# Lipid Disorder Screening in the General Population: Technical Report Prepared for the National Commission on Prevention Priorities

Version 06.1; last updated August 19, 2008

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This work was supported by the Centers for Disease Control and Prevention (CDC) and the Agency for Healthcare Research and Quality (AHRQ).

## A. USPSTF Recommendation

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians routinely screen men aged 35 years and older and women aged 45 years and older for lipid disorders and treat abnormal lipids in people who are at increased risk of coronary heart disease (A recommendation).[1] The USPSTF found good evidence that lipid measurement can identify asymptomatic middle-aged people at increased risk of coronary heart disease and good evidence that lipid-lowering drug therapy substantially decreases the incidence of coronary heart disease in people with abnormal lipids, and causes few major harms. The USPSTF concludes that the benefits of screening for and treating lipid disorders in middle-aged and older people substantially outweigh harms.

## B. Choice of Screening Tools and Intervals

The USPSTF does not specify a specific cholesterol measure (LDL-C, HDL-C, TC or a ratio), a specific treatment goal, or an optimal interval for screening. Similarly, the data that are available to build estimates of clinically preventable burden (CPB) and cost effectiveness (CE) are based upon various screening measures and treatment goals. Therefore, we provide a general estimate of the value of cholesterol screening and treatment that reflects the available data rather than a detailed estimate of a specific screening and treatment strategy.

## C. Literature Search and Abstraction

### C.1 Effectiveness Literature

The literature examining pharmacological treatments for lipid disorders is considerable. To most efficiently identify key studies on the treatment of lipid disorders, we performed a literature search to identify meta-analyses and systematic reviews of lipid disorder treatments. This literature search identified 125 articles from PubMed between January 1987 and March 2004. Meta-analysis and systematic review articles were obtained and these articles were examined to identify key lipid treatment trials. A total of 65 major trials were identified, and articles for these trials were obtained. To identify observational studies that examined the treatment of lipid disorders, we performed Level 1 and Level 2 literature searches.[2] This observation study search identified 679 articles from PubMed between January 1992 and March 2004 .

We abstracted those studies that compared treatment with a control group that received either a placebo or no treatment. Outcomes in the articles needed to include at least one of the following outcomes: Coronary heart disease (CHD) incidence (fatal and nonfatal events), CHD deaths, stroke incidence (fatal and nonfatal events), stroke deaths, cardiovascular deaths, or all-cause mortality. Of the articles identified, 17 effectiveness articles were abstracted that assessed the effectiveness of treatment.[3-19] Fifteen articles concerned 12 major randomized trials,[3-5;7-16;18;19] and 2 articles concerned 2 observational studies.[6;17]

### C.2 Cost-effectiveness Literature

We performed Level 1 and Level 2 literature searches[2] to identify cost-effectiveness (CE) studies published between January 1992 and June 2004. This identified 529 articles from PubMed. Forty-two articles that examined the cost-effectiveness of screening for cholesterol and the cost-effectiveness of pharmaceutical treatment of lipid disorders were obtained for potential abstraction. None of the articles on the cost effectiveness of screening were suitable for

abstraction, but we abstracted three cost-effectiveness articles about statin treatment for high cholesterol in order to explore the possibility of building a CE estimate of screening from one or more of them.[20 21;22]Ultimately, however, we built a new CE estimate from the data summarized in our CPB estimate, since none of the abstracted articles provided the necessary information.

**D. Clinically Preventable Burden Estimate**

Conceptually, CPB is the burden addressed by the service multiplied by the effectiveness of the service. Table 1 shows the summary calculations for CPB. Some of the data points in Table 1 are estimates from the literature and others are calculated based upon other data in the table. The "Data Source" column in Table 1 shows either the references for estimates or the formula used to calculate the variable. The alphanumeric codes in the formulas refer to the row labels (leftmost column) for the data on which the calculation is based. The "Base Case" column shows the best available estimate for each variable that was used in our calculation of CPB, and the "Range" column shows the range over which the point estimates were varied in our sensitivity analyses.[2] We created additional tables (not shown) to summarize the evidence and perform supporting calculations. The contents of these tables are described below.

D.1 Burden of Disease:

D.1.1. Coronary Heart Disease Mortality: Rows a1-a3.

CPB is based on the delivery of the service to a one-year U.S. birth cohort (the size of which is defined consistently in this study as 4 million) over the age range recommended by the USPSTF for this service. CHD mortality (row a1) is estimated from 1998 death rates data using the CDC Wonder engine,[23] which included mortality data for ICD-9 codes of 410 to 414 (ischemic heart disease). Whenever U.S. population estimates are needed for calculations, the 2000 census data are used.[24] The number of CHD deaths in a birth cohort of 4 million individuals is estimated and stratified by 10-year age groups, with men only for ages 35-44 years. The attributable fraction of high cholesterol in CHD has been estimated at 42.7% (row a2).[25] This estimate is applied as a proxy for the portion of CHD that occurs among persons with high cholesterol. An estimate of 348,334 CHD deaths among individuals with high cholesterol (row a3) is obtained by multiplying all CHD deaths in the birth cohort by the attributable fraction.

D.1.2. Delivery Rates: Row a4.

This estimate reflects cumulative (lifetime risk) CHD deaths among persons with high cholesterol in a birth cohort given current cholesterol screening and treatment practices. To estimate the total value of screening and treatment, we first predicted what the burden would be in the absence of screening by adjusting for current screening and treatment rates. We used the 1999 United States cholesterol screening rate of 70.8% (row a4) estimated from the Behavioral Risk Factor Surveillance Survey (BRFSS) as the delivery rate of screening to the service population.[26] We used an estimate by Ansell that 43% (row a5) of patients with high cholesterol requiring pharmacologic treatment are receiving such therapy.[27] This estimate is used because it appears to directly address the treatment gap for patients with high cholesterol. It is further supported by two studies in other types of patients. One study published in 1998 included patients with CHD and the authors found that 33% were treated.[28] A second study published in 2004 included hypertensive patients with dyslipidemia and found that treatment rate ranged from 13% in black men to 33% in white men.[29]

D.1.3. Predicted Deaths in the Absence of Screening: Row a7.

