Who Needs Laboratories and Who Needs Statins?

Comparative and Cost-Effectiveness Analyses of Non–Laboratory-Based, Laboratory-Based, and Staged Primary Cardiovascular Disease Screening Guidelines

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Background—Early detection and treatment of cardiovascular disease (CVD) risk factors produces significant clinical benefits, but no consensus exists on optimal screening algorithms. This study aimed to evaluate the comparative and cost-effectiveness of staged laboratory-based and non–laboratory-based total CVD risk assessment.

Methods and Results—We used receiver operating characteristic curve and cost-effectiveness modeling methods to compare strategies with and without laboratory components and used single-stage and multistage algorithms, including approaches based on Framingham risk scores (laboratory-based assessments for all individuals). Analyses were conducted using data from 5998 adults in the Third National Health and Nutrition Examination Survey without history of CVD using 10-year CVD death as the main outcome. A microsimulation model projected lifetime costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios for 60 Framingham-based, non–laboratory-based, and staged screening approaches. Across strategies, the area under the receiver operating characteristic curve was 0.774 to 0.780 in men and 0.812 to 0.834 in women. There were no statistically significant differences in area under the receiver operating characteristic curve between multistage and Framingham-based approaches. In cost-effectiveness analyses, multistage strategies had incremental cost-effectiveness ratios of $52 000/QALY and $83 000/QALY for men and women, respectively. Single-stage/Framingham-based strategies were dominated (higher cost and lower QALYs) or had unattractive incremental cost-effectiveness ratios (>$300 000/QALY) compared with single-stage/non–laboratory-based and multistage approaches.

Conclusions—Non–laboratory-based CVD risk assessment can be useful in primary CVD prevention as a substitute for laboratory-based assessments or as the initial component of a multistage approach. Cost-effective multistage screening strategies could avoid 25% to 75% of laboratory testing used in CVD risk screening with predictive power comparable with Framingham risks. **(*Circ Cardiovasc Qual Outcomes*. 2014;7:25-32.)**

Key Words: diagnosis ■ economics ■ primary prevention

The clinical benefits from early detection and treatment of cardiovascular disease (CVD) risk factors are significant and well established.[1,2] There is less agreement on what form an optimal CVD screening strategy should take in light of the various screening mechanisms available to stratify high- and low-risk persons for intervention.[3–6] A recent review of CVD screening guidelines from major professional organizations in Western countries found that most guidelines called for assessments based on total CVD risk scores, and all of these risk scores included ≥1 laboratory-based component (ie, total and high-density lipoprotein cholesterol).[7]

Non–laboratory-based risk assessment approaches use risk factors that can be assessed in a 5- or 10-minute clinical evaluation (such as age, smoking, blood pressure, and body mass index) to predict CVD risk using less time and fewer resources compared with laboratory-based risk scores.[8] We previously found that a non–laboratory-based CVD risk score discriminated CVD mortality risk similar to the Framingham risk scores in a representative US population in men, but there were significant differences in women.[9] A potential 2-staged CVD screening strategy could incorporate non–laboratory-based risk assessment as an initial step to identify patients who would benefit the most from further laboratory-based testing (eg, using Framingham risk) and recommend treatment decisions accordingly (ie, those determined to be high risk at either stage would receive treatment, others would not), thus optimizing the trade-offs in predictive accuracy and

Received June 10, 2013; accepted December 6, 2013.

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The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.113.000397/-/DC1.

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Circ Cardiovasc Qual Outcomes **is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/CIRCOUTCOMES.113.000397**

WHAT IS KNOWN

- Identifying high-risk individuals for statin initiation is a widely-recommended primary prevention strategy.
- Most primary cardiovascular disease (CVD) prevention guidelines in developed countries recommend assessing CVD risk using total risk scores, such as the Framingham risk score, that require cholesterol information.
- A simple, non–laboratory-based CVD risk score has been developed and validated for the US population that could be used as a substitute for or in conjunction with laboratory-based scores.

WHAT THE STUDY ADDS

- Up to 75% of cholesterol laboratory testing used for primary CVD prevention in the United States could be avoided under a multistage screening approach (that uses non–laboratory-based screening as an initial test) without significant reductions in CVD mortality prediction.
- Non–laboratory-based CVD risk assessment could represent a cost-effective primary prevention screening approach in the United States, either as single test or as part of a multistage screening framework.

cost compared with purely laboratory- or non–laboratory-based approaches.[10]

The objectives of this study were to evaluate the potential role of multistage screening using 2 types of analysis: (1) an external validation of the risk discrimination performance of various multistage specifications compared with the Framingham CVD risk score and (2) a cost-effectiveness analysis (CEA) of various multistage specifications compared with Framingham- and non–laboratory-based screening strategies.

Methods

Primary CVD screening strategies were evaluated using 2 types of analyses: (1) receiver operating characteristic (ROC) curve analysis using observational data from the Third National Health and Nutrition Examination Survey (NHANES III) and (2) model-based CEA using data from the 2005 to 2006 and 2007 to 2008 NHANES populations and other published sources. We considered 3 general types of screening strategies for our study: (1) single-stage/Framingham-based strategies, where all individuals aged 25 to 74 years were characterized as high or low risk based on their Framingham CVD risk (this approach is most consistent with current statin treatment guidelines for developed countries)[6]; (2) single-stage/non–laboratory-based strategies, which were similar to the single-stage/Framingham-based approach except that there was no cholesterol testing, and risk characterization was based on non–laboratory-based total risk; and (3) multistage screening, where only a subset of individuals with intermediate-level risk results in a non–laboratory-based assessment would go on to receive laboratory testing, and individuals could be characterized as high risk from stage 1 (based on their non–laboratory-based risk) or stage 2 (based on their Framingham CVD risk).[11]

Multistage Screening Strategy

Stage 1 in the proposed multistage screening approach was to calculate an individual's total CVD risk (ie, risk of having a fatal or nonfatal CVD event) using the following non–laboratory-based risk factors: age, sex, smoking status, history of diabetes mellitus, blood pressure treatment, systolic blood pressure, and body mass index.[8] The resulting total risk predictions were used to identify 3 types of patients from stage 1: (1) high-risk patients, (2) intermediate-risk patients who were identified for laboratory-based risk assessment, and (3) low-risk patients. Framingham-based risk assessment results from stage 2 dictated dichotomous risk characterization (ie, high or low risk) for patients at intermediate risk (as identified by the stage 1). This type of multistage screening strategy was therefore defined by 3 variables: (1) an upper bound for the non–laboratory-based risk assessment (to identify high-risk individuals from the first stage), xU; (2) a lower bound for the non–laboratory-based risk assessment (to identify low-risk individuals from the first stage), xL; and (3) a Framingham-based treatment threshold for those at intermediate risk from the first stage, xT. In the risk discrimination analysis, we compared the Framingham CVD risk score (single-stage/laboratory-based strategy) with 3 versions of the multistage strategy that only used laboratory-based risk assessment for 75%, 50%, and 25% of the population. Appendix A1 in the Data Supplement describes these strategies in more detail. Figure 1 shows how a hypothetical multistage screening strategy would dictate laboratory screening and statin treatment decisions in the model-based CEA.

Study Population for ROC Analysis

NHANES III is a complex, multistage, nationally representative US sample that contains health and nutrition information for 33 394 persons aged ≥2 months.[12] Baseline values were collected from 1988 to 1994, and cause-specific mortality status is available for adults up to 2006, providing ≥10-year follow-up data for these individuals. The general methodology and results for the NHANES III are described elsewhere.[13] Among the 20 050 adults in the NHANES III population, 14 973 were between the ages of 25 and 74 years and 1742 of these individuals were excluded from our study sample for history of myocardial infarction, heart failure, stroke, or cancer, resulting in 13 248 individuals who met our inclusion criteria. Among these individuals, 5999 had complete data required to calculate the Framingham and non–laboratory-based risk scores. Although we focused our study on the population with complete data, we used imputed data to address the possibility of confounding attributable to missing values in our analysis. Appendix A2 in the Data Supplement describes the missing data and imputation approaches used in the risk discrimination analysis.

Risk Discrimination Analyses Using ROC Analysis

The performance in risk discrimination for each screening strategy was assessed using the individual score-specific ranks, with 10-year CVD death as the outcome of interest. Causes of death for the NHANES III population were verified by National Death Index death certificate match. CVD deaths were defined by having an underlying cause of (*International Classification of Diseases*, *Tenth Revision* codes in parentheses) acute myocardial infarction (I21–I22), other acute ischemic heart disease (I24), atherosclerotic cardiovascular disease (I25.0), all other forms of chronic ischemic heart disease (I20, I25.1–I25.9), or cerebrovascular diseases (I60–I69). Sex-specific ROC curves were generated, and areas under the ROC curve (AUCs) were compared for the Framingham CVD risk score and 3 versions of the multistage screening approach defined by different boundary thresholds for intermediate risk. Sensitivity, specificity, positive predictive value, and negative predictive value were also calculated for each screening approach based on a commonly used risk threshold (10-year Framingham CVD risk >10%[6]). The Hosmer–Lemeshow statistic for reclassification index could not be calculated because of the outcome data being restricted to fatal CVD events (the risk scores predict fatal and nonfatal CVD outcomes).[14] We assumed a monotonic relationship between the risk of fatal CVD

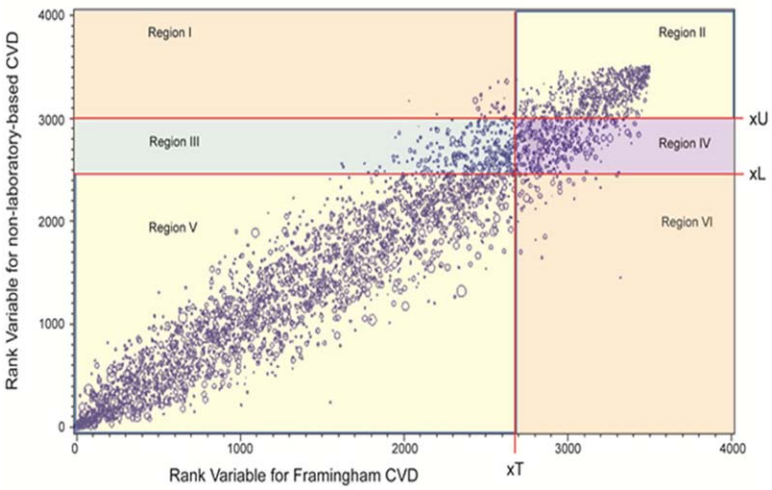

Figure 1. A hypothetical 2-staged primary cardiovascular disease (CVD) screening strategy that incorporates non–laboratory-based risk assessment. In a multistage screening framework, all individuals are assessed using non–laboratory-based risk assessment initially, and those at intermediate risk from the first stage are ultimately assessed using laboratory-based (Framingham) risk. xT is the laboratory-based treatment threshold, xL is the lower bound for laboratory testing (based on non–laboratory-based risk assessment), and xU is the upper bound for laboratory testing (based on non–laboratory-based risk assessment). Compared with laboratory-based risk assessment strategy for all individuals, a multistage strategy would only result in different treatment decisions for individuals in regions I and VI. Regions I and II would be characterized as high risk and recommended for statin treatment but not recommended for laboratory testing from stage 1. Region III would be characterized as intermediate risk and recommended for laboratory testing from stage 1, but not recommended for statin treatment based on stage 2. Region IV would be characterized as intermediate risk and recommended for laboratory testing from stage 1 and recommended for statin treatment based on stage 2. Regions V and VI would characterized as low risk and not be recommended for either laboratory testing or statin treatment from stage 1.

events observed in the data and the composite outcomes predicted by the CVD risk scores in the ROC curve analysis because of this data limitation. The non–laboratory-based score predicted both fatal and nonfatal CVD events similarly compared with laboratory-based scores in its derivation study, which supports our assumption of this monotonic relationship.[8]

Model-Based CEA

We developed a CVD microsimulation model to assess the cost-effectiveness of single-stage and multistage screening strategies that informed laboratory testing and statin treatment decisions. The model projected the lifetime health outcomes and CVD-related costs of 10 000 men and 10 000 women sampled from representative NHANES populations (2005–2006 and 2007–2008 waves) without history of CVD. Figure 2 shows the model structure in terms of general disease states and possible annual transitions. This structure was based on a previously published CVD Markov model in which CVD risk is based on Framingham (laboratory based) risk functions.[15,16] Because this study focuses on primary CVD prevention, all of the individuals started in the disease free (without treatment) health state. Individuals in this health state were screened for CVD using non–laboratory-based (and potentially laboratory based) risk assessment every 5 years at a routine general physician visit, until they were characterized as high risk and received treatment, experienced a coronary heart disease or stroke event, or died. Appendix A3 in the Data Supplement contains detailed information about the model structure, population, input parameters, and calibration of the disease model. Figure 2 depicts the microsimulation model structure.

