# Calcium Channel Blockers Review

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## *FDA-approved Indications*

| Drug | Manufacturer | Vasospastic Angina | Angina | Ventricular Rate Control | Hypertension |
|---|---|---|---|---|---|
| **Dihydropyridines** | | | | | |
| amlodipine (Norvasc®) | generic | X | X | -- | X |
| felodipine ER (Plendil®) | generic | -- | -- | -- | X |
| isradipine | generic | -- | -- | -- | X |
| isradipine SR (Dynacirc CR®) | Reliant | -- | -- | -- | X |
| nicardipine (Cardene®) | generic | -- | X | -- | X |
| nicardipine SR (Cardene SR®) | Roche | -- | -- | -- | X |
| nifedipine (Procardia®) | generic | X | X | -- | -- |
| nifedipine ER, nifedipine SA, nifedipine SR (Adalat CC®, Afeditab CR, Nifediac CC, Nifedical XL, Procardia XL®) | generic | X | X | -- | X |
| nimodipine (Nimotop®) | generic | | | | |
| nisoldipine ER (Sular®) | generic, Sciele Pharma | -- | -- | -- | X |
| **Nondihydropyridines** | | | | | |
| diltiazem (Cardizem®) | generic | X | X | X | -- |
| diltiazem ER (Cardizem LA®) | Abbott | -- | X | -- | X |
| diltiazem ER (Cardizem CD®, Cartia XT, Dilacor XR®, Dilt CD, Taztia XT, Tiazac®) | generic | X | X | -- | X |
| diltiazem ER (Dilt XR) | generic | -- | X | -- | X |
| diltiazem ER (Diltia XT) | generic | -- | -- | -- | X |
| verapamil (Calan®) | generic | X | X | X | X |
| verapamil ER (Covera-HS®) | Pfizer | -- | X | -- | X |
| verapamil ER (Verelan PM®) | generic | -- | -- | -- | X |
| verapamil SR (Calan SR®, Isoptin SR®, Verelan®) | generic | -- | -- | -- | X |

Amlodipine is also indicated for angiographically documented coronary artery disease (CAD).[1] Nimodipine is indicated only for use in subarachnoid hemorrhage. Verapamil is also indicated for unstable angina.

## *Overview*

Hypertension affects over 30 percent of adult Americans.[2] Hypertension is an independent risk factor for the development of cardiovascular disease. The more elevated the blood pressure, the higher the risk of myocardial infarction (MI), stroke, heart failure, and kidney disease. To reduce the risk of cardiovascular events, the current blood pressure goal is less than 140/90 mm Hg. For patients with chronic renal disease or diabetes, the current goal for blood pressure therapy is less than 130/80 mm Hg.[3,4,5] Attainment of blood pressure goals results in a reduced risk of cardiovascular events.[6] There is inter-patient variability in response to various antihypertensive classes. In the absence of compelling indications, reaching target blood pressure is central in determining cardiovascular benefit in patients with hypertension, not the specific agent used.[7,8,9,10]

Calcium channel blockers (CCBs) are widely used in the treatment of hypertension and angina pectoris. While other antihypertensives may be considered first line therapy, according to the JNC-VII guidelines for the treatment of hypertension, CCBs could be used in patients who have diabetes or are at high risk for coronary heart disease.[11] The American Diabetes Association 2008 guidelines recommend that dihydropyridine CCBs should be used as second-line drugs for patients who cannot tolerate the other preferred classes [angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB,) or thiazide diuretics]) or who require additional agents to achieve the target blood pressure.[12]

Recent trials have shown several long-acting CCBs to have decreased hospitalization and revascularization procedures associated with them.[13,14,15,16]

Hypertension

CCBs have been shown to effectively reduce blood pressure. In isolated systolic hypertension (ISH), CCBs have been shown to reduce the systolic blood pressure (SBP) more than diastolic blood pressure (DBP) thereby reducing the pulse pressure. In patients with ISH, treatment with nitrendipine, a CCB not available in the U.S., reduced the stroke rate by 42 percent and cardiovascular morbidity by 30 percent.[17] In the ALLHAT study, the primary endpoint of combined fatal CHD and nonfatal acute MI were similar amongst chlorthalidone, amlodipine, and lisinopril treatment arms. Amlodipine demonstrated higher risk of heart failure and hospitalization related to heart failure or fatal heart failure compared to chlorthalidone, among diabetics and non-diabetics (RR 1.42, 95% confidence interval (CI), 1.23-1.64). CCBs and diuretics in other comparative published trials have been shown to have similar risk reductions and rates of major CHD events and stroke.[18,19,20,21,22] A recent ALLHAT post hoc analysis found that in patients with metabolic syndrome and particularly in black patients, the findings do not support preferring a CCB, ACE inhibitor or alpha blocker to a thiazide diuretic despite their more favorable metabolic profiles.[23] A subgroup analysis of ALLHAT showed that despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, cardiovascular disease outcomes in older hypertensive adults with metabolic syndrome, as compared with treatment with CCBs and ACE inhibitors.[24] A reanalysis of the ALLHAT data showed the higher risk of heart failure with amlodipine and lisinopril versus chlorthalidone was greatest in the first year (RR 2.2, 95% CI, 1.68 to 2.98 and RR 2.08, 95% CI, 1.56 to 2.78, respectively), whereas the unadjusted risk of hospitalized or fatal heart failure remained higher for amlodipine versus chlorthalidone (RR 1.35, 95% CI, 1.21 to 1.50) and lisinopril (RR 1.23, 95% CI, 1.09 to 1.38).[25]

