The systematic review by Manolio et al.[79] suggests that the pattern of risk associated with hyperlipidemia in middle-aged women is similar to that for middle-aged men (increased risk for CHD mortality with higher total cholesterol, LDL-C and triglycerides, and with lower HDL-C). However, the pattern of risk among older women appears to be different than in men (i.e., CHD risk was increased among older men with higher total cholesterol and LDL-C, but not in older women). In addition, CHD risk was increased among older women with low HDL-C and high triglycerides, but not among older men with these lipid abnormalities. There are several limitations to the review by Manolio et al.,[79] including an outdated and incomplete literature search and the lack of adjusted results. Evidence provided by the systematic review by Jacobs et al.[80] is not very helpful, as summary data was provided only for total cholesterol levels. The systematic review by Hokanson, et al.[81] and Austin et al.[82] strongly suggests that elevated triglyceride level is a risk factor for CVD, and that this elevated risk is higher in women than in men.

The suggestion that the pattern of risk associated with lipoprotein abnormalities in women is different than in men could be clinically important. This is especially true because statins, which are the most widely used lipid-lowering drugs, primarily reduce LDL-cholesterol. If elevated LDL-C is a weaker risk factor in women than low HDL-C, these drugs may be less effective for lowering risk in women than in men. A systematic review of the literature to address the association of lipoproteins and risk for CHD in women is feasible and would likely contribute important clinical information.

Treatment of Hyperlipidemia to Reduce Risk of CHD Events in Women

The best evidence concerning the effect of lipid-lowering on CHD risk in women is provided by the systematic review by LaRosa et al.[87] Both women and men with hypercholesterolemia had a 30 percent reduction in risk of major CHD events. Men also experienced a 20 percent reduction in total mortality. The effect on total mortality in women was not provided, perhaps because only 13 percent of the participants in the five trials reviewed were women. A recent large randomized trial[89] among persons with CHD or at high risk for CHD found that treatment with simvastatin reduced risk of major vascular events about 25 percent in both men and women, regardless of cholesterol level.

The review by LaRosa et al.[87] included only clinical trials of statin drugs for lipid-lowering, only one quantitative estimate of the effect of lipid lowering on risk for CHD events in women and no separate assessments of the effectiveness for primary and secondary prevention. A systematic review focused on the effects of lipid-lowering in women could provide important clinical information.

3.04a Homocysteine as a risk factor for CHD in women

Systematic Reviews

F.1. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA 1995;274(13):1049-57.[90]

In this systematic review, standard methods were used to determine the association between homocysteine and risk for CVD events. Overall, 27 observational studies were identified that fulfilled the inclusion criteria of providing data on the association of serum homocysteine level and risk for vascular disease. Nine of the 27 included studies were considered high quality because they were prospective cohorts or population-based case-control studies. Coronary disease was defined as fatal and nonfatal MI and angiographically confirmed occlusion of at least one major coronary artery. Only three studies provided data on women. Assuming a linear relation between homocysteine and outcomes, the summary odds ratios, based on a 5 µmol/L increase in homocysteine are given below:

	All (N=NA)			Women (N=NA)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
CHD events	1.7	1.5-1.9	NA	1.8	1.4-2.3	NA

Each 5 µmol/L increase in serum homocysteine level was associated with a 70 percent increased risk of CHD events among all participants and an 80 percent increased risk of CHD events in women.

This article was rated fair quality based on lack of information regarding analysis methods.

3.04b Treatment to reduce homocysteine levels to reduce risk of CHD events in women

There were no systematic reviews identified for this topic. Folate supplementation is known to reduce serum homocysteine levels in men.[91] Whether reductions in homocysteine lead to a decreased risk of CHD events has not been tested in a randomized controlled trial.

Summary and Recommendations

Homocysteine as a Risk Factor for CHD in Women

A systematic review of observational studies suggests that higher serum homocysteine levels are strongly associated with higher risk for CHD events in both men and women.[90] Each 5 µmol/L increase in serum homocysteine level was associated with a 70 percent higher risk of CHD events among both men and women. This systematic review is relatively old and did not rate studies by degree of statistical adjustment for potential confounding variables. An updated systematic review of this topic is feasible and could provide important evidence.

Treatment to Lower Homocysteine Levels to Reduce Risk of CHD Events in Women

There is insufficient evidence in women to address this question.

3.05a C-reactive protein as a risk factor for CHD events in women

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed two reports from the Women's Health Study that evaluated the association between C-reactive protein and the risk of CVD events in 28,263 healthy postmenopausal women.[92, 93] After adjustment for markers of inflammation, lipoprotein measures and other coronary heart disease risk factors, the relative risk of a CVD event associated with a one-quartile increase in the concentration of C-reactive protein levels was 1.5 (95% CI, 1.1-2.1; p = .02).

G.1. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 1998;98(8):731-3.[92]
G.2. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342(12):836-43.[93]

3.05b Treatment to reduce C-reactive protein levels to reduce risk of CHD events in women

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.

Summary and Recommendations

C-Reactive Protein as a Risk Factor for CHD Events in Women

One large cohort study[93] suggests that higher C-reactive protein levels are associated with increased risk for CVD events in women. A systematic review of this topic is not feasible due to lack of data.

