Hypertension Screening: Technical Report Prepared for the National Commission on Prevention Priorities

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Prepared by

Michael V. Maciosek, PhD*

Nichol M. Edwards, MS*

Winnie W. Nelson, PharmD

Margaret K. Davis, MS

Dana A. McGree*

*HealthPartners Research Foundation
8100 34th Ave S
PO Box 1524, MS 21111R
Minneapolis MN 55440-1524

** Partnership for Prevention
1015 18th Street NW, Suite 200
Washington, DC 20036

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A. USPSTF Recommendation

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians screen adults aged 18 and older for high blood pressure (A recommendation).[1] The USPSTF found good evidence that blood pressure measurement can identify adults at increased risk for cardiovascular disease due to high blood pressure, and good evidence that treatment of high blood pressure substantially decreases the incidence of cardiovascular disease and causes few major harms. The USPSTF concludes the benefits of screening for, and treating, high blood pressure in adults substantially outweigh the harms.

B. Choice of Screening Tools, Intervals and Treatment

Blood pressure is most commonly measured in a clinical setting using a sphygmomanometer. The USPSTF found that evidence was lacking for an optimal interval to screen adults for high blood pressure, so it was unable to include such a recommendation. We used annual frequency of blood pressure screening for our estimates.

The USPSTF found studies that evaluated the effects of pharmacological therapy on blood pressure and cardiovascular events; however, the USPSTF was unable to find studies that examined the effects of nonpharmacological therapies on cardiovascular outcomes, but did find nonpharmacological effects on blood pressure. Due to the lack of information and evidence for nonpharmacological therapies, we limited our investigation to pharmacological therapies only.

C. Literature Search and Abstraction

C.1. Effectiveness Literature

The literature examining pharmacological treatments for high blood pressure is considerable. To most efficiently identify key studies on the treatment of high blood pressure, we performed a Level 1 literature search[2] to identify meta-analyses and systematic reviews. Our meta-analysis/systematic review literature search identified 87 articles in PubMed from January 1, 1992 through January 14, 2004. Meta-analysis and systematic review articles relevant to the screening and treatment of high blood pressure were obtained and examined to identify key high blood pressure treatment trials. Using the meta-analysis and systematic review articles as well as their references of other articles, we identified 90 articles for potential abstraction.[3-92]

We examined the randomized controlled trials and the observational studies to determine which of the 90 articles should be abstracted. All articles that were abstracted were primary prevention studies that compared treatment to a control group that either received a placebo or no treatment. Outcomes in the articles needed to include at least one of the following: 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 all articles identified, 21 were abstracted that assessed the effectiveness of treatment and met these criteria.[6;16;18;19;29;31;42;46;51;55;56;69;71;72;74;75;80;84;89;93;94] During the adjudication process, 6 of these articles were fatally flawed due to greater potential for contamination of the study groups.[18;31;51;69;75;89] In addition, another study was fatally flawed due to the lack of generalizability of the study population,[72] and the final article was excluded because It did not test the association between treatment and outcomes.[74] This left 13 articles for analysis of effectiveness.[6;16;19;29;42;46;55;56;71;80;84;93;94]

C.2. Cost-effectiveness Literature

We performed Level 1 and Level 2 searches[2] to identify cost-effectiveness literature, and 438 articles were identified in PubMed between January 1, 1992 through January 1, 2004. As a result of this search and review of references in these articles, we identified a total of 57 articles for potential abstraction, but only abstracted 2 cost-effectiveness articles.[95;96] The reasons articles were not abstracted for cost effectiveness were that the studies were conducted in non-U.S. populations, evaluated costs in non-U.S. dollars, did not examine a population that was free of other medical complications outside of hypertension, studied only people with mild hypertension, did not report outcomes in life years saved, did not include net costs, used too short of a time horizon for analysis, or were not cost-effectiveness analyses, but rather pure cost analyses. During the adjudication process, the article by Edelson[95] was determined to be unusable for our purposes due to the lack of use of a birth cohort or cross section approach to the population and the fact that it only treated people until age 65. Littenberg et al.[96] is an older study published in 1990, which has the potential for various problems with adjusting costs over more than a 10 year period. Also, Littenberg et al. did not address costs of laboratory tests that are currently recommended with hypertension treatment, and used effectiveness estimates from older RCTs which may not accurately reflect effectiveness with current stepped therapy treatment with antihypertensives. To avoid these potential problems and to be consistent with our other services, we decided to create our own estimate of cost effectiveness.

D. Clinically Preventable Burden Estimate

Conceptually, clinically preventable burden (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 analysis.[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, Congestive Heart Failure and Stroke Mortality: Rows a1-a3.

CPB is based on 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 the service. For hypertension screening, CPB is based on offering screening each year to a U.S. birth cohort starting at age 20 and continuing until death.

Mortality was estimated from 1998 death rates data using the CDC Wonder engine,[97] which provided mortality data for CHD (ICD-9 codes of 410 to 414), stroke (ICD-9 codes of 430 to 438), and congestive heart failure (CHF) (ICD-9 code of 428). Whenever U.S. population estimates were needed for calculations, the 2000 census data were used.[98] The number of deaths was estimated for persons 20 years and older, stratified by 5 or 10-year age groups, as available in the data tables. Age group-specific death rates were applied to the years of life lived between corresponding age groups over the lifetime of a birth cohort of 4 million to estimate the total

deaths in the cohort. We estimated 817,949 deaths from CHD, 96,013 deaths from CHF and 286,857 deaths from strokes (rows a1-a3 in Table 1).

