

Calcium Antagonists and Beta-Blockers: Impact on Cardiovascular and Cerebrovascular Events

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It is well established that elevated blood pressure is a major risk factor for cardiovascular and cerebrovascular events, and that controlling hypertension reduces these risks. Although most classes of antihypertensive agents play a role in risk reduction, none offers blanket reductions for all adverse events. The β -blockers, while the agents of choice for those with ischemic heart disease and for disease states requiring reducing heart rate, are inappropriate first-line therapies in patients whose primary concern is stroke risk reduction. In patients who require heart rate–lowering therapy but who cannot tolerate β -blockers, long-acting nondihydropyridine calcium antagonists offer the benefits of heart rate reduction, as well as the vasodilation that is characteristic of the calcium antagonists as a class. This article reviews the data on risk reduction involving the β -blockers and calcium antagonists, as well as other antihypertensive classes that have been shown to reduce the risk of cerebrovascular and cardiovascular disease. (*Clinical Cornerstone*. 2004;6[4]:18–27) Copyright © 2004 Excerpta Medica, Inc.

It was not until the early 1960s that clinical studies began to demonstrate an association between mild hypertension and increased morbidity and mortality. In 1961, investigators published the 6-year follow-up results of the landmark Framingham Heart Study, which showed a >3-fold increase in the incidence of cardiovascular disease among hypertensive men, and an 8-fold increase among hypertensive women compared with normotensive individuals.¹ Nearly a decade later, findings from the Veterans Administration Study II showed that active treatment with antihypertensive medication can dramatically reduce the incidence of fatal and nonfatal cardiovascular events, particularly stroke, compared with placebo.²

REDUCING STROKE RISK

Hypertension is a recognized risk factor for both heart attack and stroke. It is a particularly powerful risk factor for stroke: A pooled analysis of random-

ized, controlled hypertension trials showed a progressive increase in the relative risk for stroke-related mortality with increases in systolic or diastolic blood pressure. At the highest decile of blood pressure (systolic ≥ 151 mm Hg or diastolic ≥ 98 mm Hg), the relative risk of death due to stroke was ~ 4.0 in women and 8.0 in men compared with those in the lowest decile ($< 112 / < 71$ mm Hg) (**Figure 1**).³ Aside from previous stroke or transient ischemic attack (TIA), consistently elevated blood pressure ($> 140 / 90$ mm Hg) is the most important stroke risk factor, increasing risk by up to 6-fold (**Figure 2**).⁴ The high morbidity and mortality associated with stroke demands that aggressive risk-reduction strategies be employed in patients with hypertension: Only 10% of patients achieve a complete recovery, while nearly two thirds (65%) either die or suffer from impairments requiring special care (including nursing home care).⁴

