Calcium Antagonists and Hypertension: Role of co-existent coronary disease, impaired renal function and diabetes

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Calcium Antagonists and Hypertension: Role of co-existent coronary disease, impaired renal function and diabetes

Calcium-antagonisten en Hypertensie: De rol van de bijkomende aanwezigheid van coronair lijden, verminderde nierfunctie en diabetes

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	Prof.dr. A.W. Hoes

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For all my family

PUBLICATIONS INCORPORATED IN THIS THESIS

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Chapter 5: Ruilope LM, Kirwan BA, de Brouwer S, Danchin N, Fox KAA, Wagener G, Segura J, Poole-Wilson PA, Jacobus Lubsen J, on behalf of the ACTION investigators. Uric acid and other renal function parameters in patients with stable angina pectoris participating in the ACTION trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome. J Hypertens 2005;**25**:1711-1718.

Chapter 6: Mancia G, Brown M, Castaigne A, de LP, Palmer CR, Rosenthal T, Wagener G, Ruilope LM. Outcomes with nifedipine GITS or co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). Hypertension 2003;**41**:431-6.

Chapter 7: Danchin N, Wagener G, Kirwan BA, de Brouwer S, Lubsen J, Poole-Wilson PA for the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) investigators. Efficacy and safety of long-acting nifedipine in patients with symptomatic stable angina pectoris with and without Diabetes: the ACTION trial. Submitted for publication.

TABLE OF CONTENTS

Chapter 1

Introduction

INTRODUCTION

Hypertension is the leading cause of morbidity and mortality worldwide [1]. Starting from anecdotal evidence in the 40s [2] and observational studies in the 50s [3], it has taken more than 30 years to establish that high blood pressure is a major risk factor for the development of cardiovascular disease and death, and that blood pressure lowering is an effective tool in reducing morbidity and mortality.

The relationship between high blood pressure and other risk factors and the occurrence of cardiovascular disease has been described first by the Framingham Heart Study [4], which was started in 1948. The residual lifetime risk of developing hypertension in middle aged and elderly individuals is 90% [5]. In particular in elderly normotensives, progression to hypertension may occur within only 4 years [6]. In industrialised countries with an aging population hypertension is therefore a growing public health concern.

With the exception of sub-Saharan Africa, cardiovascular disease is the leading cause of death in all other World Bank developing regions. In developing countries, hypertension is also a major risk factor for the development of cardiovascular disease [7]. Hence, developing countries are following the pattern of industrialised countries, although with a much steeper rise in cardiovascular disease – predominantly hypertension and stroke – followed by an increase in coronary heart disease [8]. With increasing urbanization, the prevalence of hypertension is expected to reach epidemic dimensions that will require cost-effective treatment strategies also in sub-Saharan Africa [9].

In 1990, 14 million patients died from cardiovascular disease, 5 million in industrialised countries and 9 million in developing countries. It is estimated that the total number of cardiovascular deaths will increase to 25 million worldwide, with an increase to 6 million in industrialised countries and a more than doubling to 19 million in developing countries [10]. About two thirds of the occurrence of stroke, one half of coronary heart disease, and about one sixth of other cardiovascular diseases can be attributed to above-optimal blood pressure [9]. Worldwide, 7.1 million deaths (about 12.8% of the total) and 64.3 million disability adjusted life years (DALYs) (4.4% of the total) are estimated to be lost due to above-optimal blood pressure levels [11]. Globally, blood pressure is ranked as the third most important cause of DALYs lost, behind malnutrition and unsafe sex [1].

The costs of complications due untreated or sub-optimally treated hypertension are enormous. In five western European countries, these costs add up to 1.2 billion US dollar because blood pressure control is not achieved in more than 26 million patients in the countries concerned [12]. For hypertensives in the United States, inadequate blood pressure control was estimated to result in 39,702 cardiovascular events, 8,374 cardiovascular disease deaths, and 964 million US dollars in direct medical expenditures. For the treated population with cardiovascular disease, the incremental cost of the failure to attain blood pressure goals was approximately 467 million US dollars [13].

Hypertension has been arbitrarily defined as blood pressure levels equal or above 140/90 mmHg. Earlier trials focused on diastolic blood pressure as the target for treatment, whereas newer trials have stressed the need to also control systolic blood pressure, which is usually more difficult to achieve [14]. Research has shown that there is a gradual relationship between blood pressure and risk of cardiovascular complications (in particular of stroke) [15]. In the HOT trial, patients with the lowest diastolic blood pressure also had the lowest cardiovascular morbidity [16]. Clinical research has also demonstrated that patients with "normal" blood pressure levels, i.e. systolic between 125 and 135 mmHg, may be at risk of cardiovascular complications due to other risk factors, such as hyperlipidemia, diabetes or renal disease [17]. Thus, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defined this particular group at risk as "pre-hypertensive" patients [18] and urged control and treatment in the presence of additional risk factors for these patients.

It follows that the use of definitions such as "hypertensive" and "normotensive" does not adequately reflect the total burden of cardiovascular disease due to elevated blood pressure. In fact, most of the burden of vascular disease in elderly patients is estimated to occur in those with a "normal" systolic blood pressure of less than 140 mmHg [19,20]. Blood pressure levels should not be dichotomised into "hypertensive" and "normotensive", as this gives the erroneous impression that those who are "normal" have no cause for concern and do not need therapy [19-21]. Indeed, recent European guidelines define the need for treatment based on the total cardiovascular risk: the higher the risk the lower the target blood pressure [17]. Recent US guidelines continue to distinguish between "hypertensive", "pre-hypertensive" and "normotensive" patients, although for certain high-risk groups such as diabetics and patients with renal disease lower target blood pressure levels are recommended [18]. This reflects that patients with diabetes and/or renal disease require particular attention because those with established target organ damage have a particularly high risk of developing cardiovascular complications. Mild renal failure (i.e. serum creatinine above 110 µmol/l in female and 120 µmol/l in male patients) has been demonstrated to be associated with a significant increase in cardiovascular risk [22]. The target blood pressure in the patients with diabetes or renal disease is less than 135/75mmHg, which is difficult to achieve even in randomized controlled clinical trials.

Patients with established renal disease, e.g. with proteinuria or microalbuminria, require strict control of blood pressure to levels below 120 / 75mmHg. In these patients, the kidney becomes a secondary target of blood pressure control in order to prevent further deleterious effects on renal function. It has also been demonstrated that the decline in renal function in diabetic patients can be stopped when blood pressure is "normalized" to levels below 120/75mmHg [23], and that strict blood pressure is beneficial [16].

APPROACHES TO THE TREATMENT OF HYPERTENSION

A multitude of placebo-controlled clinical trials have demonstrated that drugs that reduce blood pressure also reduce cardiovascular risk. Assuming that newer drugs may be more effective in reducing cardiovascular risk than older drugs (such as diuretics and β-blockers) given the same effect on blood pressure, a new era of clinical trials in hypertension comparing older to newer drugs was initiated mainly by the pharmaceutical industry.

The INSIGHT (International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment) trial compared a calcium-channel blocker based regimen with a diuretic based regimen. The underlying assumption was that in patients with elevated blood pressure, the newer calcium-channel blocker based regimen is superior in reducing cardiovascular mortality and morbidity [24]. When the results of other trials comparing different treatments suggested that the degree of blood pressure reduction is more important than the drug used, the initial superiority design of INSIGHT was changed into a non-inferiority design. INSIGHT recruited high-risk patients, i.e. patients with elevated blood pressure and at least one additional risk factor. In addition to the main analysis, pre-defined analyses in subgroups at particularly high risk, such as patients with renal impairment (Chapter 4) and diabetes (Chapter 6), were performed.

Despite moderate favourable effects of newer drugs on intermediate endpoints, such as development of new diabetes [25-28] and progression of atherosclerosis [29], no study has demonstrated that for the same degree of blood pressure reduction there is a relevant difference in outcome between newer and older drugs [24,30-33]. These findings have been confirmed by the largest ongoing prospective meta-analysis of hypertension trials [34].

The only study that showed that reduction of blood pressure is related in gradual manner to reduction of cardiovascular risk is the HOT (Hypertension Optimal Treatment) study [16]. Patients with diastolic blood pressure levels between 100 and 115 mmHg were randomised to diastolic blood pressure target levels of 90 mmHg or less, 85 mmHg or less, and 80 mmHg or less respectively. Cardiovascular risk was lowest in patients randomised to the lowest target. Importantly, this study confirmed that blood pressure and its reduction constitute a continuum rather than a threshold in cardiovascular risk reduction.

Studies of antihypertensive drugs in patients at increased risk of cardiovascular disease due to the presence of diabetes or nephropathy have confirmed that tighter control of blood pressure is more effective than less tight control in reducing morbidity and mortality [35]. A recent meta-analysis supports this hypothesis: effects of drugs that inhibit the renin-angiotensin system on renal outcomes observed in placebo-controlled trials seemed mainly due to blood pressure lowering effects, rather than to effects "beyond blood pressure lowering" [36].

HYPERTENSION AND CORONARY HEART DISEASE

Although it is generally accepted that patients with coronary heart disease and hypertension have a higher cardiovascular risk than those without, there is little data from randomised placebo-controlled clinical trials other than subgroup analyses that show a benefit of blood pressure lowering in hypertensive patients with coronary heart disease.
One trial that did address the issue of blood pressure control in patients with coronary heart disease and hypertension is the International Verapamil-Trandolapril Study (INVEST) [37]. A verapamil-based calcium antagonist treatment strategy was compared to an atenolol-based β-blockade strategy in almost 23,000 patients with hypertension and coronary heart disease. The trial showed that control of in particular systolic blood pressure in patients with coronary heart disease and hypertension is difficult and requires multiple antihypertensive drugs. Since there was no difference in the combined primary endpoint [37], it does not seem to matter whether blood pressure control in a patient with coronary heart disease is started with verapamil or with atenolol. A retrospective analysis by achieved blood pressure levels of data from the same study suggested that there may be a J-shaped relation between on-treatment blood pressure level and primary outcomes: reductions of diastolic pressure to below 60 mmHg – which was only achieved in a minority of patients – resulted in an increased risk of primary endpoints, in particular myocardial infarction [38].
Two placebo-controlled trials with drugs also used in the treatment of hypertension in patients with coronary heart disease have recently been completed. The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery (EUROPA) compared the angiotensin-converting-enzyme inhibitor perindopril to placebo in 13,655 patients with proven stable coronary disease without apparent heart failure [39]. The ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) study compared the calcium antagonist nifedipine in a long-acting once daily formulation to placebo in 7,665 patients with stable symptomatic angina pectoris and proven coronary heart disease (Chapter 2). Neither EUROPA nor ACTION restricted inclusion to patients who also had hypertension.

AIM OF THIS THESIS

The general aim of this thesis is threefold:

1. To describe the long-term evolution of blood pressure (Chapters 2 and 3) and to examine the effect of blood pressure reduction by the calcium antagonist nifedipine GITS on outcome in patients with established stable symptomatic coronary heart disease and hypertension, based on data from the ACTION trial (Chapter 3).

2. To assess the evolution of renal function and the relationship of renal function with mortality and morbidity in patients with hypertension treated in INSIGHT with either nifedipine or the diuretic co-amilozide, and in patients with symptomatic coronary heart disease treated in ACTION with either nifedipine or placebo (Chapters 4 and 5).
3. To assess the impact of diabetes in patients with hypertension and diabetes who received either nifedipine or co-amilozide in INSIGHT, and in patients with symptomatic coronary heart disease treated in ACTION with either nifedipine or placebo (Chapters 6 and 7).

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Chapter 2

Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial

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Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial

Philip A Poole-Wilson, Jacobus Lubsen, Bridget-Anne Kirwan, Fred J van Dalen, Gilbert Wagener, Nicolas Danchin, Hanjörg Just, Keith AA Fox, Stuart J Pocock, Tim C Clayton, Michael Motro, John D Parker, Martial G Bourassa, Anthony M Dart, Per Hildebrandt, Åke Hjalmarson, Johannes A Kragten, G Peter Molhoek, Jan-Erik Otterstad, Ricardo Seabra-Gomes, Jordi Soler-Soler, Simon Weber, on behalf of the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) investigators*

Cardiac Medicine, Imperial College London, Dovehouse Street, London SW3 6LY, UK (Prof P A Poole-Wilson FESC); **Department of Epidemiology and Biostatistics, Erasmus Medical Centre, Rotterdam, Netherlands** (Prof J Lubsen MD); **SOCAR Research, Nyon, Switzerland** (Prof J Lubsen, B-A Kirwan PhD, F J van Dalen); **Pharma Research Centre, Bayer Healthcare AG, Wuppertal, Germany** (G Wagener MD); **Department of Cardiology, Georges Pompidou European Hospital, Paris, France** (Prof N Danchin FESC); **University of Freiburg, Freiburg, Germany** (Prof H Just FRCPE); **Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK** (Prof K A A Fox FESC); **Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, UK** (Prof S J Pocock PhD, T C Clayton MSc); **Ringer's Research Unit, Sheba Medical Centre, University of Tel Aviv, Tel Aviv, Israel** (Prof M Motro FACC); **Division of Cardiology, University Health Network and Mount Sinai Hospitals, Toronto, ON, Canada** (Prof J D Parker FRCPC); **Department of Medicine, Montreal Heart Institute, Montreal, QC, Canada** (M G Bourassa FESC); **Cardiovascular Medicine, Alfred Hospital, Melbourne, Australia** (Prof A M Dart FRACP); **Department of Cardiology and Endocrinology, Frederiksberg University Hospital, Frederiksberg, Denmark** (P Hildebrandt MD); **Cardiovascular Institute, Sahlgrenska University Hospital, Göteborg, Sweden** (Prof Å Hjalmarson); **Atrium Medical Centre, Heerlen, Netherlands** (J A Kragten FESC); **Medisch Spectrum Twente, Enschede, Netherlands** (G P Molhoek FESC); **Division of Cardiology, Vestfold Hospital, Toensberg, Norway** (J E Otterstad FESC); **Department of Cardiology, Hospital Santa Cruz, Lisbon, Portugal** (R Seabra-Gomes FESC); **Department of Cardiology, Vall d'Hebron University Hospital, Barcelona, Spain** (Prof J Soler-Soler FESC); and **Department of Cardiology, René Descartes University, Paris, France** (Prof S Weber).

*Investigators listed in the web appendix (http://image.thelancet.com/extras/ 04art6402we-bappendix.pdf)

Correspondence to: Prof Philip A Poole-Wilson p.poole-wilson@imperial.ac.uk

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See Comment page 817

SUMMARY

Background: Calcium antagonists are widely prescribed for angina pectoris but their effect on clinical outcome is controversial. We aimed to investigate the effect of the calcium antagonist nifedipine on long-term outcome in patients with stable angina pectoris.

Methods: We randomly assigned 3825 patients with treated stable symptomatic coronary disease to double-blind addition of nifedipine GITS (gastrointestinal therapeutic system) 60 mg once daily and 3840 to placebo. The primary endpoint was the combination of death, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularisation. Mean follow-up was 4·9 years (SD 1·1). Analysis was by intention to treat.

Findings: 310 patients allocated nifedipine died (1.64 per 100 patient-years) compared with 291 people allocated placebo (1·53 per 100 patient-years; hazard ratio 1·07 [95% CI 0·91-1·25], p=0·41). Primary endpoint rates were 4·60 per 100 patient-years for nifedipine and 4·75 per 100 patient-years for placebo (0·97 [0·88-1·07], p=0·54). With nifedipine, rate of death and any cardiovascular event or procedure was 9·32 per 100 patient-years versus 10·50 per 100 patient-years for placebo (0·89 [0·83-0·95], p=0·0012). The difference was mainly attributable to a reduction in the need for coronary angiography and interventions in patients assigned nifedipine, despite an increase in peripheral revascularisation. Nifedipine had no effect on the rate of myocardial infarction.

Interpretation: Addition of nifedipine GITS to conventional treatment of angina pectoris has no effect on major cardiovascular event-free survival. Nifedipine GITS is safe and reduces the need for coronary angiography and interventions.

INTRODUCTION

Angina pectoris is the most common symptom in patients with stable atherosclerotic coronary disease. Despite advances in its management, current treatment provides no cure, and many patients remain symptomatic. Hence, continued therapy with antianginal drugs is usually needed.

For many years, nitrates, β blockers, and calcium antagonists have been the treatments of choice for angina. These drugs have been prescribed mainly on the basis of proof of efficacy in reducing symptoms. Long-term safety has been of less concern, although safety of β blockers is lent support by positive results of trials in patients with a history of acute myocardial infarction. Before trials were done with nicorandil [1] and angiotensin-converting-enzyme (ACE) inhibitors,[2,3] no hard outcome data were available from clinical trials with drugs used in patients with angina or stable coronary disease. In the mid 1990s, considerable debate took place about the long-term safety of calcium antagonists.[4-12] Consensus arising from this discussion was the need for well-designed long-term trials in patients with hypertension or with manifestations of coronary disease such as angina. ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) was designed to investigate the effects of the long-acting calcium antagonist nifedipine on clinical outcomes in patients with stable symptomatic coronary disease.

METHODS

ACTION was a multi-centre, randomised, placebo-controlled, double-blind trial to compare the effect on clinical outcomes of long-acting nifedipine or placebo in patients with angina pectoris attributable to coronary disease. A detailed description of the trial has been published elsewhere.[13] Planned follow-up ranged from 4·5 to 6 years. We undertook the study in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice, and all patients gave written informed consent. To protect patients' safety, predefined interim analyses were done by an independent safety monitoring committee that had access to the medication code. These analyses did not lead to early termination.

Patients

Between November, 1996, and December, 1998, we recruited patients in 291 centres from 19 countries. Three categories of ambulatory patients who were age 35 years or older, had angina pectoris that had been stable for at least 1 month, and needed oral or transdermal treatment either to treat or prevent anginal attacks were eligible for the study: (1) those with

a history of myocardial infarction; (2) those with angiographic coronary artery disease but no history of myocardial infarction; and (3) those with a positive exercise test or perfusion defect who had never had coronary angiography and had no history of myocardial infarction. Locally measured left-ventricular ejection fraction had to be at least 40%. Reasons for exclusion were: overt heart failure; any major cardiovascular event or intervention within the past 3 months; planned coronary angiography or intervention; known intolerance to dihydropyridines; clinically significant valvular or pulmonary disease; unstable insulin-dependent diabetes mellitus; any gastrointestinal disorder that could compromise absorption of nifedipine GITS or passage of the tablet; any condition other than coronary artery disease that limited life expectancy; symptomatic orthostatic hypotension or supine systolic blood pressure 90 mm Hg or less; systolic blood pressure at least 200 mm Hg, diastolic blood pressure at least 105mm Hg, or both; creatinine more than twice the local upper limit of normal; and alanine or aspartate transaminase greater than three times the local upper limit of normal. Women could only participate if pregnancy was not a risk.

Procedures

Investigators randomly assigned patients to addition of either nifedipine GITS or matching placebo to the basic regimen that they were taking. Randomisation was blocked and stratified by centre. The starting dose of nifedipine was 30 mg once daily, increasing to 60 mg once daily within 6 weeks if no evidence of intolerance was seen. Dose reduction or interruption was allowed. Investigators allocated treatment by means of sequentially numbered study medication packs that contained either nifedipine GITS or matching placebo in a concealed manner using identical packaging. The chair of the safety monitoring committee prepared the random allocation list. Only patients who actually took the first tablet of study drug were regarded as randomised.

We treated symptomatic angina with conventional drugs. Lipid-lowering therapy was either continued or started according to local guidelines. The following drugs could not be used in combination with study medication: calcium antagonists (2-week washout needed); cardiac glycosides (unless given for supraventricular arrhythmias); other positive inotropic agents class I or III antiarrhythmics other than amiodarone or sotalol; cimetidine; antipsychotic and antiepileptic drugs; and rifampicin.

Baseline assessments included echocardiography and a full medical history. We recorded blood pressure with a standard sphygmomanometer in the sitting position after 5 min of rest. Functional class was rated with the New York Heart Association (NYHA) scale. Patients were seen at the outpatient clinic at least every 6 months for routine clinical assessments that included NYHA class, vital signs, and adverse events. Between visits, we contacted patients by telephone.

The primary efficacy outcome was major cardiovascular event-free survival, defined as time to occurrence of the first of the following events: death from any cause, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularisation (combined primary endpoint for efficacy). The primary combined endpoint for safety, defined for planned interim analyses,[13] was death from any cause, acute myocardial infarction, and debilitating stroke. Secondary predefined outcomes were any cardiovascular event; any death, cardiovascular event, or procedure; and any vascular event or procedure.
The critical events committee classified serious adverse events that suggested a possible major cardiovascular event with predefined criteria, irrespective of the investigators' diagnosis. Cause of death was categorised as unknown, cardiovascular, or non-cardiovascular. To define acute myocardial infarction the committee required two events of typical symptoms, raised enzymes or markers, and electrocardiographic criteria: in the context of an intervention, new Q waves were needed. A definition of refractory angina required angina at rest, prolonged administration of intravenous nitrates or equivalent, and a coronary angiogram within 1 week after onset of symptoms. New overt heart failure was diagnosed when new or worsening symptoms suggesting heart failure required a change of heart failure treatment and (prolonged) admission and a non-cardiac cause could not be identified. Debilitating stroke required the presence of acute symptoms or signs suggesting stroke combined with functional impairment 30 days after onset of symptoms, or death within 30 days. Peripheral revascularisation included any vascular intervention peripheral to the coronary circulation and amputation because of a vascular condition. When more than one event was diagnosed on the same date, the critical events committee also determined the order of occurrence.

Statistical analysis

Sample size estimation and interim analysis procedures have been described elsewhere.[13] Based on the simvastatin-treated group in the Scandinavian Simvastatin Survival Study (4S),[14] the assumed rate of the primary efficacy outcome in the placebo group was 5·6 per 100patient-years (731 events). With 30 000 patient-years of follow-up, the study was estimated to have 95% power to detect an 18% reduction of the primary efficacy outcome by nifedipine GITS relative to placebo at an overall 5% level of significance.
All analyses were done by intention to treat. Events with an onset date after the planned date of the end-of-study visit were not included. We regarded deaths of unknown cause as cardiovascular. Coronary angiography and percutaneous coronary intervention on the same day were counted only as percutaneous coronary intervention. We compared treatment groups with Kaplan-Meier plots and log rank tests without adjustment for covariates or interim analysis. Event rates were taken as number of events divided by total time that patients had been at risk of the (combined) event concerned. Hazard ratios with 95% CIs were obtained with

Cox proportional-hazards models, with treatment allocation as the only covariate. Interaction tests for subgroup analyses were done with Cox proportional-hazards models.
We calculated an overall p value for comparison of mean heart rate and blood pressure levels between treatment groups from a mixed-effects model for repeated measurements, with the SAS proc mixed procedure (SAS Institute, Cary, NC, USA).

Role of the funding source

An independent research institute (SOCAR Research SA) and an independent steering committee were responsible for study design, management, data analysis, and data interpretation. The role of the sponsor was restricted to study medication supply and on-site monitor-

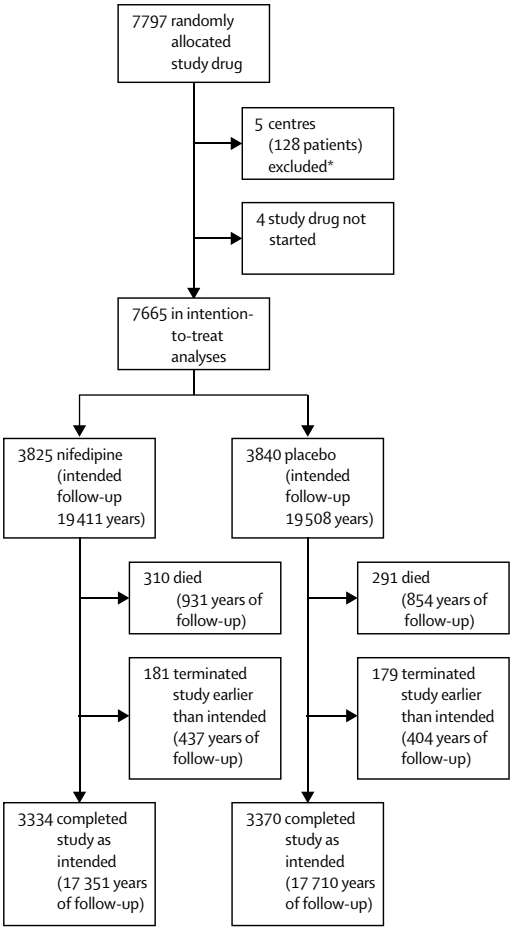


***Figure 1*: Trial profile**
*Difficulties with source data verification noted during on-site audits.

ing. A representative of the sponsor (non-voting) was in attendance at steering committee meetings. The chair of the safety monitoring committee prepared the random allocation list. The sponsor's drug safety department had to contact this person to unmask adverse drug reactions for reporting to local regulatory authorities.

RESULTS

The ACTION study was completed as planned; figure 1 shows the trial profile. Centres contributed a median of 19 patients (range 1-107); 13 centres randomised fewer than four patients. Intended follow-up (either until death, until last visit or contact within 6 weeks before planned

	Nifedipine (n=3825)	Placebo (n=3840)
Demographics		
Age (years)	63·5 (9·3)	63·4 (9·3)
Men	3041 (80%)	3043 (79%)
Clinical features		
History of myocardial infarction	1974 (52%)	1924 (50%)
With coronary revascularisation	944 (25%)	960 (25%)
Angiographic coronary artery disease, no myocardial infarction	1222 (32%)	1249 (33%)
With coronary revascularisation	766 (20%)	759 (20%)
Positive exercise or radionuclide test only	616 (16%)	646 (17%)
No history of coronary artery disease	13 (0·3%)	21 (0·5%)
Significant lesions on coronary angiogram	2632 (69%)	2634 (69%)
Normal coronary angiogram	50 (1%)	48 (1%)
Angiography not done or unknown	1143 (30%)	1158 (30%)
Past use of calcium antagonists	854 (22%)	823 (21%)
Current NYHA class II–III	1756 (46%)	1776 (46%)
Anginal attacks	3544 (93%)	3526 (92%)
History of peripheral cardiovascular disease*	494 (13%)	491 (13%)
Risk factors		
Current smoker	686 (18%)	670 (17%)
Total cholesterol ⩾5·0 mmol/L	2382 (62%)	2433 (63%)
Body-mass index ⩾30·0 kg/m^2	849 (22%)	895 (23%)
Blood pressure ⩾140/90 mm Hg	1975 (52%)	2002 (52%)
Any of the above	3291 (86%)	3362 (88%)
Diabetes mellitus	565 (15%)	545 (14%)
Treated with insulin	86 (2%)	97 (3%)
Cardiovascular variables		
Heart rate (beats per min)	64·3 (10·3)	64·4 (10·3)
Systolic blood pressure (mm Hg)	137·3 (18·8)	137·6 (18·6)
Diastolic blood pressure (mm Hg)	79·9 (9·4)	79·8 (9·5)
Ejection fraction core laboratory value (%)†	48·3 (6·4)	48·2 (6·4)
Ejection fraction local value only (%)‡	56·6 (9·1)	57·8 (9·9)

Data are number of patients (%) or mean (SD). *Stroke, transient ischaemic attacks, or claudication. †7016 core laboratory values (3519 nifedipine, 3497 placebo). ‡607 local values (286 nifedipine, 321 placebo).

Table 1: **Baseline characteristics**

	Nifedipine (n=3825)	Placebo (n=3840)
Antianginal drug		
β blocker	3032 (79%)	3066 (80%)
Organic nitrate, as needed	2157 (56%)	2175 (57%)
Organic nitrate, daily maintenance	1455 (38%)	1417 (37%)
Other vasodilator	158 (4%)	148 (4%)
Any of the above	3775 (99%)	3784 (99%)
Any two of the above	1888 (49%)	1960 (51%)
Any three or four of the above	563 (15%)	520 (14%)
Lipid-lowering		
Statin	2409 (63%)	2389 (62%)
Fibrate	242 (6%)	246 (6%)
Other	45 (1%)	68 (2%)
Any of the above	2607 (68%)	2591 (67%)
Blood-pressure lowering		
ACE inhibitor	771 (20%)	792 (21%)
Angiotensin-II antagonist	90 (2%)	93 (2%)
Diuretic	432 (11%)	447 (12%)
Other	113 (3%)	81 (2%)
Any of the above	1165 (30%)	1166 (30%)
Other cardiovascular		
Acetylsalicylic acid	3293 (86%)	3304 (86%)
Vitamin K antagonist	156 (4%)	149 (4%)
Cardiac glycoside	30 (1%)	50 (1%)
Amiodarone, sotalol, or other antiarrhythmic	138 (4%)	157 (4%)

Data are number of patients (%).

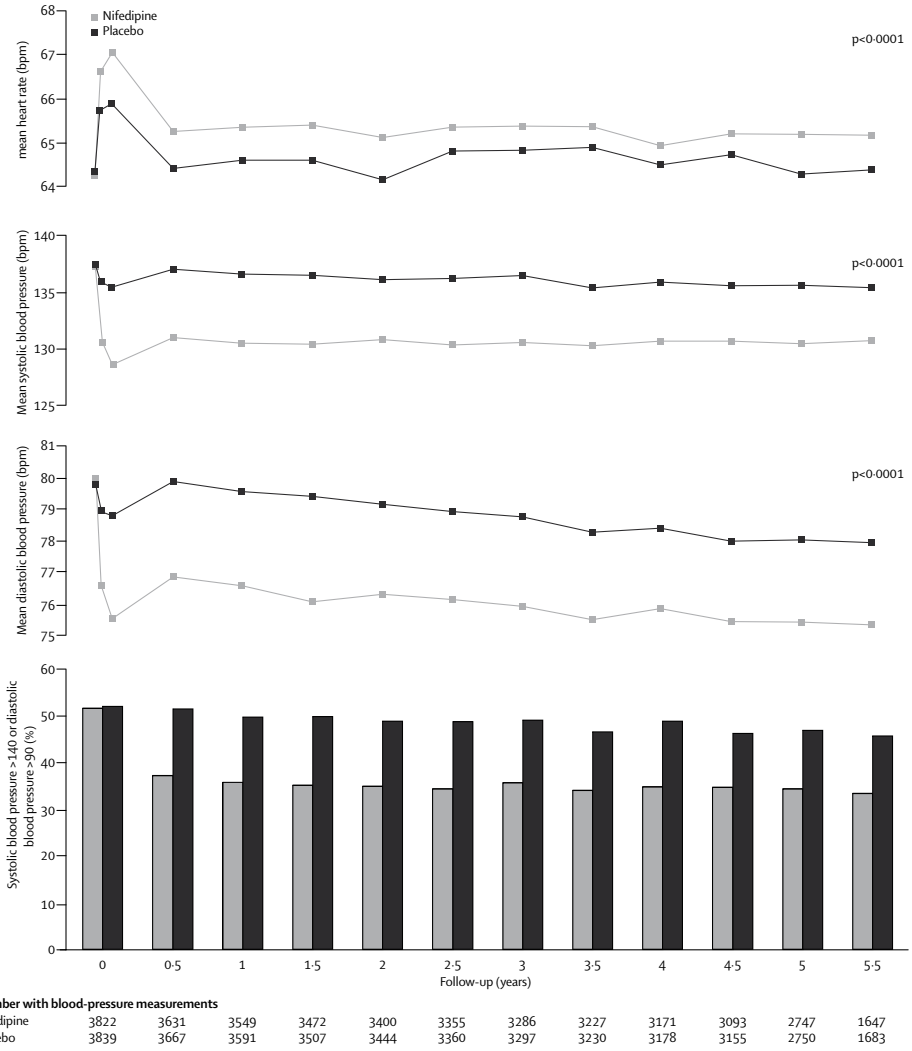
Table 2: **Concomitant treatments at baseline**

end of follow-up, or until planned date of end-of-study visit) was 38 919 patient-years (19 411nifedipine, 19 508 placebo). Actual follow-up was 37 867 patient-years (18 899 nifedipine, 18 968 placebo). Follow-up was thus 97·3% complete.