D.1.2. Hypertension Attributable Mortality. Rows a4-a9.

We estimated population attributable fractions from relative risks for CHD, CHF, and stroke among persons with and without hypertension reported in the Framingham Heart Study.[99;100] We used the prevalence of hypertension reported from the National Health and Nutrition Examination Survey (NHANES) where hypertension was defined as either systolic blood pressure greater than or equal to 140 or diastolic blood pressure greater than or equal to 90,[101] based on an average of blood pressure readings (78% had at least 3 measures). The resulting population attributable fractions were 24.6% for CHD, 33% for CHF and 38.5% for strokes (rows a4-a6). These attributable fractions were used to calculate the number of CHD, CHF, and stroke deaths attributable to hypertension 201,450, 31,641, and 110,328 respectively (rows a7-a9).

D.1.3. Predicted Deaths in the Absence of Screening. Rows a10, a11, a16-a18.

The resulting calculation estimates the number of deaths that will occur given current screening and treatment patterns. In order to estimate the total value of the service, we first predict what the number of deaths will be in the absence of screening. Current death rates are influenced by the portion of the population screened, the portion of the screened population that receives and adheres to treatment, and the efficacy of treatment in preventing deaths. The equations used to predict deaths in the absence of treatment using these factors are shown in rows a16-a18. The equations are based on algebraic manipulation of an equation that expresses deaths as a weighted average of deaths that occur among those with and without screening and treatment: current deaths = (percent screened and treated) x (deaths in those screened and treated) + (percent not screened and treated) x (deaths in those not screened and treated), where the deaths in those screened and treated = (deaths in those not treated) x (1 – efficacy of treatment).

Analyzing data from NHANES, Hajjar and Kotchen reported that 58.4% of survey participants with hypertension said they were taking medication for their hypertension (row a10).[102] It is not known what percent of those taking medication were doing so as a result of asymptomatic screening. We assumed that this would be 90% in the base case (row a11). The estimates of efficacy used in these equations to predict deaths in the absence of screening (i.e. a12-a15) are explained in the section addressing effectiveness and adherence below. After adjusting for screening and treatment, the predicted mortality in absence of hypertension treatment for CHD, CHF and stroke was 231,925, 37,564 and 148,336 respectively (rows a16 to a18).

D.1.4. Coronary Heart Disease, Congestive Heart Failure and Stroke Events: Rows a19-a21.

CHD events were approximated using hospitalizations for CHD from the 2001 National Hospital Discharge Survey.[103] As with deaths, we applied age-group specific annual rates to the birth cohort of 4 million according to the years of life lived in the corresponding age range of the birth cohort. An estimated 3,114, 203 hospitalizations for CHD will occur over the lifetime of a birth cohort of 4 million (row a19).

CHF can be caused indirectly as a sequel of nonfatal CHD events or caused directly by hypertension. An estimated 34% of acute myocardial infarction survivors are disabled by

CHF.[104] We assumed that CHF cases, both directly and indirectly, attributable to hypertension are accounted for in our estimate of the population attributable fraction for CHF (row a5) through the underlying relative risk of CHF with hypertension. An estimated 550,000 new CHF cases occur each year in the current cross-section.[105] Applying an annual incidence rate based upon this number to the years of life lived in the birth cohort results in an estimated 624,626 CHF cases over the lifetime of the birth cohort (row a20). This estimate was based on a single average incidence rate for all ages because age-group specific rates were not available. As a result, 624,626 CHF cases is likely to be an understatement because, relative to the current U.S. population, the hypothetical birth cohort will have relatively more years of life lived at older ages when the risk of CHF is higher.

Similarly, an estimated 500,000 first strokes occur each year in the U.S.,[105] and applying the corresponding incidence rate to the birth cohort results in 567,842 first strokes in the lifetime of a birth cohort of 4 million (row a21). As with lifetime CHF cases, this is likely to be a low estimate.

To estimate the number of CHD hospitalizations, lifetime CHF, and lifetime strokes that are attributable to hypertension (rows a22-a24) we used the same population attributable fractions as we used for mortality. We then made the same calculations as for deaths to predict events in the absence of screening and treatment, and estimated that 832,633 CHD hospitalizations, 295,004 lifetime CHF cases and 307,204 lifetime first strokes attributable to hypertension will occur in a birth cohort of 4 million (rows a28-30).

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: Rows a12-a14, a25-a27

The thirteen abstracted articles[6;16;19;29;42;46;55;56;71;80;84;93;94] produced 41 effectiveness estimates: 5 estimates for CHD deaths,[29;46;55;56;94] 8 estimates for CHD events,[16;19;42;46;55;56;71;84] 8 estimates for fatal stroke,[6;16;19;46;55;56;93;94] 8 estimates for nonfatal stroke,[16;19;42;46;55;56;80;93] 8 estimates for fatal cardiovascular events,[6;16;19;42;46;55;56;93] and 4 estimates for nonfatal CHF events.[6;16;42;55] The medians for these estimates are used in the CPB calculation to minimize the effects of extreme values. The medians are 20% for CHD deaths (row a12), 12% for CHD events (row a25), 39% for fatal stroke (row a14), 44% for nonfatal stroke (row a27), 24% for fatal cardiovascular events (row a13), and 46% for CHF events (row a26). The effectiveness estimates are applied to rows a16 to a18 (mortality section) and a28 to a30 (morbidity section) of Table 1.

