



Department of Vermont Health Access

Therapeutic Class Review Calcium-Channel Blocking Agents (Dihydropyridines)

Overview/Summary

Calcium-channel blocking agents have multiple roles in treating cardiovascular disease. The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.¹⁻² Calcium-channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked, which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance.^{3,4} In addition, calcium-channel blocking agents (also called calcium-channel blockers or CCBs) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle.⁵ Both coronary and systemic vasodilation serve to reduce cardiac workload.⁶ There are two classes of CCBs dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally miscellaneous group.

Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle.¹ They have a lesser effect, or even no effect, upon cardiac muscle contractility or conduction. All available dihydropyridine agents can be used in the treatment of hypertension, with the exception of nimodipine. Although not a first-line treatment for hypertension, the dihydropyridines are generally effective but differ somewhat in other properties and effects. Amlodipine, oral nifedipine and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia.²

Long-acting CCBs are recommended in patients with stable angina if β -adrenergic blocking agents (β -blockers) are contraindicated. Alternatively, they may be used with β -blockers if initial treatment was not successful.⁷ Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. The European Society of Cardiology recommends the use of CCBs in patients with angina who can't tolerate β -blockers and who have had a myocardial infarction and who do not have heart failure.⁶ CCBs are recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions.⁸

In general, hypertension guidelines recommend the use of CCBs in patients with certain compelling indications including high coronary disease risk and diabetes.^{9,10} Patients with hypertension and stable angina should be treated with a β -blocker or a long-acting CCB.¹⁰

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Amlodipine (Norvasc ^{®*})	Calcium-channel blocking agents (dihydropyridines)	✓
Felodipine ER*	Calcium-channel blocking agents (dihydropyridines)	✓
Isradipine* (Dynacirc CR [®])	Calcium-channel blocking agents (dihydropyridines)	✓
Nicardipine* (Cardene IV ^{®*} ,	Calcium-channel blocking agents	✓

Generic Name (Trade Name)	Medication Class	Generic Availability
Cardene SR [®]	(dihydropyridines)	
Nifedipine (Adalat CC ^{®*} , Afeditab [®] , Nifediac CC ^{®*} , Nifedical XL ^{®*} , Procardia ^{®*} , Procardia XL ^{®*})	Calcium-channel blocking agents (dihydropyridines)	✓
Nimodipine (Nimotop ^{®*})	Calcium-channel blocking agents (dihydropyridines)	✓
Nisoldipine (Sular ^{®*})	Calcium-channel blocking agents (dihydropyridines)	✓

CR=controlled-release, ER=extended-release, IV=intravenous, SR=sustained-release

*Generic is available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications¹¹⁻²⁵

Generic Name	Chronic Stable Angina	Hypertension	Sub-arachnoid Hemorrhage	Coronary Artery Disease in Patients Without Heart Failure or an Ejection Fraction <40%	Vasospastic Angina (Prinzmetal's or Variant Angina)
Amlodipine (Norvasc [®])	✓ *	✓ †		✓	✓ *
Felodipine ER		✓ †			
Isradipine IR		✓ ‡			
Isradipine CR (Dynacirc CR [®])		✓ ‡			
Nicardipine IR	✓ §	✓ †			
Nicardipine SR (Cardene SR [®])		✓ †			
Nicardipine IV (Cardene IV [®])		✓			
Nifedipine IR (Procardia [®])	✓				✓
Nifedipine ER (Adalat CC [®] , Afeditab CR [®] , Nifediac CC [®])		✓ †			
Nifedipine ER, osmotic-release tablets (Nifedical XL [®] , Procardia XL [®])	✓	✓ †			✓
Nimodipine (Nimotop [®])			✓ ¶		
Nisoldipine (Sular [®])		✓ †			

CR=controlled-release, ER=extended-release, IR=immediate-release, IV=intravenous, SR=sustained-release

* Alone or in combination with other antianginal agents.

† Alone or in combination with other antihypertensive drugs.

‡ As monotherapy or concurrently with thiazide-type diuretics.

§ Immediate Release only; alone or in combination with β-adrenergic blocking agents.

|| Short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, patients should be transferred to oral medication as soon as their clinical condition permits.

¶ Indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V).

Pharmacokinetics**Table 3. Pharmacokinetics**^{1,11-26}

Generic Name	Bio-availability (%)	Protein Binding (%)	Active Metabolites (%)	Elimination (%)	Half-Life (hours)
Amlodipine	64 to 90	93	None	Urine (10% of parent compound and 60% of inactive metabolites)	30 to 50
Felodipine ER	20	>99	None	Feces (10); urine (70)	26.7 to 33.2
Isradipine IR	90 to 95	95	None	Feces (25 to 30); urine (60 to 65)	8
Isradipine CR	15 to 24	95	None	Feces (25 to 30); urine (60 to 65)	8
Nicardipine IR	35	>95	None	Feces (35); urine (60)	8.6
Nicardipine SR	35	>95	None	Feces (35); urine (60)	8.6
Nicardipine IV	100	>95	None	Feces (43); urine (49)	14.4
Nifedipine IR	40 to 77	92 to 98	None	Urine (80)	2
Nifedipine ER	84 to 89*	92 to 98	None	Urine (80)	7
Nifedipine ER, osmotic-release tablets	86*	92 to 98	None	Urine (80)	7
Nimodipine	13	>95	None	Feces (32); urine (50)	8 to 9†
Nisoldipine	5	>99	Yes (10% of the activity of parent compound)	Urine (60 to 80)	13.7

CR=controlled-release, ER=extended-release, IR=immediate release, IV=intravenous, SR=sustained-release

* Relative to the immediate-release product.

†Early elimination rates of one to two hours necessitates frequent (every four hours) dosing.

Clinical Trials

The dihydropyridine calcium channel blockers are indicated to treat hypertension and angina and the agent nimodipine is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage. Clinical trials have demonstrated the efficacy of these agents for their respective indications. For the treatment of angina, amlodipine and felodipine have been shown to be more effective than placebo, though no significant difference between active treatment groups was observed.²⁷ Two studies comparing amlodipine and diltiazem in the treatment of angina demonstrated no significant differences between active treatments in time to onset of angina, time to 1-mm ST-segment depression and heart rate.^{28,29} Frishman and colleagues compared amlodipine and verapamil monotherapy with the combination of amlodipine and atenolol on exercise tolerance and found that amlodipine monotherapy resulted in a significantly greater duration of ischemic episodes compared to verapamil monotherapy and amlodipine plus atenolol combination therapy.³⁰ In-class comparisons for the treatment of hypertension have found better compliance and a higher response rate with amlodipine compared to felodipine, though van der Krogt and colleagues also found similar decreases in overall systolic and diastolic blood pressures between groups.^{31,32} Other studies have shown similar blood pressure lowering efficacy between agents.³³⁻³⁸

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Angina				
Koenig et al ²⁷ Amlodipine 5 to 10 mg Daily vs felodipine ER 5 to 10 mg Daily	DB, PRO, RCT, XO Patients 30 to 80 years of age who have a history of angina, a positive exercise-stress test or positive 24-hour ambulatory monitoring, and ≥ 6 ischemic episodes in 24 hours	N=52 8 weeks (4 weeks of each treatment)	Primary: Number of ST-segment depressions in 24 hours of ambulatory monitoring Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression, length of ischemic episode, adverse events	Primary: Significant reductions from baseline were seen in both groups for the number of ST-segment depressions, from 19.9 at baseline for both groups to 2.3 for the amlodipine group and 2.4 for the felodipine group ($P<0.001$ for both groups from baseline; $P=0.83$ between treatments). Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression and length of ischemic episode were significantly different from baseline for both treatment groups but treatments were not significantly different ($P<0.001$ for all from baseline, $P=0.53, 0.40, 0.68, 0.35$ respectively between treatments). Adverse event rates similar between the treatment groups (P value not reported).
Chugh et al ²⁸ Diltiazem 240 mg Daily for 2 weeks then 360 mg Daily for 2 weeks vs amlodipine 5 mg Daily for 2 weeks then 10 mg Daily for 2 weeks	DB, DD, PG, RCT Patients with stable angina, BP in the range of 100/60 to 170/110 mm Hg and a positive ischemic response on a treadmill test, history of angiography	N=67 4 weeks	Primary: Treadmill exercise test: time to onset of angina, time to 1-mm ST-segment depression Secondary: Heart rate, BP, number of angina episodes and use of nitrates	Primary: Both treatment groups, and all doses, had significant increases in time to onset of angina from baseline ($P<0.001$ for all). There was no significant difference between the treatment groups ($P=0.838$) and between dose levels ($P=0.144$) in time to onset of angina. Both treatment groups, and all doses, had significant increases in time to 1-mm ST-segment depression from baseline, except the low-dose amlodipine group ($P<0.004$, except $P=0.063$). There was no significant difference between the treatment groups and between dose levels ($P=0.114$) in time to 1-mm ST-segment depression ($P=0.691$). Secondary: There was no significant difference between the groups in heart rate at rest or maximal exercise. There was no significant difference between the groups in BP at rest or maximal exercise, except SBP at rest was higher in the diltiazem group (137 to 143 vs 129 to 135 mm Hg; $P=0.029$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Both treatments reduced the number of angina episodes and the use of nitrates, but these results were not statistically different between the groups (<i>P</i> value not reported).
van Kesteren et al ²⁹ Diltiazem CR 90 to 120 mg BID vs amlodipine 5 to 10 mg Daily	DB, MC Men and women 41 to 77 years of age with a history of stable angina pectoris, a positive exercise tolerance test, and positive thallium scan or positive coronary angiogram	N=132 8 weeks	Primary: Exercise tolerance test: time to 1-mm ST-segment depression, time to onset of chest pain, time to end of exercise (exercise duration) Secondary: Safety	Primary: Diltiazem and amlodipine treatment resulted in significant increases in time to 1-mm ST-segment depression as compared to baseline (<i>P</i> <0.0001). Treatments were not significantly different from each other (<i>P</i> >0.05). Diltiazem and amlodipine treatment resulted in significant increases in time to onset of chest pain at four and eight weeks, (10 and 13% for amlodipine; <i>P</i> <0.0001; 5 and 7% for diltiazem; <i>P</i> =0.009). Treatments were not significantly different from each other (<i>P</i> >0.05). Amlodipine treatment resulted in a significant increase in total exercise duration as compared to baseline (<i>P</i> =0.0002), however the change from baseline for diltiazem was not significantly increased (<i>P</i> =0.43). There was no significant difference between the treatment groups at endpoint. Secondary: Ten patients (15.2%) in the amlodipine group and 17 patients (25.8%) in the diltiazem group reported an adverse event; two patients from the amlodipine group and six patients from the diltiazem group subsequently withdrew from the study.
Frishman et al ³⁰ Verapamil 240 to 480 mg at bedtime vs amlodipine 5 to 10 mg Daily vs	DB, MC, PC, PG, RCT Patients 30 to 80 years of age with chronic stable angina pectoris, evidence of exercise-induced ST-segment depression ≥1 mm and other evidence	N=551 4 week	Primary: Exercise tolerance test (symptom-limited exercise duration, time ≥1-mm ST-segment depression and time to moderate angina) Secondary: 48-hour Holter-determined number of	Primary: Treatment with verapamil, amlodipine, and amlodipine plus atenolol resulted in significantly better results than treatment with placebo in: symptom-limited exercise duration, time ≥1-mm ST-segment depression and time to moderate angina (<i>P</i> ≤0.01 for all vs placebo). Secondary: Treatment with verapamil, amlodipine, and amlodipine plus atenolol resulted in significantly fewer ischemic episodes in 48-hour Holter monitoring (<i>P</i> =0.003 for verapamil vs placebo). Treatment with amlodipine monotherapy resulted in a significant increase