We projected the average per-person costs and quality-adjusted life years (QALYs) accrued using 20 total risk thresholds for each single-stage strategy and 20 combinations of thresholds for each multistage approach (Appendix A4 in the Data Supplement contains more detail about all 60 strategies evaluated). Strategies were ranked by cost, and then incremental cost-effectiveness ratios were calculated; inefficient strategies were ruled out by strong dominance (higher incremental costs and lower incremental QALYs) or weak dominance (if they had higher incremental costs per QALY than a more effective strategy) per conventional CEA rules.[17] Costs and QALYs were each discounted at 3% as recommended by the US Panel on Cost-Effectiveness in Health and Medicine.[18] Risk thresholds were evaluated separately for men and women because of sex-specific differences in CVD prevalence and severity.

For multistage strategies, we included a sensitivity analysis that allowed for the possibility of higher retention and treatment initiation for patients identified as high risk from stage 1 compared with those identified as intermediate risk in stage 1 and high risk in stage 2 based on the premise that immediate treatment initiation would result in better adherence relative to delayed medication decisions. There is some evidence for the effect of statin initiation timing on adherence for secondary CVD prevention, but there is no analogous study for primary CVD prevention.[19] Therefore, we assumed modest differential rates of 100% initiation for stage 1 and 95% for stage 2 (ie, 5% of individuals characterized as high risk from stage 2 would not receive treatment because of lack of follow-up of laboratory results) in a sensitivity analysis.[20]

We varied the values of all input parameters across plausible ranges in deterministic sensitivity analyses to assess the robustness of model-based CEA results. Given the relative importance of our

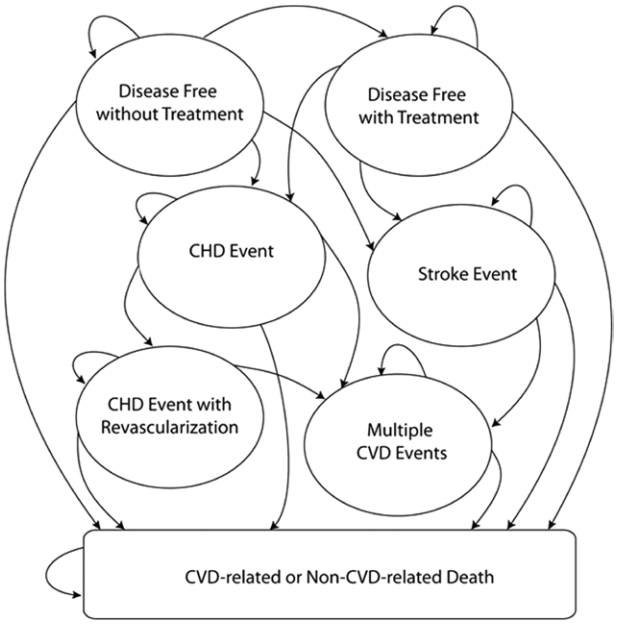

Figure 2. Simplified depiction of the cardiovascular disease (CVD) model. In the microsimulation model, all individuals begin in the disease free without treatment state. Transitions to disease free with treatment depend on the type of screening strategy being evaluated. All other transitions are based on published estimates, with adjustments made for statin treatment when applicable. CHD indicates coronary heart disease.

assumptions around treatment initiation and additional physician visit costs associated with stage 2, we performed 2-way sensitivity analyses around these parameters. We also performed a probabilistic sensitivity analysis to assess the overall uncertainty of our CEA results with respect to joint uncertainty around all model parameters. Detailed deterministic and probabilistic sensitivity analysis methods are described in Appendix A5 in the Data Supplement. There was no need for Institutional Review Board approval because there were no human subjects or animal subjects used for any of our analyses.

Results

Table 1 shows the risk profile characteristics of the NHANES III population used in the risk discrimination analysis by sex for the subpopulation for whom complete data were available. Appendix A6 in the Data Supplement shows the same information for the full population, which includes imputed values for missing data. From 10-year follow-up data for each individual (excluding those with imputed risk characteristics values), there were 118 and 58 CVD deaths for men and women, which represented 26.6% and 25.3% of the total deaths within the 10-year follow-up period, respectively.

Figure 3A and 3B show the ROC curves for the Framingham CVD risk score and the 3 versions of the multistage screening strategy evaluated in the risk discrimination analysis (where 75%, 50%, or 25% of the population would receive laboratory testing). In men, the AUC for the Framingham CVD risk score was 0.776 and the multistage strategies had AUCs of 0.774 to 0.780, with no significant differences between the Framingham and any multistage strategies (all $P>0.5$). In women, the AUC for the Framingham CVD risk score was 0.834 and the multistage strategies had AUCs of 0.812 to 0.827, with no significant differences between the Framingham and any multistage strategies (all $P>0.05$). Table 2 contains detailed information (AUCs with 95% confidence intervals, P values compared with Framingham, sensitivity, specificity, positive predictive value, negative predictive value) for all screening approaches analyzed in the risk discrimination analyses, and Appendix A6 in the Data Supplement contains these results for the imputed population analysis.

Table 3 shows the lifetime, discounted, per-person total cost, and QALY results for the nondominated single-stage/Framingham-based, single-stage/non–laboratory-based, and multistage screening strategies included in the model-based CEA. In the base-case analysis, there were no single-stage/Framingham-based strategies on the efficient frontier (ie, all of the single-stage/Framingham-based strategies were dominated) for men and only 1 for women (at the highest cost and QALY result, with an incremental cost-effectiveness ratio of $330 000/QALY). At a willingness to pay for health estimate of $50 000/QALY, single-stage/non–laboratory-based thresholds of >2% and >7.5% would be optimal primary CVD screening strategies for men and women, respectively. At a WTP for health estimate of $100 000/QALY, different forms of multistage screening strategies would be optimal for men and women. Various forms of single-stage/non–laboratory-based and multistage strategies would be optimal at lower WTP estimates ($8000–$45 000/QALY).

Table 1. Population Characteristics of the NHANES III Population Who Met Inclusion Criteria

	Men (n=3501)	Women (n=2497)
Age, y	47.0	45.6
Currently smoker, %	53.8	59.4
History of diabetes mellitus, %	6.5	7.8
Blood pressure treatment, %	11.1	13.5
Systolic blood pressure, mm Hg	129.1	122.3
Total cholesterol, mg/dL	205.1	206.5
HDL cholesterol, mg/dL	47.4	54.6
Body mass index, kg/m^2	26.7	27.4

HDL indicates high-density lipoprotein; and NHANES III, Third National Health and Nutrition Examination Survey.

Model-based CEA results were most sensitive to variations in stage-specific physician costs and treatment initiation assumptions, statin costs, disutility associated with taking statins, statins-induced diabetes mellitus, and model time horizons. Specifically, excluding extra physician costs (to follow up on laboratory results) associated with stage 2 favored approaches that involved laboratory testing (ie, single stage/Framingham based and multistage), higher treatment initiation from stage 1 favored the single-stage/non–laboratory-based approach, whereas higher statin costs, larger disutility from taking statins, statin-induced diabetes mellitus risks, or lower model time horizons favored stricter (ie, higher) treatment thresholds for all types of strategies. Probabilistic sensitivity analysis results were similar to the base-case findings. Appendices A5 and A7 in the Data Supplement contain details on the methods and results of the sensitivity analysis, respectively.

Discussion

In this study, we proposed and evaluated a multistage primary CVD screening framework for adults in the United States without history of CVD. Our discrimination analysis showed that multistage screening approaches discriminated risk of CVD death comparably with the Framingham risk score while avoiding 25% to 75% of laboratory tests that would be used for primary CVD prevention. We also found that cost-effective screening guidelines (assuming commonly used cost-effectiveness thresholds of $50 000–100 000/QALY) included non–laboratory-based risk assessment as a single-stage or as part of multistage screening approach. Single-stage/Framingham-based screening, which is the approach that is most consistent with current screening recommendations in developed countries, was dominated or offered poor value for money based on typical standards for cost-effectiveness ratios (eg, with incremental cost-effectiveness ratio >$300 000/QALY, which significantly exceeds oft-used benchmarks of $50 000 or $100 000 per QALY) in our base-case CEA.[21] Our cost-effectiveness results were most sensitive to assumptions regarding statin costs, disutility associated with taking statins, statin-induced diabetes mellitus, model time horizon, extra physician visit costs associated with laboratory testing, and the effect of treatment initiation timing on statin adherence.

Our risk discrimination results would confirm the intuition physicians might hold for low- and high-risk individuals screened for primary CVD risk, which is that laboratory testing will not change the risk assessment and treatment

