Review

Are β-Blockers Efficacious as First-line Therapy for Hypertension in the Elderly?

A Systematic Review

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Objective.—To assess antihypertensive efficacy of β-blockers and their effects on cardiovascular morbidity and mortality and all-cause morbidity compared with diuretics in elderly patients with hypertension.

Data Source.—A MEDLINE search of English-language articles published between January 1966 and January 1998 using the terms *hypertension (drug therapy)* and *elderly* or *aged* or *geriatric*, and *cerebrovascular* or *cardiovascular diseases*, and *morbidity* or *mortality*. References from identified articles were also reviewed.

Data Selection.—Randomized trials lasting at least 1 year, which used as first-line agents diuretics and/or β-blockers, and reported morbidity and mortality outcomes in elderly patients with hypertension.

Data Synthesis and Results.—Ten trials involving a total of 16 164 elderly patients (≥60 years) were included. Two thirds of the patients assigned to diuretics were well controlled on monotherapy, whereas less than a third of the patients assigned to β-blockers were well controlled on monotherapy. Diuretic therapy was superior to β-blockade with regard to all end points and was effective in preventing cerebrovascular events (odds ratio [OR], 0.61; 95% confidence interval [CI], 0.51-0.72), fatal stroke (OR, 0.67; 95% CI, 0.49-0.90), coronary heart disease (OR, 0.74; 95% CI, 0.64-0.85), cardiovascular mortality (OR, 0.75; 95% CI, 0.64-0.87), and all-cause mortality (OR, 0.86; 95% CI, 0.77-0.96). In contrast, β-blocker therapy only reduced the odds for cerebrovascular events (OR, 0.75; 95% CI, 0.57-0.98) but was ineffective in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality (ORs, 1.01, 0.98, and 1.05, respectively).

Conclusions.—In contrast to diuretics, which remain the standard first-line therapy, β-blockers, until proven otherwise, should no longer be considered appropriate first-line therapy of uncomplicated hypertension in the elderly hypertensive patient.

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ANTIHYPERTENSIVE treatment should, in addition to lowering blood pressure, reduce the incidence of cardiovascular morbidity and mortality and total mortality. Although numerous studies attest to the safety and efficacy of diuretics in this regard, the data for β-blockers in elderly patients with hypertension are less clear. In fact, the 1997 Joint National Committee[1] no longer recommends β-blockers as first-line antihypertensive treatment for elderly patients, unlike the recommendations in 1993.[2] Interestingly, the change in recommendations between 1993 and 1997 occurred despite the fact that no new evidence regarding safety and efficacy of β-blocker treatment in the elderly had been put forward. However, β-blockers remain an important treatment for patients after myocardial infarctions,[3] regardless of their age, and in other clinical settings. To clarify indications for use of β-blockers in elderly patients with hypertension, we performed a meta-analysis to determine the efficacy of β-blockers compared with diuretics. We specifically evaluated the β-blockers' effect on blood pressure and on cardiovascular morbidity and mortality and all-cause mortality.

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Dr Messerli has received honoraria from several pharmaceutical companies, some of which manufacture β-blockers and diuretics.

METHODS

The MEDLINE database was searched for English-language articles published between January 1966 and January 1998 using the terms *hypertension (drug therapy)* and *elderly* or *aged* or *geriatric*, and *cerebrovascular* or *cardiovascular diseases*, and *morbidity* or *mortality*. The CARDLINE database (1986-1997) was also searched. Pertinent articles cited as references in the identified trials and reviews were also culled.

From the 791 identified articles, we selected randomized trials that lasted at least 1 year and used diuretics and/or β-blockers as first-line agents. We included only trials that evaluated effects of drug treatment on morbidity or mortality in elderly persons with hypertension (≥60 years). Trials that examined therapy of younger subjects were included if they stratified results by age 60 years and older.