Several large clinical trials have compared CCBs with other types of antihypertensives. Some of the recent trials include ALLHAT, CAMELOT, VALUE, INVEST, CONVINCE and ASCOT-BPLA.[26,27,28,29,30,31] The comparator antihypertensives have included ACE inhibitors, diuretics, angiotensin receptor blockers, and beta-blockers and combinations of antihypertensives. Many

of these large trials have demonstrated that CCBs have beneficial effects on composite cardiovascular outcomes or individual clinical outcomes; however, most of the trials only demonstrate equivalence to the comparator antihypertensives rather than superiority. [32,33,34]

Angina

CCBs improve clinical symptoms and are well tolerated. Long-acting CCBs (the guidelines do not specify DHP or NDHP) are recommended for the treatment of chronic stable angina when beta-blockers are not tolerated or do not relieve symptoms.[35,36] Vasospastic or Prinzmetal's angina is effectively treated with CCBs by reducing the frequency of anginal attacks.

## *Pharmacology[37,38]*

CCBs inhibit calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The reduction in afterload, which results in a decrease in myocardial oxygen consumption, is thought to be responsible for the treatment of angina. There are three classes of CCBs: diphenylalkylamines (i.e., verapamil), benzothiazepines (i.e., diltiazem), and dihydropyridines (i.e., amlodipine, felodipine ER, isradipine, nicardipine, nifedipine, nimodipine, and nisoldipine ER). The dihydropyridines are potent vasodilators and can increase or have a neutral effect on vascular permeability.[39] The nondihydropyridine verapamil, and to a lesser extent diltiazem, are less potent vasodilators, but they have a greater depressive effect on cardiac conduction and contractility.

### *Pharmacokinetics*

| Drug | Bioavailability (%) | Half-Life (hr) | Metabolism | Excretion (%) |
|---|---|---|---|---|
| **Dihydropyridines** | | | | |
| amlodipine (Norvasc)[40,41] | 64-90 | 30-50 | Inactive metabolites | Urine: 70 |
| felodipine ER (Plendil)[42] | 20 | 11-16 for immediate release | Six metabolites, no activity; concentration is 23 percent of parent | Urine: 70<br>Feces: 10 |
| isradipine/SR (Dynacirc CR)[43] | 15-24 (Dynacirc CR) | 8 | Several inactive metabolites | Urine: 60-65<br>Feces: 25-30 |
| nicardipine/SR (Cardene/SR)[44,45] | 35 | 8.6 | Metabolized extensively | Urine: 60<br>Feces: 35 |
| nifedipine (Procardia/XL)[46, 47] | 40-77 (Procardia) 86 (Procardia XL relative to IR) | 2 | Inactive metabolites | Urine: 60-80 |
| nimodipine (Nimotop)[48] | 13 | 1-2 | Inactive metabolites | -- |
| nisoldipine ER (Sular)[49] | 5 | 9.4-18 | 5 metabolites; one active, 10 percent activity of parent; concentration equal to parent | Urine: 60-80 |
| **Nondihydropyridines** | | | | |
| diltiazem (Cardizem)[50] | 40-60 | 3.5-9 | desacetyl diltiazem is 25-50% as potent as parent; concentration is 10-20 percent of parent | -- |
| diltiazem ER (Cardizem LA)[51] | 40 | 6-9 | desacetyl diltiazem is 25-50% as potent as parent; concentration is 10-20 percent of parent | -- |
| diltiazem ER (Cardizem CD)[52] | -- | 5-8 | -- | -- |
| verapamil (Covera HS, Verelan PM)[53,54] | 33-65 (varies with rate and extent of release from dosage forms) | -- | 13 metabolites; norverapamil is 20 percent as potent as parent; concentration equal to parent | Urine: 70-74<br>Feces: 16 |

Chronotherapeutics is the concept of administering antihypertensives by delayed release mechanisms to lower blood pressure during the rapid rise associated with awakening. It is unclear if this concept actually lowers morbidity and mortality.[55]

### *Contraindications/Warnings*

Diltiazem and verapamil are contraindicated in sick sinus syndrome, second or third degree atrioventricular block (except in patients with a functioning artificial pacemaker), hypotension (SBP<90 mm Hg). Diltiazem is contraindicated in acute MI and pulmonary congestion. Verapamil is contraindicated in severe left ventricular dysfunction, atrial flutter or fibrillation, and an accessory bypass graft. Diltiazem and verapamil should be used with caution in hepatic or renal dysfunction.

Nimodipine capsules should not be administered intravenously or by any other parenteral method as this could result in death. Short-acting nifedipine has been related to increased coronary mortality in patients with a history of MI and should not be used for the treatment of hypertension.[56,57]

Peripheral edema is a common adverse event of CCBs and usually occurs within two to three weeks of starting therapy.

