

Calcium Antagonists and Mortality Risk in Men and Women With Hypertension in the Framingham Heart Study

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Background: Several recent studies have suggested that calcium antagonist drugs, which are widely used for the treatment of hypertension, are associated with increased risk of cardiovascular disease. These studies have cast doubts on the long-term safety of calcium antagonists.

Objective: To examine the association of calcium antagonist use with mortality in subjects with hypertension followed up in the Framingham Heart Study.

Subjects and Methods: We stratified 3539 subjects (mean \pm SD age, 64 ± 13 years) from the Framingham Heart Study who had hypertension at routine clinic examinations, according to the use of calcium antagonists and presence of coronary heart disease at the baseline examination. At each follow-up examination (every 2-4 years), subjects were reclassified with regard to the use of calcium antagonists. The end point of the study was all-cause mortality. Hazard ratios and 95% confidence intervals associated with the use of calcium antagonists were obtained using Cox proportional hazards regression models.

Results: There were 970 deaths during follow-up. Hazard ratios for mortality associated with the use of calcium antagonists were 0.93 (95% confidence interval, 0.72-1.21; $P = .59$) for subjects with hypertension without coronary heart disease, and 0.92 (95% confidence interval, 0.69-1.24; $P = .58$) for those with coronary heart disease at baseline. All models were adjusted for age, sex, current smoking, systolic and diastolic blood pressure, use of β -blockers, and use of other antihypertensive medications.

Conclusions: In this cohort of 3539 subjects with hypertension there were no differences in mortality among subjects with hypertension using a calcium antagonist compared with those who were not. Results were similar among subjects with hypertension with and without coronary heart disease. The results of ongoing long-term, randomized clinical trials will provide more definitive data on the safety of calcium antagonists.

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HYPERTENSION is well established as a risk factor for cardiovascular disease morbidity and mortality.¹⁻³ Meta-analyses of several clinical trials⁴⁻⁷ on hypertension have demonstrated reductions in cardiovascular mortality in response to treatment with diuretics and β -blockers alone or in combination.

Calcium antagonists, a heterogeneous group of drugs, have been used widely in recent years for the treatment of systemic hypertension⁸⁻¹¹ and stable coronary artery disease.¹² Several of these drugs have been approved by the US Food and Drug Administration for the treatment of hypertension based on their effects of lowering blood pressure; however, until recently they have not been evaluated thoroughly in randomized clinical trials or in prospective studies to assess their long-term effects on cardiovascular disease morbidity and mortality.¹³

Despite several advantages to the use of calcium antagonists, such as good tol-

erability, few adverse effects, and efficacy in lowering blood pressure,⁸⁻¹¹ several recent studies¹⁴⁻¹⁸ have suggested that the use of calcium antagonists may increase the risk of cardiovascular disease. These studies¹⁹⁻²¹ have cast doubts on the long-term safety of calcium antagonists.

The objective of the present study was to examine the association of calcium antagonist use with mortality in subjects with hypertension followed up in the Framingham Heart Study.

RESULTS

There were 3539 subjects with hypertension, of whom 174 were taking a calcium antagonist at baseline. During follow-up (mean, 7.7 years; maximum, 12.9 years), 572 additional subjects began taking calcium antagonists; 2793 subjects never used calcium antagonists during the period of observation. **Table 1** summarizes the baseline clinical characteristics of subjects with hypertension according

SUBJECTS AND METHODS

The Framingham Heart Study, a population-based cohort study, has followed up its participants since 1948 to evaluate risk factors and outcomes for cardiovascular disease. Offspring of the original cohort participants and their spouses were entered in a second prospective study in 1971. Selection criteria and study design have been described previously.^{22,23} As part of each routine examination, Framingham participants were asked about use of drugs and dosage, including antihypertensive drugs. A physical examination was performed as were 2 physician-obtained blood pressure measurements and a 12-lead electrocardiogram.

Hypertension was defined in accordance with the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V)²⁴ as a blood pressure of 140 mm Hg or higher systolic or 90 mm Hg diastolic or the current use of antihypertensive medication.

