

# **ACTION**

## **A Coronary disease Trial Investigating Outcome with Nifedipine GITS**

### **Best evidence in class**

- ACTION – A Coronary disease Trial Investigating Outcome with Nifedipine GITS – is the first large-scale, long-term trial to assess clinical outcomes with an anti-anginal drug in patients with symptomatic stable angina.
- ACTION was a multicentre, randomised, placebo-controlled, double-blind, parallel group trial comparing the effects of long-acting nifedipine GITS with placebo in patients with coronary artery disease (CAD) who were already receiving the current standard of medical care.
- Patients were recruited between November and December 1996 and the study was completed in September 2003.

## Study design (1)

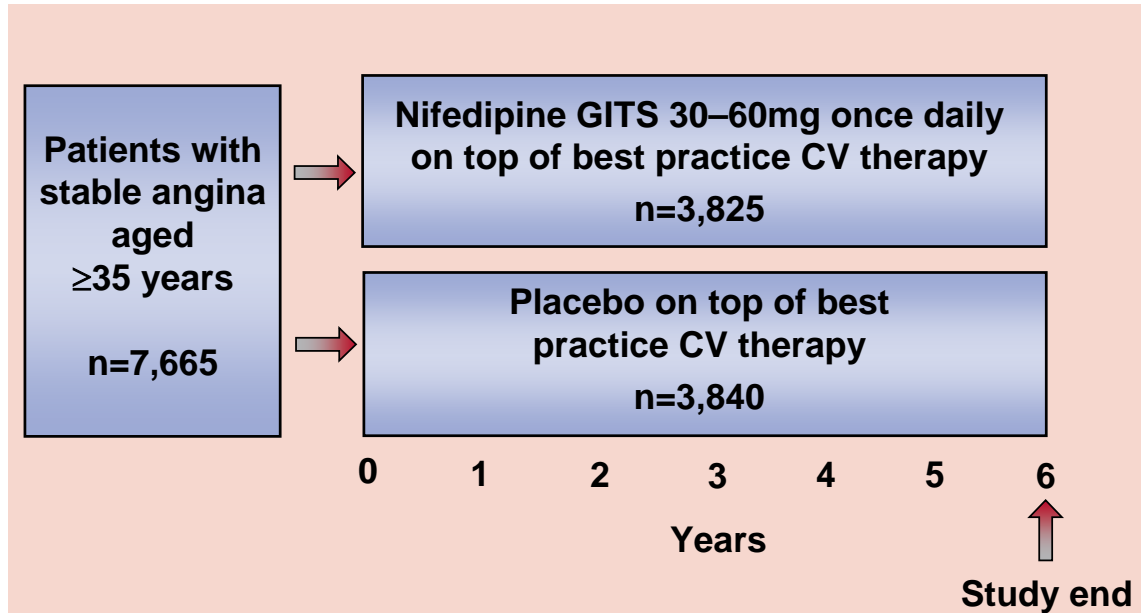
- First-ever randomised, placebo-controlled clinical outcome trial of an anti-anginal drug in patients with symptomatic stable angina pectoris
- Designed to assess the effects of nifedipine GITS on CV event-free survival
- Patients pre-treatment met best practice criteria at time of recruitment

- The findings of a meta-analysis, published in 1995,<sup>1</sup> raised concerns over the long-term safety of short-acting calcium channel blockers (CCBs) and established the need for well-designed long-term trials.
- This led to the inception of the ACTION trial – to date, the only large-scale and long-term trial of anti-anginal therapy examining the effects of a long-acting CCB on clinical outcomes in patients with stable angina.
- The primary objective of ACTION was to assess, relative to placebo, the effect of nifedipine GITS on the cardiovascular (CV) event-free survival of patients who were otherwise receiving optimal treatment for stable angina.
- Patients in ACTION were required to have at least one of the following:<sup>2</sup>
  - A history of myocardial infarction (MI) with angina
  - A previous coronary revascularisation procedure, but persistent angina
  - Angina due to CAD, with no history of MI or revascularisation, but a positive exercise test.

1. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326–31.

2. Lubsen J, Poole-Wilson PA, Pocock SJ, et al. Design and current status of ACTION: A Coronary disease Trial Investigating Outcome with Nifedipine GITS. *Eur Heart J* 1998;19(suppl I):120–32.

## Study design (2)



- Study medication, which was additional to ongoing medical therapy for CAD, consisted of either nifedipine GITS or placebo. The starting dose was 30mg once daily, which was titrated to 60mg once daily within 6 weeks if well tolerated. Study medication was continued at this dose until the end of the trial (i.e., at least 4 years for the last patient started on study medication).<sup>1</sup>
- The aim was to maintain patients on study medication for as long as possible; therefore, dose reduction or interruption was allowed.
- After the start of study medication, all patients continued to receive the concomitant treatment regimen on which they had been previously stabilised.
- Other CCBs could not be combined with study medication.

1. Lubsen J, Poole-Wilson PA, Pocock SJ, et al. Design and current status of ACTION: A Coronary disease Trial Investigating Outcome with Nifedipine GITS. *Eur Heart J* 1998;19(suppl I):120–32.

