Assessing the Economic Value of Antihypertensive Medications

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Abstract

Objective: **To assess the economic value of antihypertensive medications by comparing the likelihood of coronary heart disease and stroke events and subsequent event treatment costs.**

Study Design: **Duration of blood pressure reduction was used to profile event risk reduction of three antihypertensive medications.**

Methods: **We used clinical data to determine the duration of blood pressure reduction achieved with use of two angiotensin converting enzyme inhibitors and one angiotensin II receptor antagonist. We then used trough-to-peak ratios to calculate the reduction in risk of coronary heart disease and stroke events associated with each medication.**

Results: **Across a number of different event treatment cost and population size estimates, the economic value of different medications can be assessed.**

Conclusion: **Our method for assessing the economic value of antihypertensive medications can be applied to other drug classes and can be further refined by integrating patient population and other risk-related data.**

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In recent years, medication choices for treating mild to moderate hypertension have increased considerably. Traditional first-line therapies (diuretics and ß-blockers) have been supplemented by other drug classes that better mitigate cardiovascular risk factors.[1-3] Evidence suggests that angiotensin converting enzyme inhibitors, calcium channel blockers, and alpha-blockers have more beneficial effects on cardiovascular risk factors, including elevated blood pressure and plasma lipid levels, left ventricular hypertrophy, diabetes, and insulin sensitivity, than do diuretics and ß-blockers.[1] Thus the choice of medication for patients with hypertension has become more complex, and only in a highly restrictive formulary environment are physicians' first-line treatment choices simple.

Economic Value Study

We conducted this study to demonstrate the usefulness of an analytic approach for judging the economic value of a set of antihypertensive medications. The premise was straightforward—the medication that provides the most effective and consistent blood pressure reduction over time will be the most effective in lowering the risk of subsequent cardiovascular events, such as coronary heart disease and stroke. The medication that best minimizes risk translates economically into fewer coronary heart disease and stroke events and greater cost savings. Managed care companies, for instance, could achieve a cost savings if competing drugs were found to have different risk advantages and physicians prescribed the medication that offered the best risk–cost profile. However, there are three challenges in comparing such cost savings for different antihypertensive medications: (1) the relationship between blood pressure control and cardiovascular risk reduction must be established, specifically the quantitative relationship between blood pressure reduction in mm Hg and the number of cardiovascular events avoided; (2) pharmacodynamic profiles of different medications are needed for valid comparisons of factors related to the duration of blood pressure reduction; and (3) cardiovascular events must be estimated for populations taking each medication, depending on the pharmacodynamic blood pressure control effects of each medication. Once these challenges are met, the direct costs of a medication (eg, average wholesale price) and cost savings (fewer cardiovascular events leading to avoided costs) can be compared and the best economic value determined.

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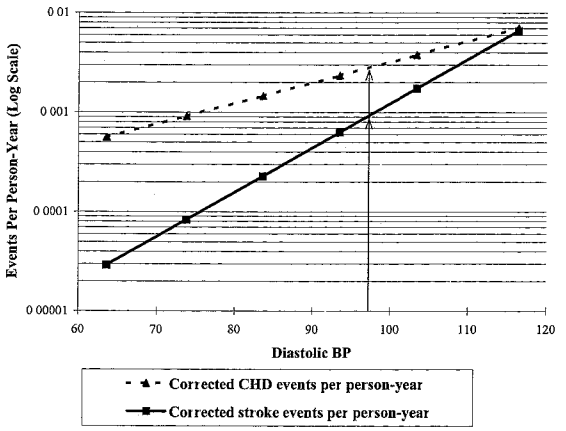
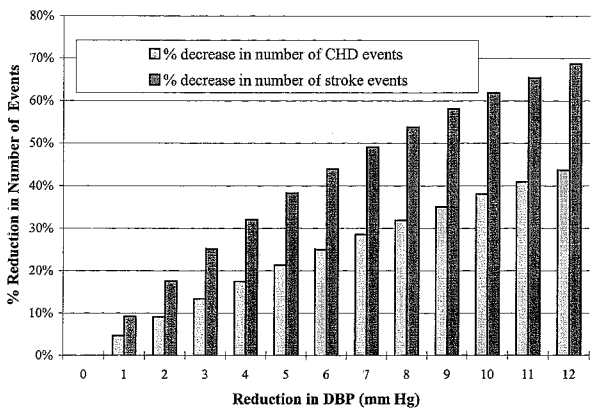
In this article, we describe our approach for addressing these challenges. We first present epidemiologic and clinical meta-analyses used to develop a quantitative relationship between blood pressure reduction and cardiovascular risk reduction for hypertensive patients (ie, patients with a diastolic blood pressure >90 mm Hg).[4,5] We then discuss the blood pressure control profiles of three medications (two angiotensin converting enzyme inhibitors and one angiotensin II receptor antagonist), focusing on their trough-to-peak ratios. Next, we estimate the coronary heart disease risk reduction for each medication, specifically addressing the number of coronary heart disease and stroke events avoided by use of each drug, and calculate and compare the economic value of each medication. We conclude by discussing the significance of these findings for managed care organizations, the applicability of this approach to other drug classes, and possible refinements for estimating economic value.

