Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study

J A Dens, W J Desmet, P Coussement, I K De Scheerder, K Kostopoulos, P Kerdsinchai, C Supanantaroek, J H Piessens

Background: Earlier angiographic studies have suggested that calcium antagonists may prevent the formation of new coronary lesions and the progression of minimal lesions. Conversely, a meta-analysis suggested that these drugs may increase cardiovascular mortality and morbidity in patients with coronary heart disease.

Objective: To investigate whether nisoldipine retards the progression of coronary atherosclerosis or reduces the occurrence of clinical events.

Design and setting: The NICOLE study (NIsoldipine in CoRonary artery disease in LEuven) is a single centre, randomised, double blind, placebo controlled trial with coronary angiography at baseline, six months, and three years of follow up.

Patients: 826 patients who had undergone successful coronary angioplasty were randomised to nisoldipine 40 mg once daily or placebo. The intention to treat and per protocol population consisted of 819 and 578 patients, respectively.

Results: In the per protocol population, 625 of the nisoldipine treated and 655 of the placebo treated patients (NS) showed angiographic progression in at least one coronary arterial segment, defined as an increase in diameter stenosis of ≥13%. The average minimum luminal diameter of the non-dilated lesions decreased by 0.163 mm and 0.167 mm in the nisoldipine and placebo groups, respectively (NS). The respective numbers of new lesions detected were 7 and 13 (NS). In the intention to treat population, the rates of death, stroke, and acute myocardial infarction were similar in both treatment groups. However, nisoldipine use was associated with fewer revascularisation procedures and thus the percentage of patients with any clinical event was lower (44.6% vs 52.6%, p = 0.02).

Conclusions: Nisoldipine has no demonstrable effect on the angiographic progression of coronary atherosclerosis or the risk of major cardiovascular events but its use is associated with fewer revascularisation procedures.

METHODS

Study population

The study design was randomised, double blind, and approved by the ethics committee of our institution. All patients less than 75 years old who underwent an elective and successful single or multiple vessel PTCA without stenting were considered for inclusion. A PTCA was considered successful when the immediate postprocedural residual stenosis was visually estimated as <50% of vessel diameter. Between June 1995 and July 1997, 2750 patients were screened, of whom 826 were included in the study. Patients with a history of coronary artery bypass grafting (CABG) and patients with homozygotic familial hypercholesterolaemia were excluded, because in general such individuals have diffuse disease that complicates the angiographic measurement of non-dilated vessel cardiovascualr events. In this paper we report the results of the primary objective and the cardiovascular events.

Abbreviations: CABG, coronary artery bypass graft; GOT, glutamate-oxalate-acetate-transaminase; INTACT, international nifedipine trial on anti-atherosclerotic therapy; LDL, low density lipoprotein; MHIT, Montreal Heart Institute trial; NICOLE, nisoldipine in coronary artery disease in Leuven; PTCA, percutaneous transluminal coronary angioplasty; PREVENT, the prospective randomised evaluation of the vascular effects of Norvasc trial.
Table 1  Baseline clinical characteristics of the intention to treat (n = 819) and per protocol population (n = 582)

<table>
<thead>
<tr>
<th></th>
<th>Intention to treat</th>
<th>Per protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nisoldipine (n=408)</td>
<td>Placebo (n=411)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>78.7</td>
<td>79.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.4 [8.76]</td>
<td>60.2 [8.83]</td>
</tr>
<tr>
<td>Hypertension (%)*</td>
<td>41.7</td>
<td>39.4</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)†</td>
<td>47.3</td>
<td>50.6</td>
</tr>
<tr>
<td>Current and ex-smoker (%)</td>
<td>71.3</td>
<td>71.0</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>58.3</td>
<td>55.7</td>
</tr>
<tr>
<td>Previous AMI (%)</td>
<td>44.1</td>
<td>40.9</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>10.5</td>
<td>10.2</td>
</tr>
<tr>
<td>Anginal class (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>23.3</td>
<td>18.0</td>
</tr>
<tr>
<td>CCS I</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>CCS II</td>
<td>24.8</td>
<td>24.6</td>
</tr>
<tr>
<td>CCS III</td>
<td>17.6</td>
<td>21.9</td>
</tr>
<tr>
<td>CCS IV</td>
<td>32.6</td>
<td>33.1</td>
</tr>
</tbody>
</table>

Values are mean (SD) or %.

