

Cost-Minimization and the Number Needed to Treat in Uncomplicated Hypertension

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The goal of this study was to compare the direct costs associated with the prescription of thiazide diuretics, β -receptor blockers (β -blockers), angiotensin converting enzyme inhibitors (ACEI), α -receptor blockers (α -blockers), and calcium channel blockers (CCB) for the prevention of stroke, myocardial infarction (MI) and premature death in uncomplicated hypertension.

We performed a cost-minimization analysis based on numbers-needed-to-treat (NNT) derived from the metaanalysis of 15 major clinical trials of hypertension treatment, and the average wholesale prices of both the most commonly prescribed and the least expensive drugs in each class. The inclusion criteria for clinical trials were that they be randomized, controlled trials of drug therapy of uncomplicated mild-to-moderate hypertension with stroke, MI, or death as endpoints. The wholesale drug costs and the total direct outpatient treatment costs to prevent a stroke, MI or death among middle-aged and elderly hypertensives were our outcome measures. The estimated wholesale drug acquisition cost to prevent one major event (MI or stroke or

death) ranged from \$4730 to \$346,236 among middle-aged patients, and from \$1595 to \$116,754 in the elderly; generic diuretic or β -blocker therapy was more economical than treatment with an ACEI, α -blocker, or CCB. The associated 5-year NNT was 86 for middle-aged patients and 29 for elderly patients. Diuretic therapy remained more cost-effective even under the unlikely assumption that the newer drugs were 50% more effective than diuretics at preventing these major events. The costs associated with potassium supplementation did not eliminate the advantage of diuretics.

Treatment costs to prevent major hypertensive complications are much lower with diuretics and β -blockers than with ACEI, CCB, or α -blockers, especially in middle-aged patients. Am J Hypertens 1998;11:618-629 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Cost analysis, hypertension treatment, drug choice, diuretic, β -blocker, angiotensin converting enzyme inhibitor, α -blocker, calcium channel blocker.

Treatment of uncomplicated hypertension with diuretics and β -adrenergic blockers (β -blockers) has been shown to reduce morbidity and mortality among middle-aged and older patients in randomized clinical trials.¹⁻³ Since

those trials, angiotensin converting enzyme inhibitors (ACEI), calcium channel blockers (CCB), and long-acting α -receptor blockers (α -blockers) have become available for the treatment of hypertension. These newer drugs are useful alternatives for selected pa-

Received January 28, 1997. Accepted October 20, 1997.

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tients who have a medical contraindication to diuretics and β -blockers, cannot tolerate them, have failed to respond adequately, or have a comorbid condition for which the newer medications have proven efficacy. The popularity and prescription rates of these newer agents have grown steadily over the past decade,^{4,5} but their effectiveness in patients with mild-to-moderate hypertension for the primary prevention of myocardial infarction (MI), stroke, or premature death, compared to older agents, remains uncertain.^{6–8} Their widespread use as initial monotherapy in uncomplicated hypertension is controversial and has spawned considerable debate.^{9–15} It has been estimated that medications account for 50% to 90% of the direct costs of hypertension treatment.^{16–18} The choice of drug(s) has a major effect on direct treatment costs because many of the estimated 43 million Americans who have hypertension must be treated to prevent major complications in relatively few.

The purpose of this study was to compare the cost-effectiveness of first-line antihypertensive drug classes for the prevention of stroke, MI, or premature death in patients with uncomplicated mild-to-moderate hypertension.

METHODS

We performed a cost minimization analysis from the perspective of providers and payors interested in the direct costs required to prevent major hypertensive complications. We use the term cost-effectiveness in reference to the costs of drugs and other direct medical expenses required to prevent one MI, stroke, or death. Our drug cost estimates are based on national survey data, and we calculated our estimates of effectiveness directly from major clinical trials, thus avoiding complex assumption-laden economic models. Separate analyses were done for middle-aged and elderly patients. Sensitivity analyses were used to address uncertainties about the comparative efficacy among antihypertensive drug classes, equipotent drug doses, and direct nondrug treatment costs, including those associated with diuretic-induced hypokalemia.

We combined data from all randomized clinical trials published in English evaluating drug treatment (versus placebo or usual care) of uncomplicated mild-to-moderate hypertension that included MI, stroke, or death as a priori endpoints in two metaanalyses: one for middle-aged patients, and one for elderly patients. These clinical trials were identified through previous overviews,^{1–3} the MEDLINE electronic literature database, and review of references in the papers found. Recommended methods for study selection and data synthesis for metaanalyses were followed.^{19–22} Ultimately, 15 studies fitting our criteria were identified and combined.^{23–39}

Event rates for each study were calculated as the number of events divided by the person-years of observation, and were based on intention-to-treat analyses. The duration of observation was based on the mean follow-up interval published for each clinical trial. The risk difference (RD) was used to calculate the number-needed-to-treat (NNT) to prevent a major hypertensive complication.⁴⁰ Because the average duration of the clinical trials was 5 years, the NNT in person-years was then converted to the number of patients treated for 5 years to prevent one event (5-year NNT).