We applied the cardiovascular death estimate in place of CHF deaths (row a13). In the clinical trials, CHF is included as one of several cardiovascular endpoints, but an estimate of the effect of treatment on CHF mortality was not reported separately. We assumed that the treatment effect on CHF is similar to that on other cardiovascular events.

D.2.3. Patient Adherence: Rows a15, a31-a33

Estimates of adherence in clinical trials are needed to calculate efficacy of antihypertensive treatment for the prediction of cardiovascular disease in the absence of screening and treatment discussed above. The estimates of adherence were based on our study definition: effectiveness = efficacy x adherence. Reporting of adherence was limited within the clinical trials that we abstracted. Most of the studies incorporated a stepped therapy treatment with various antihypertensive medications. Among the studies that contributed data to our summary estimates of effectiveness, the Medical Research Counsel (MRC) study reported 30% non-adherence with diuretics and beta-blockers,[56] the Systolic Hypertension in the Elderly Program (SHEP) trial reported 10% non-adherence with stepped therapy of diuretic (Chlorthalidone), or beta blocker (Atenolol or Reserpine if Atenolol was contraindicated),[55] Coope and Warrender reported 5% non-adherence with stepped therapy of beta-blocker (Atenolol), diuretic (Bendrofluazide), or alpha agonist (Alpha-methyldopa)[16] and the European Working Party on High Blood Pressure in the Elderly (EWPHE) study reported 35% non-adherence with diuretics.[6] In addition, as a proxy for antihypertensive compliance, Waeber et al. reported 22% non-adherence with aspirin or placebo measured by electronic monitoring devices in a Hypertension Optimal Treatment (HOT) substudy.[106] These data are insufficient to estimate efficacy on a trial-by-trial basis. Therefore, based on these sparse data, we assigned an average adherence of 80% (row a15) in order to calculate efficacy for each type of event as the effectiveness in clinical trials divided by 80%. This calculation is built into the equations in rows a16-a18 and a28-a30. Even with this adjustment, efficacy may be understated due to contamination of control groups in the clinical trials, although we excluded studies that had the highest potential for contamination.

In order to obtain an estimate of the effectiveness in usual practice, we needed to estimate adherence in usual practice rather than adherence in research trials. In the CPB calculation, we differentiated two types of medication non-adherence. First, not all patients will accept treatment. This may manifest as a direct refusal when offered medication, or as never filling a prescription. We expect that out-of-pocket cost, fear of adverse effects, the asymptomatic nature of hypertension, and other decision making processes underlie the patient's non-adherence response. Lacking prevalence data on this type of non-adherence, we assumed that 10% of patients refuse medication treatment when offered (90% initiate treatment: row a32).

The second type of patient non-adherence involves taking less of the medication than directed. The adherence estimates from the self-selected patients into heavily monitored clinical trials noted above is very unlikely to be representative of the general population in usual care. Several recent studies have documented long-term adherence with antihypertensive medications among individuals with pharmacy insurance benefits. Caro et al. reported persistence with antihypertensives among participants in the Saskatchewan provincial health insurance plan with a diagnosis of hypertension. Among those who filled a prescription for an antihypertensive, after having filled a prescription for at least 12 months prior, 46% were using an antihypertensive 4.5 years after the initial dispense.[107] Persistence was lower among those whose initial prescription was a diuretic (40%) and higher among those whose initial prescription was an ACE inhibitor (53%).[108] In another analysis of the Saskatchewan data, Bourgault et al. reported substantially lower persistence at 5 years (22%) and 7 years (20%).[109] Their definition of persistence was substantially more stringent than that of Caro and colleagues. Bourgault et al. required continued use of an antihypertensive in the same class. They allowed changes to the dosing of the initial antihypertensive, but did not allow changes of the antihypertensive class or additions of another antihypertensive to the original prescription. In addition, the persistence reported by Bourgault et

al. may be lower because they excluded individuals who were taking antihypertensives for reasons other than hypertension (such as migraine) as well as those with a recent CHD event or taking medications used in the management of CHF or angina. These exclusions served to limit the analysis to individuals with 'uncomplicated hypertension', but excluding individuals who used other medication may have eliminated a sub-population that was more adherent with medications in general. Finally, in an analysis of a Merck-Medco pharmacy database, Conlin et al. reported 4-year persistence by class of antihypertensive.[110] Like Bourgault et al., they measured persistence with the initial antihypertensive dispensed, but appear to not have excluded individuals who added antihypertensives from other classes or to have excluded individuals taking other medications. At four years, the average persistence across classes was 38%. However, persistence was 47% and 51% among ACE and ACE-II inhibitors (lorastan) respectively. Persistence in the best performing classes provides an indication of what persistence would be if measured such that switches to other classes were counted towards persistence.

Based loosely on these data, we chose a base-case estimate of 40% long-term adherence in usual practice (row a33). Each of the studies discussed above observed declining, yet 'flattening' persistence between the ultimate and penultimate year of observation. This estimate may be too high for the general U.S. population because long-term adherence may be lower in uninsured populations. However, the estimate may be too low as applied in our CPB calculation because higher rates of short-term adherence observed in these and other studies (up to 70% at 2 years, and higher in year 1) provide a higher level of short-term benefit.

We assumed that 100% of patients will accept hypertension screening when offered because it is a non-invasive procedure routinely performed during most office visits (row a31). Availability of blood pressure measurement opportunities during community events (such as health fairs) and automated machines available at clinics and pharmacies also help promote the procedure to patients.

