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Safety of Nifedipine in Angina Pectoris

A Meta-Analysis

William B. Stason, Christopher H. Schmid, Donna Niedzwiecki, Gregory W. Whiting, Jean-Francois Caubet, Douglas Cory, Don Luo, Susan D. Ross, Thomas C. Chalmers†

Abstract—Our objective was to compare cardiovascular event rates in patients with stable angina receiving nifedipine as monotherapy or combination therapy and in active drug controls. A MEDLARS search of published articles from 1966 to 1995 in English, French, German, Italian, or Spanish, supplemented by a manual search of bibliographies, identified 60 randomized controlled trials that met protocol criteria. Blinded articles were extracted by 2 physicians. The pooled risks of death, withdrawal, and cardiovascular event were computed and expressed as odds ratios (ORs) for all nifedipine formulations and relative to same study control drug regimens. Thirty cardiovascular events were reported in 2635 nifedipine exposures (1.14%) and 19 events in 2655 other active drug exposures (0.72%). Unadjusted ORs for nifedipine versus controls were 1.40 (95% CI, 0.56 to 3.49) for major events (death, nonfatal myocardial infarction, stroke, revascularization procedure), 1.75 (95% CI, 0.83 to 3.67) for increased angina, and 1.61 (95% CI, 0.91 to 2.87) for all events (major events plus increased angina). Episodes of increased angina were more frequent on immediate-release nifedipine (OR, 4.19 [95% CI, 1.41 to 12.49]) and on nifedipine monotherapy (OR, 2.61 [95% CI, 1.30 to 5.26]). The OR for immediate-release nifedipine was significantly higher than that for sustained-release/extended-release nifedipine ($P=0.001$), and the OR for nifedipine monotherapy was higher than that for nifedipine combination therapy ($P=0.03$). Increased risks of cardiovascular events in patients with stable angina on nifedipine were due primarily to more episodes of increased angina, confined to the immediate-release formulation and to nifedipine monotherapy. (*Hypertension*. 1999;33:24-31.)

Key Words: angina pectoris ■ meta-analysis ■ nifedipine ■ safety

Calcium channel blockers (CCBs), including nifedipine, are widely used in the management of chronic stable angina and are approved by the Food and Drug Administration as monotherapy for vasospastic angina and in combination with other drugs for angina due to coronary artery disease.

Two recent studies, however, have questioned the safety of CCBs in general and nifedipine in particular. A meta-analysis of randomized, controlled trials (RCTs) of nifedipine involving patients with myocardial infarction (MI) or unstable angina or patients with coronary artery disease who were undergoing coronary angiography concluded that the use of immediate-release (IR) nifedipine was associated with a significant, dose-related increase in mortality.¹ A case-control study of patients with hypertension enrolled in the Group Health Cooperative of Puget Sound reported that CCBs were associated with a statistically significant, dose-related increase in MI.² On the basis of these and other studies, the authors recommended against the use of CCBs in patients with acute coronary syndromes and for restricted use in hypertensive patients until results from ongoing, large-scale, clinical trials become available.³⁻⁶

To assess the safety of nifedipine in patients with stable angina pectoris participating in clinical trials, we performed a meta-analysis of published RCTs to examine rates of adverse cardiovascular events for (1) nifedipine compared with other active drugs; (2) nifedipine formulation effects (IR, sustained-release [SR], and extended-release [ER] formulations); and (3) nifedipine monotherapy compared with its combination with other drugs (combination therapy). Outcomes of interest were deaths, nonfatal MIs, nonfatal strokes, revascularization procedures during the study period, and episodes of increased angina. Other reasons for early withdrawals from trials were also examined. The results of a companion analysis of studies of hypertensive patients have been recently published.⁷ This report provides results in studies of stable angina patients.

Methods

This study used techniques for meta-analysis of RCTs described by Chalmers et al.⁸ A prospectively designed protocol defined the objectives, eligibility criteria for studies, key data elements to be extracted, and analytical methods to be used. To be included, a study had to be a published RCT that enrolled ≥ 10 patients with stable

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angina; that compared any nifedipine formulation, either as monotherapy or combination therapy, with a nondihydropyridine active drug or a placebo control for ≥ 1 week's duration; and that reported adverse clinical events by treatment group.

