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Review Article

Nicardia® XL (Nifedipine Extended Release): Technologically Advanced GITS Formulation Ensures Robust Efficacy and Assured Safety

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Abstract



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Nifedipine is a classical dihydropyridine calcium channel blocker (CCB) indicated for the management of hypertension, vasospastic angina and chronic stable angina. Prestigious regulatory bodies like USFDA, EMA, CDSCO and TGA have approved long-acting Nifedipine for the management of hypertension and angina. Nifedipine was 1st introduced in United States as Adalat® (Bayer) in 1981 and in India as Nicardia® (J. B. Chemicals & Pharmaceuticals) in 1985.

Conventional Nifedipine shows the rapid onset and short duration of action which results in prompt and marked hypotensive effect but exhibits reflex SNS activation leading to flushing, tachycardia, worsening myocardial ischemia, and cerebrovascular ischemia. Nifedipine gastrointestinal therapeutic system (GITS) formulation addresses many of the concerns surrounding the older formulations of Nifedipine. Nifedipine GITS is a gold standard once-daily formulation of Nifedipine which allows relatively constant plasma drug concentrations over 24 hours. Nifedipine GITS provides a controlled release and gradual onset of action of Nifedipine, avoiding the reflex SNS activation resulting in improved tolerability and compliance.

Clinical studies suggest that long-acting formulations of Nifedipine have slightly greater antihypertensive actions than Amlodipine. Nifedipine was also found to be more efficient than other CCBs like Amlodipine, Nicardipine, and Isradipine in resistant hypertensive patients. The addition of Nifedipine GITS to the conventional treatment of angina pectoris is safe and reduces the need for coronary angiography and interventions.

Several landmark trials have demonstrated that long-acting Nifedipine improves endothelial function and arterial stiffness and reduces albuminuria, LV hypertrophy, atherosclerotic plaques and cardiovascular and cerebrovascular complications.

This comprehensive review focuses on the superiority of the Nifedipine GITS formulation over the conventional Nifedipine and elaborates on the role of long-acting Nifedipine as a CCB of choice for the management of hypertension, resistant hypertension, angina pectoris and coronary artery disease.

Keywords – Calcium Channel Blockers, Nifedipine, Long-Acting Nifedipine, Nifedipine GITS, Nifedipine Extended Release, Nicardia XL.

HYPERTENSION – AN EVER-GROWING BURDEN

Hypertension is one of the leading health-related risk factors in India, with the largest contribution to the burden of disease and mortality¹. An astonishing 1 out of every 3 adults in India is affected by hypertension, making it one of the highly prevalent diseases in the country². The number of people living with hypertension world-wide has doubled to 1.3 billion since 1990³. Globally, hypertension accounts for a staggering 10.4 million deaths every year⁴. Hypertension is diagnosed when blood pressure is consistently ≥ 130 and/or ≥ 80 mm Hg⁵.

Studies have shown that most hypertensive patients on conventional treatment have uncontrolled blood pressure^{6,7}.

Globally, nearly 1 billion individuals are living with uncontrolled hypertension with a proportion of 66.8% and 61.6% in developed and developing countries respectively⁶. Resistant hypertension is defined as hypertension that remains uncontrolled with three antihypertensives (including one diuretic) or blood pressure that is controlled on four medications, while refractory hypertension is the one which remains uncontrolled on five or more antihypertensives of different classes including a diuretic and a mineralocorticoid receptor antagonist⁸. Uncontrolled hypertension is one of the most important cardiovascular risk factors and contributes to an elevated risk of stroke, myocardial infarction, heart failure, and renal failure⁹.

Hypertension is managed by a combination of lifestyle changes and pharmacological therapy. Some effective life-style strategies include decreasing salt intake, increasing potassium intake from vegetables and fruits, weight control, limiting alcohol intake, and quitting smoking. The drugs commonly used for the treatment of hypertension either alone or in combination include calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEi), beta-blockers, alpha-blockers and diuretics¹⁰.

CALCIUM CHANNEL BLOCKERS – A PROVEN ANTI-HYPERTENSIVE THERAPY

Calcium channel blockers, also called as calcium channel antagonists, are a popular class of antihypertensive drugs. CCBs are the 1st line drugs for the management of hypertension. CCBs are the only class of agents deemed desirable for combination with all the other four classes of antihypertensive drugs including ARB, ACEi, Beta-blocker and Diuretics¹¹.

These agents are classified into two major categories, non-dihydropyridines or dihydropyridines. The non-dihydropyridines include Verapamil and Diltiazem while the dihydropyridines include drugs like Nifedipine, Amlodipine, Cilnidipine, Azelnidipine, Benidipine etc. (Table 1).

Calcium channel antagonists block the inward movement of calcium by binding to the L-type “long-acting” voltage-gated calcium channels in the heart, vascular smooth muscle, and pancreas.

Table 1 - Classification of Calcium Channel Blockers

Non-dihydropyridines	Dihydropyridines
Verapamil	Nifedipine
Diltiazem	Amlodipine
	Cilnidipine
	Azelnidipine
	Benidipine

The non-dihydropyridines have inhibitory effects on the sinoatrial, and atrioventricular nodes which result in slowing of cardiac conduction and contractility. This allows for the treatment of hypertension, reduces oxygen demand, and helps to control the rate of tachydysrhythmias. The dihydropyridines have a little direct effect on the myocardium, and instead, are more often peripheral vasodilators¹².

Dihydropyridine CCBs have been determined to be appropriate for first-line therapy in patients with hypertension, particularly in those with left ventricular hypertrophy, asymptomatic atherosclerosis, angina pectoris, permanent atrial fibrillation, peripheral artery disease, isolated systolic hypertension, metabolic syndrome, and pregnancy¹³.

It is important to note that not all CCBs are alike. CCBs are a heterogenous class of antihypertensives. Therefore, each agent needs to be considered individually.