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
amlodipine 5 to 10 mg Daily plus atenolol 50 mg Daily vs placebo	of cardiac disease		ischemic episodes, mean and total duration of ischemia, maximal depth of ST depression, heart rate at onset of ischemia	in duration of ischemic episode ($P \leq 0.05$ vs verapamil vs amlodipine plus atenolol and vs placebo). Treatment with verapamil and amlodipine plus atenolol resulted in a decrease in duration of ischemic episodes as compared to treatment with amlodipine and placebo ($P \leq 0.05$ for each). Heart rate at the onset of ischemic episode was significantly lower in the verapamil group and in the amlodipine plus atenolol group ($P \leq 0.05$ vs amlodipine) and higher in the amlodipine group ($P \leq 0.05$ vs verapamil, vs amlodipine plus atenolol and vs placebo).
Parameshwar et al ³⁹ Nicardipine 20 mg TID increased to 30 mg TID vs atenolol 50 mg Daily increased to 100 mg Daily vs combination of nicardipine and atenolol	RCT, XO Patients 41 to 70 years of age with chronic stable angina	N=30 6 week treatment blocks (3 blocks, XO design)	Primary: Exercise duration, time to 1-mm ST-segment depression, time to onset of angina, ejection fraction, peak filling rate, time to peak filling rate, left ventricular end diastolic volume, angina attacks, glyceryl trinitrate use Secondary: Not reported	Primary: Exercise duration was significantly prolonged in the atenolol and nicardipine groups compared to the placebo group ($P < 0.001$). No significant difference between active treatment groups was observed. Time to onset of angina was prolonged in the nicardipine and combination therapy groups compared to the placebo group ($P < 0.01$ and $P < 0.001$ respectively). No significant change was observed in the atenolol group. No significant change in ejection fraction, peak filling rate or time to peak filling rate was observed. There was a significant increase in the first third filling friction in atenolol and combination therapy groups compared to the placebo group ($P < 0.001$). There was a significant increase in left ventricular end diastolic volume in the atenolol and combination groups compared to the placebo group ($P < 0.05$). There were no significant differences between groups in the frequency of angina attacks or glyceryl trinitrate use. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>Savanitto et al⁴⁰ IMAGE</p> <p>Weeks 1 to 6: Metoprolol ER 200 mg Daily</p> <p>vs</p> <p>nifedipine 20 mg BID</p> <p>Weeks 7 to 10: metoprolol ER 200 mg Daily plus placebo</p> <p>vs</p> <p>metoprolol ER 200 mg Daily plus nifedipine 20 mg BID</p> <p>vs</p> <p>nifedipine 20 mg BID plus placebo</p>	<p>DB, MC, RCT</p> <p>Patients with typical angina symptoms that had been stable for approximately 6 months, who showed a positive response to exercise stress testing with 23 minutes of exercise tolerance and were in sinus rhythm and had an analyzable ST segment on ECG</p>	<p>N=280</p> <p>6 weeks</p>	<p>Primary: Angina frequency, exercise tolerance, safety</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>At week six, metoprolol (mean change, -1.95; 95% CI, -1.25 to -2.64) and nifedipine (-1.57; 95% CI, -0.69 to -2.45) significantly reduced the frequency of angina compared to baseline, but there was not a significant difference between the two treatments (<i>P</i> value not reported). At the end of 10 weeks, there was not a significant difference observed between the two treatments.</p> <p>At week six, metoprolol and nifedipine significantly increased the mean exercise time to 1 mm ST-segment depression compared to baseline (<i>P</i><0.01 for both); but metoprolol was significantly more effective than nifedipine (<i>P</i><0.05).</p> <p>At week 10, the combination therapies had a further increase in time to 1 mm ST-segment depression (<i>P</i><0.05 vs placebo).</p> <p>There were 14 cardiovascular events including one sudden death, three acute MIs, eight cases of unstable angina, one of syncope and one of stroke. The incidences of these events did not differ among the treatments (<i>P</i> values were not reported).</p> <p>Secondary: Not reported</p>
Hypertension				
<p>Wright et al⁴¹</p> <p>Diltiazem graded-release 360 to 540 mg Daily</p> <p>vs</p> <p>amlodipine 5 to 10 mg Daily</p>	<p>AC, DB, MC, PG, RCT</p> <p>Male and female African Americans patients 18 to 80 years of age with hypertension (DBP 85 to 109 mm Hg and SBP <180 mm</p>	<p>N=268</p> <p>12 weeks</p>	<p>Primary: Change from baseline in DBP during first four hours of awakening as recorded by ambulatory BP monitoring</p> <p>Secondary:</p>	<p>Primary: Reductions in DBP during the first four hours after awakening, and from 6AM to noon, were significantly greater in the diltiazem group than in the amlodipine group (-13.12 vs -9.65 mm Hg; <i>P</i>=0.0049 and -11.97 vs -8.75 mm Hg; <i>P</i>=0.0019).</p> <p>Secondary: Reductions in SBP during the first four hours after awakening and between 6AM and noon, were similar between the groups (<i>P</i><0.0768 and <i>P</i><0.9470).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	Hg)		Changes from baseline in BP, heart rate, rate-pressure product, safety	<p>Mean 24-hour SBP reductions were significantly greater in the amlodipine group than in the diltiazem group (-14.08 vs -10.64; $P=0.0022$).</p> <p>Reductions in heart rate were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: -4.88 vs 1.77; $P<0.0001$).</p> <p>Reductions in rate-pressure product were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: -1,493 vs -881; $P<0.0008$).</p> <p>In the diltiazem and amlodipine groups respectively, 1.5 and 2.2% discontinued early due to adverse events.</p>
<p>Sheehy et al³¹</p> <p>Amlodipine Daily, initial dose 2.5 to 10 mg Daily</p> <p>vs</p> <p>felodipine Daily, initial dose 2.5 to 10 mg Daily</p>	<p>RETRO</p> <p>Patients 65 years of age and older with hypertension</p>	<p>N=7,818</p> <p>(amlodipine, 5,818; felodipine, 2,630)</p>	<p>Primary: Prescription renewal, drug switch rates, compliance rates, office visits</p> <p>Secondary: Not reported</p>	<p>Primary: Patients prescribed amlodipine had a greater compliance rate, 67.9%, than those prescribed felodipine 66.2% ($P<0.01$).</p> <p>Discontinuation rates were higher in the felodipine group by 27%.</p> <p>Amlodipine treatment resulted in more continuous months of treatment (69.2), than felodipine treatment (57.8; $P<0.01$).</p> <p>Renewal rates were significantly larger in the amlodipine group (89.0%), than the felodipine group (85.6%; $P<0.01$).</p> <p>Switch rates were significantly larger, five times, in the felodipine group (10.2%) than the amlodipine group (1.9%; $P<0.01$).</p> <p>Visits to specialists occurred significantly more in patients treated with amlodipine than patients treated with felodipine, respectively (OR, 1.14; 95% CI, 1.08 to 1.20).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>Van der Krogt et al³²</p> <p>Amlodipine 5 to 10 mg Daily</p> <p>vs</p> <p>felodipine ER 5 to 10 mg Daily</p>	<p>DB, MC, PG, RCT</p> <p>Patients 18 to 75 years of age with mild to moderate hypertension (DBP ≥ 95 and ≤ 114 mm Hg)</p>	<p>N=201</p> <p>12 weeks</p>	<p>Primary: Number of responders (DBP ≤ 90 mm Hg after 12 weeks of monotherapy or decrease of >10 mm Hg if baseline DBP >100 mm Hg) who did not experience serious adverse events</p> <p>Secondary: BP, adverse events</p>	<p>Primary: Amlodipine treatment resulted in significantly more responders than felodipine treatment ($P=0.046$).</p> <p>Sixty eight percent (69 of 101) of the amlodipine group were responders.</p> <p>Fifty three percent (49 of 92) of the felodipine group were responders.</p> <p>Thirty two percent (32 of 101) of the amlodipine group were not responders.</p> <p>Forty seven percent (43 of 92) of the felodipine group were not responders.</p> <p>Secondary: The decreases in SBP and DBP from baseline were significant within each group but similar between the groups (amlodipine SBP and DBP 12 weeks vs baseline; $P<0.001$, felodipine SBP and DBP 12 weeks vs baseline; $P<0.001$, amlodipine 12 week change vs felodipine 12 week change; $P>0.05$).</p> <p>Adverse events were experienced by 33% of the amlodipine group and 42% of the felodipine group.</p> <p>Significantly more patients in the felodipine group experienced serious adverse events (nine patients who experienced 17 serious events vs two patients who experienced three serious events; $P=0.048$).</p>
<p>Mounier-Vehier et al³³</p> <p>Amlodipine 5 mg Daily</p> <p>vs</p> <p>nicardipine 60 mg/daily, divided BID to TID times daily</p>	<p>DB, MC, PG, RCT</p> <p>Patients 60 years of age and older with isolated systolic hypertension (SBP 160 to 208 mm Hg) and DBP <90 mm Hg</p>	<p>N=133</p> <p>90 days</p>	<p>Primary: Mean difference in SBP from baseline to day 90</p> <p>Secondary: Mean difference in DBP, pulse pressure, heart rate, percent of patients with normal</p>	<p>Primary: The decrease in SBP from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline; $P=0.0001$, nicardipine day 90 vs baseline; $P=0.0001$, amlodipine 90 day change vs nicardipine 90 day change; $P=0.38$).</p> <p>Secondary: The decrease in DBP from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline; $P=0.0001$, nicardipine day 90 vs baseline; $P=0.0003$, amlodipine 90 day change vs</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			BP (<140/90 mm Hg), safety	<p>nicardipine 90 day change; $P=0.12$).</p> <p>The decrease in pulse pressure from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline; $P=0.0001$, nicardipine day 90 vs baseline; $P=0.0001$, amlodipine 90 day change vs nicardipine 90 day change; $P=0.88$). There was no difference between the groups in heart rate ($P=0.60$).</p> <p>At day 90, 25.9 and 23.4% of the amlodipine and nicardipine groups had achieved normal BP ($P=0.76$).</p> <p>The numbers of people in each group reporting at least one adverse event were similar, 23 in the amlodipine group and 20 in the nicardipine group (P value not reported).</p>
<p>Kes et al³⁴</p> <p>Amlodipine 5 to 10 mg Daily</p> <p>vs</p> <p>nifedipine 30 to 60 mg Daily</p>	<p>MC, OL, RCT</p> <p>Patients with hypertension</p>	<p>N=155</p> <p>12 weeks</p>	<p>Primary: Change in DBP</p> <p>Secondary: Not reported</p>	<p>Primary: There was no significant difference in DBP between the amlodipine group and nifedipine group at 12 weeks ($P=0.436$).</p> <p>Secondary: Not reported</p>
<p>Ryuzaki et al⁴²</p> <p>i-TECHO</p> <p>Amlodipine 2.5 to 10 mg Daily</p> <p>vs</p> <p>nifedipine CR 20 to 80 mg Daily</p>	<p>OL, RCT, XO</p> <p>Patients treated for hypertension (SBP >140 mm Hg or DBP >90 mm Hg)</p>	<p>N=55</p> <p>12 weeks (6 weeks per treatment)</p>	<p>Primary: Average home BP readings, pulse rates, clinic BP and pulse readings</p> <p>Secondary: Not reported</p>	<p>Primary: The morning home SBP and DBP readings were lower in the nifedipine group than the amlodipine group (SBP 131±8 vs 133±10 mm Hg; $P<0.05$, DBP 80±8 vs 81±8 mm Hg; $P<0.05$).</p> <p>There were no significant differences in evening home BP readings between the groups ($P>0.05$).</p> <p>There was no significant difference in rates of achieving target BP between the groups ($P<0.05$).</p> <p>Morning home pulse rates were greater in the nifedipine group than the amlodipine group (70±9 vs 69±9 bpm; $P<0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				<p>There were no significant differences between the groups in evening home pulse rates ($P>0.05$).</p> <p>The clinic SBP and DBP readings were significantly lower in the nifedipine group than in the amlodipine group ($P<0.05$).</p> <p>There were no significant differences between the groups in clinic pulse rates ($P>0.05$).</p> <p>Secondary: Not reported</p>
<p>Gustin et al³⁵</p> <p>Felodipine 5 to 10 mg Daily</p> <p>vs</p> <p>nifedipine 30 to 60 mg Daily</p>	<p>XO</p> <p>Patients with hypertension, stable on nifedipine for at least 3 months were switched to felodipine</p>	<p>N=127</p> <p>2 months</p>	<p>Primary: BP</p> <p>Secondary: Side effects and use of supplemental antihypertensive agents</p>	<p>Primary: There was no difference in SBP before and after switching agents. However, there was a difference in DBP, which was slightly lower (-2 ± 2 mm Hg) with felodipine treatment than with nifedipine treatment ($P<0.05$).</p> <p>Secondary: Reported adverse events by patients and providers did not differ between the agents, with the most commonly reported side effect for both treatments being leg swelling/edema.</p> <p>There was no difference in use of supplemental antihypertensive agents and heart rate between treatments ($P>0.05$ for both).</p>
<p>Saito et al⁴³</p> <p>ADVANCE-Combi</p> <p>Amlodipine 2.5 to 5 mg Daily</p> <p>vs</p> <p>nifedipine CR 20 to 40 mg Daily</p> <p>Valsartan 40 to 80 mg</p>	<p>DB, RCT</p> <p>Patients with untreated essential hypertension with sitting SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg; or previously treated with sitting SBP ≥ 150 mm Hg or DBP ≥ 95 mm Hg</p>	<p>N=514</p> <p>16 weeks</p>	<p>Primary: Target BP, achievement rate</p> <p>Secondary: Safety</p>	<p>Primary: Target BP achievement rates were higher for the nifedipine group than the amlodipine group ($P<0.001$).</p> <p>Patients in the amlodipine group were more likely to require additional treatment with valsartan or a dose increase of amlodipine ($P<0.05$).</p> <p>The reduction in BP from baseline was greater in the nifedipine group ($-34.0/-20.1$) than in the amlodipine group ($-27.0/-15.9$; $P<0.05$).</p> <p>Secondary: Adverse event rates were not significantly different between the groups</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
daily was added on if BP goal not met.				(12.4% of the nifedipine group vs 7.6% of the amlodipine group; $P=0.07$).
Pepine et al ³⁶ CESNA-II Amlodipine 5 to 10 mg Daily vs nisoldipine ER 20 to 40 mg Daily	DB, DD, PG, MC, RCT Men and women with hypertension (DBP 90 to 109 mm Hg) and coronary artery disease	N=not specified 6 weeks	Primary: Change from baseline in DBP at six weeks Secondary: Exercise duration, antihypertensive responder rate (percent of patients with DBP <90 mm Hg), exercise test responder rate (increase in time by 20% and 60 seconds)	Primary: At six weeks, the mean SBP and mean DBP for the two treatment groups were not significantly different from each other and mean reductions in BP were similar (amlodipine SBP/DBP, 138/83 mm Hg, a decrease of 13/11 mm Hg, vs nisoldipine, 137/81 mm Hg, a decrease of 15/13 mm Hg; all P values not significant). Secondary: Both treatment groups experienced increases in exercise duration, increased by 21 seconds in the amlodipine group and 23 seconds in the nisoldipine group ($P=0.268$). Antihypertensive and exercise responder rates were similar between the groups (antihypertensive rates, 78% for the amlodipine group and 87% for the nisoldipine group; $P>0.05$ for both).
Whitcomb et al ⁴⁴ Amlodipine 2.5 to 10 mg Daily vs nisoldipine ER 10 to 40 mg Daily	DB, DD, MC, RCT Men and women 21 to 75 years of age with hypertension	N=161 8 weeks	Primary: Between treatment comparison of change from baseline in DBP Secondary: Change from baseline in SBP, heart rate, percent of patients who responded	Primary: Treatment with amlodipine resulted in a significantly larger change from baseline, between-group difference of 2.7 mm Hg; $P=0.005$. However, a pre-specified difference of >5 mm Hg in least mean squares, here 1.1 to 4.3 mm Hg, showed that the treatments were similar in reduction of DBP. Secondary: Amlodipine treatment resulted in a significantly larger change from baseline in SBP than nisoldipine treatment (P value not reported, least mean square difference >5 mm Hg). At week eight, more patients in the amlodipine group were responders, 79%, as compared to the nisoldipine group, 60% ($P=0.004$).