Table 1 presents baseline characteristics. Mean age was 63·5 years (SD 9·3), 6084 (79%) patients were men, and 7540 (98%) were of white ethnic origin.

Table 2 shows treatments prescribed at the time of randomisation. Treatment groups were well balanced at baseline.

Addition of nifedipine GITS to the basic regimen was generally well tolerated. At 6 weeks, 3366 (88%) patients allocated nifedipine and 3533 (92%) assigned placebo were on the full dose. Study drugs were taken for 79% of total follow-up time by individuals randomised to nifedipine and for 82% of follow-up for those allocated placebo. A reduction to half-dose happened for 16% of total follow-up for patients assigned nifedipine and for 6% of follow-up for those given placebo. Study drugs were withdrawn permanently 2 or more days before death or end of follow-up in 1305 (34%) started on nifedipine and 1179 (31%) allocated placebo. In 389 nifedipine and 172 placebo patients, the reason was occurrence of an adverse event, the most frequent events of which were peripheral oedema (139 nifedipine, 20 placebo) and



Number with blood-pressure measurements

Nifedipine	3822	3631	3549	3472	3400	3355	3286	3227	3171	3093	2747	1647
Placebo	3839	3667	3591	3507	3444	3360	3297	3230	3178	3155	2750	1683

Figure 2: **Change in mean heart rate and blood pressure**

SEs were less than 0·5 bpm for heart rate and less than 1·0 mm Hg for both systolic blood pressure and diastolic blood pressure at all time points. P value calculated with test for repeated measurements.

headache (43 nifedipine, 20 placebo). As shown in figure 2, nifedipine raised mean heart rate during follow-up by 1 beat per min (p<0·0001), and it was associated with significant mean reductions of systolic and diastolic blood pressure relative to placebo. During follow-up, the proportion of patients with blood pressure of 140/90 mm Hg or more (52% at baseline) averaged 35% for patients assigned nifedipine, and 47% for those allocated placebo.

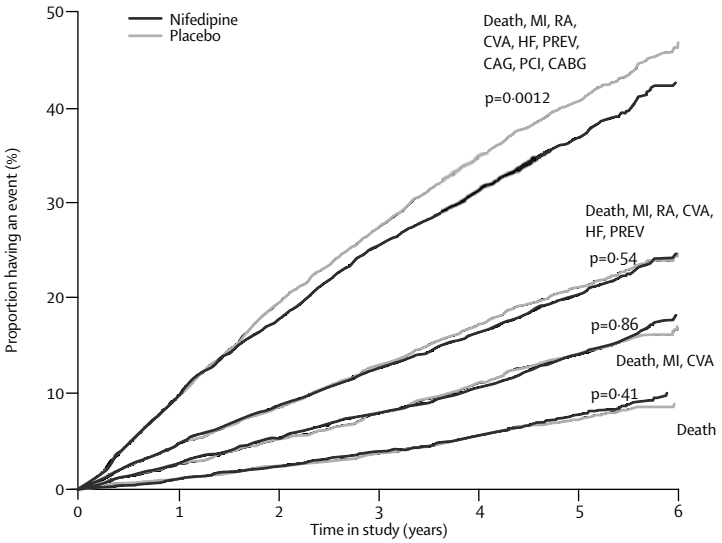
	Nifedipine (n=3825)		Placebo (n=3840)		Hazard ratio* (95% CI)	p
	Total number of events	Number of patients with event (incidence per 100 patient-years at risk)	Total number of events	Number of patients with event (incidence per 100 patient-years at risk)		
All-cause mortality	310	310 (1·64)	291	291 (1·53)	1·07 (0·91–1·25)	0·41
Non-cardiovascular	132	132 (0·70)	114	114 (0·60)	1·16 (0·90–1·49)	0·24
Cardiovascular or unknown†	178	178 (0·94)	177	177 (0·93)	1·01 (0·82–1·24)	0·93
Myocardial infarction	320	267 (1·46)	296	257 (1·39)	1·04 (0·88–1·24)	0·62
Refractory angina	171	150 (0·81)	190	174 (0·94)	0·86 (0·69–1·07)	0·18
New overt heart failure	117	86 (0·46)	158	121 (0·65)	0·71 (0·54–0·94)	0·015
Debilitating stroke	82	77 (0·41)	108	99 (0·53)	0·78 (0·58–1·05)	0·10
Peripheral revascularisation	187	146 (0·79)	144	118 (0·63)	1·25 (0·98–1·59)	0·073
Coronary angiography	1200	895 (5·46)	1357	1068 (6·69)	0·82 (0·75–0·90)	<0·0001
Percutaneous coronary intervention	512	385 (2·15)	548	417 (2·34)	0·92 (0·80–1·06)	0·25
Coronary bypass surgery	299	294 (1·62)	373	371 (2·06)	0·79 (0·68–0·92)	0·0021

*Comparison of nifedipine with placebo. †Includes cause unknown (24 nifedipine, 28 placebo).

***Table 3*: Incidence of clinical events**

Table 3 shows event rates for every outcome included in predefined combined endpoints, and figure 3 shows time-to-event data for all-cause mortality. 310 people started on nifedipine and 291 allocated placebo died; of these, 103 deaths in the nifedipine group and 97 in the placebo group happened while the patient was on study drug. Cardiovascular (including cause unknown) and non-cardiovascular death rates were similar between treatment groups (table 3). Nifedipine significantly reduced the rate of new overt heart failure (p=0·015), and need for coronary angiography (p<0·0001) and bypass surgery (p=0·0021).

Table 4 presents results of the combined primary endpoints for efficacy and safety and predefined secondary endpoints, and figure 3 shows corresponding time-to-event plots for end-



Number at risk at death

Nifedipine	3825	3732	3651	3568	3478	2966	386
Placebo	3840	3746	3666	3582	3483	2963	394

***Figure 3:* Time to first occurrence of clinical events**

MI=myocardial infarction. RA=refractory angina. CVA=debilitating stroke. HF=new overt heart failure. PREV=peripheral revascularisation. CAG=coronary angiography. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting.

	Primary endpoint for efficacy		Primary endpoint for safety		Cardiovascular events		Death, cardiovascular events, or procedures		Vascular events	
	Nifedipine (n=3825)	Placebo (n=3840)	Nifedipine (n=3825)	Placebo (n=3840)	Nifedipine (n=3825)	Placebo (n=3840)	Nifedipine (n=3825)	Placebo (n=3840)	Nifedipine (n=3825)	Placebo (n=3840)
Mean follow-up at risk (days)*	1668	1660	1740	1739	1668	1660	1475	1434	1574	1556
Percentage of time at risk on any dose of study drug (%)	80%	85%	80%	84%	80%	85%	83%	88%	81%	86%
Percentage of time at risk on full dose of study drug (%)	60%	76%	60%	75%	60%	76%	62%	79%	61%	77%
Event that terminated event-free follow-up										
Non-cardiovascular death	110	92	118	100	†	†	98	79	†	†
Cardiovascular or unknown death	82	92	111	112	82	92	77	74	88	92
Myocardial infarction	234	225	264	253	234	225	190	186	215	214
Refractory angina	135	154	†	†	135	154	113	125	128	137
New overt heart failure	50	82	†	†	50	82	44	60	†	†
Debilitating stroke	64	83	69	93	64	83	58	72	64	81
Peripheral revascularisation	129	100	†	†	129	100	109	77	115	92
Coronary angiography	†	†	†	†	†	†	629‡	779‡	†	†
Percutaneous coronary intervention	†	†	†	†	†	†	116	127	243	266
Coronary artery bypass grafting	†	†	†	†	†	†	5	4	173	239
Any of the above (rate§)	804 (4·60)	828 (4·75)	562 (3·08)	558 (3·05)	694 (3·97)	736 (4·22)	1439 (9·32)	1583 (10·50)	1026 (6·22)	1121 (6·85)
Any first event on study drug	528	552	313	331	507	536	1036	1206	734	829

*Until first of: any event considered; last visit or contact; planned date of end-of-study visit. †Not included in the combined endpoint concerned. ‡On same day as percutaneous coronary intervention, counted as percutaneous coronary intervention only. §Number of patients with event per 100 patient-years at risk.

Table 4: **Incidence of combined endpoints**

points that include all-cause mortality. The frequency of the primary endpoint for efficacy did not differ between patients assigned nifedipine and those allocated placebo (hazard ratio 0·97 [95% CI 0·88-1·07], p=0·54). The primary endpoint for safety was similar in both groups (1·01 [0·90-1·14], p=0·86). Any death, cardiovascular event, or procedure was significantly less frequent in patients assigned nifedipine than in those allocated placebo (0·89 [0·83-0·95], p=0·0012), but the frequency of cardiovascular events alone did not differ between treatment groups (0·94 [0·85-1·05], p=0·26). Nifedipine prolonged mean event and procedure-free survival by 41days. The difference between treatment groups for this combined endpoint was mainly attributable to fewer patients started on nifedipine who had coronary angiography as first event. Nifedipine also reduced the occurrence of any vascular event (0·91 [0·83-0·99], p=0·027).

Figure 4 shows predefined subgroup analyses for the primary endpoint for efficacy. Only blood pressure level seemed to be a modifier of the effect of nifedipine (interaction test, p=0·02). In patients with systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more, the noted incidence of primary endpoints for efficacy for nifedipine was less than for placebo.

DISCUSSION

ACTION has established the safety of nifedipine GITS, a long-acting dihydropyridine calcium antagonist, in the treatment of patients with stable angina pectoris already on conventional treatment. No significant difference was noted with respect to the primary efficacy endpoint, but secondary endpoints for all vascular events and procedures did show benefit.

Compared with short-acting compounds, long-acting calcium antagonists have been shown to reduce the risk of cardiovascular events in patients treated for hypertension.[15] Although

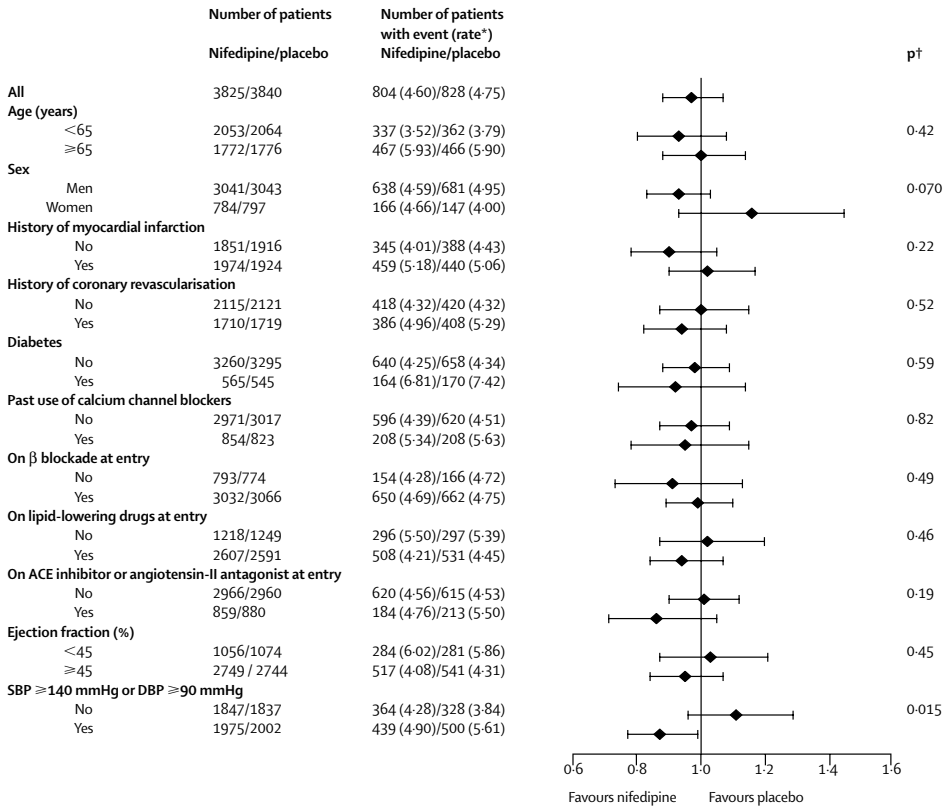


Figure 4: **Effect of nifedipine on primary endpoint for efficacy in predefined subgroups**
ACE=angiotensin-converting enzyme. SBP=systolic blood pressure. DBP=diastolic blood pressure.
*Number of events per 100 patient-years of follow-up at risk. †For effect modification (interaction test).

several large trials in hypertension have shown the efficacy and safety of nifedipine GITS [16] and other drugs in this class,[17,18] their effect on long-term clinical outcome in patients with coronary disease was unknown. Two other large studies reported on the use of another class of drug, ACE inhibitors, in patients either at risk of coronary disease or with some manifestation of coronary disease.[2,3] A study that compared atenolol, nifedipine, and their combination in patients with stable angina [19] was not placebo controlled and lacked power for showing differences between treatment groups with respect to clinical outcome.

ACTION started in 1996 and went to completion with no alteration of the protocol. Both the number of patients recruited and the number of events in the placebo group were higher than we anticipated. The difference in blood pressure levels between treatment groups shows that we did achieve a contrast between nifedipine and placebo. The formulation of nifedipine used in ACTION was not the short-acting preparation but the GITS formulation, which modifies release of the drug to provide stable long-term concentrations in plasma.

The chosen primary endpoint for efficacy did not differ between treatment groups; however, we did show that nifedipine is not unsafe. Secondary endpoints showed a benefit of nifedipine on cardiovascular outcomes, largely manifested by a substantial reduction of the need for coronary procedures and interventions for symptoms. These findings were achieved in patients who were already receiving antianginal, blood pressure, and lipid-lowering treatment, as decided by the patient's doctor.

ACTION confirmed that stable angina has a good prognosis. The mortality rate in the placebo group was just 1·53 per 100 patient-years and was essentially the same as the rate reported in a similar study in patients with presumed coronary disease.[3] In participants assigned nifedipine the mortality rate was 1·64 per 100 patient-years; hence, the absolute difference in mortality was 1·1 deaths per 1000 patient-years of follow-up, which was almost all non-cardiovascular and is well within the play of chance.

One reason we did not note a difference between groups in the primary endpoint for efficacy could be that a further reduction of cardiovascular events by addition of other drugs is not realistic in patients with stable angina who are already treated with antianginal, blood pressure, and lipid-lowering drugs in near-optimum manner. In ACTION, 80% of patients were on β blockers compared with 39% [2]and 62% [3]in two trials of angiotensin-converting-enzyme inhibitors;[2,3] the proportion on lipid-lowering drugs was 68% in ACTION and 28% [2] and 57% [3] in these trials. A second reason might be that use of nifedipine was associated with an increase in peripheral vascular procedures, which was a component of the combined primary endpoint. Peripheral vascular disease and coronary disease typically coexist. Patients whose angina is relieved by treatment might then manifest symptoms of peripheral vascular disease and seek treatment for that disorder.

Nifedipine GITS did have a positive effect on two of the three predefined secondary combined endpoints. The combined rate of death, major cardiovascular events, revascularisation, and coronary angiography was reduced by 11%, the main reason being the pronounced reduction in the need for coronary angiography (150 fewer coronary angiograms as first event in nifedipine than in placebo). Any vascular event was reduced by 9%, the main reason being the reduced need for percutaneous coronary interventions and bypass surgery (in total, 89 fewer procedures as first event in nifedipine than in placebo).

ACTION did not accord with past claims that nifedipine induces myocardial infarction or heart failure. Rates of myocardial infarction were similar in both groups. Although peripheral oedema was more common in patients assigned nifedipine than in those assigned placebo, nifedipine reduced the incidence of new overt heart failure by 29%. We used strict criteria for diagnosis of heart failure, which required more symptoms than merely presence of peripheral oedema. This definition could account for our seemingly unexpected result concerning heart failure, which might also be attributed to long-term reduction of ischaemic episodes or reduction of blood pressure by nifedipine. We excluded patients with left-ventricular systolic dysfunction because, at the time the trial was designed, nifedipine was contraindicated in

such patients. Our findings concerning heart failure suggest that a trial with nifedipine GITS in patients with coronary disease and left-ventricular systolic dysfunction might be of interest. The recorded 22% reduction of the incidence of debilitating stroke by nifedipine, although not significant, accords with results from trials and meta-analyses in hypertension.[17,18]

Several predefined subgroup analyses were done in ACTION and caution is needed in their interpretation. Patients who had raised blood pressure levels at baseline seemed to benefit from addition of nifedipine to the basic regimen because the combined rate of death and major cardiovascular events in this subgroup was reduced by 13%. This argument is plausible since the benefit of blood pressure reduction is known.

The design of ACTION differs from similar studies.[2,3] We did not use a run-in period to remove patients who did not tolerate nifedipine GITS, which must be taken into account when comparing withdrawal of study drugs and tolerance in ACTION with other studies that incorporated this design feature. Because of the fairly low total mortality expected, we used a combined outcome that incorporated non-fatal clinical events but we did not exclude non-cardiovascular death from the primary outcome. We chose to do this because a reduction of cardiovascular death by treatment increases the total number of non-cardiovascular deaths even if the treatment does not affect the rate of non-cardiovascular death per unit person-time of follow-up; this effect is directly related to the treatment and should therefore be accounted for when assessing clinical benefit.[20] We included peripheral revascularisation in the primary outcome because of the putative anti-atherosclerotic action of nifedipine. Hence, the primary outcome included all clinically relevant events that might be affected either positively or negatively by nifedipine, which allowed the net benefit of treatment with nifedipine to be assessed by one unequivocal criterion. Since we believe this conveys important additional information,[21] we also report for combined endpoints the events that terminated event-free survival.

Nifedipine GITS can be used safely for the long-term treatment of patients with coronary disease and angina pectoris because, in addition to relieving symptoms of angina, it prolongs cardiovascular event and procedure-free survival.

Contributors

P A Poole-Wilson was study chairman. J Lubsen designed the study and drafted the study protocol and the report. B A Kirwan was study director and managed the data. F J van Dalen had the idea for the study. G Wagener represented the sponsor on the steering committee and acted as liaison. N Danchin was chairman of the critical events committee. H Just, M Motro, and J D Parker were co-chairman of the steering committee. K A A Fox, M Bourassa, A M Dart, J-M Detry, P Hildebrandt, A Hjalmarson, J A Kragten, G P Molhoek, J-E Otterstad, R Seabra-Gomes, J Soler-Soler, and S Weber were members of the steering committee and country coordinators. S J Pocock was chairman of the data monitoring and ethical review committee and T C Clayton did the interim analyses. M Motro, J D Parker, M Bourassa, A M

Dart, J-M Detry, P Hildebrandt, J A Kragten, G P Molhoek, J-E Otterstad, R Seabra-Gomes, J Soler-Soler, and S Weber were also principal investigators. P A Poole-Wilson, N Danchin, K A A Fox, H Just, SJ Pocock, B-A Kirwan, and F J van Dalen critically revised the report. Committee members and principal investigators are listed in the webappendix (http://image.thelancet.com/extras/04art6402webappendix.pdf).

Conflict of interest statement

Members of the steering committee were not involved in any directly competing trial. Members of committees were funded by SOCAR Research SA to attend meetings related to the trial. Outside the context of ACTION, HJ, KAAF, MM, JDP, AMD, PH, and RS-G have served as consultants to or received travel expenses, payment for speaking at meetings, or funding for research from Bayer. PAP-W, JL, HJ, KAAF, SJP, MM, JDP, MGB, AMD, PH, ÅH, JAK, GPM, JES, RS-G, and SW have served as consultants to or received travel expenses, payment for speaking at meetings, or funding for research from other pharmaceutical companies. GW is a full-time employee of Bayer Healthcare AG; BAK and FJvD are full-time employees of SOCAR Research SA.

Acknowledgments

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Chapter 3

Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial.

Lubsen J, Wagener G, Kirwan BA, Brouwer S,
Poole-Wilson PA.

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Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial

Jacobus Lubsen[a,b], Gilbert Wagener[c], Bridget-Anne Kirwan[a], Sophie de Brouwer[a] and Philip A. Poole-Wilson[d] on behalf of ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) investigators

[a]SOCAR Research, Nyon, Switzerland, [b]Department of Epidemiology and Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands, [c]Pharma Research Center, Bayer Healthcare AG, Wuppertal, Germany and [d]Cardiac Medicine, Imperial College, London, UK.

Objective: To examine the effects of nifedipine GITS on clinical outcome in patients with concurrent stable angina and hypertension.

Methods: Data from the double-blind placebo-controlled ACTION trial was stratified for hypertension (blood pressure ≥ 140/90 mmHg), at baseline.

Results: A total of 52% of 7665 ACTION patients were hypertensive. Some 80% were on a β blocker; hypertensives were more often treated with other blood pressure-lowering drugs. Mean baseline blood pressure was 122/74 mmHg among normotensives and 151/85 mmHg among hypertensives. Follow-up blood pressures were reduced by nifedipine ($P < 0.001$) on the average by 3.9/2.4 and 6.6/3.5 mmHg among normotensives and hypertensives, respectively. Nifedipine GITS significantly ($P < 0.05$) reduced the combined incidence of all-cause mortality, myocardial infarction, refractory angina, heart failure, stroke and peripheral revascularization by 13% in hypertensives only. Nifedipine significantly reduced the incidence of any stroke or transient ischemic attack by almost 30% in both subgroups and the need for coronary angiography by 21% in normotensives and 16% in hypertensives. Among hypertensives, the incidence of new overt heart failure was significantly reduced by 38% and of debilitating stroke by 33%. Among normotensives, the need for coronary bypass grafting was significantly reduced by 32%. Nifedipine did not affect all-cause death, cardiovascular death and myocardial infarction in either normo- or hypertensives, but increased the need for peripheral revascularization.

Conclusion: The salutary effects of the addition of nifedipine GITS to the basic regimen of patients with concurrent stable symptomatic coronary artery disease and hypertension emphasize the need for blood pressure control. *J Hypertens* 23:641-648 © 2005 Lippincott Williams & Wilkins.

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Correspondence and requests for reprints to J. Lubsen, SOCAR Research SA, PO Box 2564, CH-1260 Nyon 2, Switzerland. Tel: +41 22 9944343; fax: +41 22 9944309; e-mail: jlubsen@compuserve.com
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See editorial commentary page 489

INTRODUCTION

Hypertension is a leading cause of morbidity and mortality worldwide [1] and substantially contributes to the risk of the development of cardiovascular diseases [2]. A number of placebo-controlled clinical trials have shown that blood pressure reduction reduces morbidity and mortality both in younger [3,4] and in older patients with diastolic and systolic hypertension [5-7], and in patients with isolated systolic hypertension [8,9]. Clinical trials comparing different blood pressure-lowering drugs in patients with hypertension after wash-out of previous therapy have not shown relevant differences in outcome [10-12] and the notion that available treatment options are equally effective is supported by a recent meta-analysis [13].
The dihydropyridine calcium antagonist nifedipine is widely used for the treatment of hypertension. In one large clinical outcome trial, the long-acting gastrointestinal therapeutic system (GITS) formulation of this compound was compared with co-amilozide. Both were equally effective in preventing overall cardio- and cerebrovascular complications [10]. Placebo-controlled trials with nifedipine GITS having adequate power to assess effects on morbidity and mortality have not been undertaken. Recently, the placebo-controlled ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) trial examining the effects of the same compound on clinical outcomes in 7665 patients with stable symptomatic coronary disease has been completed [14]. The main conclusion was that nifedipine GITS is safe in patients with stable symptomatic coronary disease and reduces the occurrence of new overt heart failure and the need for coronary interventions. A total of 52% of ACTION patients had a baseline blood pressure ≥ 140/ 90 mmHg, and a pre-defined subgroup analysis suggested that nifedipine GITS reduces the combined rate of death from any cause, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularization in patients with stable angina who also have elevated blood pressure [14]. This paper reports this subgroup analysis in more detail.

METHODS

Design

The ACTION design, methods and main results have been published previously [14,15]. Briefly, patients aged 35 years or older with stable symptomatic angina pectoris requiring treatment were randomized in equal proportions to the addition of either nifedipine GITS or matching placebo. In addition to angina, patients had to have either a history of myocardial infarction, or proven angiographic coronary artery disease, or a positive exercise test or perfusion defect. The left-ventricular ejection fraction had to be at least 40%. Major exclusions were: clinically significant heart failure, any major cardiovascular event or intervention within the last 3 months, planned coronary angiography or intervention, known intolerance to dihydropyridines, clinically significant valvular or pulmonary disease, unstable insulin-dependent diabetes mellitus, any gastro-intestinal condition that prohibited the use of GITS tablets, any condition other than coronary artery disease that limited life expectancy, symptomatic orthostatic hypotension or supine systolic blood pressure 90 mmHg or less, systolic blood pressure at least 200 mmHg and/or diastolic blood pressure at least 105 mmHg, and elevated creatinine or aminotransferase levels. Women could only participate if there was no risk of pregnancy. Detailed selection criteria and definitions have been described elsewhere [15].

The starting dose of nifedipine GITS or matching placebo was 30 mg once daily, increasing to 60 mg once daily within 6 weeks. Physicians were encouraged to attempt risk factor modification and to treat symptomatic angina with compatible medications. Lipid-lowering treatment was either continued or started at the same time as study medication according to internationally accepted guidelines. The following drugs could not be used in combination with study medication: calcium antagonists (2 week washout required), cardiac glycosides (unless given for supra-ventricular arrhythmias), other positive inotropic agents, class I or III antiarrhythmics other than amiodarone or sotalol, cimetidine, anti-psychotic and anti-epileptic drugs, rifampicin or rifampin.

After baseline assessments and treatment allocation, patients were seen at the out-patient clinic 2 weeks, 6 weeks and 6 months after randomization; and from then onwards every 6 months. Between visits, patients were contacted by telephone. At each clinic visit, blood pressure was recorded with a standard sphygmomanometer in the sitting position after 5 min rest.

Serious adverse events suggesting a possible major cardiovascular event were classified by the Critical Events Committee according to predefined criteria without access to the study medication code. Cause of death was classified as unknown, cardiovascular or non-cardiovascular.

STATISTICAL METHODS

Patients were excluded from the present analysis when the baseline blood pressure before start of ACTION study medication was missing. Those with available baseline blood pressures were classified as normotensive when the systolic blood pressure was below 140 and the diastolic blood pressure was below 90 mmHg. Patients with baseline blood pressures that did not meet this criterion were classified as hypertensive.

Mean blood pressure changes from baseline at selected time points during follow-up were calculated using all blood pressure measurements that were actually performed irrespective of study medication intake or prior occurrence of non-fatal clinical events. Overall mean changes from baseline were obtained by subtracting for each patient the mean follow-up value from the baseline value, and then averaging the results.

The following composite outcomes were compared: the combined rate of death from any cause, myocardial infarction, refractory angina requiring coronary angiography, new overt heart failure requiring hospitalization and peripheral revascularization (i.e. the ACTION primary endpoint for efficacy); the combined rate of death from any cause, myocardial infarction and debilitating stroke (i.e. the ACTION primary endpoint for safety); any cardiovascular event (i.e. the ACTION primary endpoint for efficacy minus non-cardiovascular death); any death, cardiovascular event or procedure (i.e. the ACTION primary endpoint for efficacy plus coronary angiography, percutaneous coronary intervention and coronary bypass surgery); and any vascular event or procedure (i.e. the ACTION primary endpoint for efficacy minus non-cardiovascular death and new overt heart failure, plus percutaneous coronary intervention and coronary bypass surgery). In addition, the combination of disabling stroke, any stroke reported by investigators that did not meet the criteria for disabling stroke, and any reported transient ischaemic attack was considered.

All analyses for composite outcomes and clinical events were done based on intention-to-treat. Deaths of unknown cause were considered as cardiovascular. Coronary angiography and percutaneous coronary intervention on the same day were counted only as percutaneous coronary intervention. Treatment groups were compared by the log-rank test without adjustment for covariates or interim analysis. Event rates were taken as number of patients with event divided by total time that patients had been 'at risk' of the event concerned. For composite outcomes, the time that the first component event occurred was used in event rate calculations. Hazard ratios with 95% confidence intervals (CI) were obtained using Cox proportional hazards models with treatment allocation as the only covariate. Interaction tests were performed by Cox proportional hazards models. An overall P-value for comparing blood pressure levels between treatment groups was obtained from a mixed effects model for repeated measurements, using the SAS proc. mixed procedure (SAS Institute, Cary, North Carolina, USA). Percentages were compared using chi-squared tests.

RESULTS

As reported elsewhere [14], ACTION was completed as planned and 7665 patients were started on study medication (3825 nifedipine GITS; 3840 placebo). Follow-up was 97.3% complete and mean follow-up was 4.9 years. From the present analysis, four patients (three nifedipine, one placebo) were excluded because the baseline blood pressure was missing. Hence, the present report concerns 7661 patients. Of these, 3684 were normotensive and 3977 were hypertensive at baseline. Baseline characteristics are given in Table 1. Patients with hypertension were older and were more often female. A history of myocardial infarction and significant lesions on a prior coronary angiogram were less frequent among patients with hypertension, while more of the latter had been treated before with a calcium antagonist. Both groups were equally frequent in NYHA class II - III and equal proportions reported anginal attacks. A history of peripheral vascular disease and of hypertension treated with drugs was more frequent among those with hypertension. Fewer patients with hypertension smoked but elevated total cholesterol and body mass index were more frequent than among normotensives. Hypertensives were more often diabetic and had a higher heart rate at baseline than normotensives.

