

Nicorandil reduced coronary events in stable angina

The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact of Nicorandil in Angina (IONA) randomised trial. *Lancet*. 2002 Apr 13;359:1269-75.

QUESTION

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

DESIGN

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

SETTING

226 U.K. centers (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 $\leq 45\%$, echocardiographic end-diastolic dimension > 55 mm, and type 1 or type 2 diabetes. Patients receiving treat-

ment 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 therapy.

MAIN OUTCOME MEASURES

The main outcome was a composite of CHD death, nonfatal MI, or unplanned hospital admission for chest pain. The secondary outcome was a composite of CHD death or nonfatal MI.

MAIN RESULTS

Analysis was by intention to treat. The incidence of the composite end point of CHD

death, nonfatal MI, or unplanned hospital admission for chest pain was lower in the nicorandil group than in the placebo group (Table). The groups did not differ for the incidence of a composite end point of CHD death or nonfatal MI (Table).

CONCLUSION

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

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*See Glossary.

Nicorandil vs placebo for stable angina with additional risk factors†

Outcomes at 1 to 3 y	Nicorandil	Placebo	RRR (95% CI)	NNT (CI)
Composite 1	13.1%	15.5%	16% (3 to 26)	41 (25 to 234)
Composite 2	4.2%	5.2%	21% (-2 to 38)	Not significant

†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 therapy had been shown to reduce morbidity or mortality in patients with CHD. Although IONA can be considered a breakthrough study, revising 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 nonfatal 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 ischemia 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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