The effect of nifedipine GITS on outcomes in patients with previous myocardial infarction: a subgroup analysis of the INSIGHT study

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Abstract

Post-myocardial infarction (MI) patients have a higher risk for subsequent cardiovascular and cerebrovascular events than the average population. This study was to test the effects on outcomes of nifedipine GITS compared to the diuretic combination co-amilozide in hypertensive patients with a history of MI on outcomes (subset of the INSIGHT study).

The multinational, randomised, double-blind International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study compared the treatment effects of nifedipine GITS 30 mg and co-amilozide (hydrochlorothiazide 25 mg plus amiloride 2.5 mg) in hypertensive patients aged 55–80 years with a blood pressure of 150/95 mmHg (or 160 mmHg systolic). This pre-specified subanalysis was performed in patients with a history of MI. The primary outcome was a composite of cardiovascular death, non-fatal stroke, MI, and heart failure.

Of 6,321 randomised patients, 383 (6.1%) had a previous MI. The percentage of primary outcomes in post-MI patients did not differ between the two treatment groups (14.9%). The number of post-MI patients with composite secondary outcomes was 53 (27.2%) in the nifedipine GITS group and 60 (31.9%) in the co-amilozide group. The incidence rates of primary and secondary outcomes were higher in patients with a previous MI than in patients without a history of MI.

For the randomised use of nifedipine GITS and co-amilozide in hypertensive patients with a previous MI, the choice seemed unimportant for outcomes and blood pressure lowering. The results of this subgroup analysis are consistent with INSIGHT's overall findings of no significant differences in efficacy, suggesting that post-MI hypertensive patients are no more likely to suffer further events when treated with long-acting nifedipine than on co-amilozide.

Key words: nifedipine GITS, co-amilozide, hypertension, post-MI.

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Introduction

Lowering the blood pressure in hypertensive patients has been shown to reduce the incidence of cardiovascular and cerebrovascular morbidity and mortality in a number of clinical trials.[1-6] Predominantly, beta blockers and diuretics have been the antihypertensives studied in long-term, controlled clinical trials. Whilst both appear to be equally effective in reducing the incidence of cerebrovascular events, diuretics have been shown to produce a greater reduction in coronary events.[6]

Until recently, there were only few data available for calcium antagonists from which to determine the effects on cardiovascular disease risks of blood pressure lowering. In addition, there had been inconsistent reports regarding adverse health effects of short-acting or immediate-release formulations of nifedipine, diltiazem hydrochloride and verapamil hydrochloride.[7,8]

A recent analysis investigated the effects of angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists and other blood pressure-lowering drugs on mortality and major cardiovascular morbidity in several populations of patients from all major published clinical studies.[9] There was strong evidence of benefits of ACE inhibitors and calcium antagonists provided by the overviews of placebo controlled trials, and weaker evidence of

Abbreviations used in article

ACTION	A Coronary disease Trial Investigating Outcome with Nifedipine GITS
bpm	beats per minute
CI	confidence interval
GITS	gastrointestinal therapeutic system
INSIGHT	International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment
MI	myocardial infarction
OR	odds ratio
SD	standard deviation

differences between treatment regimens of differing intensities and of differences between treatment regimens based on different drug classes. This analysis also included the INSIGHT study which provided, among other studies, evidence for long-acting calcium antagonists.[10] In particular, the INSIGHT study gave no indication for an increase in the risk for cardiovascular mortality and morbidity, cancer and serious bleeding. The small difference in frequency of serious adverse events between nifedipine GITS and the diuretic combination was, therefore, reassuring.

Regarding outcomes, the INSIGHT study showed equal efficacy of nifedipine GITS and co-amilozide in preventing overall cardiovascular or cerebrovascular complications in hypertensive patients with additional risk factors.

The purpose of this subanalysis was to examine whether the results of primary and secondary outcomes in patients with a previous MI were similar between the two treatment groups and would therefore confirm the results of the INSIGHT study.