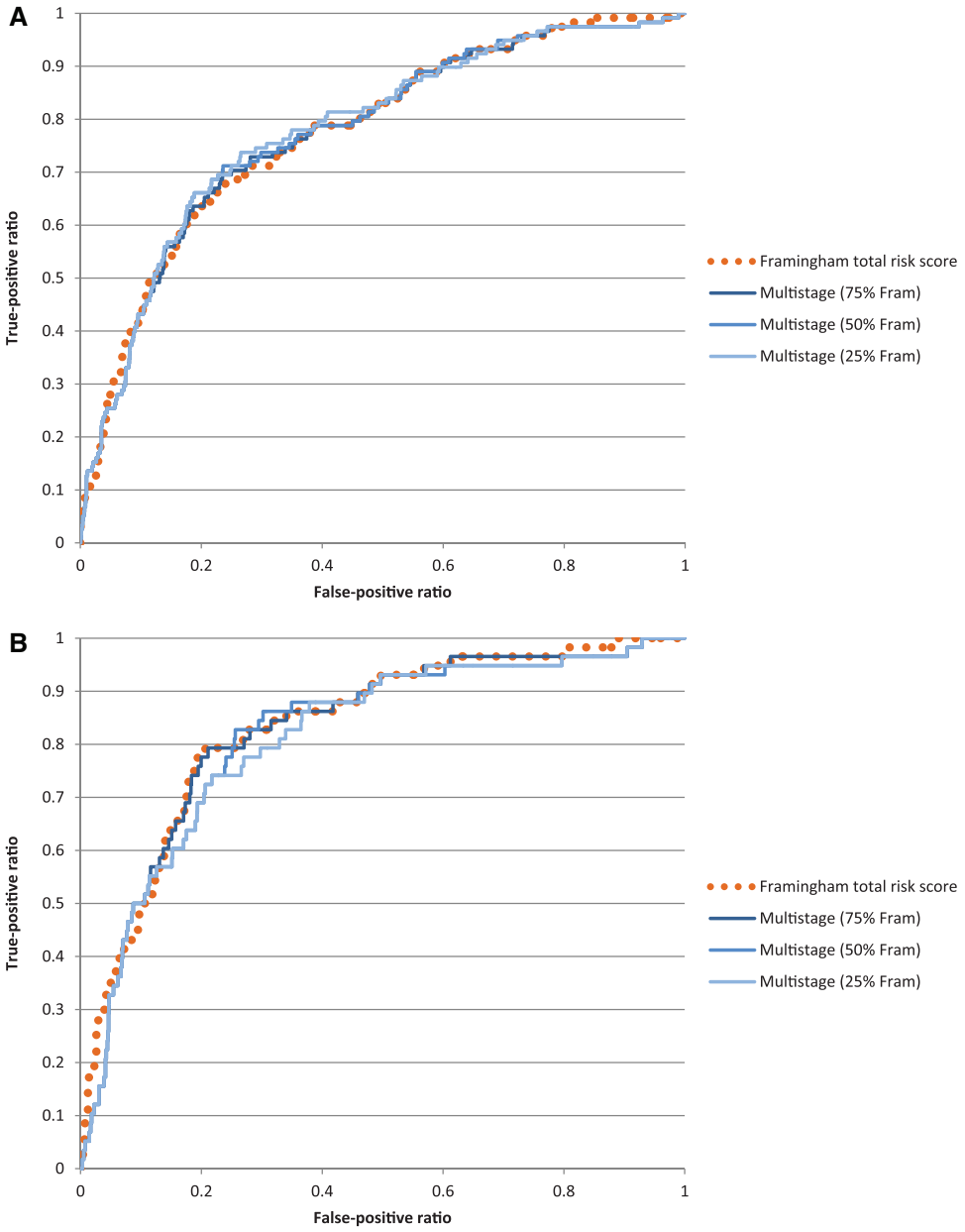

Figure 3. Receiver operating characteristic (ROC) curves (10-year cardiovascular disease [CVD] death outcome) for multistage and Framingham CVD risk scores for (**A**) men and (**B**) women. ROC curves for the 3 versions of the multistage screening strategy (with 25%, 50%, and 75% of the population receiving laboratory-based testing) and the Framingham (Fram) CVD scores, with 10-year CVD death as the outcome of interest, for individuals with complete data. For men (**A**), the performances in risk discrimination, as assessed by area under the ROC curve (AUC) were 0.776, 0.774, 0.778, and 0.780 for the Framingham CVD and multistage (75%, 50%, and 25% of adults receiving laboratory-based risk assessments) risk scores, respectively, with a *P* value for the differences compared with the Framingham score of 0.71, 0.74, and 0.57. For women (**B**), the corresponding AUC results were 0.834, 0.827, 0.819, 0.812, with *P* values for the differences compared with the Framingham score of 0.15, 0.14, and 0.06.

decisions in most cases. Cholesterol information might influence decisions for those at intermediate risk, especially considering previous evidence that there were significant differences in predicting CVD death between the Framingham and non–laboratory-based score in women.[9] In this study, we found no significant difference between the multistage screening approaches and the Framingham risk score in the same population. In our model-based CEA, we assumed that cholesterol levels influenced the underlying risk in patients (and non–laboratory-based risk assessment was only used a proxy for this true Framingham-based risk function) and still found that universal laboratory testing was an inefficient use of healthcare resources compared with non–laboratory-based or multistage approaches.

A recent modeling study by Chamnan et al[10] assessed the impact of a multistage screening framework that incorporated simple CVD risk assessment (using the Cambridge risk score) as an initial phase and found that their multistage approach could produce a similar number of CVD events avoided compared with more expensive laboratory-based strategies in the United Kingdom. Costs were not explicitly modeled in that study; however, screening and treatment

Table 2. Risk Discrimination Results for Multistage and Universal Framingham Strategies

Strategy	AUC (95% CI)	*P* Value vs Framingham	Sensitivity*	Specificity*	PPV*	NPV*
Men						
Framingham	0.776 (0.733–0.819)	…	0.814	0.516	0.055	0.988
Multistage 75%†	0.774 (0.730–0.819)	0.710	0.458	0.886	0.124	0.979
Multistage 50%†	0.778 (0.734–0.822)	0.743	0.695	0.766	0.094	0.986
Multistage 25%†	0.780 (0.736–0.824)	0.567	0.788	0.636	0.070	0.988
Women						
Framingham	0.834 (0.782–0.885)	…	0.793	0.759	0.073	0.994
Multistage 75%†	0.827 (0.773–0.880)	0.152	0.552	0.885	0.103	0.988
Multistage 50%†	0.819 (0.764–0.875)	0.140	0.741	0.761	0.069	0.992
Multistage 25%†	0.812 (0.756–0.869)	0.063	0.828	0.635	0.051	0.994

AUC indicates area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; and PPV, positive predictive value.

*Using >10% 10-year Framingham cardiovascular disease risk as positivity criterion (for multistage strategies, this is only applied to individuals at intermediate risk because Framingham risk would not be known for others). Those with non–laboratory-based risk >xU (upper bound for laboratory testing) in multistage also used for positivity criterion.

†Multistage formulations that resulted in 75%, 50%, and 25% of the population receiving laboratory testing.

thresholds were based on relatively arbitrary cutoffs (ie, 20% of Cambridge score risk distribution) as opposed to optimized thresholds informed by CEA. Despite the differences in study approaches, our risk discrimination and cost-effectiveness findings support the policy conclusions from that study, which is that non–laboratory-based and multistage screening guidelines might save enough resources from reduced laboratory tests to justify any reduction in screening accuracy from the lack of cholesterol information.

Recent studies have evaluated the cost-effectiveness of primary CVD screening guidelines for statin treatment decisions in developed countries, but none of these economic evaluations incorporated a non–laboratory-based screening component.[22–26] The non–laboratory-based and multistage screening frameworks are consistent with the evolving trend of primary risk CVD assessment, which is moving away from single risk factor–based guidelines to total risk-based (or personalized) approaches.[27] The incorporation of a non–laboratory-based component can allow physicians to make treatment decisions faster and at lower costs compared with current laboratory-based recommendations. Our study is the first to evaluate the trade-offs between risk discrimination performance, screening costs, and health benefits after incorporating simple risk assessment.

Our study has several important limitations. First, the outcome in our risk discrimination (ROC curve) analysis did not

Table 3. Base-Case Cost-Effectiveness Results for Nondominated Multistage and Single-Stage Primary CVD Screening Strategies for Adults in the United States

Strategy Type	Threshold(s)	Costs	QALYs	ICER
Men				
No treatment or laboratory screening	…	$15 988	19.593	…
Single stage, non–laboratory based	>12.5% nonlaboratory risk	$16 524	19.668	$7100
Multistage 28%*	xL=7.5%; xU=25%; xT=10%	$16 702	19.684	$12 000
Multistage 15%*	xL=3%; xU=5%; xT=5%	$17 043	19.706	$15 000
Single stage, non–laboratory based	>2% nonlaboratory risk	$17 232	19.710	$46 000
Multistage 24%*	xL=0.5%; xU=2%; xT=1%	$17 387	19.713	$52 000
Women				
No treatment or laboratory screening	…	$8971	21.301	…
Single stage, non–laboratory based	>15% nonlaboratory risk	$9748	21.344	$18 000
Single stage, non–laboratory based	>10% nonlaboratory risk	$9992	21.349	$45 000
Single stage, non–laboratory based	>7.5% nonlaboratory risk	$10 167	21.352	$50 000
Multistage 56%*	xL=1%; xU=7.5%; xT=3%	$10 589	21.358	$83 000
Single stage, Framingham based	>3% Framingham risk	$10 697	21.358	$330 000

CVD indicates cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; xL, the lower bound for laboratory testing (based on non–laboratory-based risk assessment); xT, the laboratory-based treatment threshold; and xU, the upper bound for laboratory testing (based on non–laboratory-based risk assessment).

*Multistage formulations that resulted in 28%, 15%, 24%, and 56% of the population receiving laboratory testing.

include nonfatal CVD events, but the non–laboratory-based risk score was shown to predict fatal and nonfatal CVD outcomes with similar accuracy compared with laboratory-based approaches.[8] Our model-based CEA, however, explicitly modeled both fatal and nonfatal CVD events and their cost, morbidity, and mortality implications. Second, we assumed that the benefits from statin treatment were constant for a long time horizon and across a wide spectrum of risk in the model-based CEA. Although most statin trials have not extended beyond 5 years, the former assumption is commonly made in modeling studies with lifetime horizons (with treatment adjustments made for compliance and adverse events).[23–26,28,29] The latter assumption is supported by findings from the recent Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial and Cholesterol Treatment Trialist's (CTT) Collaborators' meta-analysis, which suggested that statin benefits are not different between healthy and higher-risk individuals.[30,31] Third, we only considered age-constant screening and treatment thresholds in our study, although there is evidence that age-specific thresholds could result in efficiency gains.[22] Although we recognize that younger individuals have longer tails of life expectancy, and this could affect optimal specifications of treatment thresholds, we opted to only consider age-constant thresholds to minimize the complexity of our policy recommendations. Fourth, our microsimulation model was biased in favor of the Framingham-based screening strategies attributable to the underlying (Framingham) risk functions that determined CVD outcomes in the model. This assumption was conservative in terms of the role of non–laboratory-based and multistage risk screening strategies, which were shown to be cost effective relative to Framingham-based screening despite this bias.

Our cost-effectiveness results suggest that the benefits treating individuals for primary CVD prevention with statins would outweigh the costs and risks of taking these drugs. Some have argued that statins are overprescribed in individuals without history of CVD.[32] However, our empirical analysis of the NHANES III population shows that multistage screening could be applied to any targeted primary prevention strategy, such as smoking cessation or intensive diet and exercise interventions, if a statin-based approach is not justified. In addition, although we found that cost-effective treatment thresholds were sensitive to several statin-related model parameters (such as stain price, disutility associated with taking statins, and statin-induced diabetes mellitus), all efficient screening approaches in these scenarios were still heavily based on non–laboratory-based and multistage strategies.

Our multistage screening framework is relatively more complex than single-stage strategies, and recent modeling studies have evaluated the use of novel CVD biomarkers (such as C-reactive protein) or more detailed treatment algorithms (that vary depending on the statin type and dosage based on additional risk thresholds) that were not considered in our analysis.[25,33] Although we do not question the potential importance of these additional considerations, we opted to focus on the incorporation of the non–laboratory-based screen stage instead of attempting to simultaneously evaluate a large number of factors that could influence the efficiency of CVD screening guidelines. Future observational and model-based analyses can incorporate these considerations, and other developments related to CVD screening and treatment, into multistage screening studies.

Policy Implications and Conclusions

Previous studies have identified the potential for efficiency gains from incorporating non–laboratory-based into a multistage primary CVD screening framework. Our study explicitly evaluated the trade-off between lower costs and reduced screening accuracy from substituting simple risk assessment for conventional laboratory approaches. In our risk discrimination analyses, we found that multistage screening approaches could predict 10-year CVD death comparably with the Framingham risk score while saving 25% to 75% laboratory testing used in primary CVD screening efforts. We also found that universal laboratory-based guidelines (ie, single stage/Framingham based) were not efficient screening options compared with non–laboratory-based or multistage screening frameworks across a wide range of relevant willingness-to-pay estimates for health ($10 000–$100 000/QALY). Future studies can apply this multistage screening framework in other developed countries, as well as in low- and middle-income countries, where the screening and treatment conditions would likely lead to different formulations of optimized laboratory testing and statin treatment thresholds.

Sources of Funding

Dr Gaziano is supported by grant No. 5R01HL104284-03 from the Harvard School of Public Health from the National Heart, Lung, and Blood Institute.

Disclosures

Dr Weinstein has a consulting relationship with Optuminsight, a company that does economic analyses for the pharmaceutical and device industries. The other authors report no conflicts.