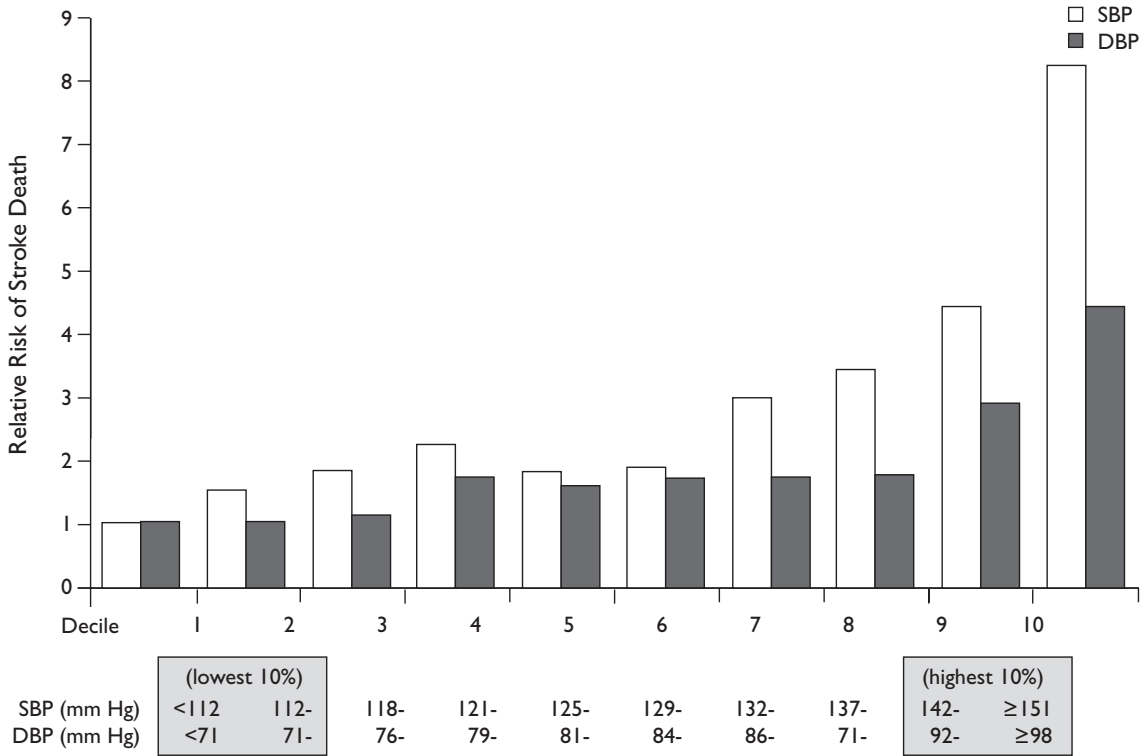


Figure 1. Stroke risk, stratified by decile of systolic blood pressure (SBP)/diastolic blood pressure (DBP). Reprinted with permission.³

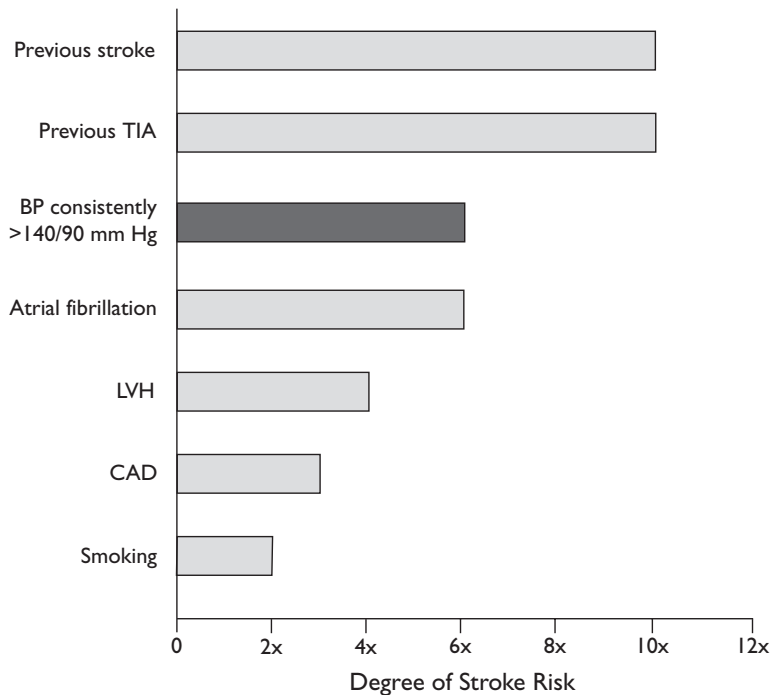


Figure 2. Risk factors for stroke. TIA = transient ischemic attack; BP = blood pressure; LVH = left ventricular hypertrophy; CAD = coronary artery disease. Reprinted with permission.⁴

KEY POINT

Aside from previous stroke or transient ischemic attack, consistently elevated blood pressure (>140/90 mm Hg) is the most important stroke risk factor, increasing risk by up to 6-fold.

