Articles

Randomised trial of effects of calcium antagonists compared with diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study

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Summary

Background Calcium antagonists are a first-line treatment for hypertension. The effectiveness of diltiazem, a non-dihydropyridine calcium antagonist, in reducing cardiovascular morbidity or mortality is unclear. We compared the effects of diltiazem with that of diuretics, β-blockers, or both on cardiovascular morbidity and mortality in hypertensive patients.

Methods In a prospective, randomised, open, blinded endpoint study, we enrolled 10 881 patients, aged 50–74 years, at health centres in Norway and Sweden, who had diastolic blood pressure of 100 mm Hg or more. We randomly assigned patients diltiazem, or diuretics, β-blockers, or both. The combined primary endpoint was fatal and non-fatal stroke, myocardial infarction, and other cardiovascular death. Analysis was done by intention to treat.

Findings Systolic and diastolic blood pressure were lowered effectively in the diltiazem and diuretic and β-blocker groups (reduction 20·3/18·7 *vs* 23·3/18·7 mm Hg; difference in systolic reduction p<0·001). A primary endpoint occurred in 403 patients in the diltiazem group and in 400 in the diuretic and β-blocker group (16·6 *vs* 16·2 events per 1000 patient-years; relative risk 1·00 [95% CI 0·87–1·15], p=0·97). Fatal and non-fatal stroke occurred in 159 patients in the diltiazem group and in 196 in the diuretic and β-blocker group (6·4 *vs* 7·9 events per 1000 patient-years; 0·80 [0·65–0·99], p=0·04) and fatal and non-fatal myocardial infarction in 183 and 157 patients (7·4 *vs* 6·3 events per 1000 patient-years; 1·16 [0·94–1·44], p=0·17).

Interpretation Diltiazem was as effective as treatment based on diuretics, β-blockers, or both in preventing the combined primary endpoint of all stroke, myocardial infarction, and other cardiovascular death.

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Introduction

The scientific background and rationale of the Nordic Diltiazem (NORDIL) study have been published previously.[1] In brief, calcium antagonists have been used extensively to treat hypertension for more than 15 years and are among the compounds listed as first-line treatment in the 1989 WHO/International Society of Hypertension guidelines for the management of mild hypertension.[2] A large trial that compared several classes of antihypertensive compounds in 1993, reported that diltiazem was more effective in lowering blood pressure than the other drugs.[3] In addition, many observations on intermediary endpoints, especially reversal of left-ventricular hypertrophy, a powerful risk indicator in hypertension,[4,5] showed that a calcium-antagonist-based antihypertensive regimen was more effective than regimens based on diuretics, β-blockers, or both.[6,7] Later meta-analyses showed calcium antagonists to be as effective as angiotensin-converting-enzyme (ACE) inhibitors.[8,9] Such findings suggested that calcium antagonists ought to be at least as effective as diuretics or β-blockers in lowering cardiovascular risks.

No data from prospective randomised intervention trials have, however, shown that antihypertensive treatment with calcium antagonists decreased cardiovascular morbidity and mortality, as had been shown for diuretics and β-blockers in 13 previous trials of this kind.[10] The first such trial data were reported in the Shanghai trial of nifedipine in the elderly (STONE),[11] and the Systolic Hypertension in Europe (Syst-Eur) trial[12] and the Systolic Hypertension in China (Syst-China) trial.[13] The latter two trials showed that a nitrendipine-based regimen significantly lowered the frequency of stroke compared with placebo. Moreover, the Swedish Trial in Old Patients with Hypertension-2 (STOP-2)[14] reported that elderly hypertensive patients were equally well protected by a regimen that included the dihydropyridine calcium antagonists felodipine and isradipine as by a conventional regimen based on diuretics, β-blockers, or both, or an ACE-inhibitor-based strategy. We started the NORDIL trial in 1992 before these data were published. All of the currently available trial data with calcium antagonists are in elderly hypertensive patients,[11–14] and mainly in patients

