The findings from early studies of short- and intermediate-acting CCBs in atherosclerosis indicated that an intrinsically long-acting agent might have better outcomes in this patient population. Amlodipine is a third-generation, long-acting dihydropyridine (DHP) calcium antagonist that has a mode of action and pharmacodynamic profile comparable to conventional compounds in this class. However, amlodipine's physicochemical properties are distinctive. At a physiologic pH of 7.4, the drug is present predominantly in the ionized form (it is positively charged). This ionized state of amlodipine may affect the accessibility of the calcium channel receptor to the drug. Furthermore, because of the charge, the rate of association/dissociation of amlodipine to its binding sites appears to be much slower, creating an intrinsically long-acting agent.

The theoretical receptor-binding mechanism for amlodipine is modeled in this slide. The slow onset of action and long duration of activity seen with amlodipine can be attributed to specific physicochemical interactions with the target cell membrane.

The charged, lipophilic amlodipine molecule partitions into the lipid matrix of the membrane where its positively charged amino group interacts with oppositely charged phospholipid headgroups. This electrostatic interaction enables the molecule to remain in the membrane and move gradually toward its target binding site on the calcium channel. In addition to a gradual onset, channel blocking by amlodipine persists as the drug remains in the lipid environment of its receptor for an extended period of time.

These physicochemical properties are thought to be responsible for amlodipine's ability to lower blood pressure gradually. The slow rate of dissociation from binding sites is thought to be responsible for its intrinsically long duration of action.

Amlodipine’s affinity for cellular membranes has been demonstrated in in vitro studies. As shown here, the membrane-based partition coefficients (a measurement of drug-membrane affinity) for several calcium channel blocking agents were compared under atherosclerotic-like conditions of elevated membrane cholesterol. Under atherosclerotic conditions, amlodipine had a greater affinity for binding to the cellular membranes than did isradipine, nimodipine, verapamil, or diltiazem.

The Treatment of Mild Hypertension Study (TOMHS) was a double-blind, placebo-controlled, randomized comparison of 6 treatments for long-term therapy in 902 patients with mild hypertension, defined as DBP between 90 and 99 mm Hg. All patients received counseling for dietary and behavioral modification and were randomized to NORVASC, enalapril, chlorthalidone, doxazosin, acebutolol, or placebo. Patients who received NORVASC 5 to 10 mg/day over the 4 years of the study (n=114) had a mean reduction of 12.2 mm Hg from baseline. Patients in the enalapril, chlorthalidone, doxazosin, and acebutolol groups experienced mean reductions of 9.7 mm Hg, 11.1 mm Hg, 11.2 mm Hg, and 11.5 mm Hg, respectively. Those in the placebo group had a mean reduction of 8.6 mm Hg.

For all groups, patients were considered controlled if the DBP was <90 mm Hg. *P = .01 for amlodipine, chlorthalidone, and doxazosin vs placebo.

*P = NS for enalapril vs placebo.

The antianginal efficacy of amlopidine in CAD is also well established. The effects of amlopidine on maximal exercise time and time to angina onset were compared with those of placebo in a parallel, randomized, double-blind, dose-response study of 134 patients with chronic stable exertional angina. Patients were maintained on β-blockers for at least 4 weeks before entering the study. After a 2-week, single-blind, run-in period of uninterrupted β-blocker treatment, patients were randomized to receive amlopidine (2.5 mg, 5 mg, or 10 mg/day) or placebo for 4 weeks. The results shown are for the 5-mg and 10-mg treatment groups (n=64) and the placebo controls (n=34). When symptom-limited exercise time was assessed, patients receiving 5 mg/day or 10 mg/day of amlopidine (n=64) experienced a mean increase of 35.8 ± 8.3 seconds from baseline, whereas those in the placebo group had a mean decrease of 0.6 ± 8.1 seconds (P < .007). Time to angina onset increased by a mean of 48.0 ± 12.2 seconds in patients receiving 10 mg/day of amlopidine compared with a mean of 19.2 ± 16.1 seconds for the placebo controls (P < .007).