Direct medication costs were calculated based on the 1996 average wholesale prices (AWP).⁴¹ The mean price for all listed generic formulations (when available) of each drug was used. Brand-name prices were used for drugs not available in generic form in the United States. The representative drugs for each class were chosen by two criteria: 1) the most-commonly prescribed in the United States⁴², and 2) the least expensive, based on the 1996 AWP. All drug costs were based on the AWP per 100 doses, then expressed as the dose-specific cost per patient for 5 years of treatment. This model required the assumption that the 1996 AWP for each drug would be stable over a 5-year period.

Costs were calculated for each drug based on equipotent doses in terms of BP reduction [compared with 25 mg/day hydrochlorothiazide (HCTZ)] as determined by a survey of five leading clinical hypertension researchers. The mean dose chosen for each drug was rounded down to the nearest available dose. The final doses were: 50 mg/day atenolol, 80 mg propranolol twice daily, 5 mg/day terazosin, 4 mg/day doxazosin, 60 mg/day nifedipine GITS, 20 mg/day nisoldipine, and 10 mg/day enalapril. At the time of our survey, benazepril was the least-expensive ACEI, but later in 1996 trandolapril became the lowest-priced ACEI, with the same AWP across its recommended dose range of 1 to 4 mg/day. There were no significant discrepancies between the final dosages used in this analysis and those recommended in two standard drug information publications.^{43,44}

The main outcome of interest was the cost to prevent a stroke, MI, or death based on the wholesale drug acquisition costs. The cost-effectiveness of each drug (CE_{drug}) was calculated as $CE_{\text{Drug}} = (\text{AWP for 5 years of treatment}) \times (5\text{-year NNT})$. We assumed that the effectiveness of the alternative drugs in reducing the rate of MI, stroke, and death was equal to that observed for diuretics and β -blockers in the major clinical trials. We also assumed that a morbid event or death averted due to treatment with any given class of antihypertensive drug resulted in direct and indirect cost savings equal to those associated with any other class of drug. Our primary analysis thus focused on

medication costs without modeling other potential direct or indirect costs, ie, those related to potential differences in quality of life.

However, we did additional analyses that included the direct costs of routine outpatient physician visits and laboratory tests in order to derive more complete estimates of cost-effectiveness. These other direct costs for hypertension management in an established patient were estimated (based on current fees at a large family practice clinic) at \$1340 per patient as follows: Three routine office visits per year @ \$70 = \$1050 over 5 years and two serum chemistry panels per year @ \$29 = \$290 over 5 years, leading to a total of \$1340 over 5 years. The overall cost-effectiveness of outpatient treatment to prevent an MI, stroke, or death was then calculated as: $CE = (AWP \text{ for 5 years of treatment} + \$1340) \times (5\text{-year NNT})$.

The cost of diuretic therapy was calculated with and without potassium chloride (KCl) supplementation. The cost of KCl supplementation included the AWP of 40 mEq/day of generic KCl @ \$45/year,⁴¹ plus two additional serum potassium levels/year @ \$20 each, for a total additional cost of \$425 per KCl-treated patient over 5 years. It was assumed that 25% of patients treated with HCTZ at 25 mg/day would actually require KCl, making the cost of KCl supplementation averaged across all patients \$106.25 per patient over 5 years. This exercise was repeated for the alternative of adding spironolactone at a dose of 25 mg twice daily (instead of KCl) to HCTZ, at the AWP of \$57/year.⁴¹ Assuming that 25% of patients would need this, the additional cost of spironolactone and potassium monitoring averaged across all patients would be \$121.25 per patient over 5 years.

Sensitivity Analyses Sensitivity analyses were done to examine the effects of our assumptions about equal drug effectiveness, equal nondrug direct outpatient costs (including correction of hypokalemia), and equipotent drug doses on the comparative cost-effectiveness of the drugs in question.

Treatment Effectiveness We examined the impact on cost-effectiveness of assuming that ACEI, CCB, and α -blockers were up to twice as effective (because of better compliance or better pharmacologic effects) as diuretics or β -blockers. This decreased the estimated NNT for each of the newer drugs to as little as one-half of the NNT for diuretics and β -blockers.

Nondrug Treatment Costs Our assumptions of equality were assessed via a threshold analysis of the amount of nondrug costs that alternative drugs would have to save, compared with those associated with HCTZ prescription, to meet the cost-effectiveness of HCTZ. Assumptions about the prevalence of hypoka-

lemia, and the costs to correct it, were also tested in this manner.

Equipotent Doses The doses of alternative drugs that were considered to be equipotent with 25 mg/day HCTZ were varied from one-half to twice the original estimate.