*Hypertension is defined as necessitating treatment.
†Hypercholesterolaemia is defined as a value of >6.8 mmol/l (250 mg/dl) or on treatment.
Differences between the two treatment groups are non-significant.

AMi, acute myocardial infarction; CCS, Canadian Cardiovascular Society.

Quantitative angiographic analysis
Coronary angiograms were obtained before and immediately after PTCA and after six months and three years of follow up. Images were acquired with a real time digital image acquisition and processing system (Polytron 1000 or Ricor, Siemens AG, Erlangen, Germany) at 25 frames a second. Thereafter, images were either analysed on-line or stored on streamer tape for later analysis. Each lesion was analysed in two approximately orthogonal projections, selected for maximal avoidance of superimposition and vessel foreshortening. Identical projections and source–patient image intensifier distances were used for pre- and post-PTCA angiograms as well as for the follow up angiograms in each patient. Before contrast injection, 200 µg of glyceryl trinitrate were injected into the coronary artery to induce maximum vasodilatation. All measurements were done on selected end diastolic frames, with lesion and adjacent “normal” segment being equally opacified. Quantitative coronary analysis was performed with a commercially available system (AWOS, Siemens AG, Erlangen, Germany), that has been validated in vitro and in vivo.13

Follow up evaluation
Patients visited their referring cardiologist after two and four months for interview, cardiac examination, electrocardiography, laboratory tests, and pill count. The same procedures were repeated at six months, when the first follow up angiogram was done at our centre. In patients with early recurrence of symptoms or evidence of silent ischaemia, coronary angiography was carried out earlier. Further, the ethical committee had requested that, if a critical restenosis in a large vessel was detected at the time of this control angiogram, an ad hoc repeat PTCA should be done, even in non-ischaemic patients. All other therapeutic decisions were left to the discretion of the operator or the attending cardiologist. Thereafter, outpatient visits to the referring cardiologist were scheduled every six months for the same procedures outlined above, until the final coronary angiogram was obtained after three years of follow up. During follow up, patients were considered treatment compliant only if at least 75% of the drug or placebo was taken, as judged from pill counts, and only those patients were included in the final per protocol analysis.

End points
The primary angiographic end point was the effect of nisoldipine, given for three years, on the angiographic progression of non-dilated coronary arterial lesions. In each patient a total of 30 predefined arterial segments had to be examined. At baseline, all non-dilated segments > 2 mm in diameter with a visually estimated > 20% but < 100% diameter stenosis were measured. When a stenosis was only present at the end of the study, a retrospective baseline measurement of the corresponding segment was carried out and these lesions were considered to be new. Progression and regression were defined categorically as a ≥ 13% absolute change in per cent diameter stenosis from baseline to follow up. This percentage represents the 95% limits of agreement when a lesion is measured twice with our system at different points in time.14 Patients were considered as progressors if there was an absolute 13% increase in diameter stenosis in at least one lesion at follow up, or if a clinical end point was reached. Otherwise, patients were counted as non-progressors. The minimum luminal diameter was evaluated as a continuous variable as well, but was not used to categorise patients as progressors or non-progressors. The primary clinical end points were cardiovascular events, including death, stroke, acute myocardial infarction, repeat PTCA, PTCA of a new or progressive lesion, or coronary artery bypass grafting (CABG).

Patients who had a repeat PTCA of a lesion that had been dilated at baseline continued the study. An acute myocardial
infarct was defined as a rise in creatine phosphokinase concentrations to more than twice the upper limit of normal. Patients who did not reach a clinical end point were excluded from the per protocol population when no angiographic follow up was available after two years. Similarly, patients were excluded when the control angiogram was obtained more than three months after discontinuation of treatment.