Questions regarding the use of calcium antagonists were first introduced at the 18th biennial examination (1983-1985) for the original study cohort and the third examination (1983-1987) for offspring participants. Subjects with hypertension at examination 18, 19, or 20 for the original cohort and the third or fourth offspring examinations were eligible for this investigation.

Subjects were classified according to the presence of coronary heart disease, defined as a history of myocardial infarction, angina, coronary artery bypass surgery, or coronary angioplasty.²⁵ Left ventricular hypertrophy was defined using electrocardiographic criteria described previously.²⁵

At each follow-up examination (every 2 years for the original cohort and every 4 years for the offspring cohort), subjects were classified as to their use of calcium antagonists and other antihypertensive drugs. Review of Framingham Heart Study charts was performed to determine the specific type of calcium antagonist used both at baseline and at each follow-up examination. Calcium antagonists

were categorized according to specific agent and class (dihydropyridine vs nondihydropyridine). Short-acting calcium antagonists were defined as those prescribed to be used more than once per day while long-acting calcium antagonists were those that were prescribed to be used once daily.

Descriptive statistics for continuous variables are presented as mean \pm 1 SD and for categorical data as counts and percentages. The end point of the study was all-cause mortality. Cox proportional hazards regression models²⁶ were used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) associated with the use of calcium antagonists using SAS PHREG software.²⁷ To minimize misclassification due to changes in treatment over time, the use of calcium antagonists was entered as a time-dependent variable. Models were adjusted for baseline values of age, sex, current smoking, systolic and diastolic blood pressure, history of diabetes, use of β -blockers, and use of other antihypertensive drugs. The use of β -blockers was included in all models because it has been shown that β -blockers reduce mortality in patients with coronary heart disease.^{28,29} Analyses were repeated among subjects with hypertension treated with drugs only ($P < .05$ was considered significant). Analyses were performed based on survival data through September 1996.

Using results from proportional hazards models, we calculated post hoc the true effect (HR) at which power would be 0.80 or higher. For comparisons of any calcium antagonist use vs nonuse, this level of power required an HR of more than 1.53 in subjects with and an HR of more than 1.46 in those without coronary heart disease. For comparison of dihydropyridine vs nondihydropyridine calcium antagonists, it required a HR of more than 2.16 in subjects with coronary heart disease and an HR of more than 2.03 for those without it; and for comparison of short-acting vs long-acting calcium antagonists, comparable values were HR of more than 2.69 in subjects with coronary heart disease and an HR of more than 2.01 in those without it. Cause-specific mortality was not addressed because of limited power to study individual end points.

Table 1. Baseline Characteristics of Subjects With Hypertension According to Coronary Heart Disease (CHD) Status and Use of Calcium Antagonist*

Characteristic	No CHD		CHD	
	Use of Calcium Antagonist (n = 60)	No Use of Calcium Antagonist (n = 2911)	Use of Calcium Antagonist (n = 114)	No Use of Calcium Antagonist (n = 454)
Mean \pm SD age, y (range)	61 \pm 12 (40-84)	62 \pm 13 (24-95)	65 \pm 10 (40-94)	70 \pm 10 (40-93)
Female, %	50	55	29	44
Mean \pm SD BMI, kg/m ²	27 \pm 6	27 \pm 5	27 \pm 4	28 \pm 4
Mean \pm SD SBP, mm Hg (range)	136 \pm 20 (98-186)	144 \pm 18 (85-240)	134 \pm 22 (96-195)	143 \pm 22 (85-212)
Mean \pm SD DBP, mm Hg (range)	79 \pm 12 (53-101)	83 \pm 10 (44-132)	75 \pm 10 (40-101)	77 \pm 11 (47-120)
LVH, %	5	2	6	5
Smoking, %	22	20	18	16
Diabetes, %	7	9	12	19
β -Blockers, %	27	19	39	51
Other Rx, %	27	40	26	49
CHF, %	5	5	11	13
Prior MI, %	54	42

*BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; other Rx, other antihypertensive medications; CHF, congestive heart failure; MI, myocardial infarction; and ellipses, not applicable.