Data on file. Pfizer Inc.
Amlodipine differs structurally from the other agents of its class by the presence of a side chain that contains a basic amino group. This group is positively charged at physiologic pH. The side chain contributes to the agent’s unique kinetics and clinical effects. It may also contribute to other mechanisms of action.

Earlier trials with CCBs provided preliminary evidence of the potential benefit of their use in the treatment of atherosclerosis. However, the properties of amlodipine that distinguish it from other CCBs raised the possibility that amlodipine might have a greater effect on atherosclerosis and clinical outcomes.


In in vitro studies, amlodipine has been shown to be a potent antioxidant, inhibiting the oxidation of lipids. The membrane antioxidative effects of amlodipine were examined and compared with other CCBs (felodipine, verapamil, diltiazem) and a sulfhydryl-containing angiotensin-converting enzyme (ACE) inhibitor, captopril, in isolated membrane vesicles that were enriched with polyunsaturated fatty acids. Captopril was included because of its demonstrated ability to exert antioxidative effects in certain cellular systems. This study was performed by Mason and colleagues specifically to evaluate the ability of amlodipine to inhibit lipid oxidation in cell membranes that contained no calcium channels.

The antioxidative properties of amlodipine were compared with those of the other agents by measuring the oxidation of phospholipids in the cell membrane into lipid peroxide (LOOH) by means of the cholesterol oxidase (CHOD)-iodide assay. Multiple measurements of control and drug-containing membrane samples were taken.

As seen in this slide, amlodipine had very potent membrane antioxidant activity. This antioxidant activity was completely independent of calcium channel blockade, and therefore may represent a newly discovered mechanism of action in the treatment of cardiovascular disease, including atherosclerosis.

Another potentially important, newly discovered mechanism of action of amlodipine that has been demonstrated in vitro is its ability to inhibit apoptosis, a form of programmed cell death. Amlodipine inhibited apoptosis of endothelial cells induced by tumor necrosis factor (TNF-α) in a dose-dependent manner.

Data on file. Pfizer Inc.
Other in vitro actions of amlodipine may support an antiatherosclerotic effect of the drug. With the addition of amlodipine to smooth muscle cell (SMC) plasma membrane preparations from atherosclerotic animals, the membrane width was reduced to that seen in nonatherosclerotic or normal membrane preparations. This membrane-stabilizing property of amlodipine has been attributed to the agent’s charged chemical structure and high affinity for the membrane. This effect on the membrane lipid bilayer may underlie amlodipine’s inhibitory effects on SMC proliferation, a key mechanism in atherogenesis.

In addition, results of in vitro and in vivo studies have shown that amlodipine inhibits SMC proliferation at concentrations significantly below those necessary for calcium channel blockade. These observations suggested a mechanism of action independent of calcium channel modulation.

Nitric oxide (NO) has also been shown to be involved in the atherosclerotic process. Zhang et al. found, using a preparation of normal small arteries and aortas from animals, that amlodipine caused a dose-dependent increase in NO production. The increase was similar in magnitude to that seen with the ACE inhibitor enalapril, but was in marked contrast to the results of studies with the CCBs diltiazem and nifedipine, neither of which increased nitrate production at any dose studied. Further studies will clarify the mechanism of action as well as the clinical implications of NO release.


Because the long-acting DHP CCB amlodipine has in vitro effects that are potentially antiatherosclerotic and has been shown to decrease the rate of atherosclerosis in a primate model, it was decided to undertake a study to investigate the effects of amlodipine on atherosclerosis in patients with symptomatic CAD. The Prospective Randomized Evaluation of the Vascular Effects of NORVASC Trial (PREVENT) was undertaken to assess the ability of amlodipine to slow the progression of early atherosclerosis in patients with CAD. This was a randomized, double-blinded study of amlodipine besylate 10 mg versus usual care (whatever medications or procedures were deemed necessary by the treating physician). The study randomized 825 patients to the treatment arms. Follow-up was 3 years. The primary outcome measure was change in progression of early atherosclerotic segments by QCA baseline and final visit. Other prospectively defined outcomes were: change in other atherosclerotic segments measured by QCA baseline and final visit, carotid atherosclerosis by B-mode carotid ultrasound, every 6 months, and clinical events.