CONVENTIONAL NIFEDIPINE – A CLASSICAL CCB

Nifedipine is the prototype dihydropyridine CCB first introduced in 1975 initially for the prevention of angina symptoms and later for the treatment of hypertension.

Nifedipine was 1st introduced in United States as Adalat® (Bayer) in 1981 and in India as Nocardia® (J. B. Chemicals & Pharmaceuticals) in 1985.

Nifedipine is a short-acting, potent vasodilator, which relaxes vascular smooth muscle by its inhibitory effect on the transmembrane influx of calcium. Nifedipine is indicated in the treatment of essential hypertension, angina resulting from coronary artery spasms, and chronic stable angina. Nifedipine exerts its effect on hypertension, as well as angina, by acting as an arterial vasodilator. Nifedipine is also very effective in the treatment of severe hypertension and hypertensive emergency. Other potential uses of Nifedipine in certain subclasses of patients include treatment of Raynaud's phenomenon, congestive heart failure, and prevention of atherosclerosis, although it must be emphasised that these are not approved indications.

Conventional Nifedipine has a rapid onset and short duration of action. The hypotensive effect of the conventional form of Nifedipine is observed maximally at 1 hour after administration and disappears within 7 hours. As a result, Nifedipine has been shown to exert a prompt and marked hypotensive effect when administered to hypertensive patients¹⁴. Rapid and profound vasodilation by short-acting Nifedipine has been associated with reflex sympathetic nervous system (SNS) activation leading to flushing, tachycardia, worsening myocardial ischemia, and cerebrovascular ischemia¹⁴. It has been suggested that a higher incidence of cardiovascular events associated with Nifedipine may be due to reflex activation of the SNS²⁰.

Also, due to the short duration of action, a q.i.d. administration of the conventional Nifedipine is essential for the maintenance of a hypotensive effect. Therefore, physicians and patients found it difficult to use the conventional form of Nifedipine for the treatment of mild to moderate hypertension.

EVOLUTION OF NIFEDIPINE FORMULATIONS

The administration of the original formulation of Nifedipine (immediate-release capsules) was associated with a profound reflex increases in heart rate and activation of the sympathetic nervous system. The Nifedipine immediate-release capsules needed a q.i.d. administration for maintenance of a hypotensive effect.

Nifedipine retard formulation was developed to overcome the limitations of the Nifedipine immediate-release capsules. The retard formulation of Nifedipine blunted the peak concentration and sustained the measurable drug levels over a longer period. The Nifedipine retard required a twice-daily administration. There was a more sustained reduction in blood pressure with Nifedipine retard, but there was still a significant increase in heart rate.

Hence, it was desirable to develop a long-acting form of Nifedipine to overcome the disadvantages observed with Nifedipine immediate-release capsule and Nifedipine retard. It was recognized that the rate of delivery of Nifedipine into the systemic circulation was a direct determinant of the rate of onset of vasodilator effect and extent of the reflex sympathetic activation. As a result, modified-release formulations of Nifedipine were then developed.

The development of the GITS formulation finally resulted in a formulation that delayed and flattened the attainment of the peak plasma concentrations of Nifedipine and thereafter sustained these levels at a relatively constant level for 24 hours. This results in a smoother, more gradual onset of the antihypertensive effect, sustained throughout 24 hours with no discernible cardioacceleration.

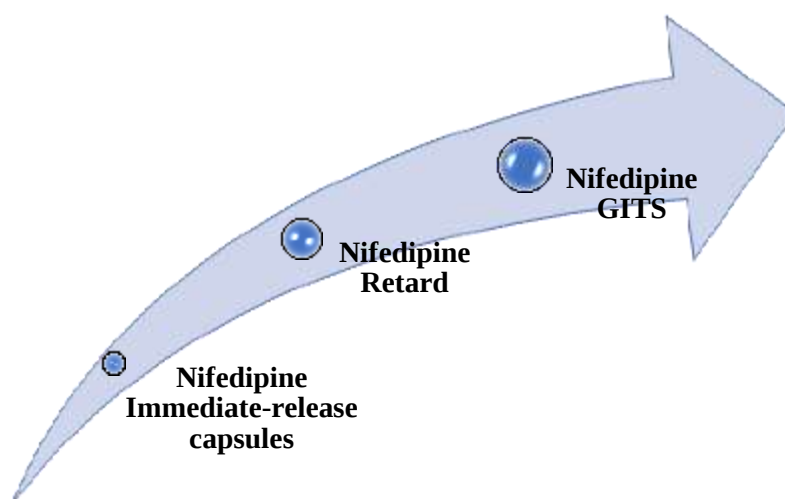


Figure 1 :- Evolution of Nifedipine Formulations

NIFEDIPINE GASTROINTESTINAL THERAPEUTIC SYSTEM (GITS) – A NOVEL DRUG DELIVERY SYSTEM

Nifedipine gastrointestinal therapeutic system (GITS) technology is the latest advancement in the Nifedipine drug delivery system which allows relatively constant plasma drug concentrations over 24 hours. Nifedipine GITS is regarded as the gold standard once-daily formulation of Nifedipine. The GITS formulation provides drug concentration which reaches a plateau within 6 hours after administration of a single Nifedipine dose and continue at that concentration until at least 24 hours after administration¹⁶.

This device utilizes a proprietary mechanism involving a 'push-pull' osmotic pump process. An osmotic pump method used in the formulation of the Nifedipine GITS, allows for nearly zero-order drug administration. The osmotic push-pull

technology-based Nifedipine GITS formulation comprises a bilayer core containing Nifedipine and an osmotically active but pharmacologically inert polymer wrapped by a semipermeable membrane (Figure 2). The pill absorbs water after entering the gastrointestinal tract, resulting in a Nifedipine suspension in the drug reservoir. The medication suspension is then extruded through the precision-drilled pore at a controlled rate over 24 hours as the polymer swells and the osmotic pressure rises. Until the formulation is exhausted, this unique osmotic delivery method releases Nifedipine into the gastrointestinal system and thus into the systemic circulation at a constant (zero-order) rate^{15,16}. This process does not depend upon pH or intestinal motility, therefore drug distribution out of the system does not vary with gastrointestinal contents or function.

