Blood Pressure Lowering and Life Expectancy Based on a Markov Model of Cardiovascular Events

Howard D. Sesso, Roland S. Chen, Gilbert J. L’Italien, Pablo Lapuerta, Won Chan Lee, Robert J. Glynn

Abstract—The life expectancy benefits of antihypertensive treatment, based on both systolic and diastolic blood pressure reduction, was estimated with a cardiovascular disease event Markov model with prospective data from 57,573 men and women. Seven patient states were defined, including (1) no cardiovascular disease, (2) stroke, (3) myocardial infarction, (4) revascularization, (5) history of cardiovascular disease, (6) noncardiovascular disease death, and (7) cardiovascular death. Risk functions were developed from gender-specific multivariate Cox proportional hazards models for primary events and age-, smoking-, and diabetes-adjusted models for secondary events. At baseline we assumed (1) hypothetical pretreatment blood pressures of 160/95 or 150/90 mm Hg; (2) strategies A and B lower blood pressure by 20/13 and 13/8 mm Hg, respectively; and (3) baseline age of 35 years. For subjects initially at 160/95 mm Hg, those with antihypertensive treatment, antihypertensive treatment and diabetes, or antihypertensive treatment, diabetes, and currently smoking had corresponding gains in life expectancy of 2.43, 2.80, and 2.43 years for Strategy A. An initial blood pressure of 150/90 mm Hg resulted in similar gains. Compared with Strategy B, with blood pressure reductions of 13/8 mm Hg, Strategy A provided additional gains in life expectancy of 0.84, 0.99, and 0.87 years for those with antihypertensive treatment, antihypertensive treatment and diabetes, or antihypertensive treatment, diabetes, and currently smoking. The initial blood pressure level did not affect the magnitude of life expectancy gains for equivalent blood pressure reductions. Greater gains in life expectancy among hypertensive and diabetic women suggest that blood pressure lowering may yield greater benefits in selected subgroups. (Hypertension. 2003;42:885-890.)

Key Words: blood pressure ■ cardiovascular diseases ■ epidemiology ■ prospective studies ■ women

The clinical benefits that result from the treatment of uncontrolled hypertension have been demonstrated in numerous studies.1–4 However, questions remain as to what benefits may be projected for different populations with different levels of blood pressure (BP) and cardiovascular disease (CVD) risk and how they compare with other medical interventions. Controversies exist in defining optimal BP treatment goals and the benefits obtained in treating below certain BP levels.5 The relative roles of systolic and diastolic BP in determining CVD risk are also a subject of ongoing research.6–9

Recently, Wright and Weinstein10 proposed a systematic way to compare the benefits of different interventions. They suggested the use of the outcome “gains in life expectancy” and provided estimates of this outcome for a number of different interventions across therapeutic areas (eg, measles vaccine and therapy for germ cell tumors). In this study, we projected the benefits of antihypertensive treatments for patients with different baseline CVD risk, measured using gains in life expectancy. To evaluate these outcomes, a Markov model was developed to accommodate different CVD risk profiles according to continuous systolic blood pressure (SBP) and diastolic blood pressure (DBP) level, age, history of diabetes, smoking status, and other risk factors. The advantage of Markov models over conventional regression models is that they allow for more flexible modeling of different risks for several different events in individuals with transitions among prespecified clinical states progressing toward death.

The long-term effects of antihypertensive treatment were previously estimated by using predictive CVD risk functions, based on the experience in two large cohorts.6 Unlike previous models used to predict the occurrence of CVD events,11,12 this model incorporates both SBP and DBP as continuous variables, allowing for comparisons of the relative impacts of different levels of BP reduction.

Methods

Markov Model Description
Probability estimates of CVD events were developed from analyses of two large primary prevention trials, the Physicians’ Health Study

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From the Division of Preventive Medicine, Brigham and Women’s Hospital (H.D.S., R.J.G.), Boston, Mass; Bristol-Myers Squibb Company (R.S.C., G.J.L., P.L.), Princeton, NJ, and Wallingford, Conn; and MEDTAP International, Inc (W.C.L.), Bethesda, Md.
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Correspondence to Howard D. Sesso, ScD, MPH, Brigham and Women’s Hospital, 900 Commonwealth Ave East, Boston, MA 02215-1204. E-mail hsesso@hsph.harvard.edu
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Markov model of primary and secondary cardiovascular (CV) events. Each arrow denotes 1-year probability of transitioning from one patient state to another. Seven patient states were defined from the Markov model: (1) no CV event history, (2) stroke, (3) myocardial infarction (MI); (4) revascularization; (5) history of CV event; (6) CV death, and (7) non-CV death. For primary events, transitions among the 7 Markov states were assumed to occur at yearly intervals, with events occurring at the midpoint of a cycle period. Secondary event probabilities were based on CV events occurring 6 months or more after the initial event, with the exception of CV death. Gender-specific transition probabilities between Markov states were estimated based on data from the PHS, WHS, and WACS.