3.06a Smoking as a risk factor for CHD in women

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We identified six prospective cohort studies evaluating the relation between cigarette smoking and risk of CHD in women. Four studies reported that smoking was independently associated with increased risk of fatal or nonfatal CHD events with a RR of about 2.[94-98] Smoking was associated with increased CHD risk in the Framingham Heart Study[99, 100] and in a study of three communities,[101] but the findings in these two cohorts were not statistically significant in women.

G.1. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1987;317(21):1303-9.[94]
G.2. Kannel WB, D'Agostino RB, Belanger AJ. Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham Study. Am Heart J 1987;113(4):1006-10.[99]
G.3. Freund KM, Belanger AJ, D'Agostino RB, Kannel WB. The health risks of smoking. The Framingham Study: 34 years of follow-up. Ann Epidemiol 1993;3(4):417-24.[100]
G.4. LaCroix AZ, Lang J, Scherr P, Wallace RB, Cornoni-Huntley J, Berkman L, et al. Smoking and mortality among older men and women in three communities. N Engl J Med 1991;324(23):1619-25.[101]
G.5. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, et al. Smoking cessation and time course of decreased risks of coronary heart disease in middle-aged women. Arch Intern Med 1994;154(2):169-75.[95]
G.6. Paganini-Hill A, Hsu G. Smoking and mortality among residents of a California retirement community. Am J Public Health 1994;84(6):992-5.[96]
G.7. Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. Circulation 1996;93(3):450-6.[97]
G.8. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998;316(7137):1043-7.[98]

3.06b Smoking cessation to reduce risk of CHD in women

Systematic Reviews

G.1. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med 2000;160(7):939-44.[102]

This systematic review of observational studies evaluated the association between smoking cessation after MI and subsequent overall mortality. The twelve international studies included in this meta-analysis were published between 1966 and 1996 and included at total of 5,878 participants. Two of the studies provided data on 185 women. Smoking status was evaluated by self-report during the first year after MI. The duration of follow-up ranged from 2 to 10 years.

	All (N=5,878)			Women (N=185; 3.1%)		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Mortality	.54	.46-.62	NA	.36	.23-.54	NA

Mortality was reduced by 50 percent among all participants and about 65 percent among women who stopped smoking after their MI, compared to persons who continued to smoke. The findings from some of the individual studies included in this meta-analysis were not adjusted for differences in CHD risk factors between persons who quit and those who continued to smoke.

Prospective Cohort Studies Not Included in the Systematic Review

We reviewed eight manuscripts based on six prospective cohort studies. Compared to women who had never smoked cigarettes, women who were former smokers had as much as a 50 percent increased risk of fatal and nonfatal coronary heart disease events, although this finding was not significant.[94, 97, 98] Among former smokers, CHD event rates approach that of non-smokers 10 to 20 years after cessation of smoking.[95, 96, 101, 103, 104]

G.2. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1987;317(21):1303-9.[94]
G.3. Omenn GS, Anderson KW, Kronmal RA, Vlietstra RE. The temporal pattern of reduction of mortality risk after smoking cessation. Am J Prev Med 1990;6(5):251-7.[103]
G.4. LaCroix AZ, Lang J, Scherr P, Wallace RB, Cornoni-Huntley J, Berkman L, et al. Smoking and mortality among older men and women in three communities. N Engl J Med 1991;324(23):1619-25.[101]

G.5. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, et al. Smoking cessation in relation to total mortality rates in women. A prospective cohort study. Ann Intern Med 1993;119(10):992-1000.[104]
G.6. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, et al. Smoking cessation and time course of decreased risks of coronary heart disease in middle-aged women. Arch Intern Med 1994;154(2):169-75.[95]
G.7. Paganini-Hill A, Hsu G. Smoking and mortality among residents of a California retirement community. Am J Public Health 1994;84(6):992-5.[96]
G.8. Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. Circulation 1996;93(3):450-6.[97]
G.9. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998;316(7137):1043-7.[98]

Summary and Recommendations

Smoking and Risk for CHD among Women

Based on the findings of six cohort studies,[94-101] smoking appears to be associated with an approximate 2-fold increased risk of CHD events in women, but no systematic review has quantified this increased risk or compared it to the increased risk among male smokers. A systematic review appears to be feasible and could provide important information.

Smoking Cessation to Reduce Risk of CHD Events among Women

A systematic review of prospective cohort studies found that smoking cessation after MI was associated with about a 50 percent lower risk of death during 2 to 10 years of observation.[102] This evidence is observational and subject to the biases associated with this study design. Of particular concern, it is not clear that the results of the studies included in the systematic review were adjusted for differences in CHD risk factors between smokers who quit and those who continued to smoke. This systematic review, though published in 2000, included only studies published before 1996. Given that the systematic review is relatively old, and the fact that only 185 women are represented in the review, we recommend a systematic review of the literature to update this topic.