Figure 1. Relationship Between Diastolic Blood Pressure (BP) and Coronary Heart Disease (CHD) and Stroke Events



Data are from Table 3 of the meta-analysis by MacMahon et al [4] The arrows are positioned at a diastolic blood pressure of 97.1 mm Hg (the weighted average of hypertensive patients' diastolic blood pressure reported in the meta-analysis).

Figure 2. Effect of Diastolic Blood Pressure (DBP) Reduction on Risk of Coronary Heart Disease (CHD) and Stroke Events



Blood Pressure Control and Cardiovascular Risk

Prospective observational studies have identified associations between blood pressure levels and the incidence of coronary heart disease and stroke. In an epidemiologic review and meta-analysis of nine studies (420,000 individuals, 4,856 coronary heart disease and 843 stroke events, 6 to 25 years of follow-up [mean follow-up, 10 years]), MacMahon et al[4] found positive and log-linear continuous associations between diastolic blood pressure and the risk of coronary heart disease and stroke. Prolonged decreases in diastolic blood pressure of 5 to 6 mm Hg were associated with a reduction in coronary heart disease and stroke risk of 25% and 44%, respectively. A meta-analysis of 17 clinical studies on antihypertensive therapy (>47,000 individuals) showed that a decrease in diastolic blood pressure of 5 to 6 mm Hg yielded mean reductions of 16% in coronary heart disease events and 38% in stroke events.[5,6] These reductions in event rate are probably conservative for coronary heart disease, since diuretics were the typical antihypertensive treatment used in these studies and these drugs are less effective in reducing cardiovascular risk than are other antihypertensive medications.[6]

Collectively, epidemiologic and clinical results strongly suggest that lower blood pressure is associated with a lower risk of vascular disease. Reducing variation in blood pressure levels also is important, since such variation is linked to deleterious cerebrovascular and cardiovascular events. For example, the rate of stroke events increases in the morning as blood pressure rises from its nocturnal nadir.[7] Damage to target organs also increases with increased blood pressure variation and with increased nighttime blood pressure, independent of patients' average daytime blood pressure.[8]

Clinical studies that compare the morbidity and mortality risk associated with short- and long-acting antihypertensive agents confirm the importance of

reducing blood pressure variation. One study of the use of angiotensin converting enzyme inhibitors for heart failure showed a significantly lower mortality risk with long-acting enalapril treatment compared with short-acting captopril treatment.[9] In the Evaluation of Losartan in the Elderly (ELITE) study, patients taking long-acting losartan (an angiotensin II receptor antagonist) for heart failure had lower mortality rates than did those receiving short-acting captopril.[10] In another study, Alderman et al[11] reported that hypertensive patients taking a long-acting calcium antagonist had a significantly lower risk of a cardiovascular event compared with those given a short-acting calcium antagonist. The authors noted that this correlated with the increased trough-to-peak ratios of the long-acting agent. These results imply that medications that produce longer and more consistent control of diastolic blood pressure (as evidenced by relatively long half-lives and high trough-to-peak ratios) are better for lowering cardiovascular risk. These findings also imply that noncompliance can adversely affect cardiovascular risk because irregular use of antihypertensive medication inhibits prolonged, consistent blood pressure reduction.

