The ACTION, EUROPA and IONA trials: similarities, differences, outcomes and expected outcome

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Abstract

The ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) study is the largest ever performed randomised trial of an anti-anginal drug in patients with chronic stable angina. Its aim is to assess the effect of nifedipine GITS 60 mg versus placebo on standard therapy for coronary artery disease on event-free survival; its composite end point includes death from any cause, acute myocardial infarction, hospitalisation for overt heart failure, emergency coronary angiography, disabling stroke and procedures for peripheral revascularisation.

ACTION is one in a series of trials assessing drug effects in chronic stable coronary artery disease. The IONA (Impact Of Nicorandil in Angina) and EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary artery disease) studies demonstrated that the K-ATP channel activator nicorandil and the angiotensin-converting enzyme inhibitor perindopril reduced the primary composite end point for cardiac events by 17% and 20%, respectively.

Nifedipine GITS is an effective antihypertensive and anti-anginal drug. In the INSIGHT trial, nifedipine GITS 30/60 mg demonstrated comparable outcomes to a diuretic combination therapy with significant effects on intermediate end points. ENCORE I (Evaluation of Nifedipine and Cerivastatin on Recovery of coronary Endothelial function) demonstrated that nifedipine GITS 30/60 mg positively affected the pathophysiology of coronary artery disease. We therefore anticipate that nifedipine will affect blood pressure, anginal symptoms and resulting complications, and the coronary atherosclerotic process in those patients randomised to receive this agent in the ACTION study.

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Introduction

Nitrates, beta-blockers and calcium channel blockers have been used as anti-anginal drugs in patients with coronary artery disease (CAD) for decades.[1] Historically, their main goal has been the reduction of anginal pain. In addition, aspirin, angiotensin-converting enzyme (ACE) inhibitors and statins reduce the risk for cardiovascular events in subgroups of patients with stable angina.[2-5] The recently published EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) and IONA (Impact Of Nicorandil in Angina) studies addressed the long-term outcomes in patients with coronary artery disease and demonstrated significant improvements in reducing major cardiovascular events with the use of the ACE inhibitor perindopril (8 mg once-daily) and the K-ATP channel activator nicorandil (20 mg twice-daily) when compared with placebo.[6,7] These publications have marked a new era of studies addressing the long-term safety of several drugs of different classes in this patient population.

The ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) study using slow-release nifedipine GITS (60 mg once-daily) is the largest ever performed, randomised, placebo-controlled clinical trial of an anti-anginal drug in patients with chronic stable angina.[8] This study addresses the on-going issue of the long-term safety of calcium channel blockers, which remains unresolved because of a lack of data from well-designed long-term trials.

This article focuses on similarities and differences between the ACTION, IONA and EUROPA trials and gives an outlook on what results might be expected from ACTION, which is due to report in 2004. The on-going PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibition trial), which is assessing the effects of ACE inhibition in patients with CAD and preserved left ventricular function, has not been considered since this is not due to report until 2004.

Patient exposure

The IONA and EUROPA trials randomised more than 5,126 and 12,218 patients with about 8,200 and 51,315 patient years of exposure to study drug, respectively. The ACTION trial has ran-

Table 1. Main inclusion criteria

ACTION	IONA	EUROPA
History of MI or coronary revascularisation with current stable angina Angina due to CAD without history of MI or revascularisation LVEF ≥ 40%	Stable angina and additional risk factors (e.g. impaired LV systolic function, LV hypertrophy, diabetes mellitus, hypertension)	CAD documented by previous MI, PTCA, stenosis CABG, ≥ 70% of one or more coronary arteries

Key: MI = myocardial infarction; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft

Table 2. Composite end points as primary efficacy variables

ACTION	IONA	EUROPA
Death from any cause	CAD death	CV death
Acute MI	Non-fatal MI	Non-fatal MI
Emergency coronary angiography for refractory angina	Unplanned hospital admission for cardiac chest pain	Cardiac arrest with successful resuscitation
Hospitalisation for overt heart failure		
Disabling stroke		
Peripheral revascularisation		

Key: MI = myocardial infarction; CAD = coronary artery disease; CV = cardiovascular disease

Table 3. Selected demographic and risk factor information

ACTION	IONA	EUROPA
Males 79%	Males 76%	Males 85%
Median age 64 years	Mean age 67 years	Mean age 60 years
Previous MI or revascularisation 70%	Previous MI 66%	Previous MI 65%
Hypertension 40%	CABG 23%	Revascularisation 55%
Diabetes mellitus 14%	PTCA 15%	Hypertension 27%
At least one risk factor 45%	Hypertension 47%	Hypercholesterolaemia 63%
Diabetes mellitus 9%	Smokers 17%	Diabetes mellitus 12%

Key: MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft

domised 7,669 patients with an expected 38,345 patient years of treatment and a mean follow-up period of five years, the longest of all three studies. PEACE has randomised 8,100 patients with an intended mean follow-up of five years thus accumulating some 45,000 patient years of follow-up.

Inclusion criteria

In the ACTION and IONA trials, the presence of stable angina with or without a history of myocardial infarction (MI) was a prerequisite for study participation. Patients were eligible for inclusion in the EUROPA trial if they had CAD documented by a previous MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG) or a ≥ 70% stenosis of one or more coronary arteries. The IONA study allowed the inclusion of patients with left ventricular (LV) dysfunction, whereas this condition was an exclusion criterion in the ACTION and EUROPA studies (table 1).

Primary end point and risk factors

All trials used composite end points as their primary efficacy variable (see table 2). Besides all-cause mortality, the composite ACTION end point may also be considered 'cardiovascular event-free survival', since – in contrast to IONA and EUROPA – it also includes cerebrovascular and peripheral vascular events. Table 3 summarises selected demographic and risk factor information for all three studies.

IONA outcome

The IONA trial demonstrated a significant improvement in outcome (HR 0.83, 95% CI 0.72, 0.96; p=0.014) with the anti-anginal nicorandil compared to placebo in patients with stable angina.[7] (This was given in addition to their usual anti-anginal therapy.) Event rates in all the primary end point components were lower in patients on nicorandil compared to placebo, each contributing to the significance of the primary end point. Total mortality, however, was unaffected. The study was underpowered to show statistical significance with regard to the secondary endpoints: CAD mortality and non-fatal MI.

It is suggested that the beneficial effects of nicorandil on outcome were mediated through disease modification, although the mechanisms remain unclear. The most plausible explanation is that nicorandil acts as a pharmacological mimetic of ischaemic preconditioning resulting in cardioprotective effects.[9,10] Since the benefit was observed when the drug was added to usual anti-anginal therapy (nitrates in most patients), the IONA results suggest that there is a likelihood that its clinical benefits are related to activation of mitochondrial K-ATP channels.[11]

EUROPA outcome

The EUROPA study showed a significant benefit with perindopril in a broad population of patients with stable CAD (HR 0.80, 95%CI 9–29; p=0.0003) versus placebo. The findings confirm the reduction in MI seen with ACE inhibitors which was shown in earlier studies in patients with congestive heart failure (CHF) or LV dysfunction.[12,13] The study also extends the observations of the

HOPE (Heart Outcomes Prevention Evaluation) study in which cardiovascular events were reduced with ACE inhibition in high-risk patients with CAD.[2] Although the high-risk level in EUROPA was slightly lower than that in the HOPE study, the relative risk reductions for MI and cardiovascular death were similar (HOPE 21%, EUROPA 20%). Benefits were in addition to other preventive measures, including aspirin, beta blockers and lipid-lowering drugs, and were consistent for all patients.

ACE inhibitors modulate the atherosclerotic process by inhibiting angiotensin II formation and reducing bradykinin breakdown.[14-21] ACE inhibitors are therefore likely to maintain endothelial function and counteract initiation and progression of atherosclerosis. There are quantitative differences among ACE inhibitors: tissue ACE inhibitors (such as ramipril and perindopril) are highly lipophilic and have strong enzyme-binding capabilities which may enable them to have greater penetration into the atherosclerotic plaque.[6] Since there was a similar treatment effect among patients with treated hypertension and those without hypertension, perindopril may have, in addition to its blood pressure-lowering effects, specific anti-atherosclerotic actions.

Expected outcome of ACTION

The INSIGHT study has confirmed that nifedipine GITS 30/60 mg effectively controls high blood pressure and reduces the relative risk for cardiovascular events by 35%.[22] INSIGHT side-arm studies and the recently published ENCORE (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function) study provide further evidence that nifedipine may have additional beneficial effects, including regression of coronary calcification, prevention of intima-media thickening and improvement of endothelial function.[23-25]

Lowering blood pressure is likely to benefit patients at increased risk of cardiovascular disease as was observed in hypertensive patients in INSIGHT. Normotensive patients in ACTION may also gain similar benefits from nifedipine's blood pressure-lowering effects.

The vascular protective effects observed in INSIGHT[22] and ENCORE[25] will possibly translate into clinical benefits in the CAD population in the ACTION study. It is anticipated that no clinically significant differences in the safety profile between nifedipine and placebo will be seen.

When interpreting the study results, it will be important to consider whether these can be explained solely by reductions in blood pressure. The risk of cardiovascular events starts to increase at blood pressures over 115/75 mmHg so, by reducing blood pressure in the ACTION patient population, it is hoped that the risk of cerebrovascular disease will also be reduced.[26] The predicted systolic blood pressure reduction in ACTION with nifedipine GITS treatment is 3–4 mmHg; this reduction corresponded to an 8% reduction in cardiovascular mortality in a previous study.[27]

Using the European Society of Hypertension/European Society of Cardiology guidelines, most patients in the ACTION study are classified as 'high risk' or 'very high risk' and are therefore recommended for antihypertensive therapy.[28] Their average baseline blood pressure was 138/86 mmHg, 40% were on treatment for hypertension or had a history of hypertension, and 36% had a blood pressure > 140/90 mmHg. It is anticipated that the predicted reduction in blood pressure in the ACTION trial will translate into benefits in reducing cardiovascular events.

Although the main benefits of antihypertensive therapy are attributed to their blood pressure lowering, different drug classes may differ in other effects, such as their efficacy in different subpopulations, their tolerability and adverse effect profiles. Such effects may influence treatment decisions and point towards a more individualised approach being adopted in the management of hypertensive patients, particularly those at additional cardiovascular risk from diabetes, CAD or post-MI.

If ACTION does show a trend towards reduced MI or angina, this will provide crucial evidence that the vasculo-protective qualities of nifedipine (i.e. the reduced intima-media thickness and coronary calcification seen in INSIGHT, and the improved endothelial function seen in ENCORE) result in actual clinical benefits in the long term.

ACTION will also look at cerebrovascular events. INSIGHT and ALLHAT have already demonstrated the advantage of calcium channel blockers over diuretics in reducing stroke in hypertensive patients and it is hoped that ACTION will provide evidence for the efficacy of nifedipine GITS at reducing stroke in this higher risk CAD patient population.

Key messages

- ACTION is the largest ever performed randomised trial of an anti-anginal drug in patients with chronic stable angina
- It has randomised 7,669 patients with coronary artery disease to nifedipine GITS 60 mg or placebo on standard therapy to assess the effect on event-free survival; mean follow-up is five years
- ACTION is one of four studies to assess drug effects in chronic stable coronary artery disease. IONA and EUROPA demonstrated that the K-ATP channel activator, nicorandil, and the ACE inhibitor, perindopril, reduced cardiac events by 17% and 20% respectively

Summary

ACTION is the largest ever performed randomised trial of an anti-anginal drug in patients with chronic stable angina. The study aims to assess whether nifedipine GITS 60 mg compared with placebo on standard therapy for CAD results in more event-free survival – its composite end point includes death from any cause, acute MI, hospitalisation for overt heart failure, emergency coronary angiography, disabling stroke and peripheral revascularisation procedures. ACTION has randomised 7,669 patients who have been followed-up for a mean of five years. The study was

completed in September 2003 and results will be presented at this year's 26th meeting of the European Society of Cardiology.

ACTION is one in a series of four trials assessing drug effects in chronic, stable CAD. Two of these studies, IONA and EUROPA, have demonstrated that the K-ATP channel activator, nicorandil, and the ACE inhibitor, perindopril, reduced the primary composite end point for cardiac events by 17% and 20%, respectively. The fourth study, PEACE, is the second trial with ACE inhibitors as a preventive strategy to reduce the incidence of cardiovascular death, non-fatal MI, or revascularisation procedures in more than 8,000 patients with stable CAD. This will also report in 2004.[29]

Nifedipine GITS is an effective antihypertensive and anti-anginal drug. With the INSIGHT trial, nifedipine GITS 30/60 mg demonstrated comparable outcomes as a diuretic combination therapy with substantial effects on intermediate end points. ENCORE I demonstrated that nifedipine GITS 30/60 mg positively affected coronary artery disease pathophysiology. Thus we anticipate that nifedipine will affect blood pressure, anginal symptoms and resulting complications, and the coronary atherosclerotic process in patients randomised in ACTION.

Conflict of interest

HJK is a principal investigator in the ACTION study and a member of the steering committee. GW is a non-voting member of the ACTION steering committee. The ACTION study was funded by Bayer.

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