



Nifedipine gastrointestinal therapeutic system (GITS) in the treatment of coronary heart disease and hypertension

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Since the 1960s, calcium antagonists have been available for the treatment of angina pectoris and hypertension. The first of this class, nifedipine, was introduced and readily accepted as the third treatment option for angina, alongside β -blockers and nitrates.

However, the short-acting formulations of nifedipine had pharmacokinetic properties that were far from ideal and in 1995, several studies involving various dosing regimens reported possible dangerous effects in secondary prevention. Since then, large-scale, randomized controlled trials with new controlled-release formulations of nifedipine have demonstrated the effectiveness and safety of this drug. As a consequence of these results, guidelines for both hypertension and angina pectoris have been recently reconsidered, and have put the modern formulations of calcium channel blockers in a pole position. Within this group of therapeutics, nifedipine gastrointestinal therapeutic system has a unique position and it cannot be replaced by other controlled-release formulations of nifedipine, the pharmaceutical properties of which have yet to be tested in large-scale outcome trials.

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Calcium channel blockers (CCBs), including nifedipine, have been commercially available since the 1960s for the treatment of angina pectoris and hypertension. CCBs exert their antihypertensive and antianginal effects by inhibiting the transport of calcium into cells via the L-type calcium channel in the cellular membrane of different tissues, including vascular and cardiac cells.

Nifedipine was initially available as an oral gelatine capsule formulation, which resulted in the immediate release of nifedipine (a phenomenon known as ‘dose dumping’). This formulation had a short duration of action, requiring multiple daily administrations (three- or four-times per day) to achieve an adequate clinical effect, which was very inconvenient for the patient.

In 1995, Furberg and colleagues published the results of a meta-analysis of randomized, secondary prevention trials of patients with acute coronary syndromes who were treated with

short-acting nifedipine capsules at a range of doses [1]. They concluded that, in patients with coronary disease, the use of short-acting nifedipine in moderate-to-high doses causes an increase in total mortality, and suggested that this effect may be particularly associated with dihydropyridine-type CCBs. The results of this analysis, in addition to those from an observational study of patients with hypertension, indicated that the use of short-acting CCBs, particularly at high doses, was associated with an increased risk of myocardial infarction (MI) [2]. This caused considerable debate and casted doubt on the safety of nifedipine and other CCBs.

As a result, a range of controlled-release formulations were developed, including nifedipine gastrointestinal therapeutic system (GITS), allowing for once-daily oral administration. Thus, nifedipine has become a key component of therapeutic regimens for patients with hypertension and coronary heart disease.

More recently, published morbidity and mortality data from large, randomized clinical trials using long-acting, slow-release CCBs in hypertensive patients, such as the International Nifedipine GITS Study: Intervention as a Goal in Hypertensive Treatment (INSIGHT) [3] and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [4]; and in patients with stable angina, such as A Coronary disease Trial Investigating Outcomes with Nifedipine GITS (ACTION) [5], have refuted the results seen with immediate-release nifedipine formulations. These recent results confirm the efficacy and safety of nifedipine GITS and other CCBs for the treatment of hypertension and angina, and have prompted a reconsideration of the current treatment guidelines [10].

This article reviews the clinical experience accumulated to date for nifedipine, with a focus on the results of recent large trials of nifedipine GITS that not only demonstrate the efficacy and safety of nifedipine for the treatment of hypertension and angina, but also show that it can significantly improve clinical outcomes in these patients and has benefits that extend beyond blood pressure control. These trials also demonstrate the superiority of a combination of CCBs and angiotensin II receptor blockers compared with the standard antihypertensive combination therapy of diuretics and β -blockers.

Overview of the market

Hypertension is recognized as one of the most important risk factors for the development of cardiovascular disease. The benefits of hypertensive treatment are known to be associated with the extent to which blood pressure is reduced, with a recommended target of less than 140/90 mmHg in patients aged more than 55 years, and a lower target in younger patients and those with diabetes mellitus.

There are several classes of agents available for the treatment of hypertension including diuretics, β -blockers, angiotensin II-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and CCBs, and these are often used in various combinations according to the needs of the individual patient. The CCBs can be broadly divided into three groups, of which the dihydropyridine types form the largest group, with many representatives including nifedipine, amlodipine, felodipine, nisoldipine, nicardipine, lacidipine and isradipine. Verapamil and diltiazem comprise the other two smaller groups within this class. Although these groups of drugs have differing chemical structures, they have a common mechanism of action.

Angina pectoris is the most common symptom in patients with stable coronary heart disease. CCBs are also one of the mainstays of treatment for the symptoms of stable angina pectoris, along with nitrates and β -blockers.

Pharmacokinetics, pharmacodynamics & the pharmaceutical compounds of nifedipine

Nifedipine is a CCB of the 1,4-dihydropyridine type. It was in fact the prototype dihydropyridine CCB and was originally marketed by Bayer Pharmaceuticals in the 1960s. The product is currently available as immediate-release capsules (10 and 20 mg) and as modified-release tablets (20, 30 and 60 mg).

Nifedipine, dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, has an empirical formula of $C_{17}H_{18}N_2O_6$, a molecular weight of 346.3 and its chemical structure is shown in FIGURE 1. It is practically insoluble in water but soluble in ethanol.

The pharmacodynamics of immediate- and modified-release nifedipine, and its pharmacokinetics in both healthy volunteers and in patients with hypertension and angina are well defined [6–8]. The pharmacokinetics of modified-release formulations have been reviewed in detail in a recent publication [9], so only a brief overview will be given here.