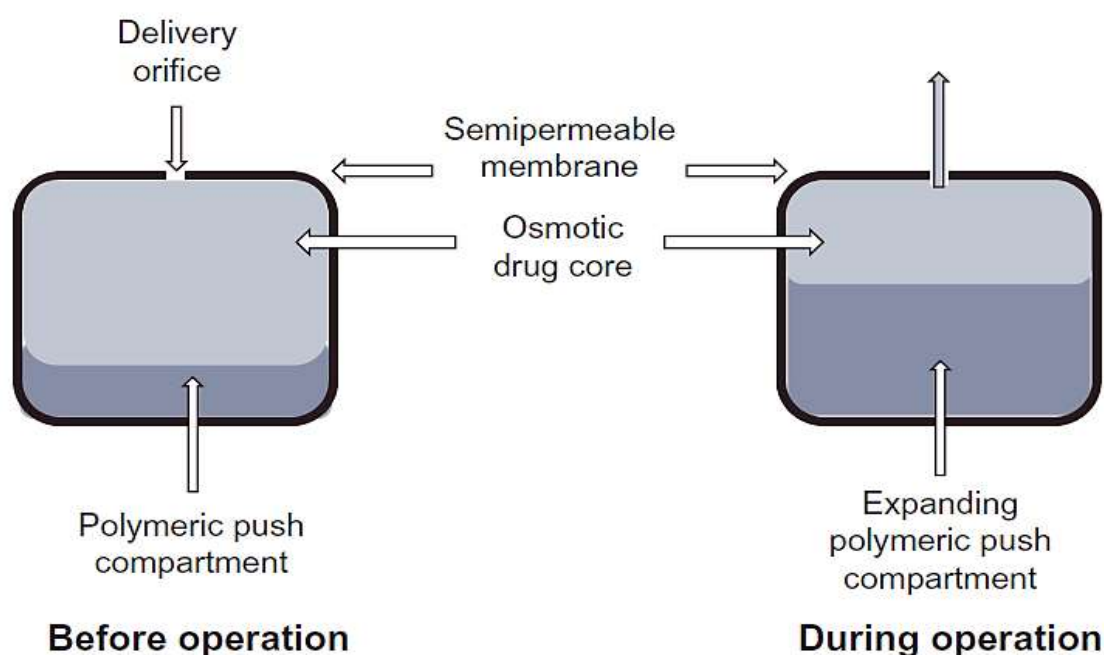


Figure 2: Diagrammatic representation of the Nifedipine gastrointestinal therapeutic system (GITS). (Image sourced from a paper by Peter A Meredith¹¹)

Nifedipine GITS provided relatively constant plasma concentrations over >18 hours intervals in a clinical study done on 23 healthy human volunteers (Figure 3). The results of this study suggest that Nifedipine drug release and

absorption are zero-order within the human GI tract, and that once-daily administration appears to be reasonable with the device¹⁷.

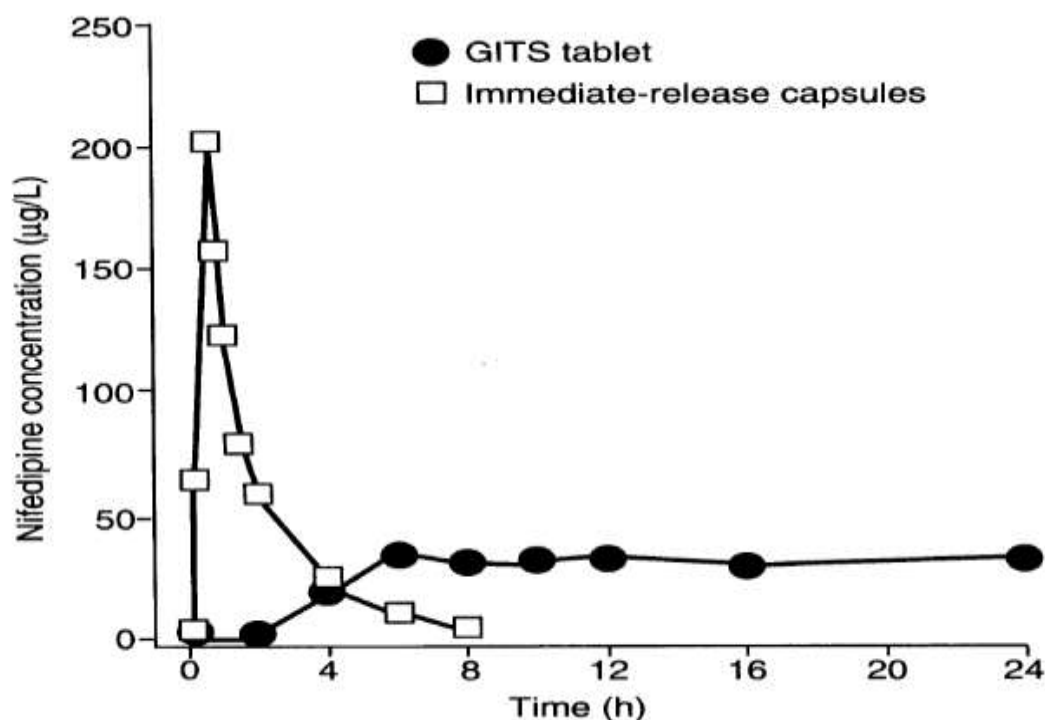


Figure 3:- Mean plasma Nifedipine concentration-time profiles in healthy volunteers (n = 23) after single doses of a Nifedipine GITS tablet (60mg) or immediate-release Nifedipine capsules (2 x 10mg)¹⁷ (Graph sourced from a study by Chung M et al.¹⁷)

