COST EFFECTIVENESS OF LABETALOL AND PROPRANOLOL IN THE TREATMENT OF HYPERTENSION AMONG BLACKS

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The cost effectiveness of labetalol and propranolol in the treatment of black adults with mild to moderate hypertension was assessed using published reports from US clinical trials of these agents among such patients. Data from these studies suggest that labetalol and propranolol lower diastolic blood pressure among black hypertensive adults by 11.2 mmHg and 8.4 mmHg, respectively. Results indicate that, for a hypothetical cohort of 1,000 patients on monotherapy, patients treated with labetalol would experience two to seven fewer strokes over a ten-year period, depending upon age and sex, and annual drug costs would be reduced by $190. For stepped care, annual costs would be $205 and $212 lower for those treated initially with labetalol. Labetalol therefore may be more cost effective than propranolol among black adults with mild to moderate hypertension.

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In 1983, approximately 18,600 US black men and women died of cerebrovascular disease (stroke), the third leading cause of black mortality after heart disease and cancer.[1] Hypertension is a major risk factor for stroke and is estimated to afflict 38 percent of black adults, compared with 29 percent of white adults.[2] Because of the resulting increase in risk of stroke and other cardiovascular diseases, treatment of hypertension in the black population is an important public health intervention.

In recent years, beta-adrenergic blockers have gained increasing favor as first-step antihypertensive agents. Clinical studies, however, suggest that they may be less effective among black than among white hypertensive patients.[3,4] In this context, the recent approval of labetalol, an alpha and beta blocker, for use in the United States is of interest. Reports from trials of labetalol indicate that, in contrast to simple beta blockers, it is as effective in controlling blood pressure in black as in white patients.[5,6] In this study, therefore, the cost effectiveness of labetalol vs propranolol is assessed in the treatment of black men and women with mild to moderate hypertension (diastolic blood pressure 90 to 114 mmHg).

METHODS

Estimating the Efficacy of Labetalol and Propranolol

The efficacy of labetalol and propranolol in controlling blood pressure was estimated by pooling data

TABLE 1. DATA USED TO CALCULATE THE INCIDENCE OF STROKE AMONG BLACK MEN AND WOMEN

Sex/Age Group	Percent Blacks, US, 1980[19]	Black/White Cerebrovascular Mortality Ratio, US, 1980[1]	Annual Incidence of Initial Stroke, per 100,000, US, 1975–1976[18]	Estimated Annual Incidence of Initial Stroke Among Blacks, per 100,000*
Men				
45–54	9.3	3.78	123	371
55–64	8.4	2.96	342	868
65–74	8.4	1.97	658	1,199
Women				
45–54	10.7	3.31	90	240
55–64	9.2	2.85	191	465
65–74	8.8	2.10	524	1,002

* Assumes equal post-stroke mortality rates for blacks and whites

from published reports of US trials of these agents among black patients. Trials conducted in the United Kingdom,[7] Africa,[8–14] and Jamaica[15] were excluded from the study because of possible differences in the etiology of hypertension and in the response to treatment. Further, the only trials used were those that employed a placebo washout period prior to treatment and that reported mean reductions in sitting or supine diastolic blood pressure.

A total of four trials met these selection criteria. Two were comparisons of labetalol and propranolol,[6,16] one was a trial of labetalol alone,[17] and one was a trial of propranolol alone.[3] Estimates of drug efficacy were therefore based on three trials of each agent. Mean reductions in sitting diastolic blood pressure were calculated by weighting reported values by the number of patients in each trial. The change in supine diastolic blood pressure was used for the one trial that did not report sitting measurements.[6]

Calculating Cost Effectiveness: Two Scenarios

The cost effectiveness of labetalol vs propranolol was examined for a hypothetical cohort of 1,000 patients with mild to moderate hypertension. The effectiveness of treatment with each agent was measured in terms of the number of cerebrovascular events, or strokes, averted over a period of ten years, and clinical protocols were used to estimate the costs of therapy. Two alternative scenarios were considered regarding the course of antihypertensive therapy.

