Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 1999; 2 (2), 163-166

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Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

Dihydropyridines and the treatment of hypertension

R. H. Fagard

Dihydropyridine calcium channel blockers reduce blood pressure and left ventricular hypertrophy in hypertensive patients. Outcome studies are at present only available in the elderly. In patients with systolic-diastolic hypertension and in patients with isolated systolic hypertension, nifedipine or nitrendipine-based antihypertensive treatment reduced the incidence of combined fatal and nonfatal strokes and of cardiovascular events. All-cause and cardiovascular mortality were significantly reduced or tended to be lower in the active-treatment groups compared to the control groups. Treatment was also beneficial in diabetics, particularly in terms of absolute risk reduction. There was no evidence of an increase of non-cardiovascular events or mortality, including cancer and bleeding, but it should be noted that the outcome trials were of relatively short duration. Finally, further studies are needed to establish whether the results obtained in the elderly would also be valid for younger patients with hypertension. *J Clin Basic Cardiol 1999; 2: 163–6*.

Key words: dihydropyridine, hypertension, calcium channel blockers, diabetes, left ventricular hypertrophy, morbidity, morality, outcome

Calcium channel blockers have been used for many years in the management of cardiovascular diseases including hypertension. There is ample evidence that verapamil, a phenylalkylamine, diltiazem, a benzothiazepine, and the dihydropyridine calcium channel blockers are capable of lowering blood pressure and all three subclasses have been used for the treatment of hypertensive patients. However, the ultimate goal of antihypertensive therapy is to prevent cardiovascular complications and to prolong life. At present, outcome trials are only available for the dihydropyridine subclass. The present paper will focus on this subclass and review the evidence for its effects on left ventricular hypertrophy, cardiovascular morbidity and mortality. Its mechanisms of action and side-effects are well-known and summarized in current textbooks and review papers and will not be addressed in the present manuscript.

Influence on left ventricular hypertrophy

High blood pressure leads to left ventricular hypertrophy [1] which is an independent risk factor for cardiovascular complications and aggravates the prognosis of the hypertensive patient [2, 3]. The reduction of left ventricular mass by antihypertensive therapy may therefore be beneficial [4]. The effect of dihydropyridine calcium channel blockers on left ventricular mass has been studied repeatedly. Because it would be unethical to leave hypertensive patients untreated, the calcium channel blocker was usually compared to another first-line agent, with the possible addition of other drugs for better blood pressure control [5]. We performed a meta-analysis of 13 prospective, comparative, randomized studies in which a calcium channel blocker was compared to a diuretic, a beta-blocker or an angiotensin converting enzyme inhibitor [6]. Left ventricular mass was reduced by 14 % (95 % confidence limits: 10–19 %) by the calcium channel blocker which was not different from the 13 % (8–18 %) change obtained with the other classes. The reduction of left ventricular mass resulted from wall thinning with unchanged internal diameter. Moreover, the changes in left ventricular structure were similar in the 4 reports in which dihydropyridine calcium channel blockers were directly compared to angiotensin converting enzyme inhibitors, which are often considered to be superior to other drug classes with regard to the reduction of left ventricular mass. More recent studies [7, 8] confirmed these findings so that it can be convincingly concluded that dihydropyridine calcium channel blockers reduce left ventricular mass and that they are at least as effective as other drug classes in this respect, including converting enzyme inhibitors.

Influence on morbidity and mortality

The major purpose of the treatment of hypertension is to reduce cardiovascular complications, such as stroke, myocardial infarction, heart failure and sudden death. Whereas the first controlled outcome trials were performed with diuretics and beta-blockers, more recent trials have used dihydropyridine calcium channel blockers as first-line therapy. One trial was performed in elderly patients with both systolic and diastolic hypertension [9], two other trials in the elderly with isolated systolic hypertension [10, 11]. Whereas all three trials have been placebo-controlled only one used proper randomization [10], the other two alternative allocation to the active-treatment and placebo groups [9, 11]. Table 1 summarizes some characteristics of these trials and the study populations.