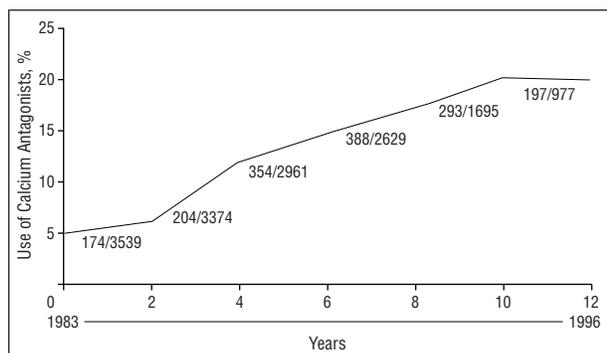


Figure 1. Proportion of study subjects using calcium antagonists at different times during follow-up. The denominator indicates the number of subjects under observation; numerator, number of subjects using a calcium antagonist. There was a sharp increase in use of calcium antagonists among subjects with hypertension, from 5% in 1983 to 20% in 1996.

Table 2. Type of Calcium Antagonist Used at Baseline and at the Last Examination Attended*

	Baseline (n = 174)	Last Examination Attended (n = 575)
Short acting		
Diltiazem	33	17
Nicardipine	1	5
Nifedipine	29	8
Verapamil	17	5
Total	80	35
Long acting		
Diltiazem	1	14
Nifedipine	2	25
Verapamil	6	19
Amlodipine or felodipine	...	7
Total	8	64
Unknown	11	1

*Numbers may not add up to 100% due to rounding. Values are percentages.

to the use of calcium antagonists and coronary heart disease status. Compared with subjects not using calcium antagonists, users of calcium antagonists, whether they had coronary heart disease or not, had lower blood pressure and were less likely to be using other antihypertensive medications.

Figure 1 shows the proportion of study subjects using calcium antagonists at different times during follow-up. There was a sharp increase in use of calcium antagonists among subjects with hypertension from 5% in 1983 to 20% in 1996. The type of calcium antagonists used also changed from baseline to the last examination attended. At baseline, short-acting preparations predominated (80%), but by the last examination attended, long-acting preparations included 64% of calcium antagonists used (**Table 2**). Although 11% of subjects were unclassified at baseline, only 1% were unclassified for purposes of the time-dependent analysis. Two thirds of subjects who were taking calcium antagonists at baseline (68% of those with and 63% of those without coronary heart disease) were still users at the last examination. Conversely, 21% of those with coronary heart disease who were nonusers of calcium antagonists at baseline were

Table 3. Mortality Among Subjects With Hypertension by Use of Calcium Antagonist at Last Examination Attended and Coronary Heart Disease (CHD) Status*

	No CHD		CHD	
	Use of Calcium Antagonist (n = 404)	No Use of Calcium Antagonist (n = 2566)	Use of Calcium Antagonist (n = 171)	No Use of Calcium Antagonist (n = 397)
Death	67 (17)	628 (24)	62 (36)	213 (54)

*Values are number (percentage).

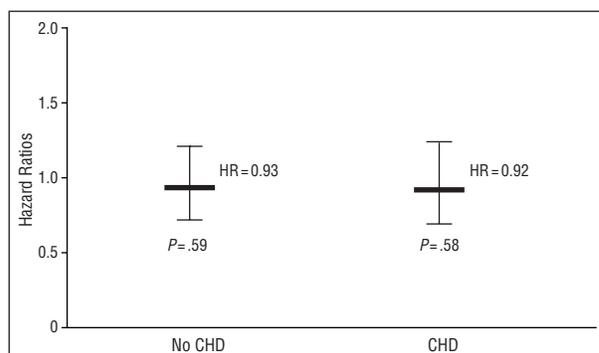


Figure 2. Time-dependent analysis of hazard ratios (HRs) for all-cause mortality associated with the use of calcium antagonists for subjects with hypertension without coronary heart disease (CHD) and for those with CHD at baseline. All models were adjusted for age, sex, current smoking, systolic and diastolic blood pressure, history of diabetes, use of β -blockers, and use of other antihypertensive medications.

users at last examination, compared with 13% for subjects without coronary heart disease at baseline.

