Am J Cardiovasc Dis 2024;14(6):396-413
www.AJCD.us /ISSN:2160-200X/AJCD0160710

Review Article

Long-acting nifedipine in the management of essential hypertension: a review for cardiologists

Prakash Kumar Hazra[1], Ashwani Mehta[2], Bhupen Desai[3], Umeshwar Pandey[4], Kapil Dev Mehta[5], Sarita Bajpai[5], Deepak Prasad[5]

[1]Manipal Hospitals Dhakuria, C.I.T Scheme, Gariahat Rd, Dhakuria, LXXII Block A, P-4 & 5, Kolkata, West Bengal 700029, India; [2]Sir Ganga Ram Hospital, A1, Sarhadi Gandhi Marg, Old Rajinder Nagar, Rajinder Nagar, New Delhi 110060, India; [3]Desai Heart Care Clinic, Level 3, Vini Elgance, Lokmanya Tilak Road, Mhatre Wadi, Borivali West, Mumbai, Maharashtra 400092, India; [4]LPS Institute of Cardiology, Rawatpur Road, Gol Chauraha, Rawat Pur, Kanpur, Uttar Pradesh 208019, India; [5]J.B. Chemicals and Pharmaceuticals Ltd., Cnergy It Park, Unit A, Appasaheb Marathe Marg, Century Bazaar, Prabhadevi, Mumbai, Maharashtra 400025, India

Received September 24, 2024; Accepted December 13, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: Calcium channel antagonists, specifically long-acting nifedipine formulations, play a crucial role in treating hypertension and angina. Originally used for angina, nifedipine has been widely employed as an antihypertensive medication for over 40 years. It offers rapid action and oral bioavailability with minimal maternal or fetal side effects, making it suitable for treating hypertensive crises during pregnancy. However, it can cause a sudden drop in blood pressure and tachycardia. Long-acting formulations, such as gastrointestinal therapeutic systems, gradually release nifedipine over 24 hours, mitigating these issues. This review aims to assess the clinical efficacy and safety of long-acting nifedipine formulations in managing essential hypertension, with a focus on improving blood pressure control and addressing challenges in uncontrolled and resistant hypertension. Furthermore, long-acting nifedipine provides therapeutic advantages beyond hypertension management, showing efficacy in treating comorbid conditions such as chronic kidney disease and diabetes. Global studies support its efficacy, suggesting that a shift toward the use of long-acting nifedipine can help address the global hypertension problem and enhance the quality of life for hypertensive patients.

Keywords: Calcium channel blockers, efficacy, hypertension, nifedipine, sustained-release, tolerability

Introduction

Essential hypertension, characterized by persistently elevated blood pressure without an identifiable secondary cause, is a major contributor to cardiovascular morbidity and mortality worldwide. Effective management of this condition is crucial for mitigating the risk of complications such as stroke, myocardial infarction, and renal failure [1]. Recognizing the global health burden, the World Health Organization (WHO) has prioritized hypertension management due to its significant role in premature mortality and its pervasive impact on public health systems. Approximately 1.28 billion people aged 30-79 worldwide have suboptimal blood pressure, with two-thirds living in low- and middle-income countries [2]. Although hypertension is often asymptomatic and termed the "silent killer", it progressively damages organs if left untreated. The prevalence of hypertension varies widely across regions, with rising rates observed in countries such as in some places like Kiribati, Tonga, Tuvalu, Indonesia (women), Uzbekistan, Argentina, and Paraguay (men). Meanwhile, Germany, Spain, Japan (women) and Germany, Switzerland, the UK, Finland, Canada (men) have seen a 12% decline. Rates remain stable in many low- and middle-income countries [3, 4].

In India, 18.1% of people aged 15 to 49 years have hypertension. Only 44.7% are aware of it, 13.3% receive treatment, and 7.9% effectively manage it [5]. In a national survey across 24 states, 30.7% of adults over 18 years of age had hypertension, with 23.7% among women and 34.2% among men [6]. A meta-analysis

https://doi.org/10.62347/RPMZ6407

found hypertension rates of 33% in urban areas and 25% in rural areas, but treatment rates are low, with 75% in rural areas and 62% in urban areas not receiving treatment [7]. India has set a target of 25% relative reduction in hypertension prevalence by 2025 [8]. If this goal is to be met, focused attention is needed to address the untreated or inadequately treated people with hypertension.

Pharmacological management of essential hypertension encompasses several key classes of antihypertensive agents, including thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, and calcium channel blockers (CCBs). Among these, CCBs are often recommended as first-line agents in clinical guidelines for essential hypertension due to their reliable efficacy in lowering blood pressure and well-documented safety profile [9]. Nifedipine, a dihydropyridine CCB, has been extensively utilized in clinical practice since its introduction in the 1970s. Its potent vasodilatory effects make it a preferred option for managing essential hypertension, particularly in patients requiring consistent blood pressure control. The immediate-release form of nifedipine provides rapid blood pressure reduction, which is useful in acute settings but may require multiple doses and can cause fluctuations and tachycardia. In contrast, long-acting formulations offer stable, sustained blood pressure control with fewer side effects, improving suitability for long-term management. Current hypertension guidelines recognize the efficacy of long-acting dihydropyridine CCBs such as nifedipine in achieving target blood pressure levels and reducing cardiovascular risk [10, 11]. This review discusses initial therapy choices for uncontrolled and resistant hypertension (RHT), emphasizing the effectiveness and safety of both immediate and sustained-release (SR) nifedipine formulations, including their role in lowering blood pressure, particularly in cases of pregnancy-induced hypertension.

Progression from uncontrolled to resistant hypertension

Global hypertension guidelines have evolved dramatically over the past two decades, progressing from no screening or treatment recommendations to targeted guidance for at-risk groups, aiming to enhance hypertension control [12]. The majority of these guidelines focus on creating limits for special populations such as elderly individuals and pregnant women (**Table 1**). The ACC/AHA guidelines 2017 classify hypertension into specific categories to guide tailored treatment and reduce cardiovascular risks. Normal BP is defined as a systolic BP<120 mmHg and diastolic BP<80 mmHg, with lifestyle recommendations to maintain these levels. Elevated BP (120-129 mmHg systolic and <80 mmHg diastolic) signals heightened risk, where preventive lifestyle changes are encouraged. Stage 1 hypertension (130-139 mmHg systolic or 80-89 mmHg diastolic) typically involves lifestyle interventions, with antihypertensive medications for patients with cardiovascular disease or high-risk profiles. Stage 2 hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) usually necessitates a combination of lifestyle and pharmacologic therapy. Hypertensive crises, defined as systolic >180 mmHg and/or diastolic >120 mmHg, are classified into urgent (without organ damage) and emergency (with organ damage), requiring immediate medical intervention [13]. Most cases of hypertension are classified as essential or primary hypertension, characterized by high blood pressure without a known secondary cause, occurring mainly due to genetic factors, excessive salt intake, and adrenergic activity, comprising 90% of hypertension cases, with potential progression to secondary hypertension if renal function deteriorates [14, 15]. Most cases of primary hypertension are asymptomatic, and are identified by routine BP checks or community screening [16].

Uncontrolled hypertension results from inadequate treatment, poor adherence, or undetected secondary causes [17, 18]. If left untreated, it can lead to resistant hypertension, often due to missing diuretics or insufficient drug doses [17, 18]. The American Heart Association defines resistant hypertension as blood pressure persistently above target levels despite three specific medications, typically a long-acting CCB, an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), and a diuretic. It can refer to either uncontrolled or controlled blood pressure, depending on the number of medications used [19]. Uncontrolled BP despite the administration of 5 antihypertensive medicines of different classes, includ-

Table 1. Blood pressure targets and initial pharmacologic therapy in patients with hypertension according to hypertension guidelines