3.07a Obesity as a risk factor for CHD in women

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed data from five cohort studies. Among women in the Framingham Heart Study,[105, 106] the Nurses' Health Study,[107-111], Atherosclerosis Risk in Communities (ARIC),[116] and the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Risk Development in Young Adults (CARDIA) studies,[112] increased weight or body mass index were associated with 1.5 to 3-fold increases in the risk of fatal and nonfatal CHD events. Fluctuating weight patterns and increased waist-hip ratios were associated with a 1.5 to 2-fold increased risk for CHD events and mortality among participants in the Iowa Women's Health Study[113-115] and the Nurses' Health Study.[109] Compared to BMI and skinfold measurements, waist-hip ratio was a better predictor of CHD among African-American women in the ARIC and CARDIA studies.[112, 116]

G.1. Harris T, Cook EF, Garrison R, Higgins M, Kannel W, Goldman L. Body mass index and mortality among nonsmoking older persons. The Framingham Heart Study. JAMA 1988;259(10):1520-4.[105]
G.2. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, et al. A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 1990;322(13):882-9.[107]
G.3. Folsom AR, Burke GL, Byers CL, Hutchinson RG, Heiss G, Flack JM, et al. Implications of obesity for cardiovascular disease in blacks: the CARDIA and ARIC studies. Am J Clin Nutr 1991;53(6 Suppl):1604S-1611S.[112]
G.4. Kannel WB, Cupples LA, Ramaswami R, Stokes J, 3rd, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham Study. J Clin Epidemiol 1991;44(2):183-90.[106]
G.5. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, et al. Body weight and mortality among women. N Engl J Med 1995;333(11):677-85.[108]
G.6. Willett WC, Manson JE, Stampfer MJ, Colditz GA, Rosner B, Speizer FE, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. JAMA 1995;273(6):461-5.[109]
G.7. Folsom AR, French SA, Zheng W, Baxter JE, Jeffery RW. Weight variability and mortality: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 1996;20(8):704-9.[113]
G.8. French SA, Folsom AR, Jeffery RW, Zheng W, Mink PJ, Baxter JE. Weight variability and incident disease in older women: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 1997;21(3):217-23.[114]
G.9. Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. Am J Epidemiol 1998;148(12):1187-94.[116]
G.10. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, et al. Abdominal adiposity and coronary heart disease in women. JAMA 1998;280(21):1843-8.[110]

G.11. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000;160(14):2117-28.[115]
G.12. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med 2001;161(13):1581-6.[111]

3.07b Weight reduction to reduce risk of CHD events in women

There were no studies identified for this topic.

Summary and Recommendations

Obesity as a Risk Factor for CHD in Women

Findings of five cohort studies[59,105-112] suggest that obesity increases risk of CHD events in women, but the measure of obesity (weight, body mass index, skinfold thickness, or waist-hip ratio) that best predicts CHD risk women is not clear. A systematic review of this topic is feasible and could be clinically useful.

Weight Reduction to Reduce Risk of CHD Events in Women

No evidence was identified to address this topic. A systematic review is not feasible due to lack of data.

3.08a Inactivity as a risk factor for CHD in women

No systematic reviews of this topic were identified.

Prospective Cohort Studies

We reviewed data from three cohort studies. Among healthy women in the Nurses' Health Study[117-119] there was a 15 to 50 percent reduction in the risk of CHD events with physical activity. However, there appeared to be a threshold above which increasing levels of activity were not associated with increased benefit. Compared to healthy women with low fitness levels, healthy women with high fitness levels were at significantly less risk for a fatal event, but not for CVD death.[120] Among healthy women in the Framingham Heart Study,[121] increased physical activity was associated with an approximate 30 percent reduction in the risk of mortality, but not with a lower risk for CVD or CVD death.

G.1. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989;262(17):2395-401.[120]
G.2. Sherman SE, D'Agostino RB, Cobb JL, Kannel WB. Physical activity and mortality in women in the Framingham Heart Study. Am Heart J 1994;128(5):879-84.[121]
G.3. Manson JE, Hu FB, Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. N Engl J Med 1999;341(9):650-8.[117]
G.4. Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical activity and coronary heart disease in women: is "no pain, no gain" passe? JAMA 2001;285(11):1447-54.[118]
G.5. Rockhill B, Willett WC, Manson JE, Leitzmann MF, Stampfer MJ, Hunter DJ, et al. Physical activity and mortality: a prospective study among women. Am J Public Health 2001;91(4):578-83.[119]

3.08b Exercise to reduce risk of CHD events in women

There were no systematic reviews identified for this topic that provide separate data on women. We know of three systematic reviews of randomized trials that assessed the effect of exercise as part of a cardiac rehabilitation program following an acute ischemic event on risk for subsequent CHD events.[122-124] However, the randomized trials included in these analyses were small and included few women.

Summary and Recommendations

Inactivity as a Risk Factor for CHD in Women

It is not clear that inactivity is a risk factor for CHD events in women. Three cohort studies suggest that risk for all-cause mortality is increased with inactivity, but the evidence regarding the association of inactivity and risk for CHD and CVD events is mixed.[117-119] The limited number of studies that provide data on women and variations in measurement of activity level limit the feasibility of a systemic review of this topic.

Exercise to Reduce Risk of CHD Events in Women

There is insufficient evidence in women to address this question.