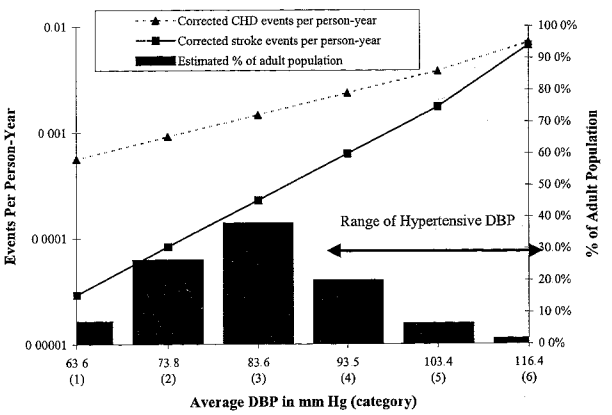
Although blood pressure variation throughout the day is associated with increased morbidity and mortality, no pharmacoeconomic or epidemiologic studies have yet determined the exact benefit of reducing this variation. For the purposes of this study, we assumed that the risk reduction benefit calculated in the nine-study meta-analysis published by MacMahon et al[4] could be time-averaged over the course of a day as blood pressure varies. Using the mean diastolic blood pressure and population size data from Table 3 of the meta-analysis,[4] we found that the relationship between diastolic blood pressure and coronary heart disease events per person-year and stroke events per person-year is positive and log-linear (Figure 1). From these data, we calculated an average diastolic blood pressure across all patients of 83.4 mm Hg, with an average number of coronary heart disease and stroke events per person-year of 0.00145 and 0.000224, respectively (see Appendix for description of calculations). Using the same data, we determined how reductions in diastolic blood pressure correspond to reductions in the number of coronary heart disease and stroke events (Figure 2).

Clinicians usually recommend antihypertensive treatment only when a patient's diastolic blood pressure exceeds 90 mm Hg.[12] In our analysis, we included patients in categories 4-6 (average blood pressure of 93.5 mm Hg and greater) (Figure 3). Using data from the epidemiologic meta-analysis published by MacMahon et al,[4] we calculated the weighted average diastolic blood pressure of hypertensive patients (those with a diastolic blood pressure >90 mm Hg) as 97.1 mm Hg. The expected number of coronary heart disease and stroke events per person-year of 0.00280 and 0.000843, respectively, was calculated using the log-linear relationship between diastolic blood pressure and cardiovascular event risk (see Appendix for description of calculations).

Blood Pressure Control Profiles of Antihypertensive Medications

After estimating the quantitative relationship between diastolic blood pressure reduction and coronary heart disease and stroke risk, we selected antihypertensive medications for comparison. The drugs we selected had to have beneficial effects on cardiovascular risk status, have long-acting effects when used as monotherapy, and have clinical pharmacodynamic data available on the onset and duration of diastolic blood pressure reduction. Two angiotensin converting enzyme inhibitors and one angiotensin II receptor antagonist met our criteria. In addition to increasing use as antihypertensive monotherapy, angiotensin converting enzyme inhibitors have beneficial effects compared with older therapies, such as diuretics and ß-blockers.[1-3,12-14] Furthermore, these drugs have similar side effect profiles and no known differences in compliance.