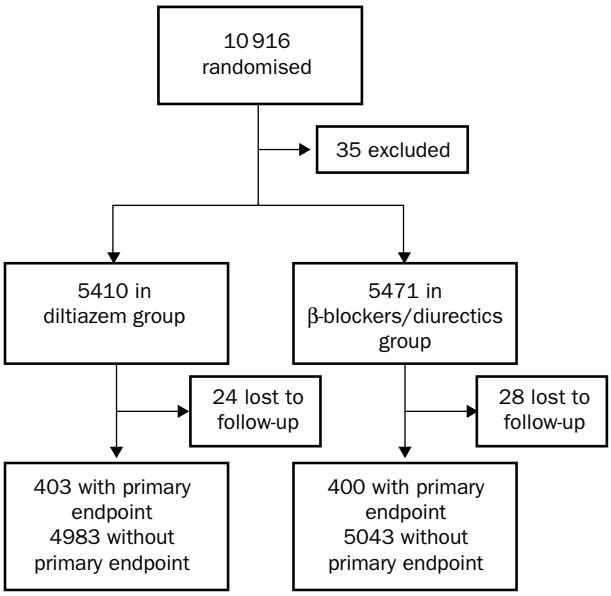


Figure 1: **Trial profile**

with isolated systolic hypertension.[12,13] Moreover, all those studies were of dihydropyridine-derived calcium antagonists[11–14] and three of the four trials showed efficacy compared only with placebo.[11–13] We did the NORDIL study, a prospective, randomised, open trial with blinded-endpoint evaluation (PROBE), which reflects routine clinical practice,[15,16] to compare the effects of diltiazem, a non-dihydropyridine calcium antagonist, with diuretics, β-blockers, or both in middle-aged patients with hypertension.

Methods

Patients

We recruited patients from Oct 9, 1992, to Oct 31, 1999 from 1032 health centres in Norway and Sweden. The baseline data for patients and the effect of treatment on blood pressure have been published previously.[17] Eligible patients had diastolic blood pressure of 100 mm Hg or more on two occasions, were aged 50–69 years (extended to 74 years during the trial), and were previously untreated. Previously treated patients could be included if they had blood pressure of 100 mm Hg or more on two consecutive visits, at least 1 week apart, during a run-in period when no antihypertensive treatment was given.

	Diltiazem group (n=5410)	Diuretics and β-blocker group (n=5471)
Demography		
Number of women	2786 (51·5%)	2805 (51·3%)
Age (years)	60·5 (6·5)	60·3 (6·5)
Clinical characteristics		
Body-mass index (kg/m²)	27·8 (4·4)	27·8 (4·3)
Systolic blood pressure (mm Hg)	173·5 (17·7)	173·4 (17·5)
Diastolic blood pressure (mm Hg)	105·8 (5·3)	105·7 (5·3)
Heart rate (beats/min)	74·6 (10·4)	74·9 (10·4)
Serum cholesterol (mmol/L)	6·45 (1·20)	6·40 (1·19)
Serum triglycerides (mmol/L)	1·78 (1·20)	1·80 (1·09)
Blood glucose (mmol/L)	5·24 (1·49)	5·27 (1·49)
Serum creatinine (mmol/L)	86·6 (17·9)	86·8 (16·9)
Previously untreated patients*	3070 (56·7%)	3062 (56·0%)
Smokers	1237 (22·9%)	1205 (22·0%)
Other disorders		
Previous myocardial infarction	112(2·1%)	118 (2·2%)
Previous other IHD	125 (2·3%)	141 (2·6%)
Previous stroke	74 (1·4%)	88 (1·6%)
Previous TIA	61 (1·1%)	64 (1·2%)
Previous atrial fibrillation	46 (0·9%)	55 (1·0%)
Diabetes mellitus	351 (6·5%)	376 (6·9%)

Data are mean (SD) unless shown otherwise. IHD=Ischaemic heart disease; TIA=transient ischaemic attacks. *No antihypertensive medication for at least 6 months before enrolment.