In common with other CCBs, nifedipine reduces the transmembranal influx of calcium ions through the slow L-type calcium channels into cells. Nifedipine is particularly effective on the cells of the myocardium and the smooth muscle cells of the coronary arteries, and the peripheral resistance vessels, thereby reducing muscle contraction. The actions of nifedipine are predominantly vasodilatory: in the heart, nifedipine dilates the coronary arteries, especially the large conductance vessels, even in the free wall segment of partially stenosed areas. Nifedipine also reduces the vascular smooth muscle tone in the coronary arteries and prevents vasospasm. This results in increased poststenotic blood flow and increased oxygen supply. In addition, nifedipine increases sodium and water excretion following both short- and long-term use. The rapid vasodilation that occurs after dosing with immediate-release nifedipine can cause baroreceptor-mediated reflex activation of the sympathetic nervous system, which results in an increase in heart rate. This does not occur with the nifedipine GITS formulation.

The pharmacokinetic profiles of the immediate-release CCBs, including nifedipine, verapamil and diltiazem, are characterized by rapid clearance with an extensive first-pass hepatic metabolism, which results in comparatively low oral bioavailability. This, coupled with their short elimination half-lives, mean that the original formulations of nifedipine needed to be administered three- or even four-times a day to achieve an adequate antihypertensive effect [10]. The comparative and widely varying pharmacokinetic profiles of selected dihydropyridine CCBs are shown in TABLE 1.

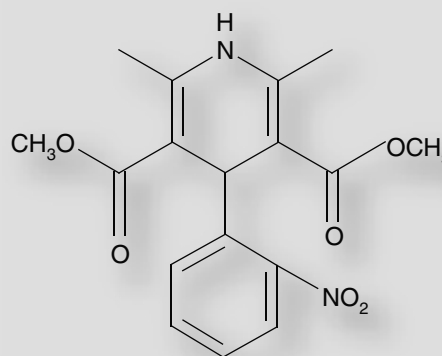


Figure 1. Nifedipine.

Table 1. Comparative pharmacokinetics of selected dihydropyridine calcium antagonists.

	Nifedipine	Nisoldipine	Felodipine	Amlodipine	Lacidipine
Oral absorption (%)	>90	>90	>90	>90	>90
Oral bioavailability (%)	30–50	5–15	10–25	60–65	5–15
Elimination half-life (h)	3–5	4–10	2–8	35–50	3–15

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It is important to note that these different CCBs show distinct differences in their pharmacokinetic, pharmacodynamic and therapeutic profiles, so it should not be assumed, for example, that all modified-release, once-daily dihydropyridine CCBs are equivalent in terms of their durations of action and overall antihypertensive efficacy [11]. For instance, the globally marketed nifedipine retard 30/60 mg (Sandoz) formula is, from a pharmacological point of view, not equivalent to the nifedipine GITS formula, although it has been presented as such [12,13].

Development of long-acting nifedipine formulations

The limitations of the pharmacokinetic and pharmacodynamic properties of the immediate-release dihydropyridine CCBs and the inconvenience of multiple daily dosing prompted the development of newer agents with longer elimination half-lives or modified-release characteristics, allowing once-daily dosing that achieves stable plasma levels over a 24-h period, which is much more convenient for the patient. Amlodipine, like nifedipine, is a hydrophilic compound, but has a slower metabolism in the human body, and thus has an intrinsically longer plasma half-life of approximately 40 h. Other newer dihydropyridine CCBs, such as lacidipine, lercanidipine and barnidipine have also been developed. These preparations have lipophilic properties and relatively short plasma half-lives but longer durations of action, attributed to a high membrane partition coefficient. At the present time, however, all compounds apart from nifedipine and amlodipine lack data from large, randomized clinical trials to support their safety and efficacy in the clinical situation.

The nifedipine GITS formulation

Nifedipine GITS is a long-acting formulation of nifedipine that releases the compound into the gastric lumen at a controlled rate over 24 h, thereby achieving sustained plasma levels. It is widely prescribed for the treatment of essential hypertension and stable symptomatic coronary heart disease (chronic stable angina).

The formulation consists of a two-layer core of nifedipine and osmotic polymer surrounded by a semipermeable membrane (FIGURE 2). The membrane

incorporates a precisely laser-drilled hole [14]. When the tablet is swallowed, water is absorbed from the GI tract through the semi-permeable membrane. The nifedipine-containing core forms a suspension, which is extruded through the laser-drilled hole at a constant rate by the expanding polymer core layer. The GITS formulation delivers nifedipine at a constant rate for approximately 18–22 h, and the resulting smooth and consistent plasma concentration profile is compatible with once-daily dosing.

There are notable differences in the pharmacokinetics and hemodynamic properties of these modified-release formulations compared with the short-acting nifedipine capsules [8,9,11]. FIGURE 3 shows the comparative pharmacokinetics and effects on heart rate and systolic blood pressure following acute administration of three different formulations of nifedipine – immediate-release nifedipine capsules, nifedipine retard and nifedipine GITS – in hypertensive patients.

Following the development of nifedipine GITS, studies demonstrated that hypertensive patients could be successfully switched from immediate-release or alternative modified-release formulations of nifedipine with comparable or improved efficacy and a resulting improvement in the side-effect profile [15–17]. In addition to being effective and having an excellent safety profile, nifedipine GITS appears to be able to maintain quality of life in patients with mild-to-moderate hypertension [18].