The efficacy estimate used in the calculation shown for row a7 is explained below in the discussions of efficacy and effectiveness. Using the calculation shown for row a7, we estimate that 385,626 CHD deaths will occur among individuals with high cholesterol in the absence of screening and treatment.

D.1.4. Coronary Heart Disease Events: Rows a8-a16.

The calculation of the CHD events in the absence of screening and treatment is similar to that from prevented CHD mortality. As a measure of acute CHD events, we used hospitalizations with a first listed diagnosis for CHD from the 2001 National Hospital Discharge Survey.[30] As with mortality, events are estimated by age group over the lifetime of a birth cohort of 4 million. These data were reported without gender stratification; hence an event rate specific to males aged 35-45 was not available. We assigned a 30% risk to the 45-64 age group based upon the relative mortality rate of males aged 35-44 and males aged 45-64.[31] The nonfatal CHD events (row a8) are multiplied by the percent attributable to high blood cholesterol and adjusted for current screening and treatment. The result is predicted lifetime hospitalizations among individuals with high cholesterol in the absence of screening and treatment – 1,460,482 events in a birth cohort of 4 million (row a11).

The most significant chronic sequela of acute CHD events is congestive heart failure (CHF) as a sequel to acute myocardial infarctions (MIs). Approximately 34% of MIs result in disabling CHF within 6 years (row a15).[32] To apply this estimate, we first calculate the lifetime MIs in the absence of screening and treatment among persons with high cholesterol in the same manner as lifetime CHD hospitalizations. This estimate is built upon a reported 565,000 annual incident MIs in the current U.S. population,[33] from which we calculate an incident rate that we apply to the years of life lived by a birth cohort of 4 million.[34] The resulting number of CHF cases as sequelae to MIs is 96,133 (row a16). The number of incident MIs was not available by age group. Applying the population average incident rate for MIs results in an understatement of cases because the age-distribution of years of life lived in the birth cohort is older than the current cross-section.

D.2 Effectiveness of Screening:

The primary distinction we make between efficacy and effectiveness is that effectiveness reflects the level of patient adherence that can be expected in every-day practice, while efficacy reflects 100% patient adherence.[2] CPB is based on effectiveness, where patient adherence is defined as the percent who accept the service once offered and adhere with follow-up treatment or advice to change behavior.

D.2.1 Effectiveness Literature:

Among the 17 effectiveness articles selected for abstraction,[3-19] 9 were excluded.[3-6;10-12;15;16] Four of the excluded articles had fatal flaws (described below), 3 articles examining the outcomes of the Heart Protection Study were excluded as it studied a high-risk population that lacked generalizability,[3-5] and 2 were not designed to measure CHD events as outcomes.[15;16] Reasons for fatally flawing four articles were:

- A high level of contamination: the comparison group received usual care instead of placebo and CHD in initial participants may represent a large % of total events[10]

- A high number of study participants with prior CHD and small event numbers[12]
- Use of medications was only reported among those who still had high cholesterol at the time of the survey. Cases and controls who had achieved lower cholesterol levels by use of medication were not included[6]
- Many study participants had prior coronary heart disease. Thirty-two percent of intervention group and 36% of control group had prior MI.[11]

D.2.2. Efficacy of Screening: Rows a17 and a19.

The 8 remaining articles [7-9;13;14;17-19] produced estimates for fatal and nonfatal events. The median for these estimates was 28% and the mean was 26%. Because these two estimates were similar, we used the midpoint for the effectiveness of pharmaceutical treatment in preventing both fatal and non-fatal events of 27% (row a19). Most studies included in this average examined the effectiveness of statins, and the mean of the statin studies was 26% -- the same as the mean with all studies included.

When estimating effectiveness of treatment for the reduction of both CHD mortality and CHD events, we made several assumptions. We assumed that if the USPSTF recommendations were followed, 90% of patients who are of service age and gender would accept screening for high cholesterol (row a17). We expected that the requirement for a fasting lipid during follow-up and the possible need to return to the clinic for the blood drawn would cause this 10% nonadherence to the screening recommendation. Following the evidence base for the USPSTF recommendation, we assumed that 100% of patients with high cholesterol requiring treatment would be offered pharmacotherapy.

D.2.3. Patient Adherence: Rows a18 and a22

In the CPB calculation, we differentiated two types of medication non-adherence. Not all patients will accept treatment which may manifest either as a direct refusal when offered medication, or by never filling a written prescription. We expected that out-of-pocket cost and fear of adverse effects among other things will cause some level of incomplete up-take. Lacking data on this type of non-adherence, we assumed that 90% of patients would accept medication treatment when offered (row a18).

A second type of patient non-adherence involves taking less of the medication than directed, either by discontinuing treatment or taking fewer pills than prescribed. When examining this type of non-adherence, we observed substantial differences among different cholesterol-lowering drug classes. Overall, non-statins, with less favorable side effect profiles, are associated with much lower adherence than statins.[35-37] Because statins have dominated the lipid-lowering market with market share of 80-90% in recent years,[38] and the summary estimate of effectiveness accurately reflects the effectiveness of statins,[39] we focused the analysis on statins, including the following discussion of adherence.

