# Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT)

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## Summary

**Background** The efficacy of antihypertensive drugs newer than diuretics and β-blockers has not been established. We compared the effects of the calcium-channel blocker nifedipine once daily with the diuretic combination co-amilozide on cardiovascular mortality and morbidity in high-risk patients with hypertension.

**Methods** We did a prospective, randomised, double-blind trial in Europe and Israel in 6321 patients aged 55–80 years with hypertension (blood pressure ⩾150/95 mm Hg, or ⩾160 mm Hg systolic). Patients had at least one additional cardiovascular risk factor. We randomly assigned patients nifedipine 30 mg in a long-acting gastrointestinal-transport-system (GITS) formulation (n=3157), or co-amilozide (hydrochlorothiazide 25 μg plus amiloride 2·5 mg; n=3164). Dose titration was by dose doubling, and addition of atenolol 25–50 mg or enalapril 5–10 mg. The primary outcome was cardiovascular death, myocardial infarction, heart failure, or stroke. Analysis was done by intention to treat.

**Findings** Primary outcomes occurred in 200 (6·3%) patients in the nifedipine group and in 182 (5·8%) in the co-amilozide group (18·2 *vs* 16·5 events per 1000 patient-years; relative risk 1·10 [95% CI 0·91–1·34], p=0·35). Overall mean blood pressure fell from 173/99 mm Hg (SD 14/8) to 138/82 mm Hg (12/7). There was an 8% excess of withdrawals from the nifedipine group because of peripheral oedema (725 *vs* 518, p<0·0001), but serious adverse events were more frequent in the co-amilozide group (880 *vs* 796, p=0·02). Deaths were mainly non-vascular (nifedipine 176 *vs* co-amilozide 172; p=0·81). 80% of the primary events occurred in patients receiving randomised treatment (157 nifedipine, 147 co-amilozide, difference 0·33% [−0·7 to 1·4]).

**Interpretation** Nifedipine once daily and co-amilozide were equally effective in preventing overall cardiovascular or cerebrovascular complications. The choice of drug can be decided by tolerability and blood-pressure response rather than long-term safety or efficacy.

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*See Commentary page xxxx*

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## Introduction

Results from trials of antihypertensive treatment in the 1970s and 1980s showed that reduction of blood pressure, mainly by use of diuretics and β-blockers, prevented stroke but did not yield the expected reduction in overall cardiovascular complications.[1] The question arose of whether this finding was attributable to undesirable properties of the available drugs or reflected a weaker contribution of hypertension to myocardial infarction than to stroke. Studies in elderly patients, mainly with isolated systolic hypertension, raised less concern about the drugs used but did not provide full reassurance about efficacy in younger patients.[2] However, placebo-controlled outcome studies of new drugs in patients in whom blood-pressure reduction had already been shown to prevent stroke were no longer ethical. The alternative, comparison of two active treatments, is expensive because of the large numbers of patients required. One solution has been to undertake open-label comparisons.[3,4]

The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) is a double-blind randomised trial of morbidity and mortality, in which the comparison is between older and newer classes of antihypertensive drugs in patients at high absolute risk of cardiovascular events. These patients are the main target for treatment in modern guidelines.[5,6] Our primary objective was to compare the efficacy in preventing the major complications from hypertension of nifedipine, a calcium-channel blocker, administered in a long-acting gastrointestinal-transport-system (GITS) formulation and co-amilozide a common and effective combination of the diuretics hydrochlorothiazide and amiloride.[7,8]

## Methods

### *Study population*

Between September, 1994, and June, 1996, inclusive, we enrolled mainly white hypertensive men and women, aged 55–80 years, from 703 centres in eight countries in western Europe and Israel. Hypertension was defined as systolic blood pressure 150 mm Hg or more and diastolic blood pressure 95 mm Hg or more, or systolic blood pressure 160 mm Hg or more. To increase the number of events expected, we required that, as well as hypertension, patients have at least one additional cardiovascular risk

| | Nifedipine (n=3157) | Co-amilozide n=3164) |
|---|---|---|
| **Demography** | | |
| Sex (M/F) | 1456 (46·1%)/ 1701 (53·9%) | 1473 (46·6%)/ 1691 (53·4%) |
| Age (years) | | |
| <60 | 759 (24·1%) | 703 (22·3%) |
| 60–70 | 1508 (47·9%) | 1554 (49·2%) |
| >70 | 883 (28·0%) | 902 (28·6%) |
| **Risk factor** | | |
| Hypercholesterolaemia | 1646 (52·1%) | 1644 (52·0%) |
| Smoker | 891 (28·2%) | 902 (28·5%) |
| Family history | 648 (20·5%) | 660 (20·9%) |
| Diabetes mellitus (types 1 or 2) | 649 (20·6%) | 653 (20·6%) |
| Left-ventricular hypertrophy | 338 (10·7%) | 336 (10·6%) |
| Coronary heart disease | 20 (6·6%) | 197 (6·2%) |
| Left-ventricular strain | 201 (6·4%) | 197 (6·2%) |
| Previous myocardial infarction | 195 (6·2%) | 188 (5·9%) |
| Peripheral vascular disease | 180 (5·7%) | 173 (5·5%) |
| Proteinuria | 98 (31·0%) | 72 (2·3%) |