RESULTS

Effectiveness of Treatment and the NNT In the clinical trials meeting the selection criteria, diuretics and β -blockers were the main therapies and mean duration of follow-up was approximately 5 years. There were 30,268 middle-aged patients (57% men) in seven trials, and 15,990 elderly patients (42% men) in eight trials. (Details of individual study characteristics are on file with the author and presented in brief in the Appendix.) Table 1 shows the combined risk ratio and the 5-year NNT for each outcome of interest, stratified by age group. The 5-year NNT to prevent one major nonfatal event or death among middle-aged patients was 86; for elderly patients the 5-year NNT was 29. The validity of the combined results was supported by statistical evidence of homogeneity among the individual study results. The only exception was stroke in middle-aged patients, for which there was statistical evidence of heterogeneity ($P = .042$). Risk ratios were similar in the two age strata, but the NNT for the elderly were one-third to one-fifth those for the middle-aged patients, due to the higher absolute risk without treatment in the elderly.

Cost of Antihypertensive Medications Table 2 shows the representative drugs, their equipotent doses, and their AWP for 5 years of treatment, based on 1996 prices. For equipotent doses of the most commonly prescribed drugs, the AWP varied 73-fold; for the least expensive drugs it varied 32-fold. The AWP for doses that were one-half and twice the estimated equipotent doses are also shown.

Drug Costs to Prevent One MI, Stroke, or Death Drug-specific cost-effectiveness ratios, expressed as the wholesale drug cost to prevent one nonfatal MI, nonfatal stroke, or death are compared in Table 3. These results reflect only drug costs and the observed effectiveness of diuretics and β -blockers, assuming that all of the drugs shown are equally effective at reducing morbidity and mortality. The estimated excess wholesale drug cost associated with using an ACEI, CCB, or α -blocker instead of HCTZ to prevent one major event (MI, stroke, or death) ranged from \$30,160 to \$115,159 in the elderly, and from \$89,440 to \$341,506 in middle-aged patients. Under the assumption that 25% of patients treated with diuretics require potassium replacement, these excess costs were only modestly reduced (\$27,879 to \$112,078 for elderly and \$80,302 to \$332,368 for middle-aged patients).

TABLE 1. NUMBERS-NEEDED-TO-TREAT (NNT) TO PREVENT CARDIOVASCULAR EVENTS OR DEATH IN PATIENTS WITH MILD-TO-MODERATE HYPERTENSION

Event	Risk Ratio (95% CI) [Treated/Control]	P for Heterogeneity† of RR	5-Year NNT (95% CI)	P for Heterogeneity† of NNT
Middle-aged patients (based on 145,595 person-years experience in seven major clinical trials)				
Fatal or nonfatal CHD	0.91 (0.79–1.04)	.626	390 (158–NA)††	.597
Fatal or nonfatal stroke	0.56 (0.30–0.71)	.071	135 (81–424)	.042
Death, any cause	0.87 (0.77–0.99)	.253	271 (97–NA)††	.100
Nonfatal event* or death	0.82 (0.75–0.90)	.581	86 (47–503)	.146
Elderly patients (based on 73,523 person-years experience in eight major clinical trials)				
Fatal or nonfatal CHD	0.82 (0.73–0.92)	.841	70 (44–167)	.885
Fatal or nonfatal stroke	0.65 (0.57–0.75)	.848	45 (32–75)	.292
Death, any cause	0.89 (0.82–0.98)	.458	72 (39–462)	.385
Nonfatal event* or death	0.84 (0.78–0.90)	.415	29 (19–61)	.233

* Nonfatal MI or nonfatal stroke.

† P > .05 indicates homogenous risk ratios across combined studies.

†† The upper 95% confidence limit cannot be estimated for NNT because the confidence limits of the risk differences include zero.

CHD, coronary heart disease; CI, confidence interval; RR, risk ratio; MI, myocardial infarction; NA, not applicable.

The overall direct outpatient treatment costs to prevent one event were estimated by adding \$1340 to cover 5 years of physician and laboratory fees to the price. The results are illustrated in Figure 1, which plots the cost to prevent one major event against any nominal 5-year outpatient treatment cost per patient. The positions on the plot of the most commonly-prescribed drugs are shown.

Sensitivity Analyses

Drug Efficacy Superior drug efficacy would lower the NNT, thereby improving cost-effectiveness through reductions in both drug and nondrug costs per event averted. Figure 2 illustrates the impact on direct costs to prevent an event of increasing the assumed efficacy of ACEI, CCB, and α -blockers, while holding the efficacy of diuretics and β -blockers constant at the level

TABLE 2. AVERAGE 1996 WHOLESALE PRICES FOR SELECTED ANTIHYPERTENSIVE DRUGS: DRUG COSTS PER PATIENT FOR 5 YEARS OF TREATMENT