Studies were identified by a MEDLARS search that exploded the Medical Subject Heading term "myocardial ischemia" and searched for "nifedipine" as a text word. The search extended from 1966 through August 1995 and included articles in English, French, Italian, German, and Spanish languages. The Current Contents CD-ROM was searched independently. Computer-based searches were supplemented by manual searches of bibliographies of retrieved articles to detect other potentially acceptable studies. Two levels of study screening were used. First, studies that were obviously ineligible, such as animal studies, pharmacokinetic-pharmacodynamic studies, or those written in ineligible languages, were excluded. Second, 2 physician reviewers assessed studies (with Results sections blinded) for fit with the aforementioned study inclusion criteria.

A total of 1764 citations were thus identified, of which 62 were ultimately accepted for data extraction. The most common reasons for rejection at the second level screening were as follows: not an RCT ($n=21$); treatment < 1 week ($n=17$); adverse clinical events not reported or not assignable by study arm ($n=21$); < 10 patients ($n=5$); the only control drug was a dihydropyridine ($n=8$); preliminary report ($n=2$); and patient selection was made only after a successful nifedipine run-in ($n=2$).

Selected studies were blinded as to source, authors, and treatment groups and then were extracted independently by 2 investigators using a data extraction form. Details of treatment regimens were extracted from unblinded articles by a third reviewer. Extraction forms were subsequently compared, and discrepancies were resolved. In 2 studies, questions of interpretation arose with respect to the assignment of adverse events by study arm; in both cases, ambiguities could not be resolved, and the study was excluded. The same reviewers also assessed the quality of each study using the scoring systems of Chalmers⁹ and Jadad.¹⁰ All data were entered into Excel spreadsheets, verified, and downloaded for analysis with the use of SAS¹¹ software.

Deaths, nonfatal MIs, nonfatal strokes, and revascularization procedures that occurred during the study were unambiguous and classified as major cardiovascular events. Episodes of increased angina were variably defined (unstable angina, crescendo angina, angina at rest, or increased frequency or severity of chest pain) and therefore were analyzed separately and in combination with major events in analyses of all cardiovascular events.

Study withdrawals were classified as due to either adverse drug reactions (ADRs) or other causes. Withdrawals for ADRs included those for drug-related symptoms, such as edema or headache, as well as the aforementioned cardiovascular events. Withdrawals for other causes included protocol violations, loss to follow-up, and lack of efficacy. Most studies reported only a single reason for withdrawal for a given patient and did not describe the clinical course after withdrawal. Hence, it is not possible to examine progression from increased angina to MI or death. The time spent on treatment from randomization to cardiovascular events or withdrawals for ADRs was rarely reported.

Because the majority of studies had no events in either the treatment or control arms, we could not compute within-study estimates of treatment effects. Heterogeneity statistics and random effects estimates could not be calculated for the same reasons.¹² Incidence rates and odds ratios (OR) with 95% CIs were calculated from the total number of events, comparing nifedipine study arms with corresponding other active drug arms in the same studies. Placebo arms were excluded from the analysis because there were too few groups with few patients and events to permit statistical pooling. We compared our results with those obtained by applying the Peto method, which excludes trials in which no event occurred in any study arm.¹³ Results were similar. In fact, unweighted pooling and the Peto method can be shown to give equivalent OR estimates when ≤ 1 event occurs during a study and the OR equals 1.0. The 2 methods give approximately equal results when the odds differ by a factor of ≤ 3.0 . All of these methods rely on asymptotic approxima-

TABLE 1. Characteristics of Studies in the Meta-Analysis of Stable Angina

Studies, subjects, drug exposures, n	
Studies	60
Study arms	141
Nifedipine	65
Other active drugs	65
Placebo	11
Subjects	3096
Drug exposures	5571
Nifedipine	2635
Monotherapy	2111
Combination therapy	524
Other active drugs*	2655
Monotherapy	2149
Combination therapy	613
Placebo	281
Study design, % of studies	
Parallel	18.3
Crossover	
With washout between phases	31.7
Without washout between phases	48.3
Washout not defined	1.7
Run-in period, % of studies	
With placebo	75.4
With active drug	18.5
No run-in	6.1
Sample size, % of studies	
10–25	56.7
26–50	23.3
51–100	10.0
≥ 101	10.0
Duration of treatment, % of studies	
1–4 wk	71.7
5–8 wk	23.3
9–12 wk	5.0
> 12 wk	0
Publication date, % of studies	
1987 or earlier	38.3
1988 or later	61.7
Study location, % of studies	
Europe	60.0
United States	35.0
Other	5.0
Study quality, mean score (range)	
Chalmers scale	29.2 (11–43)
Jadad scale	3.3 (1–5)

*Monotherapy and combination therapy treatment exposures sum to 107 more than the total because 3 control arms were used for both nifedipine monotherapy and combination therapy.

tion, which is more nearly satisfied when small number of events are added together. For analyses results that follow, ORs < 1.0 favor nifedipine.