Table 1: **Demography and additional risk factors**

factor of: hypercholesterolaemia (plasma total cholesterol ⩾6·43 mmol/L on study entry); smoker (⩾10 cigarettes per day currently or up to 1 year before entry); family history of myocardial infarction in parent or sibling before age 50 years; current left-ventricular hypertrophy, defined as current evidence confirmed by echocardiography; coronary heart disease, defined as stable angina or symptomless coronary heart disease, confirmed by coronary angiographic evidence or electrocardiographic changes on exercise testing; left-ventricular strain confirmed by electrocardiography strain pattern (down-sloping ST depression with inverted or biphasic T waves in lateral leads; peripheral vascular disease, defined as intermittent claudication, resting pain, or gangrene (Fontaine and Leriche classification stages 2–4); proteinuria (⩾0·5 g protein/24 h; table 1). Patients were followed up until June 30, 1999. The full study protocol is available at www.insight-study.com (accessed July 20, 2000).

### *Study design*

We used a prospective, double-blind, trial design with dynamic randomisation (sometimes called minimisation).[9] As well as the risk factors in table 1, randomisation also took into account patients' sex, age, and whether or not they were receiving aspirin. Randomisation was done after 4 weeks of placebo treatment, which could be shortened to 2 weeks in patients who had severe hypertension (blood pressure >180 mm Hg systolic or 110 mm Hg diastolic).

We randomly assigned patients initially nifedipine 30 mg daily, or co-amilozide (hydrochlorothiazide 25 mg amiloride 2·5 mg daily, figure 1). All patients received one active and one placebo tablet taken at the same time of day. There were four optional, dose-titration steps in patients whose blood pressure fell by less than 20/10 mm Hg or was higher than 140/90 mm Hg. These extra dose steps were: dose doubling of the randomised drug; addition of atenolol 25 mg daily (or enalapril 5 mg daily if atenolol contraindicated); dose-doubling of the additional drug; and addition of any other antihypertensive drug (other than calcium-channel blockers or diuretics). These titration steps could be done in that order at any visit from, respectively, weeks 2, 4, 8, and 12 after randomisation.

At follow-up visits, we measured blood pressure three times after 5 min of rest, with a mercury sphygmomanometer. After the initial dose-titration period, patients were seen three times a year, starting at 18 weeks after randomisation. At each visit, we measured blood

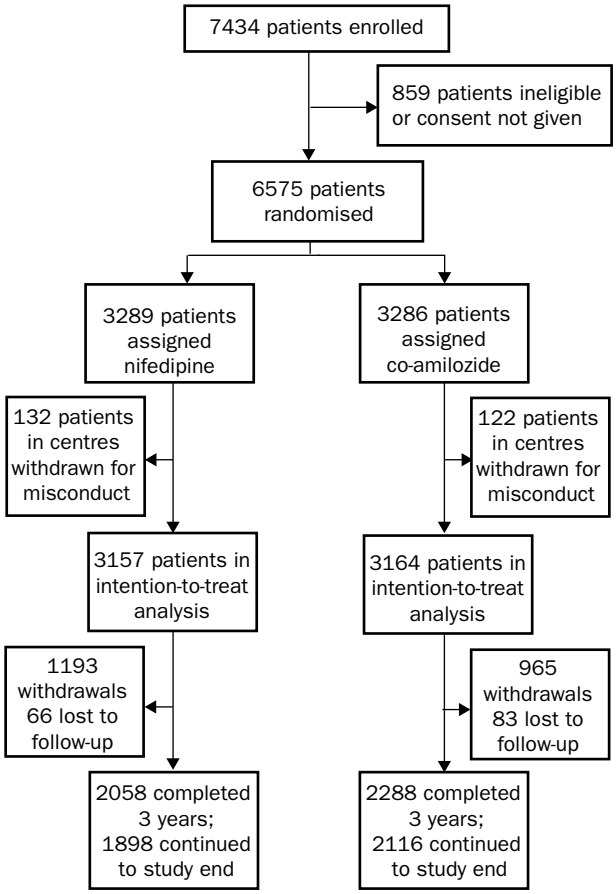



Figure 1: **Trial profile**

pressure and heart rate. Tablet counts were done at each visit and information on adverse events was collected. Laboratory tests were done during titration and annually, and electrocardiography was done annually.