3.09 Age as a Risk Factor for CHD events in women

Systematic Reviews

F.1. Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Boissel JP. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. BMJ 2001;323(7304):75-81.[125]

This is a systematic review of data from eight randomized controlled trials that studied the effect of treatment for hypertension on CVD risk and are included in the Individual Data Analysis of Antihypertensive intervention trials (INDANA) database. Pooled data from the trials were used in an prospective cohort design to determine the effect of various risk factors on CVD events and to develop a score for predicting risk of death from CVD. Baseline measures of 16 potential CVD risk factors (age, sex, height, body mass index, smoking, systolic and diastolic blood pressure, heart rate, total cholesterol, creatinine, uric acid, previous MI, stroke or diabetes, left ventricular hypertrophy on ECG and blood pressure treatment) were included in a multivariate Cox proportional hazards model. Regression coefficients from this model were used to develop a risk score for the probability of cardiovascular death within a five year interval. All participants had elevated blood pressure at entry in the trials. The primary outcomes were fatal CVD and fatal CHD events. Associations between age and fatal events are presented below:

	Men (N=27,987)			Women (N=20,802)		
Outcome	RR*	95% CI	p-value	RR*	95% CI	p-value
CVD death						
nonsmokers†	1.43	NA	<.0001	1.58	NA	<.0001
smokers†	1.33	NA	<.0001	1.46	NA	<.0001
CHD death	1.35	NA	<.0001	1.58	NA	<.0001

* per 5 year increase in age
† interaction between age and smoking status required stratified estimates for the relative risk associated with age

The risk for CVD and CHD death increased 50 to 60 percent with each 5-year increase in age among women. The effect of age is similar, but slightly weaker in men, with a 30 to 40 percent increase in risk of CVD or CHD death with each 5-year increase in age.

This study was rated fair quality because inclusion was restricted to selected clinical trials among hypertensive persons.

Prospective Cohort Studies Not Included in the Systematic Review

These two articles present risk estimates for CHD events associated with increasing age among white men and women in the Framingham Heart Study. The article by D'Agostino et al.[126] also presents associations between age and risk of CHD events stratified by race from seven other cohort studies. Data from each of the cohort studies was used to construct a multivariate Cox proportional hazards model that included age, race, sex, blood pressure, cholesterol, smoking, and diabetes as risk factors and CHD death or nonfatal MI as the outcome. Models were gender and race-specific. Multivariate relative risks for a one-year increase in age from these studies are presented below:

	Men		Women	
Race and Study*	RR†	95% CI	RR†	95% CI
White				
FHS	1.05	1.04-1.07	1.19	.97-1.45
ARIC	1.05	1.02-1.07	1.67	.73-3.38
PHS	1.01	1.00-1.02	NA	NA
CHS	1.07	0.99-1.16	2.83	.02-530.8
Black				
ARIC	1.05	1.01-1.10	.88	.33-2.33
Japanese-American				
HHP	1.06	1.04-1.08	NA	NA
Hispanic				
PR	1.03	1.00-1.05	NA	NA
Native American				
SHS	1.05	1.02-1.09	1.47	.71-3.05

*FHS = Framingham Heart Study; ARIC = Atherosclerosis Risk in Communities; PHS = Physicians' Health Study; CHS = Cardiovascular Health Study; HHP = Honolulu Heart Program; PR = Puerto Rico Heart Health Program, and SHS = Strong Heart Study.
† relative risk for CHD death and nonfatal MI for each one year increase in age

For each one-year increase in age, men of all races have about a 5 percent increase in risk of CHD events. There appears to be a greater increase in CHD risk with increasing age among women than in men, but the associations are difficult to interpret in women because the number of outcomes was small and none of the risk estimates are statistically significant. The small number of women studied also makes it difficult to determine if risk associated with increasing age differs with race.

G.2. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986;111(2):383-90.[3]
G.3. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286(2):180-7.[126]

Summary and Recommendations

Among men, cohort studies consistently show a 5 percent increase in risk of CHD events per year of age among white, black, Japanese-American, Hispanic and Native American men.[3,126] Among women, increasing age seems to be a stronger risk factor for CHD events than among men, but the evidence is inconclusive due to the small number of women included in the studies.

A systematic review of this topic could provide important information regarding the effect of aging on CHD risk and on differences in this association between men and women. Such a review would be challenging because increasing age is also associated with higher prevalence and severity of other risk factors for CHD. In addition, as indicated by the results of Pocock et al.,[125] the effects of age and gender may interact with other risk factors, such as smoking.

3.10 Age at menopause and risk for CHD

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed data from three prospective cohort studies. The Nurses' Health Study[127] and the Diagnostisch Onderzoek Mammacarcinoom (Diagnostic Investigation of Mammary Cancer)[128] found a 2 to 3 percent increased risk of CHD events with each one year decrease in age at menopause. Age at natural menopause was not a significant predictor of CHD deaths among women in the National Health and Examination Survey (NHANES).[129] Inadequate adjustment for cigarette smoking may confound the association of age at menopause and CHD risk, as smokers have an increased risk for CHD events and earlier age at menopause.[127]

G.1. Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, et al. Age at natural menopause and risk of cardiovascular disease. Arch Intern Med 1999;159(10):1061-6.[127]
G.2. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347(9003):714-8.[128]
G.3. Cooper GS, Sandler DP. Age at natural menopause and mortality. Ann Epidemiol 1998;8(4):229-35.[129]

Summary and Recommendations

Evidence that earlier age at menopause is associated with increased risk for CHD events is weak because the number of studies identified was small and their results are not consistent.[127-129] Several large community-based studies may provide sufficient data to perform a systematic review.