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Circulation
Cardiovascular Quality and Outcomes

Who Needs Laboratories and Who Needs Statins?: Comparative and Cost-Effectiveness Analyses of Non–Laboratory-Based, Laboratory-Based, and Staged Primary Cardiovascular Disease Screening Guidelines

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Circ Cardiovasc Qual Outcomes. 2014;7:25-32; originally published online January 14, 2014;
doi: 10.1161/CIRCOUTCOMES.113.000397
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713

Appendices for: Who needs labs and who needs statins? Comparative and cost effectiveness analyses of non-laboratory-based, laboratory-based, and staged primary cardiovascular disease screening guidelines.

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Appendix A1: Multistage strategies evaluated in the risk discrimination analysis

Receiver operator characteristic (ROC) curve analysis requires individual-level ranks and a binary outcome of interest (sometimes referred to as the "gold" or "reference" standard). For the Framingham risk score, individuals were ranked according to the cardinal 10-year CVD risk. For multistage strategies, risk rankings were determined using a hierarchy based on screening stage. Specifically, individuals characterized as "high-risk" in the first stage (i.e., their non-laboratory-based risk was greater than the xU threshold) were all assigned higher ranks than "intermediate-risk" individuals risk (i.e., their non-laboratory-based risk was lower than the xU but higher than the xL thresholds). Similarly, intermediate-risk individuals were all assigned ranks that were higher than low-risk individuals (i.e., their non-laboratory-based risk was lower than the xL threshold). Ranks within each group were determined by non-laboratory-based risk (for high- and low-risk individuals) or Framingham-based risk (only for intermediate-risk individuals). No Framingham-based treatment thresholds (xT) were needed for the ROC curve analysis since that threshold would not affect the rankings of individuals. Table A-1 below shows the non-laboratory-based thresholds (xL, xU) and proportions of the population characterized as high-, intermediate-, and low-risk for each multistage screening strategy evaluated in the risk discrimination analysis (for the subset of the study population with complete risk factor data).

Table A-1. Non-laboratory-based thresholds and risk characterizations for multistage screening strategies evaluated in the risk discrimination analysis (NHANES III population)

Multistage strategy	xU	xL	%high-risk*	%intermediate-risk*	%low-risk*
MEN					
MS75	32.6%	1.9%	12.5%	75%	12.5%
MS50	21.3%	3.3%	25%	50%	25%
MS25	13.6%	5.3%	37.5%	25%	37.5%
WOMEN					
MS75	27.9%	1.2%	12.5%	75%	12.5%
MS50	16.1%	2.0%	25%	50%	25%
MS25	9.4%	3.2%	37.5%	25%	37.5%

*as determined by the first (non-laboratory-based) stage in the multistage screening framework

Appendix A2: Missing data in the NHANES III population and imputation methods

The most common missing variable among individuals who met the inclusion criteria was smoking (missing in 39% and 61% of men and women, respectively), followed by total/HDL cholesterol (missing in 9% and 7% of men and women, respectively). The NHANES III data files contain five multiple imputation datasets that fill missing data with plausible values using independent draws from predictive distributions, which were generated using multivariate regression methods. The detailed methodology and performance of the NHANES III multiple imputation procedures have been previously reported.[1, 2] Imputed datasets were complete for all variables needed to calculate risk predictions for the five scores included in this study, aside from missing values for history of diabetes for 17 individuals (6 men, 11 women). As an additional analysis, we combined results from multiple imputation datasets (with adjustment for underestimated variance) using methods outlined by Rubin (1987) for scalar (i.e., one-dimensional) estimates.[2] Table A-2 shows the risk profile characteristics of the NHANES III population used in the risk discrimination analysis by sex using the imputed datasets.

Table A-2. Population characteristics of the NHANES III population (including those with imputed values) that met inclusion criteria

	MEN (n=6,273)	WOMEN (n=6,958)
Age (years)	45.5	45.5
Currently smoker (%)	38.2	23.1
History of diabetes (%)	5.3	7.8
Blood pressure treatment (%)	10.1	13.2
Systolic blood pressure (mmHg)	127.4	122.0
Total cholesterol (mg/dL)	201.8	203.9
HDL cholesterol (mg/dL)	47.3	54.7
Body-mass index (kg/m^2)	26.7	27.6

Appendix A3: CVD micro-simulation model

Lifetime health and CVD cost outcomes were projected for a representative population of adults (initially aged 25-74 years) in the U.S. without history of CVD or statin treatment. Figure 2 in the main text shows the model structure in terms of general disease states and possible annual transitions.

Transitions from either Disease Free state (with or without treatment) to CHD or stroke events were based on total risk equations derived from the Framingham Study.[3, 4] It is important to note that these risk equations are (partially) informed by total and HDL cholesterol levels, giving clinical significance to the laboratory-based screening stage. Non-CVD-based mortality was informed by age- and sex-specific U.S. life tables.[5] Acute (i.e., within one year of experiencing the event) and chronic (i.e., all years beyond the first year of the event) post-event mortality were estimated separately. Repeat and subsequent CHD and stroke events were tracked for each individual and affected mortality, quality-of-life, and costs, accordingly. Figure A-1 (from Gaziano et al. 2005)[6] shows the possible transitions from the Disease Free in more detail.

Figure A-1. Possible transitions from the Disease Free health state

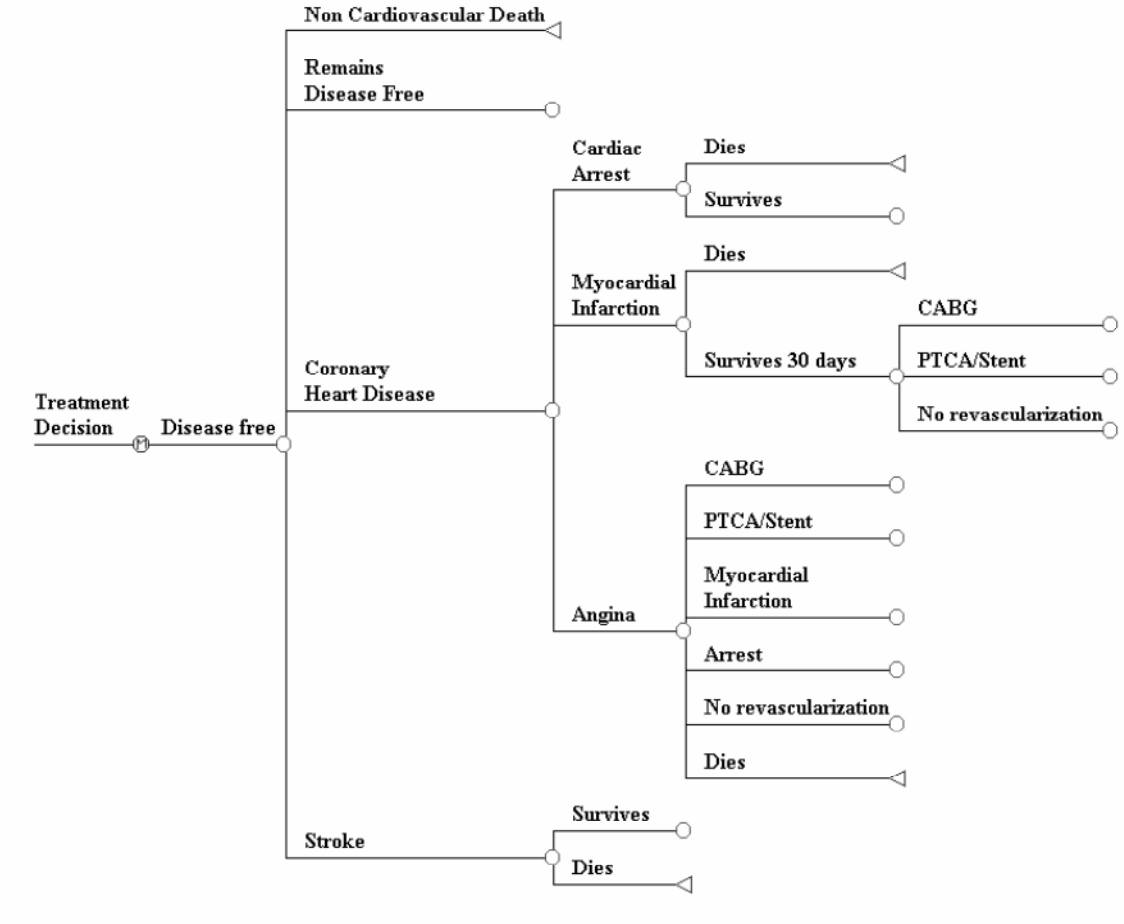


Table A-3 contains all of the disease input parameters used in the model.

Table A-3. Disease progression inputs used in the CVD micro-simulation model

Parameter	Value	Source
From Disease Free State		
Non-CVD death	Age- and sex-specific table	NCHS 2010[5]
Stroke event	RF-based equation*	Wolf 1991[4]
CHD event	RF-based equation*	Anderson 1991[3]
% Cardiac Arrest	Age- and sex-specific table	Gaziano 2005[6]
% MI (males)	0.350	NHLBI 2006[7]
% MI (females)	0.200	NHLBI 2006[7]
% Angina	Formula	100% - % Cardiac arrest - %MI
From Cardiac Arrest State		
Acute (within 1 year) death	0.954	Nichol 2008[8]
Chronic (post 1st-year) death	0.040	Assumption: same as MI
From MI State		
Acute death	Age- specific table	Roger 2002[9]
Acute CABG	0.082	Fang 2010[10]
Acute PTCA	0.300	Fang 2010[10]
% Procedure death	0.009	Dorros 1984[11]
Acute 2nd MI (no PTCA)	0.060	Capewell 2006[12]
Acute 2nd MI (after PTCA)	0.052	BARI 1996[13]
Chronic (post 1st-year) death	0.040	Law 2002[14]
>1 previous MI	0.100	Law 2002[14]
Repeat MI	0.064	Jokhadar 2004[15]
From MI and CABG State		
Acute post-CABG death	0.027	Peterson 2004[16]
Acute 2nd MI	0.051	BARI 1996[13]
Chronic (post 1st-year) death	0.040	Assumption: same as MI
>1 previous MI	0.100	Assumption: same as MI
Repeat MI	0.039	Jokhadar 2004[15]
From Angina State		
Acute death	0.045	Capewell 2006[12]
Acute cardiac arrest	0.006	Hsia 2008[17]
Acute MI	0.035	Hemingway 2003[18]
Acute CABG	0.200	Ford 2007[19]
Acute PTCA	0.300	Ford 2007[19]
Chronic (post 1st-year) death	0.030	Law 2002[14]
Chronic (post 1st-year) MI	0.035	Hemingway 2003[18]
From Angina and CABG State		
Chronic (post 1st-year) death	0.018	Law 2002[14]
Chronic (post 1st-year) MI	0.021	Hemingway 2003[18]

Table A-3. Disease progression inputs used in the CVD micro-simulation model (cont.)

Parameter	Value	Source
From Stroke State		
Acute death	0.140	Lee 2010[20]
Chronic (post 1st-year) death	0.050	Law 2002[14]
>1 previous MI	0.100	Law 2002[14]
Repeat stroke event	0.040	Hardie 2004[21]
Chronic (post 1st-year) MI	0.022	Touze 2005[22]

**RF (risk factors) included: age, sex, current smoking status, diabetes history, antihypertensive treatment, systolic blood pressure, total cholesterol, HDL cholesterol, history of CVD (for stroke risk only)*

Where: "MI" indicates myocardial infarction, "CABG" indicates coronary artery bypass graft, "PTCA" indicates percutaneous transluminal coronary angioplasty

MI and angina patients also faced probabilities of having coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) procedures. Patients receiving CABG procedures moved to separate MI-CABG and angina-CABG health states, where their risks of repeat MI were lowered (relative to not having CABG), and lower risks of death for angina-CABG. Patients receiving PTCA procedures had lower risks of acute (i.e., within one year of experiencing the initial CHD event) MI (repeat MI, for MI patients), but did not move to a different health state. Individuals in CHD health states were all at risk for subsequent MI and stroke risks. If subsequent MI or stroke risks were experienced, patients incurred short-term cost and utility consequences (same as acute costs and utilities), and moved to health states with worse prognosis (i.e., CHD patients that experienced subsequent strokes moved to the stroke health state, and angina patients that suffered later MIs moved to the MI state). Patients in CVD health states experienced the higher of constant rates (i.e., 4% for post -MI and -cardiac arrest, 3% for post-angina, and 5% for post-stroke) or age- and sex-specific all-cause mortality. Repeat MIs (>1 lifetime MIs) increased the risk of death to 10% annually.