Guideline	Population	Goal BP, mmHg	Initial drug treatment options
ESH/ESC 2018 [59]	<65 years	SBP 120-129	ACEi or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic
	Elderly 65-80 years	SBP 130-139	
	≥80 years	130-139	
	Resistant HT		Add spironolactone (25-50 mg o.d.) or other diuretic, alpha-blocker, or BB
	Pregnancy (Severe HT)		Labetalol, oral methyldopa, or nifedipine
NICE 2023, NICE guidelines (pregnancy) [95]	<80 years	<140/90	<55 y: ACEI or ARB; ≥55 y or black: CCB; thiazide-like diuretic
	≥80 years	<150/90	
	Resistant HT		Adding a fourth antihypertensive drug; diuretic therapy with low-dose spironolactone; alpha-blocker or BB
	Pregnancy	135/85	Labetalol, nifedipine, or methyldopa
2020 ISH Global Hypertension Practice Guidelines [96]	General	<140/90	Use a once-daily regimen: 24-hour BP control
	Diabetes	<130/80; <140/80 in elderly patients	An RAS inhibitor (and a CCB and/or thiazide-like diuretic)
	Pregnancy		Methyldopa, BB (labetalol), and dihydropyridine-CCB (nifedipine [not capsular], nicardipine)
	Resistant HT		Optimize the current treatment regimen including health behavior change and diuretic-based treatment
Indian Guidelines 2019 [9]	>60 years	130-140/80-90	ACEi, ARBs, CCBs, Diuretics, and Newer BBs
	<60 years	<130/80	
ACOG Guidelines 2019 [60]	Pregnancy		Labetalol, Nifedipine, Methyldopa, Hydrochlorothiazide; For Urgent BP control: Labetalol, Hydralazine, Nifedipine (immediate release)
RSSDI Guidelines 2022 [16]	Diabetes	120-130	ARBs, ACEi, BB, CCB
	Resistant HT		ARBs along with CCBs
ACC/AHA Task Force on Clinical Practice Guidelines 2017 [13]	General	130/80	Thiazide diuretics, CCBs, and ACEi or ARBs
	Pregnancy or are planning to become pregnant		To be transitioned to methyldopa, nifedipine, and/or labetalol
	Resistant HT		Maximize diuretic therapy
	Hypertensive Crises and Emergencies	<140 mmHg during the first hour and <120 mmHg in aortic dissection	CCB-dihydropyridines

ACEi: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; ASH/ISH: American Society of Hypertension/International Society of hypertension; BB: Beta-blockers; BP: Blood pressure; CAD: Coronary artery disease; CCB: calcium channel blockers; CKD: Chronic kidney disease; CV: cardiovascular; eGFR: Estimated glomerular filtration rate; ESH/ESC: European Society of Hypertension/European Society of Cardiology; GDMT: guideline-directed medical therapy; HF: Heart failure; HT: hypertension; ISH: International Society of Hypertension; JNC: Joint National Committee; NICE: National Institute for Health and Care Excellence; RAS: Renin-angiotensin-system.

ing long-acting thiazide-like diuretics and mineralocorticoid receptor antagonists, at maximal tolerated doses is referred to as refractory hypertension [20]. CCBs are the preferred as per current clinical guidelines. Nifedipine, a dihydropyridine calcium antagonist, is increasingly used for hypertension treatment.

Nifedipine: clinical indications

Nifedipine, a dihydropyridine CCB, was first introduced in 1975 for angina and hypertension. It became available in the United States as Adalat® (Bayer) in 1981 and in India as Nicardia® (J.B. Chemicals & Pharmaceuticals) in 1985. It has potential uses for Raynaud's phenomenon, congestive heart failure, and atherosclerosis prevention, pending approval. Nifedipine is indicated for severe hypertension, hypertensive emergencies, and angina resulting from coronary artery spasms, where it acts as an arterial vasodilator [10, 21].

A shift from conventional nifedipine to sustained release nifedipine formulations

The conventional rapid-release form of nifedipine, containing 10 mg of dissolved nifedipine, lowers BP within 5-10 minutes of oral intake, peaking between 30 and 60 minutes and lasting up to 6 hours [10]. However, it leads to a rapid, short-lived drop in BP, requiring four daily doses for sustained effects. This form can also cause adverse effects such as headaches, palpitations, flushing, tachycardia, and worsened heart and cerebrovascular conditions, along with heat sensations in the face and limbs [10]. To overcome these shortcomings, long-acting formulations of nifedipine have been developed and are classified into two types: twice-daily formulations - slow release, prolonged action (PA), and long action (L), and once-daily formulations - coat core (CC), continuous-release (CR) and gastrointestinal therapeutic system (GITS) [10, 22]. A comparison of the pharmacological parameters of conventional and long-acting nifedipine formulations is summarized in **Table 2**.

Slow-release nifedipine (retard tablet) offers a sustained blood pressure-lowering effect with twice-daily dosing, making it more efficient [23]. The slow-release form of nifedipine, in contrast to the conventional rapid-release version with a rapidly increasing plasma concentration-time curve and high peak levels, exhibits a longer elimination half-time, a smoother absorption and elimination profile, and low observed dose fractions (0.18-0.63), whereas the retard formulation reduces the peak concentration and prolongs detectable drug levels but leads to a significant increase in the heart rate [23].

The efficacy of nifedipine improved with the development of a 24-hour controlled-release (CR) formulation known as GITS, which was initially used for angina but later expanded to treat hypertension [24]. Nifedipine GITS is now considered the gold standard for once-daily administration, and there are various extended-release nifedipine formulations available under brand names such as Procardia XL®, Adalat CC®, Adipine XL®, Afeditab CR®, Nicardia XL®, and Folcardia XL®. Adalat CC® and Procardia XL® differ in bioavailability due to their distinct extended-release mechanisms, with Adalat CC® releasing nifedipine in successive layers, leading to peak plasma concentrations 2.5-5 hours after fasting intake and a minor secondary peak 6-12 hours later [21, 24].

On the contrary, Procardia XL® or Nicardia XL® with a gastrointestinal therapeutic mechanism (Osmotic Release Technology) administers nifedipine through an osmotic pump delivery system via an osmotically driven push-pull action (**Figure 1**). In the GITS tablet, GI fluid enters a push compartment through a semipermeable membrane. The polymeric material of tablet expands, dissolving nifedipine particles, and releases them in the GI system through a laser-drilled orifice over 24 hours in a controlled, steady manner (zero-order release profile) [25]. The tablet shell remains intact in the GI tract and is excreted in feces, a common feature of osmotic-controlled delivery devices [25].

A study comparing nifedipine CC and GITS formulations revealed equal efficacy in reducing 24-hour mean BP measurements when administered with food, while taking nifedipine CR upon waking reduces morning blood pressure surges, enhancing BP control throughout the day and potentially reducing the risk of morning cardiovascular events [26]. Other once-daily nifedipine formulations have been developed using various technologies, and peripheral edema, occurring in 10% to 30% of hypertensive patients, is dose-dependent [10].

Table 2. Comparison of the pharmacological parameters of conventional and long-acting formulations of nifedipine

Parameters	Conventional nifedipine	Long-acting nifedipine		
Type	Normal tablet	Retard tablet	Coat Core tablet	GITS tablet (Osmotically controlled drug release)
Active drug release	Rapidly releases the active drug	Slow release of active drug	Slow and sustained release of active drug	Extended-release of active drug
Onset of action	Rapid	Slow	Slow	Slow
Peak plasma level	Peak reaches 30 minutes post-dose	1.5-4.2 hours	2.5-5 hours with a second small peak or 6-12 hours post-dose	Rise gradually at a controlled rate and reaches plateau 6 hours post dose
Duration of action	Short	Long (24 hours)	Long (24 hours)	Long (24 hours)
Half-life	1.7-2 hours	7 hours	7 hours	7 hours
Bioavailability	45%-68%	75%-85%	84%-89%	86%
Dosing	Twice daily	Twice daily	Once daily	Once daily
Adverse events	SNS activation, Flushing, tachycardia, worsen myocardial and cerebrovascular ischemia	Headache, Edema (including peripheral edema), Vasodilation	Peripheral edema, Headache	Edema, Headache

GITS: Gastrointestinal therapeutic system; SNS: Sympathetic nervous system.

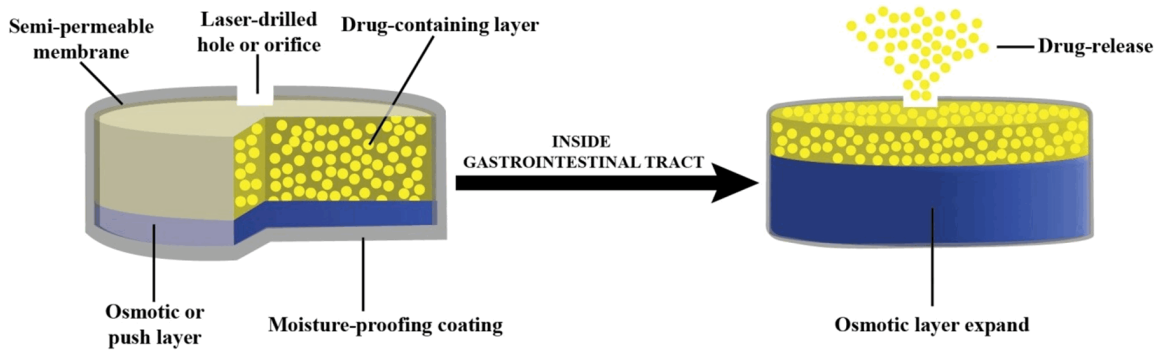

Figure 1. Administration of nifedipine through an osmotic pump delivery or gastrointestinal therapeutic system.