Figure 3. Relationship Between Average Diastolic Blood Pressure (DBP) Categories and Coronary Heart Disease (CHD) and Stroke Events



Data for diastolic BP categories 4 through 6 are from the meta-analysis by MacMahon et al.[4]

We used data on diastolic trough-to-peak ratios to estimate diastolic blood pressure control. Unfortunately, no information was available on the 24-hour variation in diastolic blood pressure reduction resulting from antihypertensive treatment. Trough-to-peak ratios, however, indicate the effects of medication 24 hours after dosage relative to its peak effect. Thus a trough-to-peak ratio of 90% indicates that an antihypertensive drug reduces blood pressure at 24 hours by 90% of the peak blood pressure reduction. The trough-to-peak ratio is becoming a common standard used by a number of regulatory agencies.[15]

About half of all angiotensin converting enzyme inhibitors have trough-to-peak ratio data in their package insert. Values fall into two distinct ranges: 50% to 60% and 75% to 100%. We selected one drug from each trough-to-peak range for our analysis. The diastolic trough-to-peak ratio for the angiotensin II receptor antagonist was 60% to 90%. We estimated the 24-hour diastolic blood pressure reduction curves for each drug from the trough-to-peak ratios. The three drugs are referred to hereafter as Drug H (high trough-to-peak ratio), Drug M (moderate trough-to-peak ratio), and Drug L (low trough-to-peak ratio) (Table 1).*

In comparing Drugs H, M, and L, we assumed that the dosages were adjusted to provide the same peak diastolic blood pressure reduction, in this case 10 mm Hg. All three compounds are pro-drugs that are rapidly absorbed (peak plasma concentrations in 1 hour) in the absence of food. They are converted to the more active form by somewhat slower liver metabolism, either through deesterification (angiotensin converting enzyme inhibitors) or oxidation (angiotensin II receptor antagonist). This slower metabolism was modeled as a 1-hour lag after dosing followed by a first-order increase to peak diastolic blood pressure effect. Although pro-drug medications have different elimination half-lives and various bound forms of the drug, the decrease from peak-to-trough diastolic blood pressure reduction also follows a first-order decay process. The resulting diastolic blood pressure reduction curves resemble (in gross detail) pharmacokinetic curves for other oral drugs.[16]

We used trough-to-peak data to plot the diastolic blood pressure reduction effects of Drugs H, M, and L over a 24-hour period (Figure 4). Each drug was modeled to achieve the same peak effect, a 10-mm Hg reduction in diastolic blood pressure, although at different times (Table 1). Twenty-four hours after dosing, the drug is at its trough level, hence the first-order decay from peak to trough. After the next dose at zero hour, an S-shaped curve is modeled, climaxing at the appropriate time to peak effect. Drug H, the drug with the highest trough-to-peak ratio, had the flattest slope because it exhibits the smallest drop-off in diastolic blood pressure reduction (ie, the smallest increase in diastolic blood pressure throughout the 24 hours) and consequently the greatest degree of risk reduction.

We calculated the change in the risk of coronary heart disease and stroke events for each drug as a function of the hourly diastolic blood pressure reduction using the method described in the appendix. An hourly risk event estimation for each drug can be made based on the diastolic blood pressure reduction curves (Figure 4). As an example, the association between diurnal variation in diastolic blood pressure reduction and hourly risk reductions for Drug H are shown in Figure 5. The consistent, or flat, bar heights indicate little fluctuation in risk owing to the low levels of diastolic blood pressure variation provided by Drug H's high trough-to-peak effect.

We averaged the results for each drug over a 24-hour period to determine the risk reduction provided by each drug and compare them to an "untreated" patient with a diastolic blood pressure of 97.1 mm Hg (Table 2). Compared with Drug L and Drug M, respectively, Drug H had an estimated difference in coronary heart disease risk reduction during the entire 24-hour period of 8.3% and 2.8% and an estimated difference in stroke risk reduction of 16.4% and 5.6%.

As previously noted, both blood pressure and risk of coronary heart disease and stroke show diurnal variation. Blood pressure usually is higher during waking hours, while the risk of coronary heart disease and stroke is probably highest in the morning.[7] Ironically, the peak for risk often overlaps with the trough of blood pressure control because morning medication dosing is often prescribed to increase patient compliance.[17,18] With evening medication dosing, the peak effectiveness of treatment overlaps with the trough of diurnal risk. However, the results presented here probably would not change considerably even if we included diurnal risk and blood pressure variation and the effects of different dosing times.