### *Drug Interactions*

Diltiazem and verapamil both inhibit CYP3A4; both can increase the effects of amiodarone, beta-blockers, lithium, digoxin, carbamazepine, and selected HMG-CoA reductase inhibitors. Grapefruit juice can increase verapamil serum concentrations, and to a lesser extent, diltiazem, serum concentrations. Nifedipine and nisoldipine should not be administered with grapefruit juice. Felodipine ER may increase tacrolimus serum levels.

Cardiovascular action of other CCBs can be enhanced by the addition of nimodipine. Blood pressure lowering effects may be additive when used concurrently with sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®).

## *Adverse Effects*

| Drug | AV Block | Constipation | Dizziness | Edema | Fatigue | Flushing | HA | Nausea |
|---|---|---|---|---|---|---|---|---|
| **Dihydropyridines** | | | | | | | | |
| amlodipine (Norvasc)[58] n=1,730 (placebo n=1,250) | nr | ≤ 1 | 1.1-3.4 (1.5) | 1.8–10.8 (0.6) | 4.5 (2.8) | 0.7 – 2.6 (0) | 7.3 (7.8) | 2.9 (1.9) |
| felodipine ER (Plendil)[59] n=861 (placebo n=334) | nr | 0.3 – 1.5 (0.9) | 2.7 – 3.7 (2.7) | 2 – 17.4 (3.3) | nr | 3.9 – 6.9 (0.9) | 10.6 – 14.7 (10.2) | 1.2 – 1.7 (1.5) |
| isradipine IR[60] | nr | nr | 7.3 (4.4) | 7.2 (3) | 3.9 (0.3) | 2.6 (0) | 13.7 (14.1) | 1.8 (1.7) |
| isradipine SR (Dynacirc CR)[61] n=422 (placebo n=186) | nr | 1.7 (0) | 4.7 (2.7) | 15.2 (2.2) | 4.3 (2.2) | 1.9 (0.5) | 13 (12.4) | 1.2 (1.6) |
| nicardipine (Cardene)[62] n=1,390 (placebo n=211) | nr | nr | 4 (0) | 8 (0.9) | nr | 9.7 (2.8) | 8.2 (4.7) | 2.2 (0.9) |
| nicardipine SR (Cardene SR)[63] n=322 (placebo n=140) | nr | nr | 1.6 (0.7) | 5.9 (1.4) | nr | nr | 6.2 (7.1) | 1.9 (0.7) |
| nifedipine (Procardia)[64] n=226 (placebo n=235) | nr | <2 | 27 (15) | 7 (1) | nr | 25 (8) | 23 (20) | 11 (8) |
| nifedipine SR (Procardia XL)[65] n=707 (placebo n=266) | nr | 3.3 (2.3) | 4.1 (4.5) | 10 – 30 | 5.9 (4.1) | < 3 | 15.8 (9.8) | 3.3 (1.9) |
| nimodipine (Nimotop)[66] n=823 (placebo n=479) | nr | nr | <1 | 4 (3) | nr | nr | 7 (1) | 9 (0) |
| nisoldipine ER (Sular)[67] n=663 (placebo n=280) | ≤ 1 | nr | 3-7 (4) | 7-27 (10) | nr | nr | 22 (15) | 2 (1) |
| **Nondihydropyridines** | | | | | | | | |
| diltiazem ER (Cardizem CD)[68] | 3.3 (0) | < 1 | 3 (3) | 2.6 (1.3) | nr | 1.4 | 5.4 (5) | 1.4 |
| diltiazem ER (Cardizem LA)[69] | 3.2 | nr | 6.4 | 6.8 | 4.8 | nr | nr | nr |
| verapamil ER (Covera-HS)[70] n=572 (placebo n=261) | 1.7 (0) | 11.7 (2.7) | 4.7 (2.7) | 3 (3.1) | 4.5 (3.8) | 0.8 (0.3) | 6.6 (7.3) | 2.1 (1.9) |
| verapamil ER (Verelan PM)[71] n=297 (placebo n=116) | 1.2 | 8.8 (0.9) | 3 (0.9) | 3.7 (0.9) | 1.7 | 0.6 | 12.1 (11.2) | 1.7 (0) |

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

## *Special Populations*

*Pediatrics*

Many of the CCBs are extended release products, making them difficult to use in children. Amlodipine has been studied in a randomized, double-blind, placebo-controlled, parallel-group study with 268 hypertensive children (mean age, 12.1 ± 3.3 years).[72] Amlodipine reduced blood pressure in a dose-dependent manner with good tolerability, and only two percent of children discontinued therapy related to adverse effects. Children between six and 17 years old should receive amlodipine 2.5 to 5 mg daily for the treatment of hypertension. Safety and efficacy of other CCBs in hypertensive pediatrics have not been established. Safety and efficacy of nimodipine have not been established in children.

*Pregnancy*

All CCBs are Pregnancy Category C.

*Hepatic/Renal Impairment*

Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine ER, diltiazem, and verapamil may require dose adjustment in hepatic impairment or in cirrhosis. Isradipine, nicardipine, diltiazem, and verapamil may require dose adjustment in renal impairment.