PREVENT was designed to examine the impact of amlodipine in patients with established CAD. PREVENT was a multicenter (16 centers in the United States and Canada), randomized, placebo-controlled, double-blinded clinical trial that enrolled 825 patients with predefined angiographic evidence of CAD. Patients eligible for PREVENT underwent initial QCA. This was followed by a single-blind placebo washout screening period of 1 to 3 months. Prior to administration of the first dose of placebo, patients underwent a medical and laboratory evaluation and at selected centers were evaluated by B-mode carotid artery ultrasound and assessment of carotid arterial compliance. Patients were then randomized to placebo or to amlodipine. Amlodipine was started at 5 mg/day and the dose was raised to 10 mg over the course of a 4-week dose titration and stabilization period. B-mode ultrasound studies were conducted every 6 months over the 3 years of the study. A second QCA exam was conducted at the end of the 36-month study.


Patients aged 30-80 years with ejection fraction (EF) ≥40% were eligible for inclusion. To randomize 825 participants, 2221 angiographic films were verified for qualification and 85% (1893) were confirmed as being eligible for the trial. On QCA, eligible patients had at least 1 segment with 5% to 20% occlusion in a native vessel without MI, a focal lesion of 30% or greater occlusion in 1 segment, or less than 50% stenosis of the left main coronary artery. Of the patients with eligible films, 825 were randomized.

Patients with a previous or planned cardiac transplantation were excluded, as were those with clinically significant valvular heart disease. Patients with a history of coronary artery bypass graft (CABG) were admitted to the study, but patients for whom a CABG or percutaneous transluminal coronary angioplasty (PTCA) was planned after randomization were excluded. Also excluded were patients unable to discontinue other CCBs or ACE inhibitors (these agents strongly discouraged during study), patients with insulin-dependent diabetes mellitus or diabetes uncontrolled on oral hypoglycemics; patients with DBP >95 mm Hg; and patients with total cholesterol ≥325 mg/dL on 2 occasions.

Data on file. Pfizer Inc.


The primary outcome measure of PREVENT was the 36-month change in the mean minimal diameter of early atherosclerotic segments measured by QCA. “Early atherosclerotic segments” were operationally defined as coronary segments with a stenosis diameter of ≤30% at baseline.

Five additional analyses tested whether amlodipine reduced the rate of coronary disease progression as measured by the change in mean minimal diameter. A sixth secondary hypothesis addressed whether amlodipine reduced the rate of progression of atherosclerosis in the carotid arteries as assessed by B-mode ultrasonography. Progression was assessed by measurement of the mean maximal IMT at 12 sites. Because this outcome required fewer participants (n = 377) than the angiographic measures, this part of the trial was conducted in a subset of trial subjects.


PREVENT had several predefined clinical outcomes. They were:

I. All-cause mortality

II. Major vascular events, individually and combined
   - Fatal/nonfatal MI
   - Fatal/nonfatal stroke
   - Other fatal vascular events, including sudden death

III. Other documented nonfatal vascular events
   - Hospitalization for congestive heart failure
   - Hospitalization for unstable angina

IV. Major coronary procedures
   - CABG
   - Percutaneous coronary intervention (PTCA, PTCA with stent, atherectomies)

V. Any major documented vascular event/procedure (II, III, and IV combined)

The baseline characteristics of the patients enrolled in PREVENT are shown on the next 2 slides. There were no clinically significant differences between the 2 treatment groups with respect to any baseline characteristics. As shown here, this was a typical CAD population. Blood pressure at baseline was 129/79 mm Hg with no differences between the 2 groups. Almost half of patients had a history of MI; two thirds had a history of angina.

Shown here are the medication use and coronary anatomy of the 2 treatment groups at baseline. There were no clinically significant differences between the 2 groups. As shown, one third were on CCBs; 60% to 65% were receiving β-blockers. The study protocol stipulated that antihypertensive treatment with CCBs or ACE inhibitors be terminated during the washout period. One quarter of patients were on lipid-lowering treatments, although statin use increased over the term of the trial to approximately 50%.

Forty-two percent of patients had a PTCA associated with the qualifying angiogram. Coronary anatomy included: 45% with 1-vessel disease; 35% with 2-vessel disease; 21% with involvement of 3 or more coronary vessels.
Quantitative Coronary Angiography (QCA)

QCA, a technique that is widely used to assess changes in the extent and severity of coronary atherosclerosis, was used to measure the primary endpoint in PREVENT. The technique digitizes and displays the chosen cineframe on a video monitor. The image is calibrated using the known size of the cardiac catheter, and correction is made for pincushion distortion. The region of interest is magnified and the technician selects preliminary centerline points in the arterial segment. An automatic edge-detection program determines the arterial contours and the arterial diameter is displayed over the length of the segment, as shown on this slide. To calculate diameter stenosis, the reference diameter can be measured in a normal location in the artery selected by the operator, or can be calculated by the computer. This arteriogram shows quantitative analysis of a right coronary artery in the LAO view. The graph plots the diameter function (vertical axis) along the length of the artery (horizontal axis). The lower curve represents the area function calculated by videodensitometry. The area shaded white around the stenosis represents plaque area.

The primary quantitative angiographic endpoint in PREVENT was the change in angiographic MLD from baseline to study end at 3 years in early atherosclerotic segments that had ≤30% stenosis. As shown here, the amlodipine and placebo groups had nearly identical average reductions in MLD over the course of the study. There was no significant difference between the treatment groups with regard to the primary endpoint. Furthermore, additional analyses of coronary segments with obstruction at baseline, >30% to ≤50%, >50%, and all segments showed no significant difference between treatment groups.

PREVENT also used B-mode ultrasound, a common methodology for studying IMT, an indicator of atherosclerotic changes in the carotid arteries. This technique yields information about atherosclerotic wall changes that cannot be obtained by conventional contrast angiography. Measurements of the combined thickness of the carotid intima and media are currently used as an outcome in clinical trials. In PREVENT, ultrasonographic measurements of the maximum IMT were obtained from the near and far walls of 3 carotid artery segments of each carotid to determine the extent and severity of atherosclerosis. The outcome measure was the mean of 12 maximum IMT measurements.


The PREVENT B-mode ultrasound measurements were conducted in a prespecified subgroup of 373 patients.

In contrast to the findings from QCA in the coronary arteries, B-mode ultrasound measures of carotid IMT showed that in patients with documented heart disease, long-term therapy with amlodipine significantly retarded the progression of atherosclerosis compared with placebo. Measurements across 12 segments were obtained twice at baseline, at the end of 4-week titration, and at months 6, 12, 24, 30, and 36 (final visit). Amlodipine patients had a .013-mm reduction in IMT over 3 years of follow-up, whereas placebo subjects had a .033-mm increase ($P = .007$ between groups).

In PREVENT, treatment with amlodipine was associated with significant reductions in clinical outcomes at 3 years for patients with documented heart disease. Long-term treatment with amlodipine resulted in a 35% reduction in hospitalizations for unstable angina and CHF (P = .01) compared with placebo. Major vascular procedures, including CABG and PTCA, were reduced by 43% in amlodipine-treated patients compared with placebo controls (P = .001). The curves separated early and the treatment effect continued with time.

By 36 months, treatment with amlodipine resulted in a 31% reduction in the composite endpoint of any major cardiovascular event or procedure ($P = .01$), which was driven largely by a significant 33% reduction in hospitalizations because of unstable angina compared with the placebo group, and a significant 43% reduction in PTCA/CABG compared with placebo. The treatment effect was manifested early by separation of the curves, shown here, that continued over time. The composite endpoint included hospitalization for congestive heart failure, hospitalization for unstable angina, CABG/PTCA, fatal or nonfatal MI or stroke, and other fatal vascular events.

In PREVENT, amlodipine treatment had a salutary effect on several important clinical endpoint measures. A significant reduction occurred in any major event/procedure (P = .01) in amlodipine versus placebo patients; and significant reductions occurred in documented nonfatal vascular events (P = .01) and in major vascular procedures (P = .001) with amlodipine treatment. Important drivers of these endpoints were a 33% reduction in hospitalizations for unstable angina in patients treated with amlodipine compared with placebo and a 44% reduction in non-CABG vascular procedures in the amlodipine group. Amlodipine had no effect on all-cause mortality or major cardiovascular events (MI and strokes). However, the statistical power for detecting a treatment difference in mortality and major morbidity was low because of the relatively low incidence rates (eg, <2% per year for MI or death).

Treatment with amlodipine besylate was well tolerated throughout the 3-year trial. The frequency and types of adverse events were comparable in the active treatment and placebo groups. Edema and dizziness were observed more frequently in the amlodipine-treated patients, whereas coughing and hypertension occurred more often in the placebo controls.

In the PREVENT economic analysis, investigators examined whether amlodipine treatment could reduce the direct cost of inpatient care associated with treatment of cardiovascular disease in patients with angiographic evidence of CAD. Unit costs for clinical events were assigned in dollar values based on the Healthcare Cost Utilization Project (HCUP-3); charges were adjusted to 1997 dollars. The annual cost of amlodipine per patient (10 mg/day) was based on the 1997 Red Book.™

The net number of clinical events averted was 27.9 per 100 patients in the amlodipine group over 3 years. The total net savings associated with the averted events was estimated at $426,462, and the net savings of inpatient care in amlodipine-treated patients relative to the placebo group averaged at $628 per patient per year. Amlodipine was cost saving relative to placebo in this 3-year study. Use of amlodipine could be expected to reduce costs of inpatient care in patients with clinical CAD.

Another recently published clinical trial corroborating the results of PREVENT was completed by Jørgensen et al. The Coronary Angioplasty Amlodipine Restenosis Study, or CAPARES, was a placebo-controlled, double-blind, randomized, multicenter study that evaluated the effect of pretreatment with amlodipine 10 mg daily or placebo on restenosis and clinical outcomes in post-PTCA patients. Patients were randomized to receive either amlodipine or placebo beginning 2 weeks prior to PTCA. Effects of therapy were then assessed 4 months after the procedure. The change in MLD, as assessed by QCA at 4 months postprocedure, served as the primary angiographic endpoint. The primary clinical endpoint was a composite of death, MI, CABG, or repeat PTCA.

Evolving Paradigms in the Development, Prevention, and Treatment of Atherosclerosis

PREVENT and the Role of NORVASC

The need for repeat PTCA and the rate of composite major clinical endpoints were reduced by amlodipine therapy, despite an apparent absence of effect on restenosis as measured by QCA.

The effects of amlodipine, an intrinsically long-acting dihydropyridine CCB, have been studied in CAD in 2 clinical trials: PREVENT and CAPARES. These trials evaluated the effect of amlodipine on atherosclerosis as measured by QCA (PREVENT and CAPARES) and carotid B-mode ultrasound (PREVENT) and on clinical events (PREVENT and CAPARES). Neither trial documented an effect on lesion progression/regression or restenosis by QCA. However, this may be due to the insensitivity of QCA for measuring change in early arterial disease. In PREVENT, amlodipine treatment was associated with an attenuation of carotid atherosclerosis as measured by B-mode ultrasound. In both trials, clinical events were reduced: revascularizations and, in PREVENT, documented hospitalizations for unstable angina, as well as a combined endpoint reduction in CAPARES and PREVENT.

These 2 trials raise unanswered questions for future investigation. Future trials should further characterize the effect of amlodipine on atherosclerotic lesions and clinical events, should identify the relation between blood pressure changes and CAD progression, and should correlate progression/regression of lesions with clinical events. The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) and NORVASC for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation (NORMALISE) studies have been undertaken to address these questions.
The CAMELOT study is assessing the effects of the CCB amlodipine versus the ACE inhibitor enalapril on atherosclerosis and clinical events in a prospective, double-blind, parallel trial of patients with CAD over 24 months.

After a single-blind, placebo run-in phase, patients meeting entry criteria will be randomized to treatment with amlodipine, enalapril, or usual care in the CAMELOT study. The initial dose of 5 mg/day of amlodipine will be increased to 10 mg/day over 1 month as tolerated. Similarly, the initial dose of 10 mg/day of enalapril will be increased to 20 mg/day over 1 month as tolerated. The CAMELOT trial will study 3000 patients for cardiovascular morbidity and mortality endpoints.

A CAMELOT substudy, NORMALISE, will assess treatment effects on atherosclerotic plaque in 750 patients from CAMELOT. Patients in this cohort will receive a qualifying coronary angiogram and an IVUS assessment at the placebo run-in phase and after completion of the 24-month treatment period.

Together, these studies will

- Evaluate the effectiveness of amlodipine in preventing clinical events in patients with CAD
- Assess the correlation between blood pressure and incidence of clinical events in patients with CAD
- Measure the effect of 24 months of treatment with amlodipine on the onset or progression of coronary artery plaque by means of IVUS
- Assess the correlation between blood pressure and onset or progression of existing coronary plaque

Data on file. Pfizer Inc.
The safety of NORVASC has been evaluated in more than 11,000 patients worldwide. In general, treatment was well tolerated at doses up to 10 mg/day; discontinuation due to adverse reactions was required in only about 1.5% of patients, a rate not significantly different from the rate of 1% seen with placebo.

NORVASC has an excellent safety profile, with no known drug interactions or contraindications, except known sensitivity to amlodipine. The agent does not have clinically significant effects on heart rate or cardiac conduction and has no adverse effect on renal function. In the Treatment of Mild Hypertension Study (TOMHS), which was sponsored by the US National Institutes of Health, the vast majority of patients remained controlled on NORVASC monotherapy, even after 4 years.

In clinical trials, N O R V A S C has proven efficacy for reducing blood pressure and controlling angina. W i t h N O R V A S C once daily, 4 out of 5 patients have been able to achieve and maintain a goal blood pressure, with excellent tolerability. I n T O M H S, for example, 83% of patients maintained antihypertensive control with N O R V A S C monotherapy after 4 years. N O R V A S C reduces blood pressure gently and gradually, maintaining antihypertensive effect throughout a full 24 hours with a minimum of side effects.

N O R V A S C provides excellent control of both chronic stable angina and vasospastic (Prinzmetal) angina, with no significant change in heart rate or cardiac conduction.

A newly demonstrated benefit of N O R V A S C in PREVENT is its efficacy for reducing the complications of CAD. I n PREVENT, N O R V A S C reduced the rate of major vascular procedures (C A B G, P T C A) by 43% and of hospitalizations for unstable angina and C H F by 35%.

O v e r a 3 6 - m o n t h treatment period, N O R V A S C significantly reduced the progression of carotid atherosclerosis (the presence of carotid plaque has been directly associated with the presence of CAD as measured by I M T).

W h e n t h e reductions in events and procedures seen in PREVENT were evaluated against the cost of treatment, N O R V A S C showed a net savings in C A D - d e r i v e d healthcare costs of $628 per patient per year (calculated in 1997 U S dollars). F r o m t h e cost analysis, t h e investigators concluded that N O R V A S C “appears to be a cost-saving agent in treatment of patients with angiographic evidence of coronary artery disease.”


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Data on file. Pfizer Inc.


