ARTICLES

Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial

The IONA Study Group*

Summary

Background In addition to its anti-ischaemic effects, the antianginal drug nicorandil is thought to have cardioprotective properties. We did a randomised trial to find out whether nicorandil could reduce the frequency of coronary events in men and women with stable angina and additional risk factors.

Methods 5126 patients were randomly assigned 20 mg nicorandil twice daily (n=2565) or identical placebo (n=2561) in addition to standard antianginal therapy. The primary composite endpoint was coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain. The secondary endpoint was the combined outcome of coronary heart disease death or non-fatal myocardial infarction. Other outcomes reported include all-cause mortality, all cardiovascular events, and acute coronary syndromes. Mean follow-up was 1·6 years (SD 0·5). Analysis was by intention to treat.

Findings There were 398 (15·5%) primary endpoint events in the placebo group and 337 (13·1%) in the nicorandil group (hazard ratio 0·83, 95% CI 0·72–0·97; p=0·014). The frequency of the secondary endpoint was not significantly different between the groups (134 events [5·2%] vs 107 events [4·2%]; 0·79, 0·61–1·02; p=0·068). The rate of acute coronary syndromes was 195 (7·6%) in the placebo group and 156 (6·1%) in the nicorandil group (0·79, 0·64–0·98; p=0·028), and the corresponding rates for all cardiovascular events were 436 (17·0%) and 378 (14·7%; 0·86, 0·75–0·98; p=0·027).

Interpretation We showed a significant improvement in outcome due to a reduction in major coronary events by antianginal therapy with nicorandil in patients with stable angina.

Lancet 2002; 359: 1269–75
See Commentary page 1262

Introduction Stable angina affects 2·3–5·1% of men aged 40–59 years, and more than 10% of those older than 60 years.1 In the UK, 25% of all deaths are attributable to coronary heart disease, and 25% of all patients presenting with a first myocardial infarction have a history of stable angina.2 Therefore, stable angina is important, not only as a cause of disability, but also as a frequently observed marker for underlying coronary heart disease. Aspirin, angiotensin-converting-enzyme (ACE) inhibitors, and statins reduce the risk of cardiovascular events in subgroups of patients with stable angina;3–7 however, the effect of specific antianginal treatment on morbidity and mortality in patients with stable angina remains unknown.

Nicorandil is a nicotinamide ester with a dual mechanism of action. Its distinctive pharmacological effect is to open ATP-sensitive potassium channels (K<sub>ATP</sub>), thereby dilating peripheral and coronary resistance arterioles; but it also possesses a nitrate moiety which dilates systemic veins and epicardial coronary arteries. Thus, nicorandil increases coronary blood flow, reduces preload and after-load,8–11 and has an antianginal efficacy and safety profile similar to that of oral nitrates, β-blockers, and calcium antagonists.12–14 However, in addition to relieving symptoms of ischaemia, nicorandil has potential cardioprotective effects. These effects are probably due to its ability to mimic the powerful ischaemic preconditioning phenomenon by opening K<sub>ATP</sub> channels, as shown in clinical and preclinical studies.15–19

The objective of the Impact Of Nicorandil in Angina (IONA) study was to investigate whether or not cardioprotective effects of nicorandil could be shown in a large outcome study in stable angina.

Patients and methods

Patients

The design and conduct of the IONA study has been reported in detail previously.20 Briefly, patients with a history of angina were recruited from centres in the UK. Angina could be recently diagnosed, but not unstable or chronic. Standard background antianginal therapy was not specified, but was to be optimum treatment as judged by the investigator for the individual patient. Such treatment could include one or more oral antianginal medications including β-blockers, calcium-channel blockers, or long-acting nitrates. The inclusion and exclusion criteria have been reported previously.20 We recruited patients with clearly established coronary heart disease or a positive exercise test with additional risk factors to ensure enrolment of individuals at high risk of a primary endpoint during the period of randomised follow-up. The recruits were men older than 45 years or women older than 55 years. They were required to have a history of myocardial infarction or...
coronary bypass surgery, or a definite diagnosis of coronary heart disease by angiography or a documented positive exercise test. In this third category, there had to be one of the following high-risk features: left-ventricular hypertrophy on electrocardiography; left-ventricular ejec tion fraction of 45% or less or an echocardiographic end diastolic dimension of more than 55 mm; type 1 or type 2 diabetes; and hypertension or documented evidence of other vascular disease (peripheral or central). The most important exclusion factor apart from cardiovascular instability was concomitant treatment with a sulphonylurea, since these drugs inhibit the opening of potassium channels.