Table 1. Number of patients by treatment groups

Patient population	Nifedipine GITS	Co-amilozide	Total
Total patient population	3,157 (100.0%)	3,164 (100.0%)	6,321 (100%)
Patients with previous MI	195 (6.2%)	188 (5.9%)	383 (6.1%)

Table 2. Blood pressure and heart rate changes

Variable	Nifedipine GITS n=195	Co-amilozide n=188
Systolic blood pressure (mmHg, mean ± SD)		
Baseline	174.9 (16.0)	176.2 (15.6)
End point	142.5 (17.6)	145.8 (20.5)
Change	32.4 (17.1)	30.4 (20.0)
Diastolic blood pressure (mmHg, mean ± SD)		
Baseline	98.3 (8.8)	99.4 (8.2)
End point	81.2 (10.0)	83.5 (9.3)
Change	17.1 (10.4)	15.9 (10.8)
Heart rate (bpm, mean ± SD)		
Baseline	77.3 (11.1)	77.5 (12.0)
End point	73.8 (11.5)	73.6 (11.9)
Change	3.5 (14.6)	4.0 (13.0)

Methods

Study population

Mainly white hypertensive men and women, aged 55–80 years, were enrolled in eight western European countries and Israel. In order to increase the number of events expected, the patients had to have at least one additional cardiovascular risk factor, e.g. hypercholesterolaemia, diabetes mellitus, smoking, family history of MI, coronary heart disease, left ventricular hypertrophy, left ventricular strain, peripheral vascular disease, or proteinuria. Patients with an MI occurring less than 12 months before study initiation did not qualify for study participation.

The study was approved by ethics committees relevant to the study sites. Each patient gave written informed consent.

Study design

This was a prospective, randomised, double-blind trial using the double-dummy technique for the two treatment arms and dynamic randomisation.[11] After a four-week placebo run-in period for identification of eligible patients, patients were randomly assigned initially to nifedipine GITS 30 mg once daily or co-amilozide (hydrochlorothiazide 25 mg plus amiloride 2.5 mg) once daily. Depending on blood pressure responses, four optional titration steps could be undertaken by the physician at weeks 2, 4, 8 and 12 after randomisation. These steps were dose-doubling of the randomised drug; addition of atenolol 25 mg daily (or enalapril 5 mg daily, if atenolol was contraindicated); dose-doubling of the additional drug; and, addition of another antihypertensive medication other than calcium antagonists or diuretics. This analysis was performed in the subgroup of patients with a history of MI, which had been pre-specified in the study protocol.

An independent critical events committee assessed all end points according to pre-specified criteria.

Statistical analysis

Odds ratios (OR) and their confidence intervals (CI) were derived using logistic regression models. All computations were performed using SPSS (version 10, SPSS Inc., Chicago, 2001). Details on the statistical analysis of the main INSIGHT study have been described elsewhere.[10] The descriptive subanalyses of patients with and without a previous MI were performed on primary and secondary outcomes in the intention-to-treat population.

Results

Between September 1996 and June 1997, a total of 6,321 patients were randomised to double-blind treatment. Of these patients, 383 (6.1%) had a history of MI prior to study initiation.

Table 3. Primary and secondary outcomes in patients with and without previous myocardial infarction

Outcomes	Nifedipine GITS		Co-amilozide	
	with previous MI n=195	without previous MI n=2,962	with previous MI n=188	without previous MI n=2,976
Primary outcomes (composite)*	29 (14.9%)	171 (5.8%)	28 (14.9%)	154 (5.2%)
Secondary outcomes (composite)†	53 (27.2%)	330 (11.1%)	60 (31.9%)	337 (11.3%)

Key: * myocardial infarction, stroke, heart failure and cardiovascular death; † primary outcomes plus non-cardiovascular deaths, renal failure, angina and transient ischaemic attacks

The number of post-MI patients was slightly higher in the treatment group receiving nifedipine GITS than in the co-amilozide group (see table 1).

Table 2 summarises blood pressure and heart rate responses in patients with a previous MI comparing baseline and end point.

At end point, mean blood pressure had fallen by 32/17 mmHg (nifedipine GITS) and 30/16 mmHg (co-amilozide). Heart rate fell slightly in both treatment groups.

Table 3 summarises the frequencies of primary and secondary outcomes in patients with and without previous MI.

