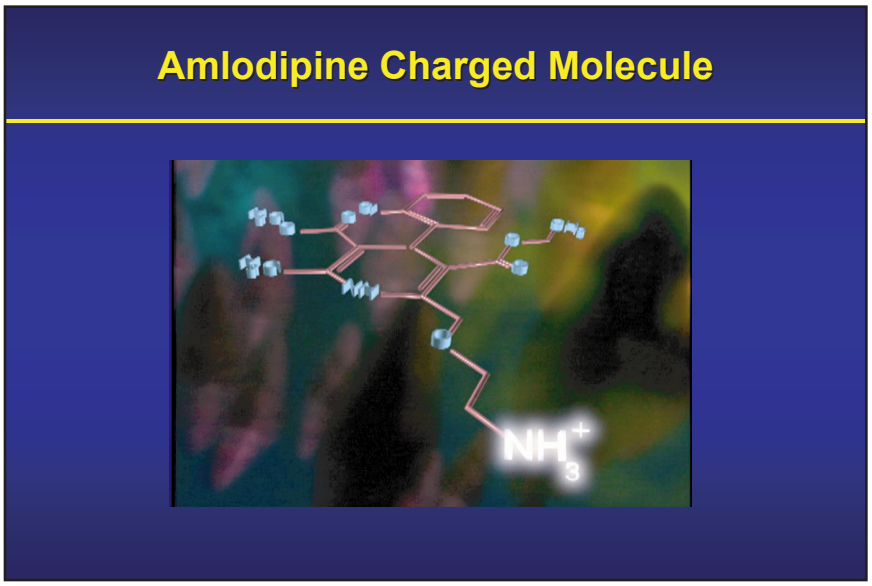
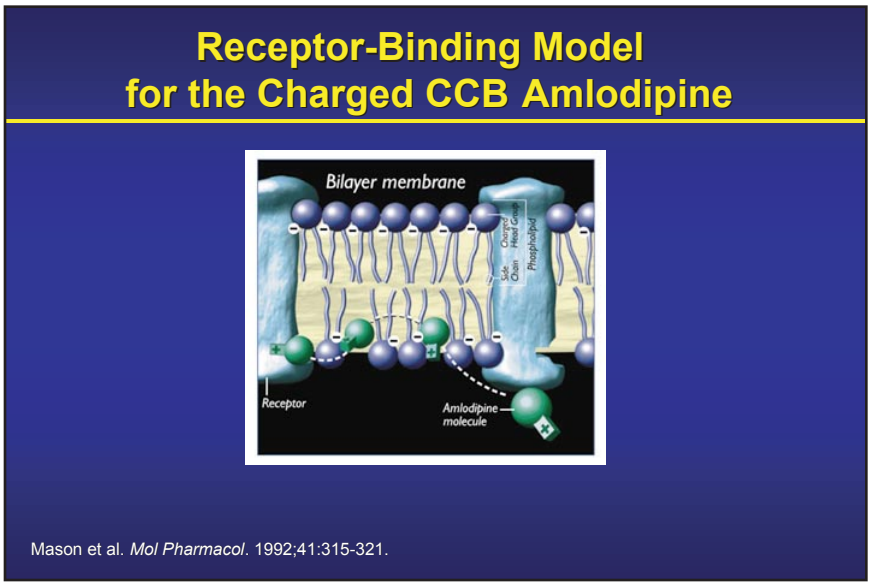


slide 30

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.

van Zwieten PA. Amlodipine: an overview of its pharmacodynamic and pharmacokinetic properties. *Clin Cardiol.* 1994; 17(suppl III):III-3-III-6.