White et al ³⁷ CESNA-III Amlodipine 5 to 10 mg	DB, MC, PRO, RCT African American	N=192 12 weeks	Primary: Ambulatory BP monitoring change from baseline in DBP	Primary: The decrease from baseline in DBP was similar between the groups: – 16.0±2.3 mm Hg for the nisoldipine group and – 15.0±2.3 mm Hg for the amlodipine group ($P=0.500$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Daily vs nisoldipine ER 20 to 60 mg Daily	patients with hypertension (BP 92 to 114 mm Hg and SBP <200 mm Hg)		in mean 24 hour period Secondary: Ambulatory BP monitoring change in SBP, awake and asleep BP, changes in clinic BP and pulse	Secondary: The decrease from baseline in SBP was similar between the groups: – 23.0±2.7 mm Hg for the nisoldipine group and –19.9±2.7 mm Hg for the amlodipine group (<i>P</i> =0.067). The changes from baseline in awake and asleep SBP and DBP were not significantly different between the groups except for awake SBP, for which the nisoldipine group had a larger reduction, –19.2 vs –15.9 mm Hg (<i>P</i> =0.045). The changes from baseline in clinic BP and pulse were similar between the groups (<i>P</i> >0.05 for SBP and DBP; <i>P</i> =0.362).
Lenz et al ³⁸ Amlodipine 5 to 10 mg Daily vs nisoldipine 10 to 20 mg Daily	OL, XO Patients 35 to 70 years of age with hypertension, (SBP 140 to 179 mm Hg and DBP 90 to 109 mm Hg), stable on amlodipine for at least 3 months prior to switch to nisoldipine	N=21 10 weeks	Primary: 24-hour ambulatory BP monitoring Secondary: Not reported	Primary: No significant difference in ambulatory BP monitoring was found after patients switched from amlodipine to nisoldipine for the following: systolic nighttime, daytime and 24-hour BP, diastolic nighttime and daytime BP (<i>P</i> >0.05 for all). 24-hour DBP was significantly lower with amlodipine treatment than with nisoldipine treatment (75.0±10.0 vs 77.0±8.5 mm Hg; <i>P</i> =0.017). Secondary: Not reported
Van Bortel et al ⁴⁵ Nebivolol vs active comparator (ARB, β-blocker, calcium channel blocker or ACE inhibitor)	MA 12 RCTs involving >25 patients with essential hypertension where nebivolol 5 mg Daily was compared to placebo or other active drugs for >1	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; <i>P</i> =0.001) and compared to the ACE inhibitors (OR, 1.92; 95% CI, 1.30 to 2.85; <i>P</i> =0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; <i>P</i> =0.283), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; <i>P</i> =0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; <i>P</i> =0.212). Overall, a higher percentage of patients obtained normalized BP with nebivolol compared to the other antihypertensive agents combined (OR,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
or placebo	month			<p>1.35; 95% CI, 1.07 to 1.72; $P=0.012$). A higher percentage of patient receiving nebivolol obtained normalized BP compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; $P=0.004$) and calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; $P=0.024$), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; $P=0.473$).</p> <p>Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; $P<0.001$) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; $P=0.482$). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; $P=0.016$), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; $P=0.007$) and calcium channel blockers (OR, 0.49; 95% CI, 0.33 to 0.72; $P<0.001$), but was similar to ACE inhibitors (OR, 0.75; 95% CI, 0.52 to 1.08).</p> <p>Secondary: Not reported</p>
<p>Wiysonge et al⁴⁶</p> <p>β-blockers (atenolol, metoprolol, oxprenolol* or propranolol)</p> <p>vs</p> <p>other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers or renin-angiotensin system inhibitors)</p>	<p>MA</p> <p>13 RCTs evaluating patients ≥ 18 years of age with hypertension</p>	<p>N=91,561</p> <p>Duration varied</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Stroke, coronary heart disease, cardiovascular death, total cardiovascular disease, adverse reactions</p>	<p>Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo therapy (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretic therapy (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitor therapy (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blocker therapy (RR, 1.07; 95% CI, 1.00 to 1.14; $P=0.04$).</p> <p>Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo therapy (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blocker therapy (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitor therapy (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretic therapy (RR, 1.17; 95% CI, 0.65 to 2.09).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				<p>Coronary heart disease risk was not significantly different between β-blocker therapy and placebo therapy (RR, 0.93; 95% CI, 0.81 to 1.07), diuretic therapy (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blocker therapy (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitor therapy (RR, 0.90; 95% CI, 0.76 to 1.06).</p> <p>The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo therapy (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blocker therapy (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretic therapy (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitor therapy (RR, 1.00; 95% CI, 0.72 to 1.3).</p> <p>There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretic therapy (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitor therapy (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blocker therapy (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.</p>
<p>Manyemba⁴⁷</p> <p>HCTZ 25 mg Daily plus reserpine 0.25 mg Daily</p> <p>vs</p> <p>HCTZ 25 mg Daily plus nifedipine SR 20 mg BID</p>	<p>OL, RCT, XO</p> <p>African American patients aged 21 to 65 years with hypertension (BP >140/95 mm Hg) after 4 weeks of daily HCTZ therapy</p>	<p>N=32</p> <p>10 weeks</p>	<p>Primary: The change in BP from baseline to the end of each four week treatment period</p> <p>Secondary: Not reported</p>	<p>Primary: Reserpine reduced SBP by 15.9 mm Hg (95% CI, 8.4 to 23.4) and DBP by 11.1 mm Hg (95% CI, 7.5 to 14.6).</p> <p>Nifedipine SR reduced SBP by 18.9 mm Hg (95% CI, 12.1 to 25.7) and DBP by 9.6 mm Hg (95% CI, 7.2 to 12.0).</p> <p>There was no significant difference between the two groups (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Ogihara et al⁴⁸</p> <p>CASE-J</p>	<p>AC, MC, OL, PG, PRO, RCT</p>	<p>N=4,703</p> <p>Up to 4 years</p>	<p>Primary: First fatal/nonfatal cardiovascular event</p>	<p>Primary: One hundred thirty four patients experienced a cardiovascular event in each treatment group (HR, 1.00; 95% CI, 0.78 to 1.27; P=0.969).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>Amlodipine 2.5 to 10 mg Daily</p> <p>vs</p> <p>candesartan 4 to 12 mg Daily</p>	<p>Patients with high risk hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg in patients < 70 years old or SBP ≥ 160 mm Hg or DBP ≥ 90 mm Hg in patients ≥ 70 years old), with either type 2 diabetes, history of stroke or ischemic attack, left ventricular hypertrophy, proteinuria or serum creatinine ≥ 1.3 mg/dL</p>		<p>(composite of sudden death, cerebrovascular events, cardiac events including heart failure, angina pectoris, acute MI, renal events, including serum creatinine increases, vascular events, including dissecting aortic aneurysm or arteriosclerotic occlusion</p> <p>Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events</p>	<p>Secondary: All-cause death rates did not differ between groups, 73 deaths in the candesartan group and 86 deaths in the amlodipine group (<i>P</i> value not reported).</p> <p>New-onset diabetes occurred in significantly fewer patients in the candesartan group than the amlodipine group (HR, 0.64; 95% CI, 0.43 to 0.97; <i>P</i>=0.033).</p> <p>One hundred twenty five (5.4%) patients in the candesartan group and 134 (5.8%) patients in the amlodipine group discontinued due to adverse events (<i>P</i> value not reported).</p>
<p>Ribeiro et al⁴⁹ LAMHYST</p> <p>Amlodipine 5 mg Daily (option to increase to 10 mg at 6 weeks)</p> <p>vs</p> <p>losartan 50 mg Daily (option to increase to 100 mg at 6 weeks)</p>	<p>DB, DD, PG, PRO, RCT</p> <p>Flexible-dose escalation study</p> <p>Males and females 18 to 79 years of age with diagnosis of mild (> 95 but < 115 mm Hg) to moderate essential hypertension and not taking an antihypertensive medication (within</p>	<p>N=194</p> <p>12 weeks, with 2 days placebo treatment, mimicking a drug holiday after 12 weeks on treatment</p>	<p>Primary: Difference between treatment groups in mean change in ambulatory BP monitoring for last nine hours of treatment and during drug holiday</p> <p>Secondary: Not reported</p>	<p>Primary: After 12 weeks, mean reductions in SBP were significantly larger in the amlodipine group than the losartan group (-18.1 vs -10.1 mm Hg; <i>P</i>< 0.001). Mean reductions in DBP were significantly larger in the amlodipine group than the losartan group (-18.1 vs -10.1 mm Hg; <i>P</i>< 0.05).</p> <p>Mean increases in SBP were similar between the groups during the two-day drug holiday (<i>P</i>> 0.05).</p> <p>After the two-day drug holiday, SBP was lower than baseline in both groups (<i>P</i>< 0.001), with the amlodipine group SBP remaining significantly lower (<i>P</i>< 0.01).</p> <p>Mean increases in DBP were similar between the groups during the two-day drug holiday (<i>P</i>> 0.05). After the two-day drug holiday, DBP was lower</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	last 4 weeks)			<p>than baseline in both groups ($P=0.0001$), with the amlodipine group DBP remaining significantly lower ($P<0.05$).</p> <p>Secondary: Not reported</p>
<p>Chrysant et al⁵⁰ COACH</p> <p>Olmesartan 10, 20 or 40 mg Daily</p> <p>vs</p> <p>amlodipine 5 or 10 mg Daily</p> <p>vs</p> <p>olmesartan 10 to 40 mg plus amlodipine 5 to 10 mg Daily (all possible combinations)</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 years of age and older with seated DBP 95 to 120 mm Hg</p>	<p>N=1,940</p> <p>8 weeks</p>	<p>Primary: Change from baseline in seated DBP at week eight</p> <p>Secondary: Change from baseline in seated SBP at week eight; mean change from baseline in seated DBP and SBP at weeks two, four, six and eight without last observation carried forward; proportion of patients achieving BP goal (<140/90 or <130/80 mm Hg), safety</p>	<p>Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week eight ($P<0.001$). Reductions in seated DBP with monotherapy ranged from -8.3 to -12.7 mm Hg; reductions with combination therapy ranged from -13.8 to -19.0 mm Hg. All combinations of combination therapy reduced seated DBP significantly greater than either component as monotherapy at the same dosage ($P<0.001$).</p> <p>Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week eight ($P<0.001$ for treatment, $P=0.024$ for placebo). All combinations of combination therapy reduced seated SBP significantly greater than either component as monotherapy at the same dosage ($P<0.001$).</p> <p>The proportion of patients achieving goal BP were 20.0 to 36.3% of patients receiving olmesartan monotherapy, 21.1 to 32.5% of patients receiving amlodipine monotherapy, 35.0 to 53.2% of patients receiving combination therapy and 8.8% of patients receiving placebo therapy. Combination therapy resulted in significantly greater achievement of goal BP than monotherapy ($P<0.005$).</p> <p>No difference in overall rates of adverse events across the different treatment groups was seen. The proportion of patients who experienced a drug-related adverse event was 26.9%.</p> <p>Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment. Platelet counts increased significantly from baseline for patients receiving amlodipine therapy, however; the increase was <10% and not deemed clinically relevant (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Cardiovascular Outcomes				
<p>Pitt et al⁵¹ PREVENT</p> <p>Amlodipine 5 to 10 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Men and women 30 to 80 years of age with angiographic evidence of coronary artery disease, DBP <95 mm Hg, total cholesterol 325 mg/dL, fasting blood glucose <200 mg/dL</p>	<p>N=825</p> <p>3 years</p>	<p>Primary: Change in mean minimal diameter with a quantitative coronary angiography</p> <p>Secondary: Progression of atherosclerosis in the carotid arteries assessed by B-mode ultrasonography for intimal-medial thicknesses, all-cause mortality, occurrence of major fatal/nonfatal vascular events or procedures, adverse events</p>	<p>Primary: Change, reduction, in the minimal diameter was similar between the amlodipine group and the placebo group (0.084 vs 0.0095; <i>P</i>=0.38).</p> <p>Secondary: Amlodipine treatment significantly decreased the progression of atherosclerosis as compared to placebo treatment, a 0.013 mm decrease for the amlodipine group vs a 0.033 mm increase with the placebo group (<i>P</i>=0.007).</p> <p>There was no difference in all-cause mortality between the amlodipine and placebo groups, respectively.</p> <p>There was no difference in occurrence of fatal and nonfatal vascular events between the treatment groups (HR, 0.82; 95% CI, 0.47 to 1.42).</p> <p>Amlodipine treatment significantly reduced the occurrence of hospitalized CHF and unstable angina (HR, 0.65; 95% CI, 0.47 to 0.91) and coronary revascularizations (HR, 0.57; 95% CI, 0.41 to 0.81) and combined overall procedures (HR, 0.69; 95% CI, 0.52 to 0.92).</p> <p>There was no significant difference between groups in rates of adverse events: cancer rate (HR, 2.13; 95% CI, 0.90 to 5.21) and bleeding episode (HR, 1.42; 95% CI, 0.88 to 2.30).</p>
<p>Lichtlen et al⁵² INTACT</p> <p>Nifedipine 80 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PRO, RCT</p> <p>Patients 65 years of age and younger demonstrating early coronary artery disease who were not candidates for invasive therapeutic</p>	<p>N=348 (282 without study deviations)</p> <p>3 years</p>	<p>Primary: Progression of coronary artery disease detected on angiogram (change in minimal diameter, percent stenosis, transition into occlusion, new stenosis)</p>	<p>Primary: In patients without study deviations, there were no significant differences in number of stenoses and occlusions per patient (nifedipine, 3.7; placebo, 3.88; <i>P</i>=0.437). The distribution among the arteries of the occlusions was not different between groups (<i>P</i> value not reported).</p> <p>The progression of stenosis was significant from baseline but changes were not significantly different between the groups (<i>P</i><0.006 for all vs baseline; <i>P</i>>0.585 for group comparisons).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	procedures		Secondary: Critical clinical events (cardiac death, nonfatal MI, unstable angina, need for procedure, heart failure, severe arrhythmias), progression of new lesions	There was no difference between nifedipine and placebo in number of critical events, 44 events in 24 patients receiving nifedipine vs 52 events in 35 patients receiving placebo ($P=0.278$). The nifedipine group had significantly fewer new lesions as compared to the placebo group: 78 (0.58 lesions/patients) vs 118 (0.8 lesions/patient; $P=0.031$).