Twelve trials fulfilled the criteria for inclusion. Excluding 2 trials that were limited to subjects who had survived a stroke, 10 studies remained for analysis.[4-13] Clinical trials were classified as either a diuretic or β-blocker trial according to the primary treatment strategy used in the active group. Trials in which the primary active treatment was either β-blocker or diuretic were included only if the results were reported separately for the different treatment regimens. For each trial the rate of blood pressure response to the first-line therapy (the percentage of patients that remained on the initial monotherapy throughout the trial) and the rate of morbidity and mortality were retrieved. Although categorization of outcomes was dependent on individual study protocols, the following guides were used. Coronary heart disease (CHD) included fatal and nonfatal myocardial infarction and sudden or rapid cardiac death. Cerebrovascular events included fatal and nonfatal stroke and transient ischemic attacks. Cardiovascular mortality included CHD and cerebrovascular mortality and also aneurysms and conges-

Table 1.—Studies Included in the Meta-analysis

Study	Age, y	No. of Patients	No. of Controls	Type of Drug
Studies of Diuretics in the Elderly				
Veterans Administrative Cooperative on Antihypertensive Agents,[4] 1972	>60	38	43	Hydrochlorothiazide
Kuramoto et al,[5] 1981	>60	44	47	Thiazide
National Heart Foundation of Australia,[6] 1981	>60	293	289	Thiazide
European Working Party on High Blood Pressure in the Elderly,[7] 1985	>60	416	424	Hydrochlorothiazide and triamterene
Hypertension Detection and Follow-up Program,[8] 1985	60-69	1204	1172	Chorthalidone
Systolic Hypertension in the Elderly Program Pilot,[10] 1989	>60	443	108	Chorthalidone
Systolic Hypertension in the Elderly Program,[11] 1991	>60	2365	2371	Chorthalidone
Medical Research Council Working Party,[13] 1992	65-74	1081	2213	Hydrochlorothiazide and amiloride hydrochloride
Total		**5884**	**6667**	
Studies of β-Blockers in the Elderly				
Coope et al,[9] 1986	60-79	419	465	Atenolol
Medical Research Council Working Party,[13] 1992	65-74	1102	2213	Atenolol
Total		**1521**	**2678**	
Other				
Swedish Trial in Old Patients,[12] 1991	70-84	812*	815	β-Blockers or hydrochlorothiazide and amiloride hydrochloride

*Sixty-seven percent of patients received β-blockers and 33% received hydrochlorothiazide and amiloride hydrochloride.

Table 2.—Response Rate to Antihypertensive Treatment in Elderly Patients With Hypertension

Study	No. of Patients	First Drug	Response Rate, %
Diuretics			
Kuramoto et al,[5] 1981	44	Thiazide	79
European Working Party on High Blood Pressure in the Elderly,[7] 1985	416	Hydrochlorothiazide and triamterene	65
Systolic Hypertension in the Elderly Program Pilot,[10] 1989	443	Chlorthalidone	88
Systolic Hypertension in the Elderly Program,[11] 1991	2365	Chlorthalidone	46
Swedish Trial in Old Patients,[17] 1991	246	Hydrochlorothiazide and amiloride hydrochloride	60
Medical Research Council Working Party,[13] 1992	1081	Hydrochlorothiazide and amiloride hydrochloride	62
β-Blockers			
Coope et al,[9] 1986	419	Atenolol	33
Swedish Trial in Old Patients,[17] 1991	219	Metoprolol	22
Swedish Trial in Old Patients,[17] 1991	180	Atenolol	32
Swedish Trial in Old Patients,[17] 1991	120	Pindolol	28
Medical Research Council Working Party,[13] 1992	1102	Atenolol	48

tive heart failure. In some studies, part of the information was not assessed or reported.

Quantitative analyses of outcomes were based on intention-to-treat results. The Programs for Epidemiologic Analysis program CASECONT[14] was used to combine measures of associations from the different studies. The procedure used computes χ^2 for each table (study) and computes the Cochran-Mantel-Haenszel pooled χ^2 statistic for test of association, with and without Yates correction for continuity, its associated 90%, 95%, and 99% confidence intervals (CIs), and a test for heterogeneity based on the Cornfield-Gart procedure.[15] The details of the computation of the CI are given by Mehta et al.[16] We pooled the estimates of the odds ratios (ORs) of cerebrovascular events, stroke mortality, CHD, cardiovascular mortality, and all-cause mortality over studies to provide a pooled OR and a CI for each end point, and we tested for heterogeneity between individual study estimates. The methods used were described in detail by Fleiss.[15] We have opted to apply the DerSimonian-Laird procedure for random-effects model when the test for heterogeneity of OR between studies was significant at the .10 level. However, this did not turn out to be the case for any of the end points considered.