Adherence with statin regimens in randomized controlled trials (RCTs) has been estimated to be approximately 85% over the length of clinical trials (typically 4 to 5 years).[40] Similar adherence has been shown for shorter durations in some observational studies. In the late 1990s, members of two Massachusetts HMOs were observed to have 85% adherence at 12 months after filling at least one prescription.[41] Because statins were a much smaller percent of the market at the time (17% in the study population) the population receiving statins in this study may not have been representative of the current population receiving statins. Three studies reported adherence in patients with CHD. Eagle et al. reported adherence of 87% at 12 months

following discharge for an inpatient stay for acute coronary syndromes.[42] Kopjar et al. observed 71% adherence at 18 months in male Veterans Administration patients with CHD.[40] Similarly, O'Connor et al. reported 88% continued use among Minnesota HMO members with heart disease who were observed retrospectively for an average of 2.5 years, but a study eligibility requirement of having two fasting LDL-C measures likely contributed to this high adherence rate.[43] Other observations, all in older populations, have shown substantially lower adherence, particularly beyond the first two years. Adherence rates of 61% at 12 months and 43% at 18 months among elderly members of a New England HMO were reported by Abughosh et al.[44] Jackevicius et al. reported that elderly outpatients with CHD in Ontario, Canada who received at least one dispense of statins, were 60% adherent at 12 months and 36% adherent at 24 months, while those without CHD were 40% adherent at 12 months and 25% adherent at 24 months.[45] Finally, Benner et al. reported 10-year follow-up data on members 65 years and older in the New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled programs.[46] Measured as the percent of days covered by prescriptions filled, adherence was 50%, 46%, 35%, and 42% at 1, 2, 5 and 10 years respectively. Measured as the percent of patients adherent, defined as at least 80% of days covered, adherence was 38%, 34%, 26%, and 32% at 1, 2, 5, and 10 years. The corresponding rates of partial adherence were 24%, 26%, 18%, and 16%. One additional source of adherence information is useful to consider. Among insured individuals with pharmacy coverage among commercial clients of a large pharmacy benefit management company using both pharmacy and mail order services, the average number of fills for any lipid therapy was 9.1 in 2003.[38] This implies an adherence of 75% among those filling at least one prescription in the year. This estimate could be considered an upper bound for adherence because the denominator excludes individuals who started a lipid agent in a prior year but had no fills in the current year. However, the number of dispenses may also reflect some individuals who take more than one type of lipid-acting agent, dispenses for more than 30 days supply, and dispenses that were not used.

The adherence rates summarized above vary greatly with the population studied and the length of follow-up. Unfortunately none of the study populations are representative of the U.S. population, making it difficult to define the expected average adherence for use in estimating CPB. The factors to consider in choosing a base-case estimate include: 1) adherence may be relatively high in younger populations and low in older populations; 2) adherence may be lower for those without insurance; 3) adherence may be lower for those screening for high cholesterol compared to those with existing CHD; 4) adherence may be very high for one or two years prior to declining, providing some initial period of higher protection from CHD; and 5) partial adherence may provide some level of protection from CHD events. We used a base-case estimate of 40% average adherence for the U.S. population diagnosed with high cholesterol (row a22). As applied in the CPB calculation, this estimate indicates the portion of potential benefit of statin therapy that is realized in the target population who are screened and who have at least one dispense of a statin. In sensitivity analysis, we used a wide range of 20% to 65% to represent the plausible extremes for the general U.S. population based upon the evidence summary above.

D.2.4 Effectiveness of Screening and Treatment: Row a24

To incorporate this estimate of adherence, we first factored-out clinical trial adherence from the estimated trial effectiveness (27%). Using the equation that reflects the primary distinction between efficacy and effectiveness in the prevention priorities study (effectiveness = efficacy x adherence), we calculated an efficacy estimate of 32% using 85% adherence in

clinical trials.[40] This efficacy estimate (rows a6 and a21) was used to adjust fatal and non-fatal events for current screening and treatment (rows a7, a11 and a14). To calculate average effectiveness in usual practice, we multiplied this efficacy rate by 40% adherence and obtained an estimate of 13% (row a23).

After adjustment for non-adherence to screening and initial non-acceptance of medication, the effectiveness of screening for high cholesterol followed by statin therapy was 10% (row a24). We did not make an additional adjustment for the sensitivity of screening tests because the definition of cholesterol-attributable burden is based on screening tests and therefore the predicted event rates among individuals with high cholesterol already reflect false negative test results.

D.3 Clinically Preventable Burden Estimate:

D.3.1. Years of Life Saved: Rows a25-a27.

The total number of deaths prevented is equal to predicted CHD deaths among individuals with high cholesterol multiplied by effectiveness of screening and treatment. The prevention service of screening for lipid disorder would prevent 39,688 deaths (row a25) if periodic screening were offered to all men older than 35 and women older 45 in a birth cohort of 4 million. For each death prevented, we tabulated the years of life saved as the life expectancy for the age at which the CHD death would have occurred.[23;24] We show the average life-expectancy weighted by the number of deaths per age group in row a26. Multiplying this average by the number of deaths prevented yields the same result as the calculations by age group: 357,946 life years saved (row a27).

D.3.2. Quality Adjusted Life Years (QALYs) Saved Through Reduced Morbidity: Rows a28-a35.

Making the same calculation as for CHD deaths prevented, 150,309 hospitalizations with a primary discharge diagnosis of CHD would be prevented over the lifetime of the birth cohort (row a28) along with 9,894 cases of CHF due to prevented MIs (row a32). QALYs saved are tabulated by multiplying each case by the duration of morbidity and the average reduction in quality of life over that time period. We assumed an average duration of 3 weeks (.058 years) for each hospitalization, which is roughly based on reported days of restricted activity for acute conditions.[47] We applied a duration of 2.3 years for CHF reported for 'established market economies' in the Global Burden of Disease study.[48] We used the quality of life reductions of 0.30 and 0.20 for CHD hospitalizations and CHF events respectively. These are the standard QALY weights for acute and chronic conditions in the prevention priorities study that are used for all conditions unless available utility scales indicate that actual quality of life reductions are substantially different.[34;49] The tabulations (shown in rows a28 – a35) yield 2,602 QALYs saved (row a31) from reduced CHD hospitalizations and 4,551 QALYs saved (row a35) from prevented cases of CHF.