However, taking nifedipine at bedtime improves ambulatory blood pressure more than morning dosing, and extended-release (ER) preparations generally offer better tolerance compared to immediate-release (IR) preparations [27].

Long-acting nifedipine: a clinical perspective

Nifedipine, especially the GITS formulation, has been compared with various antihypertensive drugs, including BBs, ACEis, and ARBs, in numerous trials. These studies include RCTs of long-acting nifedipine, which reduces both systolic and diastolic blood pressure, monotherapy and combination therapy, and placebo-controlled trials. Additionally, this section includes studies involving the use of different nifedipine formulations in specific hypertensive patient groups, such as pregnant women, elderly individuals, and those with other clinical conditions.

Blood pressure lowering effects

SR nifedipine, at various doses, effectively lowers supine systolic blood pressure over 24 hours in patients with essential hypertension. Adalat CC® and Procardia XL® also demonstrated comparable 24-hour blood pressure control in stage 1-4 hypertensive patients aged 18 to 75 years [28, 29]. The Extended Release Adalat Canadian Trial (EXACT) examined nifedipine GITS (Adalat XL®) in 1700 patients with mild-to-moderate essential hypertension, starting at 30 mg and titrating to 60 mg if the BP exceeded 95 mmHg after 3-6 weeks. At the 30 mg dose, 93% and 74% of patients achieved target DBP levels of 95 mmHg and 90 mmHg, respectively, with minimal or no adverse effects [30]. Numerous large trials have also investigated the effectiveness of long-acting nifedipine (retard, CC, GITS) in preventing hypertension-related consequences. Several other key studies have consistently shown its safety and efficacy, with details provided in **Table 3**. Trials used different comparators, dosages, and hypertension criteria. However, the results were consistent across trials with different long-acting nifedipine formulations, allowing for collective discussion.

Benefits beyond blood pressure control

Advanced controlled-release (CR) nifedipine broadens its applications to include hypertension and angina, reducing dose-related vasodilatory side effects by providing smoother peak plasma concentrations after administration compared to conventional nifedipine [24]. Nifedipine GITS, taken once daily, provides a superior approach for managing ischemic disease and exertional angina during exercise compared to conventional nifedipine, with improved patient compliance, fewer vasodilatory side effects, anti-atherosclerotic properties independent of its hypotensive effects, lower daily costs, and a simplified once-daily dosage regimen, whereas doses of nifedipine (30 to 120 mg/d given in divided doses) when used alone reduce the mean arterial pressure without adverse effects on renal function [31-33]. In patients with mild hypertension and increased pulse wave velocity aged 18-75 years, the GITS formulation is beneficial in lowering BP as well as brachial-ankle pulse wave velocity, with improvements in arterial stiffness as early as 4 weeks [34]. Nifedipine GITS improved coronary endothelial function in most constricted region after 6 months in the ENCORE I trial [35]. It also reduced the left ventricular mass index

Table 3. Summary of landmark studies involving long-acting nifedipine formulations

Trial/Reference	Study type	No. of patients	Condition	Hypertension definition followed	Intervention	Control/comparator	Conclusion	Most common AEs associated with Nifedipine therapy
Constantine et al., 1987 [97]	Clinical study	23	Pregnant women with severe hypertension	≥140/95 mmHg on at least two occasions	Slow-release nifedipine (40-120 mg/day)	Atenolol (50-100 mg rising to 100-200 mg/day)	Combining BB with nifedipine in pregnancy is effective in controlling BP	Vomiting, Ankle edema
MATH (Bravo et al., 1990) [84]	Trial	1155 (222 Elderly)	Elderly (>65 years) and non-elderly (<65 years) with mild-to-moderate hypertension in a community setting	The average sitting DBP is 95 to 110 mmHg	Nifedipine GITS 30 to 180 mg/day, 30 mg increment, titrated over 1 to 6 weeks to achieve goal BP	-	Nifedipine GITS is well tolerated and suited	Edema
Reams et al., 1991 [22]	Study for 5 weeks	12	Hypertensive patients with moderately severe renal dysfunction	DBP≥95 mmHg, but ≤114 mmHg after 2 to 4 weeks of Placebo therapy	Nifedipine GITS 30 to 180 mg/day, depending on patient tolerance	Placebo	Nifedipine GITS monotherapy improves renal function abnormalities that are encountered in hypertensive patients with renal disease	Headache, epigastric discomfort, peripheral edema, and flushing
STONE (Gong et al., 1996) [85]	Single-blind trial with prospective follow up	1632	Elderly (60-79 years) with hypertension	BP≥160/96 mmHg	Nifedipine 20 mg BD up to 60 mg/day	Placebo BD with doses 2-6 tablets/day	Nifedipine diminished the number of severe clinical outcomes in elderly hypertensives significantly	Stroke
EXACT (Toal et al., 1997) [30]	Open-label post marketing surveillance study	1326	Patients with previously or newly diagnosed with mild-to-moderate essential Hypertension	Sitting diastolic BP 95 to 114 mmHg	Nifedipine GITS 30 or 60 mg	-	When used in general medical practice, the 30 mg and 60 mg doses of nifedipine GITS were effective, well tolerated, and had minimal or no negative effects on the overall health status of treated individuals	Headache, peripheral edema and dizziness
INSIGHT (Brown et al., 2000) [93]	Prospective, double-blind, trial with dynamic randomization	6321	55-80 years old with hypertension and an additional cardiovascular risk factor	BP≥150/95 mmHg, or ≥160 mmHg systolic	30 mg in a long-acting nifedipine GITS	Co-amilozide (Hydrochlorothiazide 25 μg plus amiloride 2.5 mg) daily	Nifedipine once daily and co-amilozide were equally effective in preventing overall cardiovascular or cerebrovascular complications	Peripheral edema, headache, dizziness
PRESERVE (Devereux et al., 2001) [36]	Randomized, double-blind, parallel-group study	303	Essential hypertension and increased left ventricular mass	≥140/90 mmHg if taking antihypertensive medications or ≥150/90 mmHg if unmedicated	30 mg nifedipine GITS	10 mg enalapril	Once-daily treatment with enalapril or long-acting nifedipine, plus adjunctive hydrochlorothiazide and atenolol when needed to control BP, both had moderately beneficial and statistically indistinguishable effects on regression of LV hypertrophy	-
J-MIND (Baba and J-MIND Study Group, 2001) [91]	Open-label, prospective, randomized trial	436	Elderly under 75 years hypertensive patients with type 2 diabetes	BP>140/90 mmHg	20 mg/day Nifedipine retard	Enalapril 5 mg/day	Nifedipine retard and enalapril had a similar effect on nephropathy in hypertensive type 2 diabetic patients without overt proteinuria	Mild vasodilatory effect, mainly cough
INSIGHT (Mancia et al., 2003) [92]	Prospective, randomized, double-blind trial	6321 (1302 with diabetes)	Patients with hypertension and diabetes	BP≥150/95 or ≥160 mmHg	30 mg nifedipine GITS daily	Co-amilozide (25 mg hydrochlorothiazide and 2.5 mg amiloride) daily	Nifedipine effective as diuretic therapy in reducing cardiovascular complications in hypertensive diabetics	-
ENCORE I (Encore Investigators, 2003) [35]	Randomized, double-blind, placebo-controlled trial	343	Coronary artery disease	Symptomatic hypotension or uncontrolled hypertension	Nifedipine GITS 30 to 60 mg/d	Placebo, cerivastatin 0.4 mg/d, or their combination	Improvement in coronary endothelial function in the most constricted segment by nifedipine after 6 months' treatment	Peripheral edema