## *Dosages*

| Drug | Initial HTN Dose | Maximum HTN Dose | Angina Dose | Availability |
|---|---|---|---|---|
| **Dihydropyridines** | | | | |
| amlodipine (Norvasc) | 5 mg daily | 10 mg daily | 5-10 mg daily | 2.5, 5, 10 mg tablets |
| felodipine ER (Plendil) | 5 mg daily | 10 mg daily | -- | 2.5, 5, 10 mg tablets |
| isradipine | 2.5 mg twice daily | 10 mg twice daily | -- | 2.5, 5 mg capsules |
| isradipine SR (Dynacirc CR) | 5 mg daily | 10 mg twice daily | -- | 5, 10 mg tablets |
| nicardipine (Cardene) | 20 mg three times a day | 40 mg three times a day | 20-40 mg three times a day | 20, 30 mg capsules |
| nicardipine SR (Cardene SR) | 30 mg twice daily | 60 mg twice daily | -- | 30, 45, 60 mg capsules |
| nifedipine | -- | -- | 10 mg three times a day to max of 30 mg per dose or 180 mg per day | 10, 20 mg capsules |
| nifedipine SR | Adalat CC, Procardia XL: 30-60 mg daily | Adalat CC: 90 mg Procardia XL:120 mg daily | Adalat CC, Procardia XL: 30-90 mg daily | ER tablet: 30, 60, 90 mg tablets<br>Adalat CC, Procardia XL, Nifediac CC: 30, 60, 90 mg tablets<br>Afeditab CR, Nifedical XL: 30, 60 mg tablets |
| nimodipine (Nimotop) | -- | -- | -- | 30 mg capsules |
| nisoldipine ER | 20 mg daily | 60 mg daily | | ER tablet: 20, 30, 40 mg tablets |
| nisoldipine ER (Sular) | 17 mg daily | 34 mg daily | -- | 8.5, 17, 25.5, 34 mg tablets (new formulation) |

Nimodipine (Nimotop) is administered as 60 mg every four hours for 21 days for the reduction of the incidence and severity of ischemic deficits associated with subarachnoid hemorrhage.

Nisoldipine ER generic tablets and Sular tablets are not AB-rated and are not interchangeable.

## *Dosages (continued)*

| Drug | Initial HTN Dose | Maximum HTN Dose | Angina Dose | Availability |
|---|---|---|---|---|
| **Nondihydropyridines** | | | | |
| diltiazem (Cardizem) | -- | -- | 30 mg four times daily to a max of 360 mg per day | 30, 60, 90, 120 mg tablets |
| diltiazem ER | 120-240 mg daily | 480 mg daily<br>Tiazac: 540 mg daily | 120-480 mg daily<br>Tiazac: 120-540 mg daily | ER capsules: 120, 180, 240, 300, 360, 420 mg capsules<br>Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Dilt CD, Dilt XR, Taztia XT, Tiazac: 120, 180, 240 mg capsules<br>Cardizem CD, Cartia XT, Dilt CD, Taztia XT, Tiazac: 300 mg capsules<br>Cardizem CD, Taztia XT, Tiazac: 360 mg capsules<br>Tiazac: 420 mg capsules |
| diltiazem ER (Cardizem LA) | 180-240 mg daily | 540 mg daily | 180-360 mg daily | 120, 180, 240, 300, 360, 420 mg tablets |
| verapamil (Calan) | 80 mg three times daily | 480 mg per day | 80 mg-120 mg three times daily up to a max of 480 mg per day | 40, 80, 120 mg tablets |
| verapamil ER (Covera HS) | 180 mg at bedtime | 480 mg at bedtime | 180-480 mg at bedtime | 180, 240 mg tablets |
| verapamil ER (Verelan PM) | 200 mg at bedtime | 400 mg at bedtime | -- | 100, 200, 300 mg capsules |
| verapamil SR | 240 mg daily | 480 mg daily | -- | Calan SR, Isoptin SR:120, 180, 240 mg tablets |
| verapamil SR (Verelan) | 240 mg daily | 480 mg daily | -- | 120, 180, 240, 360 mg capsules |

## *Clinical Trials*

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. Comparative clinical trials have been performed with some of the agents in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable

clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many clinical studies were performed in the 1980 and 1990's evaluating the hemodynamic effects of the CCBs; however, clinical trials with clinical endpoints have more recently been published.

amlodipine (Norvasc) and nicardipine (Cardene)

Amlodipine and nicardipine were compared in a randomized, double-blind trial evaluating efficacy in 133 patients with isolated systolic hypertension.[73] Patients were over 60 years old. Patients were randomized to amlodipine 5 mg daily or nicardipine 60 mg per day (given in two or three divided doses). Doses were titrated up if necessary for BP control with maximum doses of amlodipine 10 mg daily and nicardipine 100 mg per day given in divided doses. After 90 days, the office blood pressure and ambulatory blood pressure monitoring (ABPM) were significantly reduced in terms of SBP and pulse pressure by both therapies. Per ABPM studies, amlodipine had a greater effect on the SBP than nicardipine. Therapy was well tolerated.

amlodipine (Norvasc) and nisoldipine ER (Sular)