An independent critical events committee assessed all endpoints according to prespecified criteria (listed at www.insight-study.com). The members of this committee were unaware of the treatment group and blood pressure of each patient. We did the study according to good clinical practice. All centres were monitored, in most countries by Quintiles or another independent company, and all source data were audited in 89 centres. The monitoring led to withdrawal of nine centres, in which existence of some patients could not be proved, or other serious violations of good clinical practice had occurred. One other centre was withdrawn when the doctor's national registration was removed after misdemeanours in another, unrelated trial. Withdrawal of centres took place during the course of the study by unanimous decision of the steering committee.

| Country | Number of patients | Number of primary events | Rates per 1000 patient-years |
|---|---|---|---|
| UK | 2032 | 149 | 21·3 |
| France | 1506 | 56 | 9·6 |
| Spain | 717 | 32 | 13·6 |
| Israel | 573 | 61 | 30·9 |
| Netherlands | 566 | 31 | 16·6 |
| Italy | 541 | 25 | 13·9 |
| Sweden | 182 | 13 | |
| Denmark | 133 | 8 | 24·0* |
| Norway | 71 | 7 | |

Single rate shown for three Scandinavian countries, where recruitment was restricted to 6 months in 1996.

Table 2: **Numbers of patients and events by country**

An independent data and safety monitoring board monitored the progress of the study, including all serious adverse events and cancers. Strict stopping rules made stopping the study early unlikely in the absence of a substantial excess of deaths in one group. Relevant ethics committees approved the study. All patients gave their informed written consent to participate.

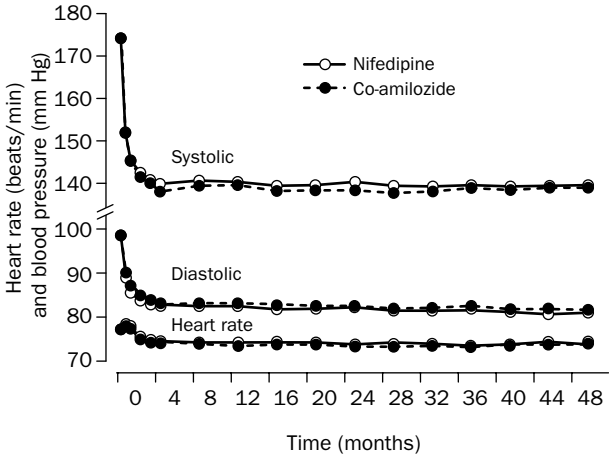
The primary outcome variable was a composite of death from any cardiovascular or cerebrovascular cause, together with non-fatal stroke, myocardial infarction, and heart failure. Three secondary variables were total mortality, death from a vascular cause, and non-fatal vascular events including transient ischaemic attacks, angina (new or worsening), and renal failure. Further planned analyses, with use of the annual biochemical data in all patients, were of renal function by the formula of Cockcroft and Gault,[10] and the development of new diabetes according to the WHO criteria.

### *Statistical analysis*

We designed the study to have a statistical power of 90% for an intention-to-treat analysis to detect a 25% relative difference in the primary outcome in a two-sided test at 5% significance between nifedipine and co-amilozide. A prestudy analysis of cardiovascular morbidity in each of the countries predicted a cumulative event rate of 8% over 3 years, and that 6592 patients were required to detect a reduction in one group to 6%. That number also gave at least 80% power to an on-treatment analysis if up to 25% of events occurred after withdrawal from randomised treatment. Initial recruits had a lower average age than that used in the power calculation, and we, therefore, adapted the protocol in two ways. First, we increased the total number to be enrolled to 7434 to include some patients from higher-risk Scandinavian countries (table 2). Second, all patients were invited after 3 years to remain in the study until a common end date 3 years after recruitment of the last patient. Analysis by intention to treat was of the first occurrence of each event in question. Cox's regression analysis was undertaken, incorporating each of the major risk factors.