ACTION trial (Poole-Wilson et al., 2004) [94]	Multicenter, randomized, placebo controlled, double-blind trial	3825	Patients with stable angina pectoris	Supine systolic BP 90 mmHg or more	Nifedipine was 30 mg once daily, increasing to 60 mg once daily	Placebo	Nifedipine GITS is safe and reduces the need for coronary angiography and interventions	Peripheral oedema
PROBE/JMIC-B (Yui et al., 2004a) [89]	Prospective, randomized, open, blinded endpoint	1650	Outpatients aged under 75 years with both hypertension and coronary artery disease	BP≥160/95 mmHg	Nifedipine retard 10-20 mg twice daily	Enalapril 5-10 mg, Imidapril 5-10 mg, or Lisinopril 10-20 mg, once daily	In Japanese hypertensive patients with coronary artery disease, nifedipine retard was as effective as ACE inhibitors	Vasodilatory effect, including hypotension, facial erythema, and hot flushes
JMIC-B (Yui et al., 2004b) [90]	Analytical and comparative study	1650	Outpatients aged under 75 years hypertensive patients with coronary artery disease with and without diabetes	BP≥160/95 mmHg	Nifedipine retard 20-40 mg/day	Enalapril 5-10 mg/day, Imidapril 5-10 mg/day, or Lisinopril 10-20 mg/day	Nifedipine retard was as effective as ACE inhibitors in reducing the incidence of cardiac events in extremely high-risk hypertensive patients with complications of diabetes and coronary artery disease	-
i-TECHO trial (Ryuzaki et al., 2007) [41]	Randomized, open-label, crossover study	41	Essential hypertension for more than 6 weeks	BP≥140/90 mmHg	20 mg Nifedipine CR	2.5 mg amlodipine	Nifedipine CR had a stronger antihypertensive effect than amlodipine during the critical morning period	Headache, palpitations, increased BP, and ankle edema
MONICA (Tanaka et al., 2013) [57]	-	35	Uncontrolled BP under treatment with valsartan 80 mg/day or amlodipine 5 mg/day	BP≥140/90 mmHg	Valsartan 80 mg/day in the morning and nifedipine CR 20 mg/day at night	Valsartan 80 mg/day and amlodipine 5 mg/day in the morning	Combination therapy with valsartan and nifedipine CR may help to control morning BP and protect the kidneys	Hypotension and pacemaker implantation
FOCUS (Park et al., 2016) [53]	Prospective, open-label, randomized, active-controlled, multicenter study	391	20-70 years with stage II or higher hypertension	BP≥160/100 mmHg	Up-titration of the nifedipine GITS dose from 30 mg (N30) to 60 mg	Up-titration of valsartan from 80 mg to 160 mg or low-dose combination of N30 and valsartan 80 mg	Up-titration of nifedipine GITS provided no additional increased safety concerns and revealed better mean reductions in BP without affecting short-term BP variability	Dizziness, headache, flushing, and palpitation were similar between the treatment groups of 30 and 60 mg
Shen et al., 2019 [98]	Comparative study of long-acting and short-acting nifedipine	300	Pregnancy-induced hypertension	BP≥160/110 mmHg	30 mg long-acting nifedipine tablets once daily	20 mg short-acting nifedipine tablets 3 times a day	Long-acting nifedipine in pregnant women with pregnancy induced hypertension (PIH) has a more stable antihypertensive effect, longer duration compared to the short-acting nifedipine	Effectively improve the eutocia rate of pregnant women and reduce the incidence of neonatal intrauterine distress and death, protecting the neonatal health
Easterling et al., 2019 [72]	Multicenter, parallel-group, open-label, randomized controlled trial	2307	Severe hypertension in pregnancy	BP≥160/110 mmHg	10 mg oral nifedipine retard	200 mg oral labetalol, or 1000 mg methyldopa	Nifedipine retard use resulted in a greater frequency of primary outcome attainment than labetalol or methyldopa use	-
ADRENAL (Lv et al., 2021) [52]	Prospective, multicenter, observational study	871	18-70 years patients with chronic kidney disease and uncontrolled hypertension	Systolic BP 140-160 mmHg or ≥160 mmHg	Nifedipine GITS 60 mg	-	Nifedipine GITS 60 mg showed effectiveness and tolerability in reducing office systolic and diastolic BP in Chinese patients with CKD and uncontrolled hypertension	-
Cleary et al., 2023 [73]	Randomized, triple-blind, placebo-controlled trial	365	Individuals with preeclampsia with severe features undergoing labor induction between 22- and 41-week gestation	Severe blood pressure (≥160/110 mmHg)	Oral extended-release nifedipine 30 mg/day	Placebo	Initiation of extended-release nifedipine is effective in reducing intrapartum acute hypertensive therapy among individuals with preeclampsia with severe features	-

ACE: angiotensin converting enzyme; AE: Adverse events; BP: Blood pressure; CR: Continuous-release; GITS: Gastrointestinal therapeutic system; SR: Slow release.

and relative wall thickness similarly to an ACE inhibitor in people with essential hypertension and left ventricular hypertrophy in the PRESERVE trial over 1 year of treatment [36]. Nifedipine XL effectively reduces arterial pressure by lowering systemic vascular resistance in liver transplant recipients with cyclosporine-associated hypertension, but its use should be limited in transplant patients due to its potential to exacerbate gingival hyperplasia when combined with cyclosporine [37].

Advantages of nifedipine: comparison with other calcium channel blockers/hypertensive agents

Long-acting nifedipine achieves comparable reductions in SBP and DBP at similar response rates as other dihydropyridine CCBs, such as amlodipine, with some studies even suggesting more favorable outcomes than amlodipine [38]. Nifedipine CC, when compared to amlodipine in essential hypertensive patients, lowers arterial stiffness, does not activate the sympathetic system, inhibits epinephrine release by the adrenal medulla, and enhances heart rate recovery, potentially leading to better outcomes during extended nifedipine treatment [39, 40]. During the critical morning phase, nifedipine CR showed a stronger antihypertensive effect than amlodipine [41]. Nifedipine coat-core exhibits 1.69 times greater overall antihypertensive potency compared to amlodipine, as assessed by the hypobaric area [38]. Studies have also compared the antihypertensive efficacy of long-acting nifedipine to that of other antihypertensives such as lisinopril [40], enalapril [42] (ACEi), losartan (ARB) [43], acebutolol [44], propranolol [45], nebivolol [46] (β-blockers), and mefruside (thiazide-like diuretic) [47]. A meta-analysis also confirmed the safety of sustained- and extended-release nifedipine combined with therapy, including diuretics, β-blockers, ACEis, and both β-blockers and diuretic, for the treatment of mild to moderate hypertension [48]. Nifedipine can be combined with other CCBs, such as diltiazem or verapamil to exert additive antihypertensive effects [49]. In summary, long-acting nifedipine not only provides comparable or even superior blood pressure reductions relative to other antihypertensive agents, such as amlodipine, ACE inhibitors, ARBs, and β-blockers but also offers specific advantages, including better control of morning BP, reduced arterial stiffness, and minimal sympathetic activation. These characteristics enhance its clinical value, particularly for patients requiring consistent BP management with a lower side-effect profile.

Role of long-acting nifedipine in addressing uncontrolled/resistant/refractory hypertension

Nifedipine is beneficial for treating resistant hypertension and is recommended for optimizing antihypertensive treatment in such cases [50]. RCT studies have shown it to be a viable alternative to step-three medications, effectively lowering blood pressure with a side effect profile similar to hydralazine. Nifedipine has also demonstrated favorable efficacy and safety, whether used alone or in combination therapy, for individuals with poorly controlled or previously drug-resistant hypertension [51].

The ADRENAL trial showed that nifedipine GITS 60 mg effectively lowered BP in Chinese patients with uncontrolled hypertension and CKD, irrespective of CKD stage [52]. The FOCUS trial found that up-titrating from 30 mg to 60 mg of nifedipine GITS resulted in greater BP reductions compared to up-titrating valsartan, without affecting short-term BP variability [53]. In individuals with mild-to-moderate hypertension who are refractory to treatment with either drug alone, a combination of nifedipine SR and arotinolol is successful in regulating BP [54]. The TIBET trial, involving patients with chronic stable angina uncontrolled on medical therapy, reported no significant impact on cardiac death, myocardial infarction, or unstable angina with nifedipine SR, atenolol, or their combination [55]. Nifedipine CR, when combined with indapamide, effectively lowers BP and improves renal function in older patients with refractory isolated systolic hypertension [56]. The MONICA trial demonstrated that combining nifedipine CR with valsartan effectively controls morning BP and offers renoprotective benefits in patients with uncontrolled BP, despite the use of medium doses of valsartan or amlodipine [57].

In 1987, Heagerty et al. successfully treated 13 patients with resistant hypertension by switching them from minoxidil to nifedipine slow-release tablets. After the switch, 9 patients maintained satisfactory blood pressure control

for at least one year, eliminating the need for loop diuretics previously required with minoxidil to manage fluid retention. Moreover, there were no indications of renal function impairment in those who continued with nifedipine [58].