Data collection and statistical analysis
All data were recorded on standardised forms and entered into the study database using double data entry. Summary statistics (n, mean, SD, 25th centile, median, 75th centile) were calculated for continuous variables, and frequency tables for categorical variables. A statistical check for homogeneity of treatment groups was carried out for age, body weight, height, and serum cholesterol using Student $t$ tests, and for sex, diabetes, hypertension, and family history of coronary heart disease by $\chi^2$ contingency table tests. For variables relating to clinical status at follow up, Fisher's exact test was used for death, acute myocardial infarction, CABG, PTCA of a new or progressive lesion, and repeat PTCA. For anginal class at follow up as well as at early angiography, and for silent ischaemia and atypical chest pain, the likelihood ratio $\chi^2$ test was used.

Statistical analysis of progression was done using a logistic regression model on the patient based data, including the factors intercept, treatment, age, sex, weight, height, diabetes, arterial hypertension, and family history of coronary artery disease. For sample size determination the three years incidence of progression of coronary lesions in placebo treated patients was estimated to be 50%. This was to be improved to 40% with nisoldipine. As the statistical analysis was done by logistic regression, the above incidence rate related to an odds ratio of 0.667. The calculated sample size was 306 per group. Taking into account 20% non-valid cases, 383 patients per group had to be randomised. The initially fixed sample size was 400 per group, but owing to a slightly increased dropout rate an additional 26 patients were included. The study was done with a one sided $\alpha$ level of 0.05 and a power of 0.80.

For angiographic end points, the intention to treat and per protocol population was used; for clinical end points the intention to treat population was considered. This latter population is defined as all randomised patients except the patients who did not take any pill.

RESULTS

Patients
In all, 2750 patients were screened, of whom 826 were randomised. Seven patients did not take any study tablet and were excluded from the intention to treat population, which consisted of 408 nisoldipine treated and 411 placebo treated.
patients. The baseline clinical characteristics of the patients are given in table 1. No significant differences between the two treatment groups were observed. The reasons for exclusion from the per protocol population, presented in fig 1, were not significantly different between treatment groups.

Overall treatment compliance was excellent: only three patients took less than 75% of the prescribed tablets. Of the nisoldipine treated patients, 23.3% stopped the study drug because of an adverse event or a side effect, compared with 14.5% of the placebo treated patients. The main side effect was ankle oedema. In the intention to treat and the per protocol population, 32% of the nisoldipine treated patients versus only 14% of the placebo treated patients (p < 0.0001) had to be downtitrated to the lower dose regimen because of side effects. Progression was a reason for premature termination of the study in an extra 8% of nisoldipine treated patients (n = 31) and an extra 15% of placebo treated patients (n = 60). In each treatment group the most frequent concomitant drugs used during the study period were β receptor blockers, lipid lowering drugs, and angiotensin converting enzyme inhibitors. In the nisoldipine group, the use of these three types of drug was recorded in, respectively, 79%, 41%, and 25% of the patients. The placebo treated patients took slightly more concomitant drugs in all three classes, but in none of them was the difference significant compared with the nisoldipine treated patients.

Effects of nisoldipine on the angiographic end points
At baseline, in the intention to treat population, 1977 lesions were measured in the nisoldipine group and 2107 in the placebo group. In the per protocol population the respective numbers were 1593 and 1763. There were no significant differences in lesion severity or lesion location between the two treatment groups (table 2). As is to be expected in a PTCA population, the severity of the non-dilated lesions was only moderate. In the intention to treat population the number of lesions evaluable both at baseline and at study end was 3373, compared with 3100 in the per protocol population. In table 3 the changes in minimum luminal diameter and per cent diameter stenosis during the follow up period are given. Irrespective of the population considered, these variables did not differ significantly between treatment groups, but within each treatment group there was a reduction in minimum luminal diameter from baseline to follow up (p < 0.01).

### Table 2 Baseline angiographic characteristics of the non-dilated lesions in the intention to treat (n = 4084) and per protocol population (n = 3356)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intention to treat</th>
<th>Placebo</th>
<th>Per protocol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nisoldipine (n=1977)</td>
<td>Placebo (n=2107)</td>
<td>Nisoldipine (n=1593)</td>
<td>Placebo (n=1763)</td>
</tr>
<tr>
<td>MLD [mm]</td>
<td>1.94 (0.68)</td>
<td>1.95 (0.65)</td>
<td>1.94 (0.67)</td>
<td>1.96 (0.65)</td>
</tr>
<tr>
<td>DS (%)</td>
<td>36.8 (11.7)</td>
<td>36.5 (11.3)</td>
<td>36.6 (11.5)</td>
<td>36.2 (11.2)</td>
</tr>
<tr>
<td>Location (%)</td>
<td>LAD</td>
<td>31</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>LCx</td>
<td>29</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>RCA</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>≤20%</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;20%, &lt;50%</td>
<td>85</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>≥50%</td>
<td>12</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

Values are mean (SD) or %. Differences between treatment groups are non-significant.