Borhani et al ⁵³ MIDAS Isradipine 2.5 to 5 mg BID vs HCTZ 12.5 to 25 mg Daily	DB, MC, positive-control, RCT Patients with an average age of 58.5 years with hypertension	N=883 3 years	Primary: Rate of progression of intimal-medial thickness in carotid arteries Secondary: Rate of cardiovascular events (MI, stroke, CHF, angina, sudden death), rate of nonmajor cardiovascular events and procedures (transient ischemic attacks, dysrhythmia, aortic valve replacement, femoral popliteal bypass graft), BP	Primary: There was no difference in the rate of progression of intimal-medial thickness between the treatment groups ($P=0.68$). Secondary: The rate of cardiovascular events was greater in the isradipine group than in the HCTZ group (5.65 vs 3.17%; $P=0.07$). The rate of nonmajor cardiovascular events was greater in the isradipine group than in the HCTZ group (9.05 vs 5.22%; $P=0.02$). There was a significant decrease in SBP in the HCTZ group as compared to the isradipine group (-19.5 vs -16.0 mm Hg; $P=0.002$). There was no difference in change in DBP (both groups -13.0 mm Hg).
Julius et al ⁵⁴ (VALUE) Valsartan 80 to 160 mg Daily	DB, PG, RCT Patients 50 years of age and older with treated or	N=15,245 4.2 years (mean)	Primary: Time to first cardiac event (cardiac morbidity and mortality)	Primary: There were no differences in the primary composite end point between the valsartan and amlodipine groups (10.6 vs 10.4%; $P=0.49$). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs amlodipine 5 to 10 mg Daily	untreated hypertension and history of cardiovascular disease, stroke or diabetes; previous medications were discontinued at trial onset		Secondary: Fatal and nonfatal MI, fatal and nonfatal heart failure and fatal and nonfatal stroke, all-cause mortality, new onset diabetes	There was a higher incidence of MI (4.8 vs 4.1%; $P=0.02$) in patients receiving valsartan than patients receiving amlodipine. There was no difference in the incidence of heart failure (4.6 vs 5.3%; $P=0.12$), stroke (4.2 vs 3.7%; $P=0.08$) and all-cause mortality (11.0 vs 10.8%; $P=0.45$) between valsartan- and amlodipine-treated patients. New onset diabetes occurred less with valsartan (13.1%) vs amlodipine- (16.4%; $P<0.001$) treated patients. Limited benefit of valsartan vs amlodipine was attributed to the differences in BP lowering. Combined target BP (<140/90 mm Hg) was achieved in 58 and 62% of patients receiving valsartan and amlodipine, respectively.
Brown et al ⁵⁵ INSIGHT Nifedipine 30 mg Daily vs amloride/HCTZ 2.5/25 mg Daily Doses were doubled or atenolol 25 to 50 mg or enalapril 5 to 10 mg was added.	DB, MC, PRO, RCT Patients 55 to 80 years of age with hypertension (BP $\geq 150/95$ mm Hg or SBP ≥ 160 mm Hg) and at least 1 cardiovascular risk factor	N=6,575 3 years	Primary: Composite death from any cardiovascular cause together with nonfatal stroke, MI, or heart failure Secondary: Total mortality, death from a vascular cause, nonfatal vascular event	Primary: There was no difference in composite cardiovascular deaths between the groups. Events occurred in 200 (6.3%) patients in the nifedipine group and 182 (5.8%) patients in the amloride/HCTZ group (18.2 vs 16.5 events per 1,000 patient-years; $P=0.34$). Secondary: There was no difference in all-cause mortality ($P=0.62$), death from a vascular cause ($P=0.67$) and in nonfatal vascular events ($P=0.50$) between the treatment groups.
Dahlöf et al ⁵⁶ ASCOT-BPLA Amlodipine 5 to 10 mg Daily (with option to add perindopril 4 to 8 mg Daily as required) vs	DB, MC, PRO, RCT Patients 40 to 79 years of age with hypertension and at least 3 other cardiovascular risk factors	N=19,257 5.5 years	Primary: Nonfatal MI and fatal coronary heart disease Secondary: All-cause mortality, total stroke, primary endpoint minus silent	Primary: There was no significant difference in rates of nonfatal MI and fatal coronary heart disease between amlodipine and atenolol (8.2 events per 1,000 patient-years vs 9.1 events per 1,000 patient-years (HR, 9.1; 95% CI, 0.79 to 1.02). Secondary: The amlodipine group had significant reductions in the following endpoints as compared to the atenolol group: nonfatal MI (excluding silent MI) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atenolol 50 to 100 mg Daily (with option of adding bendroflumethiazide 1.25 to 2.5 mg Daily as required)			MI, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart impairment	fatal coronary heart disease ($P=0.0458$), total coronary events ($P=0.0070$), total cardiovascular events and procedures ($P<0.0001$), all-cause mortality ($P=0.0247$), cardiovascular mortality ($P=0.001$), fatal and nonfatal stroke ($P=0.0003$).
<p>Nissen et al⁵⁷ CAMELOT</p> <p>Amlodipine (5 mg/day) and placebo enalapril capsule</p> <p>vs</p> <p>placebo amlodipine tablet and enalapril (10 mg/day)</p> <p>vs</p> <p>placebo amlodipine tablet and placebo enalapril capsule</p> <p>Doses were doubled (amlodipine 10 mg/day and enalapril 20 mg/day) after 2 weeks if the initial dose was tolerated.</p> <p>Participants were instructed to take only 1 tablet and 1 capsule of study medication each</p>	<p>DB, MC, PC, RCT</p> <p>Men and women 30 to 79 years of age requiring coronary angiography for evaluation for chest pain or percutaneous intervention and a diastolic pressure <100 mm Hg, with or without treatment; patients with left main coronary artery obstruction >50%, left ventricular ejection fraction <40% or moderate-to-severe CHF were excluded</p>	<p>N=1,991</p> <p>2 years</p>	<p>Primary: Incidence of adverse cardiovascular events (cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or nonfatal stroke or transient ischemic attack, and any new diagnosis of peripheral vascular disease), nominal change in percent atheroma volume (substudy)</p> <p>Secondary: Incidence of adverse events; all-cause mortality, incidence of revascularization in vessels that had undergone previous stent placement</p>	<p>Primary: Adverse cardiovascular events occurred in 23.1% of placebo-treated patients, 16.6% amlodipine-treated patients (HR, 0.69; 95% CI, 0.54 to 0.88; $P=0.003$) and 20.2% enalapril-treated patients (HR, 0.85; 95% CI, 0.67 to 1.07; $P=0.16$).</p> <p>The most frequent component of the primary end point, coronary revascularization, was reduced in the amlodipine group from 15.7 to 11.8% (HR, 0.73; 95% CI, 0.54 to 0.98; $P=0.03$). Hospitalization for angina was reduced in the amlodipine group from 12.8 to 7.7% (HR, 0.58; 95% CI, 0.41 to 0.82; $P=0.002$).</p> <p>Individual components of the primary end point generally showed fewer events with enalapril treatment vs placebo treatment, but none of the comparisons reached statistical significance.</p> <p>The primary end point comparison for enalapril treatment vs amlodipine treatment was not significant (HR, 0.81; 95% CI, 0.63 to 1.04; $P=0.10$).</p> <p>For components of the primary end point, only the rate of hospitalization for angina showed a statistically significant difference between amlodipine treatment and enalapril treatment (HR, 0.59; 95% CI, 0.42 to 0.84; $P=0.003$). A trend toward fewer episodes of revascularization in patients undergoing intervention at baseline was observed for amlodipine treatment vs enalapril treatment (HR, 0.66; 95% CI, 0.40 to 1.06; $P=0.09$).</p> <p>The mean change in percent atheroma volume was 0.5% for amlodipine treatment ($P=0.12$ vs placebo treatment), 0.8% for enalapril treatment ($P=0.32$ vs placebo treatment) and 1.3% for placebo treatment. In patients</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>day if they experienced any intolerable adverse effect thought to be related to the study drug while at full dose.</p>				<p>with SBP greater than the mean, the amlodipine group showed a significantly slower progression (0.2%) compared to the placebo group (2.3%; $P=0.02$). Compared to baseline, intravascular ultrasound showed progression in patients receiving placebo ($P<0.001$), a trend toward progression in patients receiving enalapril ($P=0.08$) and no progression in patients receiving amlodipine ($P=0.31$). For the amlodipine group, correlation between BP reduction and progression was $r=0.19$ ($P=0.07$).</p> <p>Secondary: Discontinuation from the study for treatment-emergent adverse events was low, averaging 0.4% and not statistically significant between the three treatment groups (P value not reported).</p> <p>The only statistically significant difference in secondary end points was that amlodipine treatment demonstrated a significant reduction in revascularization after previous stent placement compared to placebo treatment (4.1 vs 7.9%; HR, 0.49; 95% CI, 0.31 to 0.78; $P=0.002$). The rate of revascularization was lower than enalapril treatment (6.2%) but not statistically significant (HR, 0.66; 95% CI, 0.40 to 1.06; $P=0.09$).</p>
<p>Estacio et al⁵⁸ ABCD Enalapril 5 to 40 mg/day vs nisoldipine 10 to 60 mg/day</p>	<p>DB, PRO, RCT Patients between 40 and 74 years of age with non insulin dependent diabetes, baseline DBP ≥ 90 mm Hg and receiving no antihypertensive medications at the time of randomization</p>	<p>N=470 67 months</p>	<p>Primary: Effect of intensive (target DBP 75 mm Hg) or moderate (target DBP 80 to 89 mm Hg) BP control on the incidence and progression of complications of diabetes; compare enalapril to nisoldipine as a first-line antihypertensive agent</p> <p>Secondary: Incidence of MI</p>	<p>Primary: Analysis of the 470 patients in the trial who had hypertension (DBP ≥ 90 mm Hg) showed similar control of BP, blood glucose and lipid concentrations between the two study medications throughout the five years of follow-up.</p> <p>Secondary: Nisoldipine was associated with a higher incidence of fatal and nonfatal MI than enalapril (RR, 7.0; 95% CI, 2.3 to 21.4; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>ALLHAT Collaborative Research Group⁵⁹ ALLHAT</p> <p>Lisinopril 10 to 40 mg/day</p> <p>vs</p> <p>amlodipine 2.5 to 10 mg/day</p> <p>vs</p> <p>chlorthalidone 12.5 to 25 mg/day</p> <p>Doses were titrated to achieve a goal BP <140/90 mm Hg.</p>	<p>DB, MC, RCT</p> <p>Patients ≥55 years of age with hypertension and at least 1 additional coronary heart disease risk factor</p>	<p>N=33,357</p> <p>4.9 years (mean follow-up)</p>	<p>Primary: Composite of fatal coronary heart disease or nonfatal MI</p> <p>Secondary: All-cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease, cancer, end stage renal disease</p>	<p>Primary: There was no significant difference in the primary outcome between amlodipine- and chlorthalidone-treated patients, or between lisinopril- and chlorthalidone-treated patients (RR, 0.98; 95% CI, 0.90 to 1.07; <i>P</i>=0.65 and RR, 0.99; 95% CI, 0.91 to 1.08; <i>P</i>=0.81).</p> <p>Secondary: In a comparison of lisinopril- and chlorthalidone-treated patients, the secondary endpoints of all-cause mortality, combined coronary heart disease, peripheral arterial disease, cancer or end-stage renal disease did not significantly differ.</p> <p>However, there were higher rates of stroke (RR, 1.15; 95% CI, 1.02 to 1.30; <i>P</i>=0.02), combined cardiovascular disease (RR, 1.10; 95% CI, 1.05 to 1.16; <i>P</i><0.001), heart failure (RR, 1.19; 95% CI, 1.07 to 1.31; <i>P</i><0.001), angina (hospitalized or treated [RR, 1.11; 95% CI, 1.03 to 1.20; <i>P</i>=0.01]) and coronary revascularizations (RR, 1.10; 95% CI, 1.00 to 1.21; <i>P</i>=0.05) observed in lisinopril-treated patients compared to chlorthalidone-treated patients.</p> <p>The secondary endpoints did not differ between amlodipine- and chlorthalidone-treated patients for all-cause mortality, combined coronary heart disease, stroke, combined cardiovascular disease, angina, coronary revascularization, peripheral arterial disease, cancer or end-stage renal disease. However, heart failure and hospitalized/fatal heart failure, components of combined cardiovascular disease, occurred at higher rates in amlodipine-treated patients compared to chlorthalidone-treated patients (RR, 1.38; 95% CI, 1.25 to 1.52; <i>P</i><0.001 and RR, 1.35; 95% CI, 1.21 to 1.50; <i>P</i><0.001, respectively).</p>
<p>Hansson et al⁶⁰ STOP-2</p> <p>Conventional group: Atenolol 50 mg Daily plus HCTZ 25 mg Daily in combination with</p>	<p>MC, OL, RCT</p> <p>Patients 70 to 84 years of age with treated or untreated essential hypertension (SBP</p>	<p>N=6,614</p> <p>60 months</p>	<p>Primary: Combined fatal stroke, MI and other fatal cardiovascular disease, combined fatal and nonfatal stroke, MI and other</p>	<p>Primary: The combined fatal mortality endpoints occurred in 221 of the 2,213 patients receiving conventional therapy and in 438 of the 4,401 patients receiving newer drugs (RR, 0.99; 95% CI, 0.84 to 1.16; <i>P</i>=0.89).</p> <p>The combined fatal and nonfatal mortality endpoints occurred in 460 patients receiving conventional therapy and in 887 patients receiving newer</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
either amiloride 2.5 mg Daily, metoprolol 100 mg Daily or pindolol 5 mg Daily vs newer drug group: ACE inhibitors (enalapril 10 mg Daily or lisinopril 10 mg Daily) or calcium antagonists (felodipine 2.5 mg Daily or isradipine 2 to 5 mg Daily)	≥180 mm Hg, DBP >105 mm Hg or both) on 3 separate occasions		cardiovascular mortality Secondary: Not reported	drugs (RR, 0.96; 95% CI, 0.86 to 1.08; <i>P</i> =0.49). Secondary: Not reported
Lewis et al ⁶¹ IDNT Irbesartan 300 mg Daily vs amlodipine 10 mg Daily vs placebo	DB, MC, PC, PRO, RCT Patients 30 to 70 years of age, with type 2 diabetes mellitus, hypertension and nephropathy	N=1,715 2.6 years	Primary: Composite of risk of doubling serum creatinine, end stage renal disease or death from any cause Secondary: Composite of death from cardiovascular causes, nonfatal MI, heart failure requiring hospitalization, permanent neurologic deficit caused by a cerebrovascular event or lower limb amputation	Primary: Compared to placebo, irbesartan 300 resulted in a 20% lower relative risk of the composite primary outcome (<i>P</i> =0.02). Irbesartan was associated with a 33% lower risk of doubling serum creatinine (<i>P</i> =0.003) and 23% trend towards lower risk of end stage renal disease (<i>P</i> =0.07) compared to placebo. There was no significant difference in risk of death from any cause for irbesartan compared to placebo (<i>P</i> =0.57). Compared to amlodipine, irbesartan resulted in a 23% lower risk of composite primary outcome (<i>P</i> =0.006). Irbesartan was associated with a 37% lower risk of doubling serum creatinine vs amlodipine (<i>P</i> <0.001) and 23% trend towards lower risk of end stage renal disease vs amlodipine (<i>P</i> =0.07). There was no significant difference in risk of death from any cause (<i>P</i> =0.80). Secondary: There were no significant differences in the secondary cardiovascular composite end point (<i>P</i> =0.40 and <i>P</i> =0.79 for irbesartan vs placebo and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
amlo地平ine, respectively).				
Subarachnoid Hemorrhage				
Schmid-Elsaesser et al ⁶² Nimodipine continuous infusion of 1 mg/hour for 6 hours, followed by 2 mg/hour vs magnesium sulfate bolus infusion 10 mg/kg, followed by continuous infusion of 30 mg/kg Daily	RCT Patients with aneurismal subarachnoid hemorrhage	N=104 7 days	Primary: Incidence of clinical vasospasm and transcranial doppler/angiographic vasospasm, and infarction attributable to vasospasme Secondary: Incidence of angiographic vasospasm	Primary: There was no significant difference between the groups in number of patients experiencing clinical vasospasm or transcranial doppler/angiographic vasospasm: 14 patients (27%) in the nimodipine group vs eight patients (15%) in the magnesium group ($P=0.193$); 17 patients (33%) in the nimodipine group vs 20 patients (38%) in the magnesium group ($P=0.792$). No difference between the groups was found in incidence of cerebral infarction, 11 patients (22%) in the nimodipine group vs 10 patients (19%) in the magnesium group (P value not reported). Secondary: There were no significant differences in incidence of angiographic vasospasm, neuronal markers (P values not reported) or Glasgow outcome scores (all values; $P>0.05$).