Nifedipine GITS formulation allows controlled release of the drug and thus prolongs the duration of action and reduces the risk of adverse events as compared to conventional Nifedipine. The diameter of the pre-drilled opening limits the rate at which the drug exits the system, thus preventing a dose-dumping effect. The prevention of dose dumping by GITS technology also contributes to smooth BP management. Another important advantage of the Nifedipine GITS is that the trough/peak (T/P) effect ratio following once-daily administration is maintained above 50%, as recommended by the United States Food and Drug Administration¹⁶. Studies with the Nifedipine GITS have reported T/P ratios between 66 and 98.6%¹⁶.

Further, the extended 24-hours duration of action reduces the frequency of drug intake from two or three tablets (in conventional Nifedipine) to once daily. Once-daily dose administration with Nifedipine GITS would help improve patient compliance and the long-term treatment outcomes.

With respect to age, no or only slight differences were found in Nifedipine GITS pharmacokinetic parameters after single or multiple doses in young and elderly volunteers, and thus no dosage adjustment is apparently necessary¹⁶. Similarly, impaired renal function in patients does not appear to

significantly affect the plasma concentrations of Nifedipine even following multiple doses of the Nifedipine GITS, and thus dosage adjustment seems unnecessary¹⁶.

It should be noted that, in GITS systems, the tablet shell does not dissolve but passes through the gastrointestinal system intact and is expelled upon defecation.

LONG-ACTING NIFEDIPINE – THE NEXT-GEN REVAMPED CCB

Recently, long-acting formulations of Nifedipine were developed and made available to the clinicians. These newer formulations were designed to address many of the concerns raised by earlier formulations of Nifedipine. Long-acting formulations of Nifedipine have a longer duration of action, greater bioavailability, and lesser incidences of adverse events than the conventional preparations¹⁸. Regulatory bodies like USFDA, EMA, CDSCO and TGA have approved long acting Nifedipine for hypertension and angina. Numerous extended-release formulations of Nifedipine are available worldwide and have been shown to be equally efficacious as compared to other antihypertensives such as ARBs, β -blockers, and diuretics in the management of hypertension¹³.

Table 2: Comparative Analysis of Conventional Nifedipine and Long acting Nifedipine Over Various Pharmacological Parameters

Parameters	Conventional Nifedipine	Long-Acting Nifedipine
1. Technology	Normal tablet	Osmotically controlled drug release oral delivery system (OROS)
2. Drug release	Rapidly releases the active drug	Slow and sustained release of active drug
3. Onset of action	Rapid	Slow
4. Duration of action	Short	Long (24 hours)
5. Half-life	1.7 hours	7 hours
6. Bioavailability	45%–68%	75% - 85%
7. Dosing	Twice daily	Once daily
8. Blood Pressure	Rapidly decreases blood pressure	Smoother, more gradual decrease in blood pressure
9. Norepinephrine (NE) level	Increases significantly both acutely and chronically, reaching peak 3 hours after drug administration	Decreases plasma NE levels significantly 6 hours after the dose and the effect is maintained throughout the dosing interval
10. Heart Rate (HR)	Increases HR	No significant change in HR
11. Edema	High incidence	Low incidence
12. Side-effects	SNS activation Flushing Tachycardia Worsens myocardial & cerebrovascular ischemia	Lesser side-effects as compared to short-acting formulations

LONG-ACTING NIFEDIPINE – INSIGHTS FROM CLINICAL TRIALS

According to AHA Scientific Statement, dihydropyridine CCBs such as Nifedipine extended release and Amlodipine are the most studied in the setting of hypertension¹⁹. Till date, a staggering >24,000 publications and >2700 clinical trials are being published on Nifedipine in the scientific journals.

In adults with essential hypertension, monotherapy with modified-release Nifedipine (irrespective of formulation) for ≥8 weeks led to similar reductions in systolic and diastolic BP, and achieved similar response rates, to those seen with comparator agents, including Amlodipine, Lacidipine, extended-release Verapamil, Enalapril, Lisinopril, Losartan (with or without Hydrochlorothiazide) and Nebivolol³⁶.

The extended-release formulation of Nifedipine significantly reduced SBP and DBP due to its longer duration of action (24 hours)^{20,21}. The Nifedipine GITS formulation was associated with a more gradual decrease in BP without an increase in NE, potentially due to the fact that plasma drug levels were lower than those obtained by Nifedipine retard²⁰.

Clinical studies suggest that long-acting formulations of Nifedipine have slightly greater antihypertensive actions than

Amlodipine^{22,23,24}. In a study conducted by Keisuke Kuga et al., the total anti-hypertensive power of Nifedipine coat-core, measured by the hypobaric area, was found to be 1.69 times more potent than that of Amlodipine²³.

In a 10-week, multi-center, double-blind study, 102 patients received Nifedipine GITS 30 or 60 mg daily, Hydrochlorothiazide 25 or 50 mg daily, or placebo. Both treatments, Nifedipine GITS and Hydrochlorothiazide were found to be significantly better than placebo in decreasing SBP and DBP with 71% of the Hydrochlorothiazide group and 67% of the Nifedipine group achieving a sitting DBP <90 mmHg. This study concluded that Nifedipine GITS monotherapy decreases BP with efficacy similar to that of Hydrochlorothiazide²⁵.

In another double-blind study, patients received Nifedipine GITS or sustained-release Propranolol for 8 weeks. In this study, sitting SBP has decreased a mean of 15.9 mmHg in the Nifedipine group compared to 5.7 mmHg in the Propranolol group ($p < 0.001$). The proportion of patients receiving Nifedipine who achieved target sitting and standing SBP was 61% and 52%, respectively, as compared to 25% and 28% in the Propranolol group²⁶.