Analyses of cardiovascular events were stratified by type of nifedipine formulation (IR [TID or QID dosing], SR [BID dosing], or

TABLE 2. Characteristics of Patients and Drug Regimens in Study Arms

Patient characteristics				
Mean age (range of means), y	58.2 (49–63)			
Sex, % male	74.5			
	Study Arms	%	Drug Exposures	%
Nifedipine arms				
Nifedipine	48	73.8	2111	80.1
Nifedipine + β -blockers	12	18.5	373	14.2
Nifedipine + nitrates*	1	1.5	24	0.9
Nifedipine + other CCBs	1	1.5	11	0.4
Nifedipine + β -blockers + nitrates*	3	4.6	116	4.4
Subtotal	65	99.9	2635	100
Other active drug arms				
β -blockers	27	41.5	1632	61.5
Other CCBs	19	29.2	457	17.2
Nitrates*	8	12.3	274	10.3
Other monotherapy	1	1.5	39	1.5
β -Blockers + other CCBs	7	10.8	137	5.2
β -Blockers + nitrates* + CCBs	1	1.5	22	0.8
β -Blockers + nitrates*	2	3.1	94	3.5
Subtotal	65	99.9	2655	100
Placebo arms				
Placebo	11	100	281	100
Totals	141	100	5571	100
Formulation				
IR	50	76.9	1324	50.2
SR	13	20.0	1269	48.2
ER	2	3.1	42	1.6
Totals	65	100.0	2635	100.0

*Long-acting nitrate preparations.

ER [QD]) and by whether nifedipine was prescribed as monotherapy or combination therapy. To test whether the unadjusted ORs differed between the type of formulation and monotherapy versus combination therapy, we fit 2 logistic regression models, each including a term for type of drug (nifedipine versus other), 1 of the stratification factors (type of formulation or monotherapy/combination therapy), and an interaction term. The interaction term was used to determine whether the OR for drug type differed by the stratification factor.

To investigate whether treatment effects were confounded with study level covariates, we fit multiple logistic regression models and computed the adjusted ORs for treatment.¹⁴ Covariates of interest were drug run-in before randomization, duration of treatment, parallel or crossover study design, quality score, date of publication, and study location. Drug regimen characteristics (nifedipine versus control drugs and monotherapy versus combination therapy) and their interactions were included in all models. Dose relationships could not be explored because most studies that titrated dosages did not report the distribution of doses patients received.

Results

Characteristics of Studies

Characteristics of the 60 studies in the meta-analysis^{15–74} are summarized in Table 1. These studies have 141 study arms (65 nifedipine, 65 other active drugs, 11 placebo), 3096

subjects, and 5571 treatment exposures (2635 to nifedipine, 2655 to other active drugs, 281 to placebo). The majority of studies were crossover designs; had placebo or drug run-in periods; were of small size, ie, ≤ 25 subjects; and were ≤ 4 weeks in duration. The majority were performed in Europe and were published since 1987.

Population Characteristics and Drug Regimens

All patients had chronic stable angina. Their mean age was 58.2 years (range of means, 49 to 63 years), and a large majority were male (Table 2). Patients with recent MIs or congestive heart failure had been systematically excluded. Nifedipine was used as monotherapy in the majority of nifedipine study arms and drug exposures. Most nifedipine combination therapy groups used β -blockers. Control arms consisted of other active drugs given as monotherapy in most studies, with β -blockers accounting for 56.9% of control arms and 70.0% of exposures.