| | Nifedipine (n=3157) | | Co-amilozide (n=3164) | | p |
|---|---|---|---|---|---|
| | n (%) | Number of patients withdrawn | n (%) | Number of patients withdrawn | |
| **Adverse events** | | | | | |
| All adverse events | 1546 (49%) | 539 | 1327 (42%) | 304 | <0·0001 |
| Serious adverse events | 796 (25%) | 198 | 880 (28%) | 245 | 0·02 |
| **Symptomatic adverse events** | | | | | |
| Peripheral oedema | 896 (28%) | 267 | 137 (4·3%) | 14 | <0·0001 |
| Syncope | 47 (1·5%) | 9 | 89 (2·8%) | 6 | 0·0004 |
| Headcache | 384 (12%) | 63 | 292 (9·2%) | 32 | 0·0002 |
| Palpitation | 81 (2·5%) | 4 | 86 (2·7%) | 8 | 0·71 |
| Peripheral vascular disorder | 95 (3·0%) | 3 | 168 (5·3%) | 13 | <0·0001 |
| Impotence | 50 (1·6%) | 5 | 60 (1·9%) | 6 | 0·34 |
| Flushing | 135 (4·3%) | 40 | 74 (2·3%) | 18 | <0·001 |
| Diabetes | 96 (3·0%) | 1 | 137 (4·3%) | 8 | 0·01 |
| Dizziness | 254 (8·0%) | 21 | 318 (10·0%) | 17 | 0·006 |
| Gout | 41 (1·3%) | 0 | 67 (2·1%) | 1 | 0·01 |
| Accidental injury | 41 (1·2%) | 4 | 69 (2·2%) | 4 | 0·007 |
| Depression | 124 (3·9%) | 6 | 182 (5·7%) | 13 | 0·0009 |
| **Metabolic adverse events** | | | | | |
| Hypokalaemia | 61 (1·9%) | 0 | 195 (6·2%) | 8 | <0·0001 |
| Hyponatraemia | 8 | 0 | 61 (1·9%) | 12 | <0·0001 |
| Hyperlipidaemia | 127 (4·0%) | 0 | 202 (6·3%) | 0 | <0·0001 |
| Hyperglycaemia | 178 (5·6%) | 0 | 244 (7·7%) | 4 | 0·001 |
| Hyperuricaemia | 40 (1·3%) | 3 | 201 (6·4%) | 1 | <0·0001 |
| Impaired renal function | 58 (1·8%) | 3 | 144 (4·6%) | 18 | <0·0001 |

Table 3: **Adverse events reported by investigators**




**Patients remaining on treatment**

| Month | 0 | 4 | 12 | 24 | 36 | 48 |
|---|---|---|---|---|---|---|
| Nifedipine | 3157 | 2735 | 2498 | 2234 | 2058 | 831 |
| Monotherapy (%) | | 72 | 68 | 66 | 63 | 69 |
| Blood pressure controlled (%) | | 56 | 54 | 54 | 56 | 58 |
| Co-amilozide (n) | 3164 | 2877 | 2693 | 2469 | 2288 | 944 |
| Monotherapy (%) | | 66 | 66 | 65 | 63 | 72 |
| Blood pressure controlled (%) | | 59 | 57 | 59 | 57 | 57 |

Figure 2: **Blood-pressure response to study drugs**

In response to results of the Swedish Trial in Old Patients with Hypertension (STOP)-2[4] in 1999, which suggested that calcium-channel blockade and diuretic treatment have similar efficacy in preventing complications, and, before treatment status was revealed and data were analysed in our own study, we followed the European Medicines Agency's recommended procedure to plan and announce a secondary, non-inferiority analysis (www.eudra.org/humandocs/PDFs/EWP/048299en.pdf accessed July 20, 2000).[11] That procedure requires that the absolute difference in event rate between the groups is not significant, and has an upper 95% confidence limit below a prespecified level. We set this level at 2%, which corresponded to the minimum difference required to show superiority. This secondary, non-inferiority analysis was done in patients remaining on randomised treatment and corroboration sought in the intention-to-treat population.

## Results

6575 patients were randomised. After exclusion of 254 patients from centres withdrawn for misconduct (132 nifedipine, 122 co-amilozide), there were 3157 and 3164 patients assigned these drugs, respectively (figure 1). Of these 6321 patients, there were 2929 men and 3392 women, mean age 65 years (SD 6·5), mean body-mass index 28·2 kg/m$^2$ (4·6). At screening, when 87% of patients had been previously treated, overall mean blood pressure was 167/96 mm Hg (16/9). After the 2–4 week placebo phase before randomisation, mean blood pressure was 173/99 mm Hg (14/8). 1498 (23·7%) patients had isolated systolic hypertension (≥160/<95 mm Hg). Demography and distribution of risk factors for inclusion did not differ significantly between the groups (table 1).