Rows a34-a39 show our estimated effectiveness of screening in reducing the six types of cardiovascular outcomes measured above. These estimates reflect the probability of an individual with hypertension accepting screening (100% in the base case), the probability of accepting initial treatment if diagnosed, the efficacy of antihypertensives for each cardiovascular outcome, and long-term adherence with antihypertensives in usual practice. We did not include an estimate of the probability of screening positive (sensitivity of screening) because the prevalence estimates underlying the calculation of the population attributable fractions are already lowered by false negative test results. As a result, the burden estimates do not reflect cardiovascular disease in individuals with false negative screens. Therefore, accounting for false negatives in the effectiveness estimates would double-count false negatives in the CPB estimate.

D.3 Clinically Preventable Burden Estimate:

D.3.1. Years of Life Saved Through Reduced Mortality: Rows a46-a49.

The effectiveness of screening in reducing hypertension attributable mortality (rows a34-a36) was multiplied by the estimates of mortalities attributable to hypertension to determine the number of CHD, CHF, and stroke deaths prevented by offering screening and appropriate antihypertensive therapy to the birth cohort starting at age 20 (rows a40-a42). Total years of life saved are estimated by multiplying the deaths prevented during each range by the life-expectancy at each range. The average years of life expectancy across all ages, weighted according to the age distribution of deaths prevented, are shown in rows a43-a45. Multiplying

these weighted averages by the total deaths produced the same estimate as the age-range-specific tabulations. An estimated 437,554 years of life are saved by screening (row a49), where 190,318, 28,764, and 218,472 are attributable to CHD, CHF, and stroke deaths prevented respectively (rows a46-a48).

D.3.2. Quality Adjusted Life Years (QALYs) Saved Through Reduced Morbidity: Rows a59-a62

Using the respective estimates of the effectiveness of screening in preventing events (rows a37-a39); we estimated the number of CHD hospitalizations, CHF cases, and first strokes that would be prevented over the lifetime a birth cohort (rows a50-a52). 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.[111] We applied the CHF duration of disability of 2.3 years and the stroke duration of disability of 7.8 years reported for 'established market economies' in the Global Burden of Disease study.[113] 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 were used for all conditions unless available utility scales indicate that actual quality of life reductions are substantially different.[114;115] The QALYs lost per year for stroke of .40 (range .25 to .55) was based on published estimates from utility scales rather than the standard QALY weight for chronic conditions because the utility scales indicate that strokes have substantially higher quality of life losses per year than most other chronic conditions[112;116-121] The total QALYs saved based on these durations and quality of life estimates were 778, 28,090, and 189,778 for CHD hospitalizations, CHF cases, and first strokes respectively (rows a59-a61), and the total QALYs saved through reduced morbidity was 218,647 (row a62).

D.3.3 Clinically Preventable Burden Result: Row a63

CPB is the total of quality adjusted life years saved from mortality and morbidity prevented by offering periodic screening and pharmaceutical treatment for high blood pressure over the lifetimes of men and women starting at age 20 in a birth cohort of 4 million individuals: 656,201 QALYs saved (row a63).

D.4 Sensitivity Analysis for Clinically Preventable Burden:

For the purpose of sensitivity analysis, we treated several sets of variables as a single variable (changing the value of each at the same time) to test for the effects of systematic error in measurement. For CPB these combined variables were average years of life lost for three causes of hypertension-attributable mortality, the average duration of illness for the three types of morbidity, and the average quality of life reduction for the three types of morbidity.

In single-variable sensitivity analysis, CPB was found to be most sensitive to five variables:

- percent of stroke mortality and morbidity that is attributable to hypertension;
- percent of patients who accept treatment among those who screen positive;
- percent of patients who continue treatment among those who accept initial treatment;
- effectiveness of antihypertensives on CHD deaths in clinical trials; and
- effectiveness of antihypertensives on stroke deaths in clinical trials.

CPB changed by 22-35% in the either the positive (higher CPB) or negative direction with changes to each of these variables in the ranges for sensitivity analysis shown in Table 1. The largest change (+35%) occurred when the percent of stroke mortality and morbidity that is attributable to hypertension was increased to 60% from the base case estimate of 38.5%.

Other variables to which CPB was moderately sensitive (14% to 19% change in CPB with changes to variables inside their sensitivity analysis ranges) include:

- percent of CHD mortality and morbidity attributable to hypertension;
- effectiveness of antihypertensives on nonfatal strokes in clinical trials;
- adherence to therapy in clinical trials; and
- combined quality of life reduction.

In multivariate sensitivity analysis, several combinations of three of these variables led to changes in CPB of approximately -50% in the negative direction and +100% in the positive direction. In the positive direction, the largest change (+123%) resulted from simultaneously changing the percent of stroke mortality attributable to hypertension, the effectiveness of antihypertensives on stroke deaths in clinical trials, and adherence in clinical trials. In the negative direction, the largest change (-54%) resulted from simultaneously changing the percent of stroke mortality attributable to hypertension, the percent of patients accepting treatment, and the percent of patients continuing treatment. These combinations produced our overall range from multiple variable sensitivity analysis that we use as our key indicator of uncertainty of CPB in comparing services: 299,400 to 1,461,500 QALYs saved.