Systolic hypertension is an independent risk factor for stroke: The Multiple Risk Factor Intervention Trial was one of the largest (nearly 350,000 men) and longest-duration (>12 years) studies to demonstrate an association between stroke and high blood pressure in general, and stroke and isolated systolic hypertension in particular.⁵

Two major large-scale trials in the 1990s—the Systolic Hypertension in the Elderly Program (SHEP)⁶ and Systolic Hypertension in Europe (Syst-Eur)⁷ trial—demonstrated that reducing blood pressure decreases stroke incidence. SHEP, a stepped-care-based diuretic (chlorthalidone) antihypertensive regimen reduced stroke by 36% compared with placebo in elderly patients (aged ≥ 60 years) with isolated systolic hypertension.⁶ In Syst-Eur, a calcium antagonist-based regimen (nitrendipine), conferred a stroke reduction of 42% compared with placebo in elderly patients with isolated systolic hypertension.⁷

The marked benefit seen in these studies with multiple antihypertensive classes has led some to conclude that any drug that lowers blood pressure will reduce the risk of stroke. With regard to the other classes of antihypertensives, at least 4 independent trials have failed to show a reduction in stroke risk with the use of β -blockers, despite significant reductions in blood pressure. Two trials by the Medical Research Council, 1 in the elderly ($N = 4396$) and 1 in patients aged 35 to 64 years ($N = 17,354$), demonstrated significant stroke reductions with the use of a diuretic but not with β -blocker monotherapy (propranolol or atenolol).^{8,9} In the Dutch TIA Trial, which enrolled 1473 patients treated with acetylsalicylic acid who had a history of TIA or ischemic stroke, there was no significant reduction in nonfatal stroke, myocardial infarction, or vascular mortality with atenolol compared with placebo.¹⁰ Finally, in the

Norwegian Tenormin After Stroke and TIA Study, no significant benefit in secondary stroke prevention was seen with atenolol over a mean of 31 months.¹¹

Of interest are the findings of the recent Morbidity and Mortality After Stroke—Eprosartan Study, in which the angiotensin receptor blocker (ARB) eprosartan was compared to a calcium antagonist and showed a 25% greater reduction in the total occurrence and recurrence of fatal and nonfatal cerebrovascular events, as well as a 30% reduction in first-time cardiovascular events.¹²

CALCIUM ANTAGONISTS

The calcium antagonists exert blood pressure-lowering effects through vasodilation and decreased peripheral resistance. They are available as dihydropyridine and nondihydropyridine derivatives, and as short-acting and long-acting agents. Short-acting forms include a sublingual formulation of nifedipine, which was once widely used for hypertensive emergencies but is now used rarely due to its association with a number of adverse events, including cerebrovascular ischemia, stroke, and acute myocardial infarction.¹³ These events were a result of nifedipine's powerful vasodilator effects, which triggered an increase in sympathetic activity, raising plasma norepinephrine levels and causing reflex tachycardia.¹⁴ An analysis of 46 studies of calcium antagonists involving >1250 patients demonstrated that short-acting calcium antagonists significantly increase heart rate and plasma norepinephrine levels after acute administration.¹⁴ When given long term, short-acting agents, both dihydropyridine and nondihydropyridine continued to increase plasma norepinephrine levels (**Figure 3A**). With chronic use of long-acting dihydropyridine calcium antagonists, sympathetic activation was also increased, although less pronounced. With long-acting nondihydropyridine calcium antagonists, however, sympathetic activity was decreased significantly ($P < 0.001$), as shown by reductions in plasma norepinephrine levels (**Figure 3B**).¹⁴

Increases in sympathetic activity are of concern due to their association with adverse cardiovascular sequelae, including heart failure, atherosclerosis, and diabetes (**Figure 4**).¹⁵ Thus, provided that blood pressure reductions are equal, agents that reduce sympathetic tone, such as long-acting calcium antagonists, should have advantages over agents that increase sympathetic tone.