Economic Aspects of Antihypertensive Medications

We used two ways to translate the reductions in the coronary heart disease and stroke events associated

*The actual products used in the analysis were ramipril (angiotensin converting enzyme inhibitor, Drug L), losartan (angiotensin II receptor antagonist, Drug M), and perindopril (angiotensin converting enzyme inhibitor, Drug H).

with each antihypertensive drug into economic values: (1) multiplying reductions in events per person-year by the average cost associated with treating each type of event; and (2) combining the cost savings resulting from event reduction with the drug costs to determine the annual (or monthly) economic value of each drug.

Multiplying reductions in events per person-year by the average cost associated with treating each type of event provides an event reduction cost savings. Although cost estimates vary, we used annual direct costs (ie, costs associated with hospitalization and medications) of $45,000 for coronary heart disease and $43,000 for stroke.[12,19] Even though each drug offers cost savings because of diastolic blood pressure reduction, the better control and duration profile of Drug H translates into the highest event reduction cost savings (Table 3).

Because estimates of coronary heart disease and stroke event costs vary depending on the location of treatment, patient profiles, treatment protocols, survival time, and so forth, we conducted a sensitivity analysis using high, moderate, and low event costs derived from a number of published studies and reports.[12,19-22] Costs per person-year for coronary heart disease were $20,000 (low), $45,000 (moderate), and $70,000 (high). For stroke, costs per person-year were $20,000 (low), $43,000 (moderate), and $66,000 (high). Table 4 shows the value of Drug H relative to Drug L at each cost estimate (note that the moderate–moderate value of $10.17 is the sum of the difference in cost per person-year for Drug H–Drug L as shown in Table 3 [ie, $7.29 + $2.88 = $10.17]). As expected, a linear relationship exists between event cost and drug cost savings.

By combining the event reduction cost savings with the drug costs, we determined the annual (or monthly) economic value of each drug. Drug L has an average wholesale price of approximately $80 per 100 and Drug M has an average wholesale price of approximately $110

Figure 4. Comparison of 24-hour Diastolic Blood Pressure (DBP) Reduction Among Drugs with High (Drug H), Moderate (Drug M), or Low (Drug L) Trough-to-Peak Ratios

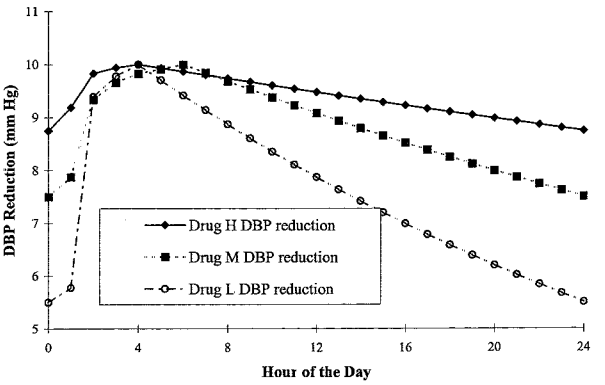


Table 1. Trough-to-Peak Profiles

	Trough-to-Peak Ratio Range (%) (Mean Value Used in Calculation)	Time Range of Peak After Dose (h) (Value Used in Calculation)	Peak Diastolic Blood Pressure Reduction (mm Hg)
Drug H	75-100 (87 5)	3-5 (4)	10
Drug M	60-90 (75)	5-7 (6)	10
Drug L	50-60 (55)	3-6 (4)	10