(PHS), the Women’s Health Study (WHS), and the Women’s Antioxidant Cardiovascular Study (WACS), which includes women with multiple coronary risk factors or preexisting CVD.

The use of Markov chain models is a technique commonly used to simulate long-term progressive diseases. These models represent recurring events associated with an ongoing risk, assuming that patients reside in one of a finite number of health states. Subjects may transition from one health state to another during a defined interval of time called a cycle.

In the present analysis, we defined 7 relevant patient states that reflected the potential effects of BP lowering: (1) no CV event history; (2) stroke; (3) myocardial infarction (MI); (4) revascularization; (5) history of CV event; (6) CV death; and (7) non-CV death (Figure). Transitions among Markov states were assumed to occur at yearly intervals, with events occurring at the midpoint of a cycle period. Microsoft Excel 97 (Microsoft) was programmed to convert transition probabilities into gains in life expectancy, based on the aforementioned 7 patient states.

With the exception of the effect of revascularization on subsequent MI, the probability of a secondary CV event was assumed to be independent of the type of preceding CV event. Secondary events occurred 6 months or more after the initial event, except CV death.

Outcome Ascertainment
Participants reported CV events on annual follow-up questionnaires. Medical records were obtained and reviewed by an independent committee of physicians for reports of MI or stroke using standard clinical criteria for MI, stroke, and CV death. WHS and WACS but not PHS also confirmed revascularizations by hospital records. Rates of morbidity and mortality follow-up exceeded 99% in all three cohorts.

Probabilities of CV Events and Risk Estimates
Transition probabilities between states were derived from gender-specific Cox proportional hazards models from the PHS, the WHS, and the WACS. Treatment benefits were evaluated on the basis of hypothetical BP-lowering effects for patients with different baseline CV risk profiles described below.

The PHS and WHS cohorts were used to develop gender-specific risk estimates of primary CV events for patients starting in the “no CV event history” state. Primary prevention models included major coronary risk factors and study-specific randomized treatment assignments. A history of diabetes was self-reported, having validation rates of 97.5% in the WHS with similar findings expected among similar health professionals in the PHS and WACS. Based on previously reported multivariate prediction models, both SBP and DBP were significantly associated with CV events (P<0.001) in men, whereas only SBP (P<0.001) predicted CV death in women. Therefore, models of men in PHS included both SBP and DBP, whereas models of women in WHS only included SBP. After excluding subjects with missing covariates, the models consisted of 17873 men from PHS and 36721 from WHS.

The PHS and WACS cohorts were used to develop gender-specific estimates of the risk of secondary CV events among those with a history of CV, adjusting for age, diabetes, and smoking status with new baseline values as of the date of their preceding CV event. After excluding subjects with missing covariates, the models consisted of 3925 men from PHS and 2979 women from WACS.

To estimate the annual rates of each end point by age, the risk functions were evaluated at the midpoint of yearly intervals starting at age 35 (for ages >85 years, the age-85 risk estimates were used). Overall mortality rates were calibrated on the basis of gender-specific life-tables published by the National Center for Health Statistics.

Determining Gains in Life Expectancy
At baseline, we assumed that subjects had hypothetical pretreatment BPs of 160/95 or 150/90 mm Hg. Antihypertensive treatments of different presumed BP-lowering efficacy (arbitrary reductions of 20/13 [Strategy A] and 13/8 [Strategy B] mm Hg were selected) were used as inputs to the Markov model. We selected BP reductions of 20/13 and 13/7 mm Hg to capture two attainable BP reductions that may be expected in a clinical setting. As expected, the consideration of smaller or larger reductions in BP versus those presented corresponded with smaller or larger gains in life expectancy. Based on previous studies with data from the PHS, WHS, and WACS (Peter J. Mason, unpublished data, 2003), spline models have shown no evidence of a nonlinear association between BP and cardiovascular disease.