Model validation and calibration

To assess the validity of our model projections in the U.S. setting, we compared model-generated CVD incidence to observed rates from large U.S. cohort studies. Specifically, we used the

Framingham Offspring Cohort (observation years 1980-2003) and Atherosclerosis Risk in Communities (ARIC, observation years 1987-2001) as benchmarks for age- and sex-specific CHD and stroke incidence rates. When model-generated rates fell outside of the upper and lower observed rates from the Framingham Offspring and ARIC cohort studies, we manually calibrated sex-specific CHD and/or stroke incidence parameters such that the resulting model incidence rates fell between the observed ranges. Consistent with other CHD simulation models[23], we started our calibration exercise by adjusting the intercept coefficients for the underlying CHD and stroke risk functions.[3, 4] Beta coefficients for age were also calibrated if further adjustments were needed to meet calibration targets.

Model calibration results

Prior to calibration, for men our model predicted CHD events well but underestimated stroke events, while for women the reverse was true. After model calibration, the CHD and stroke incidence rates produced by the calibrated model fell within observed ranges (based on the Framingham Offspring and ARIC cohorts) for 13 out of 16 outcomes (sex-specific CHD and stroke incidence for 35-44, 45-54, 55-64, and 75-84 year age groups) and were within 0.5 events per 1000 person-years for all 16 target ranges.

For men, no underlying CHD risk function[3] parameters were calibrated, but the intercept term for the underlying stroke risk function was changed from 5.677 (coefficient value reported in literature[4]) to 5.300. For women, the intercept term ("Theta 0") was changed from 0.9145 to 0.3000, and the beta coefficients for log(age) ("Beta 2"), log(age)*female ("Beta 4"), and log(age)*log(age) ("Beta 5") were all adjusted (from -1.4792 to -1.4800, -14.4588 to -14.4550, and 1.8515 to 1.7800, respectively). The stroke intercept term for women was changed from 7.5766 to 6.6150.

Figure A-2 shows the age-specific model calibration results for CHD incidence in men (panel 1-2a) and women (panel A-2b), and stroke incidence in men (panel A-2c) and women (panel A-2d). The Framingham Heart Study (FHS) offspring had higher rates compared to ARIC population, in part due to a

larger CHD definition (MI, angina, coronary insufficiency, fatal CHD) compared to ARIC (MI or death from CHD). The ranges for older age groups had the largest discrepancies between the FHS offspring and ARIC rates due to the small number of person-years in those age groups (~1,600 and ~2,800 person-years in the FHS offspring and ARIC cohorts in the 75-84 year age groups, compared to person-years of ~10,000 and ~49,000 in the 65-74 year age groups, respectively).[7]

Figure A-2a. Calibration results for CHD incidence, men

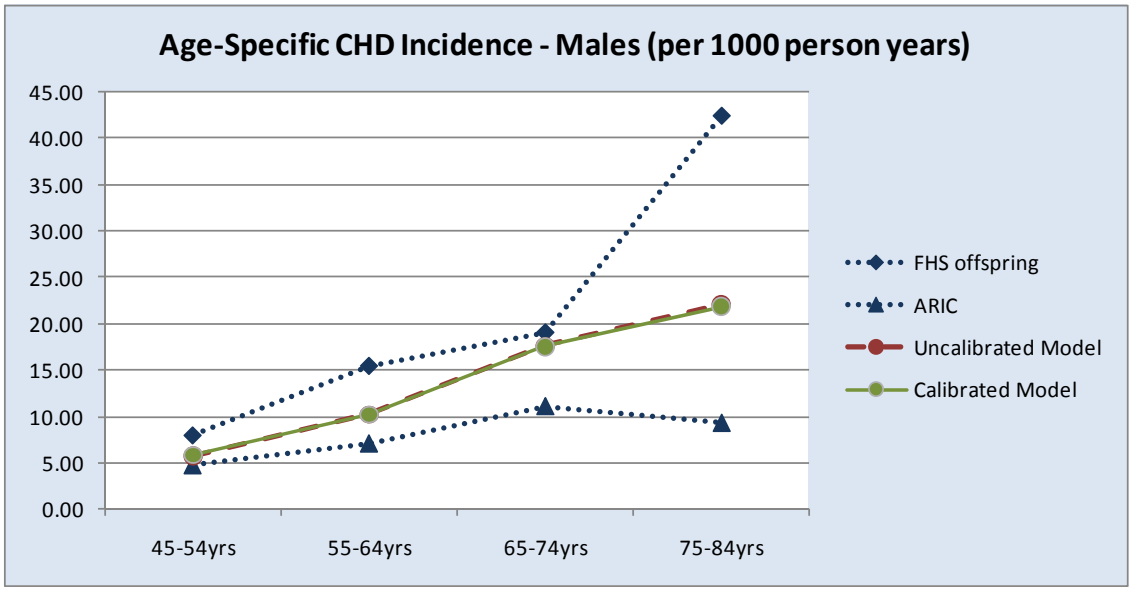


Figure A-2b. Calibration results for CHD incidence, women

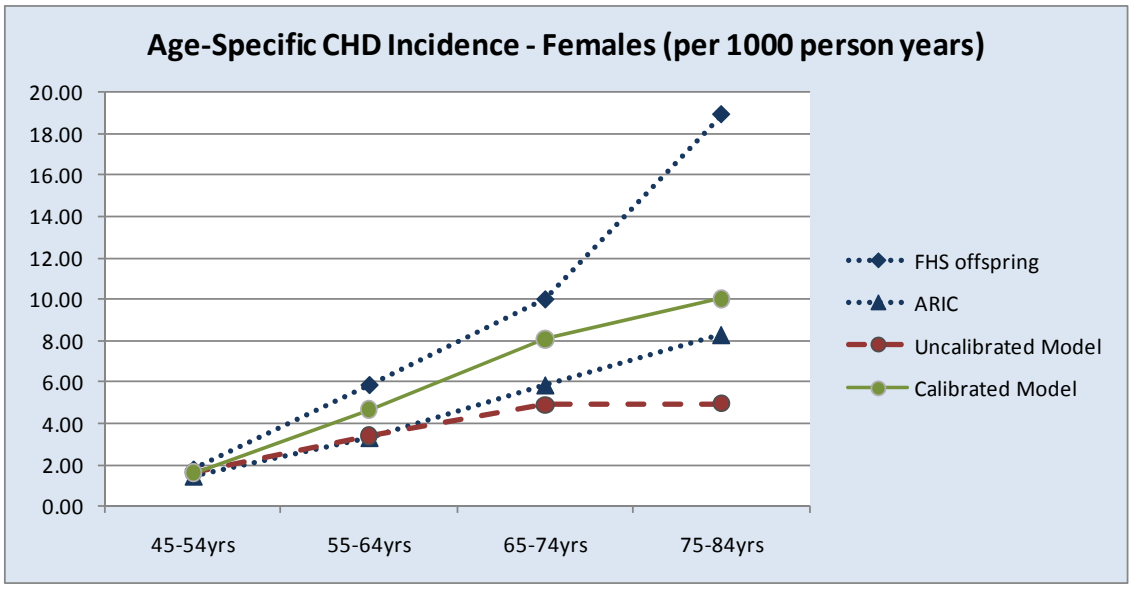


Figure A-2c. Calibration results for stroke incidence, men

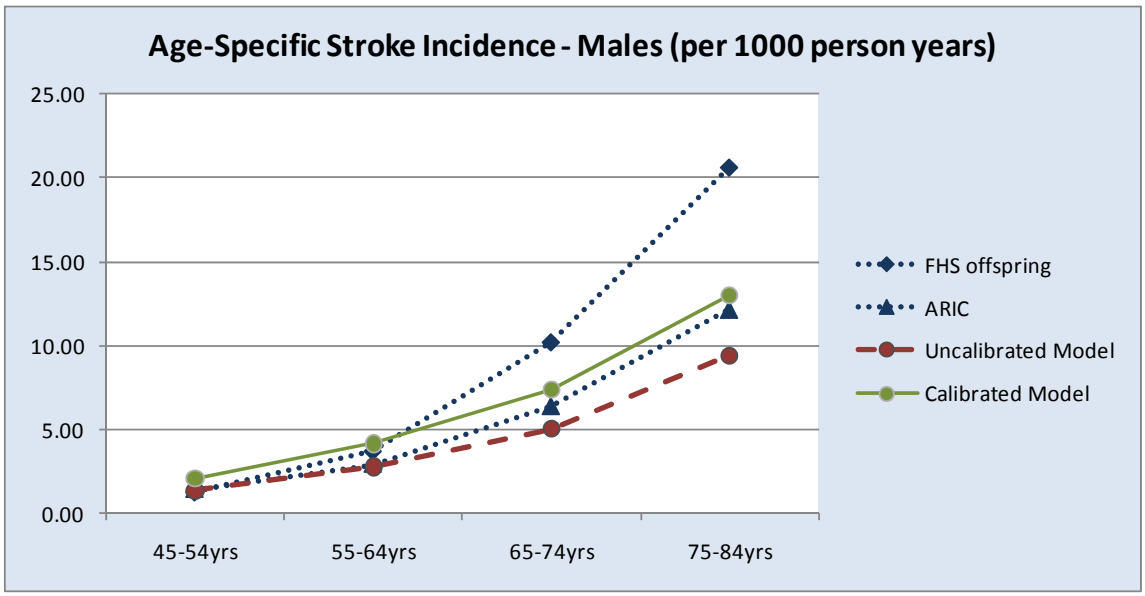
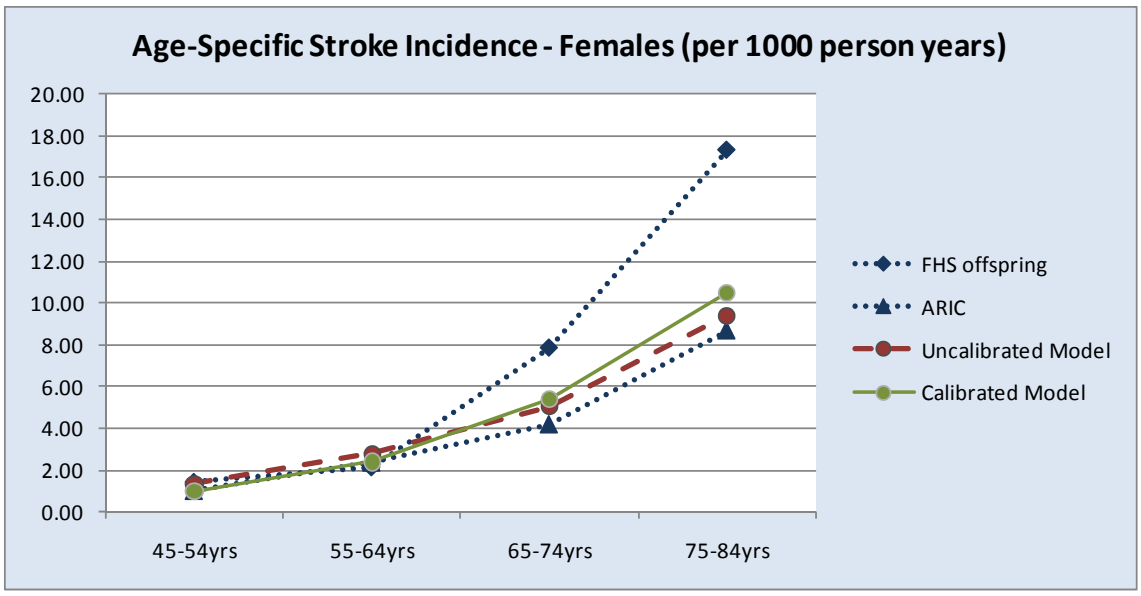


Figure A-2d. Calibration results for stroke incidence, women



Costs and utilities

Like post-event mortality, CVD event costs were estimated separately for acute and chronic events. Base-case event-based cost values were estimated from a recent analysis of a large managed care population in the U.S., and Medicare reimbursement rates were used in sensitivity analyses. Base-case statin costs were estimated from the lowest Red Book prices for generic 40 mg simvastatin

($93/year), and were increased to the average of simvastatin and atorvastatin ($1150/year) in sensitivity analyses (average statin price of $620/year). Primary CVD screening and statin-related adverse event costs were comprised of general practitioner visits and/or laboratory fees. We assumed additional costs for one extra physician visit and cholesterol panel for laboratory-based risk assessment, but evaluated scenarios without the extra physician costs in one-way and two-way sensitivity analyses. Table A-4 describes the cost inputs used in the base-case model and deterministic sensitivity analyses.