Table 1 Patient characteristics by baseline blood pressure classification

	Normotensive	Hypertensive	*P**
Total number of patients	3684	3977	
Mean (SD) age (years)	61.8 (9.4)	65.0 (8.9)	< 0.001
Male gender	83	76	< 0.001
History of MI	53	49	0.003
Angiographic CAD, no MI	32	33	0.4
Positive exercise or radionuclide test only	15	18	0.005
Significant lesions on coronary angiogram	71	66	< 0.001
Angiography not performed or unknown	28	32	< 0.001
Past use of calcium antagonists	19	24	< 0.001
Current NYHA class II–III	46	46	0.9
Anginal attacks	92	92	0.9
History of peripheral vascular disease†	11	15	< 0.001
History of hypertension treated with drugs	28	54	< 0.001
Additional risk factors			
Current smoker	20	16	< 0.001
Total cholesterol $\geq$ 5.0 mmol/l	61	66	< 0.001
Body mass index $\geq$ 30.0 kg/m^2	19	26	< 0.001
Any of the above	73	77	< 0.001
Diabetes mellitus	12	17	< 0.001
Treated with insulin	2.0	2.7	0.04
Mean (SD) heart rate (beats/min)	63.5 (10.0)	65.1 (10.5)	0.003

Data are percentage of patients unless indicated otherwise. SD, standard deviation; MI, myocardial infarction; CAD, coronary artery disease; NYHA, New York Heart Association.*P-values for comparing all normo- with all hypertensives. †Stroke, transient ischemic attacks or claudication.

Data on the use of additional blood pressure-lowering medication for normotensives and hypertensives at baseline are given in Table 2 by assigned ACTION study medication. The majority of patients were on a β blocker and patients with hypertension were more often treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and diuretics than normotensives. Irrespective of the presence of hypertension, patients assigned nifedipine or placebo were well matched at baseline as regards use of additional blood pressure-lowering medication.

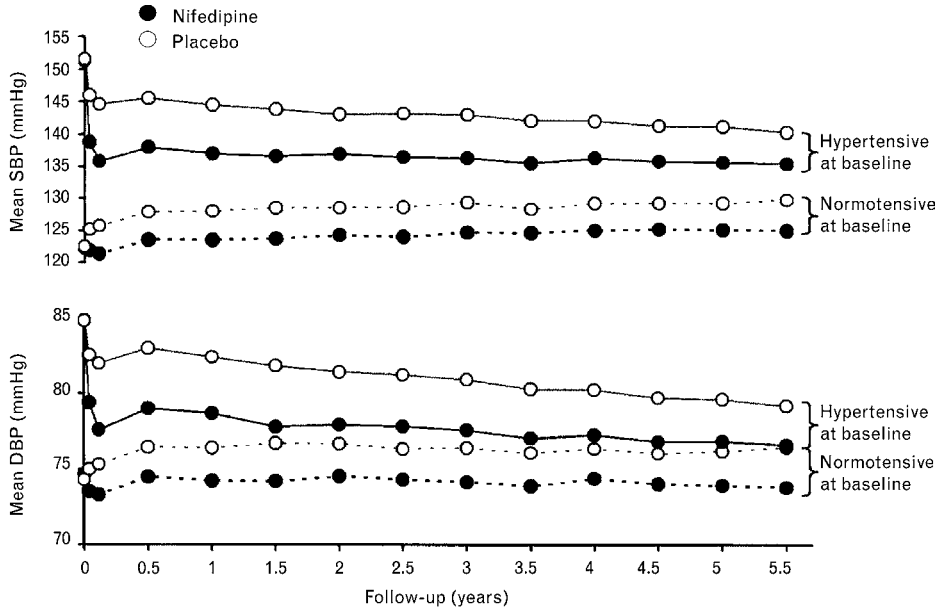
Table 2 **Use of additional blood pressure-lowering drugs by baseline blood pressure classification**

	Normotensive			Hypertensive		
	Nifedipine	Placebo	*P**	Nifedipine	Placebo	*P**
Baseline						
No. of patients	1847	1837		1975	2002	
Any calcium ant.†	0.4%	0.2%	–	0.6%	0.3%	–
β blocker	82%	81%	–	77%	79%	–
ACE-i or ARB	17%	17%	–	28%	28%	–
Diuretic	7.5%	8.6%	–	15%	14%	–
Any BP lowering	87%	87%	–	88%	88%	–
At 4 years						
No. of patients	1576	1554		1592	1623	
Any calcium ant.‡	83%	5.3%	< 0.001	84%	10%	< 0.001
β blocker	78%	78%	1.0	77%	79%	0.4
ACE-i or ARB	25%	28%	0.02	35%	49%	< 0.001
Diuretic	13%	15%	0.1	26%	32%	< 0.001
Any BP lowering	100%	87%	< 0.001	100%	93%	< 0.001

ant., antagonist; ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure. *P-values comparing nifedipine with placebo for normo- and hypertensives, respectively. †In the percentage of patients shown, calcium antagonists were not washed out before baseline assessments, as required by the protocol. ‡Either active study medication (i.e. nifedipine GITS) or any other calcium antagonist.

The use of additional blood pressure-lowering drugs at 4 years after start of study medication is shown in Table 2. Normotensives were overall more often using non-β blocking blood pressure-lowering drugs at 4 years than at baseline, and normotensives assigned placebo were

Fig. 1



Evolution of mean blood pressure for normo- and hypertensives at baseline, respectively. SBP, systolic blood pressure; DBP, diastolic blood pressure. Horizontal axis: time in years of follow-up. Standard errors of the means were too small to plot. Numbers of patients with blood pressure measurements are given also.

more often on such blood pressure-lowering drugs than normotensives assigned nifedipine. Similar but more pronounced differences were present among hypertensives.

The evolution of mean systolic and diastolic blood pressure over time by assigned treatment for normotensives and hypertensives at baseline respectively are shown in Figure 1. Mean follow-up blood pressures were consistently lower among patients assigned nifedipine than among those assigned placebo in both normotensives and hypertensives at baseline. Blood pressure data at baseline, and changes from baseline at 4 years and overall are given in Table 3.

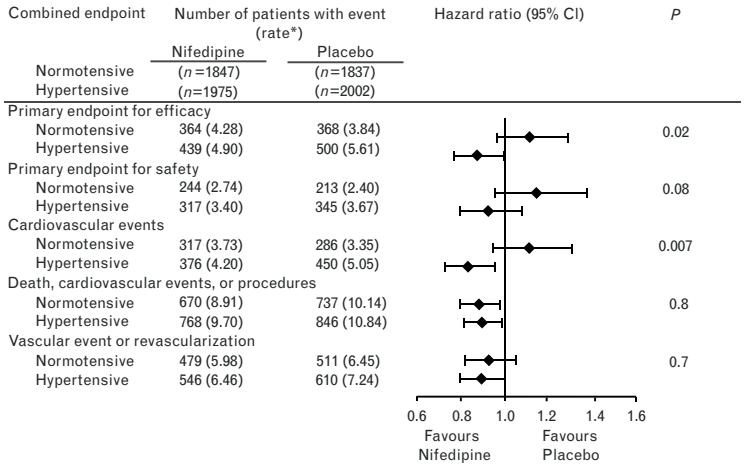
Table 3 Evolution of blood pressure (BP) by baseline blood pressure classification

	Normotensive			Hypertensive		
	Nifedipine	Placebo	*P**	Nifedipine	Placebo	*P**
No. of patients	1847	1837		1975	2002	
Baseline						
Mean SBP (SD)	122.3 (9.2)	122.4 (9.3)		151.3 (14.0)	151.5 (13.5)	
Mean DBP (SD)	74.6 (7.2)	74.3 (7.2)		84.8 (8.6)	84.8 (8.6)	
SBP $\geq$ 140 mmHg	–	–		94%	94%	
DBP $\geq$ 90 mmHg	–	–		42%	42%	
At 4 years						
No. of patients	1576	1554		1592	1623	
Mean Δ SBP (SD)	3.0 (15.0)	7.0 (16.0)	$<$ 0.001	$-$14.6 (19.1)	$-$9.1 (19.2)	$<$ 0.001
Mean Δ DBP (SD)	$-$0.3 (9.5)	2.1 (9.9)	$<$ 0.001	$-$7.6 (10.6)	$-$4.5 (10.7)	$<$ 0.001
BP $\geq$ 140/90 mmHg	23%	33%	$<$ 0.001	47%	64%	$<$ 0.001
SBP $\geq$ 140 mmHg	21%	31%	$<$ 0.001	45%	62%	$<$ 0.001
DBP $\geq$ 90 mmHg	6%	10%	$<$ 0.001	13%	21%	$<$ 0.001
Overall						
Mean Δ SBP (SD)	1.9 (14.7)	5.8 (15.7)	$<$ 0.001	$-$14.5 (18.2)	$-$7.9 (19.1)	$<$ 0.001
Mean Δ DBP (SD)	$-$0.5 (9.3)	1.9 (9.6)	$<$ 0.001	$-$7.0 (10.0)	$-$3.5 (10.3)	$<$ 0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure (mmHg, cuff method); SD, standard deviation; D, change from baseline. *P-values comparing nifedipine with placebo for normo- and hypertensives, respectively.

In Figure 2, the effects of nifedipine (relative to placebo) on pre-defined ACTION combined end-points are compared between normo- and hypertensives at baseline. Numbers of events and event-rates (expressed as number of patients with event per 100 patient-years at risk) are given also. As evidenced by 95% confidence intervals that do not include 'no effect' (hazard ratio = 1), nifedipine significantly reduced the hazard of all combined endpoints analysed among hypertensives at baseline, with the exception of the primary endpoint for safety. For the primary endpoint for efficacy and for cardiovascular events, the effects of nifedipine differed significantly among normo- and hypertensives at baseline.

Fig. 2



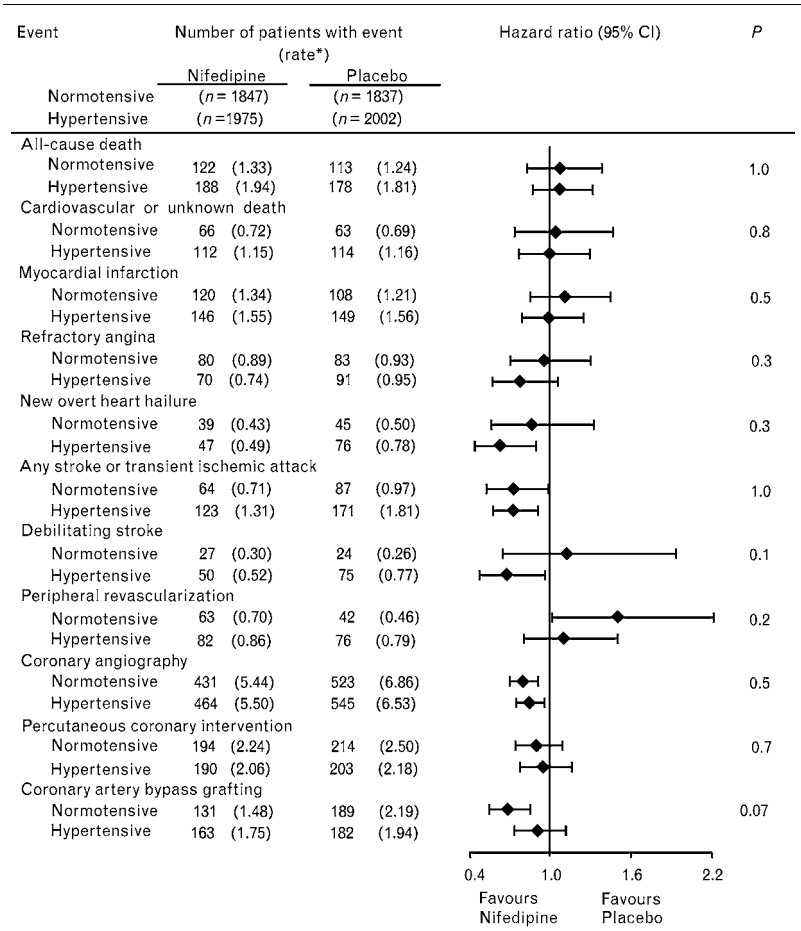
Effect of nifedipine on predefined combined endpoints for normo- and hypertensives at baseline, respectively. *Rates in number of events per 100 patient years of follow-up 'at risk'. P-values for effect modification (interaction test). CI, confidence interval.

Figure 3 shows results for separate clinical events in a similar manner as Figure 2. The rates of new overt heart failure and of debilitating stroke were significantly reduced by nifedipine among hypertensives, but not among normotensives. Rates of any stroke or transient ischaemic attack and of coronary angiography were significantly reduced by nifedipine both among normo- and among hypertensives at baseline. Nifedipine significantly increased the rate of peripheral revascularization among normo- but not among hypertensives. The opposite was the case for coronary artery bypass grafting.

DISCUSSION

In addition to lowering blood pressure, calcium antagonists are known to be an effective treatment for symptoms of angina pectoris, and are widely used for this indication. The ACTION study was initiated in response to the debate in the 1990s about the safety of calcium antagonists in particular in patients with coronary disease [16,17], and was designed to assess the effect of nifedipine GITS on clinical outcome in patients with stable angina irrespective of blood pressure level at baseline. In clinical practice, coronary disease and hypertension often occur concurrently. In ACTION, 52% of patients had baseline blood pressures 140/90 mmHg. The presence of so many patients provides an opportunity to examine the effects of nifedipine, relative to placebo, on the mortality and morbidity of patients who have both stable symptomatic angina and hypertension.

Fig. 3



Effect of nifedipine on clinical events for normo- and hypertensives at baseline, respectively. *Rates in number of events per 100 patient years of follow-up 'at risk'. P-values for effect modification (interaction test). CI, confidence interval.

The main findings from the current analysis are that nifedipine GITS given to patients who were hypertensive at baseline reduced the incidence of the combined endpoints that were pre-specified for the ACTION study with the exception of the primary endpoint for safety (Fig. 2). As shown in Figure 3, the main reason for this is the marked effect of nifedipine on new overt heart failure (38% reduction; 95% CI hazard ratio 0.43 - 0.90), any stroke or transient ischemic attack (28% reduction; 95% CI hazard ratio 0.57 - 0.91), debilitating stroke (33% reduction; 95% CI hazard ratio 0.47 - 0.96), and the need for coronary angiography (16% reduction; 95% CI hazard ratio 0.75 - 0.96). The rates of all-cause death, cardiovascular death, and myocardial infarction were not affected by nifedipine in both normotensive and hypertensive patients at baseline. The preventive effect of controlling hypertension on stroke is well-established, also

for dihydropyridines. This is the first time however, that a similar effect on new overt heart failure has been described for a calcium channel blocker. These findings also emphasize the need for blood pressure control, in particular in patients with target organ damage, such as established coronary artery disease. Corroborating similar findings for another dihydropyridine [18], a positive effect of nifedipine on the need for coronary angiography was present in both normo- and hypertensives at baseline. In a similar study with an ACE inhibitor [19] no such effect was observed even though ACE inhibitors also reduce blood pressure. These findings suggest that the effect of nifedipine on the need for coronary angiography as observed in ACTION is probably related to its well-established anti-anginal effect rather than its effect on blood pressure. Another possible explanation may be a positive effect of nifedipine GITS on the progression of coronary atherosclerosis as has been suggested previously [20,21].

As shown in Table 2, the majority of patients were at least on a β blocker at baseline. Among hypertensives, 12% of patients were not receiving any additional blood pressure-lowering medication. In this subgroup, follow-up blood pressures trended downward relative to baseline due to regression-to-the-mean (Fig. 1). As expected, these reductions were consistently larger in patients assigned nifedipine than in patients assigned placebo. Overall, the reduction in hypertensive patients assigned nifedipine was, relative to placebo, 6.6/3.5 mmHg (Table 3). This reduction was achieved despite the higher intensity of blood pressure-lowering treatment at 4 years in hypertensive patients assigned placebo (Table 2). Apparently, nifedipine reduced the need to prescribe additional blood pressure-lowering medication in patients with hypertension and stable symptomatic coronary disease. Considering active double-blind study medication (i.e. nifedipine GITS) as blood pressure-lowering medication, 100% of hypertensives assigned nifedipine were on any blood pressure-lowering treatment at 4 years. Nonetheless, 47% of patients with four-year blood pressure measurements in this subgroup were also hypertensive at that time. Recent surveys have shown that hypertension in patients with coronary disease is not always controlled in clinical practice [22]. Our results in hypertensive ACTION patients assigned nifedipine show how difficult it is to achieve control. One reason for this must be the large within-subject variability of blood pressure, causing the same patient to be 'hypertensive' at one visit, but not at the next (Table 3).

Among normotensives at baseline, follow-up blood pressure levels trended upwards (Fig. 1) and in patients assigned placebo, 33% were hypertensive at 4 years (Table 3). Again, this is partly attributable to regression-to-the-mean. At the same time, blood pressure levels in patients assigned nifedipine were consistently lower by 3.9/2.4 mmHg relative to patients assigned placebo. These reductions were not attenuated by differences in the intensity of additional blood pressure-lowering treatment during follow-up as among normotensives at baseline the percentages of patients using blood pressure-lowering medications other than calcium antagonists were similar at 4 years (Table 2). There has been considerable debate about the so-called J-shaped relationship between blood pressure reduction and risk of cardiovascular events [23], the implication being that larger blood pressure reductions eventually

may have an untoward effect. The data presented here do not directly address the relationship between blood pressure reduction and event-risk. Nonetheless, our data for normotensives are compatible with the existence of a J-shaped relationship (or more correctly a reverse L-shaped relationship) since in this subgroup there were non-significant trends towards higher rates of the primary combined endpoints for efficacy and safety, and of combined cardiovascular events (Fig. 2). We doubt that this is clinically relevant because the combined rate of death, cardiovascular events or procedures was significantly reduced by nifedipine both in normo- and hypertensives at baseline. We have no clear explanation as to why there was no suggestion of a J-shaped relationship for new overt heart failure, and why on the other hand the rate of peripheral revascularization was significantly increased by nifedipine in normotensives at baseline (Fig. 3). One explanation may be that J-shaped relationships affect different cardiovascular events in different manner. New overt heart failure may be prevented by afterload reduction also in normotensives. On the other hand, hypo-perfusion of the peripheral circulation due to large drops in blood pressure in individual normotensive patients assigned nifedipine may have contributed to their increased need for peripheral revascularization. An alternative explanation in this regard is that patients had less angina as a consequence of taking nifedipine and, being able to exercise more, were more often limited by intermittent claudication.

In conclusion, the present analysis shows that the addition of nifedipine GITS to the basic treatment regimen of patients with symptomatic CAD and hypertension results in a significant reduction of cardiovascular morbidity. The fact that this analysis concerns a sub-group of patients in a trial that was not specifically designed to assess the effect of nifedipine in patients with concurrent symptomatic coronary artery disease and hypertension is a limitation. On the other hand, the sub-group of patients with hypertension at baseline consists of more than half of ACTION patients and was pre-specified. Hence, the present analysis provides substantial additional supporting evidence that long-acting calcium channel blockers such as nifedipine GITS are effective in controlling high blood pressure and reducing major vascular events, even in patients who are already treated with other blood pressure-lowering drugs. This conclusion is supported by the recently published VALUE trial [24]. The data on patients in ACTION with hypertension at baseline supports the emphasis on blood pressure control in patients with a high global cardiovascular risk and/or established coronary artery disease in the current guidelines for the treatment of hypertension [25,26].

Acknowledgement

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Chapter 4

Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial.

de Leeuw PW, Ruilope LM, Palmer CR, Brown MJ, Castaigne A, Mancia G, Rosenthal T, Wagener G.

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Clinical Significance of Renal Function in Hypertensive Patients at High Risk

RESULTS FROM THE INSIGHT TRIAL

Peter W. de Leeuw, MD, PhD; Luis M. Ruilope, MD, PhD; Christopher R. Palmer, PhD; Morris J. Brown, MD, PhD; Alain Castaigne, MD, PhD; Giuseppe Mancia, MD, PhD; Talma Rosenthal, MD, PhD; Gilbert Wagener, MD

Background: Increasing evidence suggests renal involvement in hypertension-related cardiovascular and cerebrovascular complications. To assess this role of renal function in more detail, we studied the evolution of renal function and the relationship of renal function with mortality and morbidity in the Intervention as a Goal in Hypertension Treatment (INSIGHT) study.

Methods: The INSIGHT study was a double-blind, randomized, multicenter trial in patients with hypertension and at least 1 additional cardiovascular risk factor. Treatment consisted of nifedipine gastrointestinal therapeutic system, 30 mg/d, or hydrochlorothiazide-amiloride (25 mg/d of hydrochlorothiazide and 2.5 mg/d of amiloride hydrochloride). Primary outcome was a composite of cardiovascular death, myocardial infarction, heart failure, and stroke. Renal function was assessed by measuring creatinine clearance, serum creatinine level, and serum uric acid level and by the presence of proteinuria.

Results: Creatinine clearance fell more in nifedipine recipients than in hydrochlorothiazide-amiloride recipients. Renal insufficiency developed in 2% of nifedipine recipients and 5% of hydrochlorothiazide-amiloride recipients. Primary outcomes occurred in 15% of patients with increased serum creatinine levels and 6% of patients with normal levels (odds ratio [OR] 2.89; 95% confidence interval [CI], 1.92-4.36; *P*<.001). Primary outcomes were more likely in patients with low creatinine clearance (60 mL/min) than in those with higher clearances (9% vs. 5%, respectively [OR 1.51, 95%CI 1.22-1.88; *P*<.001]).

Conclusions: Renal function is an important predictor of risk in hypertensive patients at high risk. Antihypertensive treatment with a long-acting dihydropyridine calcium channel blocker may better preserve renal function than would treatment with diuretics.

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Author Affiliations are listed at the end of this article.

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Evidence is accumulating that the kidney contributes to the development of cardiac and cerebral complications. Recent data indicate that, besides microalbuminuria, serum creatinine level also acts as a marker of risk.[1,2] Interestingly, the predictive power of serum creatinine is already demonstrable with relatively normal values.[2,3] In hypertensive populations, relationships have been found between serum creatinine level and cardiovascular events, but in most of the studies either the type of treatment was not accounted for or patients were at relatively low risk. Consequently, only limited information is available regarding the effect of renal function on cardiovascular prognosis in patients who are already at high risk. We have addressed this question using the results from the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial. The INSIGHT trial was a large, prospective, double-blind, randomized, controlled trial that compared the effects of nifedipine gastrointestinal therapeutic system (GITS) with a diuretic combination (hydrochlorothiazide and amiloride hydrochloride) on cardiovascular outcome in hypertensive patients with additional cardiovascular risk factors. The main results of this trial have been described elsewhere.[4] In the present study, we report on the evolution of renal function during treatment and on the post hoc analysis of the relationship between renal function at baseline and cardiovascular complications. As markers of renal function, serum creatinine, creatinine clearance, serum uric acid, and proteinuria were used.

METHODS

Trial design

Inclusion criteria for the INSIGHT trial were age 55 to 80 years, hypertension (blood pressure [BP]: ≥150 mm Hg systolic *and* ≥95 mm Hg diastolic, or ≥160 mm Hg systolic regardless of diastolic BP), and at least 1 additional cardiovascular risk factor. The design of the trial has been described previously.[4] Briefly, after 4 weeks of placebo treatment, during which baseline measurements of BP and laboratory values were obtained, patients from 8 countries in Western Europe and Israel were randomized to either treatment with nifedipine, 30 mg/d, or hydrochlorothiazide-amiloride (25 mg/d of hydrochlorothiazide and 2.5 mg/d of amiloride hydrochloride) (step 1). Patients whose BP fell by less than 20/10 mm Hg or remained higher than 140/90 mm Hg received 1 of 4 dose titration steps (steps 2-5): dose doubling of the randomized drug; addition of 25 mg/d of atenolol (or 5 mg/d of enalapril maleate if atenolol was contraindicated); dose doubling of the additional drug; and addition of any other antihypertensive drug except calcium channel blockers or diuretics. Renal function was never a contraindication to any of these drugs.

Blood pressure was always measured 3 times after a 5-minute rest, with a calibrated mercury sphygmomanometer. After dose titration, patients were seen 3 times a year for BP and heart rate assessment. Laboratory tests (including serum creatinine and serum uric acid measure-

ments and urinalysis) were done during the titration phase and annually thereafter. The main marker of reduced renal function was a serum creatinine level higher than 1.5 mg/dL (133 µmol/L) in men or higher than 1.4 mg/dL (124 µmol/L) in women. Other markers included creatinine clearance below 60 mL/min (1.00 mL/s) [1] (as calculated with the Cockcroft and Gault formula [5]), serum uric acid level of 7 mg/dL or higher (416 µmol/L), presence of proteinuria (defined as protein excretion 0.5 g/24h) and any of these 4 measures.

The primary outcome of the trial was the composite end point of incidence of cardiovascular death, myocardial infarction, heart failure, and stroke. Secondary outcomes were all-cause mortality, death from a vascular cause, and death from a nonvascular cause, including transient ischemic attacks, angina, and renal failure. The latter was defined as a serum creatinine level of 2.94 mg/dL or higher (260 µmol/L) on 2 repeated measurements. All end points were validated from source documents by an independent critical events committee according to pre-specified diagnostic criteria.[6] The study complied with the principles of good clinical practice and the Declaration of Helsinki and was approved by the relevant ethics committees. All patients gave written informed consent.

STATISTICAL ANALYSIS

We assessed differences in group means or frequencies with the unpaired *t* test and the chi-square test, respectively. Relative risks and 95% confidence intervals (CIs) are quoted for randomized comparisons. Odds ratios (ORs) and 95% CIs are quoted for nonrandomized comparisons of patients with and without renal impairment at baseline. We used logistic regression to adjust for the possible effects of confounding factors. Data are expressed as mean ±SD unless stated otherwise.

RESULTS

Altogether, 6321 patients were included in the primary analysis of the INSIGHT trial. Baseline serum creatinine levels were missing in 4 patients (2 in each treatment group) leaving 6317 patients (2927 men and 3390 women) for analysis. Uric acid data were available for 6296 patients (2914 men and 3382 women) and data on protein excretion for all patients. Serum creatinine was elevated at baseline in 192 patients (3%), while creatinine clearance was below 60 mL/min (1.00 mL/s) in 1839 patients (29%). Increased serum uric acid level was present in 934 patients (15%) and proteinuria was observed in 170 patients (3%). In 2550 patients (40%), at least 1 of the 4 markers of renal impairment was found.

Patients with increased serum creatinine level were slightly older, but the difference was not statistically significant. While the prevalence of increased serum creatinine concentrations or

Table 1. Demographic Characteristics and Risk Factors at Baseline*

Characteristic	Normal Serum Creatinine Level			Elevated Serum Creatinine Level†			*P* Value‡
	Nifedipine	Hydrochlorothiazide-amiloride	Combined	Nifedipine	Hydrochlorothiazide-amiloride	Combined	
Patients	3048 (97)	3077 (97)	6125 (97)	107 (3)	85 (3)	192 (3)	
Men	1382 (45)	1409 (46)	2791 (46)	73 (68)	63 (74)	136 (71)	<.001
Women	1666 (55)	1668 (54)	3334 (54)	34 (32)	22 (26)	56 (29)	<.001
Age, y							
<60	752 (25)	693 (23)	1445 (24)	7 (7)	9 (11)	16 (9)	≥.05
60-70	1455 (48)	1511 (49)	2966 (48)	52 (49)	42 (50)	94 (49)	≥.05
>70	835 (27)	869 (28)	1704 (28)	47 (44)	33 (39)	80 (42)	≥.05
Risk factor							
Hypercholesterolemia	1595 (52)	1603 (52)	3198 (52)	51 (48)	40 (47)	91 (47)	≥.05
Smoker	868 (28)	885 (29)	1753 (29)	23 (22)	17 (20)	40 (21)	<.05
Family history of MI§	627 (21)	647 (21)	1274 (21)	19 (18)	12 (14)	31 (16)	≥.05
Diabetes mellitus	619 (20)	622 (20)	1241 (20)	30 (28)	31 (36)	61 (32)	<.001
LVH	316 (10)	322 (10)	638 (10)	22 (21)	13 (15)	35 (18)	<.001
Coronary heart disease	192 (6)	185 (6)	377 (6)	17 (16)	12 (14)	29 (15)	<.001
Left-ventricular strain	188 (6)	181 (6)	369 (6)	13 (12)	15 (18)	28 (15)	<.001
Previous MI	178 (6)	172 (6)	350 (6)	17 (16)	15 (18)	32 (17)	<.001
Peripheral vascular disease	166 (5)	164 (5)	330 (5)	14 (13)	9 (11)	23 (12)	<.001
Proteinuria	75 (2)	57 (2)	132 (2)	23 (22)	15 (18)	38 (20)	<.001

Abbreviations: LVH, left ventricular hypertrophy; MI, myocardial infarction.

* Data are given as number (percentage) of patients unless otherwise specified.

† Men, higher than 1.5 mg/dL (>133 µmol/L); women, higher than 1.4 mg/dL (>124 µmol/L).

‡ For the difference between all patients with an elevated serum creatinine level and all patients with a normal serum creatinine level.

§ In parent or sibling before age 50 years.

of reduced creatinine clearance increased with age, hyperuricemia and proteinuria were not related to age. As given in Table 1, demographic characteristics and risk factors were well balanced between the nifedipine and hydrochlorothiazide-amiloride treatment groups, irrespective of renal function. Patients with increased serum creatinine levels were more often men and smokers. In addition, they had a higher prevalence of diabetes mellitus, coronary heart disease, previous myocardial infarction, left ventricular hypertrophy or strain, peripheral vascular disease, and proteinuria. Essentially, the same results were obtained with the other markers of kidney function.

EVOLUTION OF CREATININE CLEARANCE DURING TREATMENT

Estimated creatinine clearance at baseline averaged 74 ± 24 mL/min (1.24 ± 0.40 mL/s) in the nifedipine group and 73 ± 22 mL/min (1.22 ± 0.37 mL/s) in the hydrochlorothiazide-amiloride group. During the trial it decreased in both groups to 72 ± 24 mL/min (1.20 ± 0.40 mL/s) and 68 ± 22mL/min (1.14 ± 0.37mL/s), respectively (Figure 1). The difference between the groups was statistically significant ($P<.05$) and independent from baseline renal function. Renal insufficiency occurred in 2% of patients receiving nifedipine and 5% of patients receiving the diuretic combination ($P<.01$).

