

Interpreting the ACTION study – benefits in patients with stable angina and raised blood pressure

Despite advances in the clinical management of patients with stable coronary artery disease, many patients remain symptomatic, with angina as the most common symptom. In these patients, there are few long-term trial results on which further improvements in care can be based.

The ACTION trial using nifedipine GITS is the first long-term drug study to address treatment in this particular group of patients and to provide evidence for prolonged cardiovascular event-free survival. This strategic view of the independently conducted ACTION trial was presented to South African specialists at the SA Heart Congress by Dr Freek Verheugt, Head of the Department of Cardiology, University of Nijmegen, Netherlands.

Referring to much earlier studies aimed at evaluating the long-term benefits of surgical intervention in the treatment of stable angina patients, Dr Verheugt noted that CASS (Coronary Artery Surgery Study) could not show better survival between surgical and medical groups (who were then not on β -blockers, only nitrates). After seven years of follow-up, 87% of the patients assigned to surgical and 84% of those assigned to medical treatment were alive.¹

Neither could a more recent long-term outcome trial of coronary angioplasty versus modern medical treatment, RITA² (second Randomised Intervention Treatment of Angina), show a reduced risk of death or MI in this group of patients. Initially PTCA (percutaneous transluminal coronary angioplasty) was associated with improved anginal symptoms and exercise time, but these benefits were narrowed over the seven-year study period, mainly because of coronary interventions in medical patients with severe symptoms. The authors concluded that patients with stable CAD and angina can safely be managed with continued medical therapy, but percutaneous intervention is appropriate if symptoms are not controlled.

The ACTION trial in stable, symptomatic angina patients without any signs of clinical heart failure sought

to address the value of nifedipine GITS in patients with stable angina who required treatment.³ According to Dr Verheugt, the study was also designed to exclude any safety problem with this long-acting calcium channel blocker. The patients (7 665) included in the study were followed for a mean of 4.9 years. The clinical and risk profile of the patients is provided in Table I.

In 22% of patients in both the nifedipine and placebo arm, there was a past history of the use of calcium antagonists. Patients who were on these drugs

were placed on a two-week washout period prior to study entry. All patients were on anti-anginal drug therapy at study entry – 80% were also being treated with a β -blocker.

Results

- ‘The heart rate was significantly higher – 2 beats/min – not large, but significant’, Dr Verheugt noted.
- Systolic and diastolic blood pressure was effectively lowered and 50% of patients were normotensive within a year. ‘There was a rapid

TABLE I. CLINICAL AND RISK PROFILE OF PATIENTS IN ACTION

	<i>Nifedipine</i> (n = 3 825)	<i>Placebo</i> (n = 3 840)
<i>Demographics</i>		
Age (years)	63.5 (\pm 9.3)	63.4 (\pm 9.3)
Men	3 041 (80%)	3 043 (79%)
<i>Clinical features</i>		
History of myocardial infarction	1 974 (52%)	1 924 (50%)
With coronary revascularisation	944 (25%)	960 (25%)
Angiographic coronary artery disease, no myocardial infarction	1 222 (32%)	1 249 (33%)
With coronary revascularisation	766 (20%)	759 (20%)
Positive exercise or radionuclide test only	616 (16%)	646 (17%)
Significant lesions on coronary angiogram	2 632 (69%)	2 634 (69%)
Normal coronary angiogram	50 (1%)	48 (1%)
Part use of calcium antagonists	854 (22%)	823 (21%)
Current NYHA class II-III	1 756 (46%)	1 776 (46%)
Anginal attacks	3 544 (93%)	3 526 (92%)
History of peripheral cardiovascular disease	494 (13%)	491 (13%)
<i>Risk factors</i>		
Total cholesterol \geq 5.0 mmol/l	2 382 (62%)	2 433 (63%)
Body-mass index \geq 30.0 kg/m ²	849 (22%)	895 (23%)
Blood pressure \geq 140/90 mmHg	1 975 (52%)	2 002 (52%)
Diabetes mellitus	565 (15%)	545 (14%)

TABLE II. PATIENT TREATMENT AT STUDY ENTRY

	<i>Nifedipine</i> (n = 3 825)	<i>Placebo</i> (n = 3 840)
<i>Antianginal drug</i>		
β -blocker	3 032 (79%)	3 066 (80%)
Organic nitrate	2 157 (56%)	2 175 (57%)
Other vasodilator	158 (4%)	148 (4%)
Any of the above	3 755 (99%)	3 784 (99%)
<i>Lipid-lowering</i>		
Statin	2 409 (63%)	2 389 (62%)
<i>Blood-pressure lowering</i>		
ACE inhibitor	771 (20%)	792 (21%)
Angiotensin-II antagonist	90 (2%)	93 (2%)
Diuretic	432 (11%)	447 (12%)
<i>Other cardiovascular</i>		
Acetylsalicylic acid	3 293 (86%)	3 304 (86%)

action of nifedipine GITS in this trial', Dr Verheugt pointed out.

- Nifedipine was well tolerated and only showed normal side effects – peripheral oedema (4%) and headaches (1%).
- Addition of nifedipine GITS to conventional treatment of angina pectoris did not achieve additional benefits with regard to the primary end points, but a reduction in the need for coronary angiography and interventions in patients assigned to nifedipine was significant, particularly in the light of the CASS and RITA-2 studies. These studies had shown how many angina patients who were managed medically, required coronary intervention to deal with continuing severe symptoms. In RITA-2, 35.4% of the medical group required myocardial revascularisation: 15% in the first year and an annual rate of 3.6% after two years.

In conclusion, Dr Verheugt noted that ACTION has established the safety of nifedipine GITS in the treatment

of patients with stable angina pectoris who are already on conventional treatment. It offers these patients significant, prolonged cardiovascular event-free survival.

1. Killip T, *et al.* Coronary artery surgery study (CASS): a randomized trial of coronary bypass surgery. Eight years follow-up and survival in patients with reduced ejection fraction. *Circulation* 1985; **72**(6 Pt 2): V 102–109.

2. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, *et al.* Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003; **42**(7): 1161–1170.
3. Poole-Wilson PA, *et al.* Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomized controlled trial. *Lancet-online*. August 31, 2004.

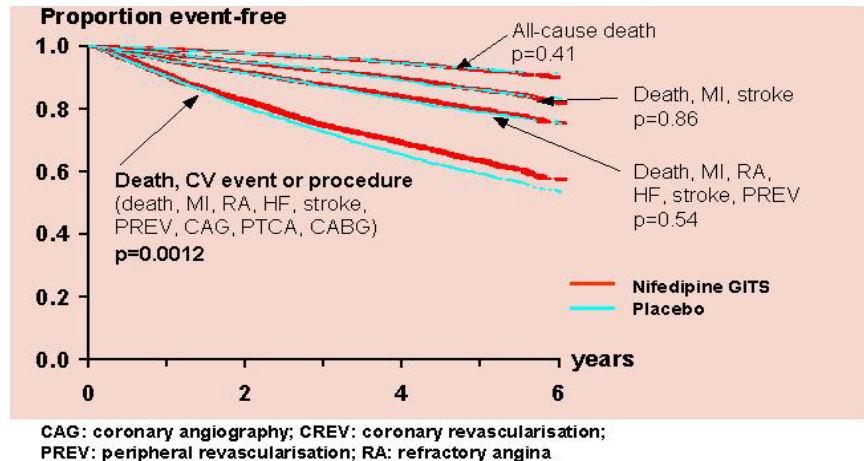


Fig. 1. Time to first occurrence of clinical events.