Table 1: **Baseline characteristics**

Time (months)	Diltiazem group	Diuretic and β-blocker group
0	173·5 (17·7)/105·8 (5·3)	173·4 (17·5)/105·7 (5·3)
6	156·2 (16·3)/90·2 (7·6)	153·5 (17·9) 90·4 (8·1)
12	156·3 (16·4)/90·0 (7·5)	153·1 (17·4)/90·1 (7·7)
24	155·2 (16·3)/88·8 (7·8)	151·5 (17·4)/88·6 (7·5)
36	154·7 (16·7)/88·4 (7·8)	151·2 (17·07)/88·2 (7·7)
48	153·2 (16·5)/87·8 (8·1)	150·3 (17·3)/87·7 (7·9)
60	152·2 (16·4)/87·6 (7·6)	149·1 (16·7)/87·4 (7·7)

Table 2: **Blood pressure (mm Hg) at baseline and during study**

Study design

We randomly assigned hypertensive patients, through a central randomisation centre, a diltiazem-based regimen or conventional antihypertensive treatment with diuretics, β-blockers, or both (figure 1). Investigators called the randomisation centre at Clinical Data Care in Lund, Sweden, to obtain randomisation numbers and treatment assignment. All patients could receive additional antihypertensive treatment in several steps to lower diastolic blood pressure to less than 90 mm Hg.[1]

In the diltiazem group, as step one, patients were given 180–360 mg diltiazem daily. Initially, we used a short-acting formulation. After 1997, this agent was replaced by a longer-acting formulation. In step two, an angiotensin-converting-enzyme (ACE) inhibitor was added, and in step three, a diuretic or α-blocker was added to the ACE inhibitor. Any other antihypertensive compound could be added as step four. In the diuretic and β-blocker group, step one was a thiazide diuretic or a β-blocker. In step two, the two were combined. In step three an ACE inhibitor or α-blocker was added. In step four, any other antihypertensive compound could be added except a calcium antagonist.

The combined primary endpoint was fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, and other cardiovascular death. All endpoints were assessed by an independent endpoint committee, according to strict and prespecified criteria for the

Class of drug	Diltiazem group	Diuretics and β-blocker group
Thiazide diuretics	222	726
Loop diuretics	369	458
Potassium-sparing diuretics	60	138
Fixed-ratio thiazides plus potassium-sparing diuretics	265	1044
Non-selective β-blockers	56	177
β_1-selective blockers	590	3336
α-blockers and β-blockers	40	122
Diltiazem	3849	77
Dihydropyridine calcium antagonists	261	375
Verapamil	22	18
ACE inhibitors	806	618
Fixed-ratio ACE inhibitors plus thiazide	167	221
AT_1 antagonists	391	418
Fixed-ratio AT_1 antagonist plus thiazide	96	124
α-blockers	183	241
Hydralazine or similar vasodilators	233	167
α-methyldopa or clonidine	2	3
No antihypertensive treatment	292	200

AT_1=angiotensin II, type 1 antagonist. Patients could take more than one drug.

Table 3: **Antihypertensive treatment at final visit**

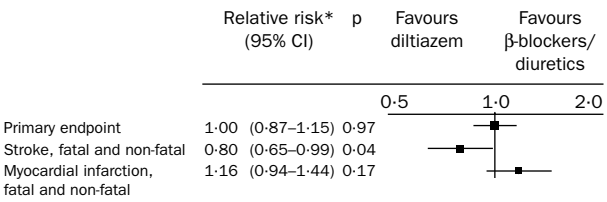


Figure 2: **Relative risk of cardiovascular endpoints**

approval of endpoints.[1] The members of the committee were unaware of treatment status and the blood pressures of patients with reported endpoints. The secondary endpoints were fatal plus non-fatal stroke and fatal plus non-fatal myocardial infarction.

Statistical methods

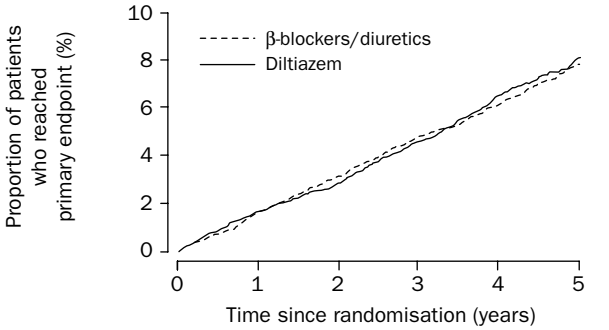
We calculated that 640 patients had to have a primary event to give the study 80% power to detect a 20% difference in the frequency of the primary endpoint, and designed the study accordingly. All p values were two-sided at a 5% significance level. Analysis was done by intention to treat. We used Cox's regression analysis to calculate relative risks with 95% CI, with use of time since randomisation as non-parametrically modelled time variable. The model was adjusted for sex, and baseline age, systolic blood pressure, and diabetes and smoking status. We compared the proportion of patients who reached the primary endpoint in the two groups with Kaplan-Meier curves. We did all calculations on Stata software (version 6).

