



# Nicorandil

C Ferguson, G McKay, M Fisher\*

## Introduction

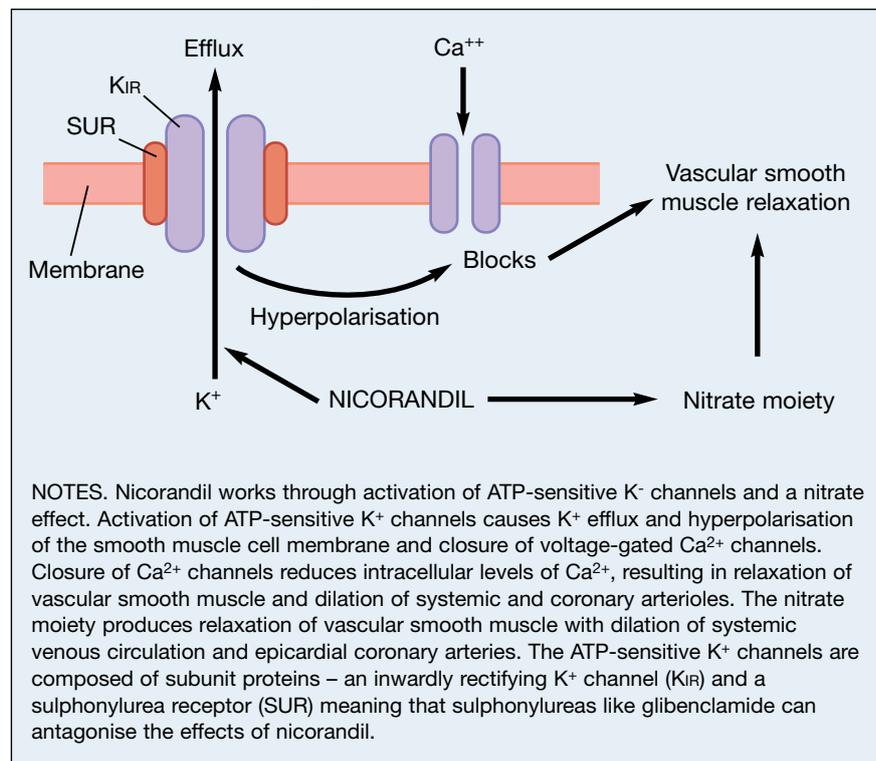
Nicorandil is an anti-anginal drug, originating from Japan in the early 1980s, and is the sole member of its pharmacological class. Licensing permits use of nicorandil as long-term prophylactic treatment in patients with angina pectoris. Initially, this compound was thought to have an efficacy and safety profile similar to nitrates. However, the IONA (Impact Of Nicorandil in Angina) trial<sup>1</sup> suggested that nicorandil had multiple benefits in patients with angina, leading to further consideration of its pharmacological mechanisms, and an elevated clinical profile in cardiovascular medicine.

## Pharmacology

Figure 1 outlines the pharmacological action of nicorandil, a nicotinamide ester with dual properties, acting as a hybrid nitrate and an activator of ATP-dependent potassium channels (K<sub>ATP</sub>). Nicorandil allows simultaneous dilation and relaxation of arterial and venous vasculature via its affect on smooth muscle. The nitrate component causes dilation of systemic venous circulation and of epicardial coronary arteries. Activation of potassium channels triggers dilation of systemic and coronary arterioles. Thus, coronary blood flow is maximised, whilst reducing both cardiac pre-load and after-load.

Early animal studies suggested additional cardioprotection might be conferred by the novel K<sub>ATP</sub> opening action of nicorandil. It was hypothesised that such benefit is achieved by ischaemic pre-conditioning: repeated bursts of ischaemia encourage endogenous protection and limitation of

**Figure 1.** The pharmacological action of nicorandil which has dual effects (see 'Notes' below the diagram)



myocardial damage in subsequent situations of prolonged myocardial ischaemia. During ischaemia, reduction of cytosolic ATP levels results in the activation of the adenosine A<sub>1</sub> receptor and promotes the simultaneous opening of K<sub>ATP</sub> channels. This phenomenon has subsequently been supported by human studies, particularly in subjects undergoing percutaneous coronary intervention.

## Trials of safety and efficacy

The SWAN study recruited 121 patients with stable angina, and compared the effect of amlodipine and nicorandil on anginal symptoms and ECG changes on exercise

tolerance test (ETT).<sup>2</sup> Standard combination anti-anginal therapy was permitted. At the eight-week endpoint of the study, the effects of nicorandil and amlodipine were comparable, and both groups reported increased time to onset of anginal pain at ETT as compared with baseline measurements.