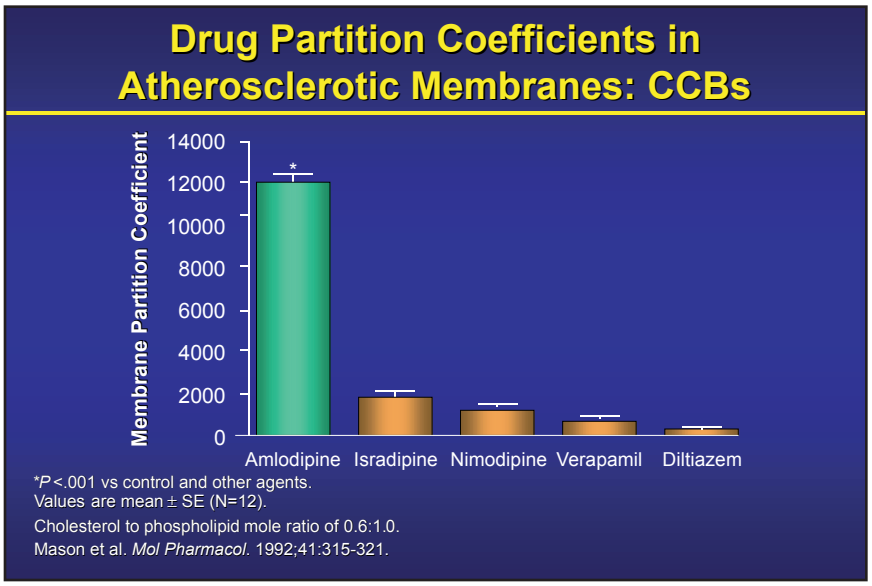
slide 31

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.

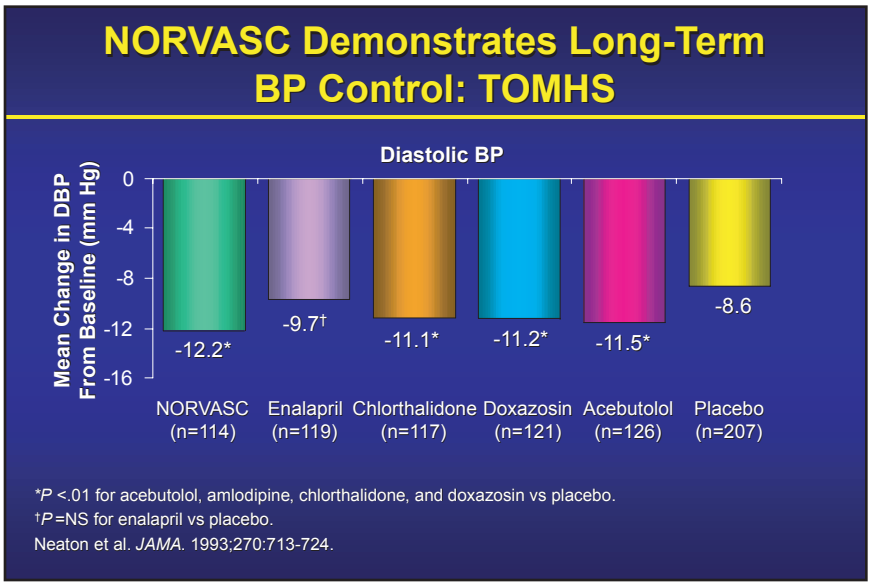
Mason RP, Moisey DM, Shajenko L. Cholesterol alters the binding of Ca^{2+} channel blockers to the membrane lipid bilayer. *Mol Pharmacol.* 1992;41:315-321.



slide 32

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.

Mason RP, Moisey DM, Shajenko L. Cholesterol alters the binding of Ca^{2+} channel blockers to the membrane lipid bilayer. *Mol Pharmacol.* 1992;41:315-321.