Drug Class	Most Commonly Prescribed		Least Expensive	
Diuretic	HCTZ		HCTZ	
	25 mg daily	\$55	25 mg daily	\$55
β -Blocker	Atenolol		Propranolol	
	25 mg daily	\$1097	40 mg twice daily	\$563
	50 mg daily	\$1222	80 mg twice daily	\$637
	100 mg daily	\$1745	160 mg twice daily	\$1274
ACE inhibitor	Enalapril		Trandolapril	
	5 mg daily	\$1734	1 mg daily	\$1095
	10 mg daily	\$1820	2 mg daily	\$1095
	20 mg daily	\$2590	4 mg daily	\$1095
α -Blocker	Terazosin		Doxazosin	
	2 mg daily	\$2260	2 mg daily	\$1675
	5 mg daily	\$2260	4 mg daily	\$1758
	10 mg daily	\$2260	8 mg daily	\$1847
Calcium blocker	Nifedipine GITS		Nisoldipine	
	30 mg daily	\$2327	10 mg daily	\$1495
	60 mg daily	\$4026	20 mg daily	\$1495
	90 mg daily	\$4645	40 mg daily	\$1495

HCTZ, hydrochlorothiazide.

Doses in boldface type represent equipotent doses.

TABLE 3. WHOLESALE DRUG ACQUISITION COSTS TO PREVENT ONE MI, STROKE OR DEATH AMONG PATIENTS WITH UNCOMPLICATED MILD-TO-MODERATE HYPERTENSION

Drug Class	Most Common Treatment			Least Expensive Treatment		
	Treatment	Middle-Aged	Elderly	Treatment	Middle-Aged	Elderly
Diuretic	HCTZ	\$4730	\$1595	HCTZ	\$4730	\$1595
β -Blocker	Atenolol	\$105,092	\$35,438	Propranolol	\$54,782	\$18,473
ACE inhibitor	Enalapril	\$156,520	\$52,780	Trandolapril	\$94,170	\$31,755
α -Blocker	Terazosin	\$194,360	\$65,540	Doxazosin	\$151,188	\$50,982
Calcium blocker	Nifedipine GITS	\$346,236	\$116,754	Nisoldipine	\$128,570	\$43,355

observed in clinical trials. Assuming a 50% increase in efficacy above that observed for HCTZ and \$1340 per patient over 5 years in nondrug costs, the excess direct outpatient treatment cost associated with using a CCB, ACEI, or α -blocker instead of HCTZ ranged from \$6,622 to \$63,288 per major event averted in the elderly, and from \$19,637 to \$187,681 in middle-aged patients. Under the extremely unlikely assumption of doubled efficacy, only the least expensive ACEI and CCB met the cost-effectiveness of HCTZ.

Nondrug Direct Treatment Costs Figure 3 shows the results of our threshold analysis of the amount of difference in nondrug costs between HCTZ and alternative drugs that would be required to meet the cost-effectiveness of HCTZ. This figure allows the reader to vary the assumption of comparative drug efficacy. Estimates of the cost to correct and monitor diuretic-induced hypokalemia can be included in the nondrug costs. For example, if one assumed that enalapril had equal efficacy with HCTZ, enalapril use would have to