In the first scenario, it was assumed that patients would be treated with labetalol or propranolol only, and would not receive additional medication even if blood pressure control had not been achieved. Differences in drug efficacy thus would be reflected in differences in treated blood pressures and consequently in the risk of stroke. In this monotherapy scenario, labetalol and propranolol were therefore compared in terms of treatment costs and the number of strokes averted over 10 years.

In the second scenario, it was assumed that patients would be treated according to a stepped-care strategy. Therapy was assumed to be initiated either with labetalol or propranolol, and other medication was assumed to be added as needed to achieve and maintain adequate control of blood pressure. By definition, therefore, the effectiveness of stepped-care therapy (in terms of reduction in stroke risk) was assumed to be the same regardless of the first-step agent. Differences in drug efficacy, however, would be reflected in differences in the proportions of patients requiring additional antihypertensive agents. In this scenario, therefore, labetalol and propranolol were compared in terms of total costs of treatment for stepped-care therapy.

Monotherapy Scenario

To estimate the reduction in stroke risk as a consequence of monotherapy, incidence rates for all races were obtained from the National Survey of Stroke[18] and adjusted using relative cerebrovascular mortality rates for blacks[1,19] to estimate the risk of stroke among black men and women (Table 1). Age- and sex-specific logistic functions from the Framingham Heart Study[20] were then used to calculate stroke risk (ce-

rebrovascular accident and atherothrombotic brain infarction) at an assumed pretreatment diastolic blood pressure, and at an assumed posttreatment blood pressure after treatment with labetalol or propranolol. Pretreatment diastolic blood pressure was estimated using the mean among US blacks with pressures between 90 mmHg and 114 mmHg.[2] Posttreatment diastolic blood pressure was calculated by subtracting the mean reduction in diastolic blood pressure reported in clinical trials for each agent from the pretreatment mean. The proportionate difference in stroke risk at untreated and treated blood pressure levels was defined as the maximum possible benefit of therapy.

As there is evidence that stroke risk is a function of both current and past levels of blood pressure,[21] an increasing fraction of benefit was used to model the effect of antihypertensive therapy.[22] It was assumed that the fraction of benefit in year 1 would be 50 percent, and that it would increase by 10 percentage points each year until the maximum possible benefit had been achieved in year 6 and beyond. Finally, these proportionate reductions in risk of stroke due to treatment (appropriately adjusted for fraction of benefit) were multiplied by the estimates of absolute stroke risk among black men and women to obtain numbers of incident strokes averted.

The average annual cost of propranolol and labetalol was calculated using mean dosages reported in the trials of each agent, rounded to the nearest number of whole pills. The unit price of each agent was determined by the prevailing cost at 12 Boston area pharmacies, and for propranolol, a weighted average of generic and proprietary (Inderal) prices was calculated assuming respective market shares of 40 and 60 percent. The costs of physician visits and laboratory tests were assumed not to differ for patients treated with either labetalol or propranolol. Because reports from trials indicate that the safety profiles of these agents are similar,[3,23] it was assumed that no difference would exist in the frequency, nature, or cost of treating side effects.

Stepped-Care Scenario

To estimate the proportion of patients who would require additional medication to achieve adequate control of blood pressure, it was assumed that the goal of treatment would be a diastolic blood pressure of less than 90 mmHg, and that each patient treated with labetalol or propranolol would experience the mean reduction in blood pressure reported for that agent. The distribution of all diastolic blood pressure levels in the 90 to 114 range among US black men and women[2] was used to approximate the blood pressure levels among the assumed cohort of 1,000 patients, and then that distribution was reduced by the mean blood pressure reduction for each agent. The proportion of patients with diastolic blood pressures remaining at, or above, 90 mmHg was assumed to be the proportion who would require additional antihypertensive medication.

It was assumed that patients would be given a combination diuretic agent containing 25 mg of hydrochlorothiazide and 50 mg of triamterene (Dyazide, Smith Kline & French) as a second-step agent. The cost was estimated in the same manner as that of labetalol, assuming a twice-daily dosage. Third- and fourth-step agents were not considered, as it was assumed that the proportion of patients remaining uncontrolled after the addition of a diuretic would be the same for labetalol and propranolol and thus not affect the relative costs of therapy. It was also assumed that the use of additional medication would not necessitate additional physician visits, and that it would not alter the relative side-effect profiles of labetalol and propranolol therapies.