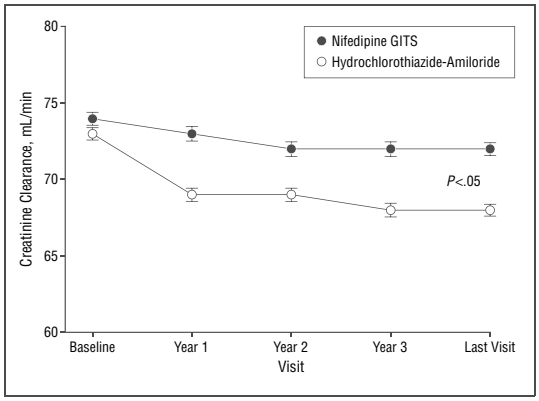

Figure 1. Creatinine clearance at baseline and at annual visits in patients treated with either nifedipine gastrointestinal therapeutic system (GITS) or hydrochlorothiazide-amiloride. The difference between groups is statistically significant (*P*<.05). Error bars indicate SD. To convert creatinine clearance to millilitres per second, multiply by 0.0167.

RENAL FUNCTION AND CONTROL OF BP AND HEART RATE

At baseline, patients with increased serum creatinine levels had significantly higher values for systolic and diastolic BP compared with those with normal serum creatinine levels (Table 2). At the end of the trial, systolic BP was still higher in the patients with increased serum creatinine levels, but the difference in diastolic BP was no longer statistically significant. When creatinine clearance was used to classify patients as those with normal or reduced renal function, systolic BP was again significantly higher in the latter at the time of randomisation (Table 2). Although the fall in systolic BP was greater in patients with reduced creatinine clearance, systolic BP remained higher in this group at the end of the trial. The opposite was found for diastolic BP, which was lower both at the start and at the end of the trial in patients with reduced creatinine clearance, with no difference in the changes of diastolic BP.

Both systolic and diastolic BPs were slightly higher in patients with increased serum uric acid levels than in those with normal concentrations, but the changes in BP during treatment were similar. When patients with or without proteinuria were considered, systolic BP was significantly higher in the former, both at the start (180 ± 18 vs. 172 ± 15 mm Hg; *P*<.001) and at the end of the trial (146 ±16 vs. 142±16 mm Hg; *P*<.001). The fall in systolic BP was also greater in patients with proteinuria (34±19 vs. 30±18mmHg; *P*<.01), but no differences in baseline and final measurements or change in diastolic BP were observed.

During treatment, heart rate fell both in patients with normal and reduced renal function. Changes were significantly greater in patients with elevated serum creatinine levels (*P*<.02), probably because more of these patients progressed to the atenolol treatment step. However, no significant

Table 2. Changes in Blood Pressure (BP) and Heart Rate During Treatment in Patients With Normal or Reduced Renal Function*

	Serum Creatinine Level			Creatinine Clearance Level		
BP and Heart Rate	Normal	Increased†	*P* Value	Normal	Reduced‡	*P* Value
Systolic BP, mm Hg						
Start	172 ± 15	179 ± 18	<.001	171 ± 14	175 ± 16	<.001
Final	142 ± 15	147 ± 22	<.001	142 ± 15	143 ± 18	<.001
Change	30 ± 18	32 ± 22	≥.05	30 ± 17	32 ± 20	<.001
Diastolic BP, mm Hg						
Start	99 ± 8	100 ± 10	.01	99 ± 8	98 ± 9	<.001
Final	82 ± 9	84 ± 11	.09	83 ± 9	81 ± 10	<.001
Change	16 ± 10	17 ± 13	≥.05	16 ± 10	16 ± 11	≥.05
Heart rate, bpm						
Start	76 ± 10	79 ± 12	≥.05	76 ± 10	77 ± 10	≥.05
Final	74 ± 11	74 ± 12	≥.05	74 ± 11	74 ± 11	≥.05
Change	3 ± 11	5 ± 14	.004	3 ± 11	3 ± 12	≥.05

Abbreviation: bpm, beats per minute.

*Data are presented as mean±SD unless otherwise specified. Renal function was determined from serum creatinine level or creatinine clearance at baseline.

†Men, higher than 1.5 mg/dL (>133 µmol/L); women, higher than 1.4 mg/dL (>124 µmol/L).

‡Below 60 mL/min (1.00 mL/s).

differences emerged when patients were divided on the basis of creatinine clearance, serum uric acid level, or proteinuria.

Although changes in BP were similar in nifedipine and hydrochlorothiazide-amiloride-treated patients, in both groups more drugs were needed in the patients with renal impairment. Indeed, while 30% of patients with normal renal function used 2 drugs and 9% used 3 drugs, these figures were 35% and 19%, respectively, in the other group (*P*<.001), with a similar proportion of patients using an angiotensin-converting enzyme inhibitor. Moreover, in patients with reduced renal function there was no difference in add-on medication between the 2 treatment groups. Figure 2 shows the proportions of patients who reached a BP of 140/90 mm Hg or below at the end of the titration phase. Both proteinuria and an elevated serum creatinine concentration significantly reduced responsiveness, whereas increased serum uric acid level or a creatinine clearance below 60 mL/min (1.00 mL/s) had no effect. When all patients with at least 1 positive marker of renal impairment were considered, response rates were similar in those with or without such an abnormality (70% in both groups).

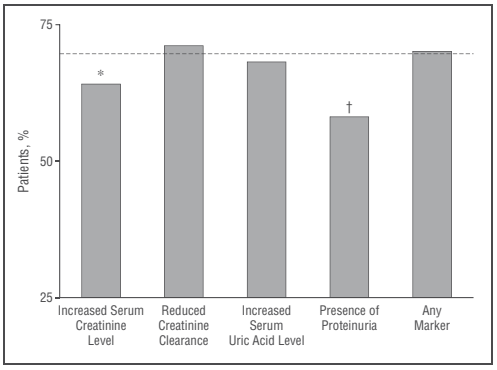

Figure 2. Percentage of patients reaching the target blood pressure level at the end of the titration phase in relation to several markers of renal impairment as determined at baseline. The dotted line indicates overall responsiveness in entire patient group (70%); the asterisk, *P*<.05 (vs. patients with normal serum creatinine levels); and the dagger, *P*<.005 (vs. patients without proteinuria).

CARDIOVASCULAR COMPLICATIONS IN RELATION TO BASELINE RENAL FUNCTION

Figure 3 summarizes risk estimates for increased serum creatinine level, reduced creatinine clearance, and presence of proteinuria when patients with such abnormalities were compared with those without. Primary outcomes occurred in 15% of patients with increased serum creatinine levels and in 6% of those with normal creatinine levels. This difference was highly significant (OR 2.89; 95% CI 1.92-4.36; *P*<.001). A similar difference was observed in the incidence of secondary outcomes (12% vs. 33%; *P*<.001). In the group with increased serum creatinine levels at baseline, the percentages of patients with primary outcomes did not differ between the nifedipine and hydrochlorothiazide-amiloride-treated groups (16% and 14%, respectively; relative risk 1.04, 95% CI 0.94-1.14). Primary outcomes were noted in 5% of the patients with a creatinine clearance above 60 mL/min (>1.00 mL/s) and 8% of the others (OR 1.51; 95% CI 1.22-1.88; *P*<.001). Non-renal secondary outcomes were also more frequent in patients with reduced creatinine clearance (17% vs. 10%; *P*<.001). When primary endpoints in patients receiving randomized treatment were compared, the results were slightly in favour of the nifedipine group (relative risk 0.93; 95% CI 0.92-0.94; *P*<.05). The risks of a primary event associated with increased serum uric acid concentration or the presence of proteinuria (OR 3.82; 95% CI 2.56-5.70; *P*<.001) showed similar patterns to those for creatinine. With regard to proteinuria, the comparison of endpoints in patients receiving randomized treatment proved nifedipine to be slightly worse than hydrochlorothiazide-amiloride (relative risk 1.16; 95% CI 1.01-1.32; *P*<.001). When cardiovascular complications were analyzed in relation to any abnormality of renal function, the same findings emerged as for the individual markers of renal function.

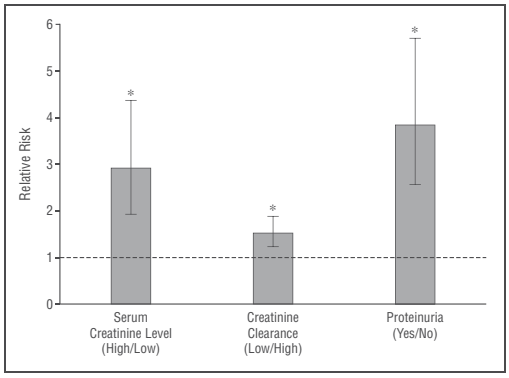

Figure 3. Risk estimates for primary end points (adjusted for other cardiovascular risk factors) associated with increased serum creatinine level, reduced creatinine clearance, or presence of proteinuria at baseline when patients with such abnormalities are compared with those without. Serum uric acid level did not emerge as an independent risk factor. The asterisks indicate *P*<.001.

Logistic regression analysis was performed to evaluate the effect of renal impairment on primary outcome with adjustments for various other risk factors. In the first model, we tested whether baseline serum creatinine is a risk factor for primary events, independent of proteinuria. This, indeed, appeared to be the case, with an OR of 2.57 (95% CI 1.68-3.93; *P*<.001) for

the presence of proteinuria and an OR of 1. 38 (95% CI 1.27-1.49; *P*<.001) for each 0.2 mg/dL (20 µmol/L) increase in serum creatinine level at baseline. In the second model, we adjusted also for other risk factors (age, sex, presence of diabetes mellitus, previous myocardial infarction, and smoking) besides proteinuria and found a high serum creatinine level to remain significant as a predictor of outcome (Table 3). With this type of analysis, however, serum uric acid level entirely lost its predictive power.

Table 3. Odds Ratios for Several Mutually Adjusted Risk Factors*

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Age	1.04 (1.02-1.05)	<.001
Male sex	1.66 (1.31-2.12)	<.001
Diabetes mellitus	1.59 (1.24-2.03)	<.001
Previous myocardial infarction	2.38 (1.73-3.28)	<.001
Smoking	1.57 (1.24-1.98)	<.001
Proteinuria	2.35 (1.52-3.63)	<.001
Creatinine level	1.23 (1.12-1.34)	<.001

*Odds ratios refer to having or not having the risk factor for the categorical variables (yes/no) or the odds ratios for a 1-unit change (1 year for age and 0.2 mg/dL [20 µmol/L] for creatinine level).

The percentages of patients with individual cardiovascular outcomes were generally similar between treatment groups within the subgroups with normal or abnormal kidney function. Meaningful statistical analyses could not be conducted for most individual cardiovascular events because of the small number of patients who had each event.

COMMENT

The first conclusion from the present study is that renal function is better preserved with the calcium channel blocker nifedipine GITS than with the diuretic combination hydrochlorothiazide-amiloride. Few studies have addressed the effects of long-term antihypertensive therapy on renal function in large cohorts of patients. In the European Working Party on High Blood Pressure in the Elderly trial, more than 800 patients received either placebo or a diuretic combination. Serum creatinine increased much more in the actively treated group than in the placebo group, and the risk of mild renal dysfunction was substantially higher in actively treated patients.[7,8] The increase in serum creatinine level correlated inversely with the fall in systolic BP, suggesting that reduced renal perfusion during diuretic treatment may underlie this phenomenon.[7] The same may be true for our data because the greatest disparity between the groups occurred during the first year with no evidence for a sustained damaging effect thereafter. Other trials in hypertensive patients, mostly using diuretics or β-blockers, also showed that active treatment is associated with a greater increase in serum creatinine level than in placebo treatment.[9,10] However, Voyaki et al. [11] provided evidence that, compared with placebo, treatment with the calcium channel blocker nitrendipine had a renopro-

tective effect in patients with isolated systolic hypertension. Thus, it may be that the type of medication plays an important role in determining renal outcome during antihypertensive treatment.

Three trials have compared the effect of a calcium channel blocker with alternative treatment on renal function in hypertensive patients. In the National Intervention Cooperative Study in Elderly Hypertensives, serum urea nitrogen level increased similarly in patients treated with nicardipine hydrochloride or a diuretic.[12] However, abnormally elevated levels were less frequent in the nicardipine group. In the Treatment of Mild Hypertension Study, hypertensive patients were randomized to placebo or 1 of 5 active drugs, which included chlorthalidone and amlodipine maleate.[13] Serum creatinine concentration increased with chlorthalidone use but was reduced by the other types of treatment. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which concluded that thiazide-type diuretics should be considered first-line therapy in patients with hypertension, also included a post hoc analysis of the changes in estimated glomerular filtration rate.[14] In this trial, the incidence of end-stage renal disease was similar for the 3 treatment arms (chlorthalidone, lisinopril, and amlodipine), but estimated creatinine clearance was significantly better preserved with amlodipine than with chlorthalidone or lisinopril. The present findings thus corroborate the data from the literature that antihypertensive treatment with a long-acting dihydropyridine calcium channel blocker may protect renal function more effectively compared with diuretics. This was true not only when changes in creatinine clearance level over time were considered but also when comparing the percentage of patients in both groups who had progressive renal deterioration. Taken together, it is fair to state that dihydropyridine calcium channel blockers confer prognostic benefit in terms of renal function. However, the mechanisms whereby this may be accomplished remain uncertain.

The second conclusion from our analysis is that in hypertensive patients at high risk, renal function is an important predictor of risk. In this respect, serum creatinine level, creatinine clearance, and urinary protein excretion may all be taken as markers of renal function. Although serum uric acid level also predicted outcome in univariate analysis, it turned out not to be an independent risk factor. The observation that serum creatinine level predicted cardiovascular morbidity and mortality fits well with data from other studies that showed an independent association between serum creatinine level and cardiovascular or overall prognosis. For example, the investigators from the Hypertension Optimal Treatment trial recently reported that in treated hypertensive patients, an elevation in serum creatinine level above 1.5 mg/dL (>132.6 µmol/L) or a reduction in estimated creatinine clearance below 60 mL/min (<1.00 mL/s) at baseline are powerful predictors of cardiovascular events and death.[1] Similar results have been described in patients with isolated systolic hypertension.[2,15,16] Importantly, in hypertensive patients, creatinine levels that are still in the normal range may already predict outcome.[3] The INSIGHT trial, however, is the first trial to examine the prognostic significance of renal function in hypertensive patients at high risk. In addition, the impact of

renal function was demonstrated for the 2 treatment groups separately. Moreover, raised serum creatinine level and presence of proteinuria were independently related to the incidence of complications.

The 3 measurements (creatinine level, serum uric acid level, and protein excretion) that we used in this study are not very sensitive or very specific markers of renal function. Moreover, they differ in strength regarding their prognostic power (greatest for proteinuria). Indeed, serum concentrations of creatinine and uric acid are also dependent on extra renal factors, and urinary protein excretion may reflect the hydraulic consequences of elevated (intra-renal) pressure rather than true glomerular damage. Despite this caveat, all markers were powerful predictors of future complications, suggesting that glomerular damage is somehow associated with progression of atherosclerotic lesions. While several investigators believe that proteinuria or elevated serum creatinine level reflects generalized endothelial dysfunction or a prothrombotic state, others argue (on equally reasonable grounds) against these possibilities. [17,18] Progression of atherosclerotic lesions in patients with reduced renal function has also been linked to enhanced oxidative stress and inflammation. Finally, increased levels of homocysteine, which is normally cleared by the kidney, may play a role. Clearly, more work has to be done before the pathophysiological connection between renal function and atherosclerotic complications can be elucidated.

One of the limitations of this study is that there may be unmeasured confounders that could have influenced our results. Although the observed relationships between renal function and cardiovascular prognosis remained statistically significant after adjustment for the other risk factors, we did not account for obesity or the newer risk factors, such as hyperhomocysteinemia, inflammation, or oxidative stress. In addition, one should bear in mind that our results apply only to hypertensive patients at high risk, treated with nifedipine GITS or hydrochlorothiazide-amiloride. Whether similar results apply to other types of treatment remains unknown. Likewise, the population we studied was predominantly white and, therefore, the implications for other races/ethnicities (e.g., African Americans) are difficult to define. Finally, we have to be aware that selection bias may have occurred in the sense that patients with more advanced renal impairment were not recruited for clinical reasons. Despite these limitations, the present findings suggest that antihypertensive treatment based on a long-acting dihydropyridine calcium channel blocker (nifedipine GITS) may offer better renoprotection compared with therapy based on the diuretic combination hydrochlorothiazide-amiloride.

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Author Affiliations: Department of Medicine, University Hospital Maastricht, Maastricht, the Netherlands (Dr de Leeuw); Unidad de Hipertension, Hospital 12 de Octobre, University of Madrid, Madrid, Spain (Dr Ruilope); Centre for Applied Medical Statistics (Dr Palmer) and Clinical Pharmacology Unit (Dr Brown), University of Cambridge, Cambridge, England; Hopital Henri-Mondor, Creteil, Paris, France (Dr Castaigne); Cattedra di Medicina Interna, Univer-

sity of Milano-Bicocca, St Gerardo Hospital, Monza, Italy (Dr Mancia); Hypertension Unit, the Chaim Sheba Medical Centre, University of Tel Aviv, Tel Aviv, Israel (Dr Rosenthal); and Bayer AG, Pharma Research Center, Wuppertal, Germany (Dr Wagener).
Correspondence: Peter W. de Leeuw, MD, PhD, Department of Medicine, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, the Netherlands (p.deleeuw @intmed.unimaas.nl).
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Chapter 5

Uric acid and other renal function parameters in patients with stable angina pectoris participating in the ACTION trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome.

Ruilope LM, Kirwan BA, de Brouwer S, Danchin N, Fox KAA, Wagener G, Segura J, Poole-Wilson PA, Jacobus Lubsen J, on behalf of the ACTION investigators.

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Uric acid and other renal function parameters in patients with stable angina pectoris participating in the ACTION trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome

Luis M. Ruilope[a], Bridget-Anne Kirwan[b], Sophie de Brouwer[b], Nicolas Danchin[c], Keith A.A. Fox[d], Gilbert Wagener[e], Julian Segura[a], Philip A. Poole-Wilson[f] and Jacobus Lubsen[b,g], on behalf of the ACTION investigators

[a]Hypertension Unit, Hospital 12 de Octubre. Madrid, Spain, [b]SOCAR Research, Nyon, Switzerland, [c]Department of Cardiology, Georges Pompidou European Hospital, Paris, France, [d]Cardiovascular Research, Division of Medical & Radiological Sciences, The University of Edinburgh, UK, [e]D-659423 Unna, Germany, [f]Cardiac Medicine, Imperial College, London, UK and [g]Department of Epidemiology and Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands

Background: Little data is available concerning the prognostic implications of renal function abnormalities, their evolution over time and the effects of nifedipine on such abnormalities in patients with stable angina pectoris.

Methods: The previously published ACTION trial compared long-acting nifedipine GITS 60 mg once daily to placebo among 7665 patients. Standard laboratory tests including creatinine and uric acid were assessed at baseline, after 6 months, 2 and 4 years, and at the end of follow-up. We assessed the impact of nifedipine on markers of renal dysfunction and determined whether evidence of renal failure alters the impact of nifedipine on the clinical outcome of patients with stable angina.

Results: Uric acid was not while creatinine level and estimated creatinine clearance were potent conditionally independent predictors of total mortality and of cardiovascular clinical events. Relative to placebo, nifedipine reduced 6-month uric acid levels by 3% ($P<0.001$) of the baseline value. This difference was maintained during long-term follow-up, was present both in normotensives and in hypertensives, and was not explained by differences in diuretic therapy or allopurinol use. Nifedipine had no effect on the occurrence of clinical renal failure. Relative to placebo, the effects of nifedipine on cardiovascular death or myocardial infarction [hazard ratio (HR)=1.01, 95% confidence interval (CI) 0.88-1.17], any stroke or transient ischaemic attack (HR=0.73, 95% CI 0.60-0.88), new overt heart failure (HR=0.72, 95% CI 0.55-0.95),

and the need for any coronary procedure (HR=0.81, 95% CI 0.75-0.88) were consistent across strata of markers of renal dysfunction.
Conclusions: We conclude that, in patients with stable angina, nifedipine reduces uric acid levels and does not affect other markers of renal dysfunction. Renal dysfunction does not alter the effects of nifedipine on clinical outcome. *J Hypertens* 25:1711-1718 © 2007 Lippincott Williams & Wilkins.
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Correspondence to Dr Luis M. Ruilope, Hypertension Unit, Hospital 12 de Octubre, Avenue Cordoba, s/n 28041, Madrid, Spain
Tel: +34 91 3908198; fax: +34 91 3908035; e-mail: ruilope@ad-hocbox.com
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INTRODUCTION

Renal dysfunction, recognized today as chronic kidney disease (CKD) [1], is an important predictor of outcome in patients with different cardiovascular (CV) conditions such as heart failure [2], myocardial infarction [3], established coronary artery disease (CAD) [4], and arterial hypertension [5,6]. Treatment of CV conditions may simultaneously influence the evolution of renal function, and both angiotensin-converting enzyme (ACE)-inhibition and dieting have been shown to slow down progression of chronic renal failure in some conditions [7,8]. Dihydropyridine calcium antagonists are both potent antihypertensive and antianginal medications widely used in the treatment of arterial hypertension and established CAD, in particular when the latter manifests itself clinically by symptoms of angina pectoris [9]. A recent review of data from hypertension trials [10] concluded that calcium channel blockers have no untoward effect on renal function and, when used in combination, do not alter the antiproteinuric effects of ACE inhibitors or angiotensin receptor blockers. Furthermore, the treatment of hypertensive patients with a dihydropyridine has been shown to increase estimated creatinine clearance or glomerular filtration rate levels relative to treatment with a diuretic [11], or an ACE inhibitor [12,13]. Recent hypertension trials with calcium antagonists have established the efficacy and safety of this class of drugs [14], and showed that earlier fears [15-19] were unjustified. Nonetheless, the evidence concerning the efficacy and safety of calcium-antagonists from placebo-controlled studies was limited until the results of the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) study became available. Relative to placebo, ACTION examined the effects on clinical outcomes of the dihydropyridine calcium antagonist nifedipine in a long-acting GITS (gastro-intestinal therapeutic system) formulation in 7665 patients with angina pectoris. The main conclusion was that the nifedipine GITS is safe in patients with stable symptomatic coronary disease and reduces both the occurrence

of new overt heart failure and the need for coronary interventions [20]. As ACTION was a randomized, double-blind, placebo-controlled trial, we could assess the impact of nifedipine GITS on markers of renal dysfunction and on renal failure, and clarify whether evidence of renal failure alters the impact of nifedipine on the clinical outcome of patients with stable angina as reported elsewhere.

METHODS

Design

The design, methods and main results of ACTION have been published previously [20,21]. Briefly, patients with stable symptomatic angina pectoris requiring treatment were randomized to the addition of either nifedipine GITS or matching placebo. The starting dose of nifedipine was 30 mg once daily, increasing to 60 mg once daily within 6 weeks if no evidence of intolerance was seen. In addition to angina, patients had to have either a history of myocardial infarction (MI), or proven angiographic CAD, or a positive exercise test or perfusion defect. The left-ventricular ejection fraction had to be at least 40%. The medical history at baseline was documented by predefined entries in the case report form, or entered as free text. The latter were coded using the ICD-9 code [22]. After baseline assessments and treatment allocation, patients were seen at the outpatient clinic 2 weeks, 6 weeks and 6 months after randomization; and from then onwards every 6 months. At each clinic visit, and at the end of the study, a standard 12-lead electrocardiogram was made. Blood pressure was recorded with a standard sphygmomanometer in the sitting position after 5 min of rest. Standard laboratory tests, which included sodium, potassium, creatinine and uric acid, were assessed in a casual blood sample at baseline, after 6 months, 2 years and 4 years and at the end of follow-up. Urinalysis was not required by the ACTION protocol. The sponsor's standard (serious) adverse event forms, based on the Council for International Organizations of Medical Sciences recommendations, were used to report and document clinical events during follow-up. Adverse events were coded using the COSTART dictionary [23].

OUTCOMES

Following definitions that have been used before [11], we defined a serum creatinine level above 1.5 mg/dl (>133 µmol/l) in men or above 1.4 mg/dl (>124 µmol/l) in women, an estimated creatinine clearance below 60 ml/min (<1.00 ml/s) as estimated by the Cockroft and Gault formula [24], and a uric acid level of 7 mg/dl or higher (416 µmol/l) as markers of reduced renal function. In addition, we defined potassium of 5 mmol/l or higher as hyperkalaemia, potas-

sium below 3.5 mmol/l as hypokalaemia, sodium of 142 mmol/l or higher as hypernatraemia, sodium below 138 mmol/l as hyponatraemia and haemoglobin below 12.5 g/dl in men, or below 11.5 g/dl in women, as anaemia.
Clinical events that occurred during ACTION follow-up were ascertained and classified as described elsewhere [21].
Any stroke or transient ischaemic attack included disabling stroke as confirmed by the critical events committee, and unconfirmed stroke or transient ischaemic attack as reported by the investigator. Any coronary procedure included angiography, percutaneous intervention and bypass surgery. We defined clinical renal failure as any adverse event coded by the following COSTART terms: acute kidney failure, creatinine clearance decreased, kidney failure, kidney function abnormal or uraemia. We defined albuminuria as any adverse event coded by the COSTART terms albuminuria or proteinuria.

STATISTICAL ANALYSIS.

We used standard statistical methods to analyse changes from baseline at 6 months. In addition, we obtained an overall P-value for comparing laboratory test levels between treatment groups from a mixed effects model for repeated measurements, using the SAS PROC mixed procedure (SAS Institute, Cary, North Carolina, USA). To assess whether nifedipine affects long-term trends in the evolution of the laboratory tests considered, we used the slope adjusted for intercept (SLAIN) method [25]. SLAIN analysis estimates the slope and intercept for each patient, using the laboratory test values measured at baseline and during follow-up as dependent, and time as an independent variable. The slopes are then correlated with study drug treatment while adjusting for intercept. We used the same method to assess whether the long-term trend in estimated creatinine clearance was related to other patient characteristics.
We used uni- and multivariate Cox proportional hazards analysis to assess whether creatinine, estimated creatinine clearance and uric acid were conditionally independent predictors of outcome. Multivariate analyses were always adjusted for age and gender, and for other predictors that contributed significantly to prediction of outcomes. As the formula used to estimate creatinine clearance takes age and gender into account, we did not adjust analyses for estimated creatinine clearance for these covariates.
To assess the impact of the three markers of renal dysfunction considered on outcomes and the effect of nifedipine, we stratified patients for the presence of the markers concerned at baseline using three strata: (i) none of the markers considered present; (ii) any one marker present; and (iii) two or three present. We took stratum-specific and overall event rates as the total number of patients who had the event concerned, divided by the total person-years of follow-up 'at risk' of event. To assess the effects of nifedipine relative to placebo, we used Cox

Table 1 Key clinical features and renal function parameters at baseline

	Nifedipine ($n = 3825$)	Placebo ($n = 3840$)
Mean (SD) age (years)	63.5 (9.3)	63.4 (9.3)
Male gender, *n* (%)	3041 (80)	3043 (79)
History of myocardial infarction, *n* (%)	1974 (52)	1924 (50)
History of coronary revascularisation, *n* (%)	1710 (45)	1719 (45)
Significant lesions on coronary angiogram, *n* (%)[a]	2632 (69)	2634 (69)
Normal coronary angiogram, *n* (%)	50 (1.3)	48 (1.3)
Angiography not performed or unknown, *n* (%)	1143 (30)	1158 (30)
Current NYHA class II–III, *n* (%)	1756 (46)	1776 (46)
History of peripheral CV disease, *n* (%)[b]	494 (13)	491 (13)
History of atrial fibrillation, *n* (%)	145 (3.8)	168 (4.4)
History of heart failure, *n* (%)	84 (2.2)	86 (2.2)
Ejection fraction $< 45\%$, *n* (%)	1056 (28)	1074 (28)
History of renal failure, *n* (%)[c]	43 (1.1)	49 (1.3)
History of proteinuria[d]	3	2
Risk factors		
Any diabetes mellitus, *n* (%)	567 (15)	546 (14)
Treated with insulin, *n* (%)	86 (2.2)	97 (2.5)
Current smoker, *n* (%)	686 (18)	670 (17)
Mean (SD) total cholesterol (mg/dl)	208.3 (41.6)	209.4 (39.9)
Total cholesterol $\geq$193 mg/dl (5.0 mmol/l)	2382 (62)	2433 (63)
Mean (SD) systolic blood pressure (mmHg)	137.3 (18.8)	137.6 (18.6)
Mean (SD) diastolic blood pressure (mmHg)	79.9 (9.4)	79.8 (9.5)
Blood pressure 140/90 mmHg or higher, *n* (%)	1975 (52)	2002 (52)
History of hypertension treated with drugs, *n* (%)	1602 (42)	1596 (42)
Blood pressure $>$ 140/90 mmHg or history of hypertension treated with drugs, *n* (%)	2509 (66)	2499 (65)
Mean (SD) body mass index (kg/m^2)	27.5 (3.8)	27.5 (3.9)
Body mass index $\geq$30.0 kg/m^2, *n* (%)	849 (22)	895 (23)
Treatment		
β-blocker, *n* (%)	2979 (78)	3024 (79)
Any organic nitrate or vasodilator, *n* (%)	2911 (76)	2949 (77)
ACE-inhibitor or ARB, *n* (%)	847 (22)	865 (23)
Diuretic, *n* (%)	436 (11)	454 (12)
Lipid-lowering, *n* (%)	2384 (62)	2370 (62)
ASA or antiplatelet, *n* (%)	3405 (89)	3400 (89)
Vitamin K antagonist, *n* (%)	153 (4.0)	148 (3.9)
Digoxin, *n* (%)	32 (0.8)	51 (1.3)
Renal function parameters		
Mean (SD) creatinine (mg/dl)[e]	1.09 (0.22)	1.09 (0.21)
$>$ 1.5 mg/dl (men) or $>$ 1.4 mg/dl (women), *n* (%)	153 (4.1)	130 (3.4)
Mean (SD) creatinine clearance (ml/min)[f]	78.3 (23.6)	78.7 (24.3)
$<$ 60 ml/min, *n* (%)	811 (22)	837 (22)
Mean (SD) uric acid (mg/dl)[g]	5.90 (1.42)	5.92 (1.43)
$\geq$ 7 mg/dl, *n* (%)	773 (21)	803 (22)
Any of the above abnormal, *n* (%)	1398 (37)	1443 (38)
Other laboratory tests		
Mean (SD) potassium (mmol/l)	4.44 (0.41)	4.45 (0.40)
$\geq$ 5 mmol/l, *n* (%)	356 (9.6)	382 (10.1)
$<$ 3.5 mmol/l, *n* (%)	26 (0.7)	15 (0.4)
Mean (SD) sodium (mmol/l)	140.8 (2.75)	140.8 (2.58)
$\geq$142 mmol/l, *n* (%)	1463 (39)	1501 (40)
$<$138 mmol/l, *n* (%)	390 (10)	348 (9.2)
Mean (SD) haemoglobin (g/dl)[h]	14.5 (1.23)	14.4 (1.22)
$<$12.5 g/dl (men) or $<$11.5 g/dl (women), *n* (%)	103 (2.7)	117 (3.1)

Values in means and standard deviations (SD) or in numbers of patients and percentages. NYHA, New York Heart Association; CV, cardiovascular; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. [a]Significant lesions in any major coronary artery; [b]Stroke, transient ischemic attacks or claudication; [c]ICD-9 581.9, 582.9, 583.0, 583.9, 585-587, 593.9; [d]ICD-9 791.0; [e]To convert values to micromole per liter, multiply by 88.339; [f]Cockroft and Gault formula [24]; [g]To convert values to micromole per litre, multiply by 59.488; [h]To convert values to mmol/l, multiply by 0.6207.

proportional hazards analysis with assigned treatment as the only covariate and obtained stratum-specific and overall hazard ratios and their 95% confidence intervals (CI).