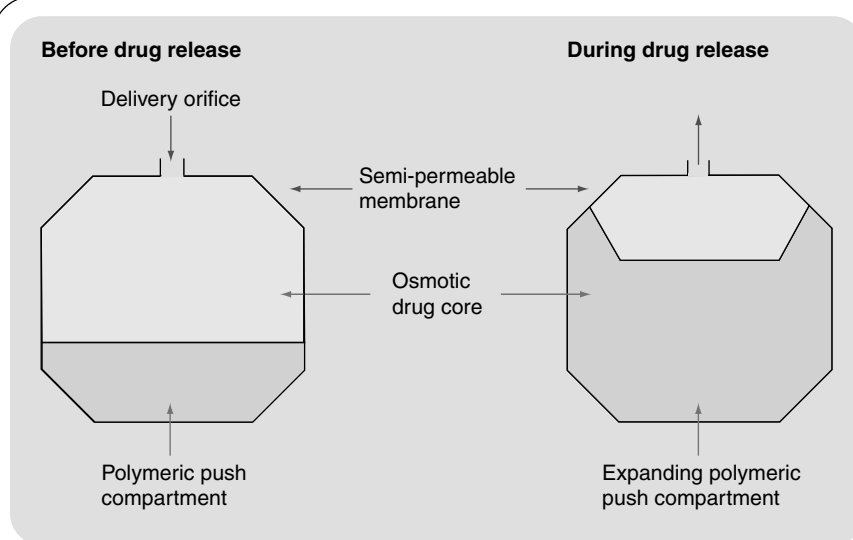
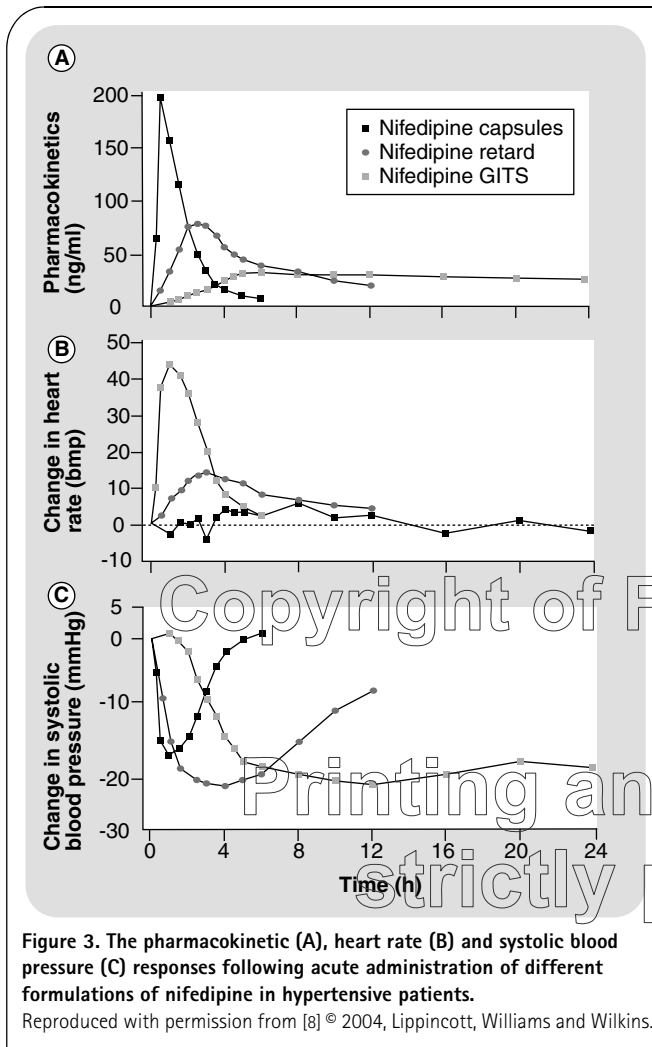


Figure 2. The nifedipine gastrointestinal therapeutic system formulation.



Interpretation of early clinical studies with short-acting nifedipine

In 1995, Furberg and colleagues published the results of a meta-analysis of randomized, secondary prevention trials of patients with acute coronary syndromes treated with a range of doses of short-acting nifedipine capsules [1]. Their analysis concluded that the use of nifedipine was associated with a significant adverse effect on total mortality, which increased with higher doses of nifedipine. They suggested that this phenomenon might be due to the established proischemic effect, negative inotropic effects, marked hypotension and prohemorrhagic effects attributed to the antiplatelet and vasodilatory actions of CCBs, and possibly to proarrhythmic effects. They postulated that other CCBs, particularly those of the dihydropyridine type, might have similar adverse effects. In addition, an observational study of patients with hypertension suggested that the use of short-acting CCBs, especially at high doses, was associated with an increased risk of MI [2]. The Furberg study was challenged and criticized in terms of both design and conclusions [19]; however, it is well recognized in evidence-based medicine that questions such as those raised about the effects of

CCBs on mortality can only be answered by conducting large, randomized, clinical outcome trials of sufficiently long duration. None were available at that time, but in recent years large studies have been undertaken and the debate has now been resolved.

Clinical efficacy: nifedipine GITS in coronary heart disease

Several clinical studies have shown that nifedipine GITS has equivalent efficacy to diltiazem and atenolol in increasing exercise tolerance in chronic stable angina patients [20–22]. Studies have also suggested that the efficacy and tolerability of nifedipine GITS is superior to long-acting nitrates as second-line therapy to β -blockade in the treatment of chronic stable angina [23] and is particularly effective in patients with chronic stable angina who were inadequately controlled on β -blockers alone. Nifedipine GITS has also been shown to have a sustained effect – a single daily dose is effective over 24 h regardless of whether it was administered in the morning or evening [24,25].

The ACTION study was designed to answer some of the questions posed by the Furberg meta-analysis about the effects of CCBs on mortality in patients with coronary artery disease [5]. ACTION was a multicenter (291 centers in 19 countries), randomized, double-blind, placebo-controlled trial, and is the largest outcome trial of an antianginal drug in patients with chronic stable angina [26]. A total of 7669 patients were randomized with an expected 38,345 patient-years of treatment and a mean follow-up period of 5 years, making it one of the longest trials of its kind in such patients.

