Table 1: List of Key Questions

Please note that the numbering of the Key Questions is used to identify the questions throughout the report and appendices.

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
1.02 exercise echocardiogram
1.03 coronary artery calcification score

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 as 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)

Table 1: List of Key Questions (continued)

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

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?**

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

Table 2: Articles identified by key question and topic

Key Question	Topic	Number Identified	Full-text Reviewed	Provided Evidence	Good Quality
1.01	exercise tolerance	138	28	4	2
1.02	exercise echo	135	22	2	2
1.03	calcium score	201	20	2	2
2.01	aspirin	393	31	6	6
2.02	beta-blockers	623	33	4	0
2.03	ACE inhibitors	561	28	7	6
2.04	calcium channel blockers	536	28	0	0
2.05	nitrates	137	11	3	1
2.06	heparin	401	15	0	0
2.07	IIb/IIIa drugs	58	17	2	1
2.08	thrombolysis	727	46	2	1
2.09	ticlopidine	58	9	0	0
2.10	clopidogrel	33	8	2	2
2.11	angioplasty/stenting	433	64	11	6
2.12	coronary bypass surgery	39	19	3	3
3.01	hypertension	622	37	8	4
3.02	diabetes	21	13	9	8
3.03	hyperlipidemia	694	97	11	5
3.04	homocysteine	6	5	1	0
3.05	C-reactive protein	15	9	2	2
3.06	smoking	28	23	17	17
3.07	obesity	28	21	12	12
3.08	inactivity	61	13	5	5
3.09	age	75	15	3	2
3.10	age at menopause	29	10	3	3
3.11	ethnicity	26	11	3	1
3.12	socioeconomic status	13	7	4	4
4.0	Differences in utilization between women & men	288	156	36	23
5.01	troponins	8	8	0	0
5.02	creatine kinase MB	14	4	0	0
5.03	myoglobin	2	2	0	0
Totals		**6403**	**810**	**162**	**118**

Table 3: Summary and Recommendations by Key Question

Key Question	Topic	Existing Evidence	Systematic Review Feasible?	Summary & Recommendations
1.01	Exercise tolerance testing	fair	yes	Two good quality systematic reviews suggest that the accuracy of exercise EKG and exercise thallium in women appears to be low with positive likelihood ratios of 2 to 3 and negative likelihood ratios of .35 to .55.[19,22] The accuracy of exercise echocardiography appears to be higher with a positive likelihood ratio of 4 and negative likelihood ratio of .2, but data are limited. However, one of the systematic reviews is outdated,[19] the other does not provide accuracy estimates stratified by gender[22] and neither addresses current myocardial perfusion imaging technology using thallium and/or technetium agents with SPECT or gated SPECT imaging in women. An updated systematic review including information on exercise SPECT is feasible and could provide important clinical information.
1.02	Exercise echocardiogram	fair	yes	
1.03	Calcium score	weak	no	Two good quality studies 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 and might be useful for ruling out disease in both men and women.[25,26]
2.01	Aspirin a. secondary prevention	good	yes	There is evidence from a good systematic review that aspirin reduces risk of CHD events about 20% in women with coronary disease or at high risk for CHD.[27] The systematic review included only studies published until 1990 and provided few data on dose, duration of therapy or adverse effects in women. A more detailed and current systematic review of the data in women is feasible. A new review is unlikely to change overall conclusions, but might provide clinically important information on dose, duration and adverse effects.
	b. primary prevention	weak	yes	Evidence from a randomized trial among persons with hypertension suggests that risk for cardiovascular events is reduced about 20% in women taking aspirin, but total mortality was not reduced.[30,31] A systematic review of aspirin for primary prevention is feasible, assuming that data stratified by gender could be obtained. However, a systematic review should likely await the results of the ongoing Women's Health Study, a randomized trial of aspirin therapy in women that may be definitive.
2.02	Beta-blockers a. secondary prevention	fair	yes	Two small meta-analyses that included data from 4 large randomized trials found that treatment with beta-blockers reduced the risk of mortality by about 30% in both men and women with CHF.[33,34] 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