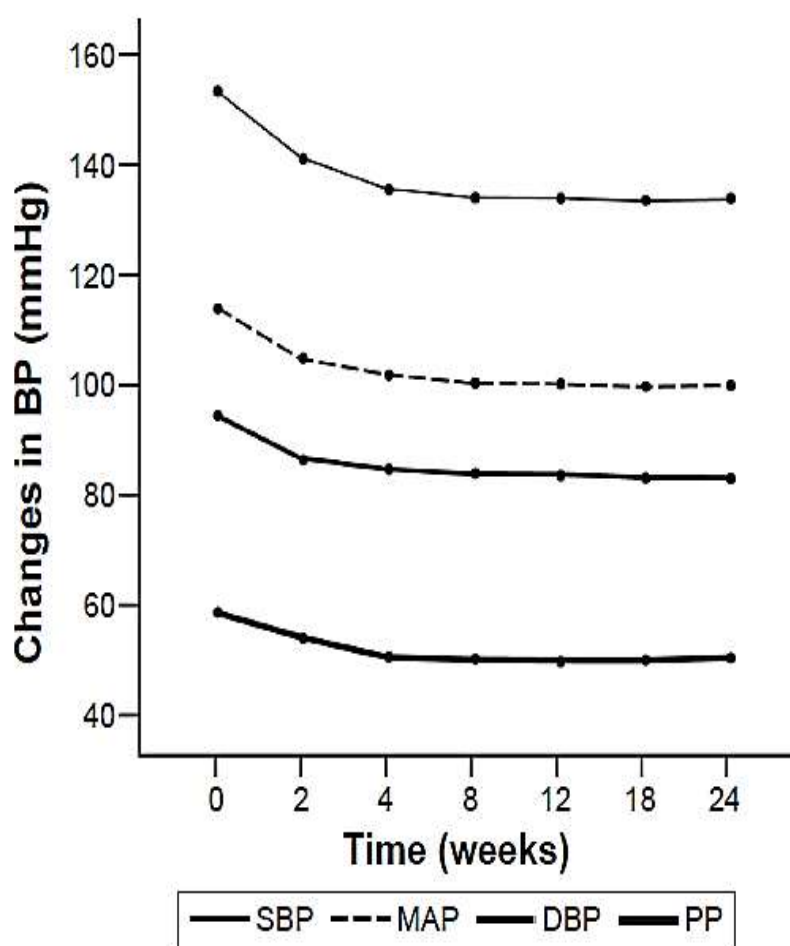


Figure 4 :- Changes in hemodynamic parameters with Nifedipine GITS (Graph sourced from a study by Jidong Zhang et al.)²⁰

LONG-ACTING NIFEDIPINE – CCB OF CHOICE IN DIFFICULT TO CONTROL/ RESISTANT HYPERTENSION/ REFRACTORY HYPERTENSION

Resistant hypertension can be managed with appropriate lifestyle modifications and escalation of antihypertensive medications. In patients with uncontrolled BP on the triple combination, it is important to first replace the existing on-going drugs with other potent molecules from the same class, before adding new drugs. For examples, the existing CCB can be replaced with a more potent CCB like long-acting Nifedipine. According to an expert review paper published in the Clinical Journal of the American Society of Nephrology, long-acting Nifedipine or Amlodipine should be the preferred CCBs for managing resistant hypertensive patients²⁷.

In several clinical trials done in refractory hypertensive patients, the high potent antihypertensive action of a single dose of long-acting Nifedipine was found to be much more efficient than two or more doses of Amlodipine, Nicardipine, and Isradipine^{24,22,28}.

Landmark MONICA Study compared the efficacy of Valsartan 80 mg + Amlodipine 5 mg per day with Valsartan 80 mg + Nifedipine controlled release (CR) 20 mg per day in thirty-five patients with uncontrolled blood pressure for 16 weeks. If the patient did not reach the target office BP at 8 weeks, they received double doses of CCBs. In the Valsartan + Nifedipine group, morning diastolic BP was found to be significantly lower than the respective values in the Valsartan + Amlodipine group at 8 weeks. The percentage of patients who required a double dose of CCB in the Valsartan + Nifedipine group was

significantly lower than that in the Valsartan + Amlodipine group. Urinary albumin/creatinine at 16 weeks was significantly less than that at 0 weeks in the Valsartan + Nifedipine group. The authors concluded that, combination therapy with Valsartan and Nifedipine CR may help to control morning BP and protect the kidneys²⁴.

In another study done in patients with an inadequate response to Candesartan, Atenolol or Diuretic monotherapy, the addition of modified release Nifedipine formulations led to significant reductions in BP³⁶.

According to the ESC/ESH guidelines for managing severe hypertension during pregnancy, drug treatment with IV Labetalol, oral Methyldopa, or Nifedipine is recommended²⁹.

Joshua Adeniyi Adebayo et al. compared Nifedipine versus Hydralazine in the management of severe hypertension in pregnancy. Both oral Nifedipine and intravenous Hydralazine were found to be equally efficacious for acute control of BP in severe hypertension in pregnancy without adverse maternal and perinatal effects. However, the average number of dosages needed to control the BP was lower in the Nifedipine arm³⁰.

LONG-ACTING NIFEDIPINE – BENEFITS BEYOND BLOOD PRESSURE CONTROL

Long-acting formulations of Nifedipine have been shown to exert several beneficial effects along with blood pressure reduction.