Table 1. Characteristics of outcome trials on dihydropyridine calcium channel blockers

	Stone [9]	Syst-Eur [10]	Syst-China [11]
Number of patients	1632	4695	2394
Selection criteria			
age (yr)	60–79	≥ 60	≥ 60
gender	m + f	m + f	m + f
blood pressure: systolic	160–219	160–219	160–219
(mmHg) diastolic	96–124	< 95	< 95
Treatment: first	nifedipine	nitrendipine	nitrendipine
second	captopril	enalapril	captopril
third	dihydrochloro-thiazide	hydrochloro-thiazide	hydrochloro-thiazide
Patient characteristics			
age (yr)	66	70	67
gender (% men)	47	33	64
blood pressure: systolic	169	174	170
diastolic	98	85	86

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The Stone-trial [9] included 1632 men and women with systolic-diastolic hypertension. The study started with a placebo run-in period. The patients were alternatively allocated to the active-treatment or to the placebo group at the beginning rather than at the end of the run-in period. Active treatment consisted of long acting nifedipine, 20 to 60 mg per day. Patients allocated to the placebo group could be switched to the active-treatment group by the attending physicians in case of severe hypertension, ie, diastolic blood pressure ≥ 110 mm Hg. In addition, all patients, including those in the placebo group, could receive active treatment, consisting of captopril or dihydrochlorothiazide, or both, for better blood pressure control. In a collaborative effort of the Chinese trialists and investigators from Montreal, the Stone study was analysed in several different ways, in which various unorthodox aspects of the design were taken into account.

The primary analysis related to the endpoints of the study which occurred in the placebo and nifedipine groups assessed by original treatment assignment, including subjects receiving comedication. The relative risk for combined cardiovascular events, which included stroke, heart failure, myocardial infarction and severe arrhythmias, was significantly reduced by 62 % by active medication. The reduction of stroke was significant and amounted to 57 % when considered separately. Non-cardiovascular events were also reduced by 58 % ($p < 0.05$). The differences between the two groups in all-cause (–45 %) and cardiovascular mortality (–26 %) did not reach conventional levels of statistical significance. These results were achieved with a systolic/diastolic blood pressure difference between the two treatment arms of 9.3/5.6 mmHg. Other analyses, ie, the on-treatment approach and analyses with exclusion of the second- and third-line active treatment yielded similar results. The trialists therefore concluded that nifedipine-based active antihypertensive therapy reduced the incidence of stroke and of cardiovascular events in elderly patients with systolic-diastolic hypertension.

The Syst-Eur trial [10] was a randomized placebo-controlled outcome trial in elderly patients with isolated systolic hypertension. Its main characteristics are given in Table 1. Patients at least 60 years old were started on masked placebo. At three run-in visits 1 month apart, their average sitting systolic blood pressure was 160–219 mmHg with a diastolic pressure lower than 95 mmHg. After stratification per centre, sex and previous cardiovascular complications, 4695 patients were randomly assigned to nitrendipine 10–40 mg daily, with the possible addition of enalapril 5–20 mg daily and hydrochlorothiazide 12.5–25 mg daily, or matching placebos. At a median of 2 years' follow-up, sitting systolic and diastolic blood pressures had fallen by 13 mmHg and 2 mmHg in the placebo group (n = 2297) and by 23 mmHg and 7 mmHg in the active-treatment group (n = 2398). The between-group differences were systolic 10.1 mmHg and diastolic 4.5 mmHg. The results on outcome are summarized in Table 2. Active treatment reduced the primary trial endpoint, ie, the incidence of fatal and non-fatal strokes, from 13.7 to 7.9 endpoints per 1000 patient-years (42 % reduction; $p = 0.003$). In the active-treatment group, all fatal and non-fatal cardiac endpoints including heart failure, myocardial infarction and sudden death declined by 26 % ($p = 0.03$). Cardiovascular mortality was slightly lower on active treatment (–27 %; $p = 0.07$), but all-cause mortality was not affected (–14 %; $p = 0.22$). Results were similar for the per-protocol or on-treatment analysis, except that also total mortality was significantly reduced in the patients who remained on study treatment (–26 %; $p = 0.05$) [12]. According to the intention-to-treat analysis, active treatment of 1000 patients for 5 years could prevent 29 strokes and 53 major cardiovascular events.

Table 2. Difference in risk, expressed as percent rate, for fatal and non-fatal events and for fatal events between the active-treatment group and the placebo group

Nature of event	Fatal and nonfatal events % rate (95% CL) P	Fatal events % rate (95% CL) P
All causes	–	–14 (–33 to +9) = 0.22
Cardiovascular	–31 (–54 to –14) < 0.001	–27 (–48 to +2) = 0.07
– cardiac	–26 (–44 to –3) = 0.03	–27 (–51 to +11) = 0.14
– heart failure	–29 (–53 to +10) = 0.12	–24 (–70 to +93) = 0.57
– myocardial infarction	–30 (–56 to +9) = 0.12	–56 (–82 to +9) = 0.08
– sudden death	–	–12 (–49 to +52) = 0.65
– stroke	–42 (–60 to –17) = 0.003	–27 (–62 to +39) = 0.33
Non-cardiovascular	–	–1 (–31 to +41) = 0.95
– cancer	–15 (–38 to +16) = 0.29	–31 (–63 to +26) = 0.22