E. Cost-effectiveness Estimate

We estimated the cost-effectiveness of screening for hypertension by adding service costs and cost-savings, and discounting to the estimate of CPB. We estimated cost effectiveness over 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 preventives services.[114;115] These methods are consistent with the 'reference case' of the Panel on Cost-Effectiveness in Health and Medicine.[122] 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 to 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 Table 2 contains references to the rows of Table 1. To simplify calculations of the costs of screening, 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 20 using U.S. life tables,[98] the portion of these years for which individuals would have hypertension (eligible for treatment; row b2), and the portion for which individuals would not have hypertension (eligible for screening; row b3). We based the distribution of years of life with and without hypertension on the age-gender prevalence for 1999-2002 reported from NHANES.[101] To estimate the number of individuals in the birth cohort of 4 million who would eventually develop hypertension, we multiplied the number of individuals in the birth cohort projected to be alive at age 20 by an estimate of lifetime incidence for each gender defined by age group prevalence rates and the portion of each gender predicted to be alive at each age according to U.S. life tables. The result is an estimated 1,938,369 individuals (row b4).

E.1. Costs of Screening, Monitoring, and Pharmacotherapy

We computed the costs of screening in three components: the lifetime costs of screening, the lifetime costs of laboratory tests and monitoring, and the lifetime costs of pharmacotherapy. The costs of screening include patient time for travel and the medical appointment, physician time to discuss screening and hypertension risk factors, 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 the clinic appointment and we used average hourly earnings plus benefits in 2000[123] to estimate the value of patient time. The resulting estimate is $42.32 per office visit in year 2000 dollars (row b5). However we assumed that only half of this time is attributable to screening (row b7) because some patients will receive one or more other services at the same time.

We assumed that half of a 10-minute evaluation and management office visit for an established patient (CPT4 99219) is required for screening, including discussion of health behaviors related to hypertension. The cost of this visit is estimated as the average of Medicare reimbursement and the median private sector charges.[124]

Recommended initial tests include 12-lead ECG, urinalysis, blood glucose, hematocrit, serum potassium, creatinine, calcium and lipid profile.[125] Because there is no Medicare reimbursement rate for laboratory tests, we assigned 75% of the median private sector charge[124] rather than the average of Medicare and the private sector median as calculated for office visit costs (rows b9-b16). 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 75% of patients who continue antihypertensive therapy would adhere to recommended blood pressure monitoring of 2 tests per year and serum potassium and creatinine tests every other year (row b21).[125] Receiving the prescription and initial tests for monitoring are likely to be the primary reason for the first visit after a diagnosis of hypertension is established. Follow-up blood pressure monitoring may be done at virtually any visit, including, in some practices, allocated drop-in times for blood pressure measurement. To represent the average of these scenarios, we assigned 50% of the cost of a 10-minute visit, including patient time and travel, to blood pressure monitoring costs (row b8).

Therapy costs were based upon an estimate of the average costs per fill of antihypertensive agents.[126] This average monthly cost ($42.54) reflects the market share of all antihypertensives among commercial clients of a large pharmacy benefits management company using both pharmacy and mail order services.[126] We believe that using the average cost of all agents given their current market share provides the best estimate of costs of implementing screening in usual care. We assumed 12 prescriptions per year at this average cost are filled for patients with complete compliance (row b17). This assumption may cause therapy costs to be over- or understated, depending on the balance between individuals who are using more than one agent, and the number of dispenses in the average cost estimate that are for more than 30 days.

The calculations for screening costs, laboratory costs, and pharmacotherapy are shown in rows b22-b24. The monitoring cost calculation is broken into two components. The calculation first shows the costs of initial laboratory tests along with associated visit costs, and then the cost of follow-up blood pressure checks and potassium and creatinine tests. 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 Illness: Rows b25-b30

We estimated the costs of events with hospitalizations, using the first year and follow-up disease costs for CHD reported by Russell et al.[127] 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.[103] 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 was $19,931 (row b25), 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 hypertension attributable CHD. Furthermore, because these costs include pharmaceutical use, our CE estimate reflects antihypertensive treatment net of antihypertensives that are used in secondary prevention following CHD. This approximation is accurate if individuals with hypertension 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.[128;129] Delea et al. report the predicted lifetime costs of CHF with and without beta-blocker therapy[128] and Cowper et al. report the predicted 5-year costs with and without beta-blocker therapy.[129] We use 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. are higher than the lifetime costs estimated by Delea at al. Both studies reported long-term 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 screening in our CE calculation. Adjusted to year 2000 dollars, the resulting average was $46,814 (row b26).

As with CHF, we identified two estimates of the long-term costs of strokes and used the average of the two after adjusting for discounting and inflation. Fagan et al. estimated the lifetime costs of stroke in a Markov model of the CE of tissue plasmionogen activator (tPA).[130] They reported lifetime costs discounted 5% in 1996 dollars of $62,716 in the placebo group of the RCT on which the CE analysis was based. We used the reported average years of life in the placebo group (7.1 years) as the basis for removing the discount rate and adjusted costs to 2000 dollars. The result is $80,159. This estimate includes the two largest components of stroke care – acute inpatient and nursing home care – but excludes prescription drugs and outpatient care attributable to strokes. Taylor et al. reported the total life-time costs of stroke as $103,576 in 1990 dollars as estimated from a cost-of-illness model.[131] From Figure 1 of their article, we estimated that the direct costs (excluding productivity losses) are approximately $46,000 in 1990 dollars and $73,745 after inflation to 2000 dollars. This estimate includes all major elements of care: acute inpatient (including the costs of recurrent stroke), nursing home, outpatient visits, and pharmaceuticals. We used the average of these two estimates, $76,952 in year 2000 dollars, as our base-case estimate for the undiscounted lifetime cost after an initial stroke (row b27).