Long-acting nifedipine formulations: a safer option

Pregnant women with hypertension

Hypertensive disorders of pregnancy (HDP) include conditions such as chronic hypertension, gestational hypertension, preeclampsia, severe preeclampsia, and eclampsia. Nifedipine is recommended by the ESC/ESH Guidelines for treating severe hypertension during pregnancy [59]. ER nifedipine is recommended for managing severely elevated BP in hospitalized pregnant women, as per American College of Obstetricians and Gynecologists' guidelines, and immediate-release nifedipine can also be used [60].

Nifedipine's pharmacokinetics, rapid onset, extended action, high oral bioavailability, and few side effects make it a suitable choice for treating hypertensive emergencies during pregnancy as an alternative to nifedipine and hydralazine by quickly reaching therapeutic blood pressure levels, improves urine output, and has no adverse effects on maternal and perinatal outcomes [61, 62]. IR oral nifedipine is recommended as a first-line treatment when intravenous access is unavailable or when labetalol (due to asthma or congestive heart failure) or hydralazine (due to tachycardia) is contraindicated [63]. A network meta-analysis revealed that nifedipine, hydralazine, and labetalol are equally effective in treating severe hypertension during pregnancy [64]. Nifedipine has been shown to increase the cardiac index (43%), reduce systemic vascular resistance, and lower mean arterial pressure, with minimal effects on heart rate in preeclamptic hypertensive emergencies [65]. It is generally safe and has minor and transient side effects such as headache, nausea, and palpitations in pregnant women with severe gestational hypertension [66]. However, short-acting nifedipine is no longer considered appropriate as a first-line treatment for hypertensive urgencies to avoid excessive pressure drops that lead to renal, cerebral, or coronary ischemia [67].

Despite having a slower onset, nifedipine tablets are as effective as nifedipine capsules for the quick treatment of severe hypertension during pregnancy [68]. SR nifedipine during pregnancy is safe in terms of malformation risks, and has no effect on major developmental impairment at 18 months of age when used for mild-moderate hypertension during pregnancy [69]. Nifedipine is more effective at preventing threatened preterm contractions and appears to be superior to 2-adrenergic-receptor agonists and magnesium sulphate as the first-line tocolytic drug for the management of preterm labor [70]. A long-term follow-up study found no significant differences in psychosocial or motor outcomes, and even better psychosocial outcomes in children (aged 9-12 years) previously exposed to nifedipine in utero [71]. Long-acting nifedipine offers a more sustained antihypertensive effect that lasts longer in pregnant women with PIH, higher rates of eutocia, and full-term births while reducing neonatal mortality, promoting neonatal health compared to short-acting nifedipine [72]. A randomized, triple-blind, placebo-controlled trial showed a beneficial effect of 30 mg extended-release nifedipine in lowering intrapartum acute hypertensive treatment in women with severe preeclampsia [73].

Pediatric patients with hypertension

Short-acting nifedipine has a rapid onset of action and does not cause central nervous system (CNS) depression, but it is associated with adverse effects such as reflex tachycardia, retinal ischemia, and myocardial ischemia and infarction; however, it is still a common treatment for severe hypertension in children [74]. Short-acting nifedipine is safe in children with severe hypertension or hypertensive crisis in a hospital environment where a rapid drop in BP is needed [75]. Over 1,000 doses of short-acting nifedipine were provided, with only 5% of the doses experiencing a mild side event, the most frequent being tachycardia [76]. It is also effective and safe for the treatment of severe hypertension secondary to acute post-streptococcal glomerulonephritis [76]. A retrospective study showed that lowering the initial nifedipine dosage to 0.25 mg/kg alleviates rapid BP drops in pediatric patients [77]. A greater mean nifedipine dose per kilogram was observed in patients who had a ≥25% reduction in the MAP

compared with those who had a <25% reduction in MAP. However, it should be used with caution in children with acute CNS damage [78].

The availability of suitable pediatric medication formulations for nifedipine is limited, posing a challenge for clinical use and optimal dosing recommendations [79]. Although long-acting formulations have been developed to address the limitations of short-acting nifedipine, there is a lack of licensed nifedipine formulations specifically designed for safe use in children, particularly those incorporating high-quality modified or sustained drug delivery systems. Additionally, the large size of the tablet, which must be ingested whole, limits its applicability in small children [79].

Elderly patients

Short-acting nifedipine has been linked to an increased risk of stroke in elderly hypertensive patients with atrial fibrillation, indicating a potential proarrhythmic effect. In contrast, longer-acting nifedipine formulations have demonstrated favorable effects [80].

A German real-world study found that elderly patients taking the IR nifedipine required more cardiovascular medications, with 30% taking six or more, compared to 16% of those taking the SR nifedipine [81]. Nifedipine SR (Adalat A.R.) 20 mg, taken twice daily for 2 weeks, results in biphasic changes with reduced systolic and diastolic BP over 24 hours in elderly patients with mild to moderate hypertension [82]. In a 12-month open study, nifedipine retarded 20 mg + atenolol 50 mg had a stronger antihypertensive effect than atenolol alone in elderly hypertensive patients with no evidence of tachyphylaxis [83]. The Modern Approach to the Treatment of Hypertension (MATH) trial showed that after 12 weeks of nifedipine treatment, both elderly and nonelderly individuals had significantly lower systolic and diastolic BP compared to their baseline levels [84]. Long-acting nifedipine also significantly reduced the relative risk of all events (including stroke, heart failure, myocardial infarction and severe arrhythmias) by 59%, independent of hypertension stage in STONE trial involving elderly hypertensive individuals [85]. However, a population-based prospective study revealed an increase in mortality risk with an average daily dose and recent (46 months) commencement of therapy among nifedipine users aged >65 years, which remained significant for prolonged-acting formulations [86].

Patients with comorbidities

Independent of the impact on systemic BP, monotherapy of nifedipine GITS (30-180 mg/day) has the potential to ameliorate the renal function abnormalities observed in hypertensive individuals with renal disease [41]. The MONICA study observed that combination therapy involving nifedipine CR at night and valsartan in the morning was more effective than amlodipine and valsartan in the morning for controlling morning BP, reducing the CCB dosage, reducing albuminuria and protecting the kidneys [57]. Prudent use of CR nifedipine tablets-valsartan therapy in elderly patients with type II diabetic nephropathy and hypertension significantly improved blood pressure, total therapeutic efficiency (98.46%), treatment satisfaction (96.92%), and blood urea nitrogen levels [87]. Individuals with severe impairment of renal function compared to those with normal renal function showed good BP control without greater accumulation of nifedipine following several doses of nifedipine GITS 60 mg [88].

According to the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) trial, nifedipine retard appeared to be equally effective as ACE inhibitors in terms of lowering the occurrence of cardiac events in extremely high-risk hypertensive patients with both hypertension and coronary artery disease [89, 90]. The Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetics (J-MIND) noted equivalent effects of nifedipine retard and enalapril on nephropathy in hypertensive type 2 diabetic patients without overt proteinuria [91]. Nifedipine GITS, which is administered once daily, is as effective as diuretics in reducing cardiovascular events in hypertensive diabetic patients. Additionally, nifedipine users were less prone to experiencing diabetes or secondary events (a composite of all-cause mortality, vascular death, and non-vascular death) compared to co-amilozide users. These findings suggest that nifedipine could be considered a first-line therapy for hypertensive diabetic patients [92].

Tolerability of long-acting nifedipine

In contrast to the conventional, immediate-release capsule nifedipine formulation, which could be associated with a rapid drop in BP and reflex sympathetic activation (expressed as tachycardia), modified-release formulations are designed to reduce fluctuations in plasma nifedipine concentrations, resulting in a more gradual drop in BP and reduced sympathetic activation [10]. The EXACT trial demonstrated only 33.9% of patients reported one or more adverse events following nifedipine GITS administration, with the most frequently reported events being headache (12.2%), peripheral edema (8.1%), and dizziness (2.9%) [30]. The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) trial noted that nifedipine is efficacious in preventing overall cardiovascular and cerebrovascular outcomes including non-fatal stroke, myocardial infarction, and heart failure [93]. Moreover, adding nifedipine GITS to standard angina pectoris therapy has been shown to have no effect on major cardiovascular event-free survival. Furthermore, nifedipine GITS is a safe medication that decreases the need for coronary angiography and interventions, according to A Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION) trial [94]. Nifedipine GITS 60 mg is safe and well tolerated in hypertensive individuals with CKD as well as those with persistent renal impairment [52]. Up-titration of the nifedipine GITS from 30 mg to 60 mg produced no extra increased safety concerns when compared to up-titration of valsartan [53].