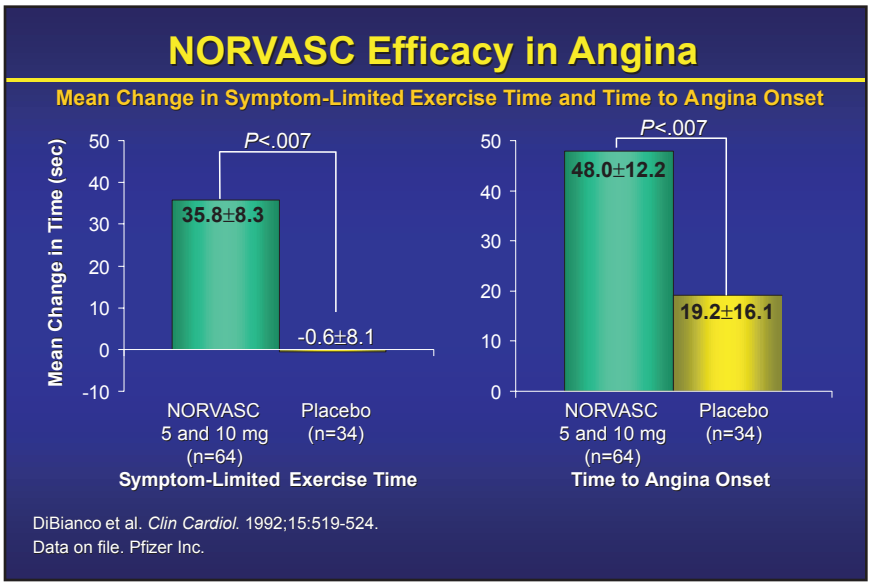


slide 33

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, doxazosin, chlorthalidone, 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, doxazosin, and acebutolol versus placebo; for enalapril, $P=$ NS versus placebo.

Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study Research Group. Treatment of Mild Hypertension Study: final results. *JAMA.* 1993;270:713-724.

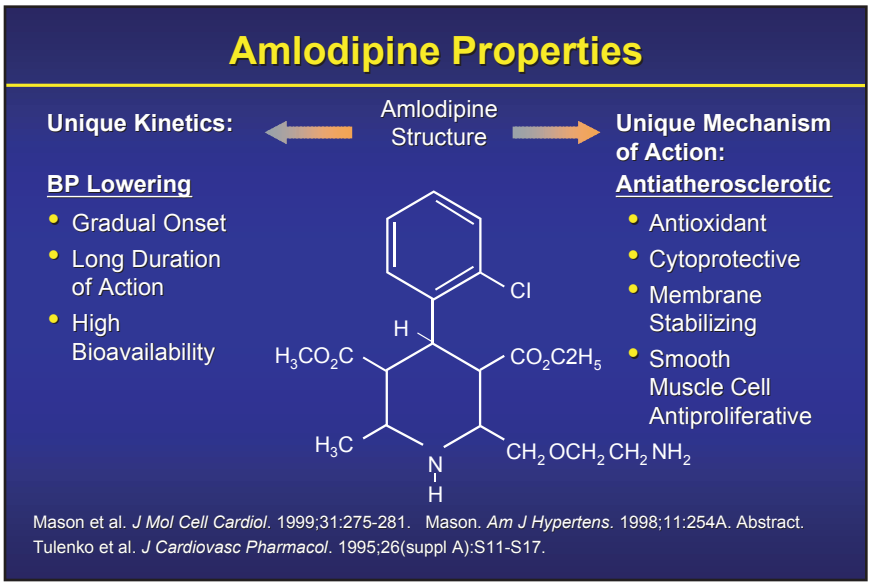


slide 34

The antianginal efficacy of amlodipine in CAD is also well established. The effects of amlodipine 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 amlodipine (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 amlodipine (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 amlodipine compared with a mean of 19.2 ± 16.1 seconds for the placebo controls ($P<.007$).

DiBianco R, Schoomaker FW, Singh JG, et al. Amlodipine combined with beta blockade for chronic angina: results of a multicenter, placebo-controlled, randomized double-blind study. *Clin Cardiol.* 1992;15:519-524.