Results

10 916 patients were randomised (figure 1). After randomisation, one centre (with 35 patients) was excluded because of uncertainty about data quality. 5290 men and 5591 women with a mean age of 60 years, therefore, remained in the study (figure 1). Of the 10 881 patients, 7108 were recruited in Sweden and 3773 in Norway. Patients were studied at primary-health-care centres by their normal physicians, but several doctors at local hospitals, who had an interest in hypertension, nephrology, or cardiology, served as local coordinators. The characteristics of the two groups were well balanced (table 1).

The mean follow-up was 4·5 years and 48 992 patient-years were accumulated. Of the 10 881 randomised patients, 52 (0·5%) were lost to follow-up (figure 1), but complete information on fatal events was available for 31 of these at the end of the trial.

Blood pressure at baseline was similar in the two treatment groups, as was previous cardiovascular



Patients at risk

β-Blockers/ diuretics	5471	5363	5244	4975	3486	1921
Diltiazem	5410	5299	5217	4932	3409	1865

Figure 3: **Kaplan-Meier curves of proportion of patients in each group who reached primary endpoint**

morbidity, including diabetes mellitus (table 1). Blood pressures during the study are shown in table 2.

The mean blood pressure during the study was 154·9/88·6 mm Hg in the diltiazem group, and 151·7/88·7 mm Hg in the diuretic and β-blocker group. Among patients who remained in the study for at least 24 months, the mean reductions in systolic and diastolic blood pressures from baseline to the last follow-up visit were 20·3/18·7 mm Hg in the diltiazem group and 23·3/18·7 mm Hg in the diuretic and β-blocker group (difference in systolic blood pressure p<0·001, table 2).

At the end of the trial, 50% of all patients in the diltiazem group were still taking their randomised monotherapy, compared with 45% in the diuretic and β-blocker group. In the diltiazem group 77% of all patients remained on their randomised treatment (diltiazem plus additions) compared with 93% in the diuretic and β-blocker group (which could consist of diuretics or β-blockers, or diuretics plus β-blockers plus additions, table 3). 283 patients in the diltiazem group were taking other calcium antagonists. This additional treatment did not affect the results, and these patients were included in the intention-to-treat analysis.

The primary endpoint occurred in 403 patients in the diltiazem group and in 400 patients in the diuretic and β-blocker group (16·6 *vs* 16·2 events per 1000 patient-years; relative risk 1·00 [95% CI 0·87–1·15], p=0·97, figure 2). The proportion of patients who reached the primary endpoint in the two groups was similar (figure 3).

Fatal plus non-fatal stroke occurred in 159 patients in the diltiazem group and in 196 in the diuretic and β-blocker group (6·4 *vs* 7·9 events per 1000 patient-years;

	Number of patients with events		Event rate per 1000 patient-years		Relative risk (95% CI)*	p
	Diltiazem group	Diuretics and β-blocker group	Diltiazem group	Diuretics and β-blocker group		
Primary endpoint	403	400	16·6	16·2	1·00 (0·87–1·15)	0·97
All stroke	159	196	6·4	7·9	0·80 (0·65–0·99)	0·04
Fatal stroke	21	22	0·8	0·9	0·96 (0·52–1·74)	0·89
All stroke plus TIA	200	236	8·1	9·5	0·84 (0·70–1·01)	0·07
All myocardial infarction	183	157	7·4	6·3	1·16 (0·94–1·44)	0·17
Fatal myocardial infarction	28	25	1·1	1·0	1·10 (0·64–1·88)	0·74
Cardiovascular death	131	115	5·2	4·5	1·11 (0·87–1·43)	0·41
Total mortality	231	228	9·2	9·0	1·00 (0·83–1·20)	0·99
All cardiac events	487	470	20·2	19·2	1·04 (0·91–1·18)	0·57
Diabetes mellitus	216	251	9·4	10·8	0·87 (0·73–1·04)	0·14
Atrial fibrillation	105	128	4·2	5·1	0·82 (0·64–1·07)	0·14
CHF	63	53	2·5	2·1	1·16 (0·81–1·67)	0·42

TIA=transient ischaemic attack; CHF=congestive heart failure. *Cox's regression model adjusted for age, sex, systolic pressure, and baseline status of diabetes mellitus and smoking.