The inclusion criteria for the study were patients with stable symptomatic angina with either a history of acute MI (AMI) or documented coronary artery disease [24]. Patients with a positive exercise test or a perfusion defect without AMI, or a documented coronary artery disease were allowed in the trial, the types of patients who would be seen in a routine cardiac clinic. A total of 3825 patients with stable symptomatic coronary disease were randomized to receive nifedipine GITS (30–60 mg once daily) and 3840 to receive placebo, in addition to current best practice therapy for their condition. The primary efficacy end point was cardiovascular event-free survival, a composite end point selected to include all clinically relevant events that patients at increased cardiovascular risk might experience, namely a combination of death, AMI, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularization. The mean follow-up period was 4.9 years and was completed in 97.3% of patients. Primary end point rates did not differ between the nifedipine- and placebo-treated groups: 4.60 per 100 patient-years for nifedipine and 4.75 per 100 patient-years for placebo (95% confidence interval [CI]: 0.97 [0.88–1.07]; $p = 0.54$) [5]. With nifedipine, the rate of death and any cardiovascular event or procedure was significantly reduced compared with placebo: 9.32 per 100 patient-years for nifedipine versus 10.50 per 100 patient-years for placebo (95% CI: 0.89 [0.83–0.95]; $p = 0.0012$) [5]. The difference was mainly attributed to a reduction in the need for coronary angiography and interventions in patients receiving

nifedipine GITS, despite an increase in peripheral revascularization. Nifedipine GITS had no effect on the rate of AMI. The investigators concluded that the addition of nifedipine GITS to conventional treatment for angina pectoris has no effect on major cardiovascular event-free survival [5]. In addition, it was found to have an excellent safety profile and reduce the need for coronary angiography and interventions. FIGURE 4A summarizes the outcomes from the overall study. Nifedipine GITS was also found to be very well tolerated [5].

The key lessons learned from these important results are that patients with coronary artery disease have a very good prognosis, with a mortality rate in the placebo group of only 1.53 per 100 patient-years. However, it should be noted that the placebo group of patients was very well treated (TABLE 2), probably explaining the lack of difference in mortality between the active and placebo group [5].

Although not designed as a hypertension study, after newly adjusted definitions of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), approximately half of the patient group in the ACTION study (n = 3977; 52%), fulfilled these criteria. In this hypertensive

subgroup, all end points were found to be significantly better in the patients treated with nifedipine GITS [27]. FIGURE 4B summarizes the outcomes from the hypertensive subgroup. Importantly, in clinical practice, slightly elevated blood pressure readings are often disregarded and left untreated. The ACTION results showed that initiation of anti-ischemic treatment in symptomatic patients resulted both in relief of symptoms and a lowering of blood pressure, and reduced the incidence of heart attacks and strokes. Both aspects probably influenced the prognosis of these patients. In a recent publication, Lubsen and colleagues using the vast database of ACTION, demonstrated that the effect of nifedipine GITS on the reduction of both stroke and the incidence of heart failure was caused by the anti-hypertensive effect of this drug. However, the effect on reducing coronary interventions was not related to the reduction in hypertension. This was related to the antianginal (probably vascular) effects of this drug. In this way, the dual effect of treatment with a long-acting CCB such as nifedipine GITS is nicely demonstrated. Treatment of coronary heart disease thus should be regarded as more than treating hypertension [15].

These findings are supported by the results of the CAMELOT study, a double-blind, randomized, multicenter trial that compared the effects of the CCB amlodipine or enalapril with placebo on cardiovascular events in patients with coronary artery disease [28]. The investigators concluded that administration of amlodipine to patients with coronary artery disease and normal blood pressure reduced the incidence of adverse cardiovascular events.

Clinical efficacy: nifedipine GITS in hypertension

Nifedipine GITS has been shown to reduce elevated blood pressure effectively in patients with mild-to-moderate essential hypertension in both placebo-controlled and noncomparative clinical trials [18,29]. Response rates were higher in elderly patients than in younger patients. Nifedipine GITS has also been shown to be effective in patients with severe hypertension. In a number of comparative trials involving CCBs (verapamil, diltiazem and felodipine), β -blockers (atenolol, propranolol) and ACE inhibitors (enalapril and lisinopril), nifedipine GITS has shown equal or superior antihypertensive efficacy [18,29]. In comparison with co-amilofide (hydrochlorothiazide/amiloride), nifedipine GITS was equivalent in effectively lowering 24-h blood pressure [18].