The area between survival curves of different interventions was calculated to estimate the gains in life expectancy for treatments with different levels of presumed effectiveness among men, among women, and then among a 50-50 sample of men and women. We considered whether primary prevention benefits do—or do not—extend into secondary prevention. Calculations were performed with the use of SAS 6.12 software.

An expanded Methods section can be found in an online supplement available at http://www.hypertensionaha.org.

Results
The average baseline age was 53.8 years, and body mass index was 24.9 kg/m² for men and 54.5 years and 26.0 kg/m² for women in primary prevention models. BP levels were similar for men and women, with a mean level of 126.0/78.8 mm Hg in men and 123.8/77.0 mm Hg for women. Median follow-up for PHS was 15.0 years; for WHS, 7.2 years; and for WACS, 5.2 years. The number of primary and secondary events in each of the studies is listed in Table 1. There were a total of 3123 primary CV events for men in the PHS, including 622 cases of MI, 679 cases of stroke, 1345 revascularizations, 477 cases of CV death, and 1564 cases of non-CV death. There were considerably fewer primary events among women in WHS despite the larger baseline

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sample size as the result of lower disease rates for middle-aged and older women versus men, plus the shorter follow-up time. In secondary prevention models, the average age of men in the PHS was 65.7 years, and for women in the WACS, the average age was 63.0 years. Including multiple events for some subjects, there were 1397 total cases of CVD for men and 425 cases of CVD for women, again with discrepancies probably as the result of shorter follow-up times in the WACS.

We first determined the gains in life expectancy in subjects without a history of CVD assuming that primary prevention benefits extend to secondary prevention models (Table 2). For all subjects with an initial BP of 160/95 mm Hg, those with antihypertensive treatment, antihypertensive treatment and diabetes, or antihypertensive treatment, diabetes, and currently smoking had corresponding gains of life expectancy of 2.43, 2.80, and 2.43 years, with a reduction in BP to 140/82 mm Hg. A lower initial BP of 150/90 mm Hg with a reduction in BP to 130/77 mm Hg resulted in similar corresponding gains in life expectancy. For those subjects with a starting BP of 160/95 mm Hg, Strategy A would yield additional gains in life expectancy of 0.84, 0.99, and 0.87 years, compared with Strategy B for patients with antihypertensive treatment, antihypertensive treatment and diabetes, or antihypertensive treatment, diabetes, and currently smoking in all subjects.

There were modest incremental gains in life expectancy associated with BP reduction when considering men with diabetes compared with men without diabetes. In contrast, women with diabetes and antihypertensive treatment had considerable gains in life expectancy from intervention resulting from BP reductions compared with women with only antihypertensive treatment. Specifically, when BP was lowered from 160/95 to 140/82 mm Hg, women with both diabetes and antihypertensive treatment gained 3.14 years in life expectancy, whereas women with only antihypertensive treatment gained 2.60 years in life expectancy.

Because previous analyses in these data and other studies have determined that correction for measurement error in BP increased risk estimates by \( \approx 50\% \), we recalculated estimates of life-years gained, accounting for potential measurement error. For all subjects with an initial BP of 160/95 mm Hg, those with antihypertensive treatment, antihypertensive treatment and diabetes, or antihypertensive treatment, diabetes, and currently smoking had corresponding gains of life expectancy that increased to 3.56, 4.05, and 3.48 years, with a reduction in BP to 140/82 mm Hg. A lower initial BP of 150/90 mm Hg resulted in similar corresponding gains in life expectancy.

### TABLE 1. Number of Primary and Secondary Prevention End Points for the PHS, WHS, and WACS

<table>
<thead>
<tr>
<th>Description</th>
<th>PHS (Men)</th>
<th>WHS (Women)</th>
<th>WACS (Women)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention models, n</strong></td>
<td>17,873</td>
<td>36,721</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>3123</td>
<td>688</td>
<td></td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>622</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>679</td>
<td>226</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1345</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>477</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>CVD death</td>
<td>1564</td>
<td>423</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary prevention models, n</strong></td>
<td>3925</td>
<td>2979</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>1397</td>
<td>425</td>
<td></td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>192</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>236</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>663</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>306</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>CVD death</td>
<td>349</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>

PHS indicates Physicians’ Health Study; WHS, Women’s Health Study; WACS, Women’s Antioxidant Cardiovascular Study; and CVD, cardiovascular disease.