### Table 3 Angiographic changes from baseline to follow up in the non-dilated lesions of the intention to treat (n = 3373) and the per protocol population (n = 3100)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intention to treat</th>
<th>Placebo</th>
<th>Per protocol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nisoldipine (n=1582)</td>
<td>Placebo (n=1791)</td>
<td>Nisoldipine (n=1483)</td>
<td>Placebo (n=1617)</td>
</tr>
<tr>
<td>MLD [mm]</td>
<td>Baseline</td>
<td>1.94 (0.68)</td>
<td>1.94 (0.67)</td>
<td>1.97 (0.64)</td>
</tr>
<tr>
<td></td>
<td>FU</td>
<td>1.78 (0.68)</td>
<td>1.77 (0.67)</td>
<td>1.80 (0.66)</td>
</tr>
<tr>
<td></td>
<td>FU–baseline</td>
<td>-0.15 (0.43)</td>
<td>-0.16 (0.41)</td>
<td>-0.16 (0.43)</td>
</tr>
<tr>
<td>Reference [mm]</td>
<td>Baseline</td>
<td>3.03 (0.80)</td>
<td>3.02 (0.80)</td>
<td>3.06 (0.77)</td>
</tr>
<tr>
<td></td>
<td>FU</td>
<td>2.89 (0.75)</td>
<td>2.87 (0.75)</td>
<td>2.90 (0.74)</td>
</tr>
<tr>
<td></td>
<td>FU–baseline</td>
<td>-0.15 (0.47)</td>
<td>-0.15 (0.48)</td>
<td>-0.15 (0.46)</td>
</tr>
<tr>
<td>Diameter stenosis [%]</td>
<td>Baseline</td>
<td>36.6 (11.6)</td>
<td>36.4 (11.5)</td>
<td>36.1 (11.1)</td>
</tr>
<tr>
<td></td>
<td>FU</td>
<td>38.5 (14.3)</td>
<td>38.7 (14.2)</td>
<td>38.3 (14.3)</td>
</tr>
<tr>
<td></td>
<td>FU/baseline</td>
<td>1.10 (0.44)</td>
<td>1.10 (0.40)</td>
<td>1.10 (0.40)</td>
</tr>
</tbody>
</table>

Values are mean (SD). Differences between treatment groups are non-significant. FU, follow up; MLD, minimum luminal diameter.
65% of the placebo treated patients showed progression. When the per protocol population was broken down according to sex, 63% of the nisoldipine treated men and 66% of the placebo treated men showed progression, while the respective values for women were 53% and 60%. When the population was broken down into non-diabetic and diabetic patients, progression was observed in 60% of the nisoldipine treated and 63% of the placebo treated non-diabetic patients; for diabetic patients the respective values were 78% and 81%. None of these differences between the two treatment groups was significant. In additional explorative analyses, interaction terms for treatment–sex and treatment–diabetes were included in a logistic regression model. This failed to show either a treatment–sex interaction (odds ratio (OR) 1.1, 95% confidence interval (CI) 0.70 to 1.77; \( p = 0.66 \)) or a treatment–diabetes interaction (intention to treat, \( p = 0.619 \), per protocol, \( p = 0.74 \)). However, irrespective of treatment, women tended to have a lower rate of progression than men (OR 0.55, 95% CI 0.29 to 1.0; \( p = 0.06 \)) and, as expected, subjects with diabetes had an increased rate (OR 2.2, 95% CI 1.0 to 4.9; \( p = 0.04 \)).