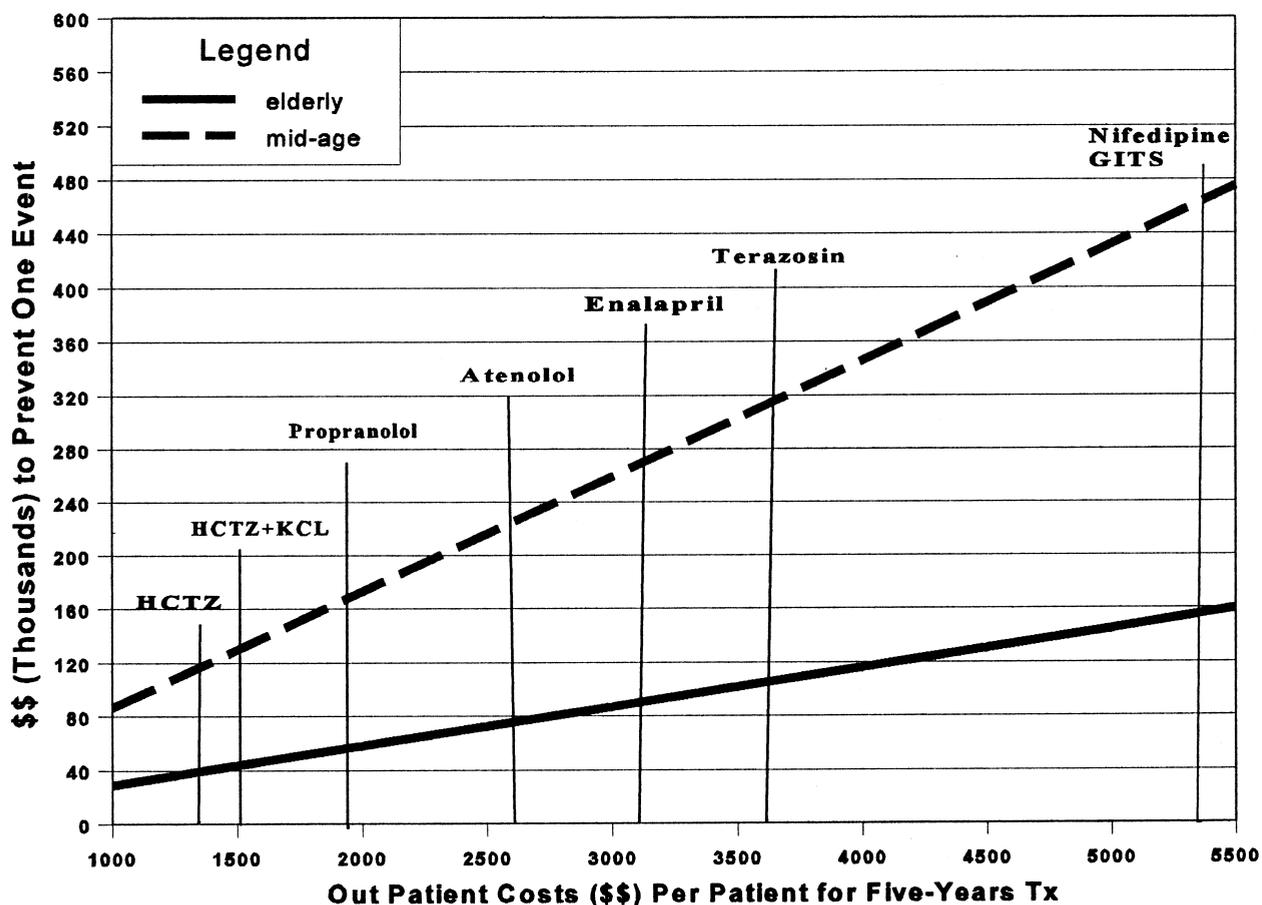
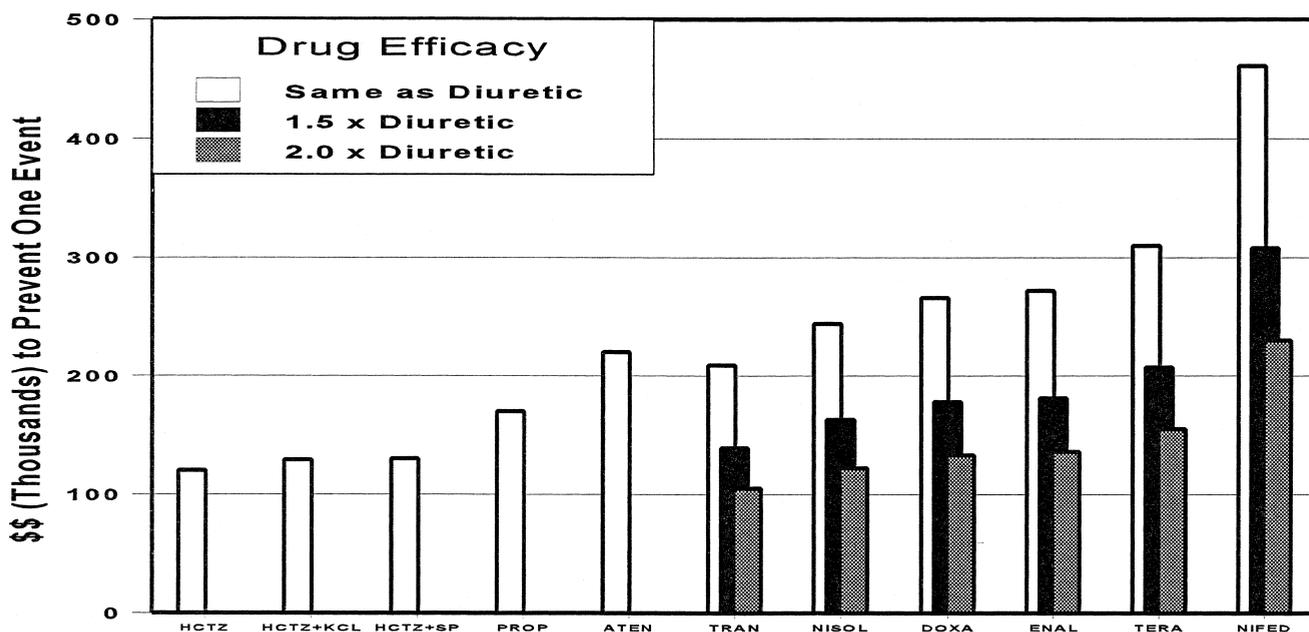


FIGURE 1. Total 5-year direct outpatient treatment costs to prevent one major event (nonfatal MI or nonfatal stroke or death by any cause). Vertical bars show per-patient costs for commonly-prescribed drugs, assuming \$1340 over 5 years in nondrug costs and assuming stable drug prices. "HCTZ + KCL" bar includes 40 mEq/day KCl supplement plus two extra serum potassium levels/year.



Total 5-yr outpatient costs to prevent a nonfatal CV event or death, based on AWP of drug plus \$1340/pt nondrug costs.