### TABLE 2. Gains in Life Expectancy in Subjects Free of CVD, With an Initial BP of 160/95 or 150/90 mm Hg, Comparing Attained BPs Assuming Primary Prevention Benefits Extend to Secondary Prevention*

<table>
<thead>
<tr>
<th>Starting BP of 160/95 mm Hg</th>
<th>Comparison of Hypothetical Attained BPs</th>
<th>Men</th>
<th>Women</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive treatment</td>
<td>2.27</td>
<td>0.82</td>
<td>2.60</td>
<td>0.88</td>
</tr>
<tr>
<td>Antihypertensive treatment and diabetes</td>
<td>2.46</td>
<td>0.90</td>
<td>3.14</td>
<td>1.18</td>
</tr>
<tr>
<td>Antihypertensive treatment, diabetes, and current smoker</td>
<td>2.17</td>
<td>0.80</td>
<td>2.69</td>
<td>0.94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Starting BP of 150/90 mm Hg</th>
<th>Comparison of Hypothetical Attained BPs</th>
<th>Men</th>
<th>Women</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive treatment</td>
<td>2.26</td>
<td>0.81</td>
<td>2.54</td>
<td>0.85</td>
</tr>
<tr>
<td>Antihypertensive treatment and diabetes</td>
<td>2.48</td>
<td>0.91</td>
<td>3.16</td>
<td>1.09</td>
</tr>
<tr>
<td>Antihypertensive treatment, diabetes, and current smoker</td>
<td>2.19</td>
<td>0.80</td>
<td>2.74</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Gains in life expectancy are expressed in years.

*All other covariates set to unexposed for discrete characteristics and for continuous characteristics the mean value in the population.
with similar magnitudes of BP reduction resulted in nearly equivalent gains in life expectancy.

We also considered alternative models, including only SBP for men and both SBP and DBP in women to examine the impact on our estimates of the gains in life expectancy. Models that only included systolic BP in men resulted in considerably smaller gains in life expectancy. For men with an initial BP of 160/95 mm Hg, those with antihypertensive treatment, antihypertensive treatment and diabetes, or antihypertensive treatment, diabetes, and currently smoking had corresponding gains of life expectancy that increased to 2.50, 2.52, and 2.45 years, with a reduction in BP to 140/82 mm Hg.

Starting BP was lowered to 150/90 mm Hg but with similar absolute reductions in BP by 20/13 mm Hg.

We again considered the impact of correcting for measurement error in BP by recalculating estimates of life-years gained assuming a 50% increase in the BP parameter estimates, assuming that primary prevention benefits do not extend to secondary prevention. For all subjects with an initial BP of 160/95 mm Hg, those with antihypertensive treatment, antihypertensive treatment and diabetes, or antihypertensive treatment, diabetes, and currently smoking had corresponding gains of life expectancy that increased to 2.50, 2.52, and 2.45 years, with a reduction in BP to 140/82 mm Hg.

Discussion

These prospective data from a large cohort of middle-aged and older men and women provide evidence that substantial gains in life expectancy, due to the reduction in both primary and secondary CVD events, can be achieved through BP lowering. This study used continuous measures of SBP and DBP in models to provide greater flexibility in model selection and statistical efficiency. These gains in life expectancy as a result of BP reductions were consistent with previously reported findings. The substantially greater gains in life expectancy among women who were both hypertensive and diabetic was unexpected and warrants further exploration into the benefits of BP reduction in high-risk women still free of baseline CVD.

Projected gains in life expectancy based on modest differences in BP reduction compare favorably to a number of well-accepted preventive interventions. For example, reduction of weight to ideal in 35-year-olds would be expected to confer gains in life expectancy of 0.5 to 0.6 years. Similarly, reduction of cholesterol to 200 mg/dL in subjects with elevated cholesterol (200 to 239 mg/dL) would translate into projected gains in life expect-
ancy of \( \approx 0.5 \) year. Assuming that primary prevention benefits extend to secondary prevention, gains in life expectancy for a 50:50 mix of men/women were projected to be 0.84 years, with a difference in BP lowering of 7/5 mm Hg obtained by two hypertension treatment strategies of different effectiveness. These findings support the clinical relevance and significance of even modest differences in BP with respect to their impact on life expectancy.