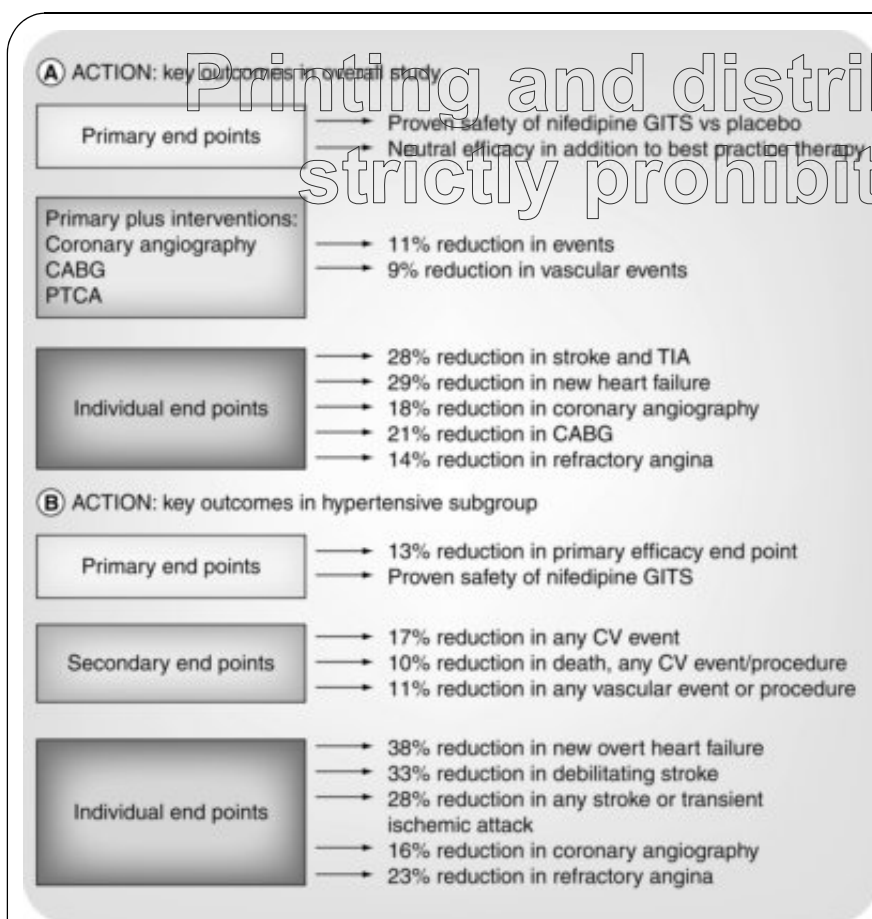


Figure 4. Key outcomes from the ACTION study. (A) Overall study. (B) Hypertensive subgroup. CABG: Coronary artery bypass graft; CV: Cardiovascular; PTCA: Percutaneous transluminal coronary angioplasty; TIA: Transient ischemic attack.

Adapted from [5].

Table 2. Incidence of clinical events in the ACTION study.

Event	Nifedipine (n = 3825)		Placebo (n = 3840)		Hazard ratio* (95% CI)	p-value
	Total number of events	Number of patients with event (incidence per 100 patient- years at risk)	Total number of events	Number of patients with event (incidence per 100 patient- years at risk)		
All-cause mortality	310	310 (1.64)	291	291 (1.53)	1.07 (0.91–1.25)	0.41
- Noncardiovascular	132	132 (0.70)	114	114 (0.60)	1.16 (0.90–1.49)	0.24
- Cardiovascular or unknown†	178	178 (0.94)	177	177 (0.93)	1.01 (0.82–1.24)	0.93
Myocardial infarction	320	267 (1.46)	296	257 (1.39)	1.04 (0.88–1.24)	0.62
Refractory angina	171	150 (0.81)	190	174 (0.94)	0.86 (0.69–1.07)	0.18
New overt heart failure	117	86 (0.46)	158	121 (0.65)	0.71 (0.54–0.94)	0.015
Debilitating stroke	82	77 (0.41)	108	99 (0.53)	0.78 (0.58–1.05)	0.10
Peripheral revascularization	187	146 (0.79)	144	118 (0.63)	1.25 (0.98–1.59)	0.073
Coronary angiography	1200	895 (5.46)	1357	1068 (6.69)	0.82 (0.75–0.90)	<0.0001
Percutaneous coronary intervention	512	385 (2.15)	548	417 (2.34)	0.92 (0.80–1.06)	0.25
Coronary bypass surgery	299	294 (1.62)	373	371 (2.06)	0.79 (0.68–0.92)	0.0021

*Comparison of nifedipine with placebo.

†Includes cause unknown (24 nifedipine, 28 placebo).

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Although the effect of diuretics and β -blockers on morbidity and mortality of hypertensive patients was well established, until the results of INSIGHT became available the effect of CCBs on long-term outcomes was unknown. The objective of the INSIGHT study was to compare fatal and nonfatal cardiovascular end points in hypertensive patients randomized to treatment with either nifedipine GITS or the diuretic co-amilofide (amilofide/hydrochlorothiazide 2.5/25 or 5/50 mg) [3]. The primary study outcome was a composite end point defined as stroke, intracerebral hemorrhage, subarachnoid hemorrhage, MI, heart failure and death of cerebrovascular or cardiovascular origin, including sudden cardiac death. Results showed that nifedipine GITS reduced mortality and morbidity as effectively as standard diuretic treatment with co-amilofide in hypertensive patients with additional risk factors, but with a reduced incidence of adverse metabolic consequences. Nifedipine GITS was found to be equally effective in preventing cardiovascular complications based on the primary end point, and the treatment arms did not differ for all-cause mortality, nonfatal end points or the combined primary and secondary end points (FIGURE 5).

Several planned subgroup analyses showed that the long-term protective effects of nifedipine GITS extended to hypertensive patients with diabetes mellitus [3], previous MI [31] and isolated systolic hypertension [32]. New-onset diabetes during the course of the study was lower in patients treated with nifedipine GITS than in those treated with co-amilofide [30].