Data on file. Pfizer Inc.



slide 35

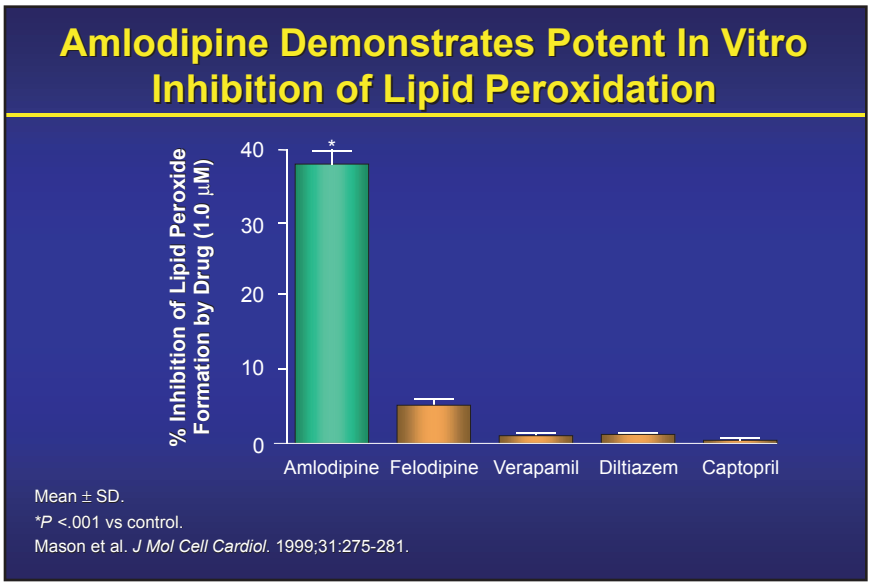
Amlodipine differs structurally from the other agents of its class by the presence of a side chain that contains a basic amino group. This group is positively charged at physiologic pH. The side chain contributes to the agent's unique kinetics and clinical effects. It may also contribute to other mechanisms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

Mason RP, Walter MF, Trumbore MW, Olmstead EG Jr, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J Mol Cell Cardiol.* 1999;31:275-281.

Mason RP. Cytoprotective properties of a long-acting calcium channel blocker: new mechanisms of action. *Am J Hypertens.* 1998;11:254A. Abstract.

Tulenko TN, Stepp DW, Chen M, Moisey D, Laury-Kleintop L, Mason RP. Actions of the charged dihydropyridine amlodipine in a cell culture model of dietary atherosclerosis. *J Cardiovasc Pharmacol.* 1995;26(suppl A):S11-S17.



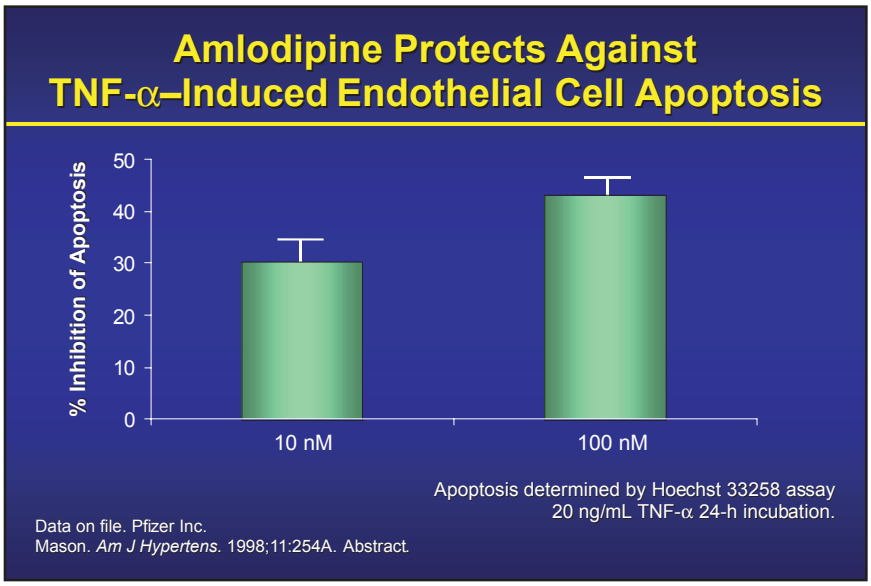
slide 36

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.

Mason RP, Walter MF, Trumbore MW, Olmstead EG Jr, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J Mol Cell Cardiol.* 1999;31:275-281.



slide 37

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.

Mason RP. Cytoprotective properties of a long-acting calcium channel blocker: new mechanisms of action. *Am J Hypertens.* 1998;11:254A. Abstract.