FIGURE 2. Sensitivity of comparative cost-effectiveness to assumptions about drug efficacy (middle-aged hypertensives). Total 5-yr outpatient costs to prevent a nonfatal CV event or death, based on AWP of drug plus \$1340/pt nondrug costs. The HCTZ + KCl bar assumes that 25% of diuretic-treated patients require KCl supplements and K^+ monitoring. The HCTZ + SP bar assumes that 25% of diuretic-treated patients require spironolactone and K^+ monitoring. HCTZ, hydrochlorothiazide; HCTZ + KCl, hydrochlorothiazide + potassium chloride; HCTZ + SP, hydrochlorothiazide + spironolactone; PROP, propranolol; ATEN, atenolol; TRAN, trandolapril; NISOL, nisoldipine; DOXA, doxazosin; ENAL, enalapril; TERA, terazosin; NIFED, nifedipine.

achieve savings of \$353/patient/year in nondrug costs (compared with HCTZ) to meet the economy of HCTZ in terms of preventing morbid events. If enalapril had 1.5 times the efficacy of HCTZ, this figure would be \$142/patient/year.

Equipotent Drug Doses The AWP for all nondiuretic drugs for one-half and twice the doses used in this analysis are shown in Table 2. The only drug for which lowering the estimated effective dose had any appreciable effect on the cost to prevent an event was nifedipine GITS, but its cost was still very high. Raising the dose of atenolol, propranolol, enalapril, or nifedipine GITS would significantly reduce the cost-effectiveness of each.

DISCUSSION

This cost minimization analysis shows that generic diuretics and β -blockers can be expected to prevent major cardiovascular events at a much lower cost than ACEI, CCB, or α -blockers among patients with uncomplicated hypertension. Diuretic therapy, with or without potassium management, retains a significant advantage, even if the other drugs are assumed to have 50% higher efficacy than was observed in major clinical trials of diuretics and β -blockers. Many must

be treated to benefit a few, especially among middle-aged patients, and choosing more expensive drugs results in significantly higher direct treatment costs to prevent one major hypertensive complication. Drug selection in the United States can result in a more than 70-fold variation in AWP. An increase in drug charges of just \$100/year/middle-aged patient raises the cost to prevent one major event by about \$43,000; a cost that must be borne by people who pay for health care. Based on previous metaanalyses and this cost minimization analysis, we conclude that diuretics and β -blockers should be the mainstay of therapy for uncomplicated hypertension. They are economical and have proven efficacy. At their current prices, the alternative drugs substantially increase the cost to prevent cardiovascular events and death without clear-cut justification.

Economic analyses of hypertension treatment have varied widely by the models chosen and their underlying assumptions.^{18,45-50} Most have been done by combining data from one or two clinical trials with cardiovascular risk estimates derived from observational epidemiologic studies.^{47,48} A few have used risk ratios from metaanalyses of multiple clinical trials in middle-aged patients combined with epidemiologic