During follow-up, there were 970 deaths. **Table 3** shows crude mortality according to the use of calcium antagonists and coronary heart disease status. Unadjusted mortality was lower among users of calcium antagonists than among nonusers for subjects both with and without coronary heart disease at baseline. The results of time-dependent proportional hazards regression models for all-cause mortality are shown in **Figure 2**. Mortality HRs associated with the use of calcium antagonists were 0.93 (95% CI, 0.72-1.21; $P = .59$) for subjects with hypertension without coronary heart disease, and 0.92 (95% CI, 0.69-1.24; $P = .58$) for those with coronary heart disease at baseline. All models were adjusted for age, sex, current smoking, systolic and diastolic blood pressure, history of diabetes, use of β -blockers, and use of other antihypertensive drugs. There were no significant differences in mortality between users of calcium antagonists and nonusers among subjects either with or without coronary heart disease. The results of time-dependent models were similar when the analyses were restricted to subjects with hypertension treated with drugs; the HR for calcium antagonist use in subjects with coronary heart disease was 0.84 (95% CI, 0.60-1.15; $P = .27$) and 0.78 (95% CI, 0.57-1.08; $P = .14$) for those without it.

Subgroup analysis by calcium antagonist class and duration of action using time-dependent analysis showed that the use of dihydropyridines was not associated with

an increased risk of mortality when compared with nondihydropyridine calcium antagonists, among subjects both with (HR, 0.74; 95% CI, 0.43-1.26; $P = .27$) and without coronary heart disease at baseline (HR, 0.93; 95% CI, 0.57-1.51; $P = .75$). In contrast, trends toward adverse risk of short-acting (vs long-acting) calcium antagonists were found among subjects both with coronary heart disease (HR, 1.79; 95% CI, 0.90-3.58; $P = .10$) and without at baseline (HR, 1.35; 95% CI, 0.83-2.19; $P = .23$).

COMMENT

Among 3539 subjects with hypertension in the Framingham Heart Study, we found no differences in mortality among subjects using calcium antagonists when compared with nonusers after adjustment for confounding variables. Results were similar in subjects with and without coronary heart disease. Adjustment for potential confounding variables yielded similar estimates of the mortality hazard associated with the use of calcium antagonists in subjects with and without coronary heart disease at baseline.

In a recently published case-control study¹⁷ of patients with hypertension, case patients and controls with myocardial infarction were analyzed with regard to the type of antihypertensive medication they were using, and the risk of myocardial infarction in relation to antihypertensive treatment was examined. Compared with the use of diuretics alone, the risk of myocardial infarction was 58% higher among users of calcium antagonists. This increased risk for myocardial infarction among users of calcium antagonists was similar in patients with and without cardiovascular heart disease.¹⁷

Similar results were reported by Pahor et al,¹⁸ who followed up a cohort of 904 elderly patients with hypertension who were treated with either a β -blocker, a short-acting calcium antagonist, or an angiotensin-converting enzyme inhibitor during a 4-year follow-up period. Compared with the use of β -blockers, the use of short-acting nifedipine was associated with a 70% increased risk of mortality. In that study, no information was available on use of drugs after baseline, creating a potential for misclassification of calcium antagonist use shortly before death.

A meta-analysis of the effects of the short-acting calcium antagonist nifedipine on the outcome in patients with coronary artery disease¹⁶ also suggested a trend toward increased mortality with increased doses of this medication. This meta-analysis has been criticized^{19,21} because of its retrospective nature, inclusion of patients with a variety of clinical syndromes including unstable angina, arbitrary study selection, and because analyses were performed on patients taking short-acting calcium antagonist preparations, which are no longer in widespread use.

By contrast, a recent cohort study³⁰ in patients with coronary disease demonstrated no difference in mortality among patients who were taking short-acting calcium antagonists compared with those who were not, after adjustment for clinical characteristics that differed between the 2 groups. That study³⁰ had a relatively short

follow-up period (mean, 3.2 years) and was limited to patients with coronary disease.