In a randomized, double blind, double-dummy, parallel group trial, amlodipine and nisoldipine ER were compared for efficacy, safety, and tolerability in 120 patients with stage one to two hypertension (DBP 90 to 109 mm Hg) and chronic stable angina.[74] The initial phase was a three-week placebo run-in phase followed by the randomization to nisoldipine ER 20 or 40 mg daily or amlodipine 5 or 10 mg daily. Doses were titrated if needed after two weeks to achieve a DBP of less than 90 mm Hg. At six weeks, nisoldipine ER (-15/-13 mm Hg) and amlodipine (-13/-11 mm Hg) effectively reduced blood pressure (p=NS). Blood pressure response rates for nisoldipine ER (87 percent) and amlodipine (78 percent) were similar (p=NS). The mean increase in total exercise time was similar in both groups (p=NS). More headache and peripheral edema were observed with nisoldipine ER, but overall, both therapies were well tolerated.

Nisoldipine ER and amlodipine were compared in 192 African-American patients with DBP of 95 to 114 mm Hg over 12 weeks.[75] Patients were randomized to nisoldipine ER 20 to 60 mg daily or amlodipine 5 to 10 mg daily in a double-blind manner. Blood pressure, using ambulatory monitoring, was significantly lower compared to baseline with nisoldipine ER (-23/-16 mm Hg) and amlodipine (-20/-15 mm Hg) (between-group comparisons, p=0.07 for SBP; p=0.5 for DBP). Neither agent had an effect on heart rate. Adverse effects were similar for both groups; most commonly reported were headache, edema, and dizziness.

diltiazem ER (Cardizem LA) and amlodipine (Norvasc)

Diltiazem ER and amlodipine were compared in 262 hypertensive African-Americans in a multicenter, randomized, double-blind, parallel-group, dose-to-effect study.[76] Patients were randomized to diltiazem ER 360 mg at bedtime (10 p.m.) or morning amlodipine 5 mg (8 a.m.) for six weeks; if blood pressure still exceeded 130/85 mm Hg, therapy was titrated to diltiazem

ER 540 mg or amlodipine 10 mg. Changes in blood pressure, heart rate, and rate-pressure product (heart rate x SBP) were measured by ambulatory blood pressure monitoring for the first four hours after awakening and over a 24-hour period. Amlodipine increased heart rate whereas diltiazem ER decreased heart rate. Greater mean reductions in heart rate and rate-pressure product were seen in the diltiazem group during all intervals ($p \leq 0.0008$). Diltiazem ER showed greater reductions in DBP during the first four hours after awakening and between 6 a.m. and noon ($p < 0.0049$ and $p < 0.0019$), but had a comparable reduction in the mean 24-hour DBP to amlodipine. Reductions in the SBP in the morning hours were comparable for both groups; however, amlodipine demonstrated a 3.4 mm Hg greater reduction in the mean 24-hour SBP ($p < 0.0022$). Therapy in both arms was well tolerated. The manufacturer of diltiazem ER funded the study.

felodipine ER (Plendil) and amlodipine (Norvasc)

In a multicenter, double-blind, parallel group trial, felodipine ER and amlodipine were compared in 535 elderly hypertensive patients (> 65 years).[77] Patients had an initial sitting DBP of 90 to 115 mm Hg or SBP of 160 to 220 mm Hg. Patients were randomized to felodipine ER 2.5 mg or amlodipine 5 mg once daily. Blood pressure was evaluated after three and six weeks; if BP reduction was not satisfactory, doses were titrated upward. After nine weeks, the average doses of felodipine ER and amlodipine were 5.5 mg and 7.3 mg. The primary endpoint of new vasodilatory adverse effects was reported by 32 percent of the felodipine ER group and 43 percent of the amlodipine group. Both treatments effectively reduced blood pressure 24 hours post-dose.

felodipine ER (Plendil) and nisoldipine ER (Sular)

A multicenter, randomized, double-blind trial compared the safety and efficacy of nisoldipine ER 20 to 40 mg daily and felodipine ER 5 to 10 mg daily in 229 patients with mild to moderate hypertension.[78] Following a two-week placebo run-in phase, patients were randomized and followed for 16 weeks. Both drugs demonstrated significant reductions in blood pressure compared to baseline. No significant differences in blood pressure reduction were observed between the two drugs. The percentage of responders was 77.8 and 66.5 percent for nisoldipine ER and felodipine ER, respectively, Edema occurred more frequently with nisoldipine ER (30 percent) compared to felodipine ER (21 percent). More patients withdrew from the nisoldipine ER group than felodipine ER group with the most common reason being edema.

nifedipine GITS

The ACTION trial was a randomized, double-blind trial evaluating the effects of nifedipine GITS on long-term outcome in 7,665 angina patients.[79] Patients with stable CAD were randomized to nifedipine GITS 60 mg daily or placebo. The primary endpoint, the composite of death, MI, angina, new heart failure, stroke, or peripheral revascularization, was similar in both groups {nifedipine 4.6 per 100-patient years; 4.75 per 100 patient-years for placebo (0.97 [0.88-1.07], p=0.54)}. The combined endpoint of death and any cardiovascular event or procedure favored nifedipine GITS (0.89 [0.83-0.95], p=0.0012). Fewer patients underwent coronary angiography and interventions with nifedipine GITS.