Table 2. Calculated Risk Events

	Coronary Heart Disease	Stroke
Expected events per person-year with Drug H	0.001787	0.000340
Expected events per person-year with Drug M	0 001838	0.000360
Expected events per person-year with Drug L	0 001949	0.000407
Expected events per person-year with diastolic blood pressure of 97 1 mm Hg, untreated	0 002804	0.000843

suggests that Drug H adds economic value when priced at approximately $85 to $90 or less per 100 at moderate coronary heart disease and stroke event costs. When comparing Drug H to Drug M, Drug M's event reduction cost savings diminish (combined coronary heart disease and stroke event reduction cost savings, approximately $3.16 per person-year). However, since the average wholesale price of Drug M is much higher than that for Drug L ($110 per 100), Drug H offers additional economic value when compared with Drug M at prices up to $110 per 100 at moderate to high coronary heart disease event costs. Also noteworthy is that different Drug L prices ($72, $80, and $88) have a more pronounced effect on marginal value than do the estimated costs for coronary heart disease and stroke events (Figure 6).

Implications for Managed Care

Our study demonstrates an approach for assessing the economic value of a set of medications. This approach is particularly useful for managed care organizations for three reasons—it shows how existing data can be leveraged to assess medication effectiveness, it provides both benefit and cost components, and it permits direct drug comparisons in economic terms. Although controlled clinical pharmacoeconomic and outcomes studies can be designed to avoid making assumptions that we could not circumvent, the costs of such studies are formidable. As such, our study provides managed care organizations with an alternative approach for comparing the economic value of comparable drugs. In the managed care environment, a drug with superior trough-to-peak effects may offer higher event reduction cost savings. Although this drug might have a higher price than its key competitors, it may still offer approximately the same or even greater economic value. When the drug with the greatest event cost saving is priced lower than its full economic value, both the managed care organization and the drug manufacturer benefit.

Cost savings to the managed care organization depend on a number of factors. Two critical ones are the number of patients taking the medications being studied and the organization's event costs per person-year. Table 5 shows the economic value of Drug H versus Drug L for three hypertensive patient population sizes (both those currently taking an angiotensin converting enzyme inhibitor and those who are candidates for switching to an angiotensin converting enzyme inhibitor) and for three event cost estimates. Because of economies of scale, larger managed care organizations may have lower event costs relative to smaller organiza-

Figure 6. Calculated per Person-Year Economic Value of Drug H Versus Drug L

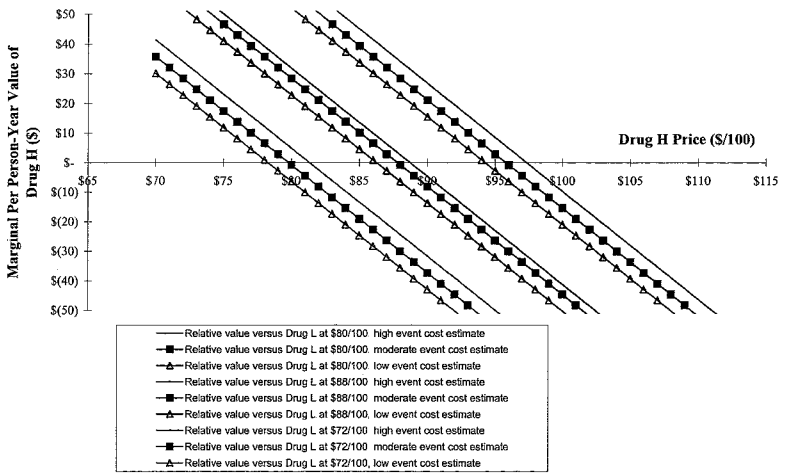


Table 5. Value Estimates Based on Population Size and Costs for Drug H Versus Drug L

Population Size	Cost Estimate		
	Low*	Moderate†	High‡
1,000	$4,577	$10,163	$15,750
5,000	$22,883	$50,817	$78,752
25,000	$114,413	$254,086	$393,759

*Low coronary heart disease cost ($20,000/event person-year) and low stroke cost ($20,000/event person-year)
†Moderate coronary heart disease cost ($45,000/event person-year) and moderate stroke cost ($43,000/event person-year).
‡High coronary heart disease cost ($70,000/event person-year) and high stroke cost ($66,000/event person-year).

tions. The data presented in Table 5 correspond to this expected size–cost relationship. This analysis shows one way that a managed care organization can more accurately calculate its potential cost savings using its own internal records.