RESULTS

Monotherapy Scenario

Results from the trials of labetalol and propranolol that met the selection criteria are displayed in Table 2. Pooling these results, it was estimated that labetalol and propranolol monotherapy lowers sitting or supine diastolic blood pressure an average of −11.2 mmHg and −8.4 mmHg, respectively, among adult black patients with mild to moderate hypertension. Because variances were not reported in all trials,[6,17] the statistical significance of this difference in blood pressure reduction cannot be determined. On the basis of the pooled trial results, two to seven fewer strokes (depending upon age and sex) were estimated over 10 years among 1,000 patients treated with labetalol, compared with the same number treated with propranolol (Table 3).

The reductions in diastolic blood pressure reported in the trials were achieved with dosages of 900 mg/d of labetalol and 480 mg/d of propranolol (rounding to the nearest number of whole pills). The average

TABLE 2. RESULTS OF CLINICAL TRIALS OF LABETALOL AND PROPRANOLOL IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION AMONG US BLACKS

	Labetalol				Propranolol			
Study	No.	Mean Daily Dose (mg)	Baseline DBP (mmHG)	Change in DBP (mmHg)	No.	Mean Daily Dose (mg)	Baseline DBP (mmHg)	Change in DBP (mmHg)
Flamenbaum (1985)[6]*	30	—	98.0	−6.0	35	—	99.0	−2.0
Saunders (1985)[16]	74	927	102.0	−11.2	79	411	102.0	−8.6
Cubberley (1985)[17]	17	624	102.3	−20.4	—	—	—	—
Veterans Administration (1982)[3]**		—	—	—	196	534	101.6	−9.5
Pooled results		872	101.1	−11.2		481	101.4	−8.4

DBP—diastolic blood pressure
* Dosages of labetalol and propranol are not reported.
** Dosage is reported for only those black patients achieving blood pressure control (DBP ≤ 90 mmHg).

TABLE 3. OUTCOMES AND COSTS FOR LABETALOL (L) AND PROPRANOLOL (P) IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION AMONG US BLACKS

	Monotherapy Scenario						Stepped-Care Scenario					
Sex and Age at Initiation of Therapy	Number (Percent) of Strokes Averted in 10 Years per 1,000 Patients*			Annual Cost of Medication per Patient			Number Requiring Additional Medication, per 1,000 Patients			Annual Cost of Medication per Patient		
	L	P	(P − L)	L	P	(P − L)	L	P	(P − L)	L	P	(P − L)
Men												
45–54	9 (24.0)	7 (18.9)	−2 (−5.1)	$436	$626	$190	264	381	117	$472	$678	$206
55–64	38 (45.6)	31 (37.4)	−7 (−8.1)	436	626	190	320	432	112	480	685	205
65–74	16 (13.9)	13 (11.3)	−3 (−2.6)	436	626	190	317	448	131	479	687	208
Women												
45–54	8 (34.8)	7 (28.1)	−2 (−6.7)	436	626	190	403	557	154	491	702	211
55–64	17 (38.0)	14 (30.8)	−3 (−7.2)	436	626	190	353	462	109	484	689	205
65–74	30 (31.2)	24 (25.4)	−6 (−5.8)	436	626	190	298	461	163	477	689	212

* Columns may not add due to rounding.

retail price of labetalol (Normodyne, Schering Plough) in 300 mg tablets is $39.83 per 100 pills; annual cost per patient is $436. The average retail prices of 80 mg tablets of proprietary and generic propranolol were $32.76 and $22.32 per 100 pills, respectively, yielding a weighted average price of $28.58 per 100 pills. The resulting annual cost per patient for propranolol is $626. Annual cost of medication is thus estimated to be $190 less per patient for those treated with labetalol than for those treated with propranolol.