Nifedipine has been shown to decrease albuminuria in hypertensive patients. MONICA study, showed that,

combination therapy consisting of Valsartan and Nifedipine CR is more useful for controlling morning BP and protecting the kidneys than the combination of Valsartan and Amlodipine. Valsartan + Nifedipine was found to significantly reduce the urinary albumin/creatinine after 16 weeks of treatment²⁴. Renal function was better preserved with Nifedipine GITS than with Co-amilofide in hypertensive patients in the INSIGHT study, while in the J-MIND study, Nifedipine had a similar effect on urinary albumin excretion (UAE) rate after 2 years to that seen with Enalapril in hypertensive diabetic patients³⁶.

Nifedipine has been shown to improve endothelial function by the virtue of its anti-hypertensive action. An improvement in endothelial function by Nifedipine GITS was demonstrated in the ENCORE study by a significant reduction in acetylcholine-induced vasoconstriction in the coronary arteries³¹.

A prospective, double-blind INSIGHT trial by Brown and colleagues evaluated the cardiovascular and cerebrovascular outcomes following Nifedipine GITS 30 mg or Co-amilofide (HCTZ 25 mg/amilofide 2.5 mg) daily therapy. The primary outcome was reported in 6.3% of patients in the Nifedipine group compared to 5.8% in the Co-amilofide group ($p = 0.34$). There was no significant difference in event rates between groups. The authors concluded that both agents were equally efficacious in preventing cardiovascular and cerebrovascular complications.³² One sub-analysis of the INSIGHT study showed that, Nifedipine and diuretics offer similar protection against cardiovascular events³³. Another sub-analysis of the INSIGHT study showed that, Nifedipine GITS and diuretics are equally efficacious in the treatment of patients with isolated systolic hypertension³⁴.

In the STONE study, Nifedipine was found to significantly reduce the risk of major clinical events compared with placebo in elderly hypertensive patients while in the JMIC-B study, Nifedipine had similar efficacy to ACE-inhibitor therapy in terms of reducing major cardiac events in patients with both hypertension and coronary artery disease³⁶.

Landmark INTACT trial provided evidence that, relative to placebo, Nifedipine GITS significantly reduced the development of new lesions (stenoses > 20% or occlusions) in

patients with mild coronary artery disease (CAD) over a 3-year trial period³⁵. In patients with CAD, Nifedipine GITS significantly improved coronary endothelial function by increasing artery diameter.⁴²

In patients with chronic stable angina pectoris, modified-release Nifedipine significantly increased the time to onset of 0.1mV ST-segment depression during exercise testing compared with baseline. Improvements were similar to those seen with Atenolol, Carvedilol or Diltiazem³⁶. In another study, modified-release Nifedipine was as effective as modified-release Isosorbide dinitrate or Nisoldipine coat-core in patients with variant angina³⁶.

Landmark ACTION trial was a large, double-blind trial in which patients were randomized to receive Nifedipine GITS 30–60 mg once daily ($n = 3825$) or placebo ($n = 3840$) in addition to standard treatment and followed up for a mean of 4.9 years. ACTION trial showed that the addition of Nifedipine GITS to conventional treatment of angina pectoris is safe and reduces the need for coronary angiography and interventions³⁷. The mean heart rate was higher by 1 bpm in the Nifedipine GITS group versus the placebo group. The risk of meeting the primary efficacy endpoint (a composite of major events including death from any cause, MI, refractory angina, new overt heart failure, debilitating stroke, peripheral revascularization), or primary safety endpoint (a composite of any death, MI or debilitating stroke) was similar for recipients of Nifedipine GITS and placebo³⁷. Looking at secondary endpoints, there was no difference for 'any cardiovascular event', but the composite endpoint 'any death, cardiovascular event or procedure' and the 'any vascular event' endpoint were significantly reduced by 11% and 9% with Nifedipine GITS compared with placebo³⁷ (Figure 5). This was largely because fewer Nifedipine GITS recipients needed coronary angiography or coronary bypass surgery (hazard ratios 0.82 [$p < 0.0001$] and 0.79 [$p = 0.0021$]). Nifedipine GITS significantly reduced the incidence of any stroke or transient ischemic attack and the need for coronary angiography by 21% in normotensives and 16% in hypertensives. Nifedipine GITS prolonged the mean cardiovascular event and procedure-free survival by 41 days.

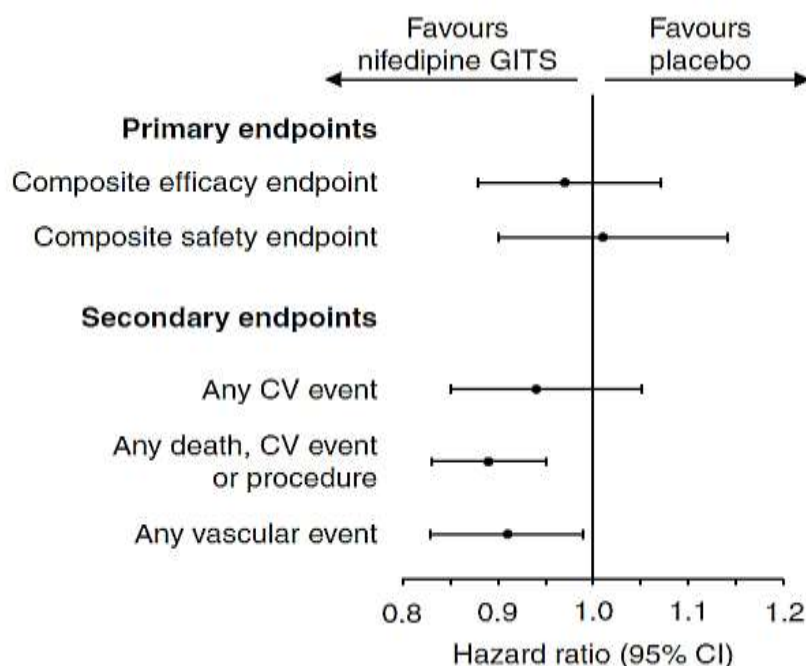


Figure 5 :- Effect of Nifedipine GITS on Cardiovascular (CV) Outcomes in Patients With Chronic Stable Angina³⁷ (Forest Plot sourced from the ACTION study³⁷)

The PRESERVE trial demonstrated the effectiveness of Nifedipine GITS in reducing LV hypertrophy. This study compared once-daily Enalapril or long-acting Nifedipine, plus adjunctive Hydrochlorothiazide and Atenolol when needed to control blood pressure. Both once-daily Enalapril and long-acting Nifedipine had moderately beneficial and statistically indistinguishable effects on regression of LV hypertrophy³⁸.