All analyses were performed based on intention-to-treat, using for laboratory tests all available values.

RESULTS

ACTION was completed as planned [21]; 7665 patients were started on study medication (3825 nifedipine, 3840 placebo). Mean follow-up was the same for both treatment groups, and was 4.94 years. Overall, follow-up was 97.3% complete [21].

The key baseline clinical features and laboratory test data are given in Table 1. Few patients had a history of renal failure or proteinuria reported as a concomitant medical condition. Less than 5% of patients had an elevated baseline creatinine level. Nonetheless, almost 40% of patients had evidence of renal dysfunction based either on baseline creatinine, or estimated creatinine clearance, or uric acid values. Both treatment groups were well matched.

Changes from baseline at 6 months of blood pressure and the laboratory tests considered are given in Table 2. As expected, nifedipine lowered blood pressure significantly relative to placebo. Mean creatinine rose at 6 months in both treatment arms, and 0.007 mg/dl more so in patients assigned nifedipine than in patients assigned placebo. Consequently, nifedipine also significantly reduced estimated creatinine clearance. The mean change of uric acid was 0.164 mg/dl lower in patients assigned nifedipine than in patients assigned placebo ($P<0.001$), which represents 3% of the baseline value. The change cannot be explained by a different percentage of patients receiving diuretic therapy or allopurinol, as can be seen in Table 3. Relative to placebo, nifedipine reduced potassium by 0.035 mmol/l ($P<0.001$), which represents less than 1% of the baseline value. Nifedipine had no effect on sodium at 6 months, and reduced haemoglobin by 0.122 g/dl ($P<0.001$, less than 1% of the baseline value).

Table 2 Changes from baseline at 6 months

	Nifedipine ($n=3825$)	Placebo ($n=3840$)	P
Systolic blood pressure (mmHg)			
Number of values at 6 months	3628	3666	
Mean change (SD)	−6.26 (17.7)	−0.48 (17.8)	< 0.001
Mean effect of nifedipine (95% CI)	−5.78 (−6.60,−4.97)		
Diastolic blood pressure (mmHg)			
Number of values at 6 months	3628	3666	
Mean change (SD)	−3.06 (9.6)	0.10 (9.8)	< 0.001
Mean effect of nifedipine (95% CI)	−3.16 (−3.61, −2.72)		
Creatinine (mg/dl)			
Number of values at 6 months	3494	3548	
Mean change (SD)	0.014 (0.14)	0.007 (0.13)	0.02
Mean effect of nifedipine (95% CI)	0.007 (0.001, 0.014)		
Creatinine clearance (ml/min)			
Number of values at 6 months	3454	3500	
Mean change (SD)	−1.38 (10.4)	−0.81 (10.2)	0.02
Mean effect of nifedipine (95% CI)	−0.56 (−1.05, −0.08)		
Uric acid (mg/dl)			
Number of values at 6 months	3364	3418	
Mean change (SD)	−0.109 (0.99)	0.055 (0.99)	< 0.001
Mean effect of nifedipine (95% CI)	−0.164 (−0.211, −0.116)		
Potassium (mmol/l)			
Number of values at 6 months	3412	3482	
Mean change (SD)	−0.063 (0.41)	−0.028 (0.41)	< 0.001
Mean effect of nifedipine (95% CI)	−0.035 (−0.054, −0.015)		

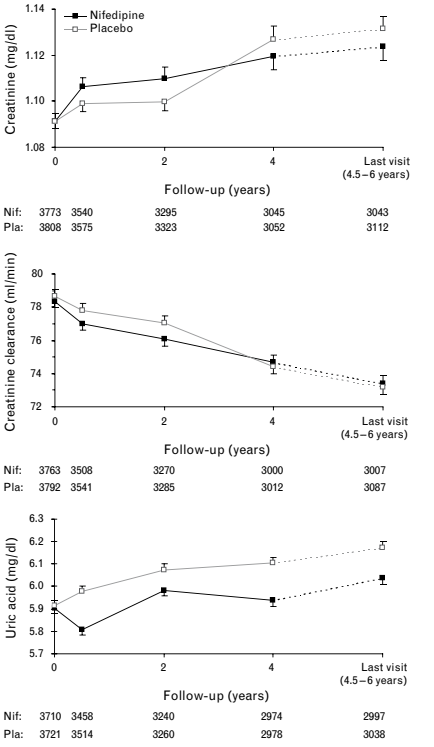
95% CI, 95% confidence interval.

Table 3 Percentage of patients receiving diuretics or allopurinol at baseline in both groups and mean percentage of time of administration during follow-up

	Baseline		Follow-up	
	Nifedipine, *n* (%)	Placebo, *n* (%)	Nifedipine mean % of time (SD)	Placebo mean % of time (SD)
Any diuretics, including aldosterone antagonists	435 (11.4)	448 (11.7)	17.97 (33.49)	20.21 (34.36)
Thiazides	257 (6.7)	281 (7.3)	8.68 (24.50)	11.80 (27.28)
Low-ceiling diuretics, excluding thiazides	73 (1.9)	47 (1.2)	1.90 (12.09)	1.80 (11.50)
High-ceiling diuretics	106 (2.8)	121 (3.2)	7.65 (22.35)	7.10 (21.35)
Potassium-sparing agents	88 (2.3)	93 (2.4)	3.94 (16.82)	3.67 (16.28)
Diuretics and potassium-sparing agents in combination	79 (2.1)	86 (2.2)	2.93 (14.93)	2.91 (15.00)
Allopurinol	117 (3.1)	100 (2.6)	3.98 (18.03)	3.68 (16.95)

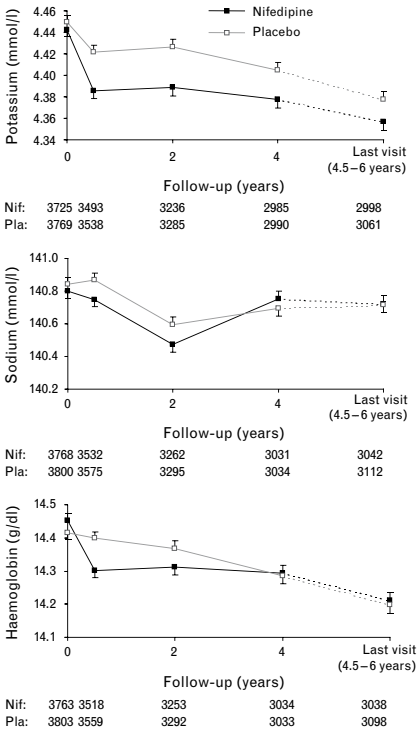
The long-term evolution of the renal function parameters and laboratory tests considered is shown in Figs 1 and 2. Differences between treatment groups in changes from baseline at 6 months for creatinine and creatinine clearance in favour of placebo reversed to differences in favour of nifedipine towards the end of the study. Follow-up uric acid levels were significantly lower ($P<0.001$, test for repeated measurements) in patients assigned nifedipine than in patients assigned placebo. The follow-up pattern of potassium levels was similar to that of uric acid ($P<0.001$, test for repeated measurements) but the difference at 6 months between treatment groups in haemoglobin disappeared towards the end of the study. SLAIN analysis showed that nifedipine had no effect on the trend over time of any of the parameters shown.

Fig. 1



Long-term evolution of the renal function parameters. Nif, nifedipine; Pla, placebo.

Fig. 2



Long-term evolution of the laboratory tests. Nif, nifedipine; Pla, placebo.

The occurrence of laboratory test abnormalities among patients with normal values at baseline who had at least one measurement for the parameter concerned during follow-up are shown in Table 4. Nifedipine significantly reduced the occurrence of elevated creatinine (P=0.018) and uric acid (P<0.001), but had no effect on the occurrence of other abnormalities considered at any time during follow-up.

Table 4 Laboratory tests abnormalities at any time during follow-up among patients with normal values at baseline

	Nifedipine		Placebo		
Abnormality	Abnormality absent at baseline	Present at any time during follow-up (%)	Abnormality absent at baseline	Present at any time during follow-up (%)	*P*
Creatinine > 1.5 mg/dl (men) or > 1.4 mg/dl (women)	3514	268 (7.6)	3591	330 (9.2)	0.018
Creatinine clearance < 60 ml/min	2870	639 (22)	2881	627 (22)	0.65
Uric acid ≥ 7 mg/dl	2844	702 (25)	2844	838 (29)	< 0.001
Any of above	2237	911 (41)	2219	977 (44)	0.026
Potassium ≥ 5 mmol/l	3271	554 (17)	3298	605 (18)	0.13
Potassium < 3.5 mmol/l	3592	104 (2.9)	3659	82 (2.2)	0.078
Sodium ≥ 142 mmol/l	2247	1257 (56)	2246	1306 (58)	0.14
Sodium < 138 mmol/l	3288	729 (22)	3370	755 (22)	0.82
Haemoglobin < 12.5 g/dl (men) or < 11.5 g/dl (women)	3554	315 (8.9)	3594	337 (9.4)	0.45

Nifedipine had no effect on the incidence of clinical renal failure (c.f. outcomes) during follow-up, which occurred in total in 298 patients [155 nifedipine, 143 placebo, hazard ratio (HR) 1.09, 95% CI=0.87-1.37].

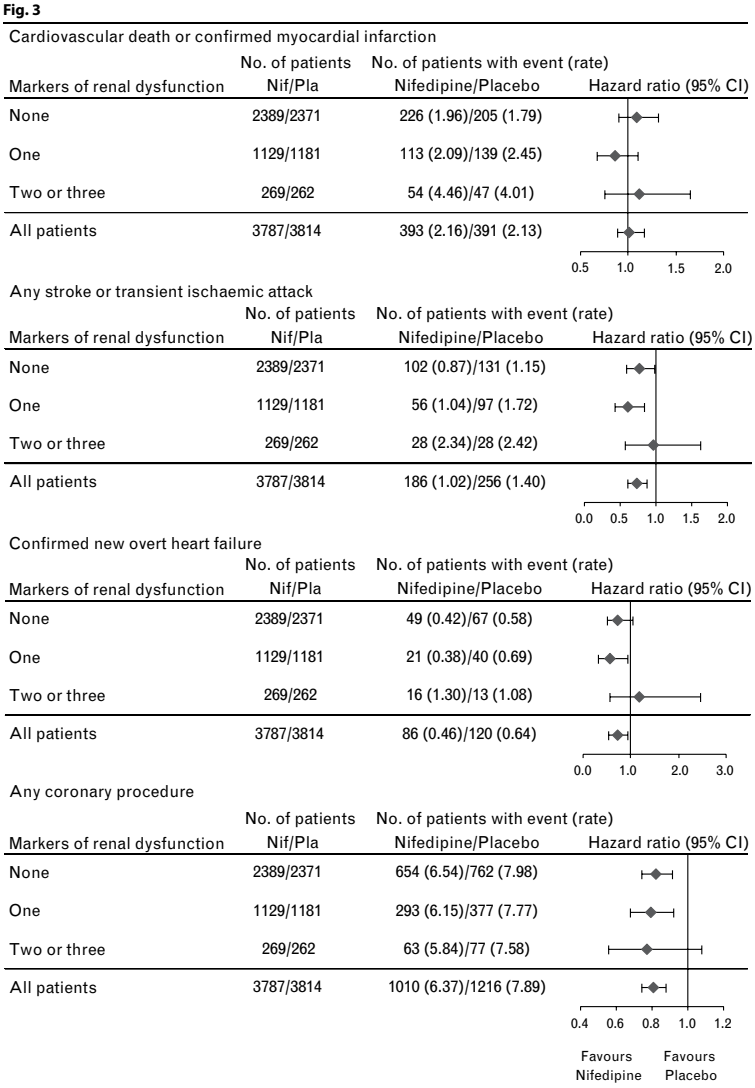
Results of unadjusted and adjusted Cox-regression analysis (adjusted for age, gender, history of MI, atrial fibrillation, peripheral cardiovascular disease, diabetes, current smoking, left ventricular ejection fraction <45%, and study treatment) showed that baseline creatinine level was a significant predictor of total mortality (unadjusted HR=3.18, 95% CI=2.31-4.37; adjusted HR=1.61, 95% CI=1.14-2.28 per mg/dl increase), of cardiovascular death or confirmed myocardial infarction (unadjusted HR=2.58, 95% CI=1.92-3.45; adjusted HR=1.75, 95% CI=1.27-2.40 per mg/dl increase), and of new overt heart failure (unadjusted HR=4.13, 95% CI=2.47-6.91, adjusted HR=1.98, 95% CI=1.11-3.54 per mg/dl increase). Unadjusted baseline creatinine was a significant predictor of any stroke or transient ischaemic attack but adjusted was not (unadjusted HR=1.91, 95% CI=1.27-2.87, adjusted HR=1.10, 95% CI=0.71-1.70 per mg/dl increase). Baseline creatinine was not a predictor of the need for any coronary procedure.

Baseline estimated creatinine clearance was a significant unadjusted and adjusted (as for creatinine but not for age and sex) predictor of total mortality (unadjusted HR=1.20, 95% CI=1.15-1.24; adjusted HR=1.19, 95% CI=1.14-1.24 per 10 ml/min decrease), of cardiovascular death or confirmed myocardial infarction (unadjusted HR=1.11, 95% CI =1.07-1.15; adjusted HR=1.11, 95% CI=1.07-1.14 per 10 ml/min decrease), of new overt heart failure (unadjusted HR =1.16, 95% CI =1.09-1.24, adjusted HR=1.13, 95% CI=1.06-1.20 per 10 ml/min decrease) and of any stroke or transient ischaemic attack (unadjusted HR=1.16, 95% CI=1.11-1.22, adjusted HR=1.13, 95% CI=1.08-1.18 per 10 ml/ min decrease). Baseline estimated creatinine clearance was also a predictor of the need for any coronary procedure (unadjusted and adjusted HR=0.96, 95% CI 0.95-0.98 per 10 ml/min decrease).

Baseline uric acid was a significant predictor of total mortality only, and only when not adjusted for other predictors (unadjusted HR=1.07, 95% CI=1.01-1.13).

Effects of nifedipine relative to placebo on clinical outcomes after stratification for markers of renal dysfunction at baseline are shown in Fig. 3. Overall, nifedipine had no effect on cardiovascular death or confirmed myocardial infarction (HR=1.01, 95% CI=0.88-1.17) and there was no evidence for an adverse effect in patients with markers of renal dysfunction. Similarly, there was no evidence that the positive effects of nifedipine on any stroke or transient ischaemic attack (overall HR=0.73, 95% CI=0.60-0.88), on new overt heart failure (overall HR=0.72, 95% CI=0.55-0.95), and on the need for coronary procedures (overall HR=0.81, 95% CI=0.75-0.88) as reported earlier [21,26] depended on the presence of markers of renal dysfunction.

Fig. 3



Effects of nifedipine relative to placebo on clinical outcomes after stratification for markers of renal dysfunction at baseline. CI, confidence interval; Nif, nifedipine; Pla, placebo.

DISCUSSION

Our main finding is that four out of ten patients have any of the three markers of reduced renal function that we could assess: (i) an elevated creatinine level; (ii) a reduced estimated creatinine clearance; and/or (iii) an elevated uric acid level. We emphasize that we were unable to include urinary albumin excretion in the present analysis as this was not measured in ACTION. Nonetheless, our findings confirm those from the HOPE study [27], and support the notion that coronary artery disease and chronic kidney disease are related phenomena [28,29].

We found that an elevated creatinine level and a reduced estimated creatinine clearance are independent predictors of death, MI, stroke and overt heart failure in patients with stable angina. In addition, we found a marked relationship between cardiovascular clinical events and the number of renal function markers that was abnormal (Fig. 3). This confirms earlier findings in patients with a variety of cardiovascular conditions [30]. Interestingly, no such relationship was observed for the need for any coronary procedure. This suggests that recurrent angina, the primary indication for coronary revascularisation, is not related to renal dysfunction. The rate of reduction of estimated creatinine clearance in the present study was approximately 1 ml/min/year, which is less than the rapid reduction observed after myocardial infarction [31], and is similar to that accompanying natural aging [32].

Nifedipine is known to have renal vasodilatory effects [33] and may therefore lower uric acid levels. Our data show that this is indeed the case as uric acid levels in patients assigned nifedipine were significantly below those of patients assigned placebo throughout the study despite both treatment groups receiving similar amounts of diuretic therapy and allopurinol. Nifedipine lowered uric acid levels, both in hypertensives and in normotensives at baseline. In all patients combined, the difference between mean uric acid changes from baseline at 6 months was 3% of the baseline value (Table 2). In the LIFE trial, which compared losartan with atenolol in patients with hypertension, the mean baseline uric acid level was 330.09 μmol/l, which is equivalent to 5.55 mg/dl and is similar to the baseline level in ACTION (Table 1). In LIFE the baseline-to-end-of-study increase in uric acid in patients assigned atenolol was 27.4 μmol/l more than in patients assigned losartan, which represents 8% of the baseline value. This difference has been claimed to account for a 29% of the benefit in CV outcome of patients assigned losartan in LIFE, and was attributed to the 'unique uric-acid lowering effect of losartan' [34]. Although the effect of nifedipine on uric acid levels may be less marked, our data show that losartan is not alone in this regard. Relative to placebo, nifedipine also significantly reduced the number of patients who developed an elevated uric acid level at any time during follow-up (Table 4).

Nifedipine had no effect on the incidence of clinical renal failure during follow-up. This is in agreement with the fact that in our data nifedipine had little or no effect on renal function parameters other than on uric acid (Table 4). In a trial comparing nifedipine with diuretics in patients with hypertension, nifedipine was associated with lower creatinine values than di-

uretics [11]. These two findings together imply that diuretics negatively affect renal function, whereas nifedipine does not.

The presence of renal function abnormalities did not affect the effect of nifedipine on outcomes in the ACTION trial (c.f. Figure 3). The addition of nifedipine GITS to conventional treatment of angina pectoris had no effect on major cardiovascular event-free survival while reducing the need for coronary angiography and interventions [21]. In patients with blood pressures of 140/90 mmHg or higher, the combined incidence of all-cause mortality, myocardial infarction, refractory angina, heart failure, stroke, and peripheral revascularisation was reduced by 13% [26]. The fact that we could not show that these effects depend on the presence of renal function abnormalities is important clinically because this shows that impaired renal function is not a contra-indication when administering nifedipine to patients with stable angina pectoris.

In conclusion, our data confirm that in patients with stable angina, creatinine and estimated creatinine clearance are potent independent predictors of total mortality, cardiovascular death or myocardial infarction, new overt congestive heart failure, and stroke or transient ischemic attack. On the other hand, uric acid is not a predictor of any of these.

In these patients, nifedipine reduces uric acid levels both in patients with and without hypertension. Otherwise, nifedipine has little effect on renal function parameters and its effects on outcome do not depend on their presence. These properties may be clinically relevant.

Acknowledgement

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Conflict of interest statement: The ACTION study was carried out by an independent Steering Committee and Research Group. L.M.R, N.D, K.A.A.F, P.A.P.-W. and J.L have served as consultants to or received travel expenses, or funding for research from other pharmaceutical companies. B.A.K. and S.deB. are full-time employees of SOCAR Research SA, which managed the study.

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Chapter 6

Outcomes with nifedipine GITS or Co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT).

Mancia G, Brown M, Castaigne A, de LP, Palmer CR, Rosenthal T, Wagener G, Ruilope LM.

Hypertension 2003;41:431-6.

Outcomes With Nifedipine GITS or Co-Amilozide in Hypertensive Diabetics and Nondiabetics in Intervention as a Goal in Hypertension (INSIGHT)

Giuseppe Mancia, Morris Brown, Alain Castaigne, Peter de Leeuw, Christopher R. Palmer, Talma Rosenthal, Gilbert Wagener, Luis M. Ruilope

Abstract—To investigate the impact of treatment on cardiovascular mortality and morbidity, we assessed outcomes in patients with hypertension and diabetes who received co-amilozide or nifedipine in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension. Participants had to be 55 to 80 years of age, with hypertension (≥150/95 or ≥160 mm Hg) and at least one additional cardiovascular risk factor. Patients received 30 mg nifedipine once daily or co-amilozide (25 mg hydrochlorothiazide and 2.5 mg amiloride) daily. Doses were doubled if target blood pressures (<140/90 mm Hg) were not achieved. Primary (composite of cardiovascular death, myocardial infarction, heart failure, and stroke) and secondary outcomes (composite of primary outcomes, including all-cause mortality and death from vascular and nonvascular causes) were assessed by means of intent-to-treat analyses. There was no significant difference in the incidence of primary outcomes between nifedipine-treated and co-amilozide-treated patients with diabetes at baseline (n=1302) (8.3% versus 8.4%; relative risk 0.99, 95% CI 0.69 to 1.42; *P*=1.00). A significant benefit for nifedipine-treated patients was seen for the composite secondary outcome (14.2% versus 18.7%; relative risk 0.76, 95% CI 0.59 to 0.97; *P=0.*03). Among patients without diabetes at baseline (n=5019), there was a significant difference in the incidence of new diabetes (nifedipine 4.3% versus co-amilozide 5.6%, *P*=0.023). Nifedipine GITS once daily is as effective as diuretic therapy in reducing cardiovascular complications in hypertensive diabetics. Nifedipine-treated patients were also less likely to have diabetes or have secondary events (a composite of all-cause mortality, death from a vascular cause, and death from a nonvascular cause) than co-amilozide recipients. Our results suggest that nifedipine could be considered as first-line therapy for hypertensive diabetics. **(*Hypertension*. 2003;41:431-436.)**

Key Words: calcium channel blockers, diabetes mellitus, diuretics, nifedipine, mortality, morbidity

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From the University of Milano-Bicocca, St Gerardo Hospital (G.M.), Monza, Milan, Italy; Clinical Pharmacology Unit, University of Cambridge (M.B.), Cambridge, UK; Hopital Henri-Mondor (A.C.), Creteil, Paris, France; the Department of Internal Medicine, University Hospital Maastricht (P.d.L.), Maastricht, The Netherlands; the Centre for Applied Medical Statistics,

University of Cambridge (C.R.P.), UK; the Hypertension Unit, The Chaim Sheba Medical Centre, University of Tel Aviv (T.R.), Israel; Bayer AG, Pharma Research Center (G.W.), Wuppertal, Germany; and Unidad de Hipertension, Hospital 12 de Octubre (L.M.R.), Madrid, Spain.
Correspondence to G. Mancia, Clinica Medica, Ospedale San Gerardo di Monza, Universita degli Studi Milano-Bicocca, Via Donizetti 106-20052, Monza (Mi), Italy. E-mail giuseppe.mancia@unimib.it

Hypertensive patients with diabetes mellitus must receive antihypertensive drugs because this therapeutic intervention substantially lowers their high absolute risk of cardiovascular morbidity and mortality.[1,2] Whether the benefit depends on the reduction in blood pressure itself or is due (at least in part) to the different protective properties of the drugs used is a matter of debate. This is because trials have so far provided conflicting results: In some trials, diabetic patients receiving treatment with ACE inhibitors or angiotensin II antagonists had lower rates of cardiovascular morbidity and mortality than patients receiving diuretics, β-blockers, or calcium antagonists.[3- 6] This has also been the case in the Appropriate Blood pressure Control in Diabetes (ABCD) trial, in which a comparison of the calcium channel blocker nisoldipine and the ACE inhibitor enalapril in patients with diabetes and hypertension revealed a significantly higher incidence of fatal and nonfatal myocardial infarction in the nisoldipine recipients.[4] However, further analysis of patients enrolled in the ABCD trial identified additional myocardial infarctions in both treatment groups that reduced the above difference without altering the overall conclusions of the study.[7] Furthermore, in several other trials, comparisons between new and conventional treatments as well as between ACE inhibitors and calcium antagonists have shown no substantial differences in cardiovascular morbidity and mortality rates.[8 -12] In a review of trials completed between 1990 and 2000, Kaplan[13] concluded that there are no concerns about the use of calcium channel blockers in patients with diabetes.

The intervention as a Goal in Hypertension (INSIGHT) study demonstrated that nifedipine and diuretic therapy with co-amilozide had comparable efficacy in preventing overall cardiovascular or cerebrovascular complications in patients with hypertension and at least one additional cardiovascular risk factor.[14] In this report, we describe cardiovascular outcomes in patients enrolled in INSIGHT who had diabetes at baseline.

METHODS

Design of the Trial

The design of INSIGHT has been described previously.[14] In brief, patients were randomly assigned to receive either 30 mg nifedipine daily or co-amilozide (25 mg hydrochlorothiazide and

2.5 mg amiloride) daily (step 1). Patients whose blood pressure fell by <20/10 mm Hg or remained >140/90 mm Hg could receive 1 of 4 dose-titration steps (steps 2 to 5): dose doubling of the randomized drug; addition of 25 mg atenolol daily (or 5 mg enalapril daily if atenolol was contraindicated); dose doubling of the additional drug; and addition of any other antihypertensive drug except calcium channel blockers or diuretics. Use of add-on medications (steps 3 to 5) was recorded during the study. The inclusion criteria for INSIGHT have been described previously and included age 55 to 80 years, hypertension (blood pressure ≥150/95 or ≥160 mm Hg), and at least one additional cardiovascular risk factor, which could include diabetes mellitus.[14]

All end points were assessed by an independent critical events committee. The progress of the study was monitored by an independent data and safety monitoring committee. The study was performed according to the principles of good clinical practice and the declaration of Helsinki and was approved by the relevant ethics committees. All patients gave informed written consent.

Blood pressure was measured 3 times after a 5-minute rest. After the initial dose-titration period, patients returned for assessment 3 times per year when blood pressure and heart rate were recorded. The primary outcome was the composite end point of incidence of cardiovascular death, myocardial infarction, heart failure, and stroke. The secondary outcome was the composite of all-cause death, death from a vascular cause, and death from a nonvascular cause. As part of our analysis, we also assessed the number of patients in whom diabetes mellitus developed during treatment. Diabetes at baseline was diagnosed using the 1985 World Health Organization (WHO) definition (i.e., the most recent definition available at the time of the initiation of the INSIGHT study), that is, a random capillary blood glucose measurement >11.0 mmol/L or use of antidiabetic drugs.

STATISTICAL ANALYSIS

The subgroup analyses in the diabetic population in INSIGHT and of the development of diabetes within the nondiabetic population were prespecified in the study protocol. INSIGHT was designed to have 90% power to detect a 25% relative difference between treatment groups at the 5% (2-sided) level of significance.[14] In the present study, relative risks and 95% CIs are quoted for the randomized comparisons. Odds ratios and 95% CIs are quoted for the nonrandomized comparisons of patients who had diabetes at baseline with those who were not diabetic. Logistic regression was used to compare multivariate and univariate results to adjust for possible effects of age and proteinuria (variables shown to be modestly imbalanced within the diabetic and nondiabetic subgroups). The Fisher exact test was used to compare all categoric data. All analyses were carried out using SPSS version 10.0 (SPSS Inc, 2001).

RESULTS

Patient Characteristics

A total of 6321 patients were enrolled in INSIGHT, of whom 1302 had diabetes at baseline. Demographic characteristics and risk factors were well balanced between the nifedipine and co-amilozide treatment groups. Combining the treatment groups revealed some differences between diabetics and nondiabetics. Diabetics were less likely than nondiabetics to have a family history of cardiovascular disease, to have hypercholesterolemia, or to be smokers but were more likely to have proteinuria (Table 1). Mean age was slightly lower in the nifedipine-treated patients with diabetes than in the co-amilozide recipients (66.0 versus 65.1 years), whereas among nondiabetics, patients in the nifedipine group were more likely to have proteinuria than patients in the co-amilozide group (Table 1).

TABLE 1. Demographic Characteristics and Risk Factors at Baseline

	Diabetes*			No Diabetes*		
	Nifedipine n (%)	Co-Amilozide n (%)	Combined n (%)	Nifedipine n (%)	Co-Amilozide n (%)	Combined n (%)
Patients, n	649	653	1302	2508	2511	5019
Demographic characteristics						
Gender						
Men	309 (47.6)	315 (48.2)	624 (47.9)	1147 (45.7)	1158 (46.1)	2305 (45.9)
Women	340 (52.4)	338 (51.8)	678 (52.1)	1361 (54.3)	1353 (53.9)	2714 (54.1)
Age, y						
<60	144 (22.2)	130 (19.9)	274 (21.0)	617 (24.6)	573 (22.8)	1190 (23.7)
60–70	327 (50.4)	318 (48.7)	645 (49.5)	1186 (47.3)	1238 (49.3)	2424 (48.3)
>70	178 (27.4)	205 (31.4)	383 (29.4)	705 (28.1)	700 (27.9)	1405 (28.0)
Risk factors						
Hypercholesterolemia	225 (34.7)	220 (33.7)	445 (34.2)	1421 (56.7)	1424 (56.7)	2845 (56.7)
Smoker	89 (13.7)	86 (13.2)	175 (13.4)	802 (32.0)	816 (32.5)	1618 (32.2)
Family history of MI†	72 (11.1)	55 (8.4)	127 (9.8)	576 (23.0)	605 (24.1)	1181 (23.5)
LVH	77 (11.9)	69 (10.6)	146 (11.2)	261 (10.4)	267 (10.6)	528 (10.5)
Coronary heart disease	39 (6.0)	47 (7.2)	86 (6.6)	170 (6.8)	150 (6.0)	320 (6.4)
Left-ventricular strain	43 (6.6)	35 (5.4)	78 (6.0)	158 (6.3)	162 (6.5)	320 (6.4)
Previous MI	41 (6.3)	38 (5.8)	79 (6.1)	154 (6.1)	150 (6.0)	304 (6.1)
Peripheral vascular disease	37 (5.7)	39 (6.0)	76 (76)	143 (5.7)	134 (5.3)	277 (5.5)
Proteinuria	45 (6.9)	38 (5.8)	83 (6.4)	53 (2.1)	34 (1.4)	87 (1.7)

*No significant differences between the nifedipine- and co-amilozide-treated groups.
†In parent or sibling before 50 years of age.