Key Question	Topic	Existing Evidence	Systematic Review Feasible?	Summary & Recommendations
2.02 (continued)	Beta-blockers a. secondary prevention (continued)			women. A systematic review of the effect of beta-blockers in women with CHF 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 fair quality systematic reviews, treatment with beta-blockers after MI in women appears to decrease mortality 20 to 25%.[35,36] Both of these reviews are over 10 years old and they 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
	b. primary prevention	none	no	There is insufficient evidence in women to address this question.
2.03	ACE inhibitors a. secondary prevention	good	yes	Among women with documented CHF, two good systematic reviews suggest that outpatient treatment with ACE inhibitors reduces the risk of mortality 15 to 20%.[37,38] Results of the HOPE trial suggest that outpatient treatment of women with cardiovascular disease or with multiple risk factors results in about a 20% reduction in risk of cardiovascular events.[39-41] A systematic review of the results of 4 large randomized trials, treatment with ACE inhibitors within 36 hours of acute MI is probably associated with about a 7% 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.[42] New systematic reviews of these topics are feasible, but are unlikely to provide additional information on use of ACE inhibitors in women.
	b. primary prevention	none	no	There is insufficient evidence in women to address this question.
2.04	Calcium channel blockers	none	no	There is insufficient evidence in women to address this question.
2.05	Nitrates	good	no	Consistent evidence from 2 large randomized trials suggests that mortality in women is not reduced after MI by early treatment with nitrates.[43,44] Further systematic review of the literature related to this question is unlikely to provide clinically useful information.
2.06	Heparin	none	no	There is insufficient evidence in women to address this question.

2.07	IIb/IIIa drugs	fair to good	yes	A recent fair quality systematic review found that among women undergoing percutaneous coronary interventions, treatment with abciximab for a maximum of 12 hours reduces risk of death, MI and urgent revascularization 40 to 50% at 6 weeks and at 6 months.[46] Risk for mortality is reduced 40% at one year. There is no difference in the effect of these drugs in men and women who are undergoing percutaneous coronary intervention. A recent good quality systematic review found that among women admitted to the hospital for acute coronary syndromes, the effect of glycoprotein IIb/IIIa inhibitor treatment may be harmful.[47] While men with acute coronary syndromes benefited from 2 to 5 days of treatment with a variety of IIb/IIIa inhibitors, risk for MI or mortality was increased 15% at 30 days in treated women. In a subset of about 1/3 of participants in whom troponins were elevated, treatment appeared to reduce risk of mortality about 20 to 25% in both men and women. However, these findings were based on post-hoc subset analyses, the findings were not statistically significant 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	fair	yes	A good quality systematic review of 9 large randomized trials demonstrates that thrombolysis reduces the risk of 5-week mortality in women and men hospitalized for suspected acute MI about 15%.[48] The systematic review, while large and well-conducted, was published in 1994. An updated systematic 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	none	no	There is insufficient evidence in women to address this question.
2.10	Clopidogrel	weak	no	Results from one large, good quality randomized trial suggest that 3 to 12 months of treatment with clopidogrel among women with acute coronary syndromes reduces risk of cardiovascular events and death about 20%.[51] Prolonged treatment (3 to 12 months) with clopidogrel among women undergoing percutaneous coronary intervention reduced risk of cardiovascular events and death about 20% more than brief treatment (2 to 4 weeks).[50] A systematic review of this topic is not feasible due to limited data.

2.11	Angioplasty/stenting	weak	no	Evidence regarding the efficacy of PTCA to reduce the risk of CHD events in women is limited. Three available clinical trials included only 100 to 250 women.[49,52,53] These trials suggest that PTCA relieves angina over the short term better than medical therapy, but there are few data regarding risk for CHD outcomes. One small trial suggested that CABG is more effective than PTCA in relieving angina, but that CABG and PTCA have similar effects on risk for CHD events at one year after the procedure among women with symptomatic multi vessel coronary disease.[52] No studies were identified that provided data on the efficacy of coronary stenting to reduce risk of CHD events in women. Whether PTCA is superior to medical management or to 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 bypass surgery	weak	no	Evidence regarding the efficacy of CABG to reduce the risk of CHD events and death in women is limited. Observational evidence suggests that despite a high perioperative mortality rate (5.3%), 8-year survival is improved in women with double or triple vessel coronary disease who undergo CABG surgery compared to initial medical management.[60] Randomized trials to compare the effectiveness of CABG and PTCA provide little evidence regarding the relative benefits of procedures in women. There is no clear evidence that either CABG or PTCA is superior with regard to mortality or CHD outcomes in women.[53] CABG is associated with a higher peri-procedure mortality but appears more effective than PTCA in relieving angina and is less likely to be followed by additional revascularization procedures. A systematic review of the findings of randomized trials regarding the efficacy of CABG for preventing CHD events in women is probably not feasible given the small numbers of trials and women participants.
3.01	Hypertension a. As a risk factor	weak	yes	Results of four large cohort studies suggest that hypertension, especially diastolic hypertension, is associated with a 2 to 3-fold increased risk for coronary heart disease events in both men and women.[62-65] A systematic review and meta-analysis would likely be feasible if additional data could be obtained from the placebo groups in large clinical trials of treatment for hypertension. Summary estimates of the effect of blood pressure on CHD risk could be important in helping identify women most likely to benefit from therapy.

