Impact of nicorandil in angina: subgroup analyses

IONA Study Group

Aims: IONA (impact of nicorandil in angina) is a randomised, double blind, placebo controlled trial of nicorandil, with a target dose of 20 mg twice daily. The consistency of benefits seen in subgroups is reported.

Methods: The primary composite end point of the study was coronary heart disease death, non-fatal myocardial infarction, or unplanned hospitalisation for cardiac chest pain. Subgroups were defined using baseline characteristics including, age, sex, histories of smoking, diabetes, hypertension, myocardial infarction, revascularisation, anginal status, anti-anginal treatment, other cardiovascular drugs, and an overall assessment of risk.

Results: A total of 5126 patients were randomised to receive nicorandil or identical placebo in addition to standard anti-anginal treatment. Overall, nicorandil reduced the incidence of the primary end point from 15.5% to 13.1% (hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.72 to 0.97; p = 0.014). There was no evidence of significant heterogeneity of benefit across all subgroups studied. The absolute risk reduction was greatest and the numbers needed to treat to prevent one event was lowest in subjects at greatest risk.

Conclusions: The IONA study demonstrates a significant improvement in outcome by nicorandil treatment across a broad range of patients with stable angina.
Figure 1  Estimated hazard ratios and 95% CI for subgroups defined by traditional risk factors analysed on the basis of the primary end point; p values are for tests of homogeneity of treatment effect. The numbers tabulated are the numbers of events/subjects for the placebo and nicorandil groups.

Figure 2  Estimated hazard ratios and 95% CI for subgroups defined by background medication risk factors analysed on the basis of the primary end point; p values are for tests of homogeneity of therapy effect. The numbers tabulated are the numbers of (subjects with events)/(total number of subjects) for the placebo and nicorandil groups.
**DISCUSSION**

The subgroup analyses provide no significant evidence of any qualitative or quantitative interactions between nicorandil treatment benefit and subgroup status. The effect of nicorandil on top of nitrates adds support to the argument that the mechanism of benefit is other than the nitrate properties of nicorandil and plausibly caused by its potassium channel opening activity. The hazard ratio for treatment benefit was at least as great in subjects receiving three anti-anginal medications as it was in those receiving one or two medications. A similarly consistent result was achieved across the categories of the CCS functional status questionnaire. Subjects taking higher numbers of anti-anginal medications, or with higher CCS functional status scores, were at particularly high risk. A reduction in relative risk that is independent of baseline risk suggests that treatment of those at highest risk will provide the greatest absolute risk reduction and possibly be the most cost effective. Our results suggest that treating subjects in the highest third of risk will prevent more than twice the number of events compared to the treatment of subjects in the lowest third. However, even in the lowest third of the risk spectrum the NNT is 63, a not unimpressive result for a relatively short period of treatment (1.6 years).

Weaknesses of the analyses that were conducted are primarily caused by the reduced power associated with the important but modest overall risk reduction. Despite this fact, the consistency of benefit across all subgroups supports the view that the overall results of the study in terms of a 17% reduction and possibly be the most cost effective. Our results suggest that treating subjects in the highest third of risk will prevent more than twice the number of events compared to the treatment of subjects in the lowest third. However, even in the lowest third of the risk spectrum the NNT is 63, a not unimpressive result for a relatively short period of treatment (1.6 years).

Current guidelines place β blockers as the first line treatment for the medical management of angina pectoris. This is probably because, in addition to being effective anti-anginal agents, they also have an impressive record in reducing major coronary events across a wide spectrum of coronary heart disease, although this has never been tested in an appropriately powered trial in stable angina. In contrast, calcium channel blockers and then long acting nitrates, which are added in or substituted in cases of inadequate efficacy or intolerance to β blockers, have not been shown to have cardioprotective effects in coronary heart disease. Therefore, it would appear that IONA has two important messages for clinical practice. Firstly, in this group of patients with established coronary heart disease, nicorandil may be added to statins, antiplatelet agents, and ACE inhibitors as a member of a class of treatments that prevent major clinical events. Secondly, the secondary prevention properties established in IONA, combined with the already known anti-anginal properties of nicorandil, suggests that nicorandil should be considered at an earlier stage in the treatment of angina ahead of calcium channel blockers and nitrates.

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**APPENDIX: IONA STUDY GROUP**

**Steering committee**

**Voting members**

Professor HJ Dargie (Chairman, Glasgow Western Infirmary, Glasgow), Professor I Ford (Glasgow University, Glasgow), Professor K M Fox (Royal Brompton Hospital, London), Professor W S Hillis (Glasgow University, Glasgow).

**Sponsor representatives (non-voting)**

Dr M Morris (Merck Pharmaceuticals Ltd), Dr M Ford (Aventis Pharma Ltd).

**Critical events committee**

Professor WS Hillis (Glasgow University, Glasgow), Professor JJV McMurray (Glasgow University, Glasgow), Dr AL Clark (University of Hull, Kingston upon Hull).

**Data and safety monitoring committee**

Professor J Hampton (Chairman, University Hospital, Nottingham), Dr A Skene (Nottingham Clinical Research Ltd), Dr J Birkhead (Northampton General Hospital, Northampton).

**Statistical and data centre**

Robertson Centre for Biostatistics, University of Glasgow, Glasgow: Professor I Ford (Director), Dr A McMahon (Study Statistician), Ms A Trainer, Ms H Christie (Database Managers), Ms A Nears (Nurse/coder), Ms C Ferrell (Study Administrator), Dr B Shaw (Clinical Co-ordinator).

**Study monitoring**

Ingenix Pharmaceutical Services: Ms V Diment (Project Manager)
Investigators
See IONA Study Group.9

REFERENCES

Giant left main coronary artery aneurysm with mitral regurgitation

A 32 year old woman presented with acute myocardial infarction and left ventricular failure leading to acute mitral regurgitation. A coronary angiogram revealed a proximal stenosis of the left anterior descending artery (LAD), occlusion of the circumflex artery, and an aneurysm of the left main coronary artery, measuring 24 x 16 mm (panel A). A transthoracic echocardiogram showed grade III mitral valve regurgitation secondary to annular dilatation and lateral wall dysfunction. The patient underwent surgery three weeks later. During the operation, the left main stem aneurysm containing multiple thrombi was over-sewn both proximally and distally. The LAD was grafted with the left internal thoracic artery, and intermediate and obtuse marginal arteries were grafted sequentially with a segment of the long saphenous vein. Failure in weaning off from cardiopulmonary bypass, because of the hypoperfusion within the LAD distribution, led to an additional vein graft to the LAD. The mitral valve was repaired using an annuloplasty band. The patient remains clinically asymptomatic; follow up computed tomographic coronary angiography six months later revealed an occluded left main stem and the aneurysm, and patent saphenous vein grafts to the LAD (panel B and C). As there are reports that such patients may also develop extracardiac aneurysms, she underwent a magnetic resonance imaging scan of head, thorax, and abdomen, which did not show any pathology.

Anneurysms of the left main coronary artery occur in 0.1% of adults. Only a few descriptions exist of a surgically treated aneurysm of the left main coronary artery. In this case, a direct approach was undertaken to close the aneurysm, and this was combined with mitral valve repair for ischaemic mitral regurgitation.