BLOOD PRESSURE CONTROL AND HEART RATE

Decreases in blood pressure were similar in nifedipine-treated and co-amilozide-treated patients in the subgroups with and without diabetes (Table 2). In patients with diabetes, systolic blood pressure decreased from 175 mm Hg in nifedipine-treated patients and 176 mm Hg in co-amilozide-treated patients at baseline to 144 and 145 mm Hg, respectively, at the final visit. In both the nifedipine-treated and co-amilozide-treated groups, diastolic blood pressure decreased from 98 mm Hg at baseline to 82 mm Hg at the final visit. Similar changes in systolic and diastolic blood pressure were noted in the patients who did not have diabetes at baseline. Heart rate decreased to a similar slight extent in nifedipine-treated and co-amilozide-treated patients both in the subgroups with and without diabetes (Table 2).

TABLE 2. Changes in Blood Pressure and Heart Rate From Baseline

	Nifedipine	Co-Amilozide	*P*
Diabetes			
Systolic blood pressure, mm Hg			
Baseline	174.7 (15.8)	175.7 (15.1)	0.263
Final	144.6 (16.1)	143.6 (17.0)	0.272
Change	30.1 (18.4)*	32.1 (20.0)*	0.065
Diastolic blood pressure, mm Hg			
Baseline	98.2 (9.2)	97.7 (9.1)	0.329
Final	81.9 (9.4)	82.4 (9.7)	0.426
Change	16.3 (10.4)*	15.4 (10.8)*	0.119
Heart rate, bpm			
Baseline	78.0 (10.5)	78.3 (10.0)	0.559
Final	75.9 (11.1)	75.4 (11.0)	0.386
Change	2.1 (11.9)*	2.9 (11.6)*	0.186
No diabetes			
Systolic blood pressure, mm Hg			
Baseline	172.0 (14.7)	171.7 (14.9)	0.500
Final	142.6 (15.6)	140.8 (15.1)	<0.001
Change	29.4 (17.8)*	30.9 (18.0)*	0.002
Diastolic blood pressure, mm Hg			
Baseline	99.0 (8.3)	99.0 (8.3)	0.771
Final	82.6 (8.9)	82.5 (8.6)	0.541
Change	16.4 (10.2)*	16.5 (10.2)*	0.773
Heart rate, bpm			
Baseline	76.3 (9.7)	76.0 (9.8)	0.303
Final	73.7 (10.7)	72.7 (10.5)	0.001
Change	2.6 (11.4)*	3.3 (11.0)*	0.024

Values are mean (SD).
*$P<0.001$ for within-group comparisons.

Diabetic patients treated with co-amilozide required significantly more add-on medication than patients treated with nifedipine (P=0.027). Patients with diabetes required more add-on therapy (steps 3 to 5) than nondiabetic patients (Table 3). Among the patients with diabetes at baseline, 57% of nifedipine-treated patients and 51% of co-amilozide recipients received no additional drugs, compared with 64% and 62%, respectively, among nondiabetics. ACE inhibitors were administered to 1933 patients (61%) in the nifedipine group and 1880 patients (59%) in the co-amilozide group. Among patients with diabetes at baseline, 697 (54%) received an ACE inhibitor, compared with 1811 (36%) of the patients with no diabetes.

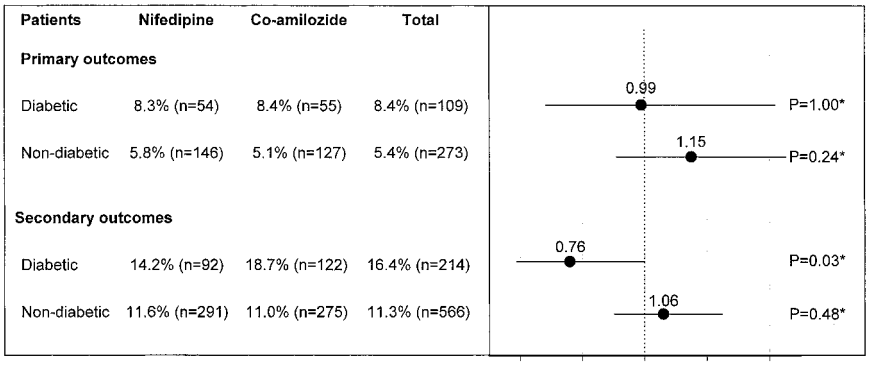
TABLE 3. Use of Add-On Medications to Achieve Blood Pressure Targets

	Diabetes		No Diabetes	
	Nifedipine n (%)	Co-Amilozide n (%)	Nifedipine n (%)	Co-Amilozide n (%)
Patients receiving add-on medication	279 (43.0)	320 (49.0)	906 (36.1)	959 (38.2)
Steps 3–5				
One additional drug, steps 3–4*	214 (33.0)	239 (36.5)	726 (28.9)	708 (28.2)
Two or more additional drugs, step 5†	65 (10.0)	81 (12.4)	180 (7.2)	251 (10.0)
	P=0.027‡		P=0.008‡	

*Enalapril (or atenolol if enalapril was contraindicated); †enalapril (or atenolol) and any other antihypertensive drug except calcium-channel blockers or diuretics.
‡ χ^2 test for trend.

OUTCOMES IN DIABETIC AND NONDIABETIC PATIENTS

In the group with diabetes at baseline, the percentages of patients with primary outcomes were similar in the nifedipine-treated and co-amilozide-treated groups (Figure). Among patients given ACE inhibitors, there were no significant differences in the percentage of patients with primary or secondary end points between the nifedipine and co-amilozide groups. Similarly, there was no significant difference in primary and secondary outcomes between the treatment groups within the subgroup of patients who were not given ACE inhibitors. In the nifedipine-treated group, 8.3% of patients had primary outcomes, compared with 8.4% in the co-amilozide-treated group (relative risk 0.99; 95% CI 0.69, 1.42; P=1.00). Significantly fewer nifedipine-treated patients had secondary outcomes (a composite of all-cause death, death from a vascular cause, and death from a nonvascular cause) than co-amilozide-treated patients (14.2% versus 18.7%; relative risk 0.76; 95% CI 0.59, 1.42; P=0.03) (Figure). There were no significant differences between the nifedipine-treated and co-amilozide-treated groups in the incidence of stroke, coronary heart disease, congestive heart failure, major cardiovascular events, cardiovascular deaths, or total deaths (P>0.05 in all cases) (Table 4).



Incidence (box) and relative risks and 95% CIs (figure) for primary and secondary outcomes in diabetic and nondiabetic patients. *Fisher exact test.

TABLE 4. Patients With Primary or Secondary Outcomes in the Diabetic Subgroup

	Nifedipine (n=649) n (%)	Co-Amilozide (n=653) n (%)	Relative Risk (95% CI)
Stroke	17 (2.6)	19 (2.9)	0.90 (0.47, 1.72)
CHD: MI and sudden death	28 (4.3)	25 (3.8)	1.13 (0.66, 1.91)
CHF	9 (1.4)	6 (0.9)	1.51 (0.54, 4.22)
Major cardiovascular events	46 (7.1)	49 (7.5)	0.95 (0.64, 1.39)
Cardiovascular mortality	19 (2.9)	19 (2.9)	1.01 (0.54, 1.88)
Total mortality	44 (6.8)	59 (9.0)	0.75 (0.52, 1.09)

CHD indicates coronary heart disease; MI, myocardial infarction; CHF, congestive heart failure; MI, myocardial infarction; and SD, standard deviation.

Because of the slight imbalances in baseline characteristics (Table 1), logistic regression analyses were performed to compare primary and secondary outcomes, with adjustment for age and proteinuria. Conclusions remained unchanged in both cases, so only the univariate analyses are reported.

In the group without diabetes at baseline, the percentages of patients with primary outcomes were similar in nifedipine- treated and co-amilozide-treated patients (Figure). In the nifedipine-treated group, 5.8% of patients had primary outcomes, compared with 5.1% in the co-amilozide-treated group (relative risk 1.15; 95% CI 0.91, 1.45; *P*=0.24). There was also no significant difference in the percentages of nifedipine-treated and co-amilozide-treated patients who had secondary outcomes (11.6% versus11.0%; relative risk 1.06; 95% CI 0.91, 1.24; *P*=0.48) (Figure)

In the combined nifedipine-treated and co-amilozide-treated groups, nondiabetic patients were less likely to have primary outcomes than diabetic patients (5.4% versus 8.4%; odds ratio 1.54, 95% CI 1.24, 1.90; *P*<0.001) (Figure). Similarly, significantly fewer nondiabetic patients had secondary outcomes than diabetic patients (11.3% versus 16.4%; odds ratio 1.46; 95% CI 1.26, 1.68; *P*<0.001) (Figure).

The percentages of patients with individual cardiovascular outcomes were generally similar between the treatment groups within the diabetic and nondiabetic subgroups. Meaningful statistical analyses could not be conducted for most individual cardiovascular events because of the small number of patients who had each event. Nondiabetic patients were more likely to have no primary or secondary events, and there was no significant difference between the nifedipine-treated and co-amilozide-treated patients (11.6% versus 11.0%, respectively; *P*=0.48).

INCIDENCE OF NEW DIABETES MELLITUS

The number of patients with no diabetes at baseline who had newly diagnosed diabetes mellitus during the study was significantly lower in the nifedipine-treated group (n=136, 4.3%) than in the co-amilozide-treated group (n=176, 5.6%; *P*=0.023). Among patients with newly diagnosed diabetes, 5 nifedipine-treated patients (0.2%) and 6 co-amilozide-treated patients (0.2%) had primary events during the INSIGHT follow-up.

DISCUSSION

The present analysis of data collected from a relatively large subgroup of diabetic hypertensive patients enrolled in INSIGHT showed that the incidence of the composite end point of myocardial infarction, stroke, congestive heart failure, and cardiovascular death in patients receiving antihypertensive treatment with nifedipine GITS was similar to that seen with co-amilozide (a combination of a thiazide and a potassium-retaining diuretic). However, compared with diuretics, treatment with nifedipine-GITS was associated with a lower incidence of (1) vascular and nonvascular deaths combined and (2) new cases of diabetes mellitus. This suggests that a long-acting dihydropyridine calcium channel blocker is as effective as conventional antihypertensive drugs for preventing major nonfatal and fatal cardiovascular events in patients with diabetes and hypertension. It also suggests that calcium channel blockers may have some advantages when all events are taken into account and that they are better than conventional treatments at counteracting the greater tendency in hypertensive patients for the development of diabetes mellitus.[15]

In nondiabetic patients enrolled in INSIGHT, the absolute difference in the percentages of patients with new diabetes between the 2 treatment groups was 1.3% over a treatment duration of ≈4 years. This was not due to differences in the number of patients who received an ACE inhibitor as added treatment because this was similar in the nifedipine and diuretic group. The difference in the development of new diabetes was not sufficient to cause a difference in cardiovascular morbidity and mortality rates over the same period. However, if the trend

continues, it is likely to lead to risk reductions over 10 to 20 years because (1) the increased risk of cardiovascular disease brought about by diabetes is considerable,[16] and (2) this is the case both for native diabetes and for diabetes induced by antihypertensive drugs.[17] A number of studies have reported increased risks for the development of diabetes in patients treated with diuretics and β-blockers,[15,18-20] but it appears that ACE inhibitors and calcium channel blockers have either no effect or reduce the likelihood of new diabetes.[21,22] Assessing the incidence of new diabetes should therefore be part of all trials that aim to determine the protective effect of antihypertensive drugs and predict the benefits beyond the actual trial duration. To date, this has been done only in some trials, most of which have shown that the incidence of new diabetes is less with calcium antagonists,[14] ACE inhibitors, and angiotensin II antagonists[3,5,23] than with diuretics and β-blockers, which appear to increase the incidence of new diabetes beyond that seen in untreated hypertensive individuals.[24] This may be accounted for by the different effects on insulin sensitivity, which are favourable with calcium antagonists, ACE inhibitors, and angiotensin II antagonists and unfavourable with diuretics and β-blockers.[25,26]

The reduction in systolic and diastolic blood pressure was similar in the diabetic and nondiabetic subgroups of INSIGHT, regardless of whether treatment was based on nifedipine or diuretics. In the nondiabetic subgroup, however, on treatment systolic blood pressure was slightly (1.8 mm Hg) but significantly less in the diuretic than in the nifedipine-treated patients, with no difference in the incidence of primary or secondary outcomes. This could be due to the fact that nifedipine has direct organ-protective properties in addition to the protection provided by the blood pressure lowering per se. It could also mean, however, that even in the high-risk patients enrolled in the INSIGHT study, a blood pressure difference of 1.8 mm Hg was too small to have a pathophysiological effect, that the duration of the study was too short for differences in outcome to become apparent, or that the sample size was insufficient to determine differences in outcome in these subgroups.

Diabetic patients had slightly higher average blood pressures at baseline, which resulted in slightly higher on-treatment values. Furthermore, add-on medications were more frequently needed in diabetic than in nondiabetic patients. Finally, in diabetic patients diastolic blood pressure was reduced well below 90 mm Hg (82 mm Hg) but systolic blood pressure remained around 140 mm Hg. These results are consistent with the conclusions of other studies that effective antihypertensive treatment in diabetic patients requires more drugs, with a limited chance of reaching the perhaps too ambitious target systolic blood pressure values (130 mm Hg) which, according to current guidelines, provide the greatest degree of protection.[27-29]

Three further points should be mentioned. First, our data on the differential incidence of new diabetes and on combined primary and secondary end points add to the evidence provided by recent studies that similar reductions in blood pressure may be accompanied by different degrees of morbidity and mortality, thereby supporting the independent roles of the blood pressure-specific and organ-protective properties of the drugs used. Second, they provide

further evidence that calcium antagonists are suitable for diabetic hypertensive patients, contrary to the contention that treatment should make selective use of drugs that interfere with the renin-angiotensin system. To date, this contention does not appear to be supported by the available data, because treating diabetic patients with systolic hypertension using a calcium antagonist markedly reduced cardiovascular morbidity and mortality rates compared with placebo.[30] Furthermore, in patients with diabetic nephropathy, administration of an angiotensin II antagonist did not affect cardiovascular morbidity to a different degree than administration of a calcium antagonist.[31] Finally, patients included in studies showing the marked renal and cardiovascular protective effects of angiotensin II antagonists or ACE inhibitors in diabetes have usually required chronic administration of a calcium antagonist to achieve effective blood pressure control.[23,32,33]

The final point concerns the fact that although diabetes is associated with greater cardiovascular morbidity, there were insufficient events in the diabetic subgroup of INSIGHT to make an adequately powered comparison of the primary end point between nifedipine and diuretic-based treatments. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, losartan was more effective than atenolol at reducing cardiovascular and all-cause morbidity and mortality in patients with hypertension, diabetes, and left ventricular hypertrophy. [34] However, the majority of studies and sub-studies have been inadequately powered to compare cardiovascular protection with different antihypertensive drug regimens in diabetes. [3-6,11,12] Meta-analysis of the available data will therefore be needed to give comparisons adequate statistical power.

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Chapter 7

Efficacy and safety of long-acting nifedipine in patients with symptomatic stable angina pectoris with and without Diabetes: the ACTION trial.

Danchin N, Wagener G, Kirwan BA, de Brouwer S, Lubsen J, Poole-Wilson PA for the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) investigators.

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Efficacy and safety of long-acting nifedipine in patients with symptomatic stable angina pectoris with and without Diabetes: the ACTION trial

N. Danchin,* G. Wagener,† B-A. Kirwan,‡ S. de Brouwer,‡ J. Lubsen,‡§ P.A. Poole-Wilson,|| for the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) investigators.

*Department of Cardiology, Georges Pompidou European Hospital, Paris, France; †Pharma Research Center, Bayer Healthcare AG, Wuppertal, Germany; ‡SOCAR Research, Nyon, Switzerland; §Department of Epidemiology and Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands; ||Cardiac Medicine, Imperial College, London, UK.
Correspondence and requests for reprints to Prof. J. Lubsen, MD, PhD; SOCAR Research SA, PO Box 2564, CH-1260 Nyon 2, Switzerland
Tel: +41 22 9944343; fax: +41 22 9944309; e-mail: jlubsen@compuserve.com

ABSTRACT

Background: Data from placebo-controlled trials with calcium antagonists in patients with symptomatic coronary artery disease and diabetes is limited.
Aims: To assess the efficacy and safety of adding long-acting nifedipine to the conventional treatment of patients with stable symptomatic angina with and without diabetes mellitus.
Methods: Results of the ACTION trial, which compared nifedipine GITS 60 mg once daily to placebo in patients who required anti-anginal treatment but had preserved left-ventricular function, were stratified for diabetes at baseline.
Results: 14.5% of 7,665 patients in ACTION were diabetics. Both among non-diabetics and diabetics, nifedipine significantly reduced blood pressure by 6/3 mm Hg. During the study, significantly fewer diabetics assigned nifedipine required insulin or additional blood pressure lowering medication. The evolution of blood glucose and serum creatinine was not affected by nifedipine. Irrespective of diabetes, nifedipine had no effect on total mortality, cardiovascular mortality or myocardial infarction but significantly reduced the combined rate of death, any cardiovascular event or procedure by 11% (p=0.001), the incidence of new overt heart failure by 29% (p=0.02), and the need for coronary angiography by 18% (p<0.0001). Among non-diabetics, nifedipine significantly reduced the incidence of any stroke or transient ischeamic attack stroke by 34% (p=0.0001), and the need for bypass surgery by 24% (p=0.002).

Conclusion: The addition of nifedipine is safe both in diabetic and non-diabetic patients with stable symptomatic coronary artery disease, does not improve major cardiovascular event-free survival but reduces cardiovascular events and the need for interventions.

INTRODUCTION

Patients with coronary artery disease (CAD) and diabetes mellitus are at particularly high risk of developing further cardiovascular (CV) complications [1]. Angiotensin converting enzyme (ACE) inhibitors have been shown to be effective in preventing complications of diabetes [2], but these drugs do not have anti-anginal effects. Patients with CAD often need anti-anginal drugs either to prevent or to treat anginal attacks. No conclusive data exist on the long-term efficacy and safety of anti-anginal medications in patients with concurrent diabetes and stable symptomatic CAD irrespective of the presence of hypertension or previous myocardial infarction (MI). Current guidelines recommend a low target for arterial blood pressure, which may require the use of multiple antihypertensive medications [3,4]. Among these, dihydropyridines offer the advantage of being both potent anti-anginal and antihypertensive medications. In the mid-1990s there was considerable debate on the safety of calcium antagonists, and in particular dihydropyridines, in patients with CAD [5,9]. More recently, a meta-analysis on the safety of mostly long-acting calcium antagonists in hypertension suggested that, although these medications had overall beneficial effects in hypertensive patients similar to other antihypertensive medications, they were associated with a higher risk of heart failure (HF) [10]. The ACTION trial [11] was designed to assess the efficacy of long-acting nifedipine GITS (gastro-intestinal therapeutic system) in stable symptomatic patients with CAD and preserved left-ventricular function. In total 7,665 patients were included, and were followed for a mean of almost 5 years. The main conclusion was that nifedipine GITS is safe in patients with stable symptomatic CAD and reduces the need for coronary interventions [12]. Almost 15% of ACTION patients were diabetics. This paper reports the effects of nifedipine GITS in a large population of diabetic patients with stable CAD, and assesses whether this compound affects diabetes-related outcomes in non-diabetics.

METHODS

Design

The design, methods and main results of ACTION have been published previously [11,12]. Briefly, patients aged 35 years or older with stable symptomatic angina pectoris requiring treatment were randomized in equal proportions to the addition of either nifedipine GITS or

matching placebo. In addition to angina, patients had to have either a history of MI, or proven angiographic CAD, or a positive exercise test or perfusion defect. The left-ventricular ejection fraction had to be at least 40%. Major exclusions were: clinically significant heart failure, any major CV event or intervention within the last three months, planned coronary angiography or intervention, known intolerance to dihydropyridines, clinically significant valvular or pulmonary disease, unstable insulin-dependent diabetes mellitus, any gastro-intestinal condition that prohibited the use of GITS tablets, any condition other than CAD that limited life expectancy, hypotension or uncontrolled hypertension, and elevated creatinine or aminotransferase levels. Women could only participate if there was no risk of pregnancy. Detailed selection criteria and definitions have been described elsewhere [11].

The starting dose of nifedipine GITS or matching placebo was 30 mg once daily, increasing to 60 mg once daily within six weeks. Physicians were encouraged to attempt risk factor modification and to treat symptomatic angina with compatible medications. Lipid-lowering treatment was either continued or started at the same time as study medication according to internationally accepted guidelines. The following drugs could not be used in combination with study medication: calcium antagonists (2-week washout required), cardiac glycosides (unless given for supra-ventricular arrhythmias), other positive inotropic agents, class I or III antiarrhythmics other than amiodarone or sotalol, cimetidine, anti-psychotic and anti-epileptic drugs, rifampicin or rifampine.

At baseline, investigators recorded whether or not diabetes was present but no specific diagnostic criteria were given. After baseline assessments and treatment allocation, patients were seen at the out-patient clinic two weeks, six weeks and six months after randomization; and from then onwards every six months. Between visits, patients were contacted by telephone. At each clinic visit, blood pressure was recorded with a standard sphygmomanometer in the sitting position after 5 minutes of rest. Blood glucose and other standard laboratory tests were measured in routine non-fasting blood samples at baseline, after 26 weeks, 2 and 4 years, and at the end of the study. Haemoglobin A1c was not routinely assessed.

Serious adverse events suggesting a possible major CV event were classified by the Critical Events Committee events according to predefined criteria without access to the study medication code. Cause of death was classified as unknown, CV or non-cardiovascular.

STATISTICAL METHODS

As no specific diagnostic criteria for the presence of diabetes were given, patients were stratified for diabetes at baseline based on the investigator's diagnosis. Mean changes from baseline at selected time points during follow-up were calculated using all available measurements irrespective of study medication intake or prior occurrence of non-fatal clinical events. Overall mean changes from baseline were obtained by subtracting for each patient the mean follow-up value

from the baseline value, and then averaging the results. An overall p-value for comparing blood pressure levels between treatment groups was obtained from a mixed effects model for repeated measurements, using the SAS® proc mixed procedure. Percentages were compared using chi-square tests.

In addition to CV clinical events and procedures, the following composite endpoints were compared: the combined rate of death from any cause, MI, refractory angina requiring coronary angiography, new overt HF requiring hospitalization and peripheral revascularization (i.e. the ACTION primary endpoint for efficacy); the combined rate of death from any cause, MI and debilitating stroke (i.e. the ACTION primary endpoint for safety); any CV event (i.e. the ACTION primary endpoint for efficacy minus non-CV death); any death, CV event or procedure (i.e. the ACTION primary endpoint for efficacy plus coronary angiography, percutaneous coronary intervention and coronary bypass surgery); and any vascular event or procedure (i.e. the ACTION primary endpoint for efficacy minus non-CV death and new overt heart failure, plus percutaneous coronary intervention and coronary bypass surgery). In addition, the combined rate of disabling stroke, any stroke reported by investigators that did not meet the criteria for disabling stroke, and any reported transient ischaemic attack was considered.

All analyses for clinical events and composite endpoints were based on intention-to-treat. CV deaths and deaths of unknown cause were combined. Coronary angiography and percutaneous coronary intervention on the same day were counted only as percutaneous coronary intervention. Event rates were taken as number of events divided by total time that patients had been 'at risk' of the event concerned. For composite endpoints, the time that the first component event occurred was used in event rate calculations. Hazard ratios comparing patients assigned nifedipine to patients assigned placebo and their 95% confidence intervals were obtained using Cox proportional hazards models with treatment allocation as the only covariate. Interaction tests were performed by Cox proportional hazards models, using the SAS® proc phreg procedure.

RESULTS

ACTION was completed as planned [12]; 7,665 patients were started on study medication (3,825 nifedipine GITS, 3,840 placebo). At baseline, 1,113 (14.5%) ACTION patients were diagnosed as diabetic by the investigator, three more than reported earlier [12]. Mean follow-up was 5.0 years for non-diabetics and 4.8 years for diabetics, and did not depend on assigned treatment. Double-blind medication was taken by non-diabetics assigned nifedipine during 79%, and by those assigned placebo during 83% of total follow-up time. Diabetics used double-blind medication during 78% of total follow-up time, with no difference between nifedipine and placebo. Overall, follow-up was 97.3% complete [12].

Baseline characteristics for non-diabetics and diabetics respectively are given in Table 1. Both groups were similar with respect to, age, sex, NYHA class, presence of anginal attacks and history

Table 1: Baseline characteristics of non-diabetics and diabetics

	Non-Diabetic (n = 6552)	Diabetic (n = 1113)	*P**
Mean (SD) age (years)	63.4 (9.4)	63.9 (8.9)	0.1
Male gender	5,224 (80%)	860 (77%)	0.06
Current NYHA class II – III	3,004 (46%)	528 (47%)	0.3
Anginal attacks	6,040 (92%)	1,030 (93%)	0.7
History of MI	3,326 (51%)	572 (51%)	0.7
Angiographic CAD, no MI	2,088 (32%)	383 (34%)	0.1
Positive exercise or radionuclide test only	1,105 (17%)	157 (14%)	0.02
Significant lesions on coronary angiogram	4,442 (68%)	824 (74%)	<0.001
Angiography not performed or unknown	2,023 (31%)	278 (25%)	<0.001
History of PTCA	1,720 (26%)	296 (27%)	0.8
History of CABG	1,486 (23%)	303 (27%)	<0.001
On drug treatment for hypertension	2,577 (39%)	621 (56%)	<0.001
On drug treatment for hyperlipidaemia	4,446 (68%)	754 (68%)	0.9
On any BG lowering drug	0	853 (77%)	N/A
Past use of calcium antagonists	1,389 (21%)	287 (26%)	<0.001
Claudication	451 (6.9%)	174 (16%)	<0.001
Transient ischaemic attack	247 (3.8%)	55 (4.9%)	0.06
Stroke	139 (2.1%)	31 (2.8%)	0.2
Any peripheral vascular disease†	752 (11%)	233 (21%)	<0.001
Mean (SD) BG (mg/dl)	99 (21.2)	177 (70.8)	<0.001
Casual BG ≥200 mg/dl §			
In pts not on any BG lowering drug	31 (0.5%)	35 (3.1%)	N/A
In pts on any BG lowering drug	N/A	292 (26%)	N/A
Mean (SD) total cholesterol (mmol/l)	209 (40)	206 (45)	0.008!!!
Mean (SD) creatinine (mg/dl)	1.1 (0.2)	1.1 (0.2)	0.9
Creatinine ≥1.2 mg/dl	1,645 (25%)	308 (28%)	0.1
Mean (SD) BMI (kg/m2)	27 (3.7)	29 (4.2)	<0.001
Mean (SD) pulse rate (beats/min)	64 (10.1)	67 (10.7)	<0.001
Mean (SD) systolic BP (mmHg)	137 (18.8)	141 (18.0)	<0.001
Mean (SD) diastolic BP (beats/min)	80 (9.5)	80 (9.4)	0.7
Additional risk factors:			
Current smoker	1,204 (18%)	152 (14%)	<0.001
Total cholesterol ≥5.0 mmol/l	4,167 (64%)	648 (58%)	<0.001
Body mass index ≥30.0 kg/m^2	1,368 (21%)	376 (34%)	<0.001
BP ≥140/90 mm Hg	3,309 (51%)	668 (60%)	<0.001
Any of the above	5,485 (84%)	933 (84%)	0.9

Data are percentage of patients unless indicated otherwise. SD, standard deviation; NYHA, New York Heart Association; MI, myocardial infarction; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; BG, blood glucose; BP, blood pressure.
*p-values for comparing non-diabetics with diabetics. † Stroke, transient ischemic attacks or claudication.
§ equivalent to 11.1 mmol/l

of MI. Diabetics had more often significant lesions in a known prior coronary angiogram, more commonly a history of bypass surgery, and were more often already on drug treatment for hy-

pertension. Diabetics also had more commonly a history of peripheral vascular disease. Baseline mean blood glucose level, body mass index, pulse rate and systolic blood pressure were all higher in diabetics than in non-diabetics. 853 (77%) of all diabetics were on any blood glucose lowering drug. Of the 260 diabetics who were not, 35 (13% of 260) had a casual baseline blood glucose level ≥ 200 mg/dl (11.1 mmol/l). There was no difference with respect to the fraction of patients who had least one of the additional risk factors listed in Table 1. Nonetheless, fewer diabetics were current smokers or had a total cholesterol ≥5.0 mmol/l, while more diabetics were obese (body mass index ≥30.0 kg/m2) or had a baseline blood pressure ≥140/90 mm Hg. At baseline, 68% of both non-diabetics and diabetics were on any lipid lowering treatment but diabetics were more often on statins than non-diabetics (63% and 58% respectively). Any anti-anginal medication other than β-blockers was used by 79% of non-diabetics and 78% of diabetics. 86% in both groups were using aspirin, and 4% were on warfarin or similar. Any anti-arrhythmic drug was used by 4% in both groups.

Data on the use of blood pressure and blood glucose lowering drugs at baseline and during follow-up is given in Table 2. At baseline, β-blockers were used to a similar extent by both non-diabetics and diabetics, but diabetics were more often on ACE-inhibitors, angiotensin receptor blockers (ARBs) or diuretics. Patients assigned nifedipine and placebo respectively were comparable at baseline as regards the medications listed in Table 2 both for non-diabetics and diabetics.

During the study, nifedipine significantly reduced the need to prescribe ACE-inhibitors, ARBs or diuretics both among non-diabetics and among diabetics (c.f. Table 2). In both groups, nifedipine had no effect on the number of patients that were prescribed any blood glucose lowering drug at any time, or were started on any blood glucose lowering drug. Among diabetics, nifedipine significantly reduced the number of patients treated with insulin at any time.