3.01 (continued)	Hypertension (continued) b. Treatment	good	yes	Two recent systematic reviews (one good- and one fair-quality) suggest that treatment of hypertension in women results in small reductions in risk of mortality (about 10%) and in CHD events (15-20%), but these benefits are primarily limited to women over age 55.[66,67] African-American women seem to derive more marked benefit than white women with about 40% reduction in risk of death and CHD events.[67] A large randomized trial in China suggests that Asian women derive marked benefit from treatment of hypertension.[69] Repeating these two relatively recent systematic reviews is unlikely to add additional clinical information.
3.02	Diabetes a. As a risk factor	good	yes	Two recent systematic reviews (one good- and one fair-quality) found that risk of CHD events is increased in both men and women diabetics compared to non-diabetics.[70,71] In women diabetics, the increased risk (RR = 2.6) appeared to be increased more markedly than in men diabetics (RR = 1.8).[71] These summary risk estimates are based on findings that were not adjusted for differences in CHD risk factors between women and men. It is feasible to update these systematic reviews and to calculate comparable, risk factor-adjusted relative risks 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 or is more likely to be associated with other risk factors in women.
	b. Treatment	none	no	There is insufficient evidence in women to address this question.
3.03	Hyperlipidemia a. As a risk factor	fair	yes	Evidence regarding the association of abnormal lipoprotein levels and CHD risk in women is inconclusive. A fair quality systematic review 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).[79] However, the pattern of risk among older women appears to be different than in men with increased risk for CHD mortality associated only with lower HDL-C and higher triglycerides. The meta-analysis is limited, however, because it is outdated, the literature search may not have been complete and unadjusted findings were summarized. An updated 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.
	b. Treatment	good	yes	A recent, good quality systematic review found that both women and men with hyperlipidemia and treated with statins had a 30% reduction in risk of major CHD events.[87] Men also experienced a 20% reduction in total mortality. The effect on total mortality in women was not provided, perhaps due to the small number of women included in the trials. A recent large randomized trial among persons with

3.03 (continued)	Hyperlipidemia b. Treatment (continued)			CHD or at high risk for CHD found that treatment with simvastatin reduced risk of major vascular events about 25% in both men and women, regardless of pretreatment cholesterol level.[89] The systematic review includes only clinical trials of statins for lipid-lowering, did not separately assess effectiveness for primary and secondary prevention, and provided only one outcome estimate specifically for women. An updated systematic review focused on the effects of lipid-lowering in women could provide important clinical information.
3.04	Homocysteine a. As a risk factor	fair	yes	A fair quality systematic review of observational studies found that each 5 µmol/L increase in serum homocysteine level was associated with a 70% higher risk of CHD events among both men and women.[90] 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.
	b. Treatment	none	no	There is insufficient evidence in women to address this question.
3.05	C-reactive protein a. As a risk factor	weak	no	One large cohort study suggests that higher C-reactive protein levels are associated with increased risk for CVD events in women.[92,93] A systematic review of this topic is not feasible due to lack of data.
	b. Treatment	none	no	There is insufficient evidence in women to address this question.
3.06	Smoking a. As a risk factor	weak	yes	Based on the findings of 6 cohort studies, smoking appears to be associated with increased risk for CHD events in women, but no systematic review has quantified this increased risk or compared it to the increased risk among male smokers.[94-101] A systematic review is feasible and could provide important information.
	b. Smoking cessation	fair	yes	A small systematic review of prospective cohort studies found that smoking cessation after MI was associated with about a 50% lower risk of death during 2 to 10 years of observation.[102] This evidence is observational, and may be 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 this, and the fact that only 185 women are represented in the review, we rated the evidence as only fair and recommend an updated systematic review.
3.07	Obesity a. As a risk factor	weak	yes	Based on the findings of five cohort studies, obesity appears to increase 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 in women is not