Nifedipine IR formulations were used in 76.9% of nifedipine study arms but in only 50.2% of exposures since studies using nifedipine SR or ER formulations had larger sample sizes. Starting doses of nifedipine were titrated upward to

TABLE 3. Cardiovascular Events During Treatment of Stable Angina

	Nifedipine		Active Drug Controls	
	No.	Occurrence Rate	No.	Occurrence Rate
Total events				
Total	30	1.14%	19	0.72%
Death	4		1	
Nonfatal acute MI	5		6	
Nonfatal stroke	0		1	
Revascularization	2		0	
Increased angina	19		11	
Events on monotherapy				
Total	28	1.33%	11	0.51%
Death	3		1	
Nonfatal acute MI	4		4	
Nonfatal stroke	0		1	
Revascularization	2		0	
Increased angina	19		5	
Events on combination therapy				
Total	2	0.38%	8	1.31%
Death	1		0	
Nonfatal acute MI	1		2	
Nonfatal stroke	0		0	
Revascularization	0		0	
Increased angina	0		6	

achieve the desired clinical responses in 41.5% of study arms and reached a maximum of ≥ 80 mg/d in 30.6% and 20% of study arms for IR and SR/ER nifedipine, respectively. The proportion of subjects who actually received higher doses was rarely specified.

Incidence of Cardiovascular Events

Nifedipine Versus Other Active Drugs

One or more cardiovascular events were reported in 35% of studies (21/60), in 1.14% of patients in nifedipine study arms, and in 0.72% of patients in active drug control arms (Table 3). In nifedipine study arms, there were 30 events, including 4 deaths, 7 other major events, and 19 episodes of increased angina. In control arms, there were 19 events, including 1 death, 7 other major events, and 11 episodes of increased angina. All episodes of increased angina on nifedipine occurred on monotherapy. Figure 1 presents the associations between the type of drug regimen, nifedipine formulation, and the risk of cardiovascular events. Overall unadjusted ORs were not significant for major cardiovascular events (OR=1.40 [95% CI, 0.56 to 3.49]), episodes of increased angina (OR=1.75 [95% CI, 0.83 to 3.67]), or all events (OR=1.61 [95% CI, 0.91 to 2.87]). ORs adjusted for type of drug regimen and other study level covariates increased to 1.45 (95% CI, 0.58 to 3.62) for major events and 1.75 (95% CI, 0.98 to 3.13) for all events but still did not reach statistical significance. Drug run-in, US location of the study, and a higher quality score were independently and significantly associated with an increased risk of all events when we controlled for drug regimen. Study design (crossover or parallel) was not associated with treatment effects.

Nifedipine Formulation

To assess the effects of nifedipine formulation, ORs were calculated separately for IR and SR/ER formulations. The latter were combined in the analysis because of small numbers of events in each alone. Compared with other active drugs, the OR was not significant for IR nifedipine for risk of major events (OR=1.96 [95% CI, 0.59 to 6.52]). However, a significantly higher risk of episodes of increased angina (OR=4.19 [95% CI, 1.41 to 12.49]) and all events combined (OR=3.09 [95% CI, 1.39 to 6.88]) was evident. Odds ratios for study arms using SR or ER formulations were not statistically significant for major events (OR=0.78 [95% CI,

Drug	Number Events	Number Exposures	Unadjusted OR (95% CI)
All Nifedipine vs. Other Active Drugs			
Major Events	Nifedipine 11	2,635	1.40 (0.56,3.49)
	Other 8	2,655	
Increased Angina	Nifedipine 19	2,635	1.75 (0.83,3.67)
	Other 11	2,655	
All Events	Nifedipine 30	2,635	1.61 (0.91,2.87)
	Other 19	2,655	
IR Nifedipine vs. Other Active Drugs			
Major Events	Nifedipine 8	1,324	1.96 (0.59,6.52)
	Other 4	1,293	
Increased Angina	Nifedipine 17	1,324	4.19 (1.41,12.49)
	Other 4	1,293	
All Events	Nifedipine 25	1,324	3.09 (1.39,6.88)
	Other 8	1,293	
SR/ER Nifedipine vs. Other Active Drugs			
Major Events	Nifedipine 3	1,311	0.78 (0.17,3.49)
	Other 4	1,362	
Increased Angina	Nifedipine 2	1,311	0.30 (0.06,1.43)
	Other 7	1,362	
All Events	Nifedipine 5	1,311	0.47 (0.16,1.36)
	Other 11	1,362	

*Squares indicate odds ratios of nifedipine compared to other active drug controls: lines indicate 95% confidence intervals