Limitations and future prospects

This review provides a comprehensive overview of the pharmacologic management of essential hypertension, focusing on the unique benefits of nifedipine and its sustained-release formulations. While global data have been included, regional variations in hypertension prevalence and treatment responses may not be fully captured, which could affect the generalizability of certain findings to specific populations with essential hypertension. Additionally, the rapid evolution of hypertension treatments means that emerging therapeutic developments and new long-term efficacy data will continue to expand future insights.

Long-acting nifedipine formulations, such as GITS, have demonstrated broader benefits beyond essential hypertension management, effectively addressing uncontrolled and resistant hypertension as well as conditions such as ischemic disease, exertional angina, chronic kidney disease, diabetes, and renal insufficiency. Future research could further explore these advantages by examining the long-term outcomes of sustained-release nifedipine in diverse patient groups and investigating novel therapeutic combinations that incorporate emerging antihypertensive agents. Such studies could help optimize clinical approaches, enhance the quality of life for patients and address the global hypertension burden effectively.

Conclusion

The initial nifedipine immediate-release capsule formulation, with its quick onset, oral effectiveness, affordability, and simplicity of administration, offers advantages over amlodipine and other antihypertensive agents. The pharmacokinetics of nifedipine make it suitable for treating hypertensive emergencies during pregnancy, although it can sometimes cause a rapid drop in blood pressure and tachycardia. Long-acting formulations are designed to mitigate these effects by gradually releasing nifedipine. Additionally, these formulations have broader benefits, including managing uncontrolled and resistant hypertension, as well as related conditions such as ischemic disease, exertional angina, chronic kidney disease, diabetes, and renal insufficiency. Safety analysis revealed that long-acting nifedipine formulations such as GITS nifedipine are well tolerated across various populations, making them a promising addition to hypertension treatment options. Shifting toward the use of long-acting nifedipine formulations in clinical practice could significantly contribute to addressing the global hypertension epidemic and improving the quality of life for hypertensive patients.

Acknowledgements

The author expresses gratitude to Clinexcel Research, Ahmedabad, for their valuable assistance in the drafting and submission of this manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kapil Dev Mehta, J.B. Chemicals and Pharmaceuticals Ltd., Cnergy It Park, Unit A, Appasaheb Marathe Marg, Century Bazaar, Prabhadevi, Mumbai, Maharashtra 400025, India. Tel: +91-78748-56742; E-mail: kapil.mehta@jbpharma.com

References

[1] Messerli FH, Williams B and Ritz E. Essential hypertension. Lancet 2007; 370: 591-603.
[2] Hypertension. https://www.who.int/news-room/fact-sheets/detail/hypertension.
[3] Fatima S and Mahmood S. Combatting a silent killer - the importance of self-screening of blood pressure from an early age. EXCLI J 2021; 20: 1326-1327.
[4] Nguyen TN and Chow CK. Global and national high blood pressure burden and control. Lancet 2021; 398: 932-933.
[5] Prenissl J, Manne-Goehler J, Jaacks LM, Prabhakaran D, Awasthi A, Bischops AC, Atun R, Bärnighausen T, Davies JI, Vollmer S and Geldsetzer P. Hypertension screening, awareness, treatment, and control in India: a nationally representative cross-sectional study among individuals aged 15 to 49 years. PLoS Med 2019; 16: e1002801.
[6] Ramakrishnan S, Zachariah G, Gupta K, Shivkumar Rao J, Mohanan PP, Venugopal K, Sateesh S, Sethi R, Jain D, Bardolei N, Mani K, Kakar TS, Kidambi B, Bhushan S, Verma SK, Bhargava B, Roy A, Kothari SS, Gupta R, Bansal S, Sood S, Nath RK, Tyagi S, Gupta MD, Girish MP, Kalra IPS, Wander GS, Gupta S, Mandal S, Senguttuvan NB, Subramanyam G, Roy D, Datta S, Ganguly K, Routray SN, Mishra SS, Singh BP, Bharti BB, Das MK, Kumar S, Goswami KC, Bahl VK, Chandra S, Banerjee A, Guha S, Deb PK, Chopra HK, Deedwania P and Seth A; CSI-Great India BP Campaign Investigators. Prevalence of hypertension among Indian adults: results from the great India blood pressure survey. Indian Heart J 2019; 71: 309-313.
[7] Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E and Prabhakaran D. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens 2014; 32: 1170-1177.
[8] Ministry of Health and Family Welfare. National Action Plan and Monitoring Framework for Prevention and Control of Non-Communicable Diseases (NCDs) in India (2017-2022). https://mainmohfwgovin/sites/default/files/National%20Multisectoral%20Action%20Plan%20%28NMAP%29%20for%20Prevention%20and%20Control%20of%20Common%20NCDs%20%282017-22%29_1pdf.
[9] Shah SN, Munjal YP, Kamath SA, Wander GS, Mehta N, Mukherjee S, Kirpalani A, Gupta P, Shah H, Rohatgi R, Billimoria AR, Maiya M, Das MK, Goswami KC, Sharma R, Rajapurkar MM, Chawla R, Saboo B and Jha V. Indian guidelines on hypertension-IV (2019). J Hum Hypertens 2020; 34: 745-758.
[10] Snider ME, Nuzum DS and Veverka A. Long-acting nifedipine in the management of the hypertensive patient. Vasc Health Risk Manag 2008; 4: 1249-1257.
[11] Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Andreotti F, Becher H, Dietz R, Fraser A, Gray H, Antolin RAH, Huber K, Kremastinos DT, Maseri A, Nesser HJ, Pasierski T, Sigwart U, Tubaro M and Weis M. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the management of stable angina pectoris of the European Society of Cardiology. Eur Heart J 2006; 27: 1341-1381.
[12] Evbayekha EO, Okobi OE, Okobi T, Ibeson EC, Nwafor JN, Ozobokeme OE, Olawoye A, Ngoladi IA, Boms MG, Habib FA, Oyelade BO, Okoroafor CC, Chukwuma VN, Alex KB and Ohikhuai EE. The evolution of hypertension guidelines over the last 20+ years: a comprehensive review. Cureus 2022; 14: e31437.
[13] Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD and Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension 2018; 71: e13-e115.
[14] Hamrahian SM. Pathophysiology of hypertension: pathogenesis of essential hypertension, factors influencing bp regulation, etiology of essential hypertension. https://emedicine.medscape.com/article/1937383-overview.

[15] Brettler J. BMJ Best Practice Essential hypertension. https://bestpractice.bmj.com/topics/en-gb/26.
[16] Kumar V, Agarwal S, Saboo B and Makkar B. RSSDI Guidelines for the management of hypertension in patients with diabetes mellitus. Int J Diabetes Dev Ctries 2022; 42: 576-605.
[17] Sarafidis PA and Bakris GL. Resistant hypertension: an overview of evaluation and treatment. J Am Coll Cardiol 2008; 52: 1749-1757.
[18] Tobe SW and Lewanczuk R. Resistant hypertension. Can J Cardiol 2009; 25: 315-317.
[19] Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, Lackland DT, Laffer CL, Newton-Cheh C, Smith SM, Taler SJ, Textor SC, Turan TN and White WB; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 2018; 72: e53-e90.
[20] Acelajado MC, Hughes ZH, Oparil S and Calhoun DA. Treatment of resistant and refractory hypertension. Circ Res 2019; 124: 1061-1070.
[21] Mavani S, Abraham M, Conjeevaram A, Singh S, Revandkar V and Birla A. Nicardia® XL (nifedipine extended release): technologically advanced GITS formulation ensures robust efficacy and assured safety. Journal of Drug Delivery and Therapeutics 2022; 12: 181-191.
[22] Reams G, Lau A, Knaus V and Bauer JH. The effect of nifedipine GITS on renal function in hypertensive patients with renal insufficiency. J Clin Pharmacol 1991; 31: 468-472.
[23] Meredith PA and Elliott HL. A review of the gastrointestinal therapeutic system (GITS) formulation and its effectiveness in the delivery of antihypertensive drug treatment (focus on nifedipine GITS). Integr Blood Press Control 2013; 6: 79-87.
[24] Cramer MP and Saks SR. Translating safety, efficacy and compliance into economic value for controlled release dosage forms. Pharmacoeconomics 1994; 5: 482-504.
[25] Vetrovec GW. Once-daily therapy for angina pectoris with nifedipine gastrointestinal therapeutic system. Dosing and clinical efficacy. Am J Med 1989; 86: 28-32.
[26] Kawano H, Ashizawa N, Toda G, Seto S and Yano K. Administration of nifedipine CR immediately after awakening prevents a morning surge in hypertensive patients. Case report of three cases. Blood Press Suppl 2003; 1: 44-48.
[27] Khan KM, Patel JB and Schaefer TJ. Nifedipine. In: StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Jayesh Patel declares no relevant financial relationships with ineligible companies. Disclosure: Timothy Schaefer declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
[28] Granberry MC, Gardner SF, Schneider EF and Carter IR. Comparison of two formulations of nifedipine during 24-hour ambulatory blood pressure monitoring. Pharmacotherapy 1996; 16: 932-936.
[29] Carr AA, Bottini PB, Feig P, Prisant LM, Mulligan S, Devane JG, Fisher L, Rhoades RB and MacCarthy EP. Effectiveness of once-daily monotherapy with a new nifedipine sustained release calcium antagonist. Am J Cardiol 1992; 69: 28E-32E.
[30] Toal CB, Mahon WA, Barnes C and Burelle D. Nifedipine gastrointestinal therapeutic system (GITS) for hypertensive patients in a primary care setting: results of the Extended Release Adalat Canadian Trial (EXACT). Clin Ther 1997; 19: 924-935.
[31] Bittar N, Corder CN, Eich R, McGrew FA 3rd, Paulk EA and Zellner S. Efficacy of nifedipine gastrointestinal therapeutic system in combination with beta blockers in the management of exertional angina. A multicenter study of 54 patients. Am J Med 1987; 83: 30-33.
[32] Ueng KC, Lin MC, Chan KC and Lin CS. Nifedipine gastrointestinal therapeutic system: an overview of its antiatherosclerotic effects. Expert Opin Drug Metab Toxicol 2007; 3: 769-780.
[33] Reams GP, Lau A and Bauer JH. Short-term and long-term renal response to nifedipine monotherapy. Am J Hypertens 1989; 2: 188-190.
[34] Zhang J, Wang Y, Hu H, Yang X, Tian Z, Liu D, Gu G, Zheng H, Xie R and Cui W. Early intervention of long-acting nifedipine GITS reduces brachial-ankle pulse wave velocity and improves arterial stiffness in Chinese patients with mild hypertension: a 24-week, single-arm, open-label, prospective study. Drug Des Devel Ther 2016; 10: 3399-3406.
[35] ENCORE Investigators. Effect of nifedipine and cerivastatin on coronary endothelial function in patients with coronary artery disease: the ENCORE I Study (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function). Circulation 2003; 107: 422-428.