3.11 Ethnicity as a risk factor for CHD in women

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed data from three cohorts, comparing risk for CHD outcomes between African-American and white women. Among participants in the Charleston Heart Study[130] the risk of coronary heart disease death and mortality did not differ significantly by race. However, case fatality rates after myocardial infarction were 1.5 to 3-times higher among African-American women compared to white women in the Atherosclerosis Risk in Communities study[131] and in the National Hospital Discharge Survey.[132]

F.1. Roig E, Castaner A, Simmons B, Patel R, Ford E, Cooper R. In-hospital mortality rates from acute myocardial infarction by race in U.S. hospitals: findings from the National Hospital Discharge Survey. Circulation 1987;76(2):280-8.[132]
G.2. Keil JE, Sutherland SE, Knapp RG, Lackland DT, Gazes PC, Tyroler HA. Mortality rates and risk factors for coronary disease in black as compared with white men and women. N Engl J Med 1993;329(2):73-8.[130]
F.3. White AD, Rosamond WD, Chambless LE, Thomas N, Conwill D, Cooper LS, et al. Sex and race differences in short-term prognosis after acute coronary heart disease events: the Atherosclerosis Risk In Communities (ARIC) study. Am Heart J 1999;138(3 Pt 1):540-8.[131]

Summary and Recommendations

The three cohort studies that we reviewed provide conflicting evidence regarding the association between race/ethnicity and coronary heart disease risk in women.[130-132] Several large community-based studies may provide sufficient data to perform a systematic review, but such a review would be challenging because relative risk estimates comparing CHD risk by ethnicity must be adjusted for other cardiovascular risk factors.

3.12 Socioeconomic status and risk for CHD

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed three cohort studies. After adjustment for age and other coronary heart disease risk factors, income,[133] socioeconomic deprivation score,[134] and postcode of residence[135] correlated with risk for CHD events, such that women with lower socioeconomic status (SES) measures were at an approximate 2-fold increased risk for CHD events compared to women with higher SES. However, among women in the Charleston Heart Study, level of education was not a significant predictor of coronary

heart disease deaths for white or African-American women after adjustment for other CHD risk factors.[130]

G.1. Keil JE, Sutherland SE, Knapp RG, Lackland DT, Gazes PC, Tyroler HA. Mortality rates and risk factors for coronary disease in black as compared with white men and women. N Engl J Med 1993;329(2):73-8.[130]
G.2. Salomaa V, Miettinen H, Niemela M, Ketonen M, Mahonen M, Immonen-Raiha P, et al. Relation of socioeconomic position to the case fatality, prognosis and treatment of myocardial infarction events; the FINMONICA MI Register Study. J Epidemiol Community Health 2001;55(7):475-82.[133]
G.3. Capewell S, MacIntyre K, Stewart S, Chalmers JW, Boyd J, Finlayson A, et al. Age, sex, and social trends in out-of-hospital cardiac deaths in Scotland 1986-95: a retrospective cohort study. Lancet 2001;358(9289):1213-7.[134]
G.4. Morrison C, Woodward M, Leslie W, Tunstall-Pedoe H. Effect of socioeconomic group on incidence of, management of, and survival after myocardial infarction and coronary death: analysis of community coronary event register. BMJ 1997;314(7080):541-6.[135]

Summary and Recommendations

Three cohort studies suggest that socioeconomic status may be associated with an increased CHD risk, but the evidence is weak due to the small number of studies identified and differences in the definition of socioeconomic status.[133-135] Several large community-based studies may provide sufficient data to perform a systematic review, but such a review would be challenging because relative risk estimates comparing CHD risk by ethnicity should be adjusted for other cardiovascular risk factors and definitions of socioeconomic status vary.

QUESTION 4

4. Are accurate tests (defined in #1), effective treatments (defined in #2), or risk factor modifications (defined in #3) underutilized in women (or among women of various race/ethnic populations) compared to men?

We searched the medical literature to identify studies that compared the use of tests, treatments and risk factor reduction for CHD in men and women. We have described results only for those subtopics for which studies were identified.

1.0 Non-invasive testing for CHD

Exercise Tolerance Testing

Cross-sectional Studies

Among patients hospitalized with ischemic chest pain, women were approximately 20-40 percent less likely than men to undergo exercise stress testing, even after adjustment for other risk factors.[136, 137] Men with positive exercise stress test results were 1.5 to 2-fold more likely to undergo invasive or non-invasive follow-up testing,[14, 136, 137] despite the fact that risk of a subsequent MI or cardiac death was 5-fold higher in women than in men.[14] Between 1995 and 1996, primary care providers in a major managed-care network were 2-fold more likely to refer men than women with ischemic symptoms for exercise stress testing ($p<.0001$).[138] Among the oldest patients in this population (age > 70 years), rates of referral for exercise testing were similar in men and women.