Quality-of-life (i.e., utility) decrements were applied to each year in spent in CVD event states, and were based on EQ-5D estimates from the Medical Expenditure Panel Survey. Event-specific utilities were multiplied to time spent in each state to calculate quality-adjust life years (QALYs). Table A-4 contains all of the utility information used in the model. We assumed a small annual utility decrement for each year spent on statin therapy (0.001 in the base-case, 0.005 and 0.000 in sensitivity separate analyses). Costs were considered from the healthcare payer perspective (in 2009 dollars), and were discounted (along with QALYs) at a 3% rate.[24]

Treatment parameters and assumptions

If patients in the Disease Free state received statin treatment, their CHD and stroke risks were multiplied by relative risk estimates of 0.77 and 0.84, respectively. Mild (muscle pain) and major (rhabdomyolysis and renal failure) adverse event rates (17.5% and 0.01%, respectively) were based on large observational studies of statin safety. Statin-induced type 2 diabetes was incorporated in a sensitivity analysis given the recent findings in statin trials and meta-analyses.[25] Since the effect of statin-induced diabetes on CVD is already reflected in the hazard ratios for statins on CVD events, we model the quality-of-life and cost impacts of statin-induced diabetes (annual incremental rate of 0.0047% for those taking statins). Exposing all individuals taking statins to this increased risk of diabetes in this scenario was conservative with respect to statin treatment, since the JUPITER trial findings suggest that only patients at with one or more major risk factors for diabetes (65% of the trial

population, which his likely higher than the proportion of adults in the U.S. without CVD with these risk factors) faced a significant risk of developing diabetes.

Drug compliance was derived from published estimates, with real-world treatment rates of 67% in the first year of statin initiation, 53% in the second year, and 50% in the third and all subsequent years. Treatment effectiveness and costs were both reduced proportionately with compliance rates. Drug initiation (i.e., having any chance to receive treatment after a "high-risk" diagnosis) was assumed to be 100% for all individuals that had been prescribed statins, but was varied in the sensitivity analyses for all strategies (using a rate of 80%) and for laboratory-based diagnoses only (this is explained further in the *Sensitivity analysis* section of the main text). Table A-4 outlines these parameters and values/ranges used in deterministic sensitivity analyses.

Table A-4. Cost (2009 US dollars), utility, and treatment inputs used in the CVD micro-simulation model

Parameter	Base-Case Value	Sensitivity Analysis Value(s)	Base-Case Source
Acute Costs for Disease States[A,B]			
Cardiac arrest	$17,790	$5,100	O'Sullivan 2011[26]
MI	$52,030	$4,860	O'Sullivan 2011[26]
Angina	$26,900	$2,550	O'Sullivan 2011[26]
Stroke	$12,610	$12,850	O'Sullivan 2011[26]
Acute Costs for Procedures[A,B]			
CABG	$34,040	$25,360	O'Sullivan 2011[26]
PTCA	$32,080	$13,940	O'Sullivan 2011[26]
Chronic Annual Costs for Disease States[B]			
All CHD states	$2,990	+/-15%	Mark 2008[27], Tsevat 2001[28]
Stroke	$1,940	+/-15%	Pignone 2006[29]
Screening Costs[B]			
Non-lab test (GP visit in Stage 1)	$65	$45-85	RBRVS 2009[30]
Cholesterol (lab) test	$32	$14-45	RBRVS 2009[30]
# extra GP visits during Stage 2	1	0	Assumption
# lab tests/year after treatment	1	Not varied	Lazar 2011[31], expert opinion
# GP visits/year after treatment	1	Not varied	Lazar 2011[31], expert opinion
Statin Drug and Adverse Event Costs			
Statin (annually)	$93	$620	Redbook 2009[32]
Statin-induced diabetes (age<45 yrs)	n/a	$3,800	AHRQ 2012[33]
Statin-induced diabetes (age≥45 yrs)	n/a	$5,090	AHRQ 2012[33]
Mild adverse event[C]	$160	$150-250	RBRVS 2006[30], Lee 2010[20]
Major adverse event[C]	$6,480	$5,300-6,900	RBRVS 2006[30], Lee 2010[20]
Utilities for Disease States[B]			
Disease free (no treatment)	1.000	Not varied	Assumption
Disease free (on treatment)	0.999	0.995, 1.000	Assumption, Greving[34]
Cardiac arrest	0.808	+/-15%	Sullivan 2006[35], Taylor 2009[36]
MI	0.778	+/-15%	Sullivan 2006[35]
Angina	0.768	+/-15%	Sullivan 2006[35]
Stroke	0.768	+/-15%	Sullivan 2006[35]
Disutilities for Repeat Events, Statin Treatment, and Statin Adverse Events[B]			
Repeat MI event	-0.049	+/-15%	Sullivan 2006[35]
Repeat Stroke event	-0.052	+/-15%	Sullivan 2006[35]
Statin-induced diabetes	n/a	-0.19	Sullivan 2006[35]
Mild adverse event	-0.005	+/-15%	Lee 2010[20]
Major adverse event	-0.038	+/-15%	Lee 2010[20]
Statin Efficacy (RR)[B]			
For CHD	0.77	0.74, 0.80	Baigent 2005[37]
For Stroke	0.83	0.78, 0.88	Baigent 2005[37]

Table A-4. Cost (2009 US dollars), utility, and treatment inputs used in the CVD micro-simulation model (cont.)

Parameter	Base-Case Value	Sensitivity Analysis Value(s)	Base-Case Source
Statin Compliance[B]			
1st year of treatment	67%	+/-15%	Avorn 1998[38], Greving 2011[34]
2nd year of treatment	53%	+/-15%	Avorn 1998[38], Greving 2011[34]
3rd year of treatment	50%	+/-15%	Avorn 1998[38], Greving 2011[34]
Statin Adverse Event Rates[B]			
Statin-induced diabetes[D]	None	0.0047	Ridker 2012[25]
Minor event	0.175	+/-15%	Kasliwal 2007[39]
Major event	0.0001	+/-15%	Alsheikh-Ali 2005[40], Lee 2010[20]
Probability die given major event	0.09	+/-15%	Alsheikh-Ali 2005[40], Lee 2010[20]
Treatment Initiation			
In Stage 1	100%	80%, 100%	Assumption
In Stage 2	100%	80%, 95%	Assumption

[A]*Source for cost sensitivity analysis: DRG Expert 2007 for CHD and procedure costs, Brown 2006 for acute stroke cost*
[B]*Values varied together (only for given sub-group) in deterministic sensitivity analysis*
[C]*For adverse events, minor adverse events related to muscle pain, and major adverse events represented rhabdomyolysis and renal failure*
[D]*Additional annual risk of developing diabetes due to statin treatment*

Appendix A4: Strategies evaluated in the model-based CEA

Single-stage/Framingham-based and single-stage/non-laboratory-based strategies were evaluated using the following thresholds (i.e., treat if CVD risk is greater that the following thresholds): treat none, >50%, >40%, >35%, >30%, >27.5%, >25%, >22.5%, >20%, >17.5%, >15%, >12.5%, >10%, >7.5%, >5%, >4%, >3%, >2%, >1%, >0.5%, and treat none. The proportion of individuals receiving laboratory-based testing ranged in the 20 multistage screening strategies evaluated from 15-75% in men to 14-77% in women. Tables A-5 and A-6 show the strategy type (single-stage/Framingham-based, single-stage/non-laboratory-based, or multistage), threshold(s) used for the top 15 strategies evaluated in the model-based CEA, along with the cost, QALY, and net monetary benefit (NMB) results for men and

women, respectively. Strategies were ranked by NMB (calculated by: QALYs*cost-effectiveness threshold – costs) using a cost-effectiveness threshold of $100,000/QALY.

Table A-5. Strategy type, proportion of population receiving laboratory testing, threshold(s) used, costs, QALYs, and NMB (given cost-effectiveness threshold of $100,000/QALY) for top 15 strategies (ranked by NMB) in the model-based CEA, men

Strategy type	%labs	Threshold(s)	Costs*	QALYs*	NMB*
Multistage	24%	xL=0.5%, xU=2%, xT=1%	$17,387	19.713	$1,953,949
Multistage	37%	xL=0.5%, xU=3%, xT=1%	$17,402	19.713	$1,953,934
Single-stage, non-lab-based	0%	>1% non-lab risk	$17,351	19.713	$1,953,903
Multistage	30%	xL=1%, xU=3%, xT=1%	$17,380	19.713	$1,953,878
Single-stage, non-lab-based	0%	>2% non-lab risk	$17,232	19.710	$1,953,808
Single-stage, non-lab-based	0%	>0.5% non-lab risk	$17,401	19.712	$1,953,805
Single-stage, Framingham-based	100%	>1% Framingham risk	$17,534	19.713	$1,953,802
Treat all	0%	n/a	$17,405	19.712	$1,953,802
Single-stage, Framingham-based	100%	>0.5% Framingham risk	$17,566	19.712	$1,953,641
Multistage	44%	xL=0.5%, xU=4%, xT=2%	$17,325	19.709	$1,953,609
Multistage	51%	xL=2%, xU=10%, xT=2%	$17,305	19.709	$1,953,603
Multistage	15%	xL=3%, xU=5%, xT=5%	$17,043	19.707	$1,953,582
Multistage	75%	xL=0.5%, xU=10%, xT=2%	$17,375	19.709	$1,953,559
Single-stage, non-lab-based	0%	>3% non-lab risk	$17,141	19.707	$1,953,550
Multistage	15%	xL=3%, xU=5%, xT=1%	$17,188	19.707	$1,953,503

**Discounted, lifetime, per-person results*

Table A-6. Strategy type, proportion of population receiving laboratory testing, threshold(s) used, costs, QALYs, and NMB (given cost-effectiveness threshold of $100,000/QALY) for top 15 strategies (ranked by NMB) in the model-based CEA, women