*Agent not currently available in the United States.

Drug regimen abbreviations: BID=twice daily, CR=controlled release, ER=extended release, SR=sustained release, TID=three times daily

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, XO=crossover

Miscellaneous abbreviations: ACE=angiotensin converting enzyme, ARB=angiotensin receptor blocker, BP=blood pressure, bpm=beats per minute, CHF=congestive heart failure, DBP=diastolic blood pressure, ECG=electrocardiogram, HCTZ=hydrochlorothiazide, MI=myocardial infarction, SBP=systolic blood pressure

Special Populations**Table 5. Special Populations**¹¹⁻²⁶

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Amlodipine	Dosage selection in elderly patients should be cautious. Safety and efficacy in patients <6 years of age is not known.	No dosage adjustment required.	Slow titration is recommended in patients with severe liver impairment.	C	Unknown
Felodipine ER	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown
Isradipine IR, CR	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown
Nicardipine IR	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients under the age of 18.	Starting dose of 20 mg three times daily is advised.	Starting dose of 20 mg twice daily is advised.	C	Minimal
Nicardipine SR	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients.	Starting dose of 30 mg twice daily is advised.	Not studied in patients with severe hepatic impairment; use with caution.	C	Minimal
Nicardipine IV	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients under the age of 18.	No dosage adjustment required.	No dosage adjustment required.	C	Minimal

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Nifedipine IR, ER, ER osmotic- release	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients.	No dosage adjustment required.	No dosage adjustment required.	C	Yes
Nimodipine	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients.	No dosage adjustment required.	30 mg every four hours is advised in patients with cirrhosis.	C	Unknown
Nisoldipine	Dosage selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients.	No dosage adjustment required.	Lower starting and maintenance doses are advised in patients with cirrhosis.	C	Unknown

CR=controlled-release, ER=extended-release, IR=immediate-release, IV=intravenous, SR=sustained-release

Adverse Drug Events

Table 6. Adverse Drug Events¹¹⁻²⁵

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Cardiovascular							
Angina (increased)	-	0.5 to 1.5	-	5.6	≤1	-	-
Arrhythmia	<1	0.5 to 1.5	-	-	≤1	-	≤1
Atrial fibrillation	-	-	0.5 to 1.0	<0.4	<1	-	≤1
Bradycardia	<1	-	-	-	<1	0.6 to 1.0	-
Cardiac arrest	-	-	-	-	<1	-	-
Cardiac failure	<0.1	-	0.5 to 1.0	-	-	-	-
Cerebrovascular accident	-	-	-	-	-	-	≤1
Chest pain	<1	0.5 to 1.5	0.5 to 1.0	✓	≤3	-	2
Congestive heart failure	-	-	-	-	✓	<1	<1
Deep-vein thrombophlebitis	-	-	-	✓	-	-	-
Deep-vein thrombosis	-	-	-	-	-	<1	-
Electrocardiogram abnormalities	-	-	-	0.6	-	1.4	≤1

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Extrasystoles (ventricular)	<0.1	-	-	-	<1	-	-
Heart block	-	-	-	<0.4	-	-	≤1
Hemopericardium	-	-	-	-	-	-	-
Hypertension	-	-	-	-	-	<1	≤1
Hypotension	<1	0.5 to 1.5	0.5 to 1.0	≤8	≤5	1.2 to 8.1	≤1
Jugular venous distension	-	-	-	-	-	-	≤1
Myocardial infarction	-	0.5 to 1.5	0.5 to 1.0	<0.4	✓	-	≤1
Orthostatic hypotension	-	-	-	-	-	-	-
Palpitations	0.7 to 4.5	0.4 to 2.5	1.2	2.8 to 4.1	≤2 to 7	<1	3
Pericarditis	-	-	-	<0.4	-	-	-
Peripheral ischemia	<1	-	-	-	-	-	-
Peripheral vascular disorder	-	-	-	✓	-	-	-
Postural hypotension	<1	-	-	0.9	<1	-	≤1
Premature beats	-	0.5 to 1.5	-	-	-	-	-
Pulmonary edema	-	-	-	-	✓	-	-
Pulse irregularity	<0.1	-	-	-	-	-	-
Rebound vasospasm	-	-	-	-	-	<1	-
Systolic ejection murmur	-	-	-	-	-	-	≤1
Tachycardia	<1	0.5 to 1.5	0.5 to 1.0	0.8 to 5.0	≤1	1.4	≤1
Vasculitis	<1	-	-	-	-	-	-
Vasodilatation/vasodilation	-	-	-	4.7 to 5.5	-	-	4
Venous insufficiency	-	-	-	-	-	-	≤1
Ventricular extrasystoles	-	-	-	✓	-	-	≤1
Ventricular tachycardia	-	-	-	✓	-	-	-
Central Nervous System							
Abnormal dreams	<1	-	-	0.4	-	-	≤1
Agitation	<0.1	-	-	-	-	-	-
Amnesia	<0.1	-	-	-	-	-	≤1
Anxiety	<1	0.5 to 1.5	-	✓	≤1	-	≤1
Apathy	<0.1	-	-	-	-	-	-
Asthenia	1 to 2	2.2 to 3.9	-	0.9 to 5.8	<3	-	-
Ataxia	<0.1	-	-	-	≤1	-	≤1
Balance difficulties	-	-	-	-	≤2	-	-
Cerebral ischemia	-	-	-	<0.4	-	-	≤1
Confusion	-	-	-	✓	<1	-	≤1
Depersonalization	<1	-	-	-	-	-	-
Depression	<1	0.5 to 1.5	0.5 to 1.0	✓	≤1	1.4	≤1
Dizziness	1.1 to 3.4	2.7 to	3.7 to	1.6 to	4 to 27	<1	3 to 7

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
		3.7	7.3	3.3			
Headache	7.3	10.6 to 14.7	10.3 to 21	6.2 to 8.2	10 to 23	1.2 to 4.1	22
Hyperkinesia	-	-	-	✓	-	-	-
Hypesthesia	-	-	-	-	<1	-	≤1
Hypoaesthesia	<1	-	-	-	≤1	-	-
Insomnia	<1	0.5 to 1.5	0.5 to 1.0	0.6	<3	-	≤1
Irritability	-	0.5 to 1.5	-	-	-	-	-
Lightheadedness	-	-	-	-	10 to 27	<1	-
Migraine	<0.1	-	-	-	≤1	-	≤1
Nervousness	<1	0.5 to 1.5	0.5 to 1.0	0.6	≤2 to 7	-	≤1
Neurological deterioration	-	-	-	-	-	<1	-
Paranoid syndrome	-	-	-	-	≤1	-	-
Paresthesia	<1	1.2 to 1.6	0.5 to 1.0	1	≤3	-	≤1
Peripheral neuropathy	<1	-	-	-	-	-	-
Sleep disturbance	-	-	-	-	≤2	-	-
Somnolence	1.4	0.5 to 1.5	0.5 to 1.0	1.1 to 1.4	<3	-	≤1
Stroke	-	-	0.5 to 1.0	-	-	-	-
Syncope	<1	0.5 to 1.5	0.5 to 1.0	0.8	≤1	-	≤1
Transient ischemic attack	-	-	0.5 to 1.0	-	-	-	-
Tremor	<1	-	-	0.6	≤1 to 8	-	≤1
Vertigo	<1	-	-	✓	≤3	-	≤1
Dermatologic							
Acne	-	-	-	-	-	1.4	≤1
Alopecia	<0.1	-	-	-	≤1	-	≤1
Cellulitis	-	-	-	-	<1	-	≤1
Cold and clammy skin	<0.1	-	-	-	-	-	-
Cutaneous angiecases	-	-	-	-	<1	-	-
Dermatitis	<0.1	-	-	-	≤2	-	-
Ecchymoses	-	-	-	-	-	-	≤1
Erythema	-	0.5 to 1.5	-	-	-	-	-
Erythema multiforme	<1	-	-	-	✓	-	-
Erythromelalgia	-	-	-	-	0.5	-	-
Exanthematpis pustulosis	-	-	-	-	✓	-	-
Exfoliative dermatitis	-	-	-	-	<0.5	-	≤1
Flushing	0.7 to 2.6	3.9 to 6.9	1.2 to 3.8	5.6 to 9.7	<3 to 25	<1.0 to 2.1	-
Fungal dermatitis	-	-	-	-	-	-	≤1
Hyperhidrosis/sweating	<1	-	0.5 to 1.0	0.6	≤2	<1	≤1

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Itching	-	-	-	-	-	<1	-
Petechiae	-	-	-	-	-	-	≤1
Photosensitivity reaction	-	-	-	-	<1	-	-
Pruritus	1 to 2	-	0.5 to 1.0	-	<3	-	≤1
Rash (erythematous or maculopapular)	1 to 2	0.2 to 2.0	1.3 to 2.6	0.4 to 1.2	≤3	0.6 to 2.4	2
Skin discoloration	<0.1	-	-	-	-	-	≤1
Skin dryness	<0.1	-	-	-	-	-	≤1
Skin ulcer	-	-	-	-	-	-	≤1
Urticaria	<0.1	0.5 to 1.5	0.5 to 1.0	-	≤2	-	≤1
Endocrine and Metabolic							
Diabetes mellitus	-	-	-	-	-	-	≤1
Gout	-	-	-	-	≤1	-	≤1
Gynecomastia	-	0.5 to 1.5	-	-	<1	-	-
Hyperglycemia	<1	-	-	-	✓	0.8	-
Thirst	<1	-	-	-	-	-	-
Thyroiditis	-	-	-	-	-	-	≤1
Gastrointestinal							
Abdominal discomfort	-	-	1.3 to 5.1	-	-	-	-
Abdominal distension	-	-	1.2	-	-	-	-
Abdominal pain	1.6	0.5 to 1.5	-	-	<3	-	-
Acid regurgitation	-	0.5 to 1.5	-	-	-	-	-
Anorexia	<1	-	0.5 to 1.0	-	-	-	≤1
Colitis	-	-	-	-	-	-	≤1
Constipation	<1	0.3 to 1.5	1.2 to 3.8	0.6	≤3.3	-	-
Cramps	-	-	-	-	≤2	-	-
Diarrhea	<1	0.5 to 1.5	0.5 to 1.1	-	<3	1.7 to 4.2	≤1
Dry mouth	<1	0.5 to 1.5	0.5 to 1.0	0.4 to 1.4	<3	-	≤1
Dyspepsia	1 to 2	0.5 to 3.9	-	0.8 to 1.5	<3	-	≤1
Dysphagia	<1	-	-	-	<1	-	-
Eructation	-	-	-	-	≤1	-	-
Esophagitis	-	-	-	-	<1	-	-
Flatulence	<1	0.5 to 1.5	-	-	<3	-	≤1
Gastritis	<0.1	-	-	-	-	-	≤1
Gastroesophageal reflux	-	-	-	-	≤1	-	-
Gastrointestinal bleeding	-	-	-	-	<1	-	-
Gastrointestinal	-	-	-	-	<1	<1	≤1

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
hemorrhage							
Gastrointestinal symptoms	-	-	-	-	-	1.2 to 2.4	-
Gum disorder	-	-	-	-	<1	-	-
Gum hemorrhage	-	-	-	-	<1	-	-
Heart burn	-	-	-	-	11	-	-
Hepatitis	-	-	-	-	<0.5	<1	-
Hepatomegaly	-	-	-	-	-	-	≤1
Increased appetite	<0.1	-	0.5 to 1.0	-	-	-	≤1
Jaundice	-	-	-	-	✓	<1	-
Loose stools	<0.1	-	-	-	-	-	-
Melena	-	-	-	-	≤1	-	≤1
Mouth ulceration	-	-	-	-	-	-	≤1
Nausea	2.9	1.0 to 1.7	1.2	1.9 to 7.0	2 to 11	0.6 to 1.4	2
Pancreatitis	<1	-	-	-	-	-	-
Vomiting	<1	0.5 to 1.5	0.5 to 1.1	0.4 to 7.0	≤1	<1	-
Genitourinary							
Breast engorgement	-	-	-	-	<1	-	-
Breast pain	-	-	-	-	≤1	-	-
Decreased libido	-	-	0.5 to 1.0	-	≤1	-	≤1
Dysuria	<0.1	0.5 to 1.5	0.5 to 1.0	-	≤1	-	≤1
Hematuria	-	-	-	-	≤1	-	≤1
Impotence	-	0.5 to 1.5	0.5 to 1.0	✓	≤3	-	-
Nocturia	<1	-	0.5 to 1.0	0.4	≤1	-	≤1
Pelvic pain	-	-	-	-	<1	-	-
Pollakiuria	-	-	0.5 to 1.0	-	-	-	-
Polyuria	<0.1	0.5 to 1.5	-	-	<3	-	-
Sexual dysfunction	<1	-	-	-	≤2	-	-
Urinary frequency/urgency	-	0.5 to 1.5	-	0.6	≤3	-	≤1
Urogenital disorder	-	-	-	-	<1	-	-
Vaginal hemorrhage	-	-	-	-	-	-	≤1
Vaginitis	-	-	-	-	-	-	≤1
Hematological							
Anemia	-	0.5 to 1.5	-	-	<0.5	<1	≤1
Eosinophilia	-	-	-	-	<1	-	-
Leukopenia	<1	-	0.5 to 1.0	-	<0.5	-	≤1
Purpura	<1	-	-	-	≤1	-	-
Thrombocytopenia	<1	-	-	✓	<0.5	<1	-
Laboratory Abnormalities							