F.1. Shaw LJ, Miller DD, Romeis JC, Kargl D, Younis LT, Chaitman BR. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994;120(7):559-66.[14]
G.2. Johnson PA, Goldman L, Orav J, Zhou L, Garcia T, et al. Gender differences in the management of acute chest pain. Support for the "Yentl Syndrome." J Gen Intern Med 1996;11:209-17.[136]
G.3. Roger VL, Farkouh ME, Weston SA, Reeder GS, Jacobsen SJ, et al. Sex differences in evaluation and outcome of unstable angina. JAMA 2000;283:646-52.[137]
F.4. Battleman DS, Callhan M. Gender differences in utilization of exercise treadmill testing: a claims-based analysis. J Healthcare Quality 2001;23:38-41.[138]

2.0 Treatments for CHD

Aspirin

Cross-sectional Studies

Compared to women, men in six large cross-sectional studies were more likely than women to receive aspirin during hospitalization for an acute MI[12, 139-142] or as secondary prophylaxis for a CVD event.[143] Rates of aspirin treatment among men compared to women were 38 percent higher at hospital admission,[12] 10 to 20 perccnt higher during hospitalization,[139, 141, 142] 6 percent higher on discharge,[140] and 40 percent higher after a CVD event.[143]

The Atherosclerotic Risk in Communities (ARIC) prospective cohort study reported similar rates of aspirin use between black women and black men (10 percent), but higher prevalence of use among white men than among white women (31 percent vs. 28 percent;p<.001). Overall, the prevalence of aspirin use was almost 3-fold greater among whites compared to blacks.[144] Between 1986 and 1990 the use of antiplatelet agents in women increased 4-fold in one study,[139] but remained unchanged in another.[144]

G.1. Steingart RM, Packer M, Hamm P, Coglianese ME, Gersh B, et al. Sex differences in the management of coronary artery disease. N Engl J Med 1991;325:226-30.[12]

G.2. Pagley PR, Yarzebski J, Goldberg R, Chen Z, Chiriboga D, et al. Gender differences in the treatment of patients with acute myocardial infarction. Arch Intern Med 1993;153:625-9.[139]

F.3. Clarke KW, Gray D, Keating NA, Hampton JR. Do women with acute myocardial infarction receive the same treatment as men? BMJ 1994;309:563-6.[140]

F.4. Tsuyuki RT, Teo KK, Ikuta RM, Bay KS, Greenwood PV, Montague TJ. Mortality risk and patterns of practice in 2,070 patients with acute myocardial infarction, 1987-92. Chest 1994;105:1687-92.[141]

G.5. Shahar E, Folsom AR, Romm FJ, Bisgard KM, Metcalf PA, et al. Patterns of aspirin use in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 1996;131:915-22.[144]

G.6. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, et al. Observations of the treatment of women in the United States with myocardial infarction. Arch Intern Med 1998;158:981-8.[142]

G.7. Rojas-Fernandez CH, Kephart GC, Sketris IS, Kass K. Underuse of acetylsalicylic acid in individuals with myocardial infarction, ischemic heart disease or stroke: data from the 1995 population-based Nova Scotia Health Survey. Can J Cardiol 1999;15(3):291-6.[143]

Beta-Blockers

Cross-sectional Studies

After adjustment for age, women were 10 to 30 percent less likely than men with symptoms of an acute MI to receive beta-blockers during hospitalization[141, 142] and approximately 45 percent less likely to be discharged on beta-blockers.[140]

Several studies found no gender difference in beta-blocker use prior to or during hospitalization for an acute MI.[12, 139] Between 1986 and 1990, the use of beta-blockers increased by 15 percent in hospitalized women (48.4 percent) and by 17 percent in hospitalized men (60.0 percent).[139]

G.1. Steingart RM, Packer M, Hamm P, Coglianese ME, Gersh B, et al. Sex differences in the management of coronary artery disease. N Engl J Med 1991;325:226-30.[12]
G.2. Pagley PR, Yarzebski J, Goldberg R, Chen Z, Chiriboga D, et al. Gender differences in the treatment of patients with acute myocardial infarction. Arch Intern Med 1993;153:625-9.[139]
F.3. Clarke KW, Gray D, Keating NA, Hampton JR. Do women with acute myocardial infarction receive the same treatment as men? BMJ 1994;309:563-6.[140]
F.4. Tsuyuki RT, Teo KK, Ikuta RM, Bay KS, Greenwood PV, Montague TJ. Mortality risk and patterns of practice in 2,070 patients with acute myocardial infarction, 1987-92. Chest 1994;105:1687-92.[141]
G.5. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, et al. Observations of the treatment of women in the United States with myocardial infarction. Arch Intern Med 1998;158:981-8.[142]

Thrombolysis

Cross-sectional Studies

Six large cohort studies found that men were 1.5 to 2-fold more likely than women to receive thrombolytic therapy during hospitalization for symptoms of acute MI.[140-142, 145-147] However, among patients who had been admitted to a coronary care unit, men and women were equally likely to receive thrombolytic treatment.[140] In the SAVE trial, the odds of receiving thrombolysis were 56 percent higher for men than women; however, after adjustment for other variables related to indication for thrombolysis, gender was not an independent predictor of thrombolytic therapy.[148] Between 1986 and 1990, the use of thrombolytics in women increased 6-fold.[139, 142]