nifedipine CC and amlodipine (Norvasc)

A total of 207 patients were enrolled in a randomized, double-blind study to compare the antihypertensive efficacy and safety of nifedipine coat-core to amlodipine.[80] In the patients with available data (n=176), mean blood pressure decreased from 160.9/101.9 mm Hg to 141.3/85.5

mm Hg in the nifedipine group and from 160.5/101.8 mm Hg to 140.7/85.9 mm Hg in the amlodipine group. Zidek and colleagues showed that both drugs are well tolerated, have equivalent antihypertensive efficacy, and have similar safety profiles.

nisoldipine ER (Sular)

The NICOLE study determined the effects of nisoldipine ER on the rate of progression of coronary atherosclerosis and the rate of clinical cardiovascular events.[81] The single-center, double-blind, randomized, placebo-controlled study enrolled 826 patients who had undergone coronary angioplasty. Patients were randomized to nisoldipine ER 40 mg daily or placebo and followed for up to three years. No significance difference was observed between the groups for the number of new coronary lesions. The average minimum luminal diameter of the non-dilated coronary lesions decreased in both groups; however, the difference between the groups was not significant. Both groups demonstrated progression of atherosclerosis in at least one coronary arterial segment, which was defined as an increase in diameter stenosis of ≥ 13 percent. Rates of death, stroke, and MI were similar between the groups; however, revascularizations were less frequent with nisoldipine ER. Therefore, nisoldipine ER patients had overall fewer clinical events compared to placebo (44.6 versus 52.6 percent, p=0.02).

controlled-onset extended release verapamil (Covera-HS) and nifedipine GITS (Procardia XL)

In a prospective, double-blind, randomized trial to compare 24-hour blood pressure control, controlled-onset extended release verapamil and nifedipine GITS were administered to 557 hypertensive patients over ten weeks.[82] Dose titration was based on blood pressure readings at baseline, four weeks, and ten weeks. The four-hour time period of one hour prior to awakening to three hours after awakening was the focus of intense evaluation. Early morning blood pressure was reported to be similar between the two groups. Nifedipine GITS lowered blood pressure significantly more during sleep (-11 mm Hg in the nifedipine GITS group versus -5.8 mm Hg in the verapamil group). Both drugs effectively reduced blood pressure throughout 24 hours.

chronotherapeutic oral drug absorption system (CODAS) verapamil (Verelan PM)

In a randomized, double-blind, placebo-controlled trial, CODAS verapamil was evaluated for efficacy in blood pressure reduction in 277 patients with mild to moderate hypertension.[83] All patients received placebo for two to four weeks prior to randomization. During the run-in placebo phase, patients must have had an initial sitting DBP of 95 to 115 mm Hg. Patients were then randomized in a double-blind manner to CODAS verapamil of 100, 200, 300, or 400 mg or placebo to be taken between 9 p.m. and 11 p.m for eight weeks. Blood pressure was measured weekly and ambulatory blood pressure monitoring was obtained. The 200, 300, and 400 mg doses of CODAS verapamil were effective in lowering DBP compared to placebo. Blood pressure reductions were the greatest between 6 a.m. and noon. Dose-dependent blood pressure reductions were observed. Adverse events were reflective of other verapamil preparations.

*Meta-analysis*

A meta-analysis of 13 major studies with nearly 104,000 pooled hypertensive patients suggests that the dihydropyridine CCBs were associated with a lower risk of stroke compared to other randomized antihypertensives (p=0.006).[84]

## *Summary*

The benefits of CCBs in controlling angina and hypertension are clearly documented.

The JNC-VII report on the treatment of hypertension recommends diuretics as a part of most antihypertensive regimens. The JNC-VII report lists compelling indications for CCBs for high-risk CHD patients and diabetic patients. CCBs should generally be used in combination with other antihypertensive agents in these two patient groups. Short-acting nifedipine has been related to increased coronary mortality in patients with a history of MI and should not be used for the treatment of hypertension.

The effect on cardiovascular morbidity and mortality with CCBs compared to other agents such as diuretics and ACE inhibitors has been less clear until recently, where the ALLHAT study showed that chlorthalidone, amlodipine, and lisinopril had similar outcomes of combined fatal CHD and nonfatal MI and confirmed that diuretics should be first-line in the treatment of hypertension. It should be noted that thiazides particularly at higher doses have shown to induce metabolic abnormalities and should be used with caution.

Several recent trials, such as CAMELOT, NICOLE, and ACTION, have demonstrated decreased hospitalization and revascularization procedures associated with several long-acting CCBs.

Many large trials including ALLHAT, CAMELOT, VALUE, INVEST, CONVINCE, and ASCOT-BPLA have demonstrated that CCBs have beneficial effects on composite cardiovascular outcomes or individual clinical outcomes; however, most of the trials only demonstrate equivalence to the comparator antihypertensives rather than superiority.