Further confirmation of the long-term safety of dihydropyridine CCBs was provided by the results of the ASCOT study, which investigated the prevention of cardiovascular events with an antihypertensive regimen of amlodipine plus perindopril as required versus atenolol plus bendroflumethiazide as required [4]. ASCOT was a multicenter, randomized controlled trial in 19,257 patients with hypertension aged 40–79 years with at least three other cardiovascular risk factors. Patients were randomized to receive either amlodipine 5–10 mg adding perindopril 4–8 mg as required (n = 9639), or atenolol 50–100 mg adding bendroflumethiazide 1.25–2.5 mg and potassium as required (n = 9618). The primary end points were nonfatal MI (including silent MI) and fatal coronary heart disease. The median follow-up was 5.5 years and accumulated a total 106.153 patient-years

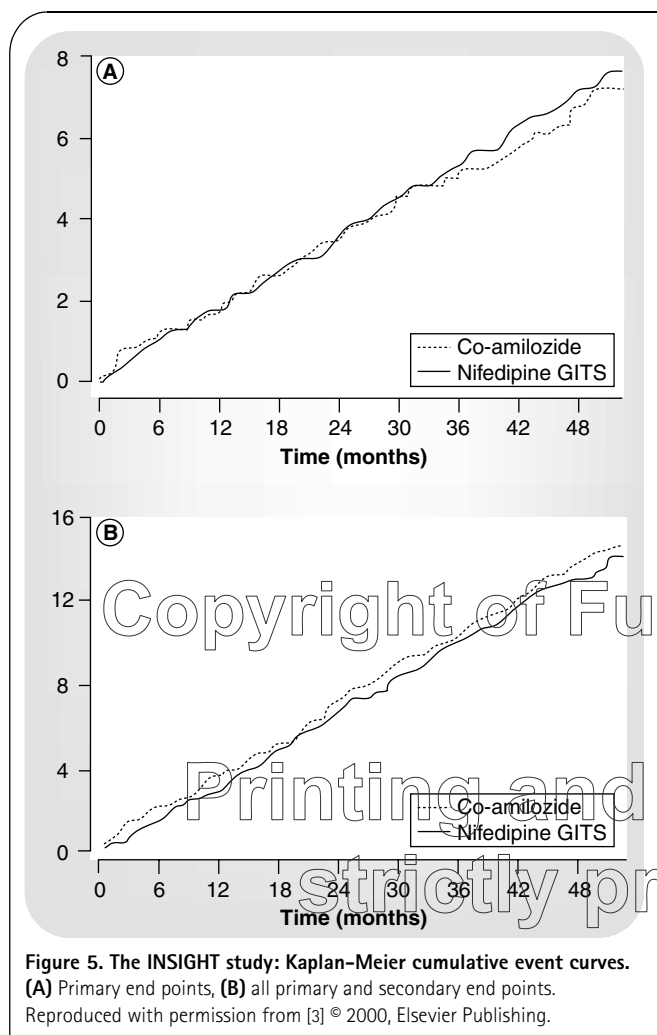


Figure 5. The INSIGHT study: Kaplan-Meier cumulative event curves.
 (A) Primary end points, (B) all primary and secondary end points.
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of observation. It was found that the amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen.

In the VALUE study, 15,245 hypertensive patients with high cardiovascular risk were randomized to valsartan or amlodipine [33]. Blood pressure was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced. There was no difference in the primary end point, a composite of cardiac mortality and morbidity, between the groups.

Safety & tolerability of nifedipine GITS

The most common adverse events experienced are those associated with the vasodilatory mechanism of action of nifedipine, namely peripheral edema, headache, dizziness and flushing. Clinical trials have demonstrated that nifedipine GITS is well tolerated, but there has been a concern about an increase of GI bleeding during treatment with CCBs. However, the Syst-Eur [34], VALUE [33] and ACTION [5] trials have shown that this risk is nonexistent. In the ACTION trial, the issue of safety and tolerability was a primary end point [5]. The total exposure of patients on nifedipine GITS in this study is over 18 years and the safety end point was definitely met.

With regards to tolerability, this same study showed that after 6 weeks of follow-up, 88% of patients allocated to nifedipine and 92% of patients allocated to placebo were receiving the full dose. The dose was reduced by half for 16% of patients allocated to nifedipine and 6% of patients allocated to placebo. With an average of 85% of the patients on active treatment, tolerability seems to be satisfactory for this drug. Adverse effects of nifedipine were mainly peripheral edema and headache. With the results of ACTION [5], the safety issues regarding the use of long-acting CCBs has since ended for nifedipine GITS.

Effect of nifedipine GITS on other cardiovascular risk factors Endothelial structure & function

Impaired endothelial cell growth and function have been suggested to be initial events leading to the development of atherosclerosis. Nifedipine GITS has been shown to improve endothelial function and thus slow the development and progression of atherosclerosis; the mechanisms by which this occurs are thought to be linked to its antioxidative properties [35].

The two substudies of INSIGHT outlined earlier compared the effects of nifedipine GITS and diuretic therapy on changes associated with the progression of atherosclerosis in high-risk hypertensive patients. The first used double-helix CT to detect, measure and compare calcification in the coronary arteries [36]. The second used ultrasonography to measure intima media thickness of the carotid arteries, which is an indicator of arterial wall thickening [37]. Nifedipine GITS significantly inhibited coronary calcium progression over a 3-year period. Although co-amlozide was associated with a significant increase in intima media thickness in the right common carotid artery far wall, there was no such progression with nifedipine GITS after 2 years of treatment. It was concluded from these two studies that nifedipine GITS has a more favourable profile than co-amlozide in these high-risk hypertensive patients. These antiatherosclerotic effects of nifedipine GITS appear to be independent of its antihypertensive effects because there was no difference between the two treatment arms in the degree of blood pressure reduction.

Evidence that nifedipine also improves endothelial function in patients with coronary artery disease was provided by the results of the Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function (ENCORE) I and II studies [38,39]. These studies were undertaken to investigate changes in endothelial function as assessed by intracoronary infusion of acetylcholine; ENCORE II was also designed to investigate atherosclerotic vascular changes and their relation to endothelial dysfunction. The objectives of the studies were to determine the effects of treatment with nifedipine GITS (compared with cerivastatin and in combination with cerivastatin) on endothelium-dependent coronary vasoconstriction in patients with stable angina and coronary stenosis of no more than 40% who were undergoing percutaneous coronary intervention. The aim was to provide an insight into atherosclerotic vascular changes and to correlate any changes in endothelial

function with those seen during the atherosclerotic process. This was measured by changes in mean luminal diameter, as assessed by quantitative coronary angiography.