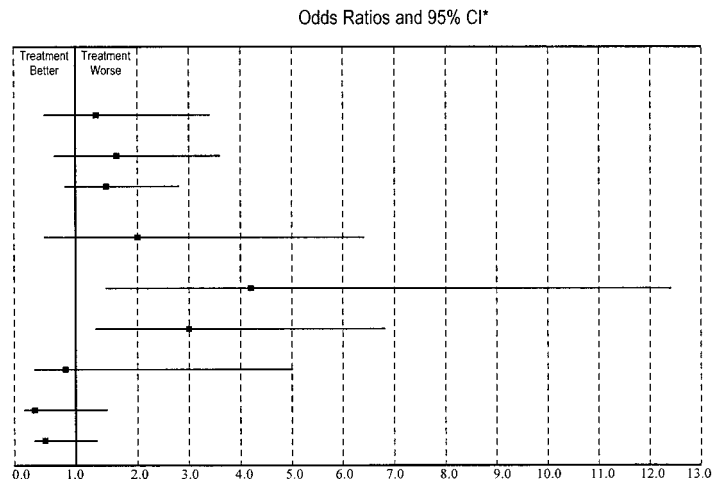


Figure 1. Associations between type of drug regimen, nifedipine formulation, and risk of cardiovascular events in patients with stable angina.

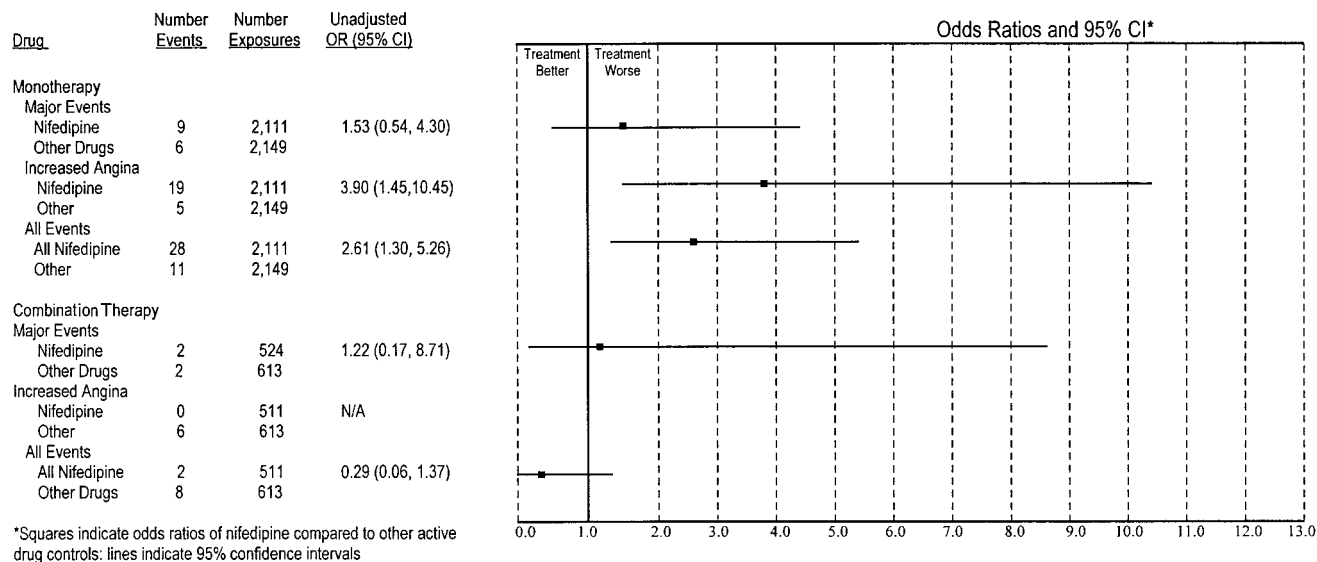


Figure 2. Associations between type of drug regimen, monotherapy vs combination therapy, and risk of cardiovascular events in patients with stable angina.

0.17 to 3.49]), for episodes of increased angina (OR=0.30 [95% CI, 0.06 to 1.43]), or for all events combined (OR=0.47 [95% CI, 0.16 to 1.36]). The OR for IR nifedipine was significantly higher than that for SR/ER nifedipine for increased angina ($P=0.001$) and all events ($P=0.006$) but not for the major events category ($P=0.36$).

Nifedipine Monotherapy Versus Combination Therapy

Figure 2 compares nifedipine monotherapy and combination therapy (all formulations) with active drug controls. In the nifedipine combination therapy group, 93.3% of patients were receiving a β -blocker. Active drug controls were from the same studies and included both monotherapy and combination therapy regimens. ORs for major cardiovascular events were 1.53 (95% CI, 0.54 to 4.30) for monotherapy and 1.22 (95% CI, 0.17 to 8.71) for combination therapy. Corresponding ORs for all events were 2.61 (95% CI, 1.30 to 5.26) and 0.29 (95% CI, 0.06 to 1.37). The effects of nifedipine monotherapy were predominantly on episodes of increased angina (OR=3.90 [95% CI, 1.45 to 10.45]). Differences in ORs between nifedipine monotherapy and combination therapy were significant for increased angina ($P=0.03$) and all cardiovascular events ($P=0.01$) but not for major events ($P=0.81$).

