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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Effects of Long-acting Calcium Channel Blockade on Cardiovascular Outcomes in Patients with Stable Angina Pectoris: The ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) Trial

Originally presented by: Philip A. Poole-Wilson, MD

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Reported and discussed by:
GORDON MOE, MD

The calcium channel blockers (CCBs) are effective agents for lowering blood pressure (BP) in patients with hypertension and for symptom relief of angina pectoris in patients with stable coronary artery disease (CAD). Earlier studies, predominantly involving short-acting CCBs, raised concerns regarding the safety of these agents. Therefore, the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) study was a large, long-term trial designed to assess the impact of a long-acting dihydropyridine CCB – nifedipine gastrointestinal therapeutic system (nifedipine GITS) – on cardiovascular outcomes in patients with stable angina pectoris. Results of the ACTION study, which were recently presented and published, is reviewed in this issue of *Cardiology Scientific Update*.

The long-acting CCBs are effective agents in the symptomatic treatment of patients with chronic angina pectoris.[1] However, previous observational studies, as well as a meta-analysis of short-term trials involving primarily the short-acting CCBs, raised concerns about the increased risk of coronary events and mortality associated with the use of these agents.[2,3] However, there has also been a general belief that the detrimental effects reported in these small observational studies and meta-analyses may not necessarily apply to the long-acting CCBs.[4] Accordingly, a large and long-term clinical trial to assess the effect of long-acting CCBs on cardiovascular outcomes in patients with hypertension and/or CAD was warranted.

ACTION was a multicentre, randomized, placebo-controlled, double-blind trial designed to compare the effect of a widely-prescribed long-acting dihydropyridine CCB, nifedipine GITS, or placebo on cardiovascular (CV) clinical outcomes in patients with CAD manifested as stable angina pectoris. Details of the trial design have been published previously.[5] Briefly, patients who were aged ≥35 years, had stable symptoms of angina pectoris for at least 1 month, and who required oral and transdermal treatment to control anginal symptoms, were eligible for recruitment. Patients were recruited if they had one of the following criteria: a history of myocardial infarction (MI); angiographically documented CAD in the absence of a history of MI; a positive exercise test or perfusion study in the absence of a history of MI and angiographic CAD.

In addition, left ventricular (LV) ejection fraction (EF) had to be ≥40%. The key exclusion criteria included clinically overt heart failure, a major CV event or intervention within 3 months, and planned coronary angiography and intervention. In addition to their baseline therapy, patients were randomized to placebo or oral nifedipine GITS beginning with 30 mg daily and increasing to 60 mg daily within 6 weeks, if tolerated. The primary composite efficacy endpoint (major CV event-free survival) was defined as time to the first event of one of the following: death from any cause; acute MI; hospitalization for new overt heart failure; refractory angina; emergency coronary angiography for refractory angina; disabling stroke; peripheral revascularization procedures.

The primary composite endpoints for safety, for the purpose of interim analysis, were combined death, MI, and disabling stroke. Secondary predefined outcomes were any CV event; any death, CV event, or procedure; and any vascular event or procedure.

Results

The results of the ACTION study were recently presented and published.[6] Between November 1996 and December 1998,

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: Baseline characteristics

	Nifedipine (n = 3825)	Placebo (n = 3840)
Mean age (years)	63.5	63.4
Male (%)	80	79
History of MI (%)	52	50
– With coronary revascularization	25	25
Angiographic CAD, no MI (%)	32	33
– With coronary revascularization	20	20
Positive stress test only (%)	16	17
Significant lesions on angiography (%)	69	69
Peripheral vascular disease (%)	13	13
Angina attacks (%)	93	92
Diabetes mellitus (%)	15	14
BP ≥140/90 mm Hg	52	52
Total cholesterol ≥5.0 mmol/L	62	63
Mean systolic BP (mm Hg)	137.3	137.6
Mean ejection fraction, local values (%)	56.6	57.8
ß-blockers (%)	79	80
Lipid-lowering therapy (%)	68	67
Aspirin (%)	86	86
ACE inhibitors (%)	20	21

7665 patients were recruited and randomized from 291 centres in 19 countries across Europe, Australia, Israel, South Africa, and Canada. Selected key baseline characteristics, including concomitant medications, are summarized in Table 1. The two study groups were comparable at baseline. Over 80% were men and almost all patients had anginal symptoms. Over half of the patients had hypertension based on contemporary definitions. Approximately 80% were on ß-blockers and substantial proportions were on antiplatelet and lipid-lowering therapy.