We did not tabulate acute MIs prevented and the associated acute quality of life reduction because these acute episodes are captured in the CHD hospitalizations (which also include hospitalized episodes of angina pectoris and hospitalizations for vascular procedures with CHD listed as the primary discharge diagnosis).

D.3.3. Clinically Preventable Burden Result. Row a36

CPB is the total of quality adjusted life years saved from mortality and morbidity prevented by offering periodic screening and pharmaceutical treatment for high cholesterol over the lifetimes of men starting at age 35 and women starting at age 45 in a birth cohort of 4 million individuals: 365,099 QALYs saved (row a36).

D.4 Sensitivity Analysis for Clinically Preventive Burden:

For the purpose of sensitivity analysis we treated the estimates of the portion of CHD mortality occurring in individuals with high cholesterol and the portion of CHD hospitalizations attributable to high cholesterol as a single variable. CPB was most sensitive to three variables: the combined variable of the portion of CHD mortality and CHD hospitalizations attributable to high cholesterol, the effectiveness of pharmacotherapy in clinical trials, and adherence with pharmacotherapy in usual practice. Changing these variables to the levels shown in the 'Range' column in Table 1 increased and decreased CPB by 28%-63% in single variable sensitivity analysis. CPB was moderately sensitive to four other variables: total CHD mortality in the birth cohort, the percent of patients accepting offers to be screened, the percent of patients who initiate pharmacotherapy among those who screen positive for high cholesterol, and the average years of life gained per CHD death prevented. Changing these variables to the levels shown in the 'Range' column in Table 1 increased and decreased CPB by 15%-20% in single variable sensitivity analysis.

In multivariate sensitivity analysis we varied three variables at time to identify a range of CPB estimates that demonstrated the uncertainty of the base case estimate.[34;49] Simultaneously changing the three variables to which CPB was the most sensitive (the combined variable of the portion of CHD mortality and CHD hospitalizations attributable to high cholesterol; the effectiveness of pharmacotherapy in clinical trials; and adherence with pharmacotherapy in usual practice) produced the widest range of CPB estimates: 92,400 to 1,023,000 QALYS saved. However, changing just two of these variables (the combined variable of the portion of CHD mortality and CHD hospitalizations that are attributable to high cholesterol and adherence with pharmacotherapy in usual practice), along with any of the variables to which CPB is moderately sensitive, produced similar estimates: 103,000 to 107,000 QALYs saved at the low end and 807,000 to 914,000 QALYs saved at the high end.

**E. Cost-Effectiveness Estimate**

We estimated the cost effectiveness of screening by adding service costs, cost-savings, and discounting to the estimate of CPB. We estimated CE for the recommended screening ages over the lifetime of a birth cohort of 4 million. We followed our methods for producing consistent estimates of CE across preventive services.[34;49] These methods are consistent with the 'reference case' of the Panel on Cost-Effectiveness in Health and Medicine.[50] The methods include use of a 3% discount rate for both costs and health benefits, the exclusion of productivity losses from disease costs, and the exclusion of medical costs that are not related the conditions prevented by the service. We used year 2000 dollars for all cost data.

Table 2 is, in effect, a continuation of Table 1 and therefore we continued the row numbering of Table 1 in Table 2. To simplify calculations of the costs of screening, laboratory monitoring, and pharmaceutical treatment over the lifetime of a birth cohort of 4 million, we computed the years of life lived after the age of 35 and 45 for men and women respectively, using U.S. life tables[24] and the portion of these years for which individuals would have high cholesterol (eligible for treatment; row a38) and the portion for which individuals would not

have high cholesterol (eligible for screening; row a39). We based the distribution of years of life with and without high cholesterol on the age-gender prevalence for 1999-2002 reported from the National Health and Nutritional Examination Survey (NHANES).[51] High cholesterol was defined as a total cholesterol of greater than 240 mg/dL in summary of survey results. To estimate the number of individuals in the birth cohort of 4 million who would eventually develop high cholesterol, we multiplied the number of individuals in the birth cohort projected to be alive at age 35 for men and 45 for women by an estimate of peak prevalence of high cholesterol for each gender. The lifetime incidence for men was defined as the prevalence in the 45-54 year old age group (23.6%), and lifetime incidence for women was defined as the prevalence in the 65-74 year old age group (32.3%).[51] The result was an estimated 1,078,000 individuals (row a40).

E.1. Costs of Screening, Monitoring, and Pharmacotherapy. Rows a41 – a59.

We computed the costs of screening in three components: the lifetime costs of screening, the lifetime costs of non-screening laboratory tests, and the lifetime costs of pharmacotherapy. The costs of screening include patient time for travel and medical appointment, physician time to discuss screening and cholesterol-related behaviors,[52] and the costs of screening. To improve consistency across the preventive services included in our study, we used our standard method of valuing time for patients to travel to the clinic and receive the service. We assumed that it takes 2 hours for travel and clinic appointment and we used average hourly earnings plus benefits in 2000[53] to estimate the value of patient time. The resulting estimate is $42.32 per office visit in year 2000 dollars (row a41). However, we assumed that only half of this time is attributable to screening (row a43) because some patients will receive one or more additional services at the same time.