[36] Devereux RB, Palmieri V, Sharpe N, De Quattro V, Bella JN, de Simone G, Walker JF, Hahn RT and Dahlöf B. Effects of once-daily angiotensin-converting enzyme inhibition and calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension: the prospective randomized enalapril study evaluating regression of ventricular enlargement (preserve) trial. Circulation 2001; 104: 1248-1254.

[37] Textor SC, Schwartz L, Wilson DJ, Wiesner R, Romero JC, Augustine J, Kos P, Hay E, Gores G and Dickson ER. Systemic and renal effects of nifedipine in cyclosporine-associated hypertension. Hypertension 1994; 23 Suppl: I220-4.

[38] Kuga K, Xu DZ, Ohtsuka M, Aonuma K, Lau AH, Watanabe Y and Ohtsuka K. Comparison of daily anti-hypertensive effects of amlodipine and nifedipine coat-core using ambulatory blood pressure monitoring - utility of "hypobaric curve" and "hypobaric area". Clin Exp Hypertens 2011; 33: 231-239.

[39] Fukuda M, Masuda T, Ogura MN, Moriya T, Tanaka K, Yamamoto K, Ishii A, Yonezawa R, Noda C and Izumi T. Influence of nifedipine coat-core and amlodipine on systemic arterial stiffness modulated by sympathetic and parasympathetic activity in hypertensive patients. Hypertens Res 2009; 32: 392-398.

[40] Richardson PJ, Meany TB, Johnston GD, Kondowe G, Grimmer SF and Breckenridge AM. Comparative efficacy of lisinopril and nifedipine retard in essential hypertension: a double-blind, placebo-controlled trial. J Cardiovasc Pharmacol 1987; 10 Suppl 10: S96-98.

[41] Ryuzaki M, Nakamoto H, Nishida E, Sone M, Nakajima S, Yoshimoto M, Suzuki Y and Itagaki K. Crossover study of amlodipine versus nifedipine CR with home blood pressure monitoring via cellular phone: internet-mediated open-label crossover trial of calcium channel blockers for hypertension (i-TECHO trial). J Hypertens 2007; 25: 2352-2358.

[42] Agabiti Rosei E, Morelli P and Rizzoni D. Effects of nifedipine GITS 20 mg or enalapril 20 mg on blood pressure and inflammatory markers in patients with mild-moderate hypertension. Blood Press Suppl 2005; 1: 14-22.

[43] Weir MR, Elkins M, Liss C, Vrecenak AJ, Barr E and Edelman JM. Efficacy, tolerability, and quality of life of losartan, alone or with hydrochlorothiazide, versus nifedipine GITS in patients with essential hypertension. Clin Ther 1996; 18: 411-428.

[44] Chamiec T, Zaleska T, Kłoś J, Pietrzykowska H, Bednarz B and Ceremuzyński L. Efficacy and tolerance of nifedipine retard vs acebutolol in patients with essential hypertension treated for 26 weeks. Mater Med Pol 1989; 21: 49-52.

[45] Frishman WH, Garofalo JL, Rothschild A, Rothschild M, Greenberg SM and Soberman J. Multicenter comparison of the nifedipine gastrointestinal therapeutic system and long-acting propranolol in patients with mild to moderate systemic hypertension receiving diuretics. A preliminary experience. Am J Med 1987; 83: 15-19.

[46] Van Nueten L, Lacourcière Y, Vyssoulis G, Korlipara K, Marcadet DM, Dupont AG and Robertson JI. Nebivolol versus nifedipine in the treatment of essential hypertension: a double-blind, randomized, comparative trial. Am J Ther 1998; 5: 237-243.

[47] Douglas-Jones AP and Mitchell AD. Comparison of nifedipine (retard formulation) and mefruside in the treatment of mild to moderate hypertension--a prospective randomized double-blind crossover study in general practice. Postgrad Med J 1984; 60: 529-532.

[48] Stason WB, Schmid CH, Niedzwiecki D, Whiting GW, Caubet JF, Cory D, Luo D, Ross SD and Chalmers TC. Safety of nifedipine in angina pectoris: a meta-analysis. Hypertension 1999; 33: 24-31.

[49] Saseen JJ, Carter BL, Brown TE, Elliott WJ and Black HR. Comparison of nifedipine alone and with diltiazem or verapamil in hypertension. Hypertension 1996; 28: 109-114.

[50] Thomas G and Rahman M. Resistant hypertension in CKD. Clin J Am Soc Nephrol 2021; 16: 467-469.

[51] Dong B, Guan S, Ge B, Yan S, Qin S, Zhang B, Pin L, Li F and Wu X. Therapeutic effect and prognostic life quality of renal denervation therapy and nifedipine combined with metoprolol tartrate in the treatment of resistant hypertension. Int J Clin Exp Med 2019; 12: 13723-13731.

[52] Lv R, Chen J, Wang H, Wang J, Cheng H, Li R, Li W, Zhang T, Wei L, Chen Q, Huang J, Yu F, Shen S, Wu H, Liu C, Hong F, Liu J, Zhang X, Xiao H and Song W. Effectiveness and tolerability of nifedipine GITS in patients with chronic kidney disease and uncontrolled hypertension: a prospective, multicenter, observational study (ADRENAL). Adv Ther 2021; 38: 4771-4785.

[53] Park JB, Shin JH, Kim DS, Youn HJ, Park SW, Shim WJ, Park CG, Kim DW, Lee HY, Choi DJ, Rim SJ, Lee SY and Kim JH; FOCUS Investigators. Safety of the up-titration of nifedipine GITS and valsartan or low-dose combination in uncontrolled hypertension: the FOCUS study. Clin Ther 2016; 38: 832-842.