Seven new lesions developed in the nisoldipine treated patients, compared with 13 in the placebo group (NS). These rates of progression in the per protocol population were observed while serum cholesterol concentrations decreased from 5.65 to 5.34 mmol/l in the nisoldipine group (\( p < 0.0001 \)) and from 5.78 to 5.42 mmol/l in the placebo treated group (\( p < 0.0001 \)), with corresponding reductions in LDL cholesterol from 3.70 to 3.50 mmol/l (\( p < 0.0001 \)) and from 5.78 to 5.42 mmol/l in the placebo treated group (\( p < 0.0001 \)), with corresponding reductions in LDL cholesterol from 3.70 to 3.50 mmol/l (\( p = 0.002 \)) and from 3.73 to 3.55 mmol/l (\( p = 0.02 \)), respectively. On the other hand, there was an increase in systolic and diastolic blood pressure over the three year study period, and this was less pronounced in the nisoldipine treated patients (3.3/0.9 mm Hg vs 1.1/3.9 mm Hg; \( p < 0.01 \)).

### Effects of nisoldipine on clinical end points

In the intention to treat population there were no differences between the two treatment groups in the rates of death, stroke, acute myocardial infarction, or PTCA of progressive or new lesions. However, the rates of repeat PTCA and CABG were lower in the nisoldipine group, at 30.6% vs 37.7% (\( p = 0.03 \)) and 5.1% vs 10% (\( p = 0.008 \), respectively. Thus fewer nisoldipine treated than placebo treated patients experienced any clinical event during follow up (44.6% vs 52.6%, \( p = 0.02 \)) (table 4).

During the course of the study, 97% of the patients reported at least one of a total of 325 different disturbing symptoms or events. The nisoldipine treated patients had less chest pain (29% vs 36%, OR 0.72, 95% CI 0.53 to 0.96; \( p = 0.03 \)) but suffered more from ankle oedema (40% vs 8%, OR 7.5, 95% CI 5.02 to 11.34; \( p < 0.0001 \)), symptomatic hypotension (9.8% vs 4.4%, OR 2.4, 95% CI 1.34 to 4.21; \( p < 0.003 \), and facial flush (5.6% vs 2.2%, OR 2.7, 95% CI 1.22 to 5.48; \( p = 0.01 \). All other differences between treatment groups were non-significant. Malignancies were diagnosed in 10 nisoldipine treated and 11 placebo treated patients, while haemorrhage was reported by five and eight patients, respectively.

### DISCUSSION

Our results show that nisoldipine, despite various promising pharmacological characteristics, did not reduce the rate of progression of coronary arterial lesions after three years of follow up. This failure of long term efficacy was observed when using a daily dose of 40 mg of nisoldipine given in a single long acting preparation. In 31% of the intention to treat and per protocol patients the target dose had to be downtitrated to 20 mg, and the study was prematurely terminated owing to adverse events in 23% of the nisoldipine treated patients. Consequently, testing the anti-atherosclerotic effect of higher doses is clinically unrealistic.

The earlier INTACT and MHIT trials, as well as the recent PREVENT trial (prospective randomised evaluation of the vascular effects of Norvasc), have already reported that the dihydropyridine calcium antagonists nifedipine, nicardipine, and amlodipine have no effect on existing coronary lesions. However, the two first studies suggested that these drugs suppress the appearance of new lesions and retard the progression of minimal lesions. In INTACT, nifedipine 80 mg daily reduced the number of new lesions per patient by 28%, and in the MHIT trial nicardipine 90 mg daily achieved a 50% reduction (in a retrospective analysis). This interesting finding was not confirmed in the present study or in PREVENT. We believe that the low rate of new lesion formation observed in these two contemporary trials precludes the detection of a possible beneficial effect of calcium antagonists. For the total study populations in the earlier trials—in INTACT over a three year period and in MHIT over a two year period—the number of new lesions per patient was 0.70 and 0.25, respectively. The corresponding value in the present study was only 0.03. For PREVENT, this figure was not reported but over the three year follow up period the minimum luminal diameter of minor lesions decreased only by a negligible 0.09 mm.