In contrast, two studies did not find a significant gender difference in thrombolytic therapy during hospitalization for acute MI.[139, 149]

F.1. Maynard C, Althouse R, Cerqueira M, Olsufka M, Kennedy JW. Underutilization of thrombolytic therapy in eligible women with acute myocardial infarction. Am J Cardiol 1991;68:529-30.[145]
G.2. Pfeffer Ma, Moye LA, Braunwald E, Basta L, Brown EJ, et al. Selection bias in the use of thrombolytic therapy in acute myocardial infarction. JAMA 1991;266:528-32.[148]
G.3. Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction. Arch Intern Med 1992;152:972-6.[146]
G.4. Pagley PR, Yarzebski J, Goldberg R, Chen Z, Chiriboga D, et al. Gender differences in the treatment of patients with acute myocardial infarction. Arch Intern Med 1993;153:625-9.[139]
F.5. Clarke KW, Gray D, Keating NA, Hampton JR. Do women with acute myocardial infarction receive the same treatment as men? BMJ 1994;309:563-6.[140]
F.6. Tsuyuki RT, Teo KK, Ikuta RM, Bay KS, Greenwood PV, Montague TJ. Mortality risk and patterns of practice in 2,070 patients with acute myocardial infarction, 1987-92. Chest 1994;105:1687-92.[141]
G.7. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (The Myocardial Infarction Triage and Intervention Registry). Am J Cardiol 1996;78:9-14.[149]
G.8. Yarzebski J, Col N, Pagley P, Savageau J, Gore J, Goldberg R. Gender differences and factors associated with the receipt of thrombolytic therapy in patients with acute myocardial infarction: a community-wide perspective. Am Heart J 1996;131(1):43-50.[147]
G.9. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, et al. Observations of the treatment of women in the United States with myocardial infarction. Arch Intern Med 1998;158:981-8.[142]

Percutaneous Transluminal Coronary Angioplasty (PTCA) and Coronary Artery Bypass Graft Surgery (CABG)

Cross-sectional Studies

We reviewed 21 cross-sectional studies comparing gender differences in revascularization procedures (PTCA and CABG). Most studies included patients who were admitted to the hospital for evaluation of acute coronary symptoms. Because women appear to be less likely than men to undergo cardiac catheterization, we categorized studies that evaluated all patients admitted for acute coronary syndromes and those that provided data on procedures subsequent to cardiac catheterization.

Procedures among all patients evaluated for acute coronary syndromes

Two European studies found significant gender differences in revascularization procedure rates among patients with known CHD, including a 50 to 60 percent higher rate for men compared to women in the United Kingdom[150] and a 36 percent higher rate for men in Austria.[151] In 1995, the lowest PTCA rates in Austria were among women over the age of 64 years.[151] These finding were similar to data from the United States, where CHD-adjusted rates of revascularization in men were 30 to 45 percent higher than in women.[13] In the same study, revascularization rates remained higher in men than in women hospitalized for an acute MI, suggesting that potential biases in admitting practices could not explain the gender differences.[13]

In adjusted models, men discharged from California hospitals in 1989 were 35 percent more likely to have undergone PTCA and 2-fold more likely to have undergone CABG than women.[152] In Massachusetts, men were 2.5-fold more likely than women to undergo PTCA following acute MI, but equally likely to undergo CABG.[153] Among patients

referred for non-invasive testing, men were twice as likely as women to undergo a subsequent revascularization procedure.[14] Data from the National Registry of Myocardial Infarction indicate that, among patients who did not receive thrombolytic therapy, 19 percent of men underwent PTCA compared with 13.8 percent of women, and 12.6 percent of men underwent CABG compared with 8.0 percent of women.[142] However, after thrombolytic therapy, 28.3 percent of women vs. 30.6 percent of men underwent PTCA and 11.0 percent of women vs. 13.5 percent of men underwent CABG.[142]

Race and gender rates of revascularization indicate that black and white women are as likely as white men to undergo PTCA, but white women are 35 percent less likely and black women 63 percent less likely to undergo CABG than white men, even after adjustment for multiple risk factors.[154] Medicare data suggest that white men have the highest rates of CABG (40.4 per 10,000 persons) and black women the lowest (6.4 per 10,000 persons).[155]

Procedures among patients who have had cardiac angiography

Among participants in the population-based Corpus Christi Heart Project,[156] age-adjusted rates of PTCA and CABG were 1.5-times higher for men than women. However, after acute MI and coronary angiography, there was no evidence of differential revascularization rates between genders. After adjustment for CHD risk factors, there were only slight differences in rates of PTCA between Mexican-Americans and non-Hispanic Whites.[156]