Amlodipine: Additional Mechanisms Under Investigation May Impact on Atherosclerosis

- Membrane-stabilizing effects
- Inhibition of smooth muscle cell migration/proliferation
- Increased nitric oxide production

Mason et al. *J Mol Cell Cardiol*. 1999;31:275-281.
Tulenko et al. *J Cardiovasc Pharmacol*. 1995;26(suppl A):S11-S17.
Zhang and Hintze. *Circulation*. 1998;97:576-580.

slide 38

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 nitrite production at any dose studied. Further studies will clarify the mechanism of action as well as the clinical implications of NO release.

Mason RP, Walter MF, Trumbore MW, Olmstead EG Jr, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J Mol Cell Cardiol*. 1999;31:275-281.

Tulenko TN, Stepp DW, Chen M, et al. Actions of the charged dihydropyridine amlodipine in a cell culture model of dietary atherosclerosis. *J Cardiovasc Pharmacol*. 1995;26(suppl A):S11-S17.

Zhang X, Hintze TH. Amlodipine releases nitric oxide from canine coronary microvessels: an unexpected mechanism of action of a calcium channel-blocking agent. *Circulation*. 1998;97:576-580.

PREVENT: Study Description

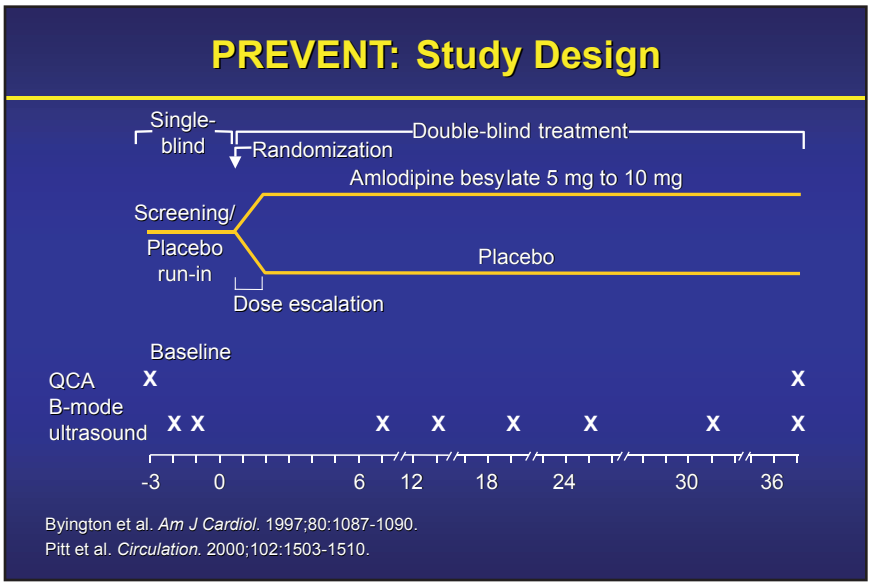
- Randomized, double-blind, placebo-controlled evaluation of amlodipine besylate 10 mg
- 825 patients with symptomatic CAD
  - Patients received "usual care" for their CAD*
- 3-year follow-up
- Prespecified outcome measures
  - Primary: progression of early atherosclerotic segments by QCA baseline and final visit
  - Progression of other atherosclerotic segments by QCA baseline and final visit
  - Carotid atherosclerosis by B-mode carotid ultrasound, every 6 months
  - Clinical events

* Whatever medications or procedures deemed necessary by the treating physician.
Byington et al. *Am J Cardiol.* 1997;80:1087-1090.

slide 39

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 qd 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 (≤30% stenosis at baseline) measured by QCA. Other prospectively defined outcomes were: change in other atherosclerotic segments measured by QCA; rate of progression of carotid atherosclerosis measured by B-mode ultrasound; and clinical events.

Byington RP, Miller ME, Herrington D, et al, for the PREVENT Investigators. Rationale, design, and baseline characteristics of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Am J Cardiol.* 1997;80: 1087-1090.



slide 40

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.