To calculate the total cots of prevented disease we multiplied each of the above lifetime costs of each CHD, CHF and stroke by the total number of events prevented to get the total costs

of CHD, CHF and stroke prevented, $896,158,199, $2,858,727,072, and $4,680,687,824 respectively (rows b28-b30).

E.3 Discounting and Cost-effectiveness Calculation

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 is beyond the study's scope, we developed alternate discounting techniques as described in our methods technical report.[115] To discount the costs of screening, we estimated the difference between median year of screening and age 20 (row b31), using the prevalence of hypertension by age group[101] to determine the age distribution of years *without* hypertension. Then we applied an appropriate discount factor based upon an annual discount rate of 3% (row b32) using present value tables developed for the Prevention Priorities Project.[115] Similarly, we used the age distribution of years living with hypertension to assign a discount factor corresponding to the median age of monitoring and antihypertensive therapy. 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 for first stroke and CHF cases prevented and associated costs was calculated relative to that of hospitalizations to reflect the fact that CHF is a sequel of MIs that are included in the CHD hospitalizations and that strokes occur at somewhat older ages than CHD events.

These discounted factors were applied to the relevant cost or health benefit in rows b41-b44. The CE ratio was calculated as the net discounted costs divided by the discounted QALYs saved. The resulting base-case estimate is 31,465 dollars per QALY saved (row b45).

D.4 Sensitivity Analysis for Cost Effectiveness

For the purposes of sensitivity analysis, we treated several sets of variables as a single variable (changing the value of each at the same time) to test for the effects of systematic error in measurement. For CE, these combined variables were average years of life lost for the three causes of hypertension-attributable mortality, the average duration of illness for the three types of morbidity, the average quality of life reduction for the three types of morbidity, the probability of ever developing hypertension and the associated portion of years of life in the birth cohort eligible for treatment ('combined hypertension prevalence variables' from here on), variables contributing to the per-person cost of screening, and variables contributing to the per-person cost of monitoring.

In single-variable sensitivity analysis, CE was found to be most sensitive to five variables:

- percent of stroke mortality and morbidity that is attributable to hypertension
- effectiveness of antihypertensives on nonfatal stroke in clinical trials
- combined screening costs variables
- combined monitoring costs variables
- cost of antihypertensives

CE changed by 29% to 50% in either the positive (higher CE ratio) or negative direction with changes to each of these variables in the ranges for sensitivity analysis shown in Table 1. The largest change (+50%) occurred when increasing the screening cost variables.

Other variables to which CE was moderately sensitive (21% to 28% change in CE with changes to variables inside their sensitivity analysis ranges) include:

- effectiveness of drug treatment on CHD deaths in clinical trials
- effectiveness of drug treatment on stroke deaths in clinical trials
- adherence to therapy in clinical trials
- combined quality of life reductions
- combined hypertension prevalence variables

In multivariate sensitivity analysis, several combinations of three of these variables led to changes in CE of approximately -80% in the negative direction and a single combination led the highest change in the positive direction (+144). In the positive direction, the largest change resulted from simultaneously changing the percent of stroke mortality attributable to hypertension, the combined screening costs variables, and the cost of antihypertensives. In the negative direction, the largest change (-88%) resulted from simultaneously changing the percent of stroke mortality attributable to hypertension, the combined screening costs variables, and the combined hypertension prevalence variables. These combinations produced our overall range from multiple variable sensitivity analysis that we used as our key indicator of uncertainty of CE in comparing services: 3,900 to 76,600 $/QALYs saved.

F. Scoring

We ranked services in the Prevention Priorities Project based upon scores for CPB and CE rather than point estimates.[2;115] 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 scope. Services having the highest CPB or best cost-effectiveness received a score of 5.

The base case estimate of 656,201 QALYs saved resulted in a CPB score of 5. Sensitivity analysis revealed several scenarios in which CPB would have received a score of 4. No scenarios in our sensitivity analysis produced CPB estimates that were consistent with scores of 3, 2 or 1.

The base-case estimate of $31,465/QALY saved resulted in a CE score of 3. Multivariate sensitivity analysis found several scenarios that generated CE estimates consistent with CE scores of 2 or 4, but none consistent with CE scores of 1 or 5.

The base-case estimates for CPB and CE produced a total score of 8. The multivariate sensitivity analysis indicated that a total score as high as 9 and as low as 6 are possible.

G. Limitations

A limitation of the CPB estimation is that the QALY loss due to disability from CHD events was an underestimate. In addition to CHF, CHD event survivors suffer other types of disability, including arrhythmia and angina pectoris. They are also more likely to experience strokes and consequently be further disabled. Outcomes data of these patients are not well documented, nor is the amount of QALY loss related to each type of disability quantified; hence, the current analysis only included CHF in the calculation.

Definitions of hypertension varied in the clinical studies, which spanned over 2 decades. Over the years, hypertension research has informed treatment guidelines and produced revised definitions of hypertension. Currently, hypertension is defined in the U.S. as blood pressure higher than 140 mmHg/90 mmHg, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).[125] The definition of hypertension in the abstracted articles used minimum systolic blood

pressures (SBP) ranging from 150 to 180 mmHg, and diastolic blood pressures (DBP) ranging from 90 to 105 mmHg. In addition, a number of studies focused on DBP only, while several others focused on SBP only. However, the effect of this less than consistent hypertension definition is likely to be minimal for the purpose of CPB estimation. The relative benefit of hypertension treatment appears to be similar across different risk levels. Thus, even though the inclusion criteria differed in the abstracted articles, the reported risk reductions are statistical estimations of the same true value.