RESULTS

Description of the Trials

Taken together, the 10 trials included a total of 16 164 patients, of whom 8217 received active treatment, followed up for an average of approximately 5 years. The characteristics of the trials are presented in Table 1. Seven trials used a diuretic as a first drug of choice.[4-8,10,11] The Medical Research Council (MRC) trial was a 3-arm trial comparing hydrochlorothiazide and amiloride hydrochloride or β-blocker with placebo.[13] Taken together, the diuretic trials include 5884 patients in the active-treatment arm. Another study[9] used a β-blocker as a first drug of choice and was therefore included in our analysis. Combining this study with the β-blocker arm of the MRC trial gives a total of 1521 patients in the active treatment arm of β-blocker trials. The Swedish Trial in Old Patients With Hypertension (STOP) study used either β-blocker (67%) or diuretic (33%) as a first drug of choice.[12] Only the blood pressure responses were reported separately for the different treatment regimens, and these results were included in the analysis.[17] However, the results for the morbidity and mortality were not broken down by different treatment regimens, and therefore they could not be included in our analysis.

Seven trials included only patients with diastolic hypertension.[4-9,12] Two trials, the Systolic Hypertension in the Elderly Program (SHEP) pilot and the subsequent larger trial, were limited to subjects with isolated systolic hypertension.[10,11] The MRC trial included either patients with moderate-to-severe isolated systolic hypertension or patients with combined systolic and diastolic hypertension.[13]

Response Rate in Patients Treated With β-Blockers and Diuretics

In several studies the response rate to the first drug of choice was reported (Table 2).[5,7,9-11,13,17] Among 4595 patients who received a diuretic as a first drug, about 66% were well controlled on monotherapy, and the remaining third required an additional agent. In contrast, among 2040 patients who received β-blocker as a first drug, less than a third were controlled on monotherapy and about two thirds required a diuretic as a supplement.

Reduction of Risk in Studies With β-Blockers and Diuretics

Both treatment regimens reduced the incidence of cerebrovascular events (Figure 1). Diuretic treatment reduced the odds for cerebrovascular events by 39% (OR, 0.61; 95% CI, 0.51-0.72), and

β-blockers reduced the odds by 26% (OR, 0.74; 95% CI, 0.57-0.98). The odds for stroke mortality were reduced by 33% with diuretics (OR, 0.67; 95% CI, 0.49-0.90), while the estimated reduction achieved with β-blockers was 24% (OR, 0.76; 95% CI, 0.48-1.22). The odds for CHD were reduced by 26% with diuretic treatment (OR, 0.74; 95% CI, 0.64-0.85), while they were not reduced with β-blockers (OR, 1.01; 95% CI, 0.80-1.29). Diuretic treatment reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64-0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78-1.23). Similarly, all-cause mortality was reduced only by diuretic therapy (OR, 0.86; 95% CI, 0.77-0.96) and not by β-blockers (OR, 1.05; 95% CI, 0.88-1.25).

We also examined whether the effect of different diuretic regimens was uniform and whether it affected the comparison with that of β-blockade. For total mortality, the following estimated ORs were associated with these regimens: thiazides only (based on 30 deaths among 661 patients): OR, 0.89; 95% CI, 0.42-1.89; thiazides with potassium-sparing diuretics: OR, 0.86; 95% CI, 0.73-1.03; $P = .10$; and chlorthalidone (the larger group of studies): OR, 0.85; 95% CI, 0.74-0.99; $P = .04$. The findings for these 3 subgroups demonstrate homogeneity and thus agree with the finding for all studies combined. Review of the other end points in terms of diuretic regimens indicates that homogeneity was striking in most examples (detailed data not shown; however, for example, the ORs for CHD were 0.79, 0.58, and 0.79, respectively, for the 3 regimens listed above). A separate consideration of 2 studies in patients with isolated systolic hypertension revealed that omission of these studies resulted in no change of the overall findings; the relative OR for total mortality is 0.85 (95% CI, 0.74-0.97; $P = .02$).[14] The above subgroup results, therefore, supported the conclusion from the overall diuretic and β-blockade comparison (Figure 1).