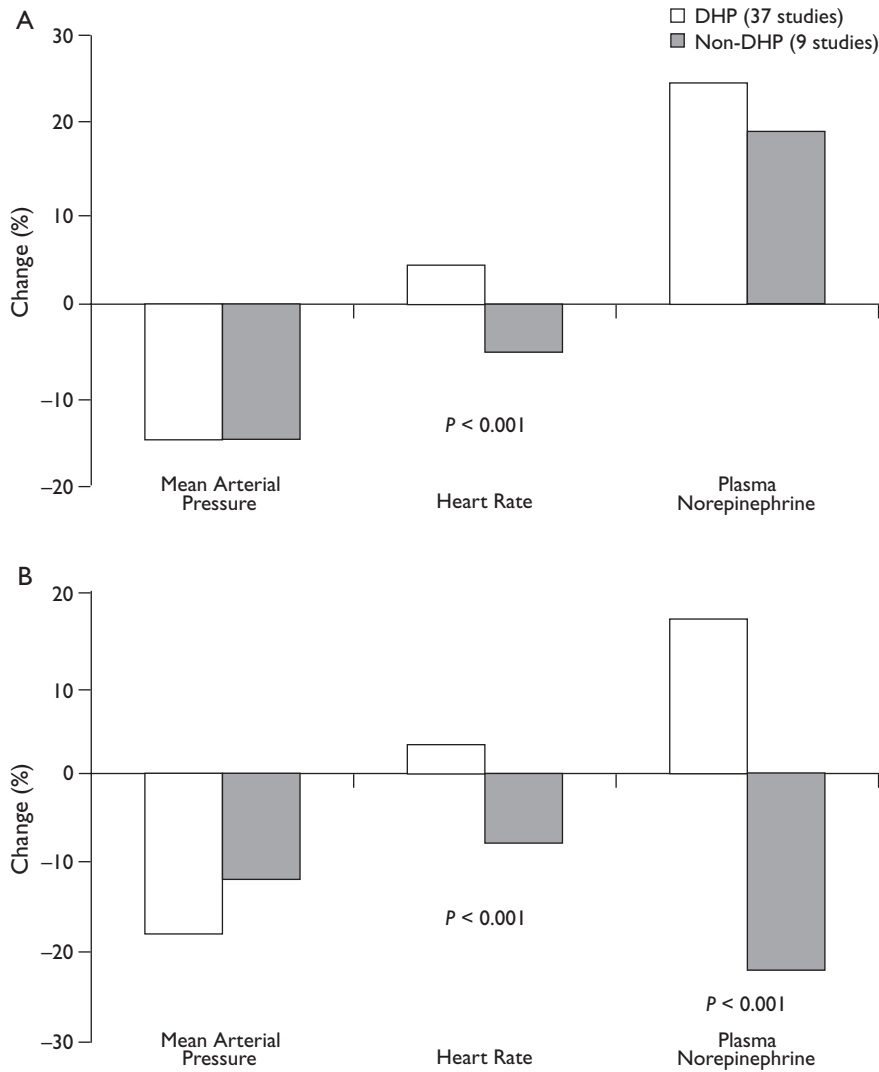


Figure 3. Long-term effects of (A) short-acting and (B) long-acting calcium channel blockers on mean arterial pressure, heart rate, and plasma norepinephrine levels. DHP = dihydropyridine. Reprinted with permission.¹⁴