The unadjusted OR for comparing primary events for those with and without previous MI is 3.02 (95% CI 2.23, 4.09), reducing to 2.43 (95% CI 1.79, 3.31) on adjusting for age and sex. Adjusting more fully for age, sex, baseline systolic blood pressure and the nine other risk factors, the OR is 2.11 (95% CI 1.51, 2.96), remaining the same on further adjusting for treatment group.

Corresponding ORs for secondary events with and without previous MI are 3.31 (95% CI 2.62, 4.18) unadjusted, 2.64 (95% CI 2.07, 3.35) age-sex-adjusted, and 2.18 (95% CI 1.68, 2.82) when fully adjusted also for baseline systolic blood pressure and nine other risk factors. Again, the latter figures remain unchanged to two decimal places on further adjusting for treatment group, confirming a lack of any treatment effect.

Figure 1 depicts the percentages of primary outcomes for patients with and without previous MI.

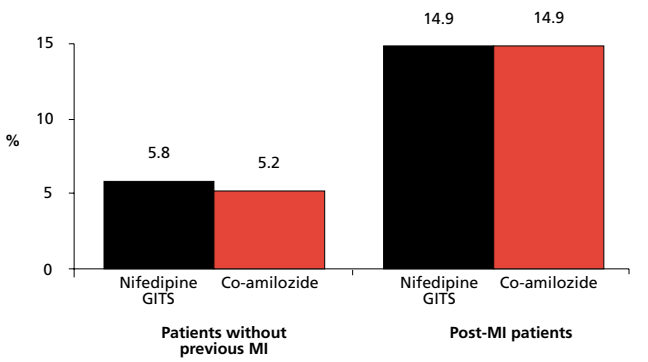
The percentage of primary outcomes in post-MI patients was 14.9% and did not differ between the two treatment groups (OR 1.00; 95% CI 0.57 to 1.75). The number of post-MI patients with composite secondary outcomes was 53 (27.2%) in the nifedipine GITS group and 60 (31.9%) in the co-amilozide group (OR 0.80; 95% CI 0.51 to 1.24).

The number of primary and secondary outcomes were more frequent in patients with a previous MI than in patients without a history of MI.

The percentages of each single secondary outcome were slightly less in patients receiving nifedipine GITS compared to the co-amilozide group, with the exception of primary non-fatal events (see table 4).

For comparison, table 5 recapitulates the primary INSIGHT data[10] for primary and secondary outcomes.

Figure 1. Primary outcomes (composite)* in patients with and without previous myocardial infarction



Key: * myocardial infarction, stroke, heart failure and cardiovascular death

Discussion

Hypertensive patients with a previous MI, treated with nifedipine GITS or co-amilozide and the selected use of atenolol or enalapril as add-on drugs, had similar primary and secondary outcomes. Although there was a slight numerical difference in outcomes between the two treatment groups in favour of nifedipine GITS, the overall small number of events does not allow statistically meaningful conclusions about true clinically relevant differences. It should be emphasised again that these results apply only to those patients whose previous MI occurred at least 12 months prior to enrolment into the INSIGHT study, which is an important caveat for interpreting the results presented in this paper.

According to epidemiological data from the Framingham Heart Study, post-MI patients have a higher risk for subsequent cardiovascular and cerebrovascular events than the average population.

- Sudden death occurs at 4–6 times the rate of the general population among people who have had a heart attack;
- 25% of men and 38% of women die within one year after having a recognised MI;
- people who survive the acute stage of a heart attack have a chance of illness and death that is 1.5–15 times higher than

Table 4. Primary and secondary outcomes in patients with previous myocardial infarction

	Nifedipine GITS n=195	Co-amilozide n=188	Odds ratio (95% CI)
Primary outcomes (composite)*	29 (14.9%)	28 (14.9%)	1.00 (0.57, 1.75)
Secondary outcomes			
Composite†	53 (27.2%)	60 (31.9%)	0.80 (0.51, 1.24)
All deaths (first event)	19 (9.7%)	20 (10.6%)	0.91 (0.47, 1.76)
All deaths	23 (11.8%)	25 (13.3%)	0.87 (0.48, 1.60)
Cardiovascular deaths	9 (4.6%)	10 (5.3%)	0.86 (0.34, 2.17)
Primary non-fatal events	20 (10.3%)	18 (9.6%)	1.08 (0.55, 2.11)
All non-fatal events	34 (17.4%)	40 (21.3%)	0.78 (0.47, 1.30)