In a study conducted by Houston MC, Nifedipine GITS significantly increased HDL, HDL2, and apolipoprotein A-I and A-II levels in patients with mild-to-moderate hypertension³⁹. In other 2 studies, Nifedipine GITS significantly reduced apolipoprotein E levels, the LDL:HDL-cholesterol ratio and the apolipoprotein B:A-I ratio in hypertensive patients^{40,41}. Nifedipine GITS was also shown to non-significantly reduce serum triglyceride levels^{39,41}.

In a single-center, prospective, Phase IV study, Jidong Zhang et al., evaluated the early intervention impact of Nifedipine GITS on arterial stiffness and pulse wave velocity (PWV) in mild hypertensive patients. Nifedipine GITS was found to significantly reduce 24-hour ambulatory BP and brachial-ankle pulse wave velocity, indicating improvement in arterial stiffness as early as 4 weeks²¹.

In animal studies, Nifedipine retarded and reversed the development of atherosclerotic plaque and improved endothelial function. Several animal studies have indicated that Nifedipine may reduce the accumulation of components of atherosclerotic plaque and, therefore, retard the development of lesions in rats, rabbits and primates. Plaque formation was inhibited dose-dependently in Nifedipine-treated (50 mg/kg) rats fed a cholesterol-enriched diet by up to 61% relative to controls⁴². In humans, Nifedipine GITS has been shown to slow the progression of various markers of early atherosclerosis, including intimal thickening, vascular calcification and luminal narrowing⁴².

LONG-ACTING NIFEDIPINE – PROVEN SAFETY & TOLERABILITY

Extended release Nifedipine appears to be relatively well tolerated, particularly compared with other antihypertensives because it does not cause depression of the central nervous system or orthostasis²⁵. The extended-release formulation of Nifedipine possesses clinically significant benefits since reflex activation of the SNS correlates with the rate of increase in plasma drug levels. Thus, the gradual rise in drug concentrations decreases SNS activation, in turn reducing adverse events associated with short-acting Nifedipine^{43,44}.

The most common types of adverse events seen, irrespective of formulation, are those relating to its vasodilatory properties, such as headache, peripheral edema not associated with heart failure, flushing and palpitations³⁶. The most significant adverse effect, edema, is dose-related and occurs in 10% to 30% of patients receiving 180 mg Nifedipine. When compared with placebo, headache and edema were more common in the Nifedipine extended-release group.

When the GITS formulation was compared to prolonged action and capsule formulations, Nifedipine GITS was better tolerated with respect to overall adverse events, particularly headache and dizziness. Only vomiting was more common in the Nifedipine GITS arm compared to the other formulations⁴⁴.

A study by Wenzel and colleagues showed that, there was no significant change in HR in the Nifedipine GITS group compared to baseline⁴⁵.

In the EXACT trial, adverse events were most commonly reported during the first few weeks of the Nifedipine GITS treatment period, and then decreased in frequency⁴⁶.

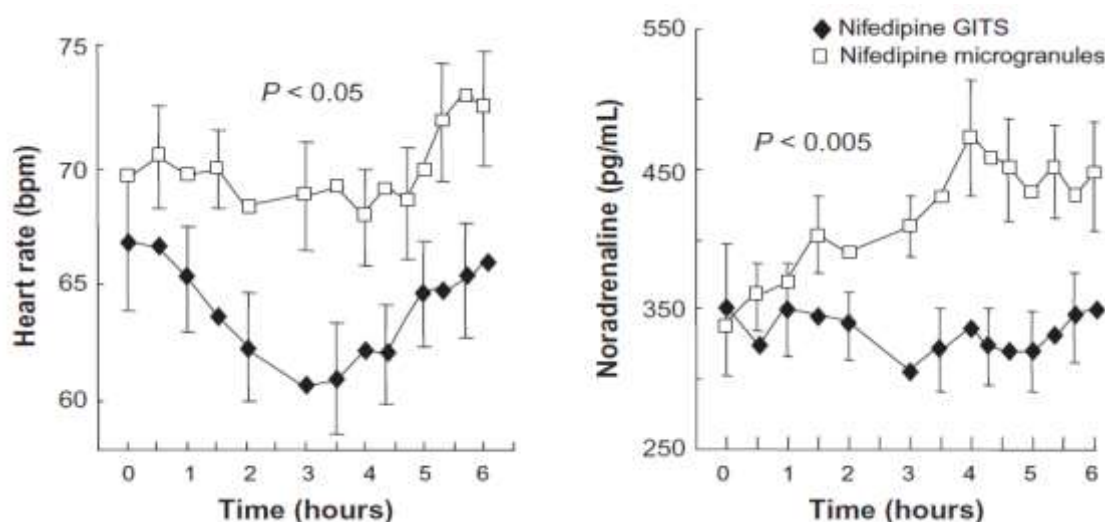


Figure 6:- Effect of Different Nifedipine Formulations on Heart Rate and Plasma Noradrenaline Level¹¹ (Graphs sourced from a paper by Peter A Meredith¹¹)