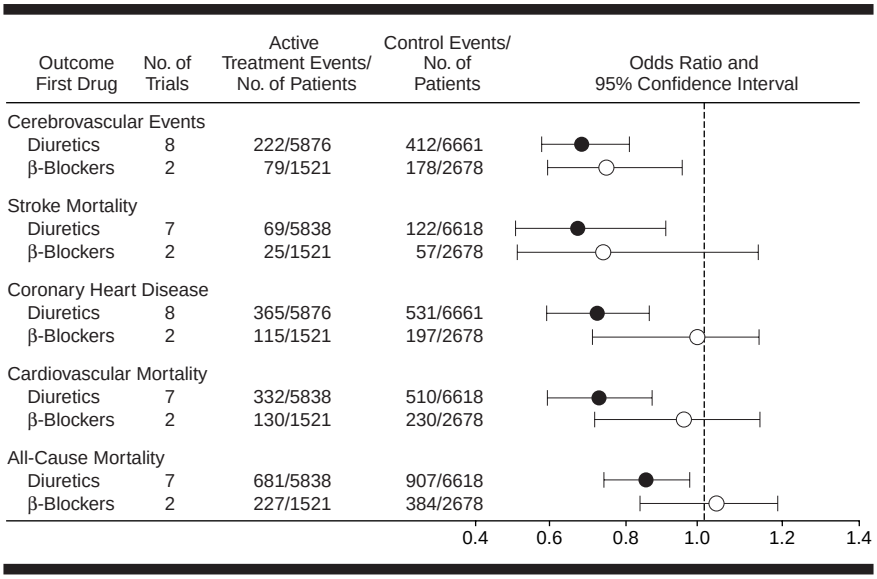

Figure 1.—Meta-analysis of prospective clinical trials in elderly patients with hypertension according to first-line treatment strategy.

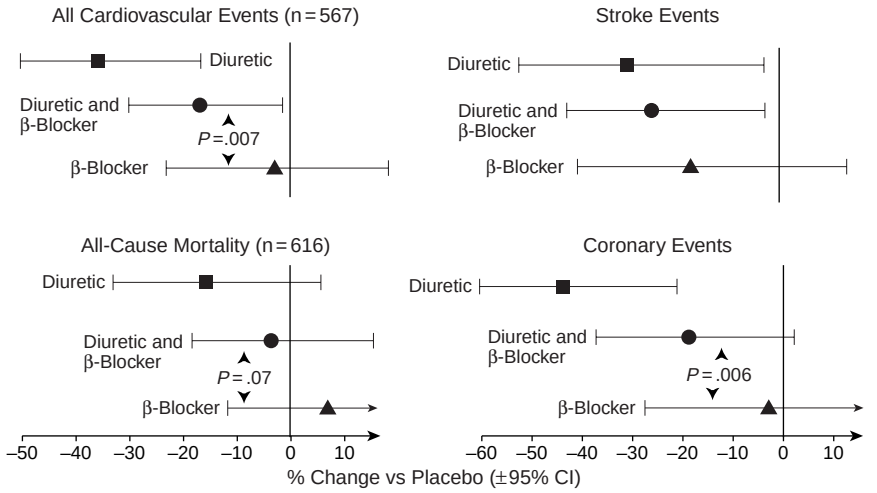

Figure 2.—Morbidity and mortality in Medical Research Council trial in older adults. Data modified with permission from Lever and Brennan.[19]