In view of the concerns about the use of calcium channel blockers as first-line antihypertensive therapy, the Syst-Eur investigators explored to which extent nitrendipine administered alone prevented cardiovascular complications [13]. Of the 2398 actively treated patients, 1327 took only nitrendipine (average dose 23.4 mg/day) and 1042 progressed to other treatments, including nitrendipine (n = 757; 35.7 mg/day), enalapril (n = 783; 13.4 mg/day) and/or hydrochlorothiazide (294; 21.0 mg/day); 29 patients randomized to active treatment were untreated or their treatment status was unreported. Compared with the whole placebo group (n = 2297), patients on monotherapy with nitrendipine had 25 % ($p = 0.05$) fewer cardiovascular endpoints, and those progressing to other active treatments showed decreases ($p < 0.01$) in total mortality (40 %), stroke (59 %) and all cardiovascular endpoints (39 %). Among the control patients, 863 used only the first-line placebo. Compared with this subgroup, patients on monotherapy with nitrendipine showed a nearly 50 % ($p \leq 0.004$) reduction of all types of endpoints, including total and cardiovascular mortality. The full relative benefit from nitrendipine was seen as early as 6 months after randomization. To ascertain that the benefit conferred by the dihydropyridine was not due to selection bias, the 1327 patients remaining on monotherapy with nitrendipine were matched by sex, age, previous cardiovascular complications and systolic blood pressure at entry with an equal number of placebo patients. In this analysis, nitrendipine reduced ($p < 0.05$) cardiovascular mortality by 41 %, all cardiovascular endpoints by 33 %, and fatal and nonfatal cardiac endpoints by 33 %. In spite of the limitations inherent to 'post-hoc' analyses, these findings suggest that the calcium channel blocker nitrendipine, given as a single antihypertensive medication, prevents cardiovascular complications in older patients with isolated systolic hypertension.

The Syst-China trial [11] was a placebo-controlled trial in elderly Chinese patients with isolated systolic hypertension. As summarized in Table 1, the general aspects of the trial and the selection criteria were similar to those of the Syst-Eur study, except for the allocation procedure and the choice of the converting enzyme inhibitor. After stratification for centre, sex and previous cardiovascular complications, alternate patients (n = 1253) were assigned nitrendipine at 10–40 mg daily, with the addition of captopril at 12.5–50 mg daily or hydrochlorothiazide at 12.5–50 mg daily, or both, if goal blood pressure had not been reached. In the remaining 1141 control patients, matching placebos were administered similarly. After 2 years of follow-up, sitting systolic and diastolic blood pressures had fallen by 10.9 mmHg and 1.9 mmHg in the placebo group and by 20.0 mmHg and 5.0 mmHg in the active treatment group, the intergroup differences being 9.1 mmHg systolic and 3.2 mmHg diastolic. Active treatment reduced all fatal

and nonfatal cardiovascular endpoints by 37 % (p = 0.004) and total strokes by 38 % (p = 0.01). All-cause mortality decreased by 39 % (p = 0.003), cardiovascular mortality by 39 % (p = 0.03) and fatal stroke by 58 % (p = 0.02). Treatment of 1000 patients for 5 years could prevent 55 deaths, 39 strokes or 59 major cardiovascular events.

Calcium channel blockers and diabetes

Hypertension and diabetes are often associated, and the combination of the two renders the patient particularly prone to cardiovascular complications. In a post-hoc analysis of the Syst-Eur study, the influence of the dihydropyridine calcium channel blocker nitrendipine on outcome was compared in diabetic and nondiabetic patients [14]. Based on a history of diabetes, treatment with antidiabetic drugs and/or blood glucose levels of ≥ 7.8 mmol/L in fasting patients and ≥ 11.1 mmol/L in nonfasting patients, 10.5 % of the patients were classified as having diabetes. Age and gender distribution were similar in diabetics (n = 492) and nondiabetics (n = 4203) but diabetics had higher systolic pressure (175.3 vs 173.7 mmHg), lower diastolic pressure (84.5 vs 85.6 mmHg) and more cardiovascular complications at entry, as well as higher blood glucose, lower HDL-cholesterol, higher serum triglycerides, and a higher prevalence of proteinuria (p < 0.001 for all); serum creatinine was similar in the two subgroups. The net difference in blood pressure between active treatment and placebo was similar in diabetics and nondiabetics. Diabetes was a significant risk factor in these elderly patients with isolated systolic hypertension. In the placebo group, the rate of cardiovascular mortality during follow-up was 12 deaths per 1000 patient-years in the nondiabetics and 45 in the diabetics. The incidence of fatal and nonfatal cardiovascular endpoints combined amounted to 31 and 58 events per 1000 patient-years, respectively. The relative benefit of active treatment on mortality and all cardiovascular events is summarized in Table 3. Moreover, by use of Cox regression analysis and with adjustment for age, gender, systolic blood pressure, smoking and cardiovascular complications at entry, it could even be shown that the effect of active treatment was significantly greater in diabetics than in nondiabetics for all-cause mortality (p = 0.04), mortality from cardiovascular causes (p = 0.02) and for all cardiovascular events (p = 0.01). In view of the high incidence of cardiovascular complications and the favourable relative effect of active therapy, it could be calculated that the absolute benefit of nitrendipine-based treatment was particularly high in diabetics: treatment of 1000 patients for 5 years prevented 97 cardiovascular deaths, 178 cardiovascular events and 91 strokes in diabetics; by contrast, these numbers were only 10, 39 and 22, respectively, in nondiabetics.