We assumed that half of a 10-minute evaluation and management office visit for an established patient (CPT4 99219) would be required for screening, including discussion of health behaviors related to cholesterol. The cost of this visit was estimated as the average of Medicare reimbursement and the median private sector charges.[54] Screening by complete lipid profile is preferred. In the base case, we assumed that 75% of those who accept screening would be screened with a full lipid panel (CPT4 80061) and 25% would be screened by total cholesterol (CPT4 82645). However, we also assumed that all individuals who are screened by total cholesterol receive the full lipid panel before they receive their initial prescription. Because there is no Medicare reimbursement rate for laboratory tests, we assigned 75% of the median private sector charge[54] rather than the average of Medicare and the private sector median as calculated for office visit costs.

Non-screening laboratory costs included the cost of an initial liver function panel, renal function panel, and thyroid function test for all individuals receiving at least one statin dispense. These laboratory tests were also valued at 75% of the median private sector charge.[54] We assumed that these panels were ordered at the same time as the 10-minute evaluation and management visit which included discussion of the initial prescription. We assumed that receiving the prescription and blood draws for monitoring were the primary reason for the visit for most patients and therefore we assigned 75% of the cost of these 10-minute visits, including patient time and travel, to cholesterol screening costs. We assumed that 75% of patients who continued statin therapy would adhere to recommended lipid monitoring of 2 tests per year and a full lipid panel would be ordered for each. Finally, we assumed that an average of 50% of patients who started therapy would have a repeat liver function test due to a dose change or symptoms of potential hepatic complications.

Therapy costs were based upon an estimate of the average per-fill costs of lipid-acting agents.[38] This average cost ($83.62) reflects the market share of all lipid-acting agents among commercial clients of a large pharmacy benefits management company using both pharmacy and mail order services, the vast majority of which are statins. We assumed 12 prescriptions per year at this average cost are filled for patients with complete compliance. This assumption may cause therapy costs to be over- or understated, depending on the balance between individuals who are screened and use more than one agent, and the number of dispenses in the average cost estimate that are for more than 30 days. We did not adjust these 2003 estimates to 2000 dollars because there appears to have been little change in per-dispense costs for the top three statins over this time period.[38]

The data points reflecting these estimates and assumptions are shown in rows a41-a56 in Table 2. The calculations for lifetime screening costs, laboratory costs, and pharmacotherapy are shown in rows a57-a59. The screening cost calculation in the source column shows, in order, the cost of initial screen and the costs of follow-up lipid panels for those screened by total cholesterol and who return for pharmacotherapy. The non-screening laboratory cost calculation is also broken into two components. The calculation first shows the costs of initial laboratory tests (renal, liver, and TSH) along with associated visit costs and then the cost of follow-up lipid and liver panels. The cost calculation for pharmacotherapy shows first the cost of therapy for all who adhere to therapy in the first year after diagnosis and then the costs of therapy reflecting average adherence in all years after the first year.

E.2. Treatment Costs of Prevented Disease. Rows a60-a63.

We estimated the costs of events with hospitalizations using the first year and follow-up disease costs for CHD reported by Russell et al.[55] We used the first-year costs for non-fatal MIs and unstable angina (both of which include a hospitalization in the first year for 100% of patients), and we weighted these estimates using the relative frequency of inpatient discharges with a first listed diagnosis of MI or angina.[30] To these costs, we added four years of follow-up costs less the costs of hospital readmissions as estimated by Russell et al. Using this method, the total cost savings assigned to each hospitalization is $19,931 (row a60), of which $18,029 of this cost occurs in the year of the hospitalization.

Both the first year costs and the follow-up costs include outpatient costs, emergency department costs, and pharmaceuticals. Therefore, applying the first year costs with additional years of follow-up costs to each hospitalization approximates the total costs of care for individuals with cholesterol attributable CHD. Furthermore, because these costs include pharmaceutical use, our CE estimate reflects lipid-pharmacotherapy net of lipid pharmacotherapy that is used in secondary prevention in the absence of screening. This approximation is accurate if individuals with cholesterol-attributable CHD have a CHD related hospitalization once every 5 years. We have no data to support that frequency.

To estimate the lifetime costs of treatment for CHF, we calculated an average from two cost-effectiveness models of beta-blocker therapy for CHF patients that reported long-term costs in U.S. dollars.[56;57] Delea et al. report the predicted lifetime costs of CHF with and without beta-blocker therapy [56] and Cowper et al. report the predicted 5-year costs with and without beta-blocker therapy.[57] We used the average of the two rather than the lifetime costs from Delea et al. alone because the 5-year estimates estimated by Cowper et al. were higher than the lifetime costs estimated by Delea at al. Both studies reported long-tern costs discounted at 3%. For both studies we calculated the average of costs for patients using and not using beta-blockers. For both

studies, we 'took-out' the 3% discount factor (assuming a median of 3 years discounting) so that we could readily discount costs back to the age of initial cholesterol screening in our CE calculation. Adjusted to year 2000 dollars, the resulting average was $46,814 (row a61).

E.3. Discounting and Cost Effectiveness Calculation. Rows a64-a79.

We discounted all costs and benefits to their present value at the age of 35 using a 3% discount rate. Because building year-by-year Markov models for each service in the prevention priorities study was beyond the study's scope, we developed alternate discounting techniques as described in our methods technical report.[34] To discount the costs of screening, we estimated the difference between median year of screening and age 35 (row a64), using the prevalence of high cholesterol by age group[51] to determine the age distribution of years *without* high cholesterol. We then applied an appropriate discount factor based upon an annual discount rate of 3% (row a65) using present value tables developed for the Prevention Priorities Project.[34] Similarly, we used the age distribution of years living with high cholesterol to assign a discount factor corresponding to the median age of laboratory monitoring and pharmacotherapy. We used the age distribution of the year of death from CHD and remaining life-expectancy at the age of death to determine a discount factor for years of life saved. We used the age distribution of hospitalizations to determine a discount factor for QALYs saved from hospitalizations and associated costs. The discount factor for QALYs saved from CHF cases prevented and associated costs was calculated relative to that of hospitalizations in order to reflect the fact that the CHF cases included in the model are sequelae of MIs.