Angiography might be an inadequate technique to assess early progression of atherosclerosis. Also the beneficial effects observed a decade after the two earlier studies most probably reflect better acceptance by the patients of cardiovascular preventive measures, including the use of effective lipid lowering agents (45% of the study population). Indeed, these measures resulted in very significant reductions in total serum cholesterol and LDL cholesterol in both treatment groups in our study, although the most recent guidelines for optimal lipid control were not yet met. Simultaneously, a rise in blood pressure was seen over the study period as an aging effect. This rise was largely attenuated by nisoldipine but the antihypertensive effect of nisoldipine was not translated into a measurable effect on the progression of coronary artery disease. Finally, we also compared the angiographic effects of nisoldipine in men versus women and in diabetic versus non-diabetic subjects. As expected, the coronary lesions progressed faster in men than in women and in diabetic than in non-diabetic subjects, but again, in neither of these subgroups was the progression rate affected by nisoldipine. The use of nisoldipine resulted in a reduction in the need for repeat PTCA and CABG, a beneficial effect already observed at the six month follow up and persisting over the three year study period. The total revascularisation rate was reduced by 11% at six months and by 8.1% at the three year follow up. As nisoldipine had no effect on the angiographic restenosis rate and no effect on the progression of coronary atherosclerosis, a reduction in the need for revascularisation is most probably

### Table 4 Percentage of patients with a clinical event in the intention to treat population (\( n = 819 \))

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>Nisoldipine (( n = 408 ))</th>
<th>Placebo (( n = 411 ))</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.9</td>
<td>3.4</td>
<td>NS</td>
</tr>
<tr>
<td>CVA</td>
<td>1.0</td>
<td>1.7</td>
<td>NS</td>
</tr>
<tr>
<td>AMI</td>
<td>3.9</td>
<td>3.2</td>
<td>NS</td>
</tr>
<tr>
<td>CABG</td>
<td>5.1</td>
<td>10</td>
<td>(&lt;0.01)</td>
</tr>
<tr>
<td>Repeat PTCA*</td>
<td>30.6</td>
<td>37.7</td>
<td>0.03</td>
</tr>
<tr>
<td>PTCA†</td>
<td>15.7</td>
<td>16.3</td>
<td>NS</td>
</tr>
<tr>
<td>Repeat PTCA and CABG</td>
<td>2.7</td>
<td>4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Repeat PTCA + PTCA†</td>
<td>6.1</td>
<td>8.8</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>44.6</td>
<td>52.6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Events are counted as not mutually exclusive.

* Repeat PTCA of a lesion dilated at baseline.
† PTCA of a lesion that was not dilated at baseline.
AM, acute myocardial infarction; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; PTCA, percutaneous transluminal coronary angioplasty.
related to the anti-ischaemic action of the drug. Indeed, the
decision for revascularisation is rarely based on angiographic
findings alone and, especially in patients with non-critical
lesions, the presence or absence of angina pectoris or silent
ischaemia may determine the therapeutic decision. Theoretically,
a drug induced suppression of ischaemic symptoms
could mask the presence of a severe stenosis, and as such, put
the patient in danger of major cardiac adverse events. This
concern seems unjustified. Indeed, the combined rate of
death, stroke, and acute myocardial infarction was 7.8% in the
patient in danger of major cardiac adverse events. This
could mask the presence of a severe stenosis, and as such, put
cally, a drug induced suppression of ischaemic symptoms
ischaemia may determine the therapeutic decision. Theoreti-
fically, a drug induced suppression of ischaemic symptoms
ischaemia may determine the therapeutic decision. Theoreti-
findings alone and, especially in patients with non-critical
decision for revascularisation is rarely based on angiographic
trials and expert manuscript preparation, and to Ms Karine Vermaelen
We are indebted to Ms Sabine Van Roey for local coordination of the
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We are indebted to Ms Sabine Van Roey for local coordination of the
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and Mr Jef Adams for the angiographic measurements. The study was
supported by a grant from Bayer AG, Wuppertal, Germany.

Conclusions
Long acting nisoldipine did not retard the angiographic
progression of coronary artery disease, nor did it affect
mortality or major disease end points. However, the drug
reduced the need for coronary revascularisation, probably
because of its antiangiinal action. These findings are in line
with those of the recent PREVENT study, in which amlodipine
reduced the need for coronary revascularisation, probably
because of its antianginal action. These findings are in line
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