All patients provided written informed consent and the study was approved by the Multicentre Research Ethics Committees of the UK. The activities of the trial centres and adherence to the principles of good clinical practice were monitored by staff from Ingenix Pharmaceutical Services.

Methods

Patients were randomly assigned nicorandil (10 mg twice daily for 2 weeks and 20 mg twice daily thereafter) or placebo in a double-blind fashion. The randomisation sequence was generated with a computerised pseudorandom number generator by an independent sequence was generated with a computerised pseudorandom number generator by an independent

investigator. Treatment allocation was obtained by a call to an interactive voice-responsive system.

Investigators were required to complete case report forms in respect of withdrawals from study medication, giving reasons where available. Patients were followed up for between 1 and 3 years, irrespective of whether or not they had withdrawn from study medication.

The study was co-ordinated by an independent statistical and data centre in the Robertson Centre for Biostatistics, University of Glasgow, and directed and overseen by committees made up of independent experts. These committees consist of a scientific steering committee headed by the study chairman, a data and safety monitoring committee, and a critical events committee. The former used p<0·001 for all-cause mortality as a guideline for stopping the trial early because of overwhelming evidence of benefit. The latter reviewed and validated all critical event data in a masked fashion, according to the formal definitions previously reported.26

The primary endpoint of the study was the combined outcome of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain. The secondary endpoint was coronary heart disease death or non-fatal myocardial infarction. Other outcomes reported in this paper include acute coronary syndromes (coronary heart disease death, non-fatal myocardial infarction, or unstable angina); all cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, hospital admission for transient ischaemic attack, and unplanned hospital admission for cardiac chest pain); cerebrovascular events (fatal and non-fatal stroke or hospital admission for transient ischaemic attack); all-cause mortality; death due to specific causes; worsening of anginal status as assessed from the Canadian Cardiovascular Society Functional classification of angina; and changes in blood pressure from baseline until the end of the study. Formal definitions of the study endpoints have been reported previously.26

Statistical analysis

With a target sample size of 5000 patients, the study had 80% power (5% significance level) to detect a 20% reduction in the rate of the primary endpoint assuming a placebo event rate of 13%, and 80% power (5% significance level) to detect a 25% reduction in the rate of the secondary endpoint assuming a placebo event rate of 8%.

All endpoints, with the exception of worsening of anginal status and changes in blood pressure, were analysed by survival analysis. For each clinical event outcome, the variable for analysis was taken to be the time to first occurrence of the event of interest. Event rates in the two treatment groups were compared by the log-rank

<table>
<thead>
<tr>
<th>Category</th>
<th>Nicorandil (n=2565)</th>
<th>Placebo (n=2561)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1962 (76%)</td>
<td>1948 (76%)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>197 (8%)</td>
<td>232 (9%)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>1197 (47%)</td>
<td>1178 (40%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>417 (16%)</td>
<td>425 (17%)</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>1696 (66%)</td>
<td>1682 (66%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>572 (22%)</td>
<td>590 (23%)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>360 (14%)</td>
<td>392 (15%)</td>
</tr>
<tr>
<td>Previous angiogram</td>
<td>1508 (59%)</td>
<td>1525 (60%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>134 (5%)</td>
<td>116 (5%)</td>
</tr>
<tr>
<td>Hospital admission for TIA</td>
<td>47 (2%)</td>
<td>55 (2%)</td>
</tr>
<tr>
<td>History of PVD</td>
<td>289 (11%)</td>
<td>335 (13%)</td>
</tr>
<tr>
<td>History of LVD</td>
<td>230 (9%)</td>
<td>206 (8%)</td>
</tr>
<tr>
<td>CCSF classification for angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>671 (26%)</td>
<td>692 (27%)</td>
</tr>
<tr>
<td>II</td>
<td>1605 (63%)</td>
<td>1583 (62%)</td>
</tr>
<tr>
<td>III</td>
<td>272 (11%)</td>
<td>275 (11%)</td>
</tr>
<tr>
<td>IV</td>
<td>15 (1%)</td>
<td>9 (&lt;1%)</td>
</tr>
<tr>
<td>Continuous risk factors, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 (8)</td>
<td>67 (9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 (9)</td>
<td>169 (9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 (15)</td>
<td>80 (15)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 (5)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>138 (19)</td>
<td>138 (19)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>79 (10)</td>
<td>79 (10)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>66 (12)</td>
<td>67 (12)</td>
</tr>
</tbody>
</table>

BMI=myocardial infarction; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; TIA=transient ischaemic attack; PVD=peripheral vascular disease; LVD=left-ventricular dysfunction; CCSF=Canadian Cardiovascular Society Functional; BMI=body-mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure.
test, and risk reductions were calculated in the form of hazard ratios and 95% CIs from Cox’s proportional hazards models with treatment fitted as the only covariate. These analyses were done on an intention-to-treat basis. Clinical outcomes were sought on all patients until death, study close-down, or withdrawal of informed consent for follow-up, whichever came first. For patients lost to follow-up, events were censored at the last visit.

Worsening of anginal status was defined as a worsening of at least one class in the Canadian Cardiovascular Society Functional classification of angina or occurrence of unplanned hospital admission for cardiac chest pain. Relative frequencies of this outcome were compared by a χ² test, and odds ratios and 95% CIs were calculated from a logistic regression model with treatment as the only covariate. Changes in blood pressure were compared by Student’s two-sample t test with associated 95% CIs.

Role of the funding source
The sponsors contributed to the design of the study and formulation of the protocol, provided funding, and had one member each in a non-voting capacity on the steering committee.

Results
5126 patients were enrolled from 226 centres in the UK between May, 1998, and August, 2000. 2565 were randomly assigned nicorandil and 2561 placebo (figure 1). Patients were recruited in about equal numbers from primary care and hospital practices. The mean follow-up was 1·6 years (SD 0·5), with the final study visit at the end of the study was 985 (43%), 1159 (50%), 162 (7%), and nine (0·1%) for nicorandil and 989 (43%), 1124 (49%), 163 (7%), and 15 (1%) for placebo. The Kaplan-Meier curves are shown in figure 2.

There was no significant difference in the rate of the secondary endpoint—coronary heart disease death or non-fatal myocardial infarction—between the nicorandil group and the placebo group (table 3, figure 3). The distributions of patients with non-fatal coronary events are given in table 3. There were fewer events in the nicorandil group in all sub-categories. We did exploratory analyses on additional composite endpoints (table 3, figure 3). Acute coronary syndromes and all cardiovascular events were significantly less common on nicorandil than placebo. All-cause mortality was not significantly different between the groups.

There was a similar number of cerebrovascular events and non-cardiovascular deaths on nicorandil as on placebo (table 3). The distribution across categories (I, II, III, and IV) of the Canadian Cardiovascular Society Functional classification of angina for patients assessed at the end of the study was 985 (43%), 1159 (50%), 162 (7%), and nine (<1%) for nicorandil and 989 (43%), 1124 (49%), 163 (7%), and 15 (1%) for placebo. Worsening of anginal status was seen in 569 (22%) patients on nicorandil and 712 (24%) patients on placebo (odds ratio 0·93, 95% CI 0·81–1·06; p=0·26).

Table 3: Distribution of major clinical outcomes

<table>
<thead>
<tr>
<th>Component events</th>
<th>Nicorandil (n=2565)</th>
<th>Placebo (n=2561)</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD death, non-fatal MI, or hospital admission for cardiac chest pain</td>
<td>337 (13·1%)</td>
<td>398 (15·5%)</td>
<td>0·83 (0·72–0·97)</td>
<td>0·014</td>
</tr>
<tr>
<td>CHD death or non-fatal MI</td>
<td>107 (4·2%)</td>
<td>134 (5·2%)</td>
<td>0·79 (0·61–1·02)</td>
<td>0·068</td>
</tr>
<tr>
<td>CHD death, non-fatal MI, or unstable angina</td>
<td>156 (6·1%)</td>
<td>195 (7·6%)</td>
<td>0·79 (0·64–0·98)</td>
<td>0·028</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>378 (14·7%)</td>
<td>436 (17·0%)</td>
<td>0·86 (0·75–0·98)</td>
<td>0·027</td>
</tr>
<tr>
<td>Ailcause mortality</td>
<td>111 (4·3%)</td>
<td>129 (5·0%)</td>
<td>0·85 (0·66–1·10)</td>
<td>0·22</td>
</tr>
</tbody>
</table>
The mean changes in blood pressure (systolic/diastolic) from baseline to the end of the study were –4·0/–2·4 mm Hg (SD 20·0/11·7) in the nicorandil group and –3·4/–2·1 mm Hg (19·8/11·3) in the placebo group (p=0·35/p=0·33 for between-group comparisons).

Overall, the rates of serious adverse events were similar in both groups, although the number of gastrointestinal events (194 vs 132) was greater in the nicorandil group. Non-serious adverse events were not collected routinely but in the nicorandil and placebo groups, respectively, the number of withdrawals from study medication were 413 (16·1%) and 163 (6·4%) at 2 weeks, 566 (22·1%) and 308 (12·0%) at 8 weeks, 758 (29·6%) and 499 (19·5%) at 6 months, and 1003 (39·1%) and 809 (31·6%) at the end of the study.

Discussion
In the IONA study, we report a significant improvement in outcome from antianginal treatment in patients with stable angina. Outcome was defined as a combination of morbidity and mortality by a composite primary endpoint of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for chest pain. Event rates in all components of the primary endpoint were lower in patients on nicorandil than on placebo and therefore each contributed to the significance of the primary endpoint.

Definitions in acute coronary disease have changed since the inception of the IONA study.21 Within the primary endpoint of IONA are all the components of “acute coronary syndromes”, which has now become the accepted term to encompass both unstable angina and
myocardial infarction, in recognition of their common underlying pathology. Thus the third component, unplanned hospital admission for chest pain, comprised three categories, namely unstable angina, definite angina, and possible angina. Unstable angina required the patient to have had parenteral therapy including heparin and to have acute electrocardiographic changes indicative of ischaemia. Myocardial infarction was defined according to the standard WHO definition. This definition required the patient to have two of the three criteria of typical clinical presentation, electrocardiographic changes consistent with acute myocardial infarction, or an appropriate increase in the concentration of cardiac enzymes. These endpoints were all adjudicated by the endpoints committee. Nicorandil therefore significantly reduced, by 21%, the rate of acute coronary syndromes, defined as coronary heart disease deaths, non-fatal myocardial infarction, or unstable angina.

The study was underpowered to show statistical significance with regard to the secondary endpoint—coronary heart disease mortality or non-fatal myocardial infarction—since the rate of this endpoint in the placebo group (5·2%) was substantially lower than predicted (8%).

Treatment with nicorandil improved outcome in terms of reducing events related to acute coronary disease and the associated requirement for admission to hospital. In view of these data, and since the rate of all cardiovascular events also fell significantly, we suggest that the beneficial effect of nicorandil on outcome was mediated through modification of the course of the underlying coronary heart disease. The trial design does not permit any conclusions as to the precise mechanism through which this might have occurred. The pharmacology of nicorandil is complex and includes nitrate effects and activation not only of sarcolemmal but also of mitochondrial KATP channels.22–24

The nitrate-like effect, together with arteriolar and venous vasodilatation due to the sarcolemmal KATP channel activation, are likely to be responsible for the efficacy of nicorandil in relieving ischaemia due to increased myocardial oxygen demand. Major coronary events, however, are thought to result from the development of instability in atheromatous plaques, and their reduction in IONA might have been related to plaque stabilisation resulting from the haemodynamic effects. However, there are no clinical or preclinical data to support this hypothesis and neither nitrates or other directly acting vasodilators have been shown previously to improve outcome in ischaemic heart disease, although the combination of nitrates and hydralazine did confer a modest survival advantage in chronic heart failure.25

The most plausible explanation is that nicorandil acts as a pharmacological mimetic of the phenomenon of ischaemic preconditioning, which has been well described in experimental studies and might represent an endogenous cardioprotective mechanism. This process is responsible for the amelioration of subsequent effects of ischaemia after an initial ischaemic event, and the role of KATP channels in this form of protection has been shown experimentally.26–28 Originally, the pharmacological basis for ischaemic preconditioning was thought to be activation of the sarcolemmal KATP channels by decreased cytosolic ATP concentrations caused by ischaemia, and resulting in a reduction potential, reduced calcium influx, and decreased contractility.22,23 An alternative, and perhaps more scientifically plausible, explanation for ischaemic preconditioning arises from the recent demonstration of preservation of mitochondrial integrity through activation of specific mitochondrial KATP channels. In the current absence of any published molecular characterisation, these “mito-KATP” channels remain possibilities only, but pharmacological evidence suggests their existence and that nicorandil exerts its preconditioning effect through their activation.29

Ischaemic preconditioning has also been invoked in several clinical phenomena including the observation that subsequent inflations during coronary angioplasty induce less ischaemia than the first,16 in “warm-up” angina in patients with stable angina, and as an explanation for the reduction in short-term mortality in patients with acute myocardial infarction preceded by unstable angina.17,20 A pilot study in patients with unstable angina, in which repeated ischaemic episodes are characteristic, showed a lower rate of arrhythmias and transient myocardial ischaemia in patients taking nicorandil than in patients on placebo.19 This effect was suggested to be due to preconditioning, since all the patients were already being treated with β-blockers, diltiazem, and nitrates, allowing little room for a haemodynamic effect. Given the pharmacological background, the consistency of the experimental data, and the results of previous clinical studies, we think that preconditioning of myocardial preconditioning is the most plausible explanation for the cardioprotective effect of nicorandil shown in IONA.

Given these favourable effects on objective evidence of ischaemia, the lack of demonstrable effect of nicorandil on symptoms as assessed by the Canadian Cardiovascular Society Functional (CCSF) classification is surprising. The reason for this lack of effect is not clear, but the CCSF might not be an appropriate instrument in the context of a clinical trial in which the main purpose was to assess outcome. No training was given to the investigators in the use of this classification, with which they would have had little previous experience. Since more patients in the nicorandil group than the placebo group survived, and since fewer patients had a major coronary event (following which symptoms of angina often improve), there would have been more patients at risk of developing worsening symptoms in the nicorandil group. Additionally, since the protocol allowed for adjustments in other antianginal medications according to anginal status, and was not held constant as in a clinical trial of antianginal efficacy, a similar symptom status in both groups is perhaps to be expected.

Overall withdrawal from randomised treatment was more frequent on nicorandil than on placebo, the absolute difference in withdrawal rates being about 10%. The reason for withdrawal was adverse events in 53% in the nicorandil group compared with 66% on placebo.16 This trend was evident from the first uptitration visit, and was mainly due to the increased incidence of headache in the nicorandil group. This trend was evident from the first uptitration visit, and was mainly due to the increased incidence of headache in the nicorandil group. The higher withdrawal rate in the nicorandil group leads to a tendency to underestimate the outcome benefit.

The favourable effects seen in this study occurred when nicorandil was given in addition to other standard antianginal therapy including β-blockers, calcium-channel blockers, or long-acting nitrates. Had all patients in IONA, rather than just over half, been taking a β-blocker, the anti-ischaemic effects of nicorandil might have been less evident when added to those of β-blockade. Although several smaller studies in stable angina have suggested a possible benefit on outcome,20–22 and although there is overwhelming evidence for morbidity and mortality benefits from β-blockade in myocardial infarction and chronic heart failure, there have been no large-scale trials...
of the effects on outcome of β-blockade in stable angina. Their putative anti-ischaemic effects in the specific situation of stable angina, therefore, remain unproven. Moreover, specific contraindications to, and side effects of, β-blockers will limit their prescription in a substantial proportion of patients.

Moreover, there are no published data on the effects of the other standard antianginal medications on clinical outcome, apart from those of the APSIS study in which the effects of verapamil and metoprolol were similar, and the TIBET study in which atenolol, nifedipine, and their combination were also similar; both studies were too small to allow definitive conclusions to be drawn. Therefore, since nisoldipine is the only antianginal agent so far to have shown a significant improvement in outcome in patients with stable angina, its use might now need to be reassessed.

**ARTICLES**

of the effects on outcome of β-blockade in stable angina. Their putative anti-ischaemic effects in the specific situation of stable angina, therefore, remain unproven. Moreover, specific contraindications to, and side effects of, β-blockers will limit their prescription in a substantial proportion of patients.

Moreover, there are no published data on the effects of the other standard antianginal medications on clinical outcome, apart from those of the APSIS study in which the effects of verapamil and metoprolol were similar, and the TIBET study in which atenolol, nifedipine, and their combination were also similar; both studies were too small to allow definitive conclusions to be drawn. Therefore, since nisoldipine is the only antianginal agent so far to have shown a significant improvement in outcome in patients with stable angina, its use might now need to be reassessed.

**ARTICLES**

of the effects on outcome of β-blockade in stable angina. Their putative anti-ischaemic effects in the specific situation of stable angina, therefore, remain unproven. Moreover, specific contraindications to, and side effects of, β-blockers will limit their prescription in a substantial proportion of patients.

Moreover, there are no published data on the effects of the other standard antianginal medications on clinical outcome, apart from those of the APSIS study in which the effects of verapamil and metoprolol were similar, and the TIBET study in which atenolol, nifedipine, and their combination were also similar; both studies were too small to allow definitive conclusions to be drawn. Therefore, since nisoldipine is the only antianginal agent so far to have shown a significant improvement in outcome in patients with stable angina, its use might now need to be reassessed.

**ARTICLES**

of the effects on outcome of β-blockade in stable angina. Their putative anti-ischaemic effects in the specific situation of stable angina, therefore, remain unproven. Moreover, specific contraindications to, and side effects of, β-blockers will limit their prescription in a substantial proportion of patients.

Moreover, there are no published data on the effects of the other standard antianginal medications on clinical outcome, apart from those of the APSIS study in which the effects of verapamil and metoprolol were similar, and the TIBET study in which atenolol, nifedipine, and their combination were also similar; both studies were too small to allow definitive conclusions to be drawn. Therefore, since nisoldipine is the only antianginal agent so far to have shown a significant improvement in outcome in patients with stable angina, its use might now need to be reassessed.

**ARTICLES**

of the effects on outcome of β-blockade in stable angina. Their putative anti-ischaemic effects in the specific situation of stable angina, therefore, remain unproven. Moreover, specific contraindications to, and side effects of, β-blockers will limit their prescription in a substantial proportion of patients.

Moreover, there are no published data on the effects of the other standard antianginal medications on clinical outcome, apart from those of the APSIS study in which the effects of verapamil and metoprolol were similar, and the TIBET study in which atenolol, nifedipine, and their combination were also similar; both studies were too small to allow definitive conclusions to be drawn. Therefore, since nisoldipine is the only antianginal agent so far to have shown a significant improvement in outcome in patients with stable angina, its use might now need to be reassessed.

**ARTICLES**

of the effects on outcome of β-blockade in stable angina. Their putative anti-ischaemic effects in the specific situation of stable angina, therefore, remain unproven. Moreover, specific contraindications to, and side effects of, β-blockers will limit their prescription in a substantial proportion of patients.

Moreover, there are no published data on the effects of the other standard antianginal medications on clinical outcome, apart from those of the APSIS study in which the effects of verapamil and metoprolol were similar, and the TIBET study in which atenolol, nifedipine, and their combination were also similar; both studies were too small to allow definitive conclusions to be drawn. Therefore, since nisoldipine is the only antianginal agent so far to have shown a significant improvement in outcome in patients with stable angina, its use might now need to be reassessed.
ARTICLES

Centre, Port Glasgow; G B Morrison, Central Health Centre, Cumbernauld; B W McGill, Motherwell Health Centre, Motherwell; J O Gallagher, Greenock Health Centre, Greenock; J Masterton, Bishopston Health Centre, Bishopston; E C Fellows, The Surgery, Dumfries; J Montgomery, Ardgowan Medical Centre, Greenock; A Robertson, Health Centre, Barhead; N Balmer, Health Centre, Stranraer; D J Wooff, Health Centre, Stranraer; D Beattie, Health Centre, Stranraer; J D Gordon, Health Centre, Stranraer; C Chapman, Abbey Medical Centre, Paisley; M Mitchell, Riverview Medical Centre, Johnstone; D Melrose, Lincludens Surgery, Uddingston; I Cannon, Peel View Medical Centre, Kirkintilloch; M Easton, The Surgery, Glasgow; B Glekin, Woodside Health Centre, Glasgow; S Goldberg, Baxterbiggens Medical Centre, Glasgow; G Naylor, Blythe Practice, Knowle; A Smithers, The Surgery, Cowenry; J Patchett, Groby Road Medical, Leicester; T Goodeing, The Atherstone Surgery, Atherstone; D Dutchman, Roebuck House Surgery, Hasting; M Sevenoaks, The Surgery, Old Cottage Hospital, Epsom; S Butt, Studholme Medical Centre, Ashford; S Hall, Grove Medical Centre, Tunbridge Wells; R Sharma, Sea Road Surgery, Bexhill on Sea; A Weaver, Winch Lane Surgery, Horfordwest; F Davies, Cwmfelin Medical Centre, Swansea; A H Jones, Talybont Surgery, Swansea; J Morris, Park Lane Surgery, Mid Glamorgan; I Farmer, Stanwell Road Surgery, Ashford; D Fernandez, The Surgery, Camberley; P Goozee, Hildenborough Medical Group, Hildenborough; G G Spence, Shetlleton Health Centre, Glasgow.

Conflict of interest statement

Members of the various committees received research grants or honoraria in respect of their contribution to this study.

Acknowledgments

The IONA study was sponsored by Merck Pharmaceuticals, Aventis in respect of their contribution to this study.

References