Stepped-Care Scenario

The numbers of patients estimated to require additional medication to achieve control of blood pressure are presented in Table 3. Among 1,000 patients starting therapy with propranolol, between 109 and 163 more would require the addition of a diuretic than among 1,000 patients starting therapy with labetalol. The average price of Dyazide is $18.60 per hundred, or $136 per year. The annual costs per pa-

tient taking labetalol or propranolol are as estimated for the monotherapy scenario. Total annual drug costs for stepped care are therefore $205 to $212 less for patients starting therapy with labetalol rather than propranolol.

Sensitivity Analysis

The sensitivity of the results was examined in relation to changes in several key parameters. The results were recalculated using alternative estimates of the efficacy of labetalol, based on limits of the 95 percent confidence interval from the only prospective study comparing labetalol with propranolol among black patients.[16] The reported mean reduction in diastolic blood pressure for labetalol in this trial[16] is equal to the pooled estimate (−11.2 mmHg) reported herein, and has lower and upper confidence limits of −9.1 mmHg and −13.3 mmHg, respectively. In the monotherapy scenario, the lower limit results in 0 to 2 additional strokes averted with labetalol compared with propranolol, while the upper limit results in 3 to 11 additional strokes averted. For stepped care, the lower limit results in annual costs per patient that are $194 to $196 less for labetalol than propranolol, while the upper limit results in annual costs per patient that are $215 to $230 less for labetalol.

An alternative method was also used to estimate the numbers of strokes averted over a ten-year period under the monotherapy scenario. The Framingham Heart Study logistic functions were adjusted to account for differences in risk factors (systolic blood pressure, total serum cholesterol, and smoking) between the Framingham cohort[24] and US black men and women in 1980[1,2] (unpublished data, Second National Health and Nutrition Examination Survey, 1976–1980, National Center for Health Statistics). The adjusted risk functions were then used to estimate the change in stroke incidence due to blood pressure reduction directly. This approach resulted in estimates of 1 to 11 additional strokes averted with labetalol than propranolol, which is similar to those presented in Table 3.

The difference in the cost of therapy between labetalol and propranolol was recalculated using, alternatively, the retail prices of generic and proprietary propranolol. At the generic price of $22.32 per 100, annual costs of therapy are lower with labetalol by $53 per patient for monotherapy and by $68 to $75 per patient for stepped care. At the proprietary price of $32.76 per 100, these differences in annual costs increase to $281 per patient for monotherapy and to $296 to $303 per patient for stepped care.

Finally, the costs of therapy under the stepped-care scenario were recalculated using a second-step agent of minimal cost (25 mg of hydrochlorothiazide once daily) rather than Dyazide. At an average retail price of $2.81 per 100 pills, the total annual cost of stepped care is $191 to $192 lower for patients starting therapy with labetalol rather than propranolol.

DISCUSSION

The cost effectiveness of labetalol vs propranolol in the treatment of black men and women with mild to moderate hypertension was examined under two alternative treatment scenarios. Assuming a monotherapy scenario, the results suggest that labetalol may be both less costly and more effective than propranolol. Under a stepped-care scenario, the results indicate that cost of treatment may be less for patients starting therapy with labetalol.

The two treatment scenarios employed in this analysis may best be interpreted as the limits of a spectrum of possible courses of therapy. The monotherapy scenario represents an extreme case; patients take medication, but no attempt is made to modify therapy for patients in whom adequate blood pressure control is not achieved. In the stepped-care scenario, on the other hand, patients are assumed to receive more aggressive care, in which clinicians adjust therapeutic regimens to achieve and maintain control of blood pressure. The typical course of antihypertensive therapy received by most patients probably lies somewhere between these two extremes.

A number of limitations of the present study should be noted. First, the cost effectiveness of labetalol was assessed only in comparison with propranolol. A number of other agents may be used as initial therapy. Nonetheless, beta blockers have been used with increasing frequency as first-step antihypertensive agents, and thus provide a relevant basis of comparison.

It also should be noted that there are only a limited number of published reports of trials of labetalol and propranolol among black patients, and only four provided usable data for this study. Thus, the estimates of drug efficacy reported here are based on relatively few randomized patients. The trial reports also did not consistently provide variance data necessary

to conduct tests of statistical significance for the pooled results. Furthermore, only one study[16] was a prospective, randomized comparison of labetalol and propranolol among black patients. The other reported comparison[6] was a post hoc subgroup analysis. It is reassuring to note, however, that the pooled estimates of efficacy reported here are quite close to the results reported from the one prospective comparison.