COMMENT

Although β-blockers have been used for the treatment of hypertension for more than 3 decades,[18] to our knowledge no study shows that their use as a single antihypertensive therapy in the elderly reduces mortality compared with placebo. Quite to the contrary, the present analysis documents that β-blockers do not reduce CHD morbidity and cardiovascular and all-cause mortality. Moreover, in the MRC trial, the elderly patients who received the combination of β-blockers and diuretics fared consistently worse than those receiving diuretics alone (Figure 2).[19] Thus, despite a "beneficial" effect on the surrogate end point, ie, blood pressure, β-blockers failed to favorably affect the clinical end point, ie, CHD and cardiovascular mortality and all-cause mortality. Similarly, in a recent case-control study, the risk of sudden cardiac death was higher in elderly patients receiving either β-blocker as monotherapy or in combination with thiazide diuretic compared with patients receiving other antihypertensive therapy (calcium antagonists, angiotensin converting enzyme inhibitors, or potassium-sparing diuretics).[20]

Part of the ineffectiveness of the β-blockers in treating hypertension in elderly patients may be related to their comparatively weak antihypertensive efficacy: less than one third of the more than 2000 patients were controlled on β-blockers monotherapy, whereas diuretic therapy controlled the blood pressure in two thirds of patients. Their weak antihypertensive efficacy notwithstanding, β-blockers were poorly tolerated in elderly patients, as illustrated by the MRC trial in which twice as many patients withdrew from the β-blocker arm because of major adverse effects than from the diuretic arm.[13] Thus, β-blocker therapy might expose elderly patients with hypertension to adverse effects and cost while conferring little if any true benefit.

Of note, in the MRC study, the diuretic was associated with a lower risk of cardiovascular events compared with the β-blocker, even after adjusting for the decrease in blood pressure.[13] This allows

Table 3.—Possible Reasons for Diminished Efficacy of β-Blockade in the Treatment of Hypertension in Elderly Patients

Pathophysiologic Entity	Specific Changes in the Elderly*	Effect of β-Blockade†
Systemic hemodynamics	Decreased cardiac output, heart rate, and elevated systemic vascular resistance[27,28]	Further decrease in cardiac output, heart rate; further increase in vascular resistance[29,30]
Blood pressure pattern	Predominantly systolic hypertension	Lesser effect on systolic blood pressure
Hypertensive heart disease	Left ventricular hypertrophy is common	Least efficient in reducing left ventricular hypertrophy[31-35]
Hypertensive renal disease	Decreased renal blood flow, glomerular infiltration rate, and increased microproteinuria[36-43]	Further decrease in renal blood flow and glomerular infiltration rate; no effect on microproteinuria[40-44]
Hypertensive vascular disease	Increased arterial stiffness, vascular hypertrophy[45]	No effect on arterial stiffness or hypertrophy (in contrast to other drugs)[46,47]
Metabolic effects	Insulin resistance, glucose intolerance, and lipid abnormalities are common	Increase the risk of developing diabetes by 4 to 6[48-52]; increase in triglycerides and decrease in high-density lipoprotein cholesterol[53-57]
β-Adrenergic responsiveness	Decreased[54,58-63]	Diminished efficacy[60]
Exercise tolerance	Decreased	Further decrease in exercise tolerance
Comorbidity	Chronic obstructive pulmonary disease, peripheral vascular disease, diabetes mellitus, depression, dementia, and sexual dysfunction are common	Affecting all of these comorbid conditions adversely

*Compared with younger patients with similar blood pressure elevation.
†With the exception of the vasodilating β-blockers.

the speculation that either the diuretic confers a specific benefit irrespective of the decrease in arterial pressure or, more concerning, that the β-blocker confers an ill effect on the cardiovascular system in the elderly that overrides the beneficial effect of a decrease in arterial pressure.