These discounted factors are applied to the relevant cost or health benefit in rows a74-a78. The CE ratio is the net discounted costs divided by the discounted QALYs saved. The resulting base-case estimate is 38,234 dollars per QALY saved (row a79).

E.4. Sensitivity Analysis for Cost Effectiveness

In single variable sensitivity analysis we treated several combinations of similar variables as a single variable to test for systematic measurement error. These included the portion of CHD mortality and CHD hospitalizations that are attributable to high cholesterol, all variables directly contributing to the cost of office visits (including patient time and travel costs), all variables directly contributing to screening costs, all variables directly contributing the cost of non-screening laboratory tests, and all discount factors. Single variable sensitivity analysis identified three variables to which the CE ratio is highly sensitive: the combination of CHD deaths and CHD hospitalizations attributable to high cholesterol; the effectiveness of statins in clinical trials; and the average annual cost of statins. Changes to these variables caused the CE ratio to increase 35% to 56% and decrease 30% to 35% when varied in the range shown in Tables 1 and 2. The CE ratio was moderately sensitive to several other variables: total CHD mortality in the birth cohort, adherence with statins in usual practice, adherence with statins in the clinical trials, average life years gained in clinical practice, the portion of years of life lived in the birth cohort for which pharmaceutical treatment could be provided, and the combined variable of all costs related to non-screening laboratory tests. Changes to these variables either increased the CE ratio 20% to 27% and/or decreased the CE ratio 15% to 26%.

In multivariate sensitivity analysis, we varied three variables at time to identify a range of CE ratios to demonstrate the uncertainty of the CE estimate.[34;49] Multiplying combinations of three variables produced ranges of CE ratios from 9,300 to 11,800 $/QALY at the low end and from 106,500 to 113,800 on the high end. At both the low and high end, changing the

combination of CHD deaths and CHD hospitalizations attributable to high cholesterol, the effectiveness of statins in clinical trials, and the average annual cost of statins simultaneously produced the low and high values that define the multivariate sensitivity analysis range of 9,300 to 113,800 $/QALY saved.

**F. Scoring**

We ranked services in the Prevention Priorities Study based upon scores for CPB and CE rather than point estimates.[2;34] For each measure, we assigned scores according to the quintile in which the service's CPB and CE estimates fall among all services included in the study. Services having the highest CPB or best cost-effectiveness received a score of 5.

For cholesterol screening, the CPB estimate resulted in a CPB score of 5. Sensitivity analysis produced scenarios in which CPB scores of 4 and 3 are possible. Sensitivity analysis produced no scenarios that would result in CPB scores of 2 or 1.

The CE estimate resulted in a score 2. Sensitivity analysis revealed scenarios in which CE would have received scores of 3 or 4. At the same time, no scenarios produced CE estimates that were consistent with scores of 5 or 1.

The resulting total score for this service was 7. The sensitivity analysis described above indicated that total scores between 5 and 9 are possible.

**G. Limitations**

The QALYs saved through prevented CHD events may be underestimated. In addition to CHF, CHD event survivors suffer other types of disability, including arrhythmia and angina pectoris. Only acute episodes of these conditions that result in hospitalizations are captured in our estimate of CPB. The CHF calculations themselves may be dated due to developments in disease management. In recent years, several landmark clinical trials have provided evidence supporting use of angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin-receptor blockers, and aldosterone blockers in the management of CHF patients.[58] Survival rates have improved significantly in the past decade, and the improvement may continue as the evidence disseminates.[59-61] Sensitivity analysis showed that none of the morbidity variables have a substantial impact on CPB. Years of life saved account for 98% of CPB in the base case. Thus, extremely large changes to the morbidity calculations would be needed to have a meaningful impact on CPB.

Another source of understatement is the exclusion of CHF after a silent MI or simply from CAD without MI that is attributable to high cholesterol. We did not find sufficient data to model this source of cholesterol-attributable disease burden.

The CPB calculation does not include effectiveness of prevention of stroke because meta-analyses have not demonstrated a reduction in stroke risk from dylipidemia agents in primary prevention. A recently updated meta-analysis found a small statistically nonsignificant effect of statins on total (fatal and non-fatal) stroke incidence in primary prevention.[62] An earlier meta-analysis found similar results: a small statistically nonsignificant reduction in non-fatal strokes (OR = .85, CI = 0.57 – 1.28) and no reduction in fatal strokes (OR = 1.00) in primary prevention.[63]

The potential differential effect of statins on fatal and non-fatal stroke can be explained by the fatality rate of different types of stroke and the mechanism of action of lipid-lowering on ischemia. The type of stroke, namely ischemic versus hemorrhagic stroke, may play a role in determining the effectiveness of lipid lowering. The majority (85%) of incident strokes were

ischemic, while the fatality rate of hemorrhagic strokes is much higher than that of ischemic strokes (40-50% as compared with 10-20%). Because lipid-lowering can improve ischemia by affecting plaque formation and stability, lipid-lowering therapy can reduce ischemic, non-fatal stroke.

Prevention of mortality accounts for a large portion of life years saved in the CPB estimation. Because treatment appears to be ineffective in preventing total stroke mortality, the CPB effect of prevention of non-fatal stroke is expected to be small if any, given the small number of strokes occurring in the service population relative to CHD fatalities. Combined with the uncertain morbidity effect of statins on stroke prevention in CHD primary prevention population, we have chosen to exclude strokes from the CPB calculations.