Most prior studies evaluating the risks associated with the use of calcium antagonists have included primarily short-acting calcium antagonist preparations. The short-acting preparations, in particular short-acting nifedipine, produce vasodilatation with reflex sympathetic activation.¹⁶ This phenomenon is less pronounced with the long-acting preparations.³¹ In our study, a gradual change from short-acting to long-acting preparations was seen; 80% of calcium antagonists used at baseline were short acting, whereas 64% were long acting at the last examination attended. Using the time-dependent Cox model, updating for the specific class of calcium antagonist, no significant difference in mortality between dihydropyridine and nondihydropyridine calcium antagonists was found in subjects with or without coronary heart disease.

We observed a trend toward increased mortality in association with short-acting vs long-acting calcium antagonists. A recent case-control study³² reported an association between the use of short-acting calcium antagonists and adverse cardiovascular outcome in patients with hypertension; however, the study was limited to 6 months of exposure time to the drug and the number of patients in each group was small.

This study has advantages such as a prospective cohort design with routine and consistent ascertainment of hypertension status, hypertension treatment, as well as risk factors and clinical characteristics at each follow-up visit. Longer follow-up time and power to detect an effect on survival are additional strengths.

Several limitations should be mentioned. This was an observational study, not a randomized clinical trial. Community physicians selected antihypertensive medications according to their patients' clinical characteristics, reflecting clinical practice in the community. In addition, there may be factors associated both with the use of calcium antagonists and mortality for which adjustment was not made. The only risk factor that differed between users and nonusers of calcium antagonists was blood pressure. Therefore, we adjusted for baseline systolic and diastolic blood pressure in the multivariate model. Although information was obtained on the type of calcium antagonist used and its duration of action, the effect of different drug doses was not analyzed. Finally, we had limited power for subgroup analysis.

CONCLUSIONS

In this cohort of 3539 subjects with hypertension we found no difference in mortality among subjects using calcium antagonists compared with nonusers. Results were similar for subjects with and without coronary heart disease at baseline. In addition, the use of dihydropyridine calcium antagonists did not confer an additional risk of mortality. There was a suggestion, however, of an increased risk of mortality associated with the use of short-acting vs long-acting calcium antagonists.

The long-term safety of calcium antagonists is best determined by controlled clinical trials. A recently published randomized, double-blind, placebo-controlled trial³³

of the calcium antagonist nitrendipine as starting treatment for older individuals with isolated systolic hypertension showed a 42% ($P < .003$) reduction in risk of stroke after a median follow-up of 2 years. In addition, the risk for fatal and nonfatal cardiac end points was reduced by 31% ($P < .001$) with active therapy. Cardiovascular mortality was slightly lower for active treatment (-27% ; $P = .07$) but all-cause mortality was not decreased significantly (-14% ; $P = .22$).

Two other large, randomized, long-term trials, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)³⁴ and STOP-Hypertension 2 (the Swedish Trial in Old Patients with Hypertension 2),³⁵ have been designed to examine differences in morbidity and mortality for different antihypertensive drugs, including a calcium antagonist. However, the results of these ongoing trials are not yet available.