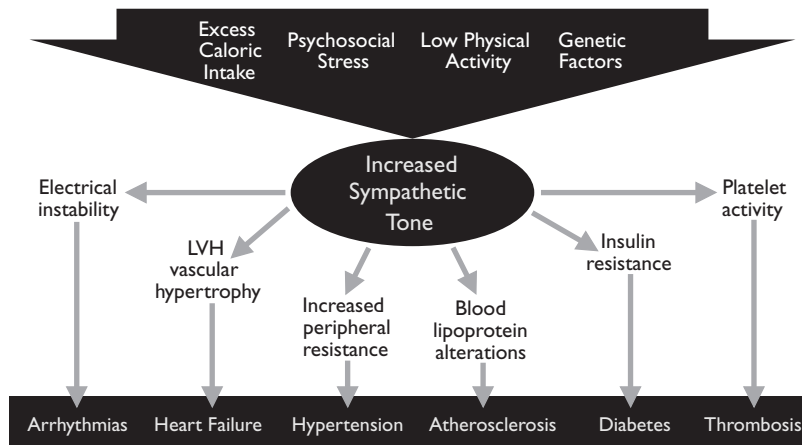


Figure 4. Pathophysiologic mechanisms underlying increases in cardiovascular disease with increased sympathetic activity. LVH = left ventricular hypertrophy. Reprinted with permission.¹⁵

KEY POINT

Agents that decrease heart rate may also decrease arterial wall stress and atherosclerosis, and cardiac work; those that decrease heart rate and sympathetic tone may also decrease the threshold for arrhythmias and improve insulin resistance and dyslipidemia.

Similarly, antihypertensive agents that reduce heart rate may offer advantages over agents that do not affect heart rate. Increased heart rate is a major but often overlooked risk factor for cardiovascular disease; data both from the Framingham Heart Study¹⁶ and Syst-Eur¹⁷ showed that all-cause mortality more than doubles in persons with heart rates ≥ 80 beats/min. Agents that decrease heart rate may also decrease arterial wall stress and atherosclerosis, and cardiac work; those that decrease heart rate and sympathetic tone may also decrease the thresh-

old for arrhythmias and improve insulin resistance and dyslipidemia.¹⁵

Reduction in heart rate is a class effect of the β -blockers. It is also a characteristic of nondihydropyridine calcium antagonists such as verapamil and diltiazem, which are available in both short- and long-acting forms. This characteristic makes heart rate–lowering calcium antagonists appropriate substitutes for β -blockers in patients who cannot tolerate β -blockers or in whom β -blockers are contraindicated.¹⁸ Verapamil shows patterns of sympathetic activation consistent with the calcium antagonists as a class, with the short-acting form increasing sympathetic tone and the long-acting form decreasing tone with chronic use (**Figure 5**).¹⁴ Verapamil is the only calcium antagonist to date that has been shown to decrease cardiovascular events after myocardial infarction. In the Danish Study Group on Verapamil on Myocardial Infarction II, cumulative mortality in postinfarction patients without heart failure was reduced by 16.7% with verapamil compared with placebo ($P = 0.02$). There was no significant reduction in patients with heart failure.¹⁹ The risk of a first cardiac event was decreased by 33%, and the risk of a first reinfarction was decreased by 29%.