In all other studies in the elderly population in which β-blockers used to treat hypertension were implied to reduce morbidity and mortality, they were used in combination with a diuretic. Thus, in the STOP trial[17] more than 70% of the patients assigned to β-blockers were receiving diuretics, and no information was available regarding the effects of a β-blocker as a first-line therapy on morbidity and mortality. The study of Coope and Warrender[9] demonstrated a significant reduction in the rate of strokes and was included as a β-blocker study in our analysis. However, whereas 70% of patients in the treatment group were receiving atenolol, 60% were receiving bendroflumethiazide; the outcome data were never reported separately.[9] In the SHEP study,[11] only 32% of patients were receiving atenolol (or reserpine), almost all of these in combination with a diuretic. A recent subanalysis of SHEP by Kostis et al[21] did not identify any benefits attributable to atenolol (or reserpine) per se that were independent of, or in addition to, the ones conferred by the diuretic. None of these studies allows us to conclude that either the β-blocker alone or the addition of the β-blocker to the diuretic antihypertensive regimen significantly and independently reduced morbidity and mortality. Conceivably, all benefits observed could be due to diuretic therapy alone. The fact that β-blockers are less appropriate first-line therapy than diuretics in the elderly was emphasized by the Working Party on Hypertension in the Elderly[22] and by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, which has changed its previous recommendation for treatment of the elderly by now stating, "When compared to each other, diuretics are superior to the β-blocker atenolol."[1]

Nevertheless, some indirect evidence suggests that β-blockers may have some benefits in treating hypertension in middle-aged and younger patients. In all 3 trials (MRC, International Prospective Primary Prevention Study in Hypertension, and Heart Attack Primary Prevention in Hypertension),[23-25] the rate of myocardial infarction, stroke, and cardiovascular death with a diuretic was similar to that with a β-blocker regimen. A meta-analysis analyzing the 3 studies showed a trend toward a decrease in total cardiovascular mortality in men by 14% and an increase in women by 16% in the β-blocker group when compared with non–β-blocker treatment.[26]

Several points may possibly account for the inefficacy of β-blockers in reducing morbidity and mortality in the elderly hypertensive patient (Table 3). The most important of these points is perhaps the hemodynamic mismatch caused by β-blockade in the elderly. The hemodynamic profile of hypertension in the elderly is characterized by a low cardiac output and a high peripheral resistance.[27,28] Most β-blockers (with the exception of few vasodilating β-blockers) lower arterial pressure by further decreasing cardiac output and increasing systemic vascular resistance.[29] A review of 85 studies on 10 different β-blockers showed an increase in peripheral resistance and a decrease in cardiac output with short-term treatment, whereas with long-term treatment, cardiac output remained depressed, although total peripheral resistance fell somewhat but remained distinctly above normal levels.[30] Thus, while lowering arterial pressure, β-blockers produce a hemodynamic effect exactly opposite to that desired in an elderly patient. By shifting the hemodynamic profile from a normal cardiac output, high vascular resistance pattern to a low cardiac output, high vascular resistance pattern, β-blockers accelerate or enhance hemodynamic changes patients with hypertension experience as they age.[27,28]

β-Blockers have been used for the treatment of hypertension for more than 3 decades.[19] Despite their well-documented potential for lowering millimeters of mercury, no study has shown that β-blockers, either alone or when added to diuretic therapy, independently diminish CHD morbidity or cardiovascular mortality and all-cause mortality when used to treat hypertension in elderly patients. Quite to the contrary, the present analysis shows few, if any, benefits of β-blocker therapy when compared with diuretic therapy. In this context it must be remembered that blood pressure is a surrogate end point that often, but not always, correlates with real end points, such as heart attacks, strokes, and sudden death. The reason for the inefficacy of β-blockers may lie in their inherent unfavorable effect on the systemic hemodynamics of elderly patients and on pathophysiologic findings in the arterial tree, the heart, the kidneys, and the brain and to a lesser extent on the metabolism of lipids and carbohydrates. Thus, although they have been shown to be beneficial in patients after myocardial infarction,[3] β-blockers appear to expose the elderly patient with uncomplicated hypertension to the adverse effects of β-blockade while conferring few, if any, true benefits. This present study reinforces the recommendation of the Joint National Committee VI that, in contrast to diuretics, β-blockers are not appropriate first-line therapy of uncomplicated essential hypertension in the elderly.

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