3.07 (continued)	Obesity a. As a risk factor (continued)			clear.[59,105-112] A systematic review of this topic is feasible and could be clinically useful.
	b. Weight reduction	none	no	There is insufficient evidence in women to address this question.
3.08	Inactivity a. As a risk factor	weak	maybe	It is not clear that inactivity is a risk factor for CHD events in women. Three cohort studies suggest that risk for mortality is increased with inactivity, but the evidence regarding the association of inactivity and risk for CHD 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.
	b. Exercise	none	no	There is insufficient evidence in women to address this question.
3.09	Age as risk factor	weak	yes	Among men, cohort studies consistently show a 5% increase in risk of CHD events per year of age among white, African-American, 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 is feasible and could provide important information regarding the effect of aging on CHD risk and on differences in this association between men and women.
3.10	Age at menopause as a risk factor	weak	maybe	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	weak	maybe	Three cohort studies 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.
3.12	Socioeconomic status as a risk factor	weak	maybe	Three cohort studies suggest that socioeconomic status may be associated with 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.
4.0	Utilization of tests, treatments and risk reduction	weak	yes	Cross-sectional 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] Differences in utilization of tests and treatment might be explained by differences in severity of disease or comorbidities between men and women, or by overuse of tests and treatments in

4.0 (continued)	Utilization of tests, treatments and risk reduction (continued)			men. A systematic review of the literature is feasible and could provide clinically important information for treatment practice guidelines.
5.01	Troponins	none	no	There is insufficient evidence in women to address this question.
5.02	Creatine kinase	none	no	There is insufficient evidence in women to address this question.
5.03	Myoglobin	none	no	There is insufficient evidence in women to address this question.

Note: Superscripted numbers correspond with citations on References, page 115.

Table 4: Findings by Level of Evidence and Key Question

No Evidence	**Weak Evidence**
2.06 heparin 2.09 ticlopidine 2.02b beta blockers – primary prevention 2.03b ace inhibitors – primary prevention 2.04 calcium channel blockers 3.02b diabetes - treatment 3.07b obesity - weight reduction 3.08b inactivity - exercise 3.04b homocysteine - treatment 3.05b C-reactive protein - treatment 5.01 troponins 5.02 creatine kinase 5.03 myoglobin	1.03 calcium score 2.01b aspirin - primary prevention 2.10 clopidogrel 2.11 angioplasty/stenting 2.12 coronary artery bypass surgery 3.01a hypertension – risk factor 3.06a smoking - risk factor 3.07a obesity - risk factor 3.08a inactivity - risk factor 3.09 age - risk factor 3.11 ethnicity - risk factor 3.12 socioeconomic status - risk factor 3.10 age at menopause - risk factor 3.05a C-reactive protein - risk factor 4.0 differences in utilization between men and women
Fair Evidence	**Good Evidence**
1.01 exercise tolerance testing 1.02 exercise echocardiography 2.02a beta-blockers for secondary prevention 2.07 IIb/IIIa drugs 2.08 thrombolysis 3.03a hyperlipidemia - risk factor 3.06b smoking cessation 3.04a homocysteine – risk factor	2.01a aspirin – secondary prevention 2.03a ACE inhibitors–secondary prevention 2.05 nitrates 3.01b hypertension – treatment 3.02a diabetes – risk factor 3.03b hyperlipidemia - treatment

participation of women and minorities in research, the National Institutes of Health, Federal Drug Administration and other funding sources should insist that primary and secondary outcome data by subgroup be published or archived.

Similarly, most systematic reviews of the literature do not provide subgroup estimates for women or minorities. This is due primarily to the difficulty of obtaining unpublished subgroup estimates, as noted above. However, as demonstrated by several excellent systematic reviews included in this report, it is possible with additional effort to obtain subgroup estimates for women and minorities. We recommend that funding agencies that support systematic reviews require inclusion of subgroup estimates in women and minorities whenever possible.

Table 5: Findings by Level of Evidence and Recommendation for Systematic Review

		Systematic Review Feasible		
Level of Evidence	Number of Key Questions	no	yes	maybe
None	13	13	0	0
Weak	15	5	6	4
Fair	8	0	8	0
Good	6	1	5	0