The 3157 patients on nifedipine and 3164 on co-amilozide completed 10 976 and 11 015 patient-years of treatment, respectively. 80% of events occurred while patients were receiving randomised treatment. 1259 patients in the nifedipine group and 1048 in the co-

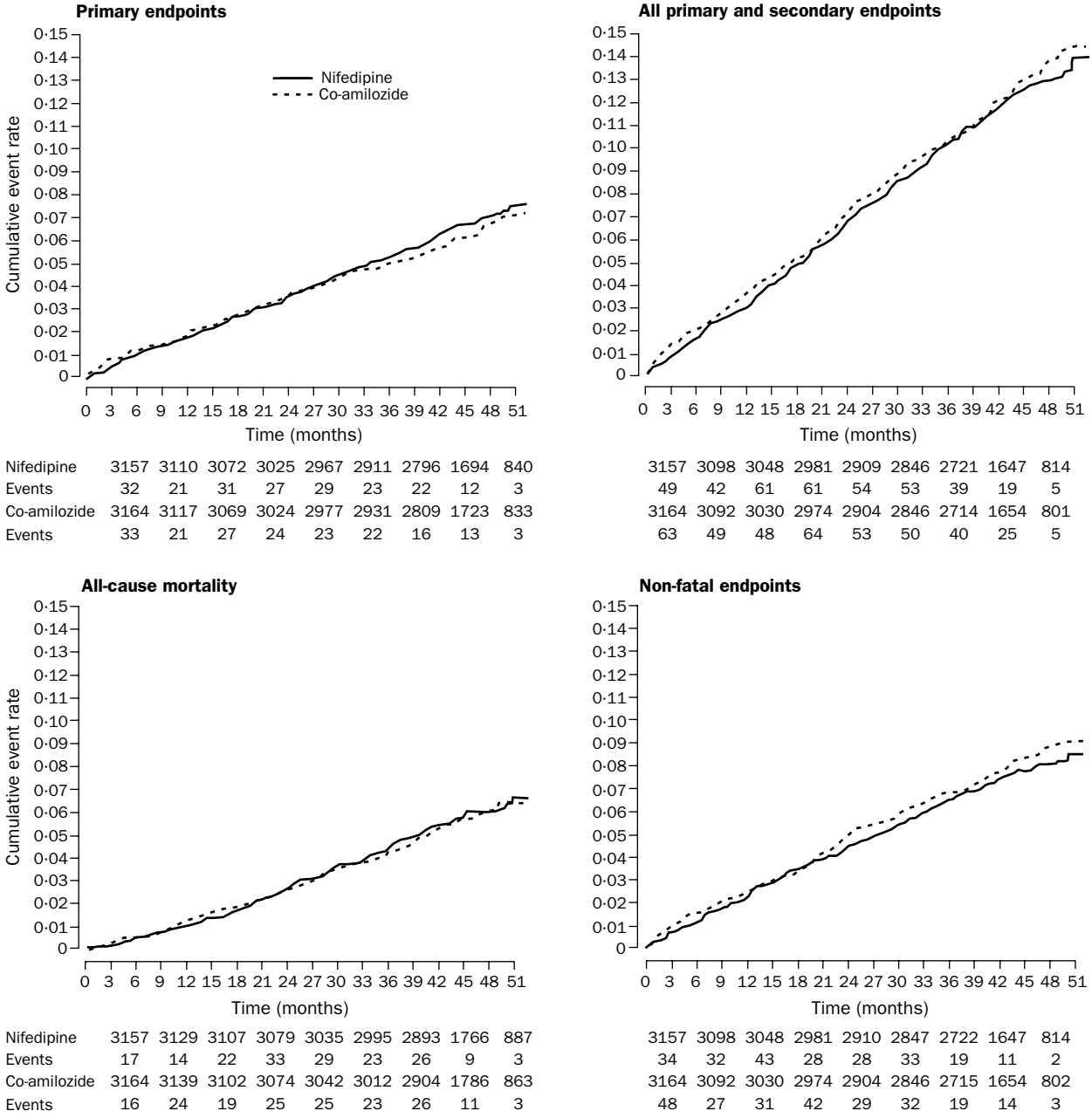



Figure 3: **Kaplan-Meier curves and life tables for survival for primary and secondary endpoints**
Life tables show numbers of patients and number of events every 6 months.

amilozide group withdrew because of: adverse events (nifedipine 725 and co-amilozide 518); non-adherence (23 and 19); withdrawn consent (200 and 186); poor control of hypertension (38 and 38); loss to follow-up (six and 83); death (71 and 70); protocol violation (86 and 79); or other reasons (49 and 55). Table 3 lists the the frequency of adverse events that differed between groups or that have previously been associated with calcium-channel blockade or diuretics. There was an early excess of withdrawals in the nifedipine group because of peripheral oedema in 255 patients during dose titration. More patients on co-amilozide than on nifedipine had metabolic disorders: hypokalaemia, hyponatraemia, hyperuricaemia, hyperglycaemia, and renal impairment. The frequency of these adverse events cited by investigators was in line with the proportion of patients who had laboratory findings outside local normal ranges at annual follow-up. There were fewer serious adverse events (defined as life-threatening, disabling, or leading to hospital admission) in the nifedipine group than in the co-amilozide group. All patients who withdrew from randomised treatment were followed up annually until the end of the study. An end-of-study form was returned by investigators for all but 2·4% patients.