It is likely that the dosage estimates derived from the trials of labetalol and propranolol are substantially higher than dosages prescribed in clinical practice. In these trials, if blood pressure control was not achieved, dosage was increased to the maximum tolerated amount. In practice, however, a second agent would usually be added rather than increasing the dosage of labetalol or propranolol to the levels achieved in the trials. Despite this shortcoming, dosage amounts from these trials were used because they generated the blood pressure reductions upon which the estimates of efficacy were based.

In using efficacy data derived from controlled trials, it was necessarily assumed that patients in clinical practice would be as compliant with therapy as those enrolled in the trials. In effect, this probably amounts to an assumption of full compliance, as trial outcomes are reported only for those patients who did not withdraw. This assumption, however, was also dictated by the use of data from clinical trials. Less than full compliance would presumably reduce both the effectiveness and cost of therapy. If extent of compliance is similar between patients using labetalol and those using propranolol, however, the *relative* cost effectiveness of these therapies should not be affected. As there appears to be no important difference in the side-effect profiles of labetalol and propranolol, the assumption of similar compliance may be reasonable.

The estimation of the benefits of antihypertensive therapy has been limited to reductions in stroke risk. Although elevated blood pressure is also associated with increased risk of coronary heart disease, trials of antihypertensive therapy have not consistently shown corresponding reductions in coronary risk.[25,26] There is also an accumulating body of evidence that antihypertensive therapy may contribute to regression of left ventricular hypertrophy. Such evidence, however, remains preliminary and was therefore conservatively disregarded in this study as a potential benefit of therapy. By comparison, the benefit of blood pressure control in reducing the risk of stroke is well established.[26–28]

Limited epidemiologic data forced us to estimate changes in the incidence of stroke among black hypertensives in an indirect fashion, using data derived largely from white populations. Although there are a number of ongoing population-based studies of cardiovascular disease among black Americans,[29–31] none has generated sufficient numbers of strokes to permit direct estimation of multivariate risk functions relating diastolic blood pressure to stroke incidence. To avoid generalizing directly from the largely white Framingham cohort to the US black population, Framingham Heart Study logistic functions were used only to predict *proportionate* changes in stroke incidence. This approach circumvents the known differences in incidence of stroke between blacks and whites, but still rests on an assumption of a similar proportionate response to changes in blood pressure.

Absolute levels of stroke incidence in the US black population were derived using relative cerebrovascular mortality for black Americans vs the entire population as a surrogate for relative risk, and applying this factor to incidence rates from the National Survey of Stroke. It was therefore assumed that, given the occurrence of a stroke, black mortality rates do not differ from those of the US population at large. If stroke survival is lower among blacks, then the use of relative mortality to estimate overall relative risk may overstate the incidence of stroke in the US black population. On the other hand, incidence rates for the black population as a whole probably provide a conservative estimate of the rates among black men and women with untreated mild to moderate hypertension.

Finally, the choice of a combination diuretic agent as second-step therapy might be questioned, but, as the sensitivity analysis shows, the particular agent chosen does not substantially affect the findings. Even with a costless second medication, stepped-care therapy begun with labetalol would be less costly than with propranolol.

The findings of this study should be of interest to clinicians, as they suggest a marked difference between black and white patients in response to therapy, and therefore in cost effectiveness. Market research indicates that, among US patients, the average annual costs of medication are $215 for labetalol, $208 for proprietary propranolol, and $150 for generic propranolol (unpublished data, IMS America, Ltd.). Thus, at average dosages among a largely white patient population, labetalol is more costly than propranolol.

In contrast, the analysis reported here suggests that labetalol is less costly than propranolol *at equivalent therapeutic dosages among black patients.* These findings underscore the importance of evaluating therapeutic interventions among well-defined patient populations. Because of differences in responsiveness to treatment across patient groups, the use of typical or recommended dosages to estimate costs of therapy may lead to mistaken assessments of cost effectiveness.

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