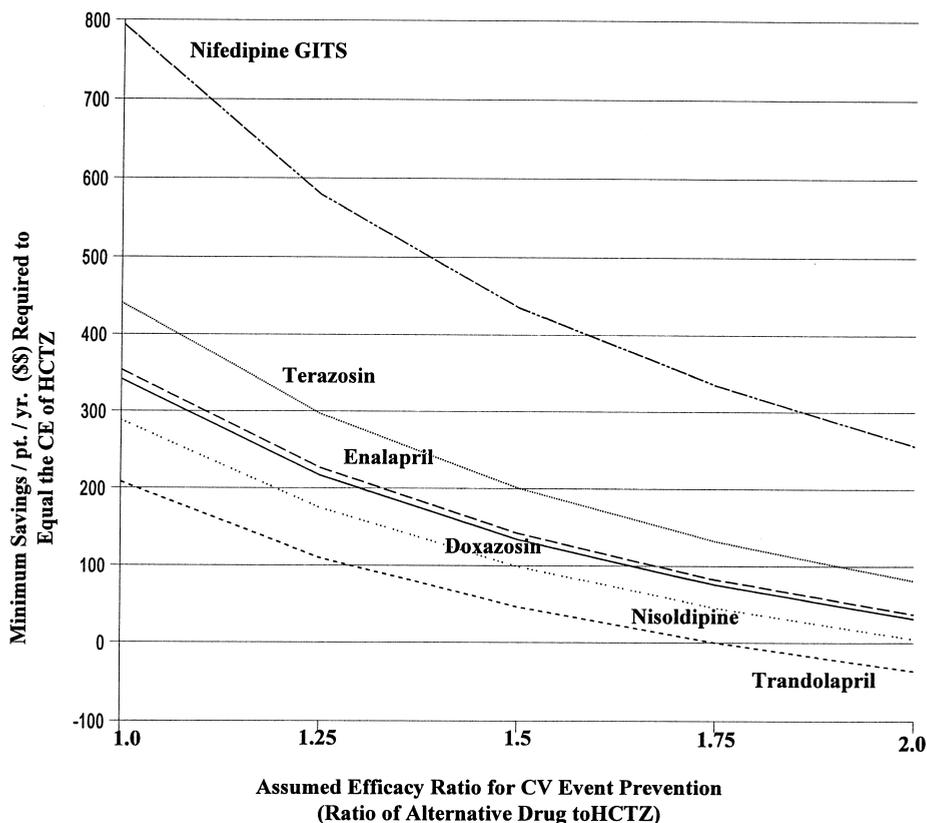


FIGURE 3. Threshold sensitivity analysis: minimum drug-specific cost savings required to make alternative drugs as cost-effective as HCTZ. Assumed Efficacy Ratio for CV Event Prevention (Ratio of Alternative Drug to HCTZ). Model includes fixed cost of \$268/patient/year for medical visits and serum chemistries.

data.^{16,17,49,50} These more comprehensive simulations have been informative, but they depend on complex models that require many assumptions. The effect of age on cost-effectiveness has been addressed, but with conflicting results.⁴⁹

This cost minimization analysis represents a more direct, if limited, approach that distinguishes it from previous economic analyses on the same subject. It rests on the NNT derived from major controlled clinical trials representing over 219,000 patient-years of observation combined in intention-to-treat analyses. It thereby eliminates major assumptions about treatment effectiveness. The definition of effectiveness is limited to the prevention of major cardiovascular events or death within a 5-year treatment period. Projections of benefit or measures of effectiveness beyond this restricted time frame are not made because data are lacking to quantify such assumptions. These features form the basis for a simple model that emphasizes what is known about the quantitative effects of anti-hypertensive therapy on cardiovascular risk, rather than relying on educated guesses derived from combining observational data with more restricted clinical trials data. We have also emphasized the importance

of age to cost-effectiveness through separate analyses for middle-aged and elderly patients.

Scope and Limitations Our conclusions are limited to the treatment of mild-to-moderate hypertension and are primarily intended to help guide decisions involving first and second attempts at therapy in relatively well patients. These results should not be extrapolated to patients with medical contraindications to diuretic and β -blocker therapy or a clear history of intolerance to these drugs. Likewise, they may not apply to patients with congestive heart failure (CHF), renal insufficiency, unstable angina, or history of an MI or stroke within the last 6 months. The results of randomized controlled trials support the use of ACEI in the presence of CHF,⁵¹ type I diabetes mellitus,⁵² and in post-MI patients with asymptomatic left ventricular dysfunction.⁵³ The CCB amlodipine may have favorable effects as adjuvant therapy in a subset of patients with severe CHF.⁵⁴ Because most of the clinical trials in this analysis drew their participants from primary care practices or community-based screenings, and excluded patients with major hypertensive complications, we believe that these results are appli-

cable to the majority of patients with mild-to-moderate hypertension treated in the primary care setting. Baseline risk status must be taken into account whenever generalizing absolute risk reduction, and cost-effectiveness of treatment increases with risk.

We have addressed the possibility of superior tolerance and efficacy for ACEI, CCB, and α -blockers compared with diuretics and β -blockers. However, our sensitivity analysis showed that under reasonable assumptions of increased effectiveness for the alternative drugs, HCTZ remained significantly more cost-effective. We did not entertain the possibility that any of the alternative drugs might be less effective than diuretics.

The differences in NNT between middle-aged and elderly patients may be confounded by diuretic dose because middle aged patients generally received higher-dose diuretic therapy than did elderly patients. Concerns about toxicity without added benefit associated with high dose diuretics have been raised.⁵⁵ Diuretic dose and age group were too highly correlated in these clinical trials to calculate the effect of dose on efficacy and, therefore, NNT. Low-dose diuretic therapy in middle-aged patients is probably more cost-effective than the main results of this analysis suggest.

Improved quality of life over that experienced with diuretic or β -blocker therapy might justify higher drug costs. We did not directly address quality of life on treatment, but available evidence argues against its being an issue in our comparisons. The randomized, double-blinded Treatment of Mild Hypertension Study (TOMHS) found no significant differences in the overall quality of life indices among the five drug classes addressed herein, with one exception: the β -blocker (acebutolol) was superior to the α -blocker (doxazosin) in that study. Also, the β -blocker and the diuretic were each associated with a better overall quality of life index than placebo, whereas the overall quality of life on the other drugs did not differ from placebo.⁵⁶ Furthermore, a recent overview found no significant differences in the effects on overall quality of life among the five antihypertensive drug classes compared in this analysis.⁵⁷

To keep this analysis straightforward, we have avoided modeling assumptions (and related costs) concerning drug switching, drug-specific side effects (except hypokalemia), and changes in AWP over time. Rates of discontinuation and medication switching have been shown to be similar among diuretics, β -blockers, ACEI, and CCB.⁵⁸ Our results are restricted to data based on 5 years of treatment, and reflect United States drug prices in effect in 1996. Our cost comparisons will require adjustment as data on longer periods of antihypertensive treatment accumulate, and as more classes of drugs go off-patent; or if the prices of patent-restricted drugs fall precipitously.