By the end of the titration phase, mean blood pressure had fallen by 33/17 mm Hg (15/9), and remained close to 138/82 mm Hg in the two groups for the rest of the study (figure 2). The proportions of patients who received monotherapy or reached blood pressures lower than 140/90 mm Hg differed slightly between treatment groups. Response in the different risk groups did not differ, except in patients with diabetes, who required more treatment, and there was no risk factor for which nifedipine or co-amilozide was more effective.[12] Heart rate fell slightly in the

| Variable | Hazard ratio (95% CI) | p |
|---|---|---|
| Smoker | 1·62 (1·29–2·04) | <0·0001 |
| Hypercholesterolaemia | 1·21 (0·98–1·51) | 0·094 |
| Diabetes | 1·47 (1·16–1·86) | 0·002 |
| Angina | 1·64 (1·19–2·26) | 0·002 |
| Peripheral vascular disease | 1·72 (1·25–2·36) | 0·001 |
| Left-ventricular hypertrophy | 1·42 (1·06–1·90) | 0·019 |
| Left-ventricular strain | 1·09 (0·75–1·57) | 0·59 |
| Previous myocardial infarction | 1·96 (1·44–2·67) | <0·0001 |
| Proteinuria | 2·08 (1·42–3·06) | <0·0001 |
| Sex (male/female) | 1·91 (1·52–2·40) | <0·0001 |
| Systolic blood pressure | 1·008 (1·002–1·015) | 0·01 |
| Age | 1·04 (1·02–1·06) | <0·0001 |
| Randomised treatment (nifedipine *vs* co-amilozide) | 1·11 (0·91–1·36) | 0·31 |
| Second drug (enalapril *vs* atenolol) | 1·16 (0·81–1·63) | 0·65 |

Hazard ratios for blood pressure and age are for 1 mm Hg and 1 year increases, respectively.

Table 4: **Cox's regression analysis of risk factors**

| | Nifedipine | Co-amilozide | Odds ratio (95% CI) | p |
|---|---|---|---|---|
| **Primary outcomes** | | | | |
| Composite | 200 (6·3%) | 182 (5·8%) | 1·11 (0·90–1·36) | 0·34* |
| Myocardial infarction | | | | |
| Non-fatal | 61 (1·9) | 56 (1·8) | 1·09 (0·76–1·58) | 0·52 |
| Fatal | 16 (0·5) | 5 (0·2) | 3·22 (1·18–8·80) | 0·017 |
| Sudden death | 17 (0·5) | 23 (0·7) | 0·74 (0·39–1·39) | 0·43 |
| Stroke | | | | |
| Non-fatal | 55 (1·7) | 63 (2·0) | 0·87 (0·61–1·26) | 0·52 |
| Fatal | 12 (0·3) | 11 (0·3) | 1·09 (0·48–2·48) | 0·84 |
| Heart failure | | | | |
| Non-fatal | 24 (0·8) | 11 (0·3) | 2·20 (1·07–4·49) | 0·028 |
| Fatal | 2 (0·1) | 1 (<0·1) | 2·01 (0·18–22·13) | 0·63 |
| Other cardiovascular death | 13 (0·4) | 12 (0·4) | 1·09 (0·50–2·38) | 0·85 |
| **Secondary outcomes** | | | | |
| Composite† | 383 (12·1) | 397 (12·5) | 0·96 (0·83–1·12) | 0·62 |
| Deaths | | | | |
| All (first event)* | 153 (4·8) | 152 (4·8) | 1·01 (0·80–1·27) | 0·95 |
| Non-cardiovascular | 71 (2·2) | 66 (2·1) | 1·08 (0·77–1·52) | 0·67 |
| Unknown cause | 22 (0·7) | 34 (1·1) | 0·65 (0·38–1·11) | 0·14 |
| Cardiovascular | 60 (1·9) | 52 (1·6) | 1·16 (0·80–1·69) | 0·45 |
| Non-fatal cardiovascular events | 230 (7·3) | 245 (7·7) | 0·94 (0·78–1·13) | 0·50 |
| Primary events | 140 (4·4) | 130 (4·1) | 1·08 (0·85–1·38) | 0·53 |
| Angina (worsening or new) | 57 (1·8) | 77 (0·4) | 0·74 (0·52–1·04) | 0·10 |
| Transient ischaemic attacks | 25 (0·8) | 25 (0·8) | 1·00 (0·57–1·75) | 1·0 |
| Renal failure | 8 (0·3) | 13 (0·4) | 0·62 (0·26–1·49) | 0·38 |

*Myocardial infarction, stroke, heart failure, and cardiovascular death. †Primary outcomes plus non-cardiovascular deaths, renal failure, angina, and transient ‡23 additional in nifedipine group and 20 in co-amilozide group occurred after a previous endpoint.