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REFERENCES

- Kannel WB. Role of blood pressure in cardiovascular morbidity and mortality. *Prog Cardiovasc Dis*. 1974;27:5-24.
- Rutan GH, Kuller LH, Neaton JD, Wentworth DN, McDonald RH, Smith WM. Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Factor Intervention Trial. *Circulation*. 1988;77:504-514.
- The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final results of the Pooling Project. *J Chronic Dis*. 1978; 31:201-306.
- MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease, I: prolonged differences in blood pressure—prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765-774.
- Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease, II: short-term reduction in blood pressure—overview of randomized drug trials in their epidemiological context. *Lancet*. 1990;335:827-838.
- Cutler J, Psaty B, MacMahon S, Furberg C. Public health issues in hypertension control: what has been learned from clinical trials. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*. 2nd ed. New York, NY: Raven Press; 1995:253-270.
- Psaty B, Furberg C. Antihypertensive treatment trials: morbidity and mortality. In: Izzo JL, Black HR, eds. *Hypertension Primer*. Dallas, Tex: American Heart Association; 1993:197-213.
- Braunwald E. Mechanism of action of calcium channel blocking agents. *N Engl J Med*. 1982;307:1618-1627.
- Weiner DA. Calcium channel blockers. *Med Clin North Am*. 1988;72:83-115.
- Frishman WH. Current status of calcium channel blockers. *Curr Probl Cardiol*. 1994;19:637-688.
- Frishman WH, Stroh JA, Greenberg SM, et al. Calcium channel blockers in systemic hypertension. *Med Clin North Am*. 1988;72:449-499.
- Braunwald E, Muller JE, Stone PH. Use of calcium channel blocker agents in the management of ischemic heart disease. *Eur Heart J*. 1985;6(suppl A):31-36.
- Yusuf S. Calcium antagonist in coronary artery disease and hypertension. *Circulation*. 1995;92:1079-1082.
- Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview of the results from randomized clinical trials. *BMJ*. 1989;229:1187-1192.
- Glasser SP, Clark PI, Lipicky RJ, Hubbard JM, Yusuf S. Exposing patients with chronic stable exertional angina to placebo periods in drug trials. *JAMA*. 1991; 265:1550-1554.
- Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation*. 1995;92:1326-1331.
- Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA*. 1995;274:620-625.
- Pahor M, Guralnick JM, Corti MC, Foley DJ, Carbonin P, Havlik RJ. Long term survival and use of antihypertensive medications in older patients. *J Am Geriatr Soc*. 1995;43:1191-1197.
- Opie LH, Messerli FH. Nifedipine and mortality: grave defects in the dossier. *Circulation*. 1995;92:1068-1073.
- Kloner RA. Nifedipine in ischemic heart disease. *Circulation*. 1995;92:1074-1078.
- Buring JE, Glynn RJ, Hennekens CH. Calcium channel blockers and acute myocardial infarction: a hypothesis formulated but not yet tested. *JAMA*. 1995;274: 654-655.
- Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci*. 1963;107:539-556.
- Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: The Framingham Offspring Study. *Am J Epidemiol*. 1979;110:281-290.
- The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med*. 1993;153:154-183.
- Kannel WB, Wolf PA, Garrison RJ. The Framingham Study: an epidemiological investigation of cardiovascular disease, section 34—some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements. In: *Framingham Heart Study, 30-Year Follow-up*. Bethesda, Md: National Heart, Lung, and Blood Institute; 1987. US Dept of Health and Human Services NIH publication 87-2703:9-19.
- Cox DR, Oakes D. *Analysis of Survival Data*. New York, NY: Chapman & Hall; 1984:91-141.
- SAS Institute Inc. *SAS/STAT Software: Changes and Enhancements Through Release 6.11 (The Phreg Procedure)*. Cary, NC: SAS Institute Inc; 1996:807-884.
- Yusuf S, Whittes J, Friedman L. Overview of results of randomized clinical trials in heart disease, I: treatment following myocardial infarction. *JAMA*. 1988;260: 208.
- Beta-Blocker Pooling Project Research Group. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trials in post-infarction patients. *Eur Heart J*. 1988;9:8-16.
- Braun S, Boyko V, Behar S, et al, and the Benzifibrate Infarction Prevention Study Participants. Calcium antagonists and mortality in patients with coronary artery disease: a cohort study of 11,575 patients. *J Am Coll Cardiol*. 1996;28:7-11.
- Frohlich ED, McLoughlin MJ, Losem CJ, et al. Hemodynamic comparison of two nifedipine formulations in patients with essential hypertension. *Am J Cardiol*. 1991; 68:1346-1350.
- Alderman MH, Cohen H, Roque R, Madhavan S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. *Lancet*. 1997;349:594-598.
- Staessen JA, Fagard R, Thijs L, et al, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomized double blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*. 1997;350:757-764.
- Davis BR, Cutler JA, Gordon DJ, et al. Rationale and design for the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). *Am J Hypertens*. 1996;9:342-360.
- Dahlof B, Hansson L, Lindholm LH, et al. STOP-Hypertension 2: a prospective intervention trial of "newer" versus "older" treatment alternatives in old patients with hypertension. *Blood Press*. 1993;2:136-141.