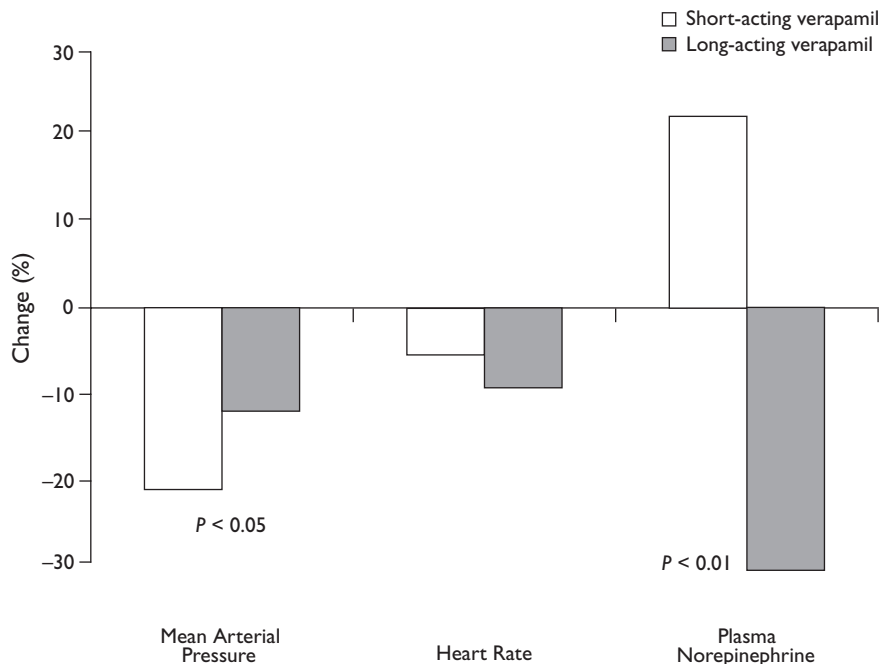


Figure 5. Sympathetic activation with verapamil, which is available in short- and long-acting formulations. The patterns of sympathetic activation with long-term use are consistent with those of the calcium channel blockers as a class. Reprinted with permission.¹⁴

KEY POINT

Because the International Verapamil SR/Trandolapril Study established equivalent efficacy with a β -blocker/diuretic and calcium antagonist/angiotensin-converting enzyme (ACE) inhibitor strategy, a calcium antagonist/ACE inhibitor regimen can be substituted for a β -blocker/diuretic regimen in patients who do not tolerate β -blockers or who have contraindications to their use.

COMPARING RISK REDUCTION WITH ANTIHYPERTENSIVE AGENTS: THE INVEST STUDY

The International Verapamil SR/Trandolapril Study (INVEST) is the largest study to date to compare the efficacy of cardiovascular risk-reduction strategies in patients with hypertension.²⁰ The study included >22,000 patients with hypertension and coronary artery disease. Half were randomized to a calcium antagonist/angiotensin-converting enzyme (ACE) inhibitor regimen, consisting of initial treatment with sustained-release verapamil 240 mg, with the addition of trandolapril 2 mg if necessary to achieve target blood pressures. The other half were randomized to a β -blocker/diuretic regimen, consisting of initial treatment with atenolol 50 mg, with the addition of hydrochlorothiazide 25 mg if necessary to achieve target blood pressures. In both groups, doses were increased as a third step if blood pressure targets were still not met, and the opposite second-line agent was added to each group as a fourth step (ie, hydrochlorothiazide to the calcium antagonist/ACE inhibitor regimen, and trandolapril to the β -blocker/diuretic regimen). Patients from both groups who had diabetes, renal dysfunction, or heart failure were given the ACE inhibitor as part of initial therapy, due to the proven benefits of the ACE inhibitor class in patients with these diseases.²⁰

The primary end points of this study were all-cause mortality, nonfatal acute myocardial infarc-

tion, and nonfatal stroke.²⁰ The 2 groups were well matched at baseline, with 32% having a previous myocardial infarction, 38% abnormal findings on angiography, 66% classic angina pectoris, and 38% a previous angioplasty or coronary artery bypass graft.

Consistent with the results of other large-scale clinical trials, the majority of patients (80%) required >1 antihypertensive agent to achieve target blood pressure goals, demonstrating that hypertension is generally managed inadequately with monotherapy.²⁰ Overall blood pressure control was impressive, with 72% in the calcium antagonist/ACE inhibitor group and 71% in the β -blocker/diuretic group achieving systolic blood pressure control at 2 years. Approximately 10% more patients met blood pressure goals in this study than in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.²¹

Blood pressure control was virtually identical in the 2 INVEST treatment arms.²⁰ At the 24-month follow-up, mean systolic pressures were reduced by 18.7 to 19.0 mm Hg, with diastolic pressures reduced by 10.0 to 10.2 mm Hg. Equal numbers of patients also remained alive and free of myocardial infarction or stroke after a mean follow-up of 2.7 years (**Figure 6**). The β -blocker-based and calcium antagonist-based strategies performed equally well on the majority of primary and secondary outcome measures, including first event, overall or cardiovascular-related mortality, nonfatal myocardial infarction or stroke, or hospitalization due to cardiovascular causes. However, in patients without diabetes at baseline, those in the verapamil-based therapy arm had reduced relative risks of new-onset diabetes; compared with β -blocker-based therapy.²⁰ The difference was not surprising, given that an increase in diabetes risk has been reported with β -blockers and diuretics.^{22,23}