In ENCORE I, 6 months of treatment with nifedipine GITS significantly improved coronary endothelial function in the most constricted segment (19 vs 10% for placebo) [38]. Unfortunately, during the ENCORE II trial, cerivastatin was withdrawn from the market. Despite this, 226 patients with stable angina were randomized to either placebo or nifedipine GITS [39]. The study investigated the effects of 18–24 months of therapy on the coronary endothelial function, as assessed by acetylcholine testing with quantitative coronary angiography, and atherosclerotic progression, as assessed by intravascular ultrasound (IVUS). Nifedipine GITS significantly improved coronary endothelial function in the most constricted segment to a greater degree than that observed after 6 months of treatment in the placebo group (18% for nifedipine GITS vs 7% for placebo). There was a trend toward a beneficial effect of nifedipine GITS on atheroma volume; however, this did not reach statistical significance. The results from the two ENCORE studies confirm the benefits of nifedipine GITS in improving endothelial function and potentially slow the atherosclerotic process.

Stroke

A study by the Blood Pressure Lowering Treatment Trialists' Collaboration investigated the effects of CCBs, ACE inhibitors and other blood pressure-lowering drugs on mortality and major cardiovascular morbidity in several patient populations [40]. The investigators reviewed the results of randomized trials comparing active treatment regimens with placebo: trials comparing more intensive versus less intensive blood pressure-lowering strategies, and trials comparing treatment regimens involving different drug classes. The overview of placebo-controlled trials of CCBs (two trials including 5520 patients mostly with hypertension) showed reductions in stroke (39%; 95% CI: 15–56) and major cardiovascular events (28%; 95% CI: 13–42). In the overviews comparing different antihypertensive regimens (eight trials; 37,872 patients with hypertension), several differences in cause-specific effects were seen between CCB-based therapy and other regimens, but these were of limited statistical significance. A subsequent study by this study group found that treatment with any commonly used regimen reduced the risk of total major cardiovascular events, and larger reductions in blood pressure produced greater risk reductions [41]. They undertook seven sets of prospectively designed overviews using data from 29 randomized trials ($n = 162,341$), with the objective of estimating the effects of strategies based on different drug classes (CCBs, ACE inhibitors, angiotensin receptor blockers and diuretics or β -blockers) or those targeting different blood pressure goals, on the risks of major cardiovascular events and death. They found that in placebo-controlled trials the relative risks of total major cardiovascular events were reduced by regimens based on ACE inhibitors (22%; 95% CI: 17–28) or CCBs (18%; 95% CI: 5–30). There were no significant differences in total major cardiovascular events between regimens based on ACE inhibitors,

CCBs or diuretics or β -blockers. There was evidence of some differences between active regimens in their effects on cause-specific outcomes. For every outcome other than heart failure, the greater the reduction in blood pressure the greater the risk reduction.

Angeli and colleagues undertook a meta-analysis to assess whether CCBs were associated with a reduced risk of stroke compared with other antihypertensive drugs [42]. Thirteen major studies conducted in a total of 103,793 hypertensive patients were included in the analysis. Overall, there were 4040 cases of stroke, of which 1789 were among the 43,053 subjects randomized to CCBs and 2251 were among the 60,740 subjects randomized to alternative antihypertensive drugs. An overall reduction in the risk of stroke was observed among patients treated with CCBs (odds ratio [OR]: 0.90; 95% CI: 0.84–0.96; $p = 0.002$). The risk of stroke was significantly lower among subjects who received dihydropyridine CCBs than among those who received alternative drugs (OR: 0.90; 95% CI: 0.84–0.97; $p = 0.006$), whereas the effect of nondihydropyridine CCBs did not reach statistical significance (OR: 0.92; 95% CI: 0.81–1.04). The protective effect on stroke was independent of the degree of blood pressure reduction.

Renal function

Results from the INSIGHT study show that in high-risk antihypertensive patients, treatment with nifedipine GITS appears to be better at preserving renal function than treatment with diuretics [43].

Re-evaluation of treatment guidelines & economic outcomes

In June 2006, the UK National Institute for Health and Clinical Excellence (NICE) and the National Collaborating Centre for Chronic Conditions, in conjunction with the British Hypertension Society (BHS), launched eagerly awaited updated clinical guidelines for the management of hypertension [3].

These new guidelines update the recommendations contained in the original NICE guidelines for the pharmacological management of hypertension that were published in August 2004 and take into account clinical trial data on hypertensive therapies that were not available at the time the original guidelines were developed. NICE and the BHS undertook a thorough review of recently published data and the resulting guidelines set the gold standard for the optimum pharmacological management of hypertension.

The NICE analysis included randomized controlled trials that compared any combination of antihypertensive drugs from the following five classes: ACE inhibitors, angiotensin receptor antagonists, β -blockers, CCBs and thiazide-type diuretics. A total of 20 studies were found that satisfied the stated inclusion criteria, including the INSIGHT and ASCOT trials of CCBs [3,4].

It was noted that in most studies included in the analysis, a significant number of patients required treatment with multiple agents to achieve adequate blood pressure control. Taking this into account, the evidence was considered to show that CCBs or thiazide-type diuretics, including nifedipine GITS, were the most likely drugs to confer benefit as first-line treatment for most patients with hypertension.