Discussion

Our approach to estimating the economic value of antihypertensive medications relies entirely on the use of established data on hypertension. Although not all disease states have such a wealth of relevant epidemiologic, meta-analytic, and clinical data, data are available for many other diseases, and our approach can be applied to an analysis of drug classes used to treat these diseases. Similarly, not all drugs within or across classes have identical measures that allow for comparisons of effectiveness. In our study, trough-to-peak data in the package inserts were available for roughly half of the angiotensin converting enzyme inhibitors on the market. Efforts to conduct analyses such as those in our study would benefit from more standardized clinical pharmacodynamic data across drugs with similar indications.

A more complete economic value analysis of medications could be made by including other factors. Individual risk factors for hypertension that were simply aggregated in the meta-analyses could be integrated into our approach. For example, within a managed care organization, estimates of coronary heart disease and stroke events could be affected by a preponderance of enrollees with an above or below average number of risk factors, such as age, obesity, and comorbid medical conditions. Compliance also should be taken into account. Noncompliance with a medication regimen can increase blood pressure variation and consequently increase the risk of coronary heart disease or stroke events. Modeling risk factors requires integrating data from additional studies on the relationship between each risk factor and diastolic blood pressure or cardiovascular events. For a managed care organization with disproportionately large Medicare and Medicaid populations, the study would need to include age as a risk factor and quantify the relationship between age and diastolic blood pressure and the risk of coronary heart disease and stroke.

When conducting economic value analyses of competing medications, managed care organizations should include as much comparable drug data as possible. Typical data include pharmacodynamic properties, indications and contraindications, side effect profiles, and any other differentiating factors. In the case of angiotensin converting enzyme inhibitors, most of these drugs share common indications, contraindications, and side effect profiles. Although we did not integrate these factors into our analysis, they could be germane to economic value studies of other drug classes. In addition, refinements to analyses can more fully identify disease states circumvented by controlling diastolic blood pressure. We did not include risks for other diseases linked to high blood pressure, such as retinopathies and renal diseases, but essentially treated each disease independently. The event reduction cost savings for coronary heart disease and stroke were added only after we compared the economic value of the drugs. In reality, many disease states are interrelated, thus cost savings from lowering diastolic blood pressure are only partially captured by the cost savings associated with reductions in coronary heart disease and stroke events. The direct and indirect costs associated with untreated high blood pressure are therefore even higher, and consequently the economic value of medications providing enduring blood pressure reduction are proportionately higher as well.

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Appendix

Data from the epidemiologic meta-analysis reported by MacMahon et al[4] show that the risk of coronary heart disease (CHD) is reduced by 25% for every 5 to 6 mm Hg decrease in diastolic blood pressure (DBP) and that the risk of stroke is reduced by 44% for every 5 to 6 mm Hg decrease in DBP. At an average DBP of 83.4 mm Hg, the average number of cardiovascular events per person-year is 0.00145 for CHD and 0.000224 for stroke.[4] Using the log-linear relationship between DBP and risk of cardiovascular events, we estimated the number of risk events per person-year at different DBP levels using the following equation: $CHDRisk\_newDBP = CHDRisk\_83.4\ mm\ Hg\ (1.0 - 0.25)^{(83.4mm-newDBP)/6mm}$ or $CHDRisk\_newDBP = 0.00145\ (1.0 - 0.25)^{(83.4mm-newDBP)/6mm}$. Based on the weighted average DBP of 97.1 mm Hg for a hypertensive patient, CHD risk events per person-year for patients with hypertension are calculated as: $CHDRisk\_97.1\ mm\ Hg = 0.00145\ (1.0 - 0.25)^{(83.4mm-97.1mm)/6mm} = 0.00280$. For calculating stroke risk events per person-year, 0.000224 is substituted for 0.00145 and 0.44 is substituted for 0.25.