Table 4: **Relative risk and occurrence of endpoints**

Adverse event	Diltiazem group	Diuretics and β-blocker group
Dizziness	505 (9·3%)	488 (8·9%)
Arthralgia	418 (7·7%)	391 (7·1%)
Headaches*	458 (8·5%)	311 (5·7%)
Chest discomfort	310 (5·7%)	322 (5·9%)
Coughing	303 (5·6%)	298 (5·4%)
Fatigue*	239 (4·4%)	353 (6·5%)
Back pain	253 (4·7%)	298 (5·4%)
Depression	198 (3·7%)	186 (3·4%)
Abdominal pain	187 (3·5%)	186 (3·4%)
Dyspnoea†	157 (2·9%)	212 (3·9%)
Myalgia	172 (3·2%)	188 (3·4%)
Impotence*	126 (2·3%)	202 (3·7%)

*p<0·001. †p=0·006.

Table 5: **12 most frequent adverse effects**

0·80 [0·65–0·99], p=0·04; figure 2). Fatal plus non-fatal myocardial infarction occurred in 183 patients in the diltiazem group and in 157 in the diuretic and β-blocker group (7·4 *vs* 6·3 events per 1000 patient-years; relative risk 1·16 [0·94–1·44], p=0·17; figure 2). No other endpoint differed significantly between groups (table 4).

Adverse events were those reported in answer to open active questioning at every visit and were not restricted to those thought to be associated with the drugs taken. Complaints were coded in accordance with WHO's code system (table 5). We present only the 12 most frequently reported adverse events or symptoms and did not include symptoms present at the time of randomisation unless they reappeared later. The frequency of four adverse events was significant—headache (p<0·001), fatigue (p<0·001), dyspnoea (p=0·006), and impotence (p<0·001).

727 patients had type 2 (non-insulin dependent) diabetes mellitus at baseline. No endpoint differed between the two treatment groups in this subgroup of patients (table 6).

Discussion

Although we used the PROBE design for the study, which aims to create conditions similar to clinical practice,[15] inclusion in an intervention trial of this kind, with the special attention that follows, may positively affect results. In analysis of prevention of the combined primary endpoint of all stroke, myocardial infarction, and cardiovascular death, the two treatment approaches were almost indistinguishable, with a relative risk of 1·00. 803 patients had such events, which gave the study an 88% power to detect a difference between groups.

The diltiazem regimen was, however, significantly more effective than the diuretic and β-blocker regimen in lowering the rate of all stroke. This finding could be due to chance, in view of the many statistical comparisons that were made.

Other reports have shown that diltiazem possibly provides a higher success rate in the lowering of blood pressure in hypertensive patients than atenolol, clonidine, prazosin, captopril, hydrochlorothiazide, or placebo[3] but in our study the reduction in diastolic blood pressure was identical and in the two groups, and for systolic blood pressure was significantly greater (3 mm Hg) in the diuretics and β-blocker group than in the diltiazem group. This difference could have been due to underdosing of diltiazem, given the results reported in a previous comparative trial.[3]

A 3 mm Hg difference in the reduction in blood pressure should have a demonstrable effect on the frequency of stroke.[10] The magnitude of effect can be compared, such as in the meta-analysis done by Collins and colleagues.[10] In that analysis of 13 intervention trials, a 10 mm Hg difference in systolic blood pressure was associated with a 42% lower risk of stroke. If such a relation between systolic blood pressure and the risk of stroke had existed in our study, the risk would have been 12% higher than that expected in the diltiazem group, and not the 20% lower frequency we saw.