In the Syst-China trial, only 4.1 % of the patients had diabetes [15]. As in Syst-Eur they were at higher risk for cardiovascular complications that the nondiabetics. The incidence of cardiovascular mortality and of fatal and nonfatal cardiovascular events was indeed about three times higher in the presence of diabetes. The relative benefit of treatment in diabetics and nondiabetics, which is summarized in Table 3, was not significantly different according to diabetic status. However, in terms of absolute risk reduction, it could be calculated that the number of events prevented per 1000 diabetic patients treated for 5 years amounted to 95 for cardiovascular death, 221 for all cardiovascular events and 100 for stroke, whereas these figures were 25, 51 and 35 in nondiabetics.

Other trials have compared the effects of dihydropyridine calcium channel blockers and of converting enzyme inhibitors and found that outcome was better with the latter drugs [16, 17]. In the absence of a control group, these results do not necessarily mean that calcium channel blockers do not favourably affect outcome, just that converting enzyme inhibitors might be better. However, the results of both studies have to be interpreted with caution because the effect on cardiovascular complications was only a secondary and not a primary endpoint. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial [16] was designed to study changes in creatine clearance and to compare more intense versus less intense reduction of blood pressure. The trial was stopped prematurely in the hypertensive arm because of a significantly higher incidence of fatal and nonfatal cases of myocardial infarction in the group of patients randomly assigned to treatment with nisoldipine (25 cases) than in the group treated with enalapril (5 cases). Several additional criticisms have been raised. More patients in the enalapril group received diuretics and beta-blockers than in the nisoldipine group and more patients in the nisoldipine group stopped taking the study medication. Furthermore, about 40 % of the patients stopped the study medication and information on initial cardiovascular events was not reported.

The primary aim of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) [17] was to assess the effects of fosinopril and of amlodipine on serum lipids and diabetes control in hypertensive patients with non-insulin-dependent diabetes mellitus. Whereas the authors failed to find differences between the treatment arms in these endpoints, cardiovascular events, ie, the combination of stroke, myocardial infarction and hospitalized angina, occurred less frequently in patients receiving fosinopril than in patients randomized to amlodipine. There were no significant differences for these endpoints taken separately, but unlike the findings in the ABCD trial, the differences in outcome between the two groups were accounted for by hospitalization for angina and stroke, and not by myocardial infarction. Other critiques on this trial were its open design and the fact that information on events was obtained by asking the patients about their occurrence. Finally the interpretation is complicated by the fact that about 30 % of the patients received both treatments because of insufficient blood pressure control.

Table 3. Difference in risk, expressed as percent rate, for fatal and nonfatal events between the active-treatment group and the placebo group in diabetics and nondiabetics

	SYST-EUR				SYST-CHINA			
	Diabetics		Nondiabetics		Diabetics		Nondiabetics	
	% rate	p	% rate	p	% rate	p	% rate	p
Mortality								
– all causes	–41	0.09	–8	0.55	–37	0.40	–39	0.005
– cardiovascular	–70	0.37	–16	0.37	–43	0.38	–37	0.06
Fatal and non-fatal endpoints								
– all cardiovascular	–62	0.002	–25	0.02	–59	0.09	–33	0.01
– stroke	–69	0.02	–36	0.02	–45	0.36	–37	0.03
– cardiac events	–57	0.06	–22	0.10	–75	0.13	–30	0.21

Acknowledgements

The secretarial assistance of N. Ausseloos is gratefully acknowledged.

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