Table 5: **Individual endpoints**

two treatment groups. 1259 and 756 patients, respectively, received atenolol or enalapril as add-on treatment, with a similar fall in blood pressure, to 141/82 mm Hg at the end of titration. More patients receiving enalapril than those receiving atenolol had diabetes (32 *vs* 19%).

382 patients had primary outcomes—200 (6·3%) in the nifedipine group, and 182 (5·8%) in the co-amilozide group (18·2 *vs* 16·5 events per 1000 patient-years, p=0·34). Time to first event and survival are shown in figure 3.

Event rates, as expected, were higher in some risk groups than others, but with no apparent differences between the two treatment groups. Patients with diabetes, for example, had primary endpoint rates of 8·3% in the nifedipine group and 8·4% in the co-amilozide group. Most of the risk factors significantly affected outcome (table 4); in separate analyses of treatment interaction with each risk factor in turn, however, no significant interactions were discerned. The event rate in the five northern European countries was higher than that in the three Mediterranean countries (20·2 *vs* 12·0 per 1000 patient years, table 2).

Groups did not differ for all-cause mortality, non-fatal endpoints, or the combined primary and secondary endpoints (figure 3). The individual endpoints are shown in table 5. Cardiovascular endpoints were more common than cerebrovascular endpoints, and the primary (vascular) causes of death were outnumbered by the secondary non-vascular causes. 56 of the latter deaths were from unexplained causes, of which exactly 50% (nifedipine 12, co-amilozide 16) were, according to the critical events committee, probably cardiovascular but did not meet the definition of sudden death. This outcome required documented cardiac symptoms in the previous 24 h. In the other 28 unexplained deaths (nifedipine ten, co-amilozide 18), inadequate data were available to the committee for classification. All 56 unexplained deaths were classified as the secondary endpoints.

The numbers of patients who remained on randomised treatment are shown in figure 2. 304 (80%) of primary endpoints and 541 (69%) of all endpoints occurred in these patients. The on-treatment analysis gave similar results to the intention-to-treat analysis, with only ten more primary endpoints in the nifedipine group than in the co-amilozide group (difference 0·33% [95% CI −0·74 to 1·40]). For all endpoints combined, there were 20 fewer events in the nifedipine group than in the co-amilozide group (−0·62% [−2·01 to 0·78]). In the intention-to-treat analysis, the differences were 0·58% (−0·59 to 1·76) for the primary outcome and −0·42% (−2·04 to 1·21) for all endpoints.

The frequency of cancers differed little between the nifedipine and co-amilozide groups (4·6 *vs* 3·9%). New diabetes occurred in 136 (4·3%) patients receiving nifedipine, and in 176 (5·6%) receiving co-amilozide (p=0·02); the overall frequency was 14·1 cases per 1000 patient-years. Other prespecified comparisons of annual biochemical safety data associated with adverse-event reporting (table 3) confirmed slight differences between the two treatment groups (in each case, co-amilozide was lower) for glomerular filtration rate (−2·3 mL/min [95% CI −3·8 to 1·9]), plasma sodium (−1·22 mmol/L [−1·43 to 1·02]), and plasma potassium (−0·16 mmol/L [−0·19 to −0·13]).

## Discussion

Nifedipine once daily and co-amilozide had a similar efficacy in these patients with hypertension and additional cardiovascular risk factors. From one standpoint, our results will be seen as negative. If a planned meta-analysis of trials of antihypertensive drugs,[13] however, confirms a lack of difference between the major classes of drugs, INSIGHT might be seen more positively, with reduction of blood pressure being accepted as a reasonable surrogate for long-term cardiovascular protection.

Single trials of hypertension do not have the power to make multiple comparisons of the individual events that make up the composite endpoints. Yet, even if clinical need is satisfied by evidence for net measures of benefit, there will be some interest in whether meta-analysis shows genuine differences between drug classes in preventing ischaemic heart disease and stroke.[14] Some caution is required, however. For example, diuretics might delay or mask the appearance of heart failure or calcium-channel blockade could alter the presentation of myocardial ischaemia. Sudden death is the most difficult diagnosis to make systematically; we achieved consistency by requiring cardiac symptoms to be present in the 24 h before death, but 50% of patients who had suspected sudden death could not be classified.