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Blood urea nitrogen increased	-	-	-	-	-	-	≤1
Creatinine kinase increased	-	-	-	-	-	-	≤1
Hepatic enzyme elevations	-	0.5 to 1.5	0.5 to 1.0	✓	-	0.2 to 1.2	≤1
Hypokalemia	-	-	-	-	-	-	≤1
Hyponatremia	-	-	-	-	-	<1	-
Hypophosphatemia	-	-	-	✓	-	-	-
Low-density lipoprotein elevations	-	-	-	-	-	0.4	-
Non-protein nitrogen increased	-	-	-	-	-	-	≤1
Serum creatinine increased	-	-	-	-	-	-	≤1
Musculoskeletal							
Arm pain	-	0.5 to 1.5	-	-	-	-	-
Arthralgia	<1	0.5 to 1.5	-	✓	<3	-	≤1
Arthritis	-	-	-	-	<1	-	≤1
Arthrosis	<1	-	-	-	-	-	-
Back pain	<1	0.5 to 1.5	0.5 to 1.0	-	≤1	-	-
Foot pain	-	0.5 to 1.5	-	-	-	-	-
Hip pain	-	0.5 to 1.5	-	-	-	-	-
Hypertonia	<0.1	-	-	✓	≤1	-	≤1
Inflammation	-	-	-	-	≤2	-	-
Joint disorder	-	-	-	-	<1	-	-
Joint pain	-	-	0.5 to 1.0	-	-	-	-
Joint stiffness	-	-	-	-	≤2	-	-
Knee pain	-	0.5 to 1.5	-	-	-	-	-
Leg pain	-	0.5 to 1.5	0.5 to 1.0	-	≤3	-	-
Muscle cramps	1 to 2	0.5 to 1.5	0.5 to 1.0	-	≤2 to 8	1.4	≤1
Muscle weakness	<0.1	-	-	-	-	-	-
Myalgia	<1	0.5 to 1.5	-	1	≤1	1.4	≤1
Myasthenia	-	-	-	-	<1	-	≤1
Myositis	-	-	-	-	-	-	≤1
Neck pain	-	-	0.5 to 1.0	-	<1	-	-
Rhabdomyolysis	-	-	-	-	-	-	-
Tenosynovitis	-	-	-	-	-	-	≤1
Twitching	<0.1	-	-	-	-	-	-
Respiratory							
Asthma	-	-	-	-	-	-	≤1

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Bronchitis	-	0.5 to 1.5	-	-	-	-	-
Cough	<0.1	0.8 to 1.7	0.5 to 1.0	-	≤1 to 6	-	≤1
Dyspnea	1 to 2	0.5 to 1.5	0.5 to 1.0	0.6	<1 to 6	1.2	≤1
Epistaxis	<1	0.5 to 1.5	0.5 to 1.0	-	≤3	-	≤1
Influenza/flu-like illness	-	0.5 to 1.5	-	-	-	-	≤1
Laryngitis	-	-	-	-	-	-	≤1
Nasal congestion	-	0.2 to 1.6	0.5 to 1.0	-	≤2 to 6	-	-
Pharyngitis	-	0.5 to 1.5	-	-	<1	-	5
Pleural effusion	-	-	-	-	-	-	≤1
Respiratory disorder	-	-	-	✓	≤1	-	-
Rhinitis	<0.1	-	-	✓	≤3	-	≤1
Shortness of breath	-	-	0.5 to 1.0	-	≤2	-	≤1
Sinusitis	-	0.5 to 1.5	-	✓	≤1	-	3
Sneezing	-	1.6	-	-	-	-	-
Sore throat	-	-	0.5 to 1.0	✓	6	-	-
Stridor	-	-	-	-	<1	-	-
Upper respiratory tract infection	-	0.5 to 1.5	-	-	≤1	-	-
Wheezing	-	-	-	-	6	<1	≤1
Other							
Abnormal lacrimation	-	-	-	-	≤1	-	-
Abnormal visual accommodation	<1	-	-	✓	≤1	-	≤1
Allergic reaction	<1	-	-	✓	<1	-	-
Amblyopia	-	-	-	-	<1	-	≤1
Anaphylaxis	-	-	-	-	✓	-	-
Angioedema	<1	0.5 to 1.5	0.5 to 1.0	-	<1	-	≤1
Blepharitis	-	-	-	-	-	-	≤1
Blurred vision	-	-	-	✓	≤2	-	-
Chills	-	-	-	-	≤2	-	≤1
Conjunctivitis	<1	-	-	✓	<1	-	≤1
Contusion	-	0.5 to 1.5	-	-	-	-	-
Decreased libido	-	0.5 to 1.5	-	-	-	-	-
Diplopia	<1	-	-	-	<1	-	-
Disseminated intravascular coagulation	-	-	-	-	-	<1	-
Ear pain/disorder	-	-	-	✓	-	-	≤1
Edema	1.8 to	-	7.2 to	-	-	0.4 to 1.2	-

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
	10.8		35.9				
Eye disorder	-	-	-	-	<1	-	-
Eye hemorrhage	-	-	-	-	<1	-	-
Eye pain	<1	-	-	-	-	-	-
Facial edema	-	0.5 to 1.5	-	-	≤1	-	≤1
Fatigue	4.5	-	2.5 to 7.6	-	4.0 to 5.9	-	-
Fever	-	-	0.5 to 1.0	-	≤2	-	≤1
Fluid retention	-	-	-	-	-	0.3	-
Gingival hyperplasia	<1	0.5 to 1.5	-	-	≤1	-	≤1
Glaucoma	-	-	-	-	-	-	≤1
Glossitis	-	-	-	-	-	-	≤1
Heat sensation	-	-	-	-	4 to 25	-	-
Hematoma	-	-	-	-	-	<1	-
Herpes simplex	-	-	-	-	-	-	≤1
Herpes zoster	-	-	-	-	-	-	≤1
Hot flush	-	-	-	✓	-	-	-
Infection	-	-	-	✓	-	-	-
Itchy eyes	-	-	-	-	-	-	≤1
Keratoconjunctivitis	-	-	-	-	-	-	≤1
Lethargy	-	-	0.5 to 1.0	-	-	-	-
Leukocytoclastic vasculitis	-	0.5 to 1.5	-	-	-	-	-
Lymphadenopathy	-	-	-	-	<1	-	-
Malaise	<1	-	-	0.6	≤1	-	≤1
Nasopharyngitis	-	-	-	-	-	-	-
Numbness	-	-	0.5 to 1.0	-	-	-	-
Otitis media	-	-	-	-	-	-	≤1
Pain	<1	-	-	0.6	<3	-	-
Parosmia	<0.1	-	-	-	-	-	-
Pedal edema	-	-	-	4.4 to 5.9	-	-	-
Peripheral edema	-	2.0 to 17.4	-	7.1 to 8.0	7 to 10	-	7 to 27
Phenytoin toxicity	-	-	-	-	-	<1	-
Phlebitis	-	-	-	-	<1	-	-
Retinal detachment	-	-	-	-	-	-	≤1
Rigors	<1	-	-	-	≤1	-	-
Taste perversion	<0.1	-	-	-	≤1	-	<1
Tinnitus	<1	-	-	✓	≤1	-	≤1
Transient blindness	-	-	-	-	<0.5	-	-
Unilateral loss of vision, temporary	-	-	-	-	-	-	≤1
Visual disturbance	-	0.5 to 1.5	0.5 to 1.0	-	-	-	-
Vitreous floater	-	-	-	-	-	-	<1

Adverse Event(s)	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Warm sensation	-	0.9 to 1.5	-	-	-	-	-
Watery eyes	-	-	-	-	-	-	≤1
Weakness	-	-	1.2	-	10 to 12	-	-
Weight gain	<1	-	0.5 to 1.0	-	≤1	-	≤1
Weight loss	<1	-	-	-	<1	-	≤1
Xerophthalmia	<0.1	-	-	-	-	-	-

✓ Percent not specified.
 - Event not reported.

Contraindications/Precautions

Dihydropyridine calcium channel blockers are contraindicated in patient with a known hypersensitivity to any component of the medication.¹¹⁻²⁵

Amlodipine

Symptomatic hypotension is possible, especially in patients with severe aortic stenosis.¹¹

Worsening of angina an acute myocardial infarction can develop after initiation or dose increase of amlodipine, especially in patients with severe obstructive coronary artery disease.¹¹

Amlodipine gives no protection against the dangers of abrupt β-blocker withdrawal.¹¹

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function. Slow titration is recommended in these patients.¹¹

Felodipine

Felodipine may precipitate significant hypotension, and rarely, syncope. Reflex tachycardia is possible, as well as precipitation of angina pectoris.¹²

The safety of felodipine in patients with heart failure has not been established. Caution should be exercised when using felodipine in patients with heart failure or compromised ventricular function, especially when used in combination with a β-blocker.¹²

A starting dose of 2.5 mg daily is recommended in patients with impaired hepatic function. Patients should have their blood pressure monitored during dosage adjustment.¹²

Peripheral edema was the most common adverse event in clinical trials and was both dose and age dependent. Peripheral edema usually occurs within two to three weeks of treatment initiation.¹²

Isradipine

Isradipine may occasionally produce symptomatic hypotension. Syncope and severe dizziness are rare.^{13,14}

Isradipine has a negative inotropic effect in vitro and possibly in some patients. Exercise caution when using in patients with congestive heart failure, especially in combination with β-blockers.^{13,14}

Peripheral edema is usually mild to moderate and not due to left ventricular dysfunction or generalized fluid retention. In patients with congestive heart failure, care should be taken to differentiate this edema from the effects of decreased left ventricular function.^{13,14}

Caution should be exercised when administering Dynacirc CR[®] to patients with pre-existing severe gastrointestinal narrowing.¹⁴

Nicardipine

Nicardipine is contraindicated in patients with advanced aortic stenosis. Reduction of diastolic pressure in these patients may worsen myocardial oxygen balance.¹⁵⁻¹⁷

A small percentage of patients may experience increased frequency, duration or severity of angina during treatment initiation and/or dosage adjustment.¹⁵⁻¹⁷

Nicardipine has negative inotropic effect in vitro and in some patients. Caution should be exercised when using this medication in patients with congestive heart failure, especially in combination with a β -blocker.¹⁵⁻¹⁷

Nicardipine does not protect against the dangers of abrupt β -blocker withdrawal.¹⁵⁻¹⁷

Nicardipine may occasionally produce symptomatic hypotension. Caution is recommended when administering to patients with sustained acute cerebral infarction or hemorrhage.¹⁵⁻¹⁷

Use with caution in patients with impaired liver function or reduced hepatic blood flow.¹⁵⁻¹⁷

Dosage adjustment is recommended in patients with renal impairment.¹⁵⁻¹⁷

Nicardipine intravenous should be administered through large peripheral veins or central veins rather than arteries or small peripheral veins. The infusion site should be changed every 12 hours.¹⁷

Nifedipine

Concomitant administration with strong P450 inducers such as rifampin is contraindicated as the efficacy of nifedipine tablets could be significantly reduced.¹⁹

Nifedipine should not be used in cases of cardiogenic shock.¹⁹

Excessive and poorly tolerated hypotension may occur. This may be more common in patients received β -blocker therapy. Immediate-release nifedipine is not approved for acute reduction of blood pressure and should not be used in this manner.¹⁸⁻²³

Severe hypotension and increased fluid volume requirements have been reported in patients receiving concomitant nifedipine and β -blocker therapy who underwent coronary artery bypass surgery using high-dose fentanyl anesthesia. This may occur in patients on nifedipine therapy alone. Physicians should be aware of these potential problems and a 36-hour washout period is recommended if possible prior to high-dose fentanyl anesthesia.¹⁸⁻²³

Nifedipine immediate-release capsules should not be used for the control of essential hypertension.¹⁸

Patients with severe obstructive coronary artery disease may rarely develop increased frequency, duration and severity of angina or acute myocardial infarction during therapy initiation or dose increases. Nifedipine immediate-release capsules should not be used within the first week or two after myocardial infarction and should be avoided in the setting of acute coronary syndrome when infarction may be imminent.¹⁸⁻²³

Patients recently withdrawn from β -blockers may develop increased angina probably related to increased sensitivity to catecholamines. Nifedipine will not prevent this occurrence and may exacerbate it by provoking reflex catecholamine release. β -blockers should be tapered rather than stopped abruptly before beginning nifedipine.¹⁸⁻³²

Rarely, patients have developed heart failure after beginning nifedipine. These patients are usually receiving concomitant β -blocker therapy. Patients with tight aortic stenosis may be at higher risk.¹⁸⁻²³

Careful monitoring of blood pressure is recommended when initiating or adjusting nifedipine therapy.¹⁸⁻²³

Mild to moderate peripheral edema may occur in patients treated with nifedipine. This edema is typically due to vasodilation and not ventricular dysfunction and usually responds to diuretic therapy. In patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this type of peripheral edema from the effects of left ventricular dysfunction.¹⁸⁻²³

Cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have also been reported.¹⁸⁻²³

There have been reports of obstructive symptoms in patients with known strictures in association with ingestion of Procardia XL[®]. Bezoars can occur in very rare cases and may require surgical intervention. Gastrointestinal ulcers in the wall surrounding the Procardia XL[®] tablet shells have been observed with and without gastrointestinal obstruction.^{22,23}

Nimodipine

Intravenous administration of the contents of nimodipine capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension and bradycardia. In patients with subarachnoid hemorrhage given nimodipine in clinical trials, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this effect. Blood pressure should be carefully monitored during treatment.²⁴

The metabolism of nimodipine is decreased in patients with impaired hepatic function. Patients should have their blood pressure and pulse closely monitored.²⁴

Nisoldipine

Patients with severe obstructive coronary artery disease may rarely develop increased frequency, duration and severity of angina or acute myocardial infarction during therapy initiation or dose increases.²⁵

Excessive and poorly tolerated hypotension may occur. Close observation is recommended.²⁵

Caution is recommended in patients with heart failure or compromised ventricular function, especially in combination with a β -blocker.²⁵

Nisoldipine should be used with caution in patients with cirrhosis and severe hepatic dysfunction.²⁵

Nisoldipine contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions. This is frequently seen in patients with an aspirin allergy.²⁵

Nimodipine has been assigned the Black Box Warning outlined below.²⁴

Black Box Warning for Nimodipine²⁴

WARNING
Do not administer nimodipine intravenously or by other parenteral routes. Deaths and serious, life threatening adverse events including cardiac arrest, cardiovascular collapse, hypotension and bradycardia have occurred when the contents of nimodipine capsules have been injected parenterally.