Byington RP, Miller ME, Herrington D, et al, for the PREVENT Investigators. Rationale, design, and baseline characteristics of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Am J Cardiol.* 1997;80:1087-1090.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.

PREVENT Inclusion/Exclusion Criteria

Inclusion

- Age 30-80 years; men; women with no childbearing potential
- EF ≥40%
- QCA documentation of qualifying coronary lesions defined as follows:
  - ≥1 segment with minimal lesion (5%-20% occlusion) in native vessel without MI
  - Focal lesion ≥30% in 1 segment
  - <50% stenosis of left main coronary artery
- Total cholesterol <325 mg/dL on 2 occasions

Exclusion

- Previous or planned cardiac transplantation
- CABG or PTCA planned after randomization (previous bypass eligible)
- Clinically significant valvular heart disease
- Patients unable to discontinue other CCBs or ACE inhibitors (these agents strongly discouraged during study)
- Insulin-dependent DM or uncontrolled DM on oral hypoglycemics
- Uncontrolled hypertension (DBP >95 mm Hg)

Data on file. Pfizer Inc.
Byington et al. *Am J Cardiol*. 1997;80:1087-1090.
Pitt et al. *Circulation*. 2000;102:1503-1510.

slide 41

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 previous MI, a focal lesion of 30% or greater occlusion in 1 segment, or less than 50% stenosis of the left main 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, those 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.

Byington RP, Miller ME, Herrington D, et al, for the PREVENT Investigators. Rationale, design, and baseline characteristics of the prospective randomized evaluation of the vascular effects of Norvasc trial (PREVENT). *Am J Cardiol*. 1997;80:1087-1090.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*. 2000;102:1503-1510.

PREVENT: Major Arterial Assessments

Primary

- 36-month change in mean minimal diameter (baseline diameter stenosis ≤30%) of coronary atherosclerotic segments, measured by QCA

Secondary

- QCA assessment of 36-month change in mean minimal diameter of
  - All segments combined
  - Segments with 0% diameter stenosis at baseline
  - Segments with >0% but ≤30% stenosis at baseline
  - Segments with >30% but ≤50% stenosis at baseline
  - Segments with >50% stenosis at baseline
- B-mode ultrasonographic assessment of 36-month change in rate of atherosclerosis progression (mean maximal IMT assessed at 12 sites) in carotid arteries

Byington et al. *Am J Cardiol.* 1997;80:1087-1090.
Pitt et al. *Circulation.* 2000;102:1503-1510.

slide 42

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.

Byington RP, Miller ME, Herrington D, et al, for the PREVENT Investigators. Rationale, design, and baseline characteristics of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Am J Cardiol.* 1997;80:1087-1090.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.

PREVENT: Predefined Major Clinical Outcomes

I. **All-cause mortality**
II. **Major vascular events**
  – 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)**

Byington et al. *Am J Cardiol.* 1997;80:1087-1090.

slide 43

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. Nonfatal vascular events requiring hospitalization, individually and combined

  –Hospitalization for congestive heart failure

  –Hospitalization for unstable angina

IV. Major coronary procedures, individually and combined

  –CABG

  –Percutaneous coronary interventions (PTCA, PTCA with stent, atherectomies)

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

Byington RP, Miller ME, Herrington D, et al, for the PREVENT Investigators. Rationale, design, and baseline characteristics of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Am J Cardiol.* 1997;80:1087-1090.

PREVENT: Baseline Patient Characteristics

	Amlodipine Besylate (n=417)	Placebo (n=408)	Overall (n=825)
Mean age (y)	56.8	57.0	56.9
% Women	20.1	19.6	19.9
% White	88.3	89.2	88.7
Mean lipid values (mg/dL)			
Total cholesterol	217	217	217
LDL-C	141	139	140
Mean blood pressure (mm Hg)	129/79	130/79	129/79
% Prior history			
MI	44.4	45.3	44.9
Stroke	3.1	2.9	3.0
Angina	67.9	69.4	68.6
Cigarette smoking (%)			
Current	22.8	26.7	24.7
Past	54.2	54.4	54.3

Pitt et al. *Circulation.* 2000;102:1503-1510.

slide 44

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.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.