Table 2: Additional medications in non-diabetics and diabetics

	Non-diabetics			Diabetics		
	Nifedipine (n=3,258)	Placebo (n=3,294)	*P**	Nifedipine (n=567)	Placebo (n=546)	P*
Baseline						
Not on BG-lowering drugs	3,258 (100%)	3,294 (100%)		133 (23%)	127 (23%)	
On insulin	0	0	-	86 (15%)	96 (18%)	-
On metformin	0	0	-	174 (31%)	159 (29%)	-
On sulfonylureas	0	0	-	302 (53%)	282 (52%)	-
On any BG-lowering drug	0	0	-	434 (77%)	419 (77%)	-
On β-blockade	2,583 (79%)	2,632 (80%)	-	450 (79%)	434 (79%)	-
On ACE-I or ARB	664 (20%)	678 (21%)	-	195 (34%)	202 (37%)	-
On a diuretic	350 (11%)	359 (11%)	-	82 (14%)	88 (16%)	-
On any blood pressure lowering drug	2,833 (87%)	2,879 (87%)	-	511 (90%)	494 (90%)	-
At any time during study						
On insulin	18 (0.6%)	21 (0.6%)	0.7	179 (32%)	206 (38%)	0.03
On metformin	81 (2.5%)	88 (2.7%)	0.6	299 (53%)	299 (55%)	0.5
On sulfonylureas	86 (2.6%)	90 (2.7%)	0.8	376 (66%)	371 (68%)	0.6
On any BG-lowering drug†	152 (4.7%)	148 (4.5%)	0.7	497 (88%)	491 (90%)	0.2
Started on BG-lowering Rx‡ (rate§)	152 (0.96)	148 (0.93)		63 (14.1)	72 (16.9)	
Hazard ratio (95% CI)	1.04 (0.83 – 1.30)		0.8	0.84 (0.60 – 1.18)		0.3
On β-blockade	2,843 (87%)	2,921 (89%)	0.1	503 (89%)	491 (90%)	0.5
On ACE-i or ARB	1,252 (38%)	1,545 (47%)	<0.001	363 (64%)	387 (71%)	0.01
On a diuretic	1,091 (33%)	1,222 (37%)	0.002	254 (45%)	285 (52%)	0.01
On any blood pressure lowering drug	3,085 (95%)	3155 (96%)	0.04	553 (98%)	529 (97%)	0.5
Started on BP-lowering Rx‡ (rate§)	252 (19.8)	276 (24.2)		42 (32.9)	35 (27.2)	
Hazard ratio (95% CI)	0.83 (0.70 – 0.98)		0.03	1.17 (0.75 – 1.83)		0.5

Numbers of patients and percentages of total number of patients at baseline, unless indicated otherwise. ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BG, blood glucose; Rx, medication; CI, confidence interval. *p-values comparing nifedipine with placebo for non-diabetics and diabetics respectively. † Includes only blood glucose lowering drugs given for at least one week. ‡ Not on blood sugar lowering medication at baseline. § Number of patients started on blood sugar lowering medication for at least one week per 100 years of follow-up of patients who were not on blood sugar lowering medication at baseline.

Relative to placebo, mean blood pressures were 6/3 mm Hg lower among patients assigned to nifedipine, both among non-diabetics (p<0.001) and among diabetics (p<0.001). In both groups, a higher percentage of patients assigned nifedipine had blood pressures below 140/90 mm Hg, or below 130/80 mm Hg, at all time points during follow-up (Figure 1).

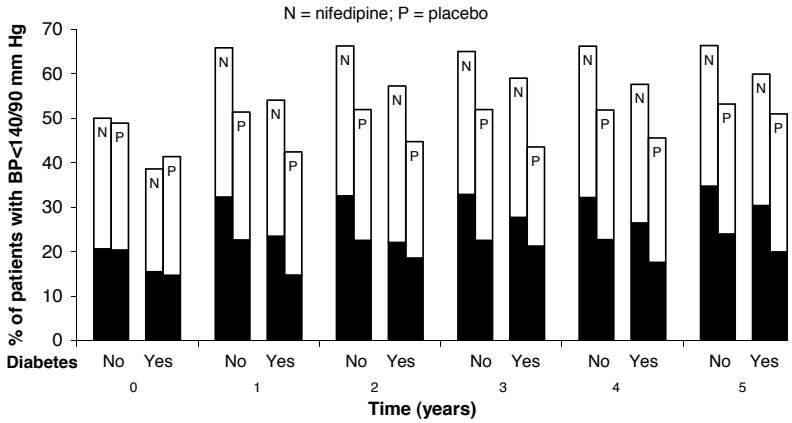
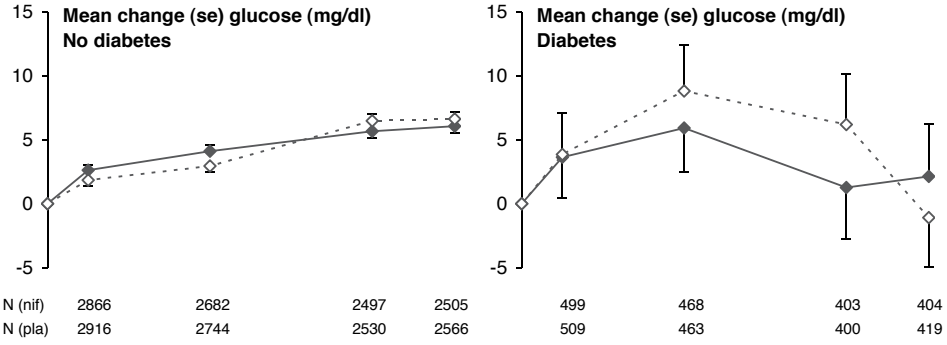


Figure 1. Evolution of fraction of patients with elevated blood pressure (BP) by diabetes at baseline as % of all patients with blood pressure measurements (irrespective of use of study medication or prior non-fatal clinical events). **Filled plus open bars**: % of patients with blood pressure below 140/90 mm Hg; **filled bars**: % of patients with blood pressure below 130/80 mm Hg.

As shown in Figure 2, blood glucose levels among non-diabetics gradually increased towards the end of the study. Among diabetics, there was an initial rise of blood glucose level during the first two years with a return to baseline towards the end of the study. There was no statistically significant and consistent effect of nifedipine on casual blood glucose levels in both non-diabetics and diabetics, and no effect on the percentage of patients with a casual blood glucose level ≥ 200 mg/dl. Baseline creatinine values increased towards the end of the study in both groups, and were not significantly affected by nifedipine. In non-diabetics, body mass index increased gradually and significantly more in patients assigned placebo than in patients assigned nifedipine. Nifedipine had no effect on the evolution of body mass index in diabetics.



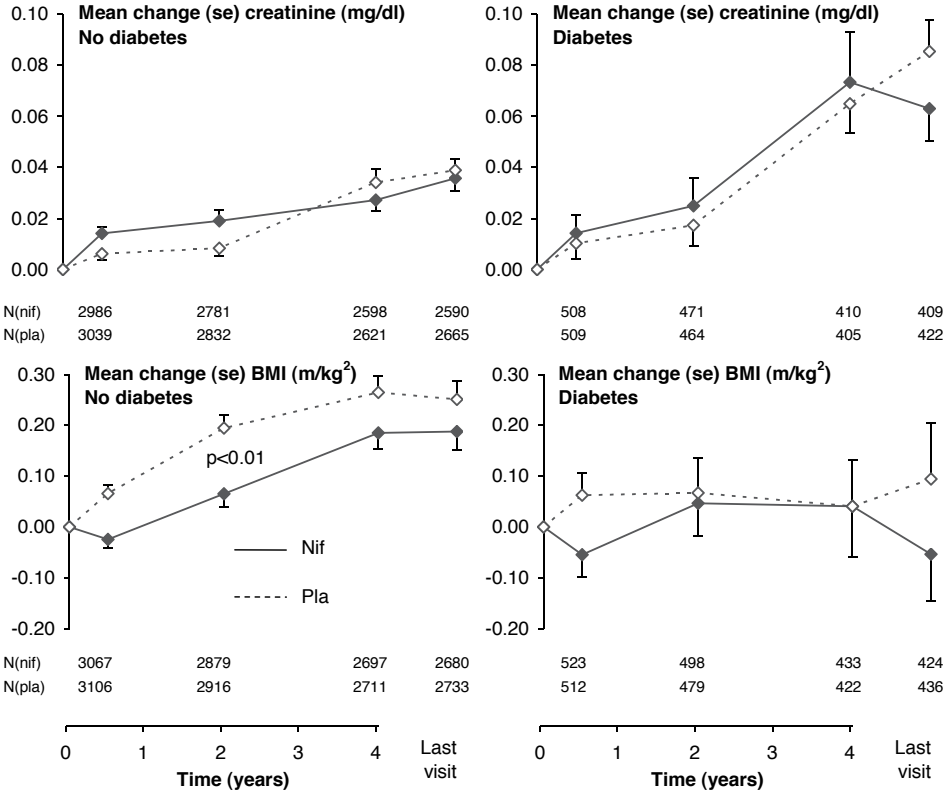


Figure 2. Mean changes from baseline of blood glucose and creatinine by diabetes at baseline. Error bars indicate standard errors of the mean. Below each graph the number of patients with available measurements (irrespective of use of study medication or prior non-fatal clinical events) is given by treatment group. N, number; nif, nifedipine; pla, placebo.

Among non-diabetics at baseline, hyperglycaemia was reported as an adverse event for 116 patients assigned nifedipine (0.73/100 patient-years of follow-up) and 120 patients assigned placebo (0.75/100 patient-years of follow-up) respectively (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.75–1.26, p=0.8). Among diabetics, hyperglycaemia was reported less often in patients assigned nifedipine (65 patients or 2.6/100 patient-years of follow-up) than in patients assigned placebo (84 patients or 3.5/100 patient-years of follow-up) respectively (HR 0.73, 95% CI 0.53–1.01, p=0.06). Similarly among diabetics, hypoglycaemia was reported less often in patients assigned nifedipine (16 patients or 0.59/100 patient-years of follow-up) than in patients assigned placebo (25 patients or 0.97/100 patient-years of follow-up) but the difference was not statistically significant (HR 0.61, 95% CI 0.33–1.14, p=0.1). As regards other possible diabetes-related side effects, there were no major differences between patients assigned nifedipine or placebo both among non-diabetics and among diabetics.

In Figure 3, the effects of nifedipine (relative to placebo) on CV clinical events are compared between non-diabetics and diabetics at baseline. For all events shown, event-rates were higher among diabetics than among non-diabetics. Rates of all-cause death, CV or unknown death and MI were similar for patients assigned nifedipine and patients assigned placebo both among non-diabetics and diabetics. Nifedipine significantly reduced the rate of any stroke or transient ischaemic attack (HR 0.66, 95% CI 0.53–0.82, p=0.0001), of debilitating stroke (HR 0.67, 95% CI 0.47–0.94, p=0.02) and the need for coronary bypass surgery (HR 0.76, 95% CI 0.64–0.90, p=0.002) in non-diabetics, but not in diabetics. The need for coronary angiography was significantly reduced by nife dipine irrespective of the presence of diabetes (HR in both diabetes groups combined 0.82, 95%CI 0.75–0.90, p<0.0001). New overt HF was reduced by

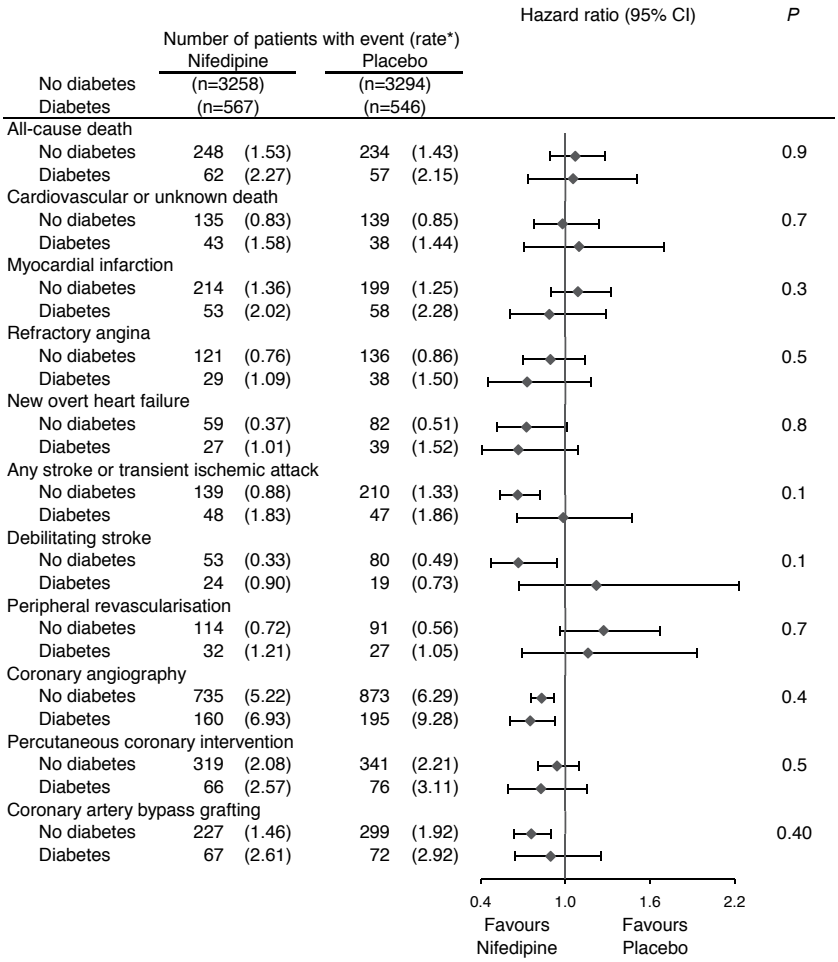


Figure 3. Effect of nifedipine on clinical events for non-diabetics and diabetics at baseline respectively. Rates in number of events per 100 patient years of follow-up 'at risk'. Hazard ratios with 95% confidence intervals (CI). P-values for effect modification (interaction test).

nifedipine to a similar extent both among non-diabetics and among diabetics (p-value for interaction = 0.8) but this effect was statistically significant only in all patients combined (HR 0.71, 95% CI 0.54–0.94, p=0.02).

Figure 4 shows results for pre-defined ACTION composite endpoints in a similar manner as Figure 3. Nifedipine had no effect on the primary endpoint for efficacy or the primary endpoint for safety both among non-diabetics and among diabetics. In both diabetes groups, nifedipine significantly reduced the combination of death, CV events and procedures. The effect on vascular events or revascularization was similar, and was statistically significant in non-diabetics (HR 0.91, 95% CI 0.83–1.00, p=0.05) and in both diabetes groups combined (HR 0.91, 95% CI 0.83–0.99, p=0.03).

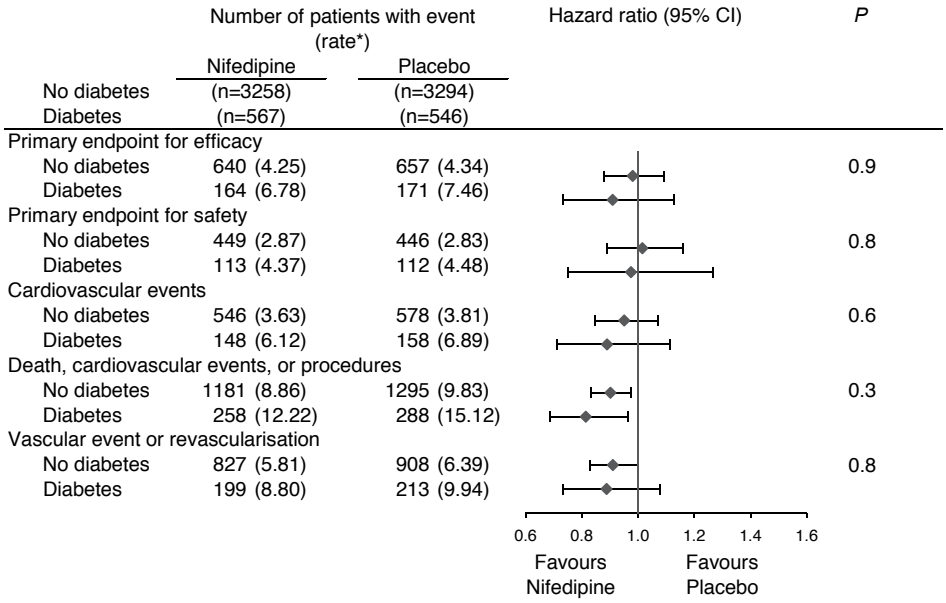


Figure 4. Effect of nifedipine on pre-defined composite endpoints for non-diabetics and diabetics at baseline respectively. Rates in number of events per 100 patient years of follow-up 'at risk'. Hazard ratios with 95% confidence intervals (CI). P-values for effect modification (interaction test).

DISCUSSION

The main finding of this subgroup analysis of data from the ACTION trial is that, although diabetics had a higher risk of events than non-diabetics, the effects of the addition of nifedipine to standard treatment on clinical outcome were similar. ACTION represents the largest long-term trial assessing the effect of an anti-anginal drug relative to placebo on clinical outcome in patients with stable CAD and preserved left-ventricular function. The majority of

patients were also on beta-blockers and lipid-lowering drugs while an important fraction was on an ACE-inhibitor or ARB. Diabetics represented 14.5% of the population in the trial and had baseline characteristics that were not substantially different from those of non diabetic patients, with the exception of obesity, hypertension and peripheral arterial disease, which were more common. Our results show that, in diabetic patients, long-acting nifedipine was neither superior nor inferior to placebo in terms of safety or efficacy as defined by corresponding predefined primary endpoints, when used on top of β-blockers and other conventional anti-anginal medications. ACE-inhibitors are known to reduce CV mortality and major morbidity in patients with hypertension or CAD [2,13]. In ACTION, more patients assigned placebo than nifedipine were prescribed ACE-inhibitors during follow-up (c.f. Table 2). This may have contributed to the lack of difference between treatment groups as regards primary endpoints. Despite this, nifedipine significantly reduced by the risk of the composite endpoint of death, any CV event or procedure both among non-diabetics and diabetics (c.f. Figure 4). Nifedipine also significantly reduced systolic and diastolic blood pressure throughout the course of the trial in both subgroups. Metabolic control during follow-up was slightly better in nifedipine-treated patients, with a lower proportion of diabetic patients needing insulin. Irrespective of the presence of diabetes, creatinine levels increased during the course of the trial in a similar fashion in patients receiving nifedipine or placebo.

Previous long-term clinical trials with calcium antagonists were performed mainly in hypertensive populations and controversial results were observed in hypertensive patients with diabetes [14]. In a secondary analysis of the ABCD trial [15], nisoldipine was associated with an increased incidence of fatal and non fatal MI in comparison to enalapril. Conversely, in the ALLHAT trial [16], amlodipine and chlorthalidone were equally effective both in diabetic or non-diabetic patients. The CONVINCE trial compared long-acting verapamil with either atenolol or hydrochlorothiazide in hypertensive patients [17], and was stopped earlier than planned. In this trial, the efficacy of verapamil appeared more marked in diabetic patients, although there was no significant heterogeneity in the trial's results according to diabetic status. The reverse was observed in the large INVEST trial [18]. In this trial, patients with CAD and hypertension were randomized to blood pressure lowering strategies based on long-acting verapamil or atenolol. The non calcium antagonist strategy appeared slightly superior (albeit not significantly so) in diabetic patients. Overall, the use of calcium antagonists in diabetic hypertensive patients appears to be safe [14]. Our results confirm that in patients with stable symptomatic CAD and preserved left ventricular function, long-acting nifedipine has no deleterious effect in terms of major CV endpoints (CV death, MI), irrespective of the presence or absence of diabetes. Importantly, the anti-anginal efficacy of nifedipine translated in improved CV outcomes in terms of CV event and intervention-free survival. New overt HF was also less frequent in patients receiving nifedipine. In addition and clinically relevant, nifedipine significantly increased the proportion of patients with appropriate blood pressure levels and reduced the need to prescribe additional blood pressure lowering drugs.

Beside their effect on major CV outcomes, there is evidence that calcium antagonists might decrease the occurrence of diabetes mellitus or improve glycaemic control at least when compared to diuretics or β-blockers as antihypertensive treatment. In the ALLHAT trial [16], fasting glucose levels were lower after two and four years in the amlodipine than in the chlorthalidone arm, although the difference was statistically significant only at two years. In the subgroup of non-diabetics, the proportion of patients with a fasting glucose ≥ 126 mg/dL was significantly lower in the amlodipine arm both at two and at four years. In the same trial enalapril was superior to chlorthalidone in this respect at all time-points. In the INVEST trial [18], in which the two antihypertensive strategies compared achieved equivalent blood pressure control, non-diabetic patients randomized to the calcium antagonist-based strategy had a statistically significant 15% lower risk of developing diabetes during the 2.7-year follow-up. In the INSIGHT trial, nifedipine significantly reduced the occurrence of new diabetes in patients without diabetes at baseline relative to co-amilozide [19]. A trend in the same direction was observed in the NORDIL study, which compared diltiazem with diuretics and β-blockers [20].
In ACTION, nifedipine was compared to placebo rather than another active agent. In diabetics, there was trend towards better glycaemic control and significantly less need for insulin in patients assigned nifedipine than in patients assigned placebo. In non-diabetics we found no evidence that nifedipine retards the occurrence of diabetes since there were no differences with respect to the introduction of anti-diabetic medications or blood glucose levels. Also, there were no differences in the occurrence of adverse events which might have been related to diabetes.
Effects on blood glucose control seem to be independent of the reduction in blood pressure. Indeed, in ALLHAT blood pressure control was if anything slightly better with chlorthalidone than with amlodipine [16]. Similarly, in the INSIGHT trial there were more episodes of hyperglycaemia reported as adverse events in the co-amilozide arm despite similar blood pressure in the nifedipine and co-amilozide arms respectively [21].
Despite the difference between nifedipine and placebo as regards blood pressure control, there was no clinically relevant difference between creatinine levels both among non-diabetics and diabetics. These results are in agreement with those of the IDNT trial [22], which showed no difference between amlodipine and placebo as regards a two-fold increase of creatinine.
In conclusion, this sub-group analysis of the results of the ACTION trial according to diabetic status at baseline documents the safety of long-acting nifedipine in patients with stable symptomatic CAD and preserved left ventricular function irrespective of the presence of diabetes. Although there was no difference in the primary endpoint of the trial, a significant reduction was observed both among non-diabetic and diabetic patients in the combined occurrence of death, CV events or cardiac procedures. In addition, nifedipine significantly improved blood pressure control but did not contribute to improved diabetes control in a manner that would

be clinically relevant. These findings lend support to existing guidelines for using calcium antagonists in diabetics with hypertension and/or angina [23].

CONFLICT OF INTEREST STATEMENT

The ACTION study was carried out by an independent Steering Committee and Research Group. The study was supported by Bayer Healthcare AG, Germany, of which GW is a full-time employee. JL and PAP-W have served as consultants to or received travel expenses, payment for speaking at meetings or funding for research from other pharmaceutical companies. BAK, SdeB and JL are full-time employees of SOCAR Research SA, which managed the study.

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Chapter 8

General discussion

Long-term evolution of blood pressure in patients with stable angina

ACTION was a multi-centre, randomised, placebo-controlled, double-blind trial designed to compare the effect on clinical outcomes of long-acting nifedipine GITS or placebo in patients with symptomatic angina pectoris attributable to coronary disease. The main results have been published (c.f. Chapter 2). Patients with symptomatic orthostatic hypotension or a supine systolic blood pressure of 90 mmHg or less, a systolic blood pressure of at least 200 mmHg and/or a diastolic blood pressure of at least 105 mmHg, were excluded. Otherwise, patients were not selected based on their screening blood pressure. Patients already on treatment for hypertension could participate as well as patients who were not.

Because patients were not selected based on screening blood pressure, the evolution of blood pressure during follow-up should not be influenced by the regression-to-the-mean phenomenon that would have been introduced by selection based on screening blood pressure values, combined with within-patient variability of measurements [1].

The evolution of blood pressure in all ACTION patients combined is shown in Figure 2 of Chapter 2. There is no explanation for the initial drop at the first two follow-up measurements after 2 and 6 weeks of treatment with either nifedipine or placebo. In the placebo group, blood pressure levels were the same at 6 months as at baseline. This indicates that there was indeed no regression-to-the-mean when all ACTION patients are considered together. During prolonged follow-up up to 5½ years, mean systolic blood pressures were essentially stable while mean diastolic blood pressure tended to decrease in both treatment groups. The mean difference between patients assigned nifedipine and placebo remained essentially stable.

That mean diastolic blood pressure levels tended to decrease is contrary to the notion that blood pressure tends to increase with age. There are several alternative explanations for the apparent decrease of mean diastolic blood pressure in ACTION. As duration of follow-up of the closed cohort concerned increases, less patients are available for blood pressure measurement. At baseline, 3822 patients assigned nifedipine had their blood pressure recorded, as opposed to 3839 patients assigned placebo. After 5 ½ years of follow-up, the corresponding numbers of patients with measurements were 1647 and 1683 respectively (c.f. Figure 2, Chapter 2). Patients with a particularly high blood pressure at baseline are at higher risk of death or myocardial infarction during follow-up, and tend therefore either to be no longer present in the cohort as follow-up increases due to death, or have decreased blood pressure values due to non-fatal myocardial infarction. Alternatively, patients admitted early on to the study during recruitment could have had lower blood pressure at baseline. This would show up as lower blood pressures in patients who have the longest duration of follow-up. Another explanation could be that patients were more intensively treated with additional blood pressure lowering drugs towards the end of the study. As shown in Table 2 of Chapter 3 there was evidence for this in the ACTION study, in particular among patients with elevated blood pressure at baseline.

The evolution of mean blood pressure for normo- and hypertensives at baseline respectively is shown in Figure 1 of Chapter 3. As expected, blood pressure in normotensives (defined in this case as systolic blood pressure below 140 and diastolic blood pressure below 90 mmHg irrespective of treatment, c.f. Chapter 3) tended to increase while the opposite was the case in hypertensives. As "normotension" was defined on baseline measurements only, the explanation for this must be regression-to-the-mean. These results underscore the difficulty of assessing the incidence of hypertension in a closed cohort of patients who are normotensive at the start of follow-up, and the need for a control group in studies that aim to demonstrate the effect of treatment on the incidence of hypertension [2].
In Chapter 3, data is given also on the blood pressure lowering effect of nifedipine GITS in normo- and hypertensives at baseline respectively (relative to placebo). As expected (c.f. Table 3, Chapter 3), nifedipine had a larger effect on follow-up blood pressures in hypertensives than in normotensives (mean reductions of 6.6/3.5 mmHg and 3.9/2.4 mmHg respectively). This shows that even in normotensives blood pressure can still be lowered by blood pressure lowering drugs. Whether this is beneficial is controversial however [3].

EFFECT OF BLOOD PRESSURE REDUCTION ON OUTCOME IN PATIENTS WITH STABLE ANGINA

The main conclusions from ACTION were that the addition of nifedipine GITS to the conventional treatment of angina pectoris has no effect on major cardiovascular event-free survival (i.e. the combination of death from any cause, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularisation; which was the pre-specified primary outcome for efficacy), that nifedipine GITS reduces the need for coronary angiography and interventions, and is safe. The safety of nifedipine GITS is an important finding as ACTION was started in response to the debate on the safety of the short-acting capsule formulation of nifedipine in patients with coronary disease that arose in the mid-1990ties (c.f. Chapters 1 and 2).
ACTION was designed to show superiority of nifedipine GITS compared to placebo. The sample size calculation has been published in detail [4]. Assuming a primary efficacy outcome rate of 5.58 per 100 patient-years and 731 patients with event among those assigned placebo, the study was designed to have 95% power to detect an 18% reduction of this outcome by nifedipine GITS, relative to placebo, at an overall 5% level of significance. As shown in Table 3 of Chapter 2, the observed rate of the primary efficacy outcome in patients assigned placebo was 4.75, and therefore slightly lower than expected. As shown in the same Table, the total number of patients with a primary outcome event – 828 – was higher than assumed. As the power is primarily dependent on the number of events rather than on the rate, the power of the study has not suffered from the lower-than-expected event-rate.

There are several reasons why nifedipine did not have the effect in ACTION that was assumed when the study was designed. The event-rate in patients assigned placebo was low, and it is difficult to reduce a low absolute rate even further by treatment. That peripheral revascularisation – a component of the primary endpoint for efficacy – was more frequent in patients assigned nifedipine was unexpected. Patients assigned placebo were more intensively treated than those assigned nifedipine (c.f. Chapter 3).

That nifedipine might have larger effects in patients with a higher risk because of co-existent hypertension was expected when the study was designed, and was the basis for prespecifying a subgroup analysis contrasting effects in patients with elevated blood pressure to the effects in patients without. Apart from the expected higher event-rates in hypertensives, the rationale underlying this subgroup analysis was that nifedipine GITS is an effective blood pressure lowering agent, and that blood pressure lowering in patients with hypertension has been shown to be effective.

The results of this and other pre-specified subgroup analyses were given in the main results report (c.f. Figure 4, Chapter 2). As shown in the figure mentioned, blood pressure level at baseline was the only baseline characteristic that showed a significant interaction with the effect of nifedipine on the primary outcome for efficacy (p=0.015, c.f. Figure 4, Chapter 2). As this was also the only subgroup analysis based on a sound a-priori rationale, this was the reason to further explore the subgroup analysis in a separate report.

As reported in Chapter 3, an almost equal number of ACTION patients were either normotensive or hypertensive based on baseline blood pressure values. Hence, this subgroup analysis has optimal statistical power. As shown in Figure 3 of Chapter 3, the rates of death, myocardial infarction, new overt heart failure, any transient ischemic attack or stroke, and debilitating stroke were higher in hypertensives than in normotensives.

As nifedipine significantly reduced the primary endpoint for efficacy in hypertensives by 16% (event-rate 4.90 nifedipine, 5.61 per 100 patient-years placebo, c.f. Figure 2 of Chapter 3), this subgroup analysis of the ACTION study supports the addition of nifedipine GITS to the basic regimen of patients with stable symptomatic coronary disease who also have elevated blood pressure, and is in agreement with the conclusion from meta-analyses that blood pressure control in patients with hypertension improves outcome [5].

In hypertensives, nifedipine significantly reduced the event rates of any transient ischemic attack or stroke, debilitating stroke and new overt heart failure, relative to placebo. That nifedipine reduced the incidence of new overt heart failure in the ACTION study is a new and therefore unexpected finding. Rather than its prevention, calcium antagonists have been associated in previous studies with an increased risk of developing new, or worsening of, heart failure [6,7]. This may have been due to the use of the immediate release, short-acting capsule formulation of nifedipine [8-11]. Short-acting nifedipine may induce a fast drop in blood pressure and a compensatory increase in heart rate [12], which may result in worsening of heart failure symptoms or even pump failure. Another possible explanation for an increased

incidence of heart failure in previous studies is peripheral oedema. The latter is a typical side effect of dihydropyridine calcium antagonists [13] that may be falsely interpreted clinically as a sign of heart failure. In the ACTION trial, peripheral oedema was indeed more commonly reported as an adverse event in patients assigned nifedipine than in those assigned placebo (c.f. Chapter 2). That the incidence of heart failure was nonetheless reduced can therefore be attributed to the strict procedures and criteria for the diagnosis of heart failure that were used by the ACTION Critical Events Committee (c.f. Chapter 2). It should be stressed in this regard that in ACTION, diagnoses by the Critical Events Committee were determined independently of the investigator diagnosis as entered on adverse events reports [14].

Interestingly, a recently published further analysis of ACTION data has suggested that the positive effect on the occurrence of heart failure and stroke can be attributed to the blood pressure lowering effect of nifedipine [15]. As uncontrolled hypertension is one of the most important modifiable risk factors for the development of heart failure, the prevention of the development of hypertension by nifedipine in patients at risk of developing heart failure should therefore also result in the reduction of new overt heart failure and stroke, as was observed in the ACTION trial.