Strategy type	%labs	Threshold(s)	Costs*	QALYs*	NMB*
Multistage	56%	xL=1%, xU=7.5%, xT=3%	$10,589	21.358	$2,125,171
Multistage	45%	xL=1%, xU=5%, xT=3%	$10,637	21.358	$2,125,167
Single-stage, Framingham-based	100%	>3% Framingham risk	$10,697	21.358	$2,125,096
Single-stage, non-lab-based	0%	>3% non-lab risk	$10,698	21.358	$2,125,095
Single-stage, non-lab-based	0%	>7.5% non-lab risk	$10,167	21.352	$2,125,082
Single-stage, non-lab-based	0%	>5% non-lab risk	$10,436	21.355	$2,125,71
Multistage	14%	xL=3%, xU=5%, xT=1%	$10,755	21.358	$2,125,038
Multistage	45%	xL=2%, xU=10%, xT=2%	$10,802	21.358	$2,124,959
Multistage	14%	xL=3%, xU=5%, xT=5%	$10,498	21.354	$2,124,915
Multistage	38%	xL=2%, xU=7.5%, xT=5%	$10,343	21.353	$2,124,914
Single-stage, non-lab-based	0%	>10% non-lab risk	$9,992	21.349	$2,124,904
Multistage	56%	xL=1%, xU=7.5%, xT=5%	$10,382	21.353	$2,124,874
Multistage	53%	xL=0.5%, xU=4%, xT=2%	$10,835	21.357	$2,124,867
Single-stage, non-lab-based	0%	>4% non-lab risk	$10,563	21.354	$2,124,866
Multistage	77%	xL=0.5%, xU=10%, xT=2%	$10,873	21.357	$2,124,857

**Discounted, lifetime, per-person results*

Appendix A5: Sensitivity analysis methods

In deterministic sensitivity analyses, we varied variables (or groups of related variables) using alternative values (or through plausible ranges) to assess the robustness of our CEA results to changes in these input parameters. In addition to the values and ranges reported in Table 2, we assessed the impact of shorter model time horizons (10 and 30 year horizons) and removing the annual disutility from daily statin treatment in separate deterministic sensitivity analyses. We also considered impact of differential treatment initiation after being classified as "high-risk" from the first (non-laboratory-based) stage relative to treatment recommendations from the second (Framingham-based) stage, as described in the main text.

We performed a probabilistic sensitivity analysis (PSA) to assess uncertainty in our CEA results. Key input parameters were assigned probability distributions, and 1000 parameter sets were generated from these distributions using 2^{nd}-order Monte Carlo simulation methods. Distribution parameters were based on the precision associated with point estimates (such as standard errors) where possible; arbitrary parameters (+/-10%) were used otherwise. Beta distributions were used for probability and utility inputs, gamma distributions from costs, and normal distributions for treatment efficacies.

For the PSA, the highest ranked strategies for each type of approach (single-stage/laboratory-based, single-stage/non-laboratory-based, and multistage) using $100,000/QALY, $50,000/QALY, $25,000/QALY, and $10,000/QALY WTP for health estimate were evaluated for each parameter set. We combined the probabilities of any time of strategy being the most cost-effective option in our cost-effectiveness acceptability curve (CEAC) to limit the number curves presented (we presented one for each strategy type, as opposed to twelve individual curves for each specific strategy type/threshold combination). Table A-7 shows the distributions assigned to variables included in the PSA.

Table A-7. Variables and Distributions used in the Probabilistic Sensitivity Analysis (PSA)

Model input parameters	Mean value	Distribution	Distribution parameters
Acute Costs for Disease States			
Cardiac Arrest	$17,790	Gamma	α = 100, λ = 177.9
MI	$52,030	Gamma	α = 100, λ = 520.3
Angina	$26,900	Gamma	α = 100, λ = 269
Stroke	$12,610	Gamma	α = 100, λ = 126.1
Acute Costs for Procedures			
CABG	$34,040	Gamma	α = 100, λ = 340.4
PTCA	$32,080	Gamma	α = 100, λ = 320.8
Chronic Annual Costs for Disease States			
All CHD events	$2,990	Gamma	α = 100, λ = 0.62
Stroke	$1,940	Gamma	α = 100, λ = 0.63
Screening Costs			
Non-lab test (GP visit in Stage 1)	$65	Gamma	α = 100, λ = 0.65
Lab test	$32	Gamma	α = 100, λ = 0.32
Acute Death Probabilities			
Cardiac Arrest	0.95	Beta	α = 95.96, β = 2303
MI <65 years	0.10	Beta	α = 95.96, β = 2304
MI ≥65 years	0.16	Beta	α = 95.96, β = 2305
Angina	0.05	Beta	α = 95.96, β = 2306
Stroke	0.14	Beta	α = 95.96, β = 2307
Chronic Death Probabilities			
Cardiac Arrest or MI	0.04	Beta	α = 95.96, β = 2303
Angina	0.03	Beta	α = 96.97, β = 3135
Stroke	0.05	Beta	α = 94.95, β = 1804
>1 MI	0.10	Beta	α = 89.9, β = 809
Utilities for Disease States			
Cardiac Arrest	0.808	Beta	α = 3133746, β = 744653
MI	0.778	Beta	α = 3359325, β = 958574
Angina	0.768	Beta	α = 3420978, β = 1033421
Stroke	0.768	Beta	α = 13683916, β = 4133683
Statin Efficacy (RR)			
For CHD	0.77	Normal	SD = 0.02
For Stroke	0.83	Normal	SD = 0.03
Statin Adverse Event Rates			
Minor event	0.175	Beta	α = 252, β = 1148
Major event	0.0001	Beta	α = 5.6, β = 99994
Probability die from major event	0.09	Beta	α = 7.2, β = 73

Appendix A6: Risk discrimination results using imputed values for the NHANES III population

The Receiver Operator Characteristics (ROC) curve results for the study population with imputed values were similar compared to the results for the population limited to those with complete data. There were no statistically significantly differences between the multistage screening strategies and the Framingham CVD risk score except for the multistage strategy with 25% of the population receiving laboratory testing (Multistage25) for women.

Table A-8. Risk discrimination results for multistage and universal Framingham strategies for the NHANES III population (including those with imputed values)

MEN						
Strategy	AUC (95% CI)	p-value vs. Framingham	Sensitivity*	Specificity*	PPV*	NPV*
Framingham	0.812 (0.780-0.842)	--	0.828	0.605	0.055	0.992
Multistage75**	0.811 (0.779-0.843)	0.967	0.515	0.886	0.111	0.985
Multistage50**	0.813 (0.781-0.845)	0.643	0.716	0.763	0.078	0.990
Multistage25**	0.812 (0.780-0.844)	0.770	0.811	0.639	0.059	0.992
WOMEN						
Strategy	AUC (95% CI)	p-value vs. Framingham	Sensitivity*	Specificity*	PPV*	NPV*
Framingham	0.839 (0.810-0.867)	--	0.727	0.794	0.069	0.993
Multistage75**	0.838 (0.809-0.866)	0.755	0.510	0.882	0.083	0.988
Multistage50**	0.828 (0.797-0.859)	0.083	0.755	0.761	0.062	0.993
Multistage25**	0.818 (0.784-0.852)	0.007	0.832	0.634	0.046	0.994

*Using >10% 10-year Framingham CVD risk as positivity criterion (for multistage strategies, this is only applied to individuals at intermediate risk, since Framingham risk would not be known for others). Those with non-laboratory-based risk >xU in multistage also used for positivity criterion.
**Multistage formulations that resulted in 75%, 50%, and 25% of the population receiving laboratory testing.

Appendix A7: Deterministic sensitivity analysis results

Tables A-9 and A-10 show the primary deterministic sensitivity analysis results for the model-based CEA for men and women, respectively. Tables A-11 and A-12 show the sensitivity analysis results for the model-based CEA for men and women, respectively. Model-based CEA results were most sensitive to variations in stage-specific physician costs and treatment initiation assumptions, statin costs, and model time horizons.

Table A-9. Primary deterministic sensitivity analysis model-based cost-effectiveness results, men

Strategy	Total costs*	QALYs*	ICER
No extra GP (physician) visit costs for Stage 2			
No statin treatment or primary CVD screening	$15,988	19.535	--
Multistage, xL = 3%, xU = 5%, xT = 5%	**$17,009**	**19.706**	**$9,000**
Single-stage/non-laboratory-based, treatment threshold >2%	$17,232	19.710	W. Dom.
Single-stage/non-laboratory-based, treatment threshold >1%	$17,351	19.713	W. Dom.
Multistage, xL = 0.5%, xU = 2%, xT = 1%	**$17,368**	**19.713**	**$51,000**
Single-stage/non-laboratory-based, treatment threshold >1%	$17,417	19.713	S. Dom.
Differential treatment initiation for Stage 1 (100%) and Stage 2 (95%)			
No statin treatment or primary CVD screening	$15,988	19.535	--
Multistage, xL = 3%, xU = 5%, xT = 5%	**$17,035**	**19.707**	**$9,200**
Single-stage/non-laboratory-based, treatment threshold >2%	**$17,232**	**19.710**	**$52,000**
Single-stage/non-laboratory-based, treatment threshold >1%	**$17,351**	**19.713**	**$56,000**
Multistage, xL = 0.5%, xU = 2%, xT = 1%	$17,382	19.712	S. Dom.
Single-stage/non-laboratory-based, treatment threshold >1%	**$17,519**	**19.713**	**$330,000**
No extra GP costs for Stage 2 and differential treatment initiation			
No statin treatment or primary CVD screening	$15,988	19.535	--
Multistage, xL = 3%, xU = 5%, xT = 5%	**$17,001**	**19.707**	**$8,900**
Single-stage/non-laboratory-based, treatment threshold >4%	$17,111	19.708	W. Dom.
Single-stage/Framingham-based, treatment threshold >2%	$17,232	19.710	W. Dom.
Single-stage/non-laboratory-based, treatment threshold >1%	**$17,351**	**19.713**	**$59,000**
Multistage, xL = 0.5%, xU = 3%, xT = 1%	$17,364	19.712	S. Dom.
Single-stage/Framingham-based, treatment threshold >1%	**$17,399**	**19.713**	**$95,000**

**All results are per-person with lifetime horizon, using 3% discount for both QALYs and costs*

Non-dominated strategies (i.e., all strategies on the efficient frontier) are in bold font

Table A-10. Primary deterministic sensitivity analysis model-based cost-effectiveness results, women

Strategy	Total costs*	QALYs*	ICER
No extra GP (physician) visit costs for Stage 2			
No statin treatment or primary CVD screening	$8,971	21.301	--
Single-stage/Framingham-based, treatment threshold >5%	**$10,083**	**21.351**	**$22,000**
Single-stage/non-laboratory-based, treatment threshold >7.5%	$10,167	21.352	W. Dom.
Multistage, xL = 2%, xU = 7.5%, xT = 5%	$10,230	21.353	W. Dom.
Single-stage/Framingham-based, treatment threshold >3%	**$10,475**	**21.358**	**$60,000**
Multistage, xL = 1%, xU = 5%, xT = 3%[A]	**$10,543**	**21.358**	**$610,000**
Single-stage/non-laboratory-based, treatment threshold >3%	$10,698	21.358	S. Dom.
Differential treatment initiation for Stage 1 (100%) and Stage 2 (95%)			
No statin treatment or primary CVD screening	$8,971	21.301	--
Single-stage/non-laboratory-based, treatment threshold >7.5%	**$10,167**	**21.352**	**$23,000**
Multistage, xL = 2%, xU = 7.5%, xT = 5%	$10,341	21.353	W. Dom.
Single-stage/Framingham-based, treatment threshold >5%	$10,351	21.352	S. Dom.
Multistage, xL = 1%, xU = 5%, xT = 3%	**$10,638**	**21.358**	**$93,000**
Single-stage/Framingham-based, treatment threshold >3%	$10,679	21.357	S. Dom.
Single-stage/non-laboratory-based, treatment threshold >3%	**$10,698**	**21.358**	**$160,000**
No extra GP costs for Stage 2 and differential treatment initiation			
No statin treatment or primary CVD screening	$8,971	21.301	--
Single-stage/Framingham-based, treatment threshold >5%	**$10,068**	**21.352**	**$22,000**
Single-stage/non-laboratory-based, treatment threshold >7.5%	$10,167	21.352	W. Dom.
Multistage, xL = 2%, xU = 7.5%, xT = 5%	$10,229	21.353	W. Dom.
Single-stage/Framingham-based, treatment threshold >3%	**$10,455**	**21.357**	**$74,000**
Multistage, xL = 1%, xU = 5%, xT = 3%	**$10,544**	**21.358**	**$110,000**
Single-stage/non-laboratory-based, treatment threshold >3%	**$10,698**	**21.358**	**$410,000**