PREVENT: Baseline Patient Characteristics (cont'd)

	Amlodipine Besylate (n=417)	Placebo (n=408)	Overall (n=825)
Medication use at screening (%)			
CCBs	33.1	34.6	33.8
ACE inhibitors	8.2	10.0	9.1
Diuretics	11.5	12.0	11.8
β-Blockers	60.0	65.7	62.8
Lipid-lowering agent	25.7	28.9	27.3
% with PTCA associated with qualifying angiogram	42.9	41.2	42.1
Clinic-defined angiographic disease (>30% stenosed vessel)			
% 1-vessel disease	44.9	44.8	44.0
% 2-vessel disease	34.6	34.5	34.5
% 3-or-more vessel disease	20.5	20.7	20.6

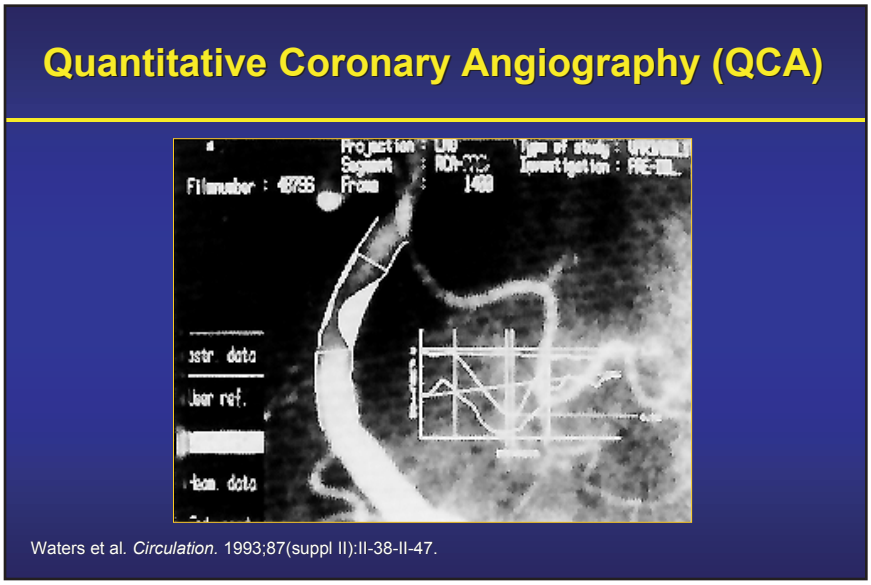
Pitt et al. *Circulation.* 2000;102:1503-1510.

slide 45

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.

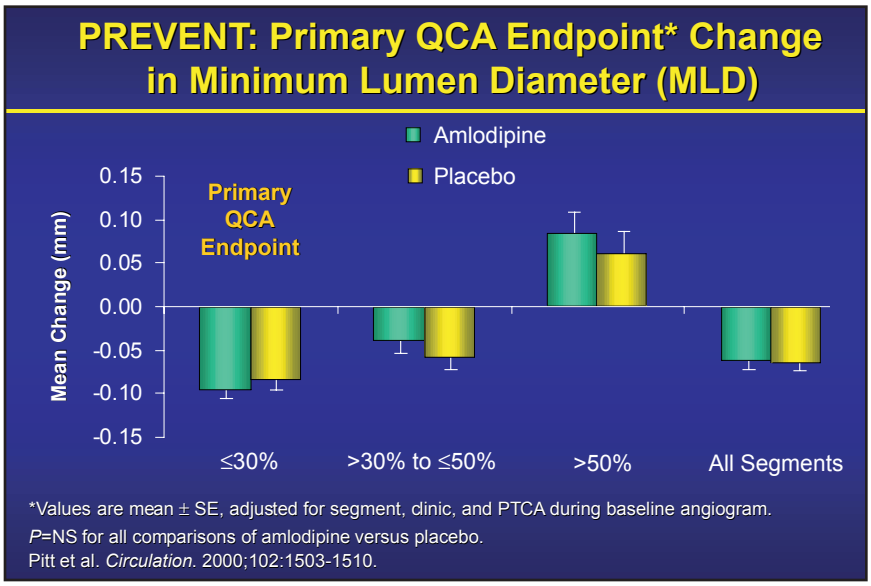
Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.



slide 46

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.