[54] Takeda K, Nakata T, Uchida A, Fujita H, Nakamura K, Takesako T, Itoh H, Sasaki S and Nakagawa M. Effect of combination therapy with

arotinolol and sustained-release nifedipine in patients with essential hypertension resistant to monotherapy. Curr Ther Res 1994; 55: 817-827.
[55] Dargie HJ, Ford I and Fox KM. Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET Study Group. Eur Heart J 1996; 17: 104-112.
[56] Liu XR, Wang CA, Tang CS, Li SH, Xiao K, Peng L and Chen CX. Influence of nifedipine controlled release tablets combined with indapamide on renal function of elderly patients with refractory isolated systolic hypertension. Journal of Clinical Medicine in Practice 2014; 79-80, 93.
[57] Tanaka T, Miura S, Tanaka M, Uehara Y, Hirano T and Saku K. Efficacies of controlling morning blood pressure and protecting the kidneys by treatment with valsartan and nifedipine CR or valsartan and amlodipine (MONICA Study). J Clin Med Res 2013; 5: 432-440.
[58] Heagerty AM, Bing RF, Thurston H and Swales JD. Nifedipine substituted for minoxidil in the treatment of refractory hypertension. J Hum Hypertens 1987; 1: 83-86.
[59] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V and Desormais I; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-3104.
[60] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 203: chronic hypertension in pregnancy. Obstet Gynecol 2019; 133: e26-e50.
[61] Adebayo JA, Nwafor JI, Lawani LO, Esike CO, Olaleye AA and Adiele NA. Efficacy of nifedipine versus hydralazine in the management of severe hypertension in pregnancy: a randomised controlled trial. Niger Postgrad Med J 2020; 27: 317-324.
[62] Sahai R, Nidhi A, Ranjan R and Lal S. Comparative study of oral nifedipine versus intravenous labetalol in severe hypertension in pregnancy: a randomized controlled study. Int J Obstet Gynecol Res 2020; 7: 75-80.
[63] Bernstein PS, Martin JN Jr, Barton JR, Shields LE, Druzin ML, Scavone BM, Frost J, Morton CH, Ruhl C, Slager J, Tsigas EZ, Jaffer S and Menard MK. National partnership for maternal safety: consensus bundle on severe hypertension during pregnancy and the postpartum period. Anesth Analg 2017; 125: 540-547.
[64] Sridharan K and Sequeira RP. Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials. Br J Clin Pharmacol 2018; 84: 1906-1916.
[65] Scardo JA, Vermillion ST, Newman RB, Chauhan SP and Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. Am J Obstet Gynecol 1999; 181: 862-866.
[66] Alam A and Zakaria S. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomized controlled trial. Int J Reprod Contracept Obstet Gynecol 2019; 8: 1921-1928.
[67] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr and Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003; 289: 2560-2572.
[68] Brown MA, Buddle ML, Farrell T and Davis GK. Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy. Am J Obstet Gynecol 2002; 187: 1046-1050.
[69] Bortolus R, Ricci E, Chatenoud L and Parazzini F. Nifedipine administered in pregnancy: effect on the development of children at 18 months. BJOG 2000; 107: 792-794.
[70] Songthamwat S, Na Nan C and Songthamwat M. Effectiveness of nifedipine in threatened preterm labor: a randomized trial. Int J Womens Health 2018; 10: 317-323.
[71] Houtzager BA, Hogendoorn SM, Papatsonis DN, Samsom JF, van Geijn HP, Bleker OP and van Wassenaer AG. Long-term follow up of children exposed in utero to nifedipine or ritodrine for the management of preterm labour. BJOG 2006; 113: 324-331.
[72] Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, von Dadelszen P, Shochet T and Winikoff B. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet 2019; 394: 1011-1021.
[73] Cleary EM, Racchi NW, Patton KG, Kudrimoti M, Costantine MM and Rood KM. Trial of intra-

partum extended-release nifedipine to prevent severe hypertension among pregnant individuals with preeclampsia with severe features. Hypertension 2023; 80: 335-342.
[74] Khan D, Badhan R, Kirby DJ, Bryson S, Shah M and Mohammed AR. Virtual clinical trials guided design of an age-appropriate formulation and dosing strategy of nifedipine for paediatric use. Pharmaceutics 2023; 15: 556.
[75] Zapata F, Fernandez C, de Rovetto C, de Castaño I, Roa JA and Echandía CA. Nifedipine and captopril in hypertensive crisis in children. Colombia Médica 2006; 37: 189-195.
[76] Yiu V, Orrbine E, Rosychuk RJ, MacLaine P, Goodyer P, Girardin C, Gowrishankar M, Ogborn M, Midgley J, Filler G and Harley F. The safety and use of short-acting nifedipine in hospitalized hypertensive children. Pediatr Nephrol 2004; 19: 644-650.
[77] Nourse PJ and McCulloch MI. Evaluation of the safety of shortacting nifedipine use in children with severe hypertension secondary to acute post-streptococcal glomerulonephritis. S Afr J Child Health 2007; 1: 34-37.
[78] Blaszak RT, Savage JA and Ellis EN. The use of short-acting nifedipine in pediatric patients with hypertension. J Pediatr 2001; 139: 34-37.
[79] Tuleu C, Grangé J and Seurin S. The need for pædiatric formulation: oral administration of nifedipine in children, a proof of concept. J Drug Deliv Sci Technol 2005; 15: 319-324.
[80] Jung SY, Choi NK, Kim JY, Chang Y, Song HJ, Lee J and Park BJ. Short-acting nifedipine and risk of stroke in elderly hypertensive patients. Neurology 2011; 77: 1229-1234.
[81] Schubert I, Hein R, Abbas S and Thürmann P. The frequency of prescription of immediate-release nifedipine for elderly patients in Germany: utilization analysis of a substance on the PRISCUS list of potentially inappropriate medications. Dtsch Arztebl Int 2012; 109: 215-219.
[82] Bonaduce D, Canonico V, Petretta M, Forgione L, Ianniciello A, Cavallaro V, Bertocchi F and Rengo F. Twenty-four-hour blood pressure monitoring during treatment with extended-release felodipine versus slow-release nifedipine in elderly patients with mild to moderate hypertension: a randomized, double-blind, crossover study. Eur J Clin Pharmacol 1997; 53: 95-100.
[83] Duckett GK and Cheadle B. Hypertension in the elderly: a study of a combination of atenolol and nifedipine. Br J Clin Pract 1990; 44: 52-54.
[84] Bravo EL, Krakoff LR, Tuck ML and Friedman CP. Antihypertensive effectiveness of nifedipine gastrointestinal therapeutic system in the elderly. The Modern Approach to the Treatment of Hypertension (MATH) Study Group. Am J Hypertens 1990; 3: 326S-332S.
[85] Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Pagé V, Ghadirian P, LeLorier J and Hamet P. Shanghai trial of nifedipine in the elderly (STONE). J Hypertens 1996; 14: 1237-1245.
[86] Wang X, Wu J, Liu L, Yang Q, Yu H, Luo W and Yan Z. Clinical effect of combined controlled-release nifedipine tablets-valsartan therapy on elderly patients suffering from type II diabetic nephropathy with hypertension. Biomed Res (India) 2018; 29: 1133-1136.
[87] Wang XJ, Wu JR, Liu L, Yang Q, Yu HL, Luo WH and Yan ZX. Clinical effect of combined controlled-release nifedipine tablets-valsartan therapy on elderly patients suffering from type II diabetic nephropathy with hypertension. Biomed Res 2018; 29.
[88] Schneider R, Stolero D, Griffel L, Kobelt R, Brendel E and Iaina A. Pharmacokinetic profile of nifedipine GITS in hypertensive patients with chronic renal impairment. Drugs 1994; 48 Suppl 1: 16-21; discussion 21-22.
[89] Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura O, Ishii M, Saruta T, Arakawa K, Hosoda S and Kawai C; Japan Multicenter Investigation for Cardiovascular Diseases-B Study Group. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. Hypertens Res 2004; 27: 181-191.
[90] Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura O, Ishii M, Saruta T, Arakawa K, Hosoda S and Kawai C. Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) subgroup analysis. Hypertens Res 2004; 27: 449-456.
[91] Baba S; J-MIND Study Group. Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. Diabetes Res Clin Pract 2001; 54: 191-201.
[92] Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, Wagener G and Ruilope LM; INSIGHT. Outcomes with nifedipine GITS or Co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). Hypertension 2003; 41: 431-436.
[93] Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T and Ruilope LM. Morbidity and mortality in patients randomised

to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000; 356: 366-372.

[94] Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J and Weber S; Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet 2004; 364: 849-857.

[95] Webster K, Fishburn S, Maresh M, Findlay SC and Chappell LC; Guideline Committee. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ 2019; 366: l5119.

[96] Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B and Schutte AE. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension 2020; 75: 1334-1357.

[97] Constantine G, Beevers DG, Reynolds AL and Luesley DM. Nifedipine as a second line antihypertensive drug in pregnancy. Br J Obstet Gynaecol 1987; 94: 1136-1142.

[98] Shen X, Yan J and Ren A. Effect of long-acting nifedipine on blood pressure level, eutocia rate and neonatal health status in patients with pregnancy-induced hypertension. Int J Clin Exp Med 2019; 12: 2605-2611.