Potential gains in life expectancy tended to be larger in women than they were in men when considering subjects with antihypertensive treatment and diabetes at baseline. However, antihypertensive use in the United States is more common in women than in men, despite roughly comparable rates of hypertension in men and women by the age of 65 years. Prevalence estimates are comparable between men and women,\(^1\) but women tend to develop hypertension at a later age.\(^2\) Therefore, these data address an apparent need for greater identification and efficacious treatment of both men and women with diagnosed hypertension as a means of not only controlling BP but also extending life expectancy.

Because we used continuous measures of SBP and DBP in models for men and SBP in models for women, more flexible simulations incorporating hypothetical attained BPs could be examined. This choice of BP parameters in models for men and women was based on previously published prediction models from these cohorts that optimally predicted the risk of CVD.\(^6\) In men, including both SBP and DBP resulted in substantially greater gains in life expectancy than Markov models with either BP parameter. The addition of DBP in models for women offered no advantage in estimating the benefits of BP reduction, thus reinforcing the greater potential clinical utility of SBP in women. These models more closely represent the combinations of coronary risk factors important in clinical practice, as patients taking antihypertensive medications present with other combinations of risk factors. Although we limited the presentation of results to men and women taking antihypertensive medications, with diabetes, or currently smoking, these models allow for greater flexibility to characterize more individualized gains in life expectancy, based on starting and attained BPs. The Markov model described here is also easily adapted to provide estimates of cost-effectiveness between different BP-lowering strategies using an outcome of cost per life-year saved.

Projections of life-years saved based on BP lowering are similar to previously published models. Tsevat et al\(^3\) predicted gains in life expectancy of 2.3 and 1.7 years in men and women, respectively, for 35-year-old individuals at risk, based on reducing DBP to 88 mm Hg if originally 95 to 104 mm Hg. Wright and Weinstein\(^4\) noted that reductions in DBP from >105 or 90 to 94 mm Hg to 88 mm Hg resulted in 5.5- and 1-year gains in life expectancy in men and women at elevated risk. However, their models did not include SBP and were not evaluated for subjects at average risk, who constituted our study population. Finally, data from the LRC Primary Prevention Trial, Framingham Heart Study, and 4S indicated more modest gains in life expectancy with antihypertensive treatment, assuming a baseline BP of 160/100 mm Hg that is reduced, albeit unsuccessfully according to JNC VII guidelines,\(^5\) to 150/93 mm Hg.\(^6\)

Several limitations need to be considered in the context of these results. First, the utilization of a single baseline assessment of BP and other coronary risk factors may be susceptible to measurement error. Correction for measurement error in BP would lead to \( \approx 50\% \) increases in risk associated with elevated BP\(^6\) and consequent increased gains in life expectancy associated with BP reduction. When we reran our models assuming 50\% increases in parameter estimates for BP, there were proportionate increases in gains in life expectancy. This finding suggests that we have conservatively estimated the benefits of BP reduction in this population of initially healthy men and women. Also, in our secondary prevention models, we did update our covariates to reflect coronary risk profiles. Updating the variables in our primary prevention models did not appreciably alter the risk functions generating the results.

Second, the generalizability of results derived from predominantly white male and female health professionals may be questioned for its use in other population groups, as lower socioeconomic groups and nonwhites may have differential responses to changes in BP and subsequent CVD risk. Along these lines, the observed death rates were consistent with US averages in men but underestimated in women. As a result, these rates with nationally representative life-tables\(^2\) improved generalizability for the models in women but at the potential expense of disconnecting the observed BP covariate data with rates of death. Third, in a limitation inherent in any epidemiologic study, it remains unclear whether average gains in life expectancy built into the prediction models apply to the individual patient. However, the impressive increases in life expectancy offer convincing evidence for the clinical utility of BP reduction. Finally, although we assumed that risk of secondary CVD events was independent of the type of preceding CVD event, it is likely that these risks are not completely independent. However, because of smaller numbers of subjects and events after specific types of prior CVD, we did not have adequate precision to warrant the increased complexity of a Markov model that incorporated different risks after different primary events.

**Perspectives**

These combined data of 57,573 men and women demonstrate that successful BP lowering in hypertensive patients and those with additional CVD risk factors such as diabetes or current smoking has the potential to provide substantial gains in life expectancy. Gains in life expectancy achieved with even modest reductions in BP lowering compare favorably to many well-accepted medical interventions.

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References


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