Conceivably, diltiazem could offer advantages over dihydropyridine-derived calcium antagonists in lowering the rate of cardiovascular complications. One potential mechanism could be via reversal of left-ventricular hypertrophy, a strong predictor of several cardiovascular events, including stroke.[4,5] The lesser sympathetic activation with diltiazem than with dihydropyridine-derived calcium antagonists[18] could be an advantage. The analysis of α-blocker group taking doxasozin in the continuing Antihypertensive and Lipid-Lowering Heart Attack Trial (ALLHAT)[19] was stopped early because of a higher frequency of major cardiovascular events in the doxazosin group than in the chlorthalidone group. This finding has led to suggestions that α-blockers should become a second-choice treatment for hypertension.[20] It is unclear whether the lower efficacy in preventing cardiovascular morbidity in the doxazosin group was because, at the given dose, the reduction in systolic blood pressure was 3 mm Hg less than that in the diuretic group, or whether other mechanisms played a part. In our study, 183 compared with 241 patients were taking α-blocker, generally doxazosin, in addition to their randomised medication. The low frequency of doxazosin use, and the use of such treatments in a similar proportion of patients in each group suggests that concomitant intake of α-blockers did not affect our results.

No other endpoint differed significantly between the two treatment groups or between patients with type 2 diabetes mellitus at baseline. These results might seem

	Number of events		Event rate per 1000 patient-years		Relative risk (95% CI)*	p
	Diltiazem	Diuretics and β-blocker group	Diltiazem	Diuretics and β-blocker group		
Primary endpoint	44	44	29·8	27·7	1·01 (0·66–1·53)	0·98
All stroke	20	20	13·3	12·3	0·97 (0·52–1·81)	0·92
Fatal stroke	1	3	0·6	1·8	0·29 (0·03–2·86)	0·29
All stroke plus TIA	20	23	13·3	14·2	0·85 (0·46–1·55)	0·6
All myocardial infarction	17	18	11·2	11·1	0·99 (0·51–1·94)	0·99
Fatal myocardial infarction	5	2	3·2	1·2	2·45 (0·47–12·8)	0·29
Cardiovascular death	15	13	9·7	7·8	1·16 (0·55–2·44)	0·71
Total mortality	28	26	18·1	15·6	1·07 (0·63–1·84)	0·80
All cardiac events	54	52	37·2	33·3	1·04 (0·71–1·53)	0·82
Atrial fibrillation	9	14	5·9	8·5	0·63 (0·27–1·46)	0·28
CHF	13	7	8·5	4·2	1·46 (0·57–3·72)	0·43

TIA=transient ischaemic attack; CHF=congestive heart failure. *Cox's regression model adjusted for age, sex, systolic pressure, and smoking.

Table 6: **Relative risk and occurrence of endpoints in patients with diabetes mellitus at baseline**

different from those in a meta-analysis of calcium-antagonist trials in hypertensive diabetic patients,[21] but most of those studies compared calcium antagonists with placebo. In comparisons of diuretics and β-blockers with ACE inhibitors in hypertensive patients with type 2 diabetes mellitus, the results differ. The CAPPP study[22] showed that several cardiovascular complications were better prevented with regimens based on ACE inhibitors than those based on diuretics and β-blockers, whereas the United Kingdom Prospective Diabetes (UKPDS) study[23] showed no difference between such regimens. This discrepancy might be explained by the different blood pressures that were attained in the CAPPP and UKPDS studies. Our findings agree with those of the STOP-Hypertension-2 study, in which cardiovascular morbidity did not differ between the calcium antagonist regimen and the diuretic and β-blocker regimen in patients with type 2 diabetes at baseline (to be published).

The two treatments were equally well tolerated. The finding that 77% of patients in the diltiazem group remained on their randomised treatment compared with 93% in the diuretic and β-blocker group probably reflects that only one drug in the diltiazem group qualified as randomised but in the other group, randomised treatment could be a diuretic or a β-blocker. Leg oedema and flushing, common side-effects of dihydropyridine-derived calcium antagonists, were not among the 12 most common adverse events in the diltiazem group.

Antihypertensive treatment with a diltiazem-based regimen did not affect total mortality or the sum of major cardiovascular events differently from a thiazide diuretic and β-blocker regimen.

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