Table 1. Summary of Clinically Preventable Burden Estimate for Hypertension

Row	Variable	Base Case	Data Source	Range for Sensitivity Analysis
	Mortality attributable to hypertension			
a1	Total CHD mortality in the birth cohort	817,949	[97]	+/-20%
a2	Total CHF mortality in the birth cohort	96,013	[97]	+/-20%
a3	Total stroke mortality in the birth cohort	286,857	[97]	+/-20%
a4	% CHD mortality attributable to hypertension	24.6%	[99;101]	15% to 40%
a5	% CHF mortality attributable to hypertension	33.0%	[100;101]	20% to 50%
a6	% stroke mortality attributable to hypertension	38.5%	[99;101]	25% to 60%
a7	Total CHD mortality in the birth cohort attributable to hypertension	201,450	a1*a4	
a8	Total CHF mortality in the birth cohort attributable to hypertension	31,641	a2*a5	
a9	Total stroke mortality in the birth cohort attributable to hypertension	110,328	a3*a6	
a10	% with hypertension receiving drug treatment	58%	[102]	40% to 60%
a11	% treatment due to asymptomatic screening	90%	Assumed	70% to 95%
a12	Effectiveness of drug treatment on CHD deaths in clinical trials	20%	[29;46;55;56;94]	10% to 35%
a13	Effectiveness of drug treatment on CHF deaths in clinical trials	24%	[6;16;19;42;46;55;56;93], see text	15% to 40%
a14	Effectiveness of drug treatment on stroke deaths in clinical trials	39%	[6;16;19;46;55;56;93;94]	25% to 60%
a15	Adherence in clinical trials	80%	See text	70% to 90%
a16	Predicted hypertension-attributable CHD deaths in absence of screening	231,925	a7/(1-a10*a11*(a12/a15))	
a17	Predicted hypertension-attributable CHF deaths in absence of screening	37,564	a8/(1-a10*a11*(a13/a15))	
a18	Predicted hypertension-attributable stroke deaths in absence of screening	148,336	a9/(1-a10*a11*(a14/a15))	
	Morbidity attributable to hypertension			
a19	Lifetime CHD hospitalizations in the birth cohort	3,114,203	[103]	+/-20%
a20	Lifetime incidence of CHF in birth cohort	624,626	[105]	+/-20%
a21	Lifetime incidence of first strokes in birth cohort	567,842	[105]	+/-20%
a22	Lifetime hypertension-attributable CHD	766,988	a19*a4	

	hospitalizations			
a23	Lifetime incidence of hypertension-attributable CHF	205,848	a20*a5	
a24	Lifetime incidence of hypertension-attributable strokes	218,398	a21*a6	
a25	Effectiveness of drug treatment on CHD events in clinical trials	12%	16;19;42;46;55;56;71;84	5% to 20%
a26	Effectiveness of drug treatment on CHF in clinical trials	46%	6;16;42;55	30% to 65%
a27	Effectiveness of drug treatment on strokes in clinical trials	44%	16;19;42;46;55;56;80;93	35% to 60%
a28	Predicted lifetime hypertension-attributable CHD hospitalizations in absence of screening	832,633	a22/(1-a10*a11*(a25/a15))	
a29	Predicted lifetime incidence of hypertension-attributable CHF in absence of screening	295,004	a23/(1-a10*a11*(a26/a15))	
a30	Predicted lifetime incidence of hypertension-attributable 1st strokes in absence of screening	307,204	a24/(1-a10*a11*(a27/a15))	
	Effectiveness of screening and treatment in typical practice			
a31	% patient accepting screening	100%	Assumed	90% to 100%
a32	% patients accepting treatment	90%	Assumed	70% to 95%
a33	% patients continuing treatment	40%	107-110	30% to 50%
a34	Effectiveness of screening on CHD deaths in typical practice	9%	a31*a32*(a12/a15)*a33	
a35	Effectiveness of screening on CHF deaths in typical practice	11%	a31*a32*(a13/a15)*a33	
a36	Effectiveness of screening on stroke deaths in typical practice	18%	a31*a32*(a14/a15)*a33	
a37	Effectiveness of screening on CHD events in typical practice	5%	a31*a32*(a25/a15)*a33	
a38	Effectiveness of screening on CHF events in typical practice	21%	a31*a32*(a26/a15)*a33	
a39	Effectiveness of screening on stroke events in typical practice	20%	a31*a32*(a27/a15)*a33	
	Years of life saved by screening and treatment			
a40	Number of CHD deaths prevented	20,873	a16*a34	
a41	Number of CHF deaths prevented	4,057	a17*a35	
a42	Number of stroke deaths prevented	26,033	a18*a36	
a43	Average life year loss of CHD death	9.1	98	+/-20%
a44	Average life year loss of CHF death	7.1	98	+/-20%
a45	Average life year loss of stroke death	8.4	98	+/-20%
a46	Number of life years saved from CHD death prevented	190,318	a40*a43	
a47	Number of life years saved from CHF death prevented	28,764	a41*a44	
a48	Number of life years saved from stroke death prevented	218,472	a42*a45	
a49	Total years of live saved	437,554	a46+a47+a48	
	Quality adjusted life years (QALYs) saved through morbidity prevented			
a50	Number of nonfatal CHD events prevented	44,962	a28*a37	
a51	Number of nonfatal CHF events prevented	61,066	a29*a38	
a52	Number of nonfatal stroke events prevented	60,826	a30*a39	
a53	Average duration of CHD event in years	0.058	See text	2 to 5 weeks

a54	Average duration of CHF in years	2.3	[113]	+/-30%
a55	Average duration of stroke in years	7.8	[113]	+/-30%
a56	CHD event disability QOL reduction per year	0.3	See text	.2 to .4
a57	CHF disability QOL reduction per year	0.2	See text	0.1 to 0.3
a58	Stroke disability QOL reduction per year	0.4	[112;116-121]	0.2 to 0.5
a59	QALY saved from prevented nonfatal CHD events	778	a50*a53*a56	
a60	QALY saved from prevented nonfatal CHF events	28,090	a51*a54*a57	
a61	QALY saved from prevented nonfatal stroke events	189,778	a52*a55*a58	
a62	Total QALYs saved through morbidity reductions	218,647	a59+a60+a61	
a63	**Clinically Preventable Burden estimate**	**656,201**	a49+a62	