The limitations of the CPB estimate are also limitations of the CE estimate. We needed to make several additional assumptions to develop a cost-effectiveness ratio. However none of these were found to be particularly important in sensitivity analysis. The assumptions regarding the portion of physician office visits and patient time costs that were attributable to laboratory testing, adherence with monitoring, and the number of repeat liver function tests were all part of the combined variable of non-screening laboratory costs to which CE was found to be only moderately sensitive. The assumptions made to tabulate costs were otherwise not influential in the CE ratio.

Both CPB and CE were more sensitive to two variables for which we had limited data: the portion of CHD mortality and the portion of CHD hospitalizations that occur in individuals with high cholesterol. We used an estimate of the high-cholesterol's attributable fraction of CHD as a proxy for these data points and we used a wide range in sensitivity analysis to reflect both the uncertainty of the estimate of the attributable fraction and the uncertainty of its adequacy as a proxy for the portion of CHD that occurs among individuals with high cholesterol. We would expect this proxy to create a small understatement of CPB because individuals with high cholesterol also have CHD that is not attributable to high cholesterol. This is expected to result in a low estimate of CPB because the effectiveness data from clinical trials measure the portion of all CHD events prevented among all study participants. These individuals likely had some level of CHD risk that was not caused by high cholesterol and thus could not be expected to be modified by lipid therapy. If the estimates of burden and effectiveness are otherwise accurate, it would be appropriate to use a slightly higher estimate of effectiveness to reflect that fact that non-cholesterol risk is not included in our CHD risk when using the attributable fraction.

This limitation section addresses concerns that are specific to the estimates for this service. Other limitations that are common to all models are addressed in the methods technical report.

**Table 1. Summary of Clinically Preventive Burden Estimate for Lipid Disorder Screening**

| Row | Variable | Base Case | Data Source | Range for Sensitivity Analysis |
|---|---|---|---|---|
| | **Mortality attributable to high cholesterol** | | | |
| a1 | Total CHD mortality in a birth cohort of 4,000,000 after the ages of 35 (men) and 45 (women) | 815,771 | [23;24] | +/-20% |
| a2 | Percent of CHD mortality attributable to high cholesterol | 42.7% | [25] | 30%-55% |
| a3 | CHD mortality in the birth cohort attributable to high cholesterol | 348,334 | a1*a2 | |
| a4 | Receipt of cholesterol screening | 70.8% | [26] | 60%-75% |
| a5 | Use of pharmacotherapy for lipid disorders among individuals with high cholesterol | 43.0% | [27] | 30%-55% |
| a6 | Efficacy of drug treatment in reducing CHD deaths | 31.8% | a19/a20 | 23%-33% |
| a7 | Predicted CHD deaths in absence of screening and treatment | 385,626 | a3/(1-a4*a5*a6) | |
| | **Acute coronary heart disease events attributable to high cholesterol** | | | |
| a8 | Total hospitalizations for CHD in birth cohort of 4,000,000 after the age of 35 (men) and 45 (women) | 3,089,571 | [24;30] | +/-20% |
| a9 | Percent of CHD hospitalizations attributable to high cholesterol | 42.7% | [25] | 30%-55% |
| a10 | CHD hospitalizations in the birth cohort attributable to high cholesterol | 1,319,247 | a8*a9 | |
| a11 | Predicted number of CHD hospitalizations in absence of screening and treatment | 1,460,482 | a10/ (1-a4*a5*a6) | |
| | **Congestive heart failure case attributable to high cholesterol** | | | |
| a12 | Incident myocardial infarctions in a birth cohort of 4,000,000 | 598,132 | [33] | +20% |
| a13 | Incident myocardial infarctions attributable to high cholesterol | 255,402 | a12*a9 | |
| a14 | Predicted incident MIs attributable to high cholesterol in the absence of screening and treatment | 282,745 | a13/(1-a4*a5*a6) | |
| a15 | Percent of MIs followed by disabling CHF | 34% | [32] | 15% to 55% |
| a16 | CHF cases subsequent to MIs attributable to high cholesterol | 96,133 | a14*a15 | |
| | **Effectiveness of screening and treatment** | | | |
| a17 | Percent of patients accepting screening | 90% | Assumed | 75%-95% |
| a18 | Percent of patients initiating treatment | 90% | Assumed | 75%-95% |
| a19 | Effectiveness of drug treatment in preventing CHD events in clinical trials | 27% | [7-9;13;14;17-19] | 20%-35% |
| a20 | Adherence with statins in clinical trials | 85% | [40] | 75%-90% |
| a21 | Efficacy of drug treatment in reducing CHD events | 31.8% | a19/a20 | |
| a22 | Adherence with drug treatment in usual practice | 40% | See text | 20%-65% |
| a23 | Effectiveness of drug treatment in preventing CHD events in usual practice | 13% | a21*a22 | |
| a24 | Effectiveness of screening and treatment in preventing CHD events in usual practice | 10% | a17*a18*a23 | |
| | **Quality adjusted life years (QALYs) saved mortality** | | | |
| a25 | Number of CHD deaths prevented | 39,688 | a7*a24 | |
| a26 | Average life years gained per CHD death prevented | 9.02 | [23;24] | +/-20% |
| a27 | Number of life years saved | 357,946 | a25*a26 | |

| | | | | |
|---|---|---|---|---|
| | **Quality adjusted life years (QALYs) saved morbidity** | | | |
| a28 | Number of CHD hospitalizations prevented | 150,309 | a11*a24 | |
| a29 | Acute QOL reduction per year | 0.3 | Assumed | .2 to .4 |
| a30 | Average duration of acute illness with hospitalization | 0.058 | Assumed | 2 to 5 weeks |
| a31 | QALYs saved from prevented acute illness | 2,602 | a28*a29*a30 | |
| a32 | Number of CHF cases prevented | 9,894 | a16*a24 | |
| a33 | CHF disability QOL reduction per year | 0.2 | Assumed | 0.1 to 0.3 |
| a34 | Average duration of CHF in years | 2.3 | [48] | +/-30% |
| a35 | QALYs saved from CHF disease prevented | 4,551 | a32 *a33*a34 | |
| a36 | Total QALYs saved **(CPB estimate)** | 365,099 | a27+a31+a35 | |