## *References*


[1] Norvasc [package insert]. New York, NY; Pfizer; August 2006.
[2] American Heart Association. Heart Disease and Stroke Statistics – 2008 Update. Dallas, Texas: American Heart Association; 2008. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1200026. Accessed October 5, 2008.
[3] American Diabetes Association. Hypertension management in adults with diabetes. Diabetes Care. 2004; 27:S65-S67.
[4] National Kidney Foundation Guidelines. K/DOQI clinical practice guideline on hypertension and antihypertensive agents in chronic kidney disease: Kidney Disease Outcome Quality Initiative. Am J Kidney Dis. 2004; 43(suppl 1):S16-S33. Available at: http://www.kidney.org/professionals/KDOQI/. Accessed October 5, 2008.
[5] American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2008; 31 (suppl 1):S5-S11. Available at: http://care.diabetesjournals.org/content/vol31/Supplement_1/. Accessed October 5, 2008.
[6] Chobanian AV, Bakris GL, Black HR and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. JAMA. 2003; 289:2560-2572.
[7] Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association council for high blood pressure research and the councils on clinical cardiology and epidemiology and prevention. Circulation 2007; 115(21):2761-2788.
[8] Mancia G, De Backer G, Dominiczak A, 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). Eur Heart J. 2007; 28(12):1462-1536.
[9] Turnball F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of random trials. Arch Intern Med. 2005; 165(12):1410-1419.
[10] Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. J Hypertens. 2003; 21(6):1055-1076.
[11] Chobanian AV, Bakris GL, Black HR and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. JAMA. 2003; 289:2560-2572.
[12] American Diabetes Association. Standards of Medical Care for Diabetes – 2008.. Diabetes Care. 2008; 31:S12-S54. Available at: http://care.diabetesjournals.org/cgi/content/full/31/Supplement_1/S12#SEC6. Accessed on October 7, 2008.
[13] Nissen SE, Tuzcu M, Libby P, et al. 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; 292(18):2217-2226.

[14] Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet. 2004; 364(9437):849-57.
[15] Dens JA, Desmet WJ, Coussement P, et al. Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. Heart. 2003; 89(8):887-92.
[16] Kizer JR, Kimmel SE. Epidemiologic review of the calcium channel blocker drugs. An up-to-date perspective on the proposed hazards. Arch Intern Med. 2001; 161(21):1145-1158.
[17] Staessen JA, Fagard R, Thijs L, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350:757-764.
[18] Staessen JA, Fagard R, Thijs L, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350:757-764.
[19] Hansson L, Lindholm LH, Ekborn T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999; 354:1751-1756.
[20] Hansson L, Hedner T, Lund-Johansen P, et al for the NORDIL Study Group. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000; 356(9227): 359-65.
[21] Pahor M, Psaty BM, Alderman MH, et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. Lancet 2000. 356(9246):1949-1954.
[22] Neal B, MacMahon S, Chapman N. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium channel antagonists, and other blood pressure lowering drugs: results of prospectively designed overviews of randomised trials. Lancet 2000; 356(9246):1955-1964.
[23] Wright JT, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2008; 168(2):207-217.
[24] Black HR, Davis B, Barzilay J, et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Diabetes Care 2008; 31(2):353-360.
[25] Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation 2006; 113(18):2201-2210.
[26] The ALLHAT Officers and Coordinators for the 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; 288:2981-2997.
[27] Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004; 363(9426):2022-31.
[28] Pepine CJ, Handberg EM, Cooper-De Hoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003; 290(21):2805-16.
[29] Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA. 2003; 289(16):2073-82.
[30] 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; 292(18):2217-25.
[31] Dahlof B, Sever PS, Poulter NR, et al for the ASCOT Investigators. 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 randomised controlled trial. Lancet. 2005; 366:895-906.
[32] Mahmud A, Feely J. Low-dose quadruple antihypertensive combination: more efficacious than individual agents-a preliminary report. Hypertension. 2007; 49(2):272-275.
[33] Kjeldsen SE, Julius S, Mancia G, et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertension. 2006; 24(7):1405-1412.
[34] Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. J Hypertension. 2006; 24(11):2163-2168.
[35] Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). 2002. Available at http://www.acc.org/qualityandscience/clinical/guidelines/stable/stable_clean.pdf. Accessed October 5, 2008.
[36] Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with 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. J Am Coll Cardiol. 2007; 50(23):2264-2772. Available at http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.187930 Accessed October 6, 2008.
[37] Grossman E, Messerli FH. Calcium antagonists. Prog Cardiovasc Dis. 2004; 47(1):34-57.
[38] Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. Am J Med. 2004; 116(1):35-43.
[39] DRUGDEX® System [Internet databse]. Greenwood, Colo: Thompson Micromedex. Updated periodically.
[40] Norvasc [package insert]. New York, NY; Pfizer; September 2005.
[41] Amlodipine [package insert]. Peapack NJ; Greenstone; April 2007.
[42] Plendil [package insert]. Wilmington, DE; AstraZeneca; November 2003.
[43] Dynacirc CR [package insert]. Liberty Corner, NJ; Reliant Pharmaceuticals; August 2005.
[44] Cardene [package insert]. Nutley, NJ; Roche Pharmaceuticals; September1999.
[45] Cardene SR [package insert]. Nutley, NJ; Roche Pharmaceuticals, January 2007.