Because the INVEST study established equivalent efficacy with a β -blocker/diuretic and calcium antagonist/ACE inhibitor strategy, a calcium antagonist/ACE inhibitor regimen can be substituted for a β -blocker/diuretic regimen in patients who do not tolerate β -blockers or who have contraindications to their use. This includes those who have metabolic syndrome or diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, or erectile dysfunction.

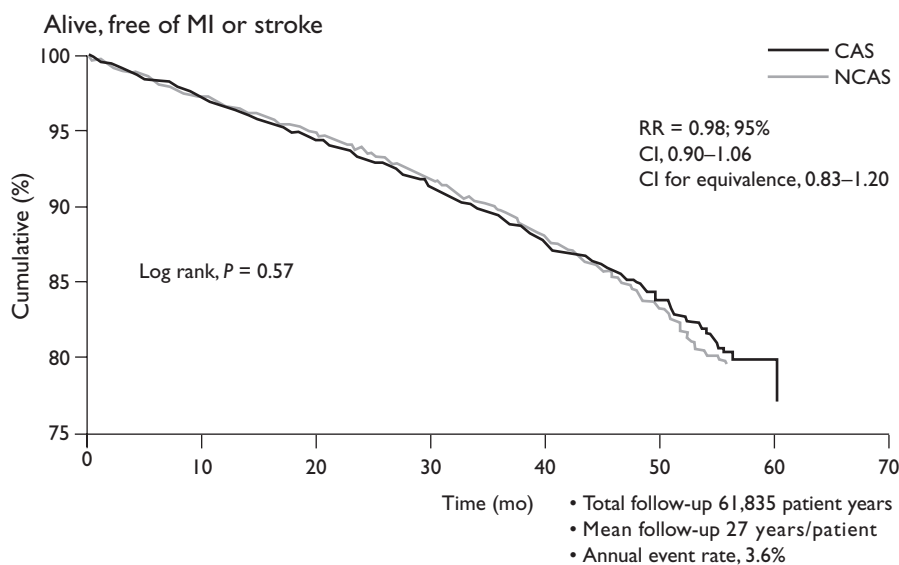


Figure 6. Kaplan-Meier graph showing cumulative survival in patients in the calcium antagonist/angiotensin-converting enzyme inhibitor and β -blocker/diuretic arms of the International Verapamil SR/Trandolapril Study. MI = myocardial infarction; CAS = calcium antagonist therapy; NCAS = non-CAS; RR = relative risk. Reprinted with permission.²⁰

LEFT VENTRICULAR HYPERTROPHY AS A CARDIOVASCULAR RISK FACTOR

Several studies have also examined the morbidity and mortality risks associated with left ventricular hypertrophy (LVH). The Framingham Heart Study established LVH as an independent risk factor for sudden death and acute myocardial infarction, and also demonstrated a progressively increased risk of cardiovascular disease with increasing left ventricular mass.^{24,25} The risk of sudden death is ~4 times higher in men and doubled in women with LVH.²⁶

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure states that all classes of agents, with the exception of direct vasodilators, are effective for reducing LVH.²⁷ The

Losartan Intervention for Endpoint Reduction in Hypertension study, however, found a distinct advantage in terms of cardiovascular events, particularly of stroke, over 4 years with the ARB losartan compared with atenolol in 9193 patients with hypertension and echocardiographically diagnosed LVH.²⁸ Blood pressure reductions were nearly identical (30.2/16.6 mm Hg for the ARB vs 29.1/16.8 mm Hg for the β -blocker). Comparing 5 classes of agents (diuretics, β -blockers, calcium antagonists, ACE inhibitors, and ARBs), Klingbeil et al²⁹ found the greatest reduction in left ventricular mass index with the ARBs and ACE inhibitors, both of which performed significantly better than β -blockers.