Table 3:- Long-Acting Nifedipine Brands Available Globally

Brand	Strength	Manufacturer
Adalat CC	30 mg, 60 mg, 90 mg	Bayer
Adipine XL	30 mg, 60 mg	Chiesi
Procardia XL	30 mg, 60 mg, 90 mg	Pfizer
Afeditab CR	30 mg, 60 mg	Actavis

Table 4:- Long-Acting Nifedipine Brands Available in India

Brand	Strength	Manufacturer
Nicardia XL	30 mg, 60 mg	J. B. Chemicals and Pharmaceuticals
Folcardia XL	30 mg	Folarix

Table 5 :- Long-Acting Nifedipine Indication and Dosage

Indications	Hypertension Vasospastic Angina Chronic Stable Angina
Dosage	30 or 60 mg once daily

DISCUSSION & CONCLUSION

Hypertension is the number one risk factor for death, affecting more than 1 billion people globally. It has been found that, despite the availability of standard medicines, most hypertensive patients on conventional treatment have uncontrolled blood pressure. CCBs are the 1st line drugs for the management of hypertension and the only class of agents deemed desirable for combination with all the other four classes of antihypertensive drugs including ARB, ACEi, Beta-blockers, and Diuretics.

Nifedipine is a classical dihydropyridine CCB introduced initially for the prevention of angina symptoms and later for the treatment of hypertension. Conventional Nifedipine had a rapid onset and short duration of action which results in prompt and marked hypotensive effect but exhibits reflex SNS activation leading to flushing, tachycardia, worsening myocardial ischemia, and cerebrovascular ischemia.

Nifedipine GITS formulation addresses many of the concerns surrounding the older formulations of Nifedipine. Nifedipine GITS is a gold standard once-daily formulation of Nifedipine which allows relatively constant plasma drug concentrations over 24 hours. Nifedipine GITS provides a controlled release and gradual onset of action of Nifedipine, avoiding the baroreceptor-mediated reflex activation of the SNS observed with conventional Nifedipine. This once-daily, long-acting formulation improves tolerability and compliance in patients with hypertension.

Esteemed regulatory bodies like USFDA, EMA, CDSCO, and TGA have approved long acting Nifedipine for hypertension and angina. Numerous extended-release formulations of Nifedipine are available worldwide and have been shown to be equally efficacious as compared to other antihypertensives such as ARBs, β -blockers, and diuretics in the management of hypertension.

According to AHA Scientific Statement, among CCBs, Nifedipine extended release and Amlodipine are the most studied in the setting of hypertension. Till date, >24,000 publications and >2700 clinical trials are being published on Nifedipine in scientific journals. Clinical studies suggest that long-acting formulations of Nifedipine have slightly greater antihypertensive actions than Amlodipine. In a study conducted by Keisuke Kuga et al., the total anti-hypertensive power of Nifedipine coat-core, measured by the hypobaric area, was found to be 1.69 times more potent than that of Amlodipine. In several clinical trials done in resistant hypertensive patients, the high potent antihypertensive action of a single dose of long-acting Nifedipine was found to be

much more efficient than two or more doses of Amlodipine, Nifedipine, and Isradipine.

Long-acting formulations of Nifedipine have been shown to exert several beneficial effects along with blood pressure reduction. In the MONICA trial, Nifedipine was found to significantly reduce the urinary albumin/creatinine after 16 weeks of treatment while in the J-MIND study, Nifedipine had a similar effect on urinary albumin excretion (UAE) rate as Enalapril in hypertensive diabetic patients after 2 years of treatment.

An improvement in endothelial function by Nifedipine GITS was demonstrated in the ENCORE study while the landmark INSIGHT trial showed the role of Nifedipine in preventing cardiovascular and cerebrovascular complications. STONE and JMIC-B trials also showed Nifedipine to significantly reduce the risk of major clinical events in elderly hypertensive patients and to reduce the major cardiac events in patients with both hypertension and coronary artery disease respectively.

Landmark INTACT trial provided evidence that, relative to placebo, Nifedipine GITS significantly reduced the development of new lesions in patients with mild coronary artery disease over a 3-year trial period. ACTION trial showed that, the addition of Nifedipine GITS to conventional treatment of angina pectoris is safe and reduces the need for coronary angiography and interventions. Nifedipine GITS prolonged the mean cardiovascular event and procedure-free survival by 41 days. The PRESERVE trial demonstrated the effectiveness of Nifedipine GITS in reducing LV hypertrophy. A prospective, Phase IV study by Jidong Zhang et al. showed that, early intervention with Nifedipine GITS significantly reduces brachial-ankle pulse wave velocity, and arterial stiffness in mild hypertensive patients.

In animal studies, Nifedipine retarded and reversed the development of atherosclerotic plaque and improved endothelial function while in humans, Nifedipine GITS has been shown to slow the progression of various markers of early atherosclerosis, including intimal thickening, vascular calcification and luminal narrowing.

Extended release Nifedipine has been proven to be safe and tolerable in several clinical trials. When the GITS formulation was compared to prolonged action and capsule formulations, Nifedipine GITS was better tolerated with respect to overall adverse events. A study by Wenzel and colleagues showed that, there was no significant change in HR in the Nifedipine GITS group compared to baseline.

Thus, to conclude, long-acting formulations of Nifedipine have a longer duration of action, greater bioavailability, and lesser incidences of adverse events than the conventional preparations. With a diminished concern for reflex SNS activation, long-acting Nifedipine has the potential to play a larger role in the management of hypertension and angina. Combination therapy, which combines long acting Nifedipine with an ACE inhibitor or ARB, and/or a thiazide diuretic, can be a game-changer in cases where traditional Nifedipine is ineffective. Nifedipine GITS can be used safely for the long-term treatment of patients with hypertension, resistant hypertension, angina pectoris, and coronary diseases. Nifedipine GITS can also be preferred in hypertensive patients with high cardiovascular risk because of its proven potential to prevent cardiovascular and cerebrovascular complications.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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