Table 2. Summary of Cost-effectiveness Estimate for Hypertension

Row	Variable	Base Case	Data Source	Range for Sensitivity Analysis
b1	Years of life in target population age range	228,214,120	[98]	
b2	Portion of years eligible for treatment	0.36	[98;101]	0.25 to 0.45
b3	Portion of years eligible for screening (no hypertension)	0.64	1 - b2	
b4	Number in birth cohort ever developing hypertension	1,938,369	[101]	+/- 20%
	Costs of screening, lab monitoring and antihypertensive therapy			
b5	Cost of patient time and travel for office visit	$42.32	[123]	+/- 50%
b6	Cost of office visit	$43.63	[124]	+/- 33%
b7	Portion of 10 minute office visit used for screen	50%	Assumed	25% to 75%
b8	Portion of 10 minute office visit used for monitoring	50%	Assumed	25% to 75%
b9	12-lead ECG	$44.38	[124]	+/- 33%
b10	Urinalysis	$9.18	[124]	+/- 33%
b11	Blood glucose	$13.70	[124]	+/- 33%
b12	Hematocrit	$9.87	[124]	+/- 33%
b13	Serum potassium	$12.79	[124]	+/- 33%
b14	Creatinine	$14.92	[124]	+/- 33%
b15	Calcium	$14.92	[124]	+/- 33%
b16	Lipid profile	$43.25	[124]	+/- 33%
b17	Average annual cost of antihypertensives, given current market share and adherence	$510	[126]	+/- 33%
b18	Average number of recommended hypertension screening tests per person year without diagnosis of hypertension	0.5	2-year interval	Na
b19	Average number of recommended hypertension monitoring tests per person year of treatment	2.0	Assumed	Na
b20	Average annual number of serum potassium and creatinine monitoring tests per person year of treatment	0.5	2-year interval	Na
b21	Adherence with monitoring among those adhering to treatment	75%	Assumed	40% to 90%
b22	Lifetime screening costs, undiscounted	$3,158,174,862	(b1*b3)*(b18*a31)*((b5+b6)*b7)	

b23	Lifetime non-screening monitoring costs, undiscounted	$2,548,683,288	a31*a32*b4* ((b5+b6)* b8 +b9+b10+b11+b12+ b13+b14+b15+b16) +(a31*a32*a33*b21) *(b1*b2)* (b19*(b5+b6)*b8 +b20*(b13+b14))	
b24	Lifetime anti-hypertensive therapy costs, undiscounted	$15,464,454,304	(a31*a32)*b4*b17 +(a31*a32*a33)* (b1*b2-b4)*b17	
	Costs savings from prevented disease			
b25	Costs of CHD hospitalizations and subsequent care	$19,931	[127]	+/- 50%
b26	Lifetime costs of CHF	$46,814	[128;129]	+/- 50%
b27	Lifetime costs of stroke	$76,952	[130;131]	+/- 50%
b28	CHD costs prevented	$896,158,199	a50*b25	
b29	CHF costs prevented	$2,858,727,072	a51*b26	
b30	Stroke costs prevented	$4,680,687,824	a52*b27	
	Discounting (all discounting to present value at age 20)			
b31	Median year of screening from age 20	20	[98;101]	
b32	Corresponding discount factor for screening	0.55	Present value tables	.50 to .60
b33	Median year of monitoring and anti-hypertensive treatment from age 20	46	[98;101]	
b34	Corresponding discount factor for monitoring and anti-hypertensive treatment	0.26	Present value tables	.21 to .31
b35	Median year of year of life prevented from age 20	55	[97;98]	
b36	Corresponding discount factor for years of life saved	0.20	Present value tables	.15 to .25
b37	Median year of acute event prevented from age 20	40	[98;103]	
b38	Corresponding discount factor for CHD morbidity QALYs and costs	0.31	Present value tables	.26 to .36
b39	Median year of chronic disease morbidity prevented from age 20	49	b37+ 5 + a55*0.5	
b40	Corresponding discount factor for CHF and Stroke morbidity QALYs and costs	0.23	Present value tables	.18 to .28
	Cost-effectiveness Calculation			
b41	Discounted costs of screening office visits	$1,748,604,849	b22*b32	
b42	Discounted costs of monitoring office visits	$654,340,098	b23*b34	
b43	Discounted costs of antihypertensive therapy	$3,970,290,304	b24*b34	
b44	Discounted savings from prevented events	$2,046,111,159	b28*b38+ b29*b40+b30*b40	
b45	Discounted QALYs	137,523	a49*b36+ a59*b38+a60*b40 +a61*b40	
b46	Discounted $/QALY **(CE Estimate)**	31,465	(b41+b42+b43-b44) /b45	

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