In similar analyses among persons who had coronary angiography, women were as likely as men to undergo PTCA but 40 percent less likely to undergo CABG.[157, 158] Gender differences in intervention rates were most significant among younger participants. Findings from several cohort studies indicate that after coronary angiography, women

were more likely to undergo PTCA[159-161] while men more likely to undergo CABG.[160, 161] After adjustment for CHD risk factors, gender was not a significant predictor of revascularization procedure in one,[161] but not all[159, 160] studies. In GUSTO-I, the rates of coronary angiography were similar in men and women (52 percent vs. 57 percent), but women were significantly more likely than men to undergo PTCA (35 percent vs. 32 percent; $p < .001$) and less likely to undergo CABG (7 percent vs. 9 percent; $p < .001$).[160] Four studies found that men were 1.5 to 2-fold more likely than women to undergo revascularization (PTCA or CABG) subsequent to acute coronary symptoms; however, once a diagnostic procedure had been performed, gender was a non-significant predictor of revascularization.[12, 146, 159, 162]

Three studies found no significant gender differences in the referral rates for PTCA or CABG after coronary angiography.[60, 149, 163] However, men were more likely to undergo revascularization procedures during the early phases of infarction,[149] or when the risk of cardiac death was low.[163] In one study, women were half as likely to undergo early intervention for MI (thrombolysis, catheterization, PTCA, CABG).[149]

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Treatment of hypertension

Systematic Review

F.1. Klungel OH, deBoer A, Paes A, Seidell JC, Bakker A. Sex differences in the pharmacological treatment of hypertension: a review of population-based studies. J

Hypertension 1997;15:591-600.[164]

In this systematic review, data from 46 population-based studies published between 1966 and 1996 were analyzed to assess gender differences in the pharmacological treatment of hypertension. Data on 108,184 men and 59,575 women with hypertension are included. Crude differences in treatment practices were also evaluated by antihypertensive drug class and by country.

	Crude Prevalence Ratio	
Outcome	Female:Male	95% CI
Any pharmacological treatment	1.33	1.32 – 1.34
Diuretics	1.12	1.09 – 1.15
β-Blockers	.82	.79 - .85
ACE inhibitors	.67	.59 - .76
Calcium antagonists	.85	.77 - .95

Women with hypertension were approximately 30 percent more likely than men to receive treatment for hypertension. Women were more likely than men to be treated with a diuretic, while men were more likely to be treated with beta-blockers, ACE inhibitors and calcium antagonists. Among participants aged 20-29, women were 2-fold more likely than men to receive treatment for hypertension. By age 60-69 the prevalence of treatment was only 22 percent higher in women than in men. Gender differences in treatment practices declined between 1970 and 1991.

Lipid lowering

Cross-sectional Studies

Three international cross-sectional studies document that rates of medication usage and gender differences in use rates vary by country.[165-167]

F.1. Sketris IS, Kephart GC, Hicks VA, Hubbard EJ, Brown MG, et al. Prescribing patterns of antilipemic drugs and prevalence of hypercholesterolemia in the Nova Scotia population more than 65 years old. Ann Pharmacother 1995;29:576-81.[165]
F.2. Magrini N, Elinarson T, Vaccheri A, McManus P, Montanaro N, Bergman U. Use of lipid-lowering drugs from 1990 to 1994: an international comparison among Australia, Finland, Italy (Emilia Romagna Region), Norway and Sweden. Eur J Clin Pharmacol 1991;53:185-9.[166]
F.3. Majeed A, Moser K, Maxwell R. Age, sex and practice variations in the use of statins in general practice in England and Wales. J Publ Hlth Med 2000;22:275-9.[167]

Summary and Recommendations

Available studies suggest that men are more likely than women to undergo diagnostic testing[14,136-138] and treatment for CHD,[12-14,60,139-163,165-167] but that women are more likely

to be treated for hypertension.[164] Several theories have been proposed to explain these gender differences.

It is possible that women have less severe CHD symptoms or findings than men and more comorbidities that contraindicate tests and procedures. This theory is supported by the fact that gender differences appear to be minimized in studies with inadequate control for potential confounding. Coronary tests and procedures may not be underused in women, but overused in men. For example, lower rates of CABG among low risk women may indicate a more appropriate treatment referral pattern among women than men. A panel of nationally recognized experts assessed the appropriateness of coronary angiography, PTCA, and CABG based on hospital data from New York and found that the rate of inappropriate cardiovascular procedures was not significantly different by gender.[168]

Women may be more reluctant than men to undergo invasive coronary procedures. Among patients scheduled for exercise stress testing, Saha et al. found that women were more willing than men to undergo coronary angiography and equally willing to undergo PTCA or CABG.[169]

A systematic review of the literature is feasible and could provide clinically important information for treatment practice guidelines.

QUESTION 5

5. What is the prognostic value of biochemical markers for acute myocardial infarction or unstable angina in women? (3 subtopics labeled 5.01-5.02)

Specifically, does the prognostic value of the following markers differ in women and men? What is the incremental prognostic benefit of new cardiac markers in addition to history, physical exam, and other laboratory data including electrocardiography?

5.01 troponin
5.02 creatinine kinase myocardial bands (CKMB) including isoforms
5.03 myoglobin

5.01 Troponins

There were no systematic reviews identified for this topic.

5.02 Creatine kinase MB

There were no systematic reviews identified for this topic.

5.03 Myoglobin

There were no systematic reviews identified for this topic.