The IONA trial<sup>1</sup> was a large double-blinded, randomised, placebo-controlled trial of 5126 patients with stable exertional angina pectoris. A diagnosis of angina was conferred using the Canadian Cardiovascular Society Functional Classification, and patients were recruited from hospital and general practice settings. Trial subjects were

Caroline Ferguson, BSc(MedSci),

MB ChB, Foundation Doctor

Gerry McKay, BSc(Hons), FRCP,

Consultant Physician

Miles Fisher, MD, FRCP, Consultant

Physician

Medical Directorate, Glasgow Royal

Infirmery, Glasgow, UK

\*Correspondence to: Dr Miles Fisher,

Wards 4 & 5, Glasgow Royal Infirmary,

84 Castle Street, Glasgow G4 0SF, UK;

e-mail: miles.fisher@ggc.scot.nhs.uk

permitted to be on any combination of standard background anti-anginal preparations, including beta blockers (57%), calcium channel blockers (55%) and long-acting nitrate preparations (87%).

Additional inclusion criteria included the presence of at least one of the following characteristics: previous myocardial infarction (MI), previous coronary artery bypass grafting (CABG), and/or proven coronary artery disease (diagnosed by positive ETT or angiography). In the presence of coronary artery disease without previous MI or CABG, one of the following additional factors also had to be present: left ventricular hypertrophy on ECG, left ventricular dysfunction on echocardiogram, age >65 years, diabetes mellitus, hypertension, and/or vascular disease (stroke, transient ischaemic attack, peripheral arterial disease). Notable exclusion criteria included those with unstable angina, very recent CABG (3/12), pre-existing treatment with nicorandil, and those receiving treatment with sulphonylureas for type 2 diabetes. The latter cohort were specifically excluded on the basis that sulphonylureas induce hypoglycaemia by blocking activation of ATP-sensitive potassium channels, thus antagonising the mechanism of nicorandil.

The primary endpoints of death due to coronary artery disease, MI (non-fatal), and cardiac chest pain requiring hospitalisation occurred in 337 of the treatment group *versus* 398 of the placebo group (13.1% *vs* 15.5%), thus demonstrating a statistically significant reduction (hazard ratio 0.83; confidence interval 0.72–0.97;  $p=0.014$ ) in the active treatment arm of the trial. Secondary endpoints of coronary artery disease death and non-fatal MI did not significantly differ, and overall mortality was not appreciably different between treatment and placebo cohorts (4.3% *vs* 5.0%;  $p=0.222$ ).

A recent trial compared nicorandil with isosorbide mononitrate in 232 patients with stable angina.<sup>3</sup> Primary outcome measures were frequency of anginal attacks and glyceryl trinitrate requirements,

### Key points

- Nicorandil is a potassium channel activator for prophylactic use in patients with angina
- In the large IONA trial it reduced cardiovascular morbidity and, in particular, hospitalisation for chest pain
- Subgroup analysis of patients with diabetes in IONA was not statistically significant, but the small numbers of patients meant that it was underpowered to show differences in outcome

changes to exercise capacity and time for development of dynamic ECG changes on ETT. A significantly enhanced exercise capacity and prolonged time to development of ECG changes on ETT were noted in both treatment groups after eight weeks of therapy, as compared with baseline measures. Furthermore, the frequency of anginal attacks was reduced in both treatment populations. This effect appears greater in the nicorandil treatment group, with 68.1% reporting a 50% reduction in anginal symptoms compared with 47.8% of the isosorbide mononitrate patients ( $p=0.048$ ).

The main adverse effects associated with nicorandil therapy are vasodilatory features: headache and facial flushing. These are not reported to be worse with nicorandil than with nitrate therapy. Oral ulceration and anal ulceration are rare but important side effects.

### Specific evidence for use in diabetes

Within the IONA trial, 429 patients with type 1 and type 2 diabetes were included, with 232 patients in the placebo arm and 197 in the treatment group. Although patients with diabetes treated with sulphonylureas were excluded, those in the study were treated with multiple modalities including insulin and oral hypoglycaemic drugs. Subgroup analysis of the original trial shows that 67 (15.6%) patients with diabetes experienced an event; 40 of these occurred in the placebo cohort (17.2%) and 27 (13.7%) in the nicorandil group.<sup>4</sup> Statistically, there was no significant difference between event rates in the population with diabetes ( $p=0.95$ ).

### Discussion

From the results of the IONA trial, it has been shown that cardiovascular morbidity was reduced by the addition of nicorandil to standard anti-anginal therapy in high risk populations. However, this effect was largely due to a reduction in cardiac chest pain requiring hospitalisation rather than a reduction in the harder endpoints of death due to coronary artery disease or non-fatal MI.

Although the small cohort with diabetes included in the IONA trial did not show significant benefit, it is well established that patients with diabetes are high risk for coronary and vascular events, and thus benefit (reduction in cardiac chest pain requiring hospitalisation) may be implied, if not statistically proven.

### Conflict of interest statement

There are no conflicts of interest.

### References

1. 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; **359**: 1269–1275.
2. The SWAN Study Group. Comparison of the antiischaemic and antianginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris: the SWAN study. *J Clin Basic Cardiol* 1999; **2**: 213–217.
3. Zhu W-L, Shan Y-D, Guo J-X, *et al*. Double-blind, multicenter, active-controlled, randomized clinical trial to assess safety and efficacy of orally administered nicorandil in patients with stable angina pectoris in China. *Circ J* 2007; **71**: 826–833.
4. IONA Study Group. Impact of nicorandil in angina: subgroup analyses. *Heart* 2004; **90**: 1427–1430.