Follow-up of randomized patients was 97% complete. The effects of the study medications on heart rate and BP are shown in Figure 1. Relative to placebo, patients assigned nifedipine

Figure 1: Heart rate and blood pressure

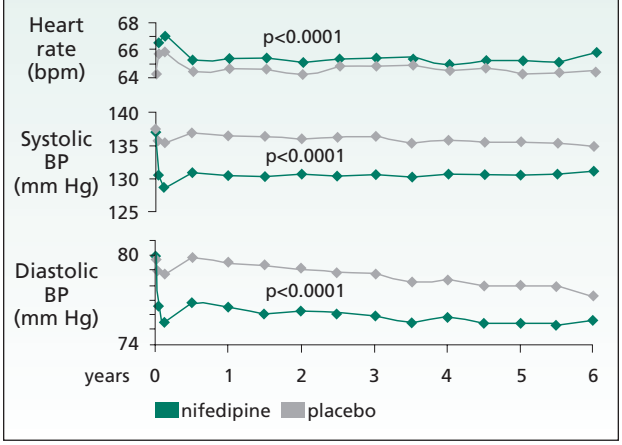
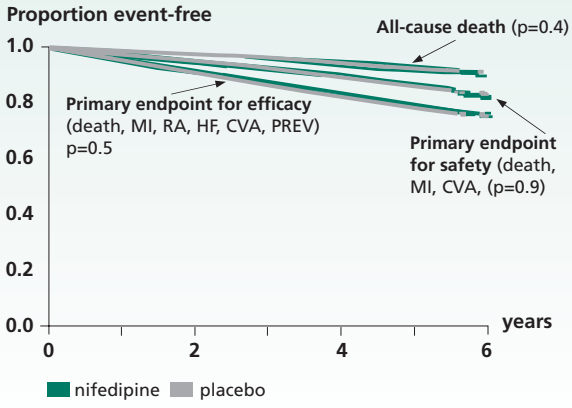


Figure 2: Primary outcomes and mortality



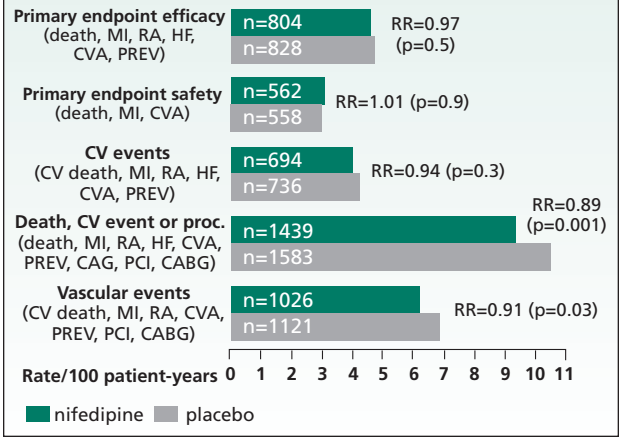
MI, myocardial infarction; RA, refractory angina; HF, heart failure; CVA, cerebral vascular accidents; PREV, peripheral vascular revascularization

experienced a small increase in heart rate (mean difference 1 beat per minute). Relative to placebo, treatment with nifedipine was associated with significant reductions in systolic and diastolic BP, averaging 6 mm Hg and 3 mm Hg, respectively. At baseline, the percentage of patients with a BP >140/90 mm Hg was 52%. During follow-up, this percentage averaged 35% for patients assigned to nifedipine, and 47% for those assigned to placebo.

Primary endpoints

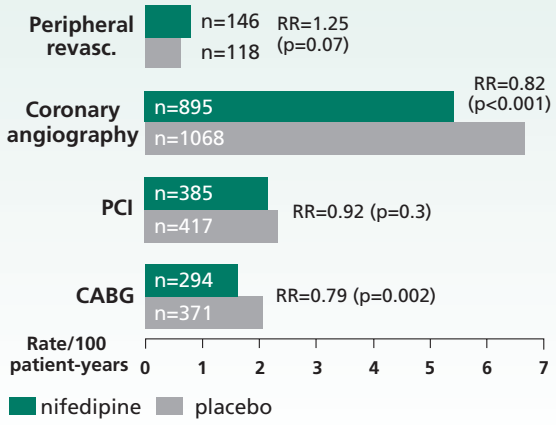
Results of the primary composite endpoints for the purpose of interim analysis, were combined (Figure 2). There were no differences between nifedipine and placebo on any of these outcomes. Three hundred and ten patients randomized to nifedipine and 291 allocated to placebo died; of these, 103 deaths in the nifedipine group and 97 in the placebo group occurred while the patient was on the study drug. Cardiovascular (including

Figure 3: Primary and secondary composite endpoints



MI = myocardial infarction; RA = refractory angina; HF = new overt heart failure; CVA = disabling stroke; PREV = peripheral revascularization; CV = cardiovascular; CAG = coronary angiogram; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

Figure 4: Cardiovascular procedures



cause unknown) and non-CV death rates were similar between the treatment groups.

Secondary endpoints

Results of the pre-defined secondary composite endpoints are summarized in Figure 3, together with the primary composite endpoints, but expressed in a different format than in Figure 2.

Table 2: All pre-defined clinical events

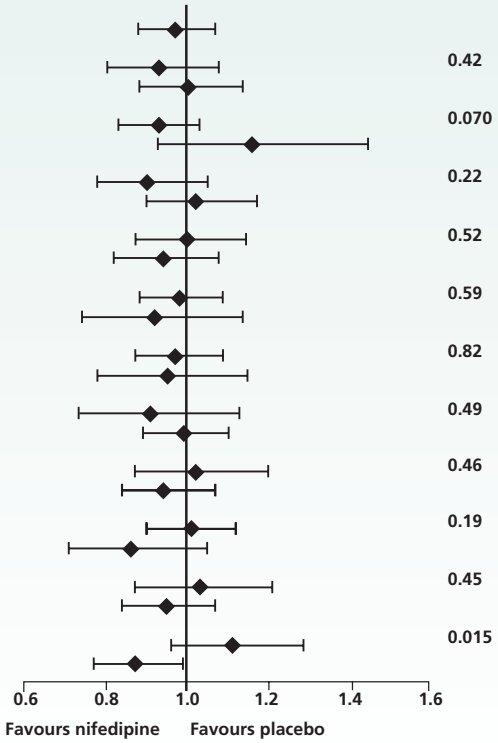
	Nifedipine (n=3825)	Placebo (n=3840)	RR (95% CI)
All death	310 (1.64)	291 (1.53)	1.07 (0.91-1.24)
CV death	178 (0.94)	177 (0.93)	1.01 (0.82-1.24)
Non-CV	132 (0.70)	114 (0.60)	1.16 (0.90-1.49)
MI	267 (1.46)	257 (1.39)	1.04 (0.88-1.24)
Refractory angina	150 (0.81)	174 (0.94)	0.86 (0.69-1.07)
New overt HF	86 (0.46)	121 (0.65)	0.71 (0.54-0.94)*
Debilitating stroke	77 (0.41)	99 (0.53)	0.78 (0.58-1.05)

RR = relative risk; CI = confidence interval; CV = cardiovascular; HF = heart failure; MI = myocardial infarction *p<0.05

Compared to placebo, nifedipine GITS had a statistically significant favourable effect on the composite endpoints of any death, CV event, or procedure, and on all vascular events combined. Data for CV procedures, which made up important components of the secondary composite endpoints, are shown in Figure 4. Nifedipine GITS had a statistically significant effect on both the need for coronary angiography and coronary bypass graft surgery (CABG). All pre-specified clinical events, which

Figure 5: Primary efficacy endpoint in predefined sub-groups

	Number of patients Nifedipine/placebo	Number of patients with event (rate) Nifedipine/placebo	p-value
All	3825/3840	804 (460)/828 (4.75)	
Age (years)			
<65	2053/2064	337 (3.52)/362 (3.79)	0.42
≥65	1772/1776	467 (5.93)/466 (5.90)	
Sex			
Men	3041/3043	638 (4.59)/681 (4.95)	0.070
Women	784/797	166 (4.66)/147 (4.00)	
History of MI			
No	1851/1916	345 (4.01)/388 (4.43)	0.22
Yes	1974/1924	459 (5.18)/440 (5.06)	
History of coronary revasc.			
No	2115/2121	418 (4.32)/420 (4.32)	0.52
Yes	1710/1719	386 (4.96)/408 (5.29)	
Diabetes			
No	3260/3295	640 (4.25)/658 (4.34)	0.59
Yes	565/545	164 (6.81)/170 (7.42)	
Past use of CCBs			
No	2971/3017	596 (4.39)/620 (4.51)	0.82
Yes	854/823	208 (5.34)/208 (5.63)	
On ß-blockade at entry			
No	793/774	154 (4.28)/166 (4.72)	0.49
Yes	3032/3066	650 (4.69)/662 (4.75)	
On lipid-lowering drugs at entry			
No	1218/1249	296 (5.50)/297 (5.39)	0.46
Yes	2607/2591	508 (4.21)/531 (4.45)	
On ACE inhibitor or ARB at entry			
No	2966/2960	620 (4.56)/615 (4.53)	0.19
Yes	859/880	184 (4.76)/213 (5.50)	
Ejection fraction (%)			
<45	1056/1074	284 (602)/281 (5.86)	0.45
≥45	2749/2744	517 (4.08)/541 (4.31)	
SBP ≥140 mm Hg or DBP ≥90 mm Hg			
No	1847/1837	364 (4.28)/328 (3.84)	0.015
Yes	1975/2002	439 (4.90)/500 (5.61)	



ARB = angiotensin II receptor blocker

formed the components of either the primary or secondary composite endpoints, are shown in Table 2. Overt heart failure was the only clinical event that was reduced by nifedipine. Therefore, given the lack of a difference in mortality and CV events, the favourable effect of nifedipine on the aforementioned secondary composite endpoints was driven by the favourable effect on coronary angiography and the need for CABG, and to a lesser extent by the reduced incidence of new-onset heart failure.

Analysis of predefined subgroups for the primary efficacy endpoint is shown in Figure 5. Among the subgroups, only BP level appeared to influence the effect of nifedipine (*p* for interaction = 0.02). In patients with systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, the noted incidence of primary endpoints for efficacy with nifedipine was less than for placebo.

In general, nifedipine was well tolerated; at 6 weeks, 88% of patients allocated to nifedipine and 92% assigned to placebo were on the full dose. Study drugs were taken for 79% of total follow-up time by individuals randomized to nifedipine and for 82% of follow-up time for those allocated to placebo. In 389 nifedipine patients and 172 placebo patients, the reason for permanent withdrawal was occurrence of an adverse event; the most frequent events were peripheral edema (139 nifedipine, 20 placebo) and headache (43 nifedipine, 20 placebo).

Comments

Results of the primary outcomes in ACTION indicate that nifedipine GITS, a widely-prescribed long-acting dihydropyridine CCB, has neutral effects on CV outcomes in stable patients with symptomatic CAD. One explanation for this neutral effect is the lack of effect of nifedipine on plaque volume. The Evaluation of Nifedipine and Cerivastatin On Recovery of Coronary Endothelial function (ENCORE II) study – presented at the same late breaking-trial session – confirmed that while nifedipine improves endothelial function, it does not have a major effect on plaque volume. The improvement in endothelial function would be expected to result in a reduction in revascularization procedures (as demonstrated in the ACTION trial), but the lack of an effect on plaque may explain why no reduction in MI was seen in the ACTION trial.[7] In the ACTION patient population (ie, patients with stable CAD, half were normotensive with the majority already treated with ß-blockers, lipid-lowering and antiplatelet therapy), the use of nifedipine GITS was safe. This observation is consistent with previous observations in hypertensive populations of the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study where nifedipine GITS had a similar impact on clinical outcomes as hydrochlorothiazide and amiloride[8] and, more recently, in the Heart Attack Trial (ALLHAT). In ALLHAT, amlodipine, another long-acting dihydropyridine CCB, exerted similar effects on clinical outcomes as chlorthalidone and lisinopril.[9] A similar lack of adverse effect from treatment with a long-acting CCB was also reported in patients with severe heart failure and reduced ejection fraction.[10] Taken together, the use of nifedipine GITS and other long-acting CCBs should be considered reasonably safe across a broad spectrum of patients with CV disease. The current data thus refute previous observations of detrimental effects from short-acting CCBs.[3,11-13] Indeed, the differential effects of short- versus long-acting CCBs on mortality in the hypertensive population have been suggested by a previous nested case-control study.[14]

In ACTION, the need for coronary angiograpy and CABG was reduced by nifedipine. These data are consistent with observations from the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) conducted in patients with stable angiographically-documented CAD where amlodipine also reduced the need for revascularization.[15] One unexpected observation in ACTION was the significant 29% reduction in new-onset heart failure by nifedipine GITS. The reason for this observation is unclear although one cannot rule out the possibility that this represents a finding by chance. This observation adds to the reassurance of the safety of nifedipine GITS with regard to heart failure, at least in patients with preserved systolic function.

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