Nifedipine had a better effect on several metabolic markers than did co-amilozide but no advantage was seen

in outcome. To address whether the drugs are equally good or equally bad, we used the Framingham equation in the British Hypertension Society risk-assessor program, to compare the observed and predicted event rates of our patients (www.hyp.ac.uk/bhs/risk.xls accessed July 20, 2000). Their baseline data predicted 34·5 primary endpoints per 1000 patient-years (excluding the extra risk of left-ventricular hypertrophy or existing vascular disease), which is twice the rate we saw overall (table 2). By contrast, the data from 1 year, when blood pressure was controlled at 138/82 mm Hg, predicted 21 primary endpoints per 1000 patient-years—slightly more than our overall rate, but similar to that in the Northern European countries. These calculations support the notion from previous placebo-controlled trials of thiazides and calcium-channel blockers that these drugs substantially lower risk.[2,15–18] Although the Framingham equation is thought by the MONICA investigators to be accurate in Mediterranean countries,[19] we used their coronary-event-rate data from different European centres to re-estimate our predicted event rates, adjusting these downwards in proportion to our numbers of Mediterranean men and women.[20] The adjusted predictions still suggested that the most conservative estimate of benefit was a reduction of 35% in primary endpoints by the two studied drugs.

We do not know whether our results are generalisable to other antihypertensive drugs, or whether they support the use of blood-pressure measurement alone as a surrogate for long-term efficacy. We can, however, say that, for the randomised use of nifedipine and co-amilozide and the selected use of atenolol or enalapril as add-on drugs, the choice seemed unimportant for blood-pressure control and outcomes. Blood pressure was lowered by use of the AB/CD strategy of starting patients older than 55 years on a calcium-channel blocker (C) or diuretic (D) and adding an inhibitor of angiotensin-converting enzyme (A) or β-blocker (B) if required.[21] This strategy lowered mean blood pressure to close to the national targets,[22] and identical to the optimum pressure described by the Hypertension Optimal Treatment (HOT) study investigators.[23] If nifedipine and co-amilozide are representative of their classes, doctors can use the better tolerated of calcium-channel blockers or diuretics in an individual, without concern about differences in long-term efficacy.

Heart failure is a troublesome endpoint for hypertension outcome trialists because of the difficulty in making uniform diagnoses, and differences in the effects of the various drug classes on symptoms. Unusually, we included all heart failure in the composite primary outcome; in STOP-2, for example, only fatal heart failure was a primary endpoint, and in the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack (ALLHAT) trial,[24] heart failure was a secondary endpoint. Whether the early excess of heart failure in the α-blocker group of ALLHAT is explained by the poorer blood-pressure control or potential for sodium retention on α-blockade is uncertain. The willingness of ALLHAT to withdraw α-blockade because of an isolated secondary-endpoint difference compared with their diuretic group seems to imply that any difference between the calcium-channel blocker and angiotensin-converting-enzyme inhibitor groups in that trial is slight.[24]

We used dynamic randomisation to prospectively assign almost equal numbers of patients to the two groups for the common risk factors. Our results suggest, therefore, that in the age-group of 55–80 years, the only compelling influence on choice of treatment is contraindications for certain drugs. The exception might be patients taken to be at risk of developing diabetes, such as those who are obese or who have a family history. The frequency of new diabetes cases in the two groups was much lower than the 29 per 1000 patient-years reported in hypertensive patients elsewhere, and the frequency in our nifedipine group was similar to that of 12% reported in normotensive people; hypertension itself, therefore, probably increases risk of diabetes, and effective blood-pressure reduction might be more important in preventing new diabetes than the class of drug used.[25]

After INSIGHT was started, certain calcium-channel blockers, compared with other classes of antihypertensive drugs, were thought to increase, rather than decrease, the risk of cardiovascular morbidity and mortality[26,27] and to increase risk of cancer and serious bleeding.[28,29] The small difference in frequency of these serious adverse events in INSIGHT was, therefore, reassuring. The equal split of deaths between the two groups means that the diuretic combination and the long-acting dihydropyridine calcium-channel blocker may be seen as similarly life-saving.

Although our primary treatments could not be separated by efficacy, we saw the largely expected differences in adverse reactions, which might influence individual preference between drugs. In choosing between the studied drugs, doctors adopting (as it were) an intention-to-treat strategy might prefer co-amilozide, with fewer withdrawals overall. On the other hand, most withdrawals on nifedipine happened early so that an on-treatment strategy might favour this drug, because of fewer serious adverse events and less need for biochemical monitoring. Identification of the optimum treatment for each individual patient can concentrate on finding the regimen that is most effective and best tolerated.

### Contributors

The listed researchers were members of the Steering Committee, who agreed the protocol, amendments and other management decisions. The initial trial design, data analysis, and preparation of the paper were undertaken in Cambridge by Morris Brown and Christopher Palmer. The clinical investigators were the principal investigators in their countries. All the listed researchers contributed to the final paper.

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