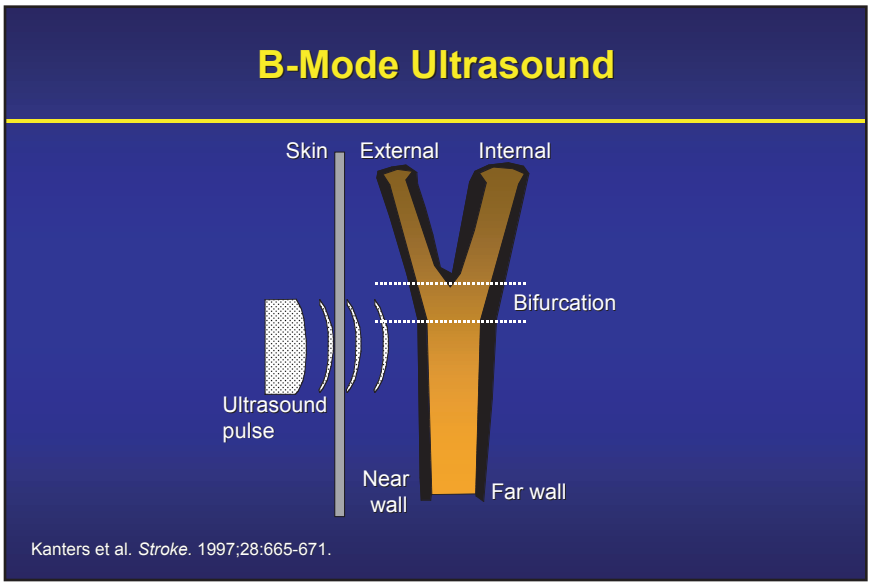
Waters D, Lesperance J, Craven TE, Hudon G, Gillam LD. Advantages and limitations of serial coronary arteriography for the assessment of progression and regression of coronary atherosclerosis: implications for clinical trials. *Circulation.* 1993;87(suppl II):II-38-II-47.



slide 47

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.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.

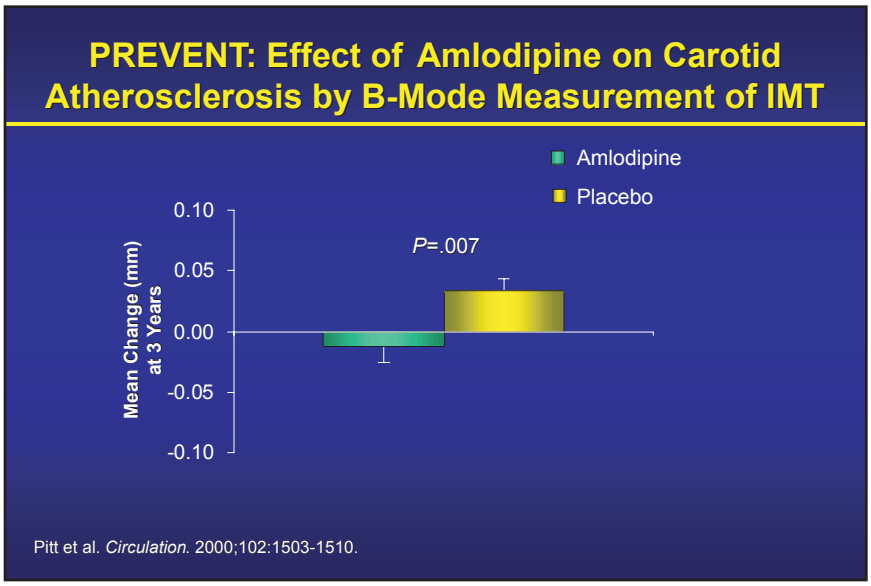


slide 48

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.

Kanters SDJM, Algra A, van Leeuwen MS, Banga J-D. Reproducibility of in vivo carotid intima-media thickