Noricandil reduced coronary events in stable angina


QUESTION: In patients with stable angina and additional risk factors, is nicorandil more effective than placebo for reducing coronary events?

Design
Randomised (allocation concealed*), blinded (clinicians and patients),* placebo-controlled trial with mean follow up of 1.6 years.

Setting
226 UK centres (primary care and hospital practices).

Patients
5126 patients (mean age 67 y, 76% men) who had stable angina with a history of myocardial infarction (MI), coronary bypass surgery, a definite diagnosis (by angiography) of coronary heart disease (CHD), or a documented positive result on the exercise test. Patients with CHD or a positive result on the exercise test were also required to have additional risk factors, including left ventricular ejection fraction ≤45%, echocardiographical end-diastolic dimension > 55 mm, and type 1 or type 2 diabetes. Patients receiving treatment with a sulfonylurea were excluded. Follow up was 100%.

Intervention
Patients were allocated to nicorandil, 20 mg twice daily (n = 2565) or placebo (n = 2561). All patients received standard antianginal treatment.

Main outcome measures
The main outcome was a composite of CHD death, non-fatal MI, or unplanned hospital admission for chest pain. The secondary outcome was a composite of CHD death or non-fatal MI.

Main results
Analysis was by intention to treat. The incidence of the composite end point of CHD death, non-fatal MI, or unplanned hospital admission for chest pain was lower in the nicorandil group than in the placebo group. The groups did not differ for the incidence of a composite end point of CHD death or non-fatal MI.

Conclusion
In patients with stable angina and additional risk factors, nicorandil was more effective than placebo for reducing coronary events.

*See glossary.

Nicorandil v placebo for stable angina with additional risk factors

<table>
<thead>
<tr>
<th>Outcomes at 1 to 3 years</th>
<th>Nicorandil</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite 1</td>
<td>13.1%</td>
<td>15.5%</td>
<td>16% (3 to 26)</td>
<td>41 (25 to 234)</td>
</tr>
<tr>
<td>Composite 2</td>
<td>4.2%</td>
<td>5.2%</td>
<td>21% (2 to 38)</td>
<td>Not significant</td>
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</tbody>
</table>

*Composite 1 = coronary heart disease death, nonfatal myocardial infarction, or unplanned hospital admission for chest pain; composite 2 = coronary heart disease death or nonfatal myocardial infarction. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Until the publication of this trial by the IONA study group, no specific antianginal treatment had been shown to reduce morbidity or mortality in patients with CHD. Although IONA can be considered a breakthrough study, revision of standards of care for patients with CHD demands further deliberation because of protocol complexity and some study limitations. The placebo group had fewer events than projected for the secondary end point of combined non-fatal MI or cardiac death, leaving the study with insufficient power to detect a difference between the groups for this outcome. Nicorandil was superior to placebo when unstable angina episodes were added to these 2 outcomes, but this analysis seems to have been post hoc.

Three decades have passed since the University Group Diabetes Program Study expressed concern about the increased mortality in patients with diabetes who had been treated with tolbutamide, but a lack of consensus still exists on this issue.1 The UK Prospective Diabetes Study found no increase in CHD mortality with sulfonylurea treatment.2 However, sulfonylurea use was associated with increased risk for in-hospital mortality in patients with diabetes who were receiving coronary angioplasty for acute MI and may reflect deleterious effects of sulfonylureas on myocardial tolerance for ischaemia and reperfusion.3 Excluding patients with type 2 diabetes receiving sulfonylureas from IONA was rational because of possible class interaction with nicorandil on opening adenosine triphosphate-sensitive potassium channels, but it limited the potential effect of nicorandil in this important and growing group of high-risk patients.

Given that 66% of patients in the trial had had previous MI but only 57% were receiving β-blockers, the authors acknowledge that the benefits of nicorandil might have been less if a higher proportion of patients had been on this proven antianginal and post-MI treatment. Only 56% of all patients received a statin and 30% an angiotensin-converting enzyme inhibitor, despite the known benefits of both classes in high-risk patients with CHD. Before nicorandil is added to the management of high-risk patients with proven CHD, primary and secondary risk factors should be managed comprehensively.

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1 Seltzer HS. A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). Diabetes 1972;21:976-9.