Key: * myocardial infarction, stroke, heart failure and cardiovascular death; † primary outcomes plus non-cardiovascular deaths, renal failure, angina and transient ischaemic attacks

Table 5. Primary and secondary outcomes in the total INSIGHT patient population

Outcomes	Nifedipine GITS n=3,157	Co-amilozide n=3164	Odds ratio (95% CI)	p
Primary outcomes (composite)*	200 (6.3%)	182 (5.8%)	1.11 (0.90–1.36)	0.34
Secondary outcomes				
Composite†	383 (12.1%)	397 (12.5%)	0.96 (0.83–1.12)	0.62
All deaths (first event)	153 (4.8%)	152 (4.8%)	1.01 (0.80–1.27)	0.95
Cardiovascular deaths	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

Key: * myocardial infarction, stroke, heart failure and cardiovascular death; † primary outcomes plus non-cardiovascular deaths, renal failure, angina and transient ischaemic attacks

that of the general population, depending on their sex and clinical outcomes;

- the risk of another heart attack, sudden death, angina pectoris, heart failure and stroke is substantial;
- within six years after a recognised heart attack, 18% of men and 35% of women have another heart attack, 7% of men and 6% of women will experience sudden death, and about 22% of men and 46% of women will be disabled with heart failure.[12]

Taking these facts into consideration, it comes as no surprise that over a mean follow-up period of 3.5 years, the incidence rates of primary and secondary outcomes were higher in post-MI patients than in those without a history of previous MI. This is consistent with previously published INSIGHT study data showing an adjusted hazard ratio for patients with previous MI of 1.96 (95% CI 1.44, 2.67).[10] However, there was no relevant difference in outcomes between the two treatment groups. Diuretics are effective in reducing the incidence of cerebrovascular events and produce a greater reduction in coronary events than beta blockers in hypertensive patients.[6] Thus, given the proven safety and efficacy of diuretics in long-term, controlled trials, the results of this subanalysis can also be taken as evidence for the efficacy and safety of long-acting nifedipine in post-MI hypertensive patients.

The observed blood pressure-lowering effects in post-MI patients were similar to those observed in the total study population (33/17 mmHg).[10] No clinically relevant differences were found between the two treatment groups.

The INSIGHT study was a unique trial in that it was the first double-blind, randomised outcome trial with a long-acting dihydropyridine calcium antagonist in hypertension to use an active control, in this case a diuretic combination. The double-blind design allowed an unbiased assessment of the clinical benefit of the two treatment regimens. The INSIGHT study added valuable information on the effects on cardiovascular disease risks of blood pressure-lowering regimens of newer classes of agents in hypertensive patients and complements evidence provided by the previously published calcium antagonist studies like the STONE study, the Syst-Eur trial, and the Syst-China study.[13-15] The currently ongoing randomised, placebo-controlled ACTION study with nifedipine GITS addresses the issue of cardiovascular outcomes in patients with stable angina pectoris and will provide additional evidence on the efficacy and safety of calcium antagonists.[16,17]

Key messages

- Following acute MI, patients are at increased risk of subsequent cardiac and cerebrovascuclar events
- Pre-specified subanalysis was performed among patients treated with nifedipine GITS and co-amilozide in the INSIGHT study
- This confirmed that the incidence rates of primary and secondary outcomes are higher in patients with previous acute MI
- Post-MI hypertensive patients are no more likely to suffer further events when treated with long-acting nifedipine than co-amilozide

Conclusions

For the randomised use of nifedipine GITS and co-amilozide and the selected use of atenolol or enalapril as add-on drugs in hypertensive patients with a previous MI, the choice seemed unimportant for outcomes and blood pressure lowering. These findings are in accordance with the main conclusions of the INSIGHT study results. As expected from epidemiological data, post-MI patients had higher incidence rates of primary and sec-

ondary outcomes compared to patients without a previous MI.

The results of this subgroup analysis are consistent with INSIGHT's overall findings of no significant differences in efficacy, suggesting that post-MI hypertensive patients are no more likely to suffer further events when treated with long-acting nifedipine than on a co-amilozide regimen.

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