CIRCADIAN VARIATION IN BLOOD PRESSURE RISK

More recent data have examined not only the effects of different classes of antihypertensive therapies but also delivery systems designed to precisely control the timing of medication. There is a significant variation in the risk of cardiovascular and cerebrovascular events that is mediated by the individual's underlying circadian rhythms, which cause a "morning surge" in blood pressure.³⁰ This morning surge, discussed in greater depth elsewhere in this issue,³¹ increases the risk of stroke, myocardial infarction, and sudden cardiovascular death in the morning

KEY POINT

More recent data have examined not only the effects of different classes of antihypertensive therapies but also delivery systems designed to precisely control the timing of medication.

hours.^{32–34} Stroke incidence, in particular, is increased by nearly 50% during the hours of 6 AM to noon, as demonstrated by a meta-analysis of 31 studies focusing on the circadian pattern of stroke timing.³²

Several chronotherapeutic forms of antihypertensive agents have been developed to deliver the most effective dose of medication during the period of the morning surge, including the calcium antagonist diltiazem and 2 forms of the calcium antagonist verapamil, and the β -blocker propranolol.

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Dialogue Box

EDITORIAL BOARD

Given their beneficial effect on blood pressure, sympathetic tone, and heart rate, why aren't β -blockers more effective in reducing the risk of stroke?

MESSERLI

The elderly (age ≥ 65 years) hypertensive patient is hemodynamically characterized by a low cardiac output, low heart rate, and very high systemic vascular resistance. A β -blocker, with the exception of carvedilol, will further lower cardiac output and heart rate and further increase total peripheral resistance, therefore making the patient hemodynamically even older. In contrast to β -blockers, all other antihypertensive drugs lower systemic vascular resistance and maintain cardiac output. Thus, β -blockade in the elderly causes a pharmacologic/physiologic mismatch.

EDITORIAL BOARD

Are there data regarding the effect other antihypertensive agents (other than CCBs and β -blockers) have on sympathetic tone?

MESSERLI

ACE inhibitors and angiotensin receptor inhibitors have some antiadrenergic effects. Of course, the old antiadrenergic drugs (eg, methyldopa, clonidine) also lower sympathetic activity. Drug classes that do not reduce sympathetic activity are the diuretics and the direct arteriolar vasodilators (eg, hydralazine, minoxidil).

EDITORIAL BOARD

If cardiac contractility and conduction are not a concern, does a medication's impact on sympathetic tone influence your choice of an antihypertensive agent?

MESSERLI

All other factors being equal (which they never are), an antihypertensive drug that lowers sympathetic activity probably should be preferred over a drug that does not reduce sympathetic activity.

EDITORIAL BOARD

What property of diuretics might account for their added benefit, beyond blood pressure control, in preventing stroke?

MESSERLI

Conceivably, the stimulation of the angiotensin II type 2 (AT_2) receptor may have some cerebroprotective effects. Drugs that stimulate the AT_2 receptor are the angiotensin receptor inhibitors, the CCBs, and the diuretics.

EDITORIAL BOARD

By what mechanisms might β -blockers and thiazide diuretics increase the risk of diabetes?

MESSERLI

β -blockers may increase the risk of diabetes because of the weight gain they cause and the decrease of insulin secretion. Diuretics could increase the risk of diabetes by causing hypokalemia and by stimulating the renin-angiotensin system.

EDITORIAL BOARD

Why would a CCB/ACE inhibitor regimen be favored in a patient with erectile dysfunction?

MESSERLI

The CCBs and blockers of the renin-angiotensin system have no negative effect on erectile dysfunction. In fact, one might argue that these drugs could increase blood flow to critical organs and therefore even facilitate erection. In contrast, β -blockers and diuretics have been documented to decrease erectile function.