# Additional proof of nifedipine GITS' dual mode of action

## Vascular protection

- 21% reduction in CABG
- 18% reduction in coronary angiography
- 14% reduction in refractory angina\*

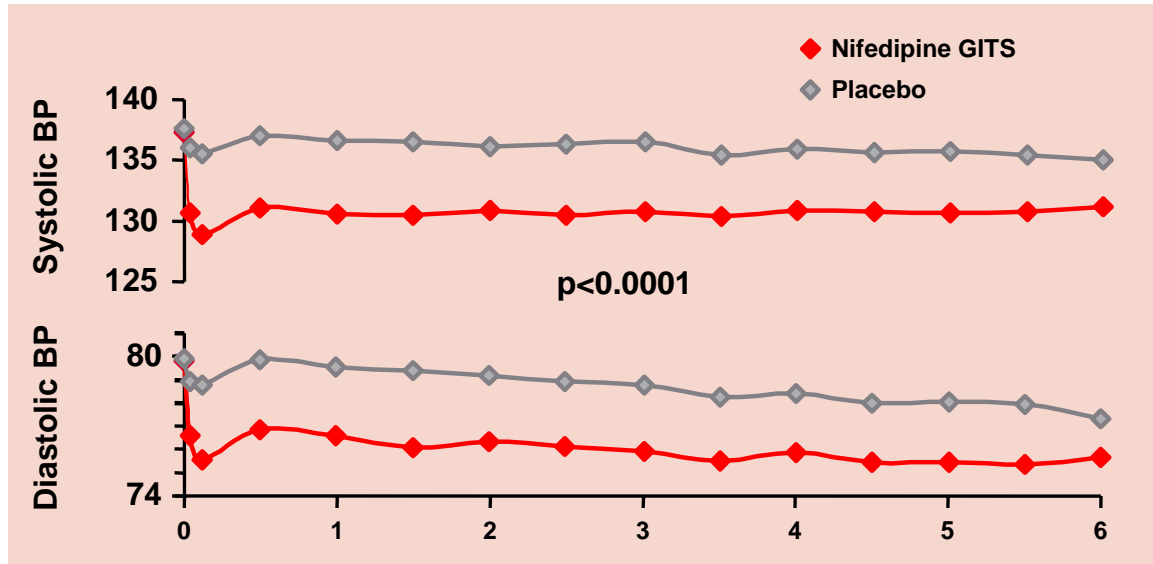
## BP lowering

- 29% reduction in new heart failure
- 22% reduction in debilitating stroke\*

\*Not statistically significant

- Nifedipine GITS works through its combined BP lowering and vascular-protective effects.
- **BP lowering:**
  - The incidence of overt HF was significantly reduced by 29% with nifedipine GITS.
  - Nifedipine GITS reduced the incidence of stroke by 22%, which was expected as significant BP lowering was achieved. The stroke definition was very stringent (debilitating with clinical signs and functional impairment present 30 days after onset of symptoms or death within 30 days), which affected the number of reported cases and likely explains why significance was not achieved.
- **Vascular protection:**
  - Nifedipine GITS was associated with a significant reduction in the need for coronary interventions such as CABG and coronary angiograms – a positive finding for patients, as quality of life is improved, and also the healthcare system, as a reduction in revascularisation procedures has serious cost-saving implications
  - Reduction in the need for coronary angiograms is an indicator of the anti-anginal effect of nifedipine GITS, resulting in relief from anginal pain and reduced atherosclerosis progression. This finding confirms the vascular-protective effects of nifedipine GITS
  - Treatment with nifedipine GITS was associated with a reduction in the incidence of refractory angina, although this did not achieve statistical significance. Development of refractory angina is a measure of disease progression, but more importantly, it is associated with an increased risk of progression to unstable angina or MI.

# Nifedipine GITS provides additional BP control on top of optimal treatment



- In addition to concomitant antihypertensive treatment, nifedipine GITS further reduced both mean systolic and diastolic BP by 6/3mmHg ( $p < 0.0001$ ) relative to placebo.
- The BP lowering achieved with nifedipine GITS in ACTION was similar to the overall BP reduction reported in the EUROPA study; however, there is evidence that the real BP effects are larger in EUROPA than described in the study.
- BP reduction with nifedipine GITS was rapid and sustained throughout the study period.
- The difference in BP levels between the two treatment groups is conclusive evidence that nifedipine GITS provides excellent BP control, and that standard intervention was not optimal for this group of CAD patients.

## Summary

- A unique study due to its design, size and scientific validity
- Proven safety and improved outcomes on top of best practice treatment:
  - **11% additional risk reduction\***
- Adding even more for hypertensive patients:
  - **13% additional risk reduction in optimally treated patients†**

\*Primary endpoint and interventions; †Primary endpoint

- ACTION is a unique study due to its robust design, large size and scientific validity.
- ACTION has established the safety of nifedipine GITS in the treatment of patients with stable angina who were already receiving optimal therapy.
- Nifedipine GITS significantly improved clinical outcomes and provided an additional 11% risk reduction on top of current optimal therapy.
- Nifedipine GITS provided even greater benefit to hypertensive patients with an additional 13% relative risk reduction in CV events.
- In conclusion, nifedipine GITS can be used safely for the long-term treatment of patients with coronary heart disease and angina as it prolongs CV event- and procedure-free survival.

# **ACTION**

**A** Coronary disease **Trial** Investigating  
**O**utcome with **N**ifedipine GITS

**Nifedipine GITS reduces  
the incidence and impact of CV events  
and coronary interventions through  
its combined BP lowering and  
vascular-protective effects**