A health economic model undertaken as part of the analysis slightly favored CCBs, with thiazide-type diuretics as the next most cost-effective option; although there was some uncertainty regarding this conclusion. Given the potential limitations of the model, it was decided that CCBs and thiazide-type diuretics should be offered as equal alternatives for clinicians to consider as first-line therapy for hypertension. They also state that β -blockers are not a preferred initial therapy for hypertension [3]. In a recently published article, Poole-Wilson and colleagues demonstrated a clear reduction in costs of disease management when a long-acting calcium blocker such as nifedipine GITS was used in a population of patients suffering coronary artery disease. Based on the vast and very solid database from the ACTION study, they were able to demonstrate that the costs of nifedipine GITS treatment, estimated to be €17,680.84 per 100 patient-years, would reduce the costs of disease management in that population with no less than €10,823.03 on savings on events and procedures as well as reduction in the use of other medication. The eventual cost of treatment was estimated to be €6857.81 per 100 years of treatment, less than one third of the net costs for drug treatment thus making the drug importantly cheaper than expected [44].

Expert commentary

It is recognized that an ideal antihypertensive agent should effectively lower blood pressure to normotensive levels while not causing any adverse metabolic changes, and should also

reverse left-ventricular hypertrophy. In several clinical studies, nifedipine GITS has been shown to fulfill these criteria and thereby provide a valuable tool for the clinician in the management of patients of all ages with hypertension and coronary artery disease. It is now recognized that modified-release formulations of nifedipine that cause a gradual onset of vasodilation are preferable to the short-acting types because they avoid baroreflex sympathetic activation. More recently, large, randomized clinical trials have confirmed that nifedipine GITS is a safe and effective first-line treatment option for patients with coronary artery disease and hypertension, including those with additional risk factors [3–5].

In the management of cardiovascular disease, there is now greater emphasis on selecting antihypertensive medications that also have an effect on other cardiovascular parameters and risk factors. Nifedipine GITS appears to have positive effects on markers of atherosclerotic disease, which may provide additional clinical benefits. Meta-analyses of randomized studies with hypertensive patients also suggest that CCBs may contribute to the prevention of stroke.

These positive results have prompted revisions to treatment guidelines for hypertensive patients such that CCBs are now recommended as a first choice for the initial therapy of hypertensive patients, alone or in combination with other agents.

Key issues

- Nifedipine gastrointestinal therapeutic system (GITS) is a long-acting calcium channel blocker that acts on the L-type calcium channels in several vessels, the myocardium and other tissues in humans.
- The nifedipine GITS formulation uses an osmotically driven 'push-pull' release mechanism that results in a slow release of nifedipine into the gastrointestinal lumen and continuous and stable blood levels of nifedipine over 24 h, making it suitable for once-daily administration.
- Nifedipine GITS administered once daily has been shown to have superior antihypertensive efficacy to both short-acting nifedipine capsules and other sustained-release nifedipine formulations.
- The different modified-release formulations of nifedipine have different pharmacokinetic properties and cannot be considered interchangeable.
- Hypertensive patients can be successfully switched to nifedipine GITS from alternative formulations of nifedipine with comparable or improved efficacy.
- Nifedipine GITS has equivalent efficacy to diltiazem and atenolol in increasing exercise tolerance in chronic stable angina patients.
- In comparative trials including calcium channel blockers, β -blockers and angiotensin-converting enzyme inhibitors, nifedipine GITS has shown equal or superior antihypertensive efficacy.
- Safety concerns raised regarding immediate-release nifedipine formulations have been challenged, and the results of recent large, randomized clinical outcomes trials confirm that the long-acting nifedipine GITS formulation is a safe and effective first-line treatment option for patients with coronary artery disease and hypertension, including those with additional risk factors.
- Revised treatment guidelines for hypertension recommend either a calcium channel blocker or a thiazide-type diuretic as the first choice for initial therapy for patients aged at least 55 years or for black patients of any age.
- Nifedipine GITS also has clinical benefits independent of blood pressure control: clinical studies have shown beneficial effects on vascular function and progression of atherosclerosis, a reduction in left-ventricular hypertrophy and preservation of renal function.

Nifedipine has been used successfully for many decades, both alone and in combination with other antihypertensive drugs, for the management of hypertension and stable angina pectoris. Nifedipine is effective and well tolerated in patients of all ages, including high-risk patients with underlying comorbidities, and is not associated with the adverse changes in lipid and glucose metabolism seen with some other classes of antihypertensive agents.

The nifedipine GITS formulation has a long duration of action and a predictable 24-h release profile that makes it suitable for convenient once-daily administration. This has the advantages of improving adherence to therapy and minimizing any potential variability in the antihypertensive and anti-ischemic effects. Nifedipine GITS has proven and well-established antihypertensive and antianginal effects. The results of large outcomes trials, such as INSIGHT and ACTION, provide definitive evidence that nifedipine GITS has beneficial effects on morbidity and mortality [3,5]. Moreover, these and other studies provide further evidence about the final version of the manuscript in taking care of the correct antiatherosclerotic effects of nifedipine.

Five-year view

The management of cardiovascular disease remains a key medical challenge, particularly in western countries, and represents a significant healthcare burden that is likely to continue. To achieve reductions in overall cardiovascular morbidity and mortality in at-risk patients, it is important that therapeutic choices include effective and well-tolerated agents that are proven to reduce cardiovascular risk factors, particularly the most modifiable risk factor – hypertension. Recent changes to hypertension treatment guidelines recommend CCBs as a first-choice initial therapy and will mean that even more patients can now benefit from agents such as nifedipine GITS, which provides effective clinical efficacy in the short-term and improved outcomes in the long-term.

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