**Table 2. Summary of Cost Effectiveness Estimate for Lipid Disorder Screening**

| Row | Variable | Base Case | Data Source | Range for Sensitivity Analysis |
|---|---|---|---|---|
| a37 | Years of life in target population age range | 149,947,228 | [24] | |
| a38 | Portion of years eligible for treatment | 0.22 | [24;51] | 0.17 to 0.27 |
| a39 | Portion of years eligible for screening (no high cholesterol) | 0.78 | 1-a38 | |
| a40 | Number in birth cohort ever developing high cholesterol | 1,078,210 | [51] | +/- 20% |
| | **Costs of screening, lab monitoring and statin therapy** | | | |
| a41 | Cost of patient time and travel for office visit | $42.32 | [53] | +/- 50% |
| a42 | Cost of office visit | $43.63 | [54] | +/- 33% |
| a43 | Portion of 10-minute office visit used for screen recommendation | 50% | Assumed | 25% to 75% |
| a44 | Portion of 10-minute office visit used for monitoring | 75% | Assumed | 40% to 90% |
| a45 | Cost of total cholesterol and HDL (non-fasting) | $14.92 | [54] | +/- 33% |
| a46 | Cost of lipid panel | $43.25 | [54] | +/- 33% |
| a47 | Cost of liver function panel | $22 | [54] | +/- 33% |
| a48 | Cost of renal function panel | $26 | [54] | +/- 33% |
| a49 | Cost of thyroid function test (TSH) | $49 | [54] | +/- 33% |
| a50 | Average annual cost of statins, given current market share and adherence | $1,003 | [38] | +/- 33% |
| a51 | Average number of recommended lipid screening tests per person year without diagnosis | 0.2 | 5-year interval | |
| a52 | Of those screened, portion initially screened with lipid panel | 75% | Assumed | 50% to 90% |
| a53 | Of those screened, portion initially screened with total cholesterol | 25% | 1-a52 | |
| a54 | Average number of recommended lipid monitoring tests per person year of treatment | 2.0 | Assumed | NA |
| a55 | Adherence with monitoring among those adhering to treatment | 75% | Assumed | 40% to 90% |
| a56 | Average number of repeat liver function panels per person treated | 0.50 | Assumed | 0.20 to 2.0 |

| | | | | |
|---|---|---|---|---|
| a57 | Lifetime screening costs, undiscounted | $1,678,276,598 | (a37*a39)*a51*a17*(((a41+ a42)*a43)+(a46*a52+a45* a53)) + (a40*a17*a53*a18*a46) | |
| a58 | Lifetime non-screening laboratory costs, undiscounted | $1,406,775,275 | a40*a17*a18* (a47+a48+a49+a41) + (a17*a18*a22*a55)*(a37* a38)* (a54*(a46+a41*a44)+a56* a47) | |
| a59 | Lifetime statin therapy costs, undiscounted | $11,190,713,209 | (a40*a17*a18*a50) + (a17*a18*a22* (a37*a38- a40)*a50) | |
| | **Costs savings from prevented disease** | | | |
| a60 | Costs of CHD hospitalizations and subsequent care | $19,931 | [55] | +/- 50% |
| a61 | Lifetime costs of CHF | $46,814 | [56;57] | +/- 50% |
| a62 | CHD costs prevented | $2,995,872,873 | a28*a60 | |
| a63 | CHF costs prevented | $463,168,150 | a32*a61 | |
| | **Discounting (all discounting to present value at age 35)** | | | |
| a64 | Median year of lipid screening from age 35 | 32 | [24;51] | |
| a65 | Corresponding discount factor for lipid screening and associated office visit | 0.39 | Present value tables | .34 to .44 |
| a66 | Median year of lab monitoring and statin treatment from age 35 | 31 | [24;51] | |
| a67 | Corresponding discount factor for laboratory tests and associated office visit | 0.40 | Present value tables | .35 to .45 |
| a68 | Median year of year of life prevented from age 35 | 40 | [23;24] | |
| a69 | Corresponding discount factor for years of life saved | 0.31 | Present value tables | .26 to .36 |
| a70 | Median year of acute event prevented from age 35 | 30 | [24;30] | |
| a71 | Corresponding discount factor for CHD morbidity QALYs and costs | 0.41 | Present value tables | .36 to .46 |
| a72 | Median year of chronic disease morbidity prevented from age 35 | 36 | a70 + 5 + a34*0.5 | |
| a73 | Corresponding discount factor for CHF morbidity QALYs and costs | 0.35 | Present value tables | .30 to .40 |
| | **Cost estimate calculation** | | | |
| a74 | Discounted costs of lipid screening tests and office visits | $651,736,957 | a57*a65 | |
| a75 | Discounted costs of non-screening laboratory tests | $562,692,026 | a58*a67 | |
| a76 | Discounted costs of statin therapy | $4,476,141,429 | a59*a67 | |
| a77 | Discounted savings from prevented events and sequelae | $1,394,067,987 | a62*a71+a63*a73 | |
| a78 | Discounted QALYs | 112,373 | a27*a69+a31*a71+a35*a73 | |
| a79 | Discounted $/QALY **(CE estimate)** | $38,234 | (a74+a75+a76-a77)/a78 | |

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