**All results are per-person with lifetime horizon, using 3% discount for both QALYs and costs*

Non-dominated strategies (i.e., all strategies on the efficient frontier) are in bold font

Table A-11. Additional deterministic sensitivity analysis model-based cost-effectiveness results, men

	Optimal strategy type and thresholds given WTP			
Scenario	$10,000/QALY	$25,000/QALY	$50,000/QALY	$100,000/QALY
Base-case	**SSNL >12.5%**	**MS, xL=3%, xU=5%, xT=5%**	**SSNL >2%**	**MS, xL=0.5%, xU=2%, xT=1%**
DRG acute event costs	SSNL >17.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%	MS, xL=0.5%, xU=2%, xT=1%
Statin costs $620/year	No treatment	SSNL >3%	MS, xL=3%, xU=15%, xT=12.5%	MS, xL=3%, xU=5%, xT=5%
High statin efficacy	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >1%	MS, xL=0.5%, xU=2%, xT=1%
Low statin efficacy	SSNL >12.5%	SSNL >12.5%	SSNL >2%	SSNL >2%
30-yr model time horizon	SSNL >30%	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%
10-yr model time horizon	MS, xL=7.5%, xU=20%, xT=15%	MS, xL=7.5%, xU=20%, xT=15%	MS, xL=7.5%, xU=20%, xT=15%	MS, xL=5%, xU=15%, xT=12.5%
High statin compliance	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%	MS, xL=0.5%, xU=2%, xT=1%
Low statin compliance	SSNL >12.5%	SSNL >3%	SSNL >2%	SSNL >2%
Low statin initiation	SSNL >7.5%	MS, xL=3%, xU=5%, xT=5%	MS, xL=3%, xU=5%, xT=5%	MS, xL=3%, xU=5%, xT=5%
High utility values	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%	MS, xL=0.5%, xU=2%, xT=1%
Low utility values	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	MS, xL=0.5%, xU=2%, xT=1%	MS, xL=0.5%, xU=2%, xT=1%
No statin disutility	SSNL >12.5%	SSNL >2%	SSNL >1%	SSNL >1%
High statin disutility	SSNL >17.5%	MS, xL=7.5%, xU=25%, xT=10%	MS, xL=3%, xU=5%, xT=5%	MS, xL=3%, xU=5%, xT=5%
Statin-induced diabetes	SSNL >20%	SSNL >17.5%	MS, xL=5%, xU=25%, xT=15%	MS, xL=5%, xU=15%, xT=12.5%
High adverse event rates	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%	SSNL >1%
Low adverse event rates	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	MS, xL=3%, xU=5%, xT=5%	MS, xL=0.5%, xU=2%, xT=1%
High chronic event costs	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%	MS, xL=0.5%, xU=2%, xT=1%
Low chronic event costs	SSNL >12.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%	MS, xL=0.5%, xU=2%, xT=1%
High screening costs	SSNL >17.5%	MS, xL=3%, xU=5%, xT=5%	SSNL >2%	MS, xL=0.5%, xU=2%, xT=1%
Low screening costs	MS, xL=7.5%, xU=25%, xT=15%	MS, xL=3%, xU=5%, xT=5%	MS, xL=0.5%, xU=2%, xT=1%	MS, xL=0.5%, xU=2%, xT=1%

Table A-12. Additional deterministic sensitivity analysis model-based cost-effectiveness results, women

	Optimal strategy type and thresholds given WTP			
Scenario	$10,000/QALY	$25,000/QALY	$50,000/QALY	$100,000/QALY
Base-case	**SSNL >30%**	**SSNL >15%**	**SSNL >7.5%**	**MS, xL=1%, xU=7.5%, xT=3%**
DRG acute event costs	SSNL >30%	SSNL >15%	SSNL >7.5%	MS, xL=1%, xU=5%, xT=3%
Statin costs $620/year	No treatment	No treatment	SSNL >25%	SSNL >15%
High statin efficacy	SSNL >30%	SSNL >10%	SSNL >7.5%	MS, xL=1%, xU=5%, xT=3%
Low statin efficacy	SSNL >30%	SSNL >15%	SSNL >7.5%	SSNL >5%
30-yr model time horizon	SSNL >30%	SSNL >30%	SSNL >30%	SSNL >15%
10-yr model time horizon	SSNL >30%	SSNL >30%	SSNL >30%	SSNL >30%
High statin compliance	SSNL >30%	SSNL >15%	SSNL >7.5%	SSNL >3%
Low statin compliance	SSNL >30%	SSNL >15%	SSNL >7.5%	MS, xL=1%, xU=7.5%, xT=3%
Low statin initiation	SSNL >15%	SSNL >15%	SSNL >15%	SSF >3%
High utility values	SSNL >30%	SSNL >15%	SSNL >15%	MS, xL=1%, xU=7.5%, xT=3%
Low utility values	SSNL >30%	SSNL >15%	SSNL >7.5%	MS, xL=1%, xU=7.5%, xT=3%
No disutility/daily statin use	SSNL >30%	SSNL >15%	SSNL >7.5%	SSNL >3%
High statin disutility	SSNL >30%	SSNL >15%	SSNL >15%	SSNL >15%
Statin-induced diabetes	SSNL >35%	SSNL >30%	SSNL >25%	SSNL >15%
High adverse event rates	SSNL >30%	SSNL >15%	SSNL >12.5%	MS, xL=1%, xU=7.5%, xT=3%
Low adverse event rates	SSNL >30%	SSNL >15%	SSNL >7.5%	MS, xL=1%, xU=5%, xT=3%
High chronic event costs	SSNL >30%	SSNL >15%	SSNL >7.5%	MS, xL=1%, xU=7.5%, xT=3%
Low chronic event costs	SSNL >30%	SSNL >15%	SSNL >7.5%	MS, xL=1%, xU=7.5%, xT=3%
High screening costs	SSNL >30%	SSNL >15%	SSNL >15%	SSNL >7.5%
Low screening costs	SSNL >15%	SSNL >15%	SSNL >7.5%	MS, xL=1%, xU=5%, xT=3%

Where "SSNL" stands for single-stage/non-laboratory-based, "SSF" stands for single-stage/Framinghma-based and "MS" stands for multistage

Appendix A8: Probabilistic sensitivity analysis (PSA) results

Figures A-3a and A-3b show the CEACs for men and women, respectively. PSA results were similar compared to the base-case model-based CEA findings.

Figure A-3a. Cost-effectiveness acceptability curve (CEAC) for the model-based CEA, men

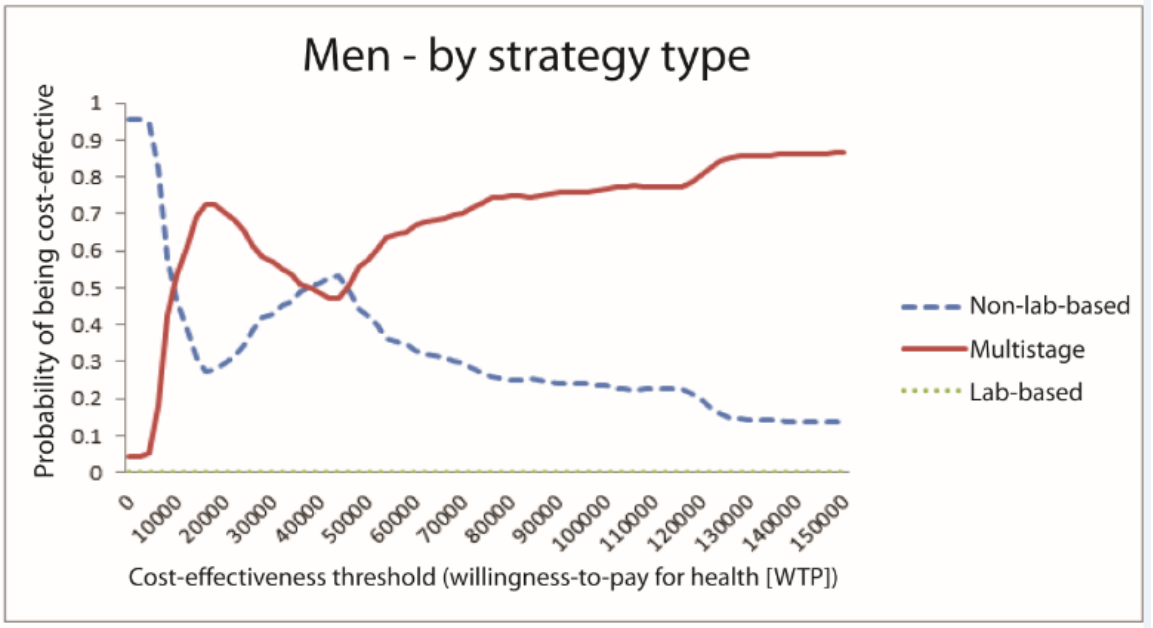
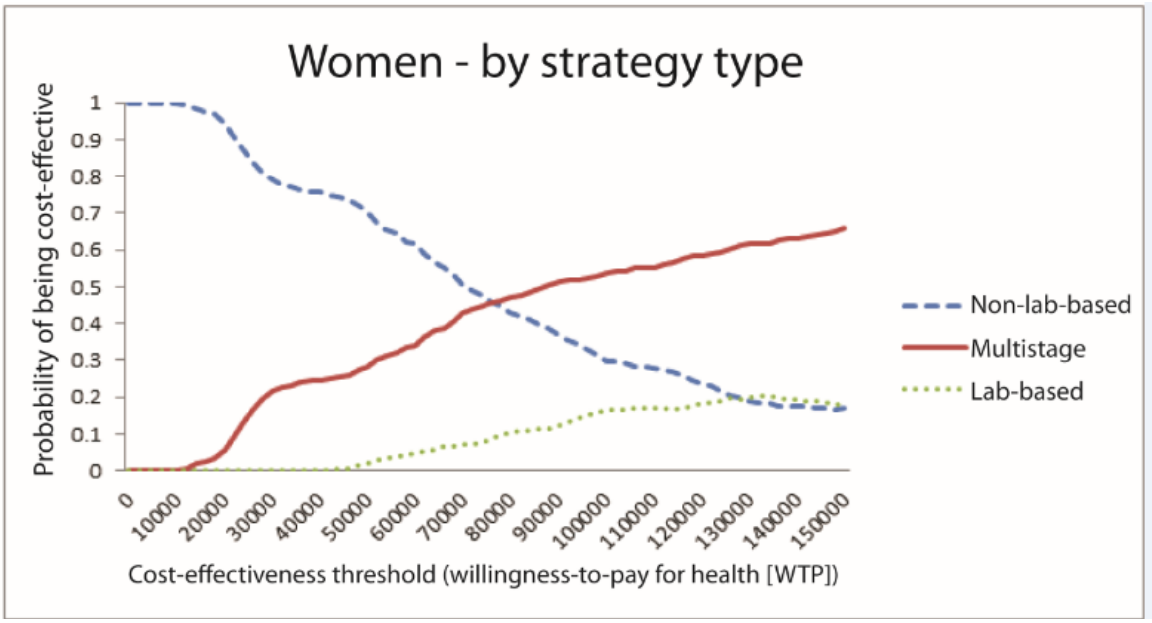


Figure A-3b. Cost-effectiveness acceptability curve (CEAC) for the model-based CEA, women



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