Additional costs unique to HCTZ prescription would have to be \$200 to \$790/patient/year to eliminate the advantage of HCTZ over the alternative drugs. In terms of tolerability, switching, and side effects (including hypokalemia), evidence to support this amount of excess cost is lacking.

The costs of generic diuretics and β -blockers to prevent an event are probably slightly underestimated to the degree that either was augmented with a second-line drug in the clinical trials. That information was not reported for most of the trials and we are not aware of any other randomized trial data involving uncomplicated hypertensives that can be used to compare rates of second-drug augmentation required among the five drug classes considered here. Also, the drug prices used in our calculations are underestimated by the amount of retail mark-up and dispensing fees, which vary widely by locality, pharmacy, and health plan. However, our calculated differences in prices among the drugs are conservative, because the absolute price increase with any percentage mark-up would increase with AWP.

Although this study provides important information as to the most economically efficient monotherapies for uncomplicated hypertension, indirect and intangible costs and benefits of various drugs are not addressed. Patient preference studies of these issues, paired with the results of ongoing randomized clinical trials comparing the effectiveness of various antihypertensive drugs,^{59,60} are needed to resolve these issues. Once available, that information can be incorporated into a comprehensive evidence-based cost-effectiveness analysis.

ACKNOWLEDGMENTS

We wish to thank Professor Michael F. Drummond, Center for Health Economics, University of York, England, and Mary Ann Sevick, ScD, Bowman Gray School of Medicine, Winston-Salem, North Carolina, for their comments and suggestions during the preparation of this manuscript.

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APPENDIX: CHARACTERISTICS OF STUDIES COMBINED

TABLE. CHARACTERISTICS OF THE CLINICAL TRIALS INCLUDED IN THIS COST-EFFECTIVENESS ANALYSIS

Study (Ref)	Number of Participants	Age Range (Years)	Mean Blood Pressure at Baseline (mm Hg)	Percent Male	Mean Follow-Up (Years)	Principal Drug(s)	Secondary Drug(s)
VA-NHLBI ¹	1012	21–50	?/93	81	1.5	Chlorthalidone	Reserpine
HDFP* ²	7503	30–59	S-I 152/96*† S-II 159/101*†	55†	5.0†	Chlorthalidone	Reserpine Methyldopa
Oslo ³	785	40–49	156/97	100	5.5	Hydrochlorothiazide	Propranolol Methyldopa
ANBPS* ⁴	2845	30–59	157/100†	63†	4.0†	Chlorothiazide	Methyldopa Propranolol Pindolol
MRC ⁵	17,354	35–64	161/98	52	5.0	Bendrofluzide or propranolol	Methyldopa
VA ⁶	380	Mean = 51	163/104	100	3.3	Hydrochlorothiazide + reserpine	Hydralazine
USPHS ⁷	389	21–55	148/99	80	7.0	Chlorothiazide + rauwolfia	
HDFP ⁸	2374	60–69	171/101	53	5.0	Chlorthalidone	Reserpine
ANBPS ⁹	582	60–69	165/101	55	3.8	Chlorothiazide	Methyldopa Propranolol Pindolol
EWPHE ¹⁰	840	60–97	182/101	30	4.7	Hydrochlorothiazide + triamterene	Methyldopa
Coope ¹¹	884	60–79	197/100	21	4.4	Atenolol	Bendroflumethiazide Methyldopa
STOP ¹²	1627	70–84	195/102	37	2.0	β-blockers or hydrochlorothiazide + amiloride	β-blocker + diuretic
SHEP-PS ¹³	551	60–>80	172/75	37	2.8	Chlorthalidone	Metoprolol Reserpine
SHEP ¹⁴	4736	60–>80	170/77	43	4.5	Chlorthalidone	Atenolol Reserpine
MRC ¹⁵	4396	65–74	185/91	42	5.8	Hydrochlorothiazide + amiloride or atenolol	Nifedipine

S-I, BP stratum I; S-II, BP stratum II.

* The HDFP and ANBPS study results are stratified by age. Mean baseline BP levels among middle-aged participants in HDFP are available only for BP strata.

† These figures apply to the entire cohorts in the HDFP and ANBPS studies.

VA-NHLBI, Veterans Administration/National Heart, Lung, and Blood Institute Cooperative Study on Antihypertensive Therapy; HDFP, Hypertension Detection and Follow-up Program; Oslo, The Oslo Study; ANBPS, Australian National Blood Pressure Study; MRC, Medical Research Council Study; VA, Veterans Administration Cooperative Study Group on Antihypertensive Agents; USPHS, US Public Health Service Hospitals Cooperative Study Group; EWPHE, European Working Party on High Blood Pressure in the Elderly; STOP, Swedish Trial in Old Patients with Hypertension; SHEP-PS, Systolic Hypertension in the Elderly Program pilot study; SHEP, Systolic Hypertension in the Elderly Program.

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