That nifedipine has potent anti-anginal effects is well established. The observation in ACTION that nifedipine reduced the need to perform coronary angiography is therefore not surprising as symptom-driven coronary angiography should be related to worsening of anginal symptoms. In contrast to heart failure and stroke, the recently published further analysis of ACTION data mentioned earlier has suggested that the significant reduction of coronary angiography – which occurred both in normo- and in hypertensives (c.f. Figure 3, Chapter 3) – cannot be attributed to blood pressure reduction [15]. This suggests, to our knowledge for the first time, that the effects of "blood pressure lowering" drugs are not necessarily all attributable to blood pressure lowering. The stroke and heart failure risk reduction by nifedipine GITS in patients with stable angina can apparently be attributed primarily to its blood pressure lowering effect. On the other hand, the effects on coronary procedures are likely to be related almost entirely to its anti-anginal effects, with blood pressure reduction being an epiphenomenon [15]. Different blood pressure lowering drugs should have different properties in this regard but there is little other information in the literature that supports this.

ACTION did not show that reduction of angina as evidenced by a reduced need for coronary angiography improves myocardial infarction-free survival in patients with stable angina and a normal blood pressure in an intention-to-treat comparison that disregards a rise in blood pressure during follow-up. Whether the results of ACTION support the addition of nifedipine GITS to the basic regimen of patients with stable angina and a normal blood pressure remains therefore a matter of debate. While nifedipine GITS can be expected to reduce the need for coronary angiography and the incidence of any transient ischaemic attack or stroke without any negative effect on the occurrence of heart failure in these patients, these positive effects

may be offset by a slightly higher rate of death and myocardial infarction due to a J-shaped relation between the occurrence of these events and treated blood pressure [3].

SIGNIFICANCE AND EVOLUTION OF RENAL FUNCTION IN PATIENTS WITH HYPERTENSION OR CORONARY DISEASE TREATED WITH NIFEDIPINE GITS

As stated in the introduction to Chapter 5, renal dysfunction is recognised as an important predictor of outcome in patients with hypertension and/or coronary disease. This poses three questions: (i) how does renal dysfunction impact on prognosis, (ii) is blood pressure control more difficult in patients with renal dysfunction, and (iii) does the choice of treatment by itself have an effect on renal dysfunction?

Both the INSIGHT and the ACTION studies have provided further evidence as regards each of these questions in patients with hypertension and with stable angina respectively. INSIGHT (c.f. Table 3, Chapter 4) revealed that patients with hypertension and proteinuria have a 2.35-fold higher odds of the combined event of cardiovascular death, myocardial infarction, heart failure and stroke than those without proteinuria, adjusted for other confounders. The adjusted odds ratio for creatinine level was 1.23 per 0.2 mg/dL (20 µmol/L) increase. ACTION (c.f. Chapter 5) revealed that the rate of all-cause death in patients with stable angina rises 1.61-fold per mg/dL increase of baseline creatinine level, adjusted for other risk factors. Similar conditionally independent associations were present for cardiovascular death or confirmed myocardial infarction, and for new overt heart failure. Estimated creatinine clearance was also significantly related to the rate of these events, but creatinine level was not. In Figure 3 of Chapter 5 event-rates in ACTION patients with stable angina are shown stratified for markers of renal dysfunction at baseline. The rate of cardiovascular death or confirmed myocardial infarction rose from 1.79 per 100 patient-years in patients assigned placebo without markers of renal dysfunction to 4.01 per 100 patient-years in patients with two or three markers. Given these findings there can therefore be little doubt that renal dysfunction has a major impact on prognosis, both in patients with hypertension and with stable angina.

The question whether elevated blood pressure is more difficult to control in patients with hypertension in INSIGHT is addressed in Chapter 4. As is shown in Table 2, blood pressure changes from baseline were similar in patients with and without elevated creatinine level or reduced creatinine clearance. But patients with renal dysfunction needed more add-on medication to reduce blood pressure. In patients with normal renal function 30% of patients used 2 drugs and 9% used 3 drugs, as opposed to 35% and 19% respectively in patients with renal dysfunction. This indicates unequivocally that blood pressure is indeed more difficult to control in hypertensives who also have renal dysfunction. In patients with stable angina who participated in ACTION, the question whether the effect of nifedipine on blood pressure levels depended on renal function was not addressed.

The effect of blood pressure lowering drugs on renal function has been a cause for concern for many years. For instance, although angiotensin-converting enzyme inhibitors were recognised when they were introduced as potent blood pressure lowering drugs useful for treating hypertension, these drugs were considered contraindicated in patients with heart failure until the results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial appeared in 1987 [16]. The reasons for this were that patients with heart failure often have impaired renal function, and that angiotensin-converting enzyme inhibitors may cause hypotension and increase creatinine levels. CONSENSUS was the first study to show that angiotensin-converting enzyme inhibitors reduce mortality in patients with heart failure despite their negative effect on creatinine levels [17], provided that an appropriately low starting dose is used to avoid hypotension.

It has long been recognised that high-dose diuretics worsen renal function and prognosis in patients with renal dysfunction [18]. As shown in Figure 1 of Chapter 4, patients with hypertension assigned in INSIGHT to a nifedipine GITS based regimen had higher estimated creatinine clearance levels during follow than those assigned to a co-amilozide based regimen. As follow-up blood pressure levels were very similar [6], the difference in creatinine clearance between the treatment arms cannot be attributed to progression of renal dysfunction due to higher blood pressure levels. Hence, the question whether creatinine clearance is increased by nifedipine GITS, or reduced by co-amilozide, cannot be answered from INSIGHT. Because of this, the data on the effect of nifedipine GITS on creatinine from the placebo-controlled ACTION trial are of considerable relevance. As is shown in Figure 1 of chapter 5, nifedipine GITS had little or no effect on creatinine or estimated creatinine clearance in ACTION. Hence, the conclusion must be that the difference in INSIGHT is caused by a negative effect of co-amilozide on renal function, rather than by a positive effect of nifedipine.

That nifedipine GITS is neutral in terms of effect on creatinine, and lowers uric acid (c.f. Figure 1 of chapter 5) is in theory a desirable property compared to diuretics and angiotensin-converting enzyme inhibitors. One might expect that this would translate into a beneficial effect of nifedipine GITS compared to co-amilozide in patients with hypertension and renal dysfunction. This subgroup analysis remains to be done in INSIGHT. As shown in Chapter 5, the effect of nifedipine GITS on outcome as observed in ACTION did not depend on renal dysfunction (c.f. Figure 3, Chapter 5). There is little doubt that renal dysfunction is associated with a poor prognosis in patients with hypertension and with coronary artery disease. The extent to which drug-induced renal dysfunction impairs prognosis remains to be elucidated however.

Significance and evolution of diabetes in patients with hypertension or coronary disease treated with nifedipine GITS

The concurrent presence of diabetes poses the same problems in patients with hypertension or stable angina as renal dysfunction. Again, the questions that must be asked relate to (i)

the impact of diabetes on prognosis, (ii) the difficulty of controlling blood pressure in these patients, and (iii) the effect that treatment may have on diabetes itself.

That the presence of diabetes is associated with an impaired prognosis has long been recognised, and was observed both in INSIGHT and in ACTION. In both INSIGHT treatment arms combined, the primary outcomes cardiovascular death, myocardial infarction, heart failure, and stroke occurred in 8.4% of hypertensives with diabetes at baseline as opposed to 5.4% of hypertensives without diabetes. The same was true for secondary outcomes, which includes all-cause death in addition to primary outcomes (16.4% among diabetics, 11.3% among non-diabetics, c.f. Figure Chapter 6). In patients with stable angina assigned placebo in the ACTION study, event-rates were higher in diabetics than in non-diabetics (c.f. Figure 3, Chapter 7). As expected, diabetes was also a conditionally independent predictor of outcome in ACTION participants when other factors are controlled for in a multivariate risk model [19].

Both INSIGHT and ACTION provided evidence on the feasibility of blood pressure control in diabetics. In INSIGHT, a similar degree of blood pressure control was achieved irrespective of treatment allocation (c.f. Table 2, Chapter 6). However, patients with diabetes required more add-on therapy than non-diabetic patients (c.f. Table 3, Chapter 6). In the ACTION study diabetics responded as well as non-diabetics to blood pressure lowering by nifedipine GITS (mean reduction of 6/3 mmHg respectively, Chapter 7). However, the prevalence of hypertension was higher in diabetics than in non-diabetics throughout the study (c.f. Figure 1, Chapter 7). Taken together, these findings imply that blood pressure control is more difficult in diabetics, as is the case in patients with renal dysfunction (see previous section).

There has been considerable debate whether blood pressure lowering drugs can induce or aggravate diabetes [20,21]. In INSIGHT, significantly more patients without diabetes at baseline in the co-amilozide group developed newly diagnosed diabetes mellitus during follow-up than in the nifedipine group (5.6% as opposed to 4.3%, P=0.023, Chapter 6). As INSIGHT did not have placebo control, these results can be explained either by a preventive effect of nifedipine on the development of diabetes, or by an adverse effect of co-amilozide. The evidence from ACTION allows the distinction to be made. Among ACTION participants who did not have diabetes at baseline, hyperglycaemia was reported as an adverse event with equal frequency in patients assigned nifedipine as in those assigned placebo (0.73 patients with event/100 patient-years of follow-up as opposed to 0.75 patients with event/100 patient-years of follow-up, P=0.8, Chapter 7). Among non-diabetics, there was also no difference in the evolution of glucose levels between nifedipine and placebo treated patients (c.f. Figure 2, Chapter 7). Assuming that patients with hypertension are equally sensitive to adverse effects of blood pressuring lowering drugs as patients with coronary disease, the evidence from INSIGHT and ACTION taken together suggest that co-amilozide induces glucose intolerance, while nifedipine does not. Indeed, most cases of newly diagnosed diabetes in patients assigned co-amilozide in INSIGHT occurred after the initial dose of this was increased [22].

This conclusion is supported by the fact that in INSIGHT, nifedipine prevented secondary outcomes relative to co-amilozide in diabetics while there was no such difference in non-diabetics (c.f. Figure, Chapter 6). On the other hand, the effects of nifedipine relative to placebo on pre-defined composite endpoints in ACTION were similar in diabetics and non-diabetics (c.f. Figure 4, Chapter 7).
Taken together, the evidence from INSIGHT and ACTION suggests that avoiding newly diagnosed diabetes is an important consideration when deciding on blood pressure lowering treatment. Nifedipine GITS appears superior to the thiazide diuretic co-amilozide in this regard.

CLINICAL IMPLICATIONS

In conclusion, both the INSIGHT and the ACTION study have important clinical implications.

1. *Evidence-based clinical medicine requires that trials such as INSIGHT and ACTION be done.*

The clinical course of patients with hypertension is unpredictable and the effect of blood pressure lowering on outcome cannot be assessed by the treating physician in individual patients. Evidence-based clinical decision making must therefore be based on the results of appropriately designed randomised clinical trials.

2. *Apparently, treating physicians do not pay sufficient attention to the need to control blood pressure.*

In the INSIGHT study, there were four dose-titration or addition of other medication steps in patients whose blood pressure fell by less than 20/10 mmHg, or was higher than 140/90 mmHg. Nonetheless, at the end of the study 42% of patients assigned nifedipine and 43% of patients assigned co-amilozide did not have their blood pressure controlled [6].
The ACTION protocol encouraged optimal medical treatment of elevated blood pressure and did not contain any restrictions as regards medications that could be added to double-blind nifedipine or placebo, provided that the medication was compatible with nifedipine. Nonetheless, of ACTION patients with a blood pressure equal or higher than 140/90 mmHg at baseline, 47% assigned nifedipine and 64% assigned placebo still had a blood pressure equal or higher than 140/90 mmHg after 4 years of follow-up (c.f. Table 3 of Chapter 3).

3. *Blood pressure control does matter, also in patients with stable angina.*

The totality of the evidence that supports blood pressure control in patients with hypertension is compelling [5]. INSIGHT showed that overall nifedipine GITS is as effective in the prevention of cardiovascular events in hypertensives as the thiazide diuretic used as comparison

[6]. While ACTION was not designed to assess the effect of nifedipine GITS in patients with stable angina and hypertension, the subgroup analysis of ACTION patients with elevated blood pressure at baseline presented in Chapter 3 shows that controlling blood pressure in these patients improves prognosis.

4. *It matters how blood pressure is controlled.*

Meta-analyses have thus far failed to show that there are important differences between blood pressure lowering drugs as regards their effects on prognosis in patients with hypertension [23]. Nonetheless, how blood pressure is controlled does matter as different drugs have different mechanisms of action and safety profiles. The INSIGHT and ACTION studies have demonstrated that nifedipine GITS has a favourable safety profile compared to a thiazide as regards preservation of renal function and glucose tolerance. While controlling blood pressure remains the primary objective of treating patients with elevated blood pressure, preservation of renal function and prevention of glucose intolerance are important additional considerations.

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Chapter 9

Summary / samenvatting

SUMMARY

It is generally accepted that blood pressure lowering drugs improve the prognosis of patients with elevated blood pressure. The dihydropyridine calcium antagonist nifedipine is a widely used blood pressure lowering drug. In the mid-1990ties questions were raised on the safety of the short-acting immediate release formulation of this drug, in particular in patients with coronary disease. To answer these questions in the absence of any prospective safety data from randomised trials, two major studies using a more optimal long-acting GITS (gastro-intestinal therapeutic system) formulation of nifedipine were mounted in the late 1990ties.

The Intervention as a Goal in Hypertension Treatment (INSIGHT) randomised double-blind trial compared 30 mg nifedipine GITS (n=3157) to co-amilozide (hydrochlorothiazide 25 µg plus amiloride 2·5 mg; n=3164) in patients aged 55-80 years with hypertension (blood pressure at least150/95 mmHg, or at least 160 mmHg systolic) who had at least one additional cardiovascular risk factor. There was no placebo-treated control group. The main results have been published elsewhere (Brown MJ et al. Lancet 2000; 356: 366–72). Up-titration followed by add-on medication was allowed and resulted in blood pressure control to a similar degree. INSIGHT showed that overall nifedipine GITS based treatment was as effective as co-amilozide based treatment in preventing cardiovascular or cerebrovascular complications.

The A Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION) study compared randomly assigned 60 mg nifedipine GITS (n=3825) to double-blind placebo (n=3840) in patients aged at least 35 years with stable angina pectoris and proven coronary artery disease. ACTION demonstrated that the addition of nifedipine GITS to the conventional treatment of angina pectoris is safe, has no effect on major cardiovascular event-free survival and reduces the need for coronary angiography and interventions. The main results of ACTION have been published (Poole-Wilson PA et al. Lancet 2004;364:849-57). The report is reproduced in this thesis as **Chapter 2**.

Results from both studies are presented in this thesis, with the following threefold **general aim**:

1. To describe the long-term evolution of blood pressure (**Chapters 2** and **3**) and to examine the effect of blood pressure reduction by nifedipine GITS on outcome in ACTION patients with stable angina and hypertension (**Chapter 3**).
2. To assess the evolution of renal function and the relationship between renal function and mortality and morbidity in patients with hypertension treated in INSIGHT with either nifedipine or co-amilozide, and in patients with stable angina treated in ACTION with either nifedipine or placebo (**Chapters 4** and **5**).
3. To assess the impact of diabetes in patients with hypertension and diabetes who received either nifedipine or co-amilozide in INSIGHT, and in patients with stable angina treated in ACTION with either nifedipine or placebo (**Chapters 6** and **7**).

First aim: Results presented in **Chapter 2** show that in all ACTION patients with stable angina combined nifedipine GITS significantly reduced both systolic and diastolic blood pressure relative to placebo throughout the follow-up of almost five years. Results of the pre-specified subgroup analysis for ACTION patients with hypertension (baseline blood pressure at least 140/90 mmHg, n=3977) are presented in **Chapter 3** (previously published: Lubsen J et al. J Hypertens 23:641-648). Nifedipine GITS significantly reduced mean follow-up blood pressures by 6.6/3.5 mmHg among hypertensives and by 3.9/2.4 mmHg among normotensives. In hypertensives, these blood pressure reductions resulted in a significant 13% reduction of the combined incidence of all-cause mortality, myocardial infarction, refractory angina, heart failure, stroke and peripheral revascularization (the ACTION primary outcome for efficacy). In normotensives, no such reduction was observed.

Nifedipine significantly reduced the incidence of any stroke or transient ischemic attack and the need for coronary angiography both in hypertensives and in normotensives with stable angina. An unexpected finding was the significant reduction by nifedipine of new overt heart failure. Nifedipine did not affect all-cause death, cardiovascular death and myocardial infarction in either normo- or hypertensives, but increased the need for peripheral revascularization.

The salutary effects of the addition of nifedipine GITS to the basic regimen emphasize the need for blood pressure control in patients with stable angina and hypertension.

Second aim: Results from INSIGHT presented in **Chapter 4** (previously published: de Leeuw PW et al. Arch Intern Med. 2004;164:2459-2464) and from ACTION in **Chapter 5** (previously published: Ruilope LM et al. J Hypertens 2005;25:1711-1718) demonstrate that renal dysfunction adversely affects the prognosis both of patients with hypertension (Chapter 4), and of patients with stable angina (Chapter 5). Patients with hypertension and renal failure needed more add-on medication to control blood pressure than those without renal failure. Overall, those assigned to a nifedipine GITS based regimen had higher estimated creatinine clearance levels during follow than those assigned to a co-amilozide-based regimen (Chapter 4). As no such difference was observed in the placebo-controlled ACTION study (Chapter 5), it appears that co-amilozide treatment is associated with a reduction of renal function.

No subgroup analysis was performed in INSIGHT to determine whether the effect of nifedipine relative to co-amilozide depended on the presence of renal failure at baseline. Such a subgroup analysis was done for the ACTION study (Chapter 5). The effects of nifedipine relative to placebo appeared not to depend on the presence of renal failure.

Third aim: Results from INSIGHT presented in **Chapter 6** (previously published: Mancia G et al. Hypertension 2003;41:431-436) and from ACTION in **Chapter 7** (submitted for publication) confirm that diabetes adversely affects the prognosis both of patients with hypertension (Chapter 6), and of patients with stable angina (Chapter 7). Patients with hypertension and diabetes in INSIGHT needed more add-on medication to control blood pressure than those without diabetes (Chapter 6). Patients with stable angina and diabetes had a higher preva-

lence of hypertension throughout the ACTION study although the blood pressure lowering effect of nifedipine GITS was the same in diabetics as in non-diabetics (Chapter 7).

In INSIGHT, significantly more patients without diabetes at baseline in the co-amilozide group developed newly diagnosed diabetes during follow-up than in the nifedipine group (Chapter 6). As no such difference was observed in the placebo-controlled ACTION study (Chapter 7), it appears that co-amilozide treatment is associated with an increased incidence of new diabetes.

In INSIGHT, nifedipine prevented secondary outcomes relative to co-amilozide in diabetics but not in non-diabetics (Chapter 6). In ACTION, effects of nifedipine relative to placebo were similar in diabetics and non-diabetics (Chapter 7). These results suggest that nifedipine GITS appears superior to a thiazide diuretic in the prevention of diabetes.

Clinical implications: The results from INSIGHT and ACTION presented in this thesis have several clinical implications.

Firstly, they underscore the need to perform large trials as basis for evidence-based clinical practice.

Secondly, treating physicians apparently do not pay sufficient attention to the need to control blood pressure. In both studies, the blood pressure of a relative large number of patients remained elevated at the end of follow-up although the protocols concerned encouraged the use of additional medication to achieve blood pressure control.

Thirdly, the present results confirm that blood pressure control with nifedipine GITS is beneficial in patients with hypertension irrespective of the presence of coronary disease.

Finally, the present results suggest that it does matter how blood pressure is controlled as the different metabolic effects of blood pressure lowering drugs may be clinically relevant. While controlling blood pressure remains the primary objective of treating patients with hypertension, preservation of renal function and prevention of glucose intolerance are important additional considerations.

SAMENVATTING

Het is algemeen aanvaard dat bloeddrukverlagende middelen de prognose van patienten met verhoogde bloeddruk gunstig beïnvloeden. De dihydropyridine calcium-antagonist nifedipine is een veel-gebruikt bloeddrukverlagend middel. Rond 1995 rezen er vragen betreffende de veiligheid van de kort-werkende capsule toedieningsvorm van dit middel, in het bijzonder bij patienten met een coronair lijden. Teneinde de gerezen vragen te beantoorden omdat prospectieve gegevens uit gerandomiseerd vergelijkend onderzoek ontbraken, werden tussen 1995 en 2000 twee grote klinische trials opgezet met een meer optimale langwerkende GITS (gastro-intestinaal therapeutisch systeem) toedieningsvorm van nifedipine.
In de "Intervention as a Goal in Hypertension Treatment" (INSIGHT) gerandomiseerde dubbelblinde trial werden 30 mg nifedipine GITS (n=3157) en co-amilozide (hydrochlorothiazide 25 µg plus amiloride 2·5 mg; n=3164) met elkaar vergeleken bij hypertensie-patienten (bloeddruk tenminste 150/95 mmHg, of systolische bloeddruk tenminste 160 mmHg) van 55-80 jaar bij wie tenminste één andere cardiovasculaire risicofactor aanwezig was. Er was geen met placebo behandelde controlegroep. De meest-belangrijke resultaten werden elders gepubliceerd (Brown MJ et al. Lancet 2000; 356: 366–72). Het was toegestaan ná randomisatie de dosis van de toegewezen medicatie te verhogen, en vervolgens zo nodig andere bloeddrukverlagende middelen toe te voegen. Op deze wijze werd bereikt dat de bloeddruk tijdens de looptijd van het onderzoek gelijk was in beide behandelingsgroepen. Er was in INSIGHT geen verschil met betrekking to het optreden van cardiovasculaire en cerebrovasculaire complicaties tussen beide behandelingsgroepen.
In de "A Coronary disease Trial Investigating Outcome with Nifedipine GITS" (ACTION) studie werd random toegewezen 60 mg nifedipine GITS (n=3825) dubbel-blind vergeleken met placebo (n=3840) bij patienten van tenminste 35 jaar met stabiele angina pectoris en een bewezen coronair lijden. ACTION toonde aan dat de toevoeging van nifedipine GITS aan de conventionele behandeling van angina pectoris veilig is, geen effect heeft op de overleving vrij van belangrijke cardiovasculaire complicaties, en de noodzaak tot het verrichten van coronaire angiografie en interventies vermindert. De meest-belangrijke resultaten werden elders gepubliceerd (Poole-Wilson PA et al. Lancet 2004;364:849-57), en zijn in dit proefschrift opgenomen als **Hoofdstuk 2**.
In dit proefschrift worden bevindingen van beide studies gepresenteerd met de volgende drie-voudige doelstelling:

1. Het beschrijven van het beloop van de bloeddruk op de lange termijn (**Hoofdstuk 2** en **3**) en het vaststellen van het effect van bloeddrukverlaging door nifedipine GITS op het klinische beloop van patienten met hypertensie en stabiele angina pectoris in de ACTION studie (**Hoofdstuk 3**)
2. Het beschrijven van het beloop van de nierfunctie en de relatie tussen nierfunctie en mortaliteit en morbiditeit in patienten met hypertensie die in INSIGHT behandeld werden met

hetzij nifedipine, hetzij co-amilozide; en bij patienten met stabiele angina pectoris die in ACTION behandeld werden met nifedipine of placebo (**Hoofdstuk 4** en **5**).

3. Het vastellen van het belang van de aanwezigheid van diabetes bij patienten met hypertensie die in INSIGHT behandeld werden met hetzij nifedipine, hetzij co-amilozide; en bij patienten met stabiele angina pectoris die in ACTION behandeld werden met nifedipine of placebo (**Hoofdstuk 6** en **7**).

Eerste doelstelling: Gegevens in **Hoofdstuk 2** laten zien dat nifedipine GITS bij alle ACTION patienten met stabiele angina tezamen een significante en blijvende bloeddrukdaling veroorzaakt in vergelijking to placebo gedurende een observatie-periode van bijna 5 jaar. Resultaten van de subgroep analyse van ACTION patienten met hypertensie (bloeddruk bij aanvang van het onderzoek tenminste 140/90 mmHg, n=3977) worden gepresenteerd in **Hoofdstuk 3** (eerder gepubliceerd: Lubsen J et al. J Hypertens 23:641-648). Nifidepine GITS verlaagde de bloeddruk significant met 6.6/3.5 mmHg by patienten met hypertensie, en met 3.9/2.4 mmHg bij patienten zonder hypertensie. Bij patienten met hypertensie ging de bloeddrukdaling gepaard met een significante vermindering van 13% van de gecombineerde incidentie van totale sterfte, myocard infarct, refractaire angina pectoris, hartfalen, cerebrovasculair accident en perifere revascularisatie (het primaire effectiviteitscriterium in ACTION). Bij patienten met een normale tensie had nifedipine geen effect op dit criterium.

Nifedipine verminderde significant het optreden van een aanval van voorbijgaande cerebrale ischaemie of een cerebrovasculair accident, en van de noodzaak tot het doen van een coronair angiogram, zowel bij patienten mèt als zónder hypertensie. Het significante minder optreden van hartfalen in de nifedipine groep was een nieuwe en daarom onverwachte bevinding. De positieve effecten van nifedipine benadrukken de noodzaak van het verlagen van de bloeddruk van patienten met stabiele angina en hypertensie.

Tweede doelstelling: Gegevens uit INSIGHT in **Hoofdstuk 4** (eerder gepubliceerd: de Leeuw PW et al. Arch Intern Med. 2004;164:2459-2464) en uit ACTION in **Hoofdstuk 5** (eerder gepubliceerd: Ruilope LM et al. J Hypertens 2005;25:1711-1718) laten zien dat een verminderde nierfunctie zowel bij patienten met hypertensie (Hoodstuk 4) als bij patienten met stabiele angina pectoris (Hoodstuk 5) gepaard gaat met een ongunstige prognose. Hypertensie patienten met een verminderde nierfunctie hadden méér bloeddrukverlagende medicatie nodig dan patienten met een normale nierfunctie. Patienten die behandeld werden met een op nifedipine gebaseerd regime hadden een hogere creatinineklaring gedurende de looptijd van de studie dan degenen die met een op co-amilozide gebaseerd regime regime behandeld werden (hoofdstuk 4). Aangezien een dergelijk verschil niet werd gezien in ACTION wanneer nifedipine wordt vergeleken met placebo volgt hieruit dat co-amilozide de nierfunctie vermindert.

Een subgroep analysie van INSIGHT om na te gaan of de effecten van nifedipine in vergelijking tot co-amilozide afhangen van de nierfunctie bij aanvang van het onderzoek is niet

uitgevoerd. Een dergelijke subgroep analyse werd wel gedaan in ACTION (Hoofdstuk 5). Deze analyse toonde aan dat de effecten van nifedipine niet afhangen van de nierfunctie.

Derde doelstelling: Gegevens uit INSIGHT in **Hoofdstuk 6** (eerder gepubliceerd: Mancia G et al. Hypertension 2003;41:431-436) en uit ACTION in **Hoofdstuk 7** (ter publicatie aangeboden) laten zien dat de aanwezigheid van diabetes zowel bij patienten met hypertensie (Hoodstuk 6) als bij patienten met stabiele angina pectoris (Hoodstuk 7) gepaard gaat met een ongunstige prognose. Patienten met hypertensie en diabetes hadden méér bloeddrukverlagende medicatie nodig dan patienten zonder diabetes (Hoodstuk 6). Patienten met stabiele angina pectoris en diabetes hadden vaker een verhoogde bloeddruk gedurende de looptijd van de ACTION studie dan patienten zonder diabetes. Het bloeddrukverlagende effect van nifedipine was hetzelfde bij diabeten en niet-diabeten (Hoodstuk 7).

Bij INSIGHT patienten in de co-amilozide groep zonder diabetes kwam voor het eerst vastgestelde diabetes gedurende de looptijd van het onderzoek significant vaker voor dan in de nifedipine groep (Hoodstuk 6). Aangezien een dergelijk verschil niet werd gezien in ACTION wanneer nifedipine wordt vergeleken met placebo (Hoodstuk 7) volgt hieruit dat co-amilozide het optreden van diabetes ongunstig beïnvloedt.

INSIGHT liet zien dat nifedipine bij diabetici met hypertensie effectiever is dan co-amilozide met betrekking tot het optreden van secondare uitkomsten (Hoofdstuk 6). Bij niet-diabetici was er geen verschil in dit opzicht. In ACTION waren de effecten van nifedipine in vergelijking tot placebo bij diabetici gelijk aan die bij niet-diabetici (Hoofdstuk 7). Deze bevindingen suggereren dat nifedipine GITS te verkiezen is boven co-amilozide met betrekking tot de preventie van diabetes.

Klinische betekenis: De INSIGHT en ACTION resultaten beschreven in dit proefschrift hebben in meerdere opzichten klinische betekenis.

In de eerste plaats benadrukken zij de noodzaak tot het doen van grote trials als basis voor "evidence-based medicine".

In de tweede plaats laten zij zien dat er in de klinische praktijk kennelijk te weinig aandacht wordt besteed aan de noodzaak een verhoogde bloeddruk te normaliseren. In beide studies hadden belangrijke aantallen patienten verhoogde bloeddruk aan het eind van het onderzoek ondanks het feit dat het gebruik van additionele medicatie ter controle van de bloeddruk werd aangemoedigd.

In de derde plaats bevestigen deze gegevens dat verlaging van de bloeddruk door nifedipine GITS effectief is bij patienten met hypertensie onafhankelijk van de aanwezigheid van een bijkomend coronair lijden.

Tenslotte suggereren deze gegevens dat het er wel degelijk toe doet hoe de bloeddruk verlaagd wordt omdat de verschillende metabole effecten van bloeddrukverlagende middelen klinisch relevant kunnen zijn. Alhoewel verlaging van de bloeddruk het eerste doel blijft van de behandeling van patienten met hypertensie, zijn het behoud van de nierfunctie en het voorkómen van glucose intolerantie belangrijke bijkomende overwergingen.

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CURRICULUM VITAE GILBERT WAGENER

1963	Born in Dortmund
1982	Abitur
1983	Military service
1984	Studies of Pharmacy and Food chemistry
1984-1990	Studies of Human Medicine
1988	Undergraduate training pharmacology
1990-1992	Postgraduate training Physiology
1992	MD thesis
1993	Research assistant Clinic for Neurology, University Hospitals of Marburg/Lahn
1993-2004	Bayer AG, Director global clinical development cardiovascular
1996-1997	MBA pharmaceutical medicine, University of Basel
Since 2005	Genzyme BV, Vice president clinical research