Study Withdrawals

Study withdrawals were significantly higher on nifedipine monotherapy (all formulations) than active drug controls for both ADRs (OR=1.7 [95% CI, 1.3 to 2.2]) and all causes (OR=1.5 [95% CI, 1.2 to 1.9]). With nifedipine combination therapy, withdrawals for neither ADRs nor for all causes were significantly different than controls (OR=0.7 [95% CI, 0.3 to 1.8] and OR=0.6 [95% CI, 0.2 to 1.5], respectively). The higher withdrawal rates for ADRs on nifedipine monotherapy were due primarily to edema and symptoms related to the effects of sympathetic stimulation and vasodilatation, such as tachycardia and

headache. Interestingly, withdrawal rates did not differ significantly between IR and SR/ER formulations.

Discussion

This meta-analysis reveals an increased risk of cardiovascular events in patients with chronic stable angina who are treated with IR nifedipine as monotherapy. The increased risk is due primarily to a greater frequency of episodes of increased angina. These findings are consistent with those of a previous meta-analysis of IR nifedipine in patients with acute MI or unstable angina pectoris.¹ They are also consistent with the Food and Drug Administration decision to approve IR nifedipine only in combination therapy with another agent for chronic stable angina.

A study published subsequent to the search cutoff date for this review reinforces these findings. The Total Ischemic Burden European Trial⁷⁵ was a multicenter, randomized, double-blind, controlled study that enrolled 682 patients with chronic stable angina. Patients were randomized to receive atenolol alone, SR nifedipine alone, or the combination and were followed for up to 3 years (mean, 2 years). A nonsignificant trend toward lower rates of cardiovascular events including unstable angina was found in the combination therapy group. Significantly higher withdrawal rates were found in the nifedipine monotherapy group (40% versus 27% for atenolol alone versus 29% for the combination).

This review cannot distinguish whether the increased risk associated with IR formulations of nifedipine is due to ADRs or diminished efficacy. Stimulation of sympathetic activity may be important to both mechanisms. IR formulations are absorbed rapidly after oral administration, reach high peak plasma concentrations, and have been associated with increased heart rates and cardiac outputs.^{76–78} The formulations designated as SR or ER are absorbed more slowly, exhibit flatter plasma concentration curves, and are thought to stimulate sympathetic activity less.^{77–79} The

lower frequency of cardiovascular events on combination therapy may be due to the effect of β -blockers in modulating the cardiostimulatory effects of nifedipine.

Withdrawals from studies may be due to an inability of patients to tolerate a drug, lack of drug efficacy, or protocol violations. Higher withdrawal rates for ADRs in this study were confined to nifedipine monotherapy. Amelioration of drug-related symptoms by the addition of a β -blocker to the regimen or the ability of combination therapy to achieve the desired therapeutic response at lower nifedipine doses is the most likely explanation.

A major strength of this meta-analysis is the inclusion of the universe of relevant published RCTs, which increases the generalizability of results and minimizes the likelihood of bias due to case-mix differences between study arms. Other strengths include the use of rigorous and explicit methods for selecting studies; the blinding of articles before data extraction; dual extraction of each article by 2 physicians; and thorough exploration of the resulting database, including multiple logistic regression.

Limitations relate to the relatively small number of adverse cardiovascular events on which analyses are based; the short duration of studies; inability to adjust per-person rates for the duration of drug treatment because available information did not permit us to determine the timing of events relative to the initiation of treatment; inability to explore dose relationships to adverse events because most studies did not provide information on actual doses received; and the paucity of patient-level data to permit case-mix adjustment across studies.

In conclusion, this systematic review of the literature suggests that adverse effects of nifedipine on cardiovascular events in patients with stable angina are due primarily to more frequent episodes of increased angina when monotherapy with IR formulations is used. SR formulations and concurrent use with β -blockers do not appear to be associated with increased risk in the studies included in this data set. Although meta-analysis has an important role in quantifying the risk of rare but important ADRs, long-term RCTs remain the gold standard required to verify these conclusions.

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