Drug Interactions**Table 7. Drug Interactions⁶³**

Drug(s)	Interaction	Mechanism
Dihydro-pyridines (felodipine, nicardipine, nifedipine, nimodipine, nisoldipine)	Grapefruit juice	Dihydropyridine serum levels may increase due to decreased metabolism resulting from inhibition of CYP3A by grapefruit juice. Coadministration should be avoided.
Dihydro-pyridines (felodipine, nifedipine, nisoldipine)	Azole antifungals (itraconazole, ketoconazole, posaconazole, voriconazole)	Dihydropyridine serum levels may increase resulting from decrease metabolism due to CYP3A4 inhibition by azole antifungal agents. Close monitoring of cardiovascular status is recommended.
Dihydro-pyridines (felodipine, nifedipine)	Barbiturates (amobarbital, butabarbital, butalbital, mephobarbital, pentobarbital, phenobarbital, primidone, secobarbital)	Dihydropyridine serum levels may decrease due to induced metabolism of dihydropyridine by barbiturates. Close monitoring of cardiovascular status is recommended, and increased dose of dihydropyridine may be required if long-term coadministration is required.
Dihydro-pyridines (felodipine, nifedipine)	Hydantoin (ethotoin, fosphenytoin, phenytoin)	Dihydropyridine serum levels may decrease due to increased first-pass metabolism of dihydropyridine caused by hydantoin. Close monitoring of cardiovascular status is recommended, and increased dose of dihydropyridine may be required if long-term coadministration is required.
Felodipine	Carbamazepine	Felodipine serum levels may decrease due to induction and increased first-pass metabolism of felodipine, caused by carbamazepine. Close monitoring of cardiovascular status is recommended, and increased dose of felodipine may be required if long-term coadministration is required.
Felodipine	Erythromycin	Felodipine serum levels may increase due to inhibition of CYP3A by erythromycin. Close monitoring of cardiovascular status is recommended.
Nicardipine	Cyclosporine	Cyclosporine serum levels may increase due to inhibited metabolism by nicardipine. Cyclosporine levels and renal function should be monitored closely if drugs are coadministered.
Nifedipine	Cisapride	Nifedipine serum levels may increase due to increase absorption of nifedipine, due to increased gastrointestinal motility caused by cisapride. Close monitoring is recommended and nifedipine doses may need to be adjusted.
Nifedipine	Melatonin	Melatonin may interfere with the antihypertensive effects of nifedipine. If melatonin use cannot be avoided, monitor the patient's response to nifedipine.
Nifedipine	Protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir,	Nifedipine plasma levels may be elevated, increasing the risk of adverse reactions. Dosage reduction of nifedipine may be necessary.

Drug(s)	Interaction	Mechanism
	lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir)	
Nifedipine	Quinidine	Serum levels of quinidine may be lower than expected and serum concentrations and actions of nifedipine may be increased. Check serum levels of quinidine when nifedipine is started or stopped and routine monitoring is recommended.
Nifedipine	Rifamycins (rifabutin, rifampin, rifapentine)	Nifedipine effects may be decreased due induced metabolism of nifedipine by CYP3A4, which is induced by rifamycins.
Nifedipine	Tacrolimus	Tacrolimus serum levels may be elevated due to inhibition of metabolism by nifedipine. Close monitoring of tacrolimus levels and renal function is recommended if coadministered.

Dosage and Administration

Table 8. Dosing and Administration¹¹⁻²⁵

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine	<u>Chronic stable, vasospastic angina, or coronary artery disease in patients without heart failure or an ejection fraction <40%:</u> 5 to 10 mg Daily; maximum, 10 mg Daily <u>Hypertension:</u> 5 mg Daily; maintenance, 5 to 10 mg Daily; maximum, 10 mg Daily	<u>Hypertension:</u> <u>age 6 to 17 years:</u> Initial, 2.5 mg Daily; maintenance, 2.5 to 5 mg Daily; maximum, 5 mg Daily Safety and efficacy in patients <6 years of age is not known.	Tablet: 2.5 mg 5 mg 10 mg
Felodipine	<u>Hypertension:</u> 5 mg Daily; range, 2.5 to 10 mg Daily	Safety and efficacy have not been established in pediatric patients.	Tablet: 2.5 mg 5 mg 10 mg
Isradipine IR	<u>Hypertension:</u> 2.5 mg BID; maximum, 20 mg/day	Safety and efficacy have not been established in pediatric patients.	Capsule: 2.5 mg 5 mg
Isradipine CR (Dynacirc CR [®])	<u>Hypertension:</u> 5 mg Daily; maintenance, 5 to 10 mg Daily; maximum, 20 mg Daily	Safety and efficacy have not been established in pediatric patients.	Tablet, controlled release: 5 mg 10 mg
Nicardipine IR	<u>Chronic stable angina and hypertension:</u> 20 mg TID; maintenance, 20 to 40 mg TID	Safety and efficacy have not been established in pediatric patients under the age of 18.	Capsule: 20 mg 30 mg
Nicardipine SR (Cardene SR [®])	<u>Hypertension:</u> 30 mg BID; maintenance, 30 to 60 mg BID	Safety and efficacy have not been established in pediatric patients.	Capsule, sustained release: 30 mg 45 mg 60 mg
Nicardipine IV (Cardene IV [®])	<u>Hypertension:</u> 0.1 mg/mL; initial, 50 mL/hour (5	Safety and efficacy have not been established in	Ampule: 2.5 mg/mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/hour); maximum, 150 mL/hour (15 mg/hour); dosage must be individualized	pediatric patients under the age of 18.	
Nifedipine IR (Procardia XL [®])	<u>Chronic stable or vasospastic angina:</u> 10 mg TID; maintenance, 10 to 20 mg TID; maximum, 20 to 30 mg TID to QID (or 180 mg/day)	Safety and efficacy have not been established in pediatric patients.	Capsule: 10 mg 20 mg
Nifedipine ER (Adalat CC [®] , Afeditab CR [®] , Nifediac CC [®])	<u>Hypertension:</u> 30 mg Daily; maintenance, 30 to 60 mg Daily; maximum, 90 mg Daily	Safety and efficacy have not been established in pediatric patients.	Tablet: 30 mg 60 mg 90 mg
Nifedipine ER, osmotic-release tablets (Nifedical XL [®] , Procardia XL [®])	<u>Chronic stable angina, hypertension and vasospastic angina:</u> 30 to 60 mg Daily; maximum, 120 mg Daily	Safety and efficacy have not been established in pediatric patients.	Tablet: 30 mg 60 mg 90 mg
Nimodipine (Nimotop [®])	<u>Subarachnoid hemorrhage:</u> 60 mg every four hours for 21 consecutive days	Safety and efficacy have not been established in pediatric patients.	Capsule: 30 mg
Nisoldipine (Sular [®])	<u>Hypertension:</u> Tablet, sustained release (new formulation): 17 mg Daily; maintenance, 17 to 34 mg Daily; maximum, 34 mg Daily Tablet sustained release (old formulation): 20 mg once Daily; maintenance, 20 to 40 mg Daily; maximum, 60 mg Daily	Safety and efficacy have not been established in pediatric patients.	Tablet, sustained release (new formulation): 8.5 mg 17 mg 25.5 mg 34 mg Tablet sustained release (old formulation): 20 mg 30 mg 40 mg

BID=twice daily, CR=controlled release, ER=extended release, IR=immediate release, QID=four times daily, SR=sustained release, TID=three times daily

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of hypertension and stable angina are presented globally, addressing the role of various medication classes in the treatment of the disease. Due to the complexity of treatment regimens for unstable angina and subarachnoid hemorrhage, the associated guideline summaries focus on the role of the calcium channel blockers in disease management.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation
American College of Cardiology/American Heart Association: 2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of	<ul style="list-style-type: none"> Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. Patients with hypertension and established coronary artery disease should be treated with blood pressure medication(s) as tolerated,

Clinical Guideline	Recommendation
<p>Patients With Chronic Stable Angina (2007)⁷</p>	<p>including angiotensin converting enzyme (ACE) inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes.</p> <ul style="list-style-type: none"> • Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) $\leq 40\%$ and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a LVEF $\leq 40\%$. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-myocardial infarction without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF $\leq 40\%$ and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
<p>European Society of Cardiology: Management of Stable Angina Pectoris (2006)⁶</p>	<p><u>Therapy to improve prognosis</u></p> <ul style="list-style-type: none"> • Aspirin 75 mg once daily is recommended in all patients without contraindications. • Statin therapy is recommended for all patients with coronary disease. • ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left ventricular dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes. • β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. • Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high risk patients with proven coronary disease. • Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. • Calcium channel blockers may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial

Clinical Guideline	Recommendation
	<p>infarction and who do not have heart failure.</p> <p><u>Therapy to improve symptoms and/or reduce ischemia</u></p> <ul style="list-style-type: none"> • Short-acting nitroglycerin therapy is recommended for acute symptom relief and situational prophylaxis. • Test the effects of a β1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. • If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. • If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. • Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. • Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. <p><u>Treatment of syndrome X</u></p> <ul style="list-style-type: none"> • Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. • Statin therapy is recommended in patients with hyperlipidemia. • ACE inhibitors are recommended in patients with hypertension. • Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil* and metabolic agents. <p><u>Treatment of vasospastic angina</u></p> <ul style="list-style-type: none"> • Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.
<p>American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-segment Elevation Myocardial Infarction (2007)⁸</p>	<ul style="list-style-type: none"> • Nitrates, morphine, β-blockers, calcium channel blockers, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents, and GP IIb/IIIa receptor antagonists can be used in the acute setting during early hospitalization. • Calcium channel blockers are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. • Treatment with nitrates and calcium channel blockers is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions. • Nitrates, β-blockers, and calcium channel blockers (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
<p>European Society of Cardiology: Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes (2007)⁶⁴</p>	<ul style="list-style-type: none"> • Calcium channel blockers may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. • Nondihydropyridine calcium channel blockers should not be used unless combined with β-blockers.
<p>Stroke Council,</p>	<ul style="list-style-type: none"> • Calcium channel blockers, specifically nimodipine, have been approved

Clinical Guideline	Recommendation
<p>American Heart Association: Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Statement for Healthcare Professionals from a Special Writing Group of the Stroke Council, American Heart Association (2009)⁶⁵</p>	<p>based on initial reports of reduction in morbidity and an improvement in functional outcome.</p> <ul style="list-style-type: none"> Reduction in morbidity and improvement in functional outcome may have been due to cerebral protection rather than an effect on the cerebral vasculature. There has been no demonstrated reduction in angiographic vasospasm in patients taking nimodipine. Intravenous nicardipine has showed a 30% reduction in spasm but no improvement in outcomes. Oral nimodipine is indicated to reduce poor outcome related to aneurysmal subarachnoid hemorrhage. The value of other oral or intravenous calcium channel antagonists remains uncertain.
<p>National Heart, Lung, and Blood Institute: The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)⁹</p>	<ul style="list-style-type: none"> Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another class (ACE inhibitors, ARBs, β-blockers, calcium channel blockers) demonstrated to be beneficial in randomized controlled outcome trials. Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs or calcium channel blockers. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), post-myocardial infarction (β-blockers, ACE inhibitors and aldosterone antagonists), high coronary disease risk (diuretics, ACE inhibitors, β-blockers and calcium channel blockers), diabetes (diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers), chronic kidney disease (ACE inhibitors and ARBs) and recurrent stroke prevention (diuretics and ACE inhibitors). The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting calcium channel blockers may also be used. For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers and aldosterone antagonists are recommended. Thiazide diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers are beneficial in reducing cardiovascular disease and

Clinical Guideline	Recommendation
	<p>stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to microalbuminuria.</p> <ul style="list-style-type: none"> • Patients with chronic kidney disease often require treatment with three or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs and β-blockers compared to calcium channel blockers and diuretics. The incidence of ACE-inhibitor-induced angioedema is two to four times higher in African Americans. • Calcium channel blockers may be useful in Raynaud's syndrome and certain arrhythmias. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
<p>World Health Organization/ International Society of Hypertension: 2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)⁶⁶</p>	<ul style="list-style-type: none"> • When used as monotherapy, a diuretic or a calcium channel blocker may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-myocardial infarction (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors and diuretics), left ventricular hypertrophy (ARBs) and cerebrovascular disease (diuretics and ACE inhibitors).
<p>European Society of Hypertension/European Society of Cardiology: 2007 Guidelines for the Management of Hypertension (2007)⁶⁷, Reappraisal of Guidelines on Hypertension Management (2009)¹⁰</p>	<ul style="list-style-type: none"> • In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage. • In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics). • Available evidence justifies the use of aliskiren in hypertension,

Clinical Guideline	Recommendation
	<p>particularly in combination with other agents.</p> <ul style="list-style-type: none"> • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, consider medications which have different and complementary mechanisms of action, and that there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and the combination is likely to be well tolerated. <ul style="list-style-type: none"> • Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor with a calcium channel blocker. • Avoid β-blocker/diuretic combination unless required for other reasons. • If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses. • A β- or α-blocker may be included in a triple therapy approach depending on clinical circumstances. • Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor, calcium channel blocker, ARB or β-blocker. • Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored. • Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Antihypertensive treatment should always be initiated in diabetic patients when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. • The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. • In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
<p>National Institute for Health and Clinical Excellence/British Hypertension Society:</p>	<ul style="list-style-type: none"> • Initial therapy in patients ≥ 55 years of age should be a calcium channel blocker or a thiazide diuretic. • Initial therapy in patients <55 years of age should be an ACE inhibitor

Clinical Guideline	Recommendation
Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006) ⁶⁸	<p>or an ARB if the patient is intolerant to ACE inhibitors.</p> <ul style="list-style-type: none"> If a second medication is required and initial therapy was with a calcium channel blocker or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a calcium channel blocker or a diuretic should be added. If three medications are required, a combination of calcium channel blocker, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.

*Agent not currently available in the United States.

Conclusions

Dihydropyridine calcium-channel blocking agents are effective in the treatment of hypertension, as demonstrated in clinical trials and confirmed in recommendations by national and international treatment guidelines. A few of the dihydropyridine agents- amlodipine, nifedipine, and nifedipine- can be used to manage angina as well. For some patients, such as those with hypertension and chronic stable angina, a calcium-channel blocking agent may be a first choice; however for most patients; they are second-line or adjunct treatment options.^{6,7} Nimodipine is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage.²⁴ This is the only indication for this agent.

Direct comparison of amlodipine and felodipine for the treatment of angina demonstrated no significant difference between the agents in the ST-segment depressions in 24 hours, total and mean duration of each ST-segment depression, maximum ST-segment depression or length of ischemic episode.²⁷ Comparisons between amlodipine and diltiazem showed no significant differences between groups for time to 1-mm ST-depression, time to onset of chest pain and total exercise duration.^{28,29} A comparison between amlodipine, verapamil and amlodipine plus atenolol showed significant increases in the duration of ischemic episode and heart rate in the amlodipine monotherapy group.³⁰

Within-class differences are seen among the dihydropyridines for the treatment of hypertension. Available comparisons of amlodipine and felodipine favor amlodipine for compliance and the achievement of blood pressure goals.^{31,32} Other within-class comparisons showed minor statistical differences between agents in lowering blood pressure; however the clinical significance of these small differences was not evaluated in the trials.³³⁻³⁸ There is no agent that is clearly more efficacious than the others within the class.

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Amlodipine	1,117	2,113	84.72%	\$31,526.94	\$14.92
Nifedipine ER	109	217	8.70%	\$19,191.07	\$88.44
Nifedical XL	52	82	3.29%	\$6,848.73	\$83.50
Felodipine ER	11	28	1.12%	\$3,325.19	\$118.76
Nifediac CC	17	23	0.92%	\$1,849.23	\$80.40
Nifedipine	15	19	0.76%	\$1,504.58	\$79.19
Afeditab CR	5	6	0.24%	\$403.00	\$67.17
Nicardipine	1	3	0.12%	\$105.85	\$35.28
Dynacirc CR	1	2	0.08%	\$685.24	\$342.62
Isradipine	1	1	0.04%	\$298.75	\$298.75
Class Total:	----	2,494	100%	\$65,738.58	\$26.36

Recommendations

No changes to the Department of Vermont Health Access (DVHA) approval criteria for dihydropyridine calcium channel blocking agents (see below) are proposed. All the available generic agents, with the exception of nisoldipine ER and isradipine, are preferred.

Non-preferred drugs:

- The patient has had a documented side effect, allergy, or treatment failure to at least three preferred drugs. (If a medication has an AB rated generic, one trial must be the generic formulation.)

References

1. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2011 [cited 2011 May 19]. Available from: <http://www.thomsonhc.com/>.
2. Kannam JP, Aroesty JM, Gersh BJ. Calcium channel blockers in the management of stable angina pectoris. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 May 19]. Available from: <http://www.uptodate.com/utd/index.do>.
3. Talbert RL. Ischemic heart disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 6th edition. New York (NY): McGraw-Hill; 2005. p. 273-90.
4. Michel T. Treatment of myocardial ischemia. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's The pharmacological basis of therapeutics [monograph on the Internet]. 11th ed. New York: McGraw-Hill; 2006 [cited 2008 Jun 5]. Available from: <http://online.statref.com/document.aspx?fxid=75&docid=305>.
5. Hoffmann BB. Therapy of hypertension. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's The pharmacological basis of therapeutics [monograph on the Internet]. 11th ed. New York: McGraw-Hill; 2006 [cited 2011 May 19]. Available from: <http://online.statref.com/document.aspx?fxid=75&docid=310>.
6. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. 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 Jun;27(11):1341-81.
7. Fraker T, Fihn S, Gibbons RJ, Abrams J, Chatterjee K, Daley J, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of chronic stable angina: a report of the American College of Cardiology/American Heart Association task force on practice guidelines writing group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *Circulation*. 2007 Dec 4;116(23):2762-72.
8. Anderson J, Adams C, Antman E, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice parameters (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction). *J Am Coll Cardiol*. 2007 Aug 14;50(7):1-157.
9. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [Internet]. Bethesda (MD): Department of Health and Human Services (US), National Institutes of Health, National Heart, Lung and Blood Institute; 2004 Aug [cited 2011 May 19]. (NIH Publication No. 04-5230.) Available from: <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf>.
10. Mancia G, Laurent S, Agabiti-Rosei E, Ambosioni E, Burnier M, Caulfield M et al. Reappraisal of European guidelines on hypertension management: a European society of hypertension task force document. *Journal of Hypertension*. 2009;27(11):2121-58.
11. Norvasc[®] [package insert]. New York (NY): Pfizer Inc; 2010 Oct.
12. Felodipine [package insert]. Morgantown (WV): Mylan Pharmaceuticals Inc.; 2009 Oct.
13. Isradipine [package insert]. Horsham (PA): PMRS Inc.; 2008 May.
14. Dynacirc CR[®] [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2009 Feb.
15. Nicardipine [package insert]. Morgantown (WV): Mylan Pharmaceuticals Inc.; 2004 Dec.
16. Cardene SR[®] [package insert]. Redwood City (CA): PDL Biopharma, Inc.; 2007 Sept.
17. Cardene IV[®] [package insert]. Bedminster (NJ): EKR Therapeutics, Inc.; 2010 Sept.
18. Procardia[®] [package insert]. New York (NY): Pfizer Inc; 2010 Nov.
19. Adalat CC[®] [package insert]. Wayne (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2011 Feb.
20. Afeditab CR[®] [package insert]. Corona (CA): Watson Laboratories Inc.; 2007 Sept.
21. Nifediac CC[®] [package insert]. Sellersville (PA): Teva Pharmaceuticals USA; 2009 Jul.
22. Procardia XL[®] [package insert]. New York (NY): Pfizer Inc; 2010 Oct.
23. Nifedical XL[®] [package insert]. Sellersville (PA): Teva Pharmaceuticals USA; 2010 Dec.
24. Nimodipine [package insert]. Detroit (MI): Caraco Pharmaceutical Laboratories, Ltd.; 2009 Dec.
25. Sular[®] [package insert]. Atlanta (GA): Shionogi Pharma, Inc.; 2010 Feb.

26. UpToDate [database on the internet]. Waltham (MA): UpToDate; 2011 [cited 2011 May 19]. Available from: <http://www.utdol.com/utd/index.do>.
27. Koenig W, Hoher M. Felodipine and amlodipine in stable angina pectoris: results of a randomized double-blind crossover trial. *J Cardiovasc Pharmacol*. 1997;29(4):520-4.
28. Chugh SK, Dignall K, Hutchinson T, McDonald CJ, Miller AJ, Lahiri A. A randomized, double-blind comparison of the efficacy and tolerability of once-daily modified-release diltiazem capsules with once-daily amlodipine tablets in patients with stable angina. *J Cardiovasc Pharmacol*. 2001 38(3):356-64.
29. van Kesteren HA, Withagen AJ. A comparative study of once-daily amlodipine versus twice-daily diltiazem controlled-release (CR) in the treatment of stable angina pectoris. *Amlodipine Study Group. Cardiovasc Drugs Ther*. 1998;12 Suppl 3:233-7.
30. Frishman WH, Glasser S, Stone P, Deedwania PC, Johnson M, Fakouhi TD. Comparison of controlled-onset, extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. *Am J Cardiol*. 1999 Feb 15;83(4):507-14.
31. Sheehy O, LeLorier J. Patterns of amlodipine and felodipine use in an elderly Quebec population [abstract]. *Can J Cardiol*. 2000;16(9):1109-17.
32. Van Der Krogt J, Brand R, Dawson E. Amlodipine versus extended-release felodipine in general practice: A randomized, parallel-group study in patients with mild-to-moderate hypertension. *Curr Therap Res*. 1996;57(3):145-58.
33. Mounier-Vehier C, Jaboureck O, Emeriau JP, Bernaud C, Clerson P, Carre A. Randomized, comparative, double-blind study of amlodipine vs nifedipine as a treatment of isolated systolic hypertension in the elderly. *Fundam Clin Pharmacol*. 2002;16(6):537-44.
34. Kes S, Caglar N, Canberk A, et al. Treatment of mild-to-moderate hypertension with calcium-channel blockers: a multicentre comparison of once-daily nifedipine GITS with once-daily amlodipine. *Curr Med Res Opin*. 2003;19(3):226-37. (Abstract)
35. Gustin G, White WB, Taylor S, Daragjati C. Clinical outcome of a mandatory formulary switch for dihydropyridine calcium-channel blocker therapy at a Veteran's Administration Medical Center. *Am J Hypertens*. 1996;9(4 Pt 1):312-6.
36. Pepine CJ, Cooper-DeHoff RM, et al. Comparative Efficacy and Safety of Nisoldipine and Amlodipine (CESNA-II) Study Investigators. Comparison of effects of nisoldipine-extended-release and amlodipine in patients with systemic hypertension and chronic stable angina pectoris. *Am J Cardiol*. 2003;91(3):274-9.
37. White WB, Saunders E, Noveck RJ, Ferdinand K. Comparative efficacy and safety of nisoldipine extended-release (ER) and amlodipine (CESNA-III study) in African American patients with hypertension. *Am J Hypertens*. 2003;16(9 Pt 1):739-45.
38. Lenz TL, Wurdeman RL, Hilleman DE. Comparison of 24-hour blood pressure profiles in patients with hypertension who were switched from amlodipine to nisoldipine. *Pharmacotherapy*. 2001;21(8):898-903.
39. Parameshwar J, Keegan J, Mulcahy D, Phadke K, Sparrow J, Sutton G, et al. Atenolol or nifedipine alone is as efficacious in stable angina as their combination: a double blind randomized trial. *Int J Cardiol*. 1993;40:135-41.
40. Savonitto S, Ardissiono D, Egstrup K, Rasmussen K, Bae EA, Omland T, et al. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. Results of the International Multicenter Angina Exercise (IMAGE) Study. *J Am Coll Cardiol*. 1996 Feb;27(2):311-6.
41. Wright JT Jr, Sica DA, Gana TJ, Bohannon K, Pascual LG, Albert KS. Antihypertensive efficacy of night-time graded-release diltiazem versus morning amlodipine in African Americans. *Am J Hypertens*. 2004;17(9):734-42.
42. Ryuzaki M, Nakamoto H, Nishida E, et al. 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 Nov;25(11):2352-8.
43. Saito I, Saruta T. Controlled release nifedipine and valsartan combination therapy in patients with essential hypertension: The Adalat CR and valsartan cost-effectiveness combination (ADVANCE-Combi) study. *J Hypertens*. 2007 Nov;25(11):2352-8.

44. Whitcomb C, Enzmann G, Pershadsingh HA, et al. A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension. *Int J Clin Pract*. 2000;54(8):509-13.
45. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. *Am J Cardiovasc Drugs*. 2008;8(1):35-44.
46. Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD002003. doi: 10.1002/14651858.CD002003.pub2.
47. Manyemba J. A randomized crossover comparison of reserpine and sustained-release nifedipine in hypertension [abstract]. *Cent Afr J Med*. 1997 Dec;43(12):344-9.
48. Ogihara T, Nakao K, Fukui T, et al; Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. *Hypertension*. 2008 Feb;51(2):393-8.
49. Ribeiro AB, Mion D Jr, Marin MJ, et al; Latin American Hypertension Study (LAMHYST) Group. Antihypertensive efficacy of amlodipine and losartan after two 'missed' doses in patients with mild to moderate essential hypertension. *J Int Med Res*. 2007 Nov-Dec;35(6):762-72.
50. Chrysant SG, Melino M, Karki S, Lee J, Heyrman R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008 Apr;30(4):587-604.
51. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. *Circulation*. 2000;102(13):1503-10.
52. Lichtlen PR, Hugenholz PG, Rafflenbeul W, et al. Retardation of coronary artery disease in humans by the calcium-channel blocker nifedipine: results of the INTACT study (International Nifedipine Trial on Antiatherosclerotic Therapy). *Cardiovasc Drugs Ther*. 1990 Aug;4 Suppl 5:1047-68.
53. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. *JAMA*. 1996; 276:785-791. (Abstract)
54. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet*. 2004 Jun 19;363(9426):2022-31.
55. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the international nifedipine GTS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet*. 2000;356:366-72.
56. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet*. 2005 Sep 10-16;366(9489):895-906.
57. Nissen SE, Tuzcu EM, Libby P, et al; for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004 Nov 10;292(18):2217-26.
58. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med*. 1998 Mar 5;338(10):645-52.
59. ALLHAT Officers and Coordinators for ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium-channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002 Dec 18;288(23):2981-97.
60. Hansson L, Lindholm LH, Ekblom T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish trial in old patients with hypertension-2 study. *Lancet*. 1999 Nov 20;354(9192):1751-6.
61. Lewis EJ, Hunsicker LG, Clarke WR, et al. Reno protective effect of angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-60.
62. Schmid-Elsaesser R, Kunz M, Zausinger S, et al. Intravenous magnesium versus nimodipine in the treatment of patients with aneurysmal subarachnoid hemorrhage: a randomized study. *Neurosurgery*. 2006 Jun;58(6):1054-6.

63. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2011 [cited 2011 May 19]. Available from: <http://online.factsandcomparisons.com>.
64. Bassand J, Hamm C, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al; Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007 Jul;28(13):1598-660.
65. Bederson J, Connolly E, Batjer H, Dacey R, Dion J, Diringer M, et al. Guidelines for the management of aneurismal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2009;40:994-1025.
66. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003 Nov;21(11):1983-92.
67. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007 Jun;25(6):1105-87.
68. National Institute for Health and Clinical Excellence, National Collaborating Centre for Chronic Conditions; British Hypertension Society. Hypertension: management of adults in primary care: pharmacological update [monograph on the Internet]. London (UK): Royal College of Physicians; 2006 Jun [cited 2011 May 19]. Available from: <http://www.nice.org.uk/guidance/index.jsp?action=download&o=30111>.