[46] Procardia [package insert]. New York, NY; Pfizer, September 2000.
[47] Procardia XL [package insert]. New York, NY; Pfizer; August 2003.
[48] Nimotop [package insert]. West Haven, CT; Bayer Corporation; December 2005.
[49] Sular [package insert]. Alpharetta, GA; First Horizon Pharmaceutical Corp; January 2008.
[50] http://clinicalpharmacology.com. Accessed October 6, 2008.
[51] Cardizem LA [package insert]. Bridgewater, NJ; Biovail; April 2006.
[52] Cardizem CD [package insert]. Bridgewater, NJ; Biovail; August 2001.
[53] Verelan PM [package insert]. Milwaukee, WI; Schwarz Pharma; March 2003.
[54] Covera-HS [package insert]. New York, NY; Pfizer; May 2004.
[55] Cooke-Ariel, H. Circadian variations in cardiovascular function and their relation to the occurrence and timing of cardiac events. Am J Health-Syst Pharm. 1998; 55(Suppl 3):S5-11.
[56] Grossman E, Messerli FH, Grodzicki T, et al. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA. 1996; 276:1328-31.
[57] Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation. 1995; 92:1326-31.
[58] Norvasc [package insert]. New York, NY; Pfizer; August 2006.
[59] Plendil [package insert]. Wilmington, DE; AstraZeneca; November 2003.
[60] Dynacirc CR [package insert]. Liberty Corner, NJ; Reliant Pharmaceuticals; April 2005.
[61] Dynacirc CR [package insert]. Liberty Corner, NJ; Reliant Pharmaceuticals; August 2005.
[62] Cardene [package insert]. Nutley, NJ; Roche Pharmaceuticals; September 1999.
[63] Cardene SR [package insert]. Nutley, NJ; Roche Pharmaceuticals; January 2007.
[64] Procardia [package insert]. New York, NY; Pfizer, September 2000.
[65] Procardia XL [package insert]. New York, NY; Pfizer; August 2003.
[66] Nimotop [package insert]. West Haven, CT; Bayer; December 2005.
[67] Sular [package insert]. Alpharetta, GA; First Horizon Pharmaceutical Corp; January 2008.
[68] Cardizem LA [package insert]. Bridgewater, NJ; Biovail; September 2007.
[69] Cardizem CD [package insert]. Bridgewater, NJ; Biovail; August 2001.
[70] Covera-HS [package insert]. New York, NY; Pfizer; May 2004.
[71] Verelan PM [package insert]. Milwaukee, WI; Schwarz; March 2003.
[72] Flynn JT, Newburger JW, Daniels SR, et al for the PATH-1 Investigators. A randomized, placebo-controlled trial of amlodipine in children with hypertension. J Pediatr. 2004; 145(3):353-9.
[73] Mounier-Vehier C, Jaboureck O, Emeriau JP, et al. Randomized, comparative, double-blind study of amlodipine vs. nicardipine as a treatment of isolated systolic hypertension in the elderly. Fundam Clin Pharmacol. 2002; 16(6):537-44.
[74] Pepine CJ, Cooper-De Hoff RM, Weiss RJ, et al. 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.
[75] White WB, Saunders E, Noveck RJ, et al. 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):739-45.
[76] Wright JT Jr, Sica DA, Gana TJ, et al. Antihypertensive efficacy of night-time graded-release diltiazem versus morning amlodipine in African Americans. Am J Hypertens. 2004; 17(9):734-42.
[77] Schaefer RM, Aldons PM, Burgess ED, et al. Improved tolerability of felodipine compared with amlodipine in elderly hypertensives: a randomised, double-blind study in 535 patients, focusing on vasodilatory adverse events. The International Study Group. Int J Clin Pract. 1998; 52(6):381-6.
[78] Hoglund C, Hutchinson HG. A comparison of nisoldipine coat-core and felodipine in the treatment of mild to moderate hypertension. Int J Clinical Practice. 1998; 52:221-225.
[79] Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet. 2004; 364(9437):849-57.
[80] Zidek W, Spiecker C, Knaup G, et al. Comparison of the efficacy and safety of nifedipine coat-core versus amlodipine in the treatment of patients with mild-to-moderate essential hypertension. Hypertension Study Group. Clin Ther. 1995; 17:686-700.
[81] Dens JA, Desmet WJ, Coussement P, et al. Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. Heart. 2003; 89(8):887-92.
[82] White WB, Black HR, Weber MA, et al. Comparison of effects of controlled onset extended release verapamil at bedtime and nifedipine gastrointestinal therapeutic system on arising on early morning blood pressure, heart rate, and the heart rate-blood pressure product. Am J Cardiol. 1998; 81:424-431.
[83] Smith DH, Neutel JM, Weber MA. A new chronotherapeutic oral drug absorption system for verapamil optimizes blood pressure control in the morning. Am J Hypertens. 2001; 14:14-19.
[84] Angeli F, Verdecchia P, Reboldi GP, et al. Calcium channel blockade to prevent stroke in hypertension: a meta-analysis of 13 studies with 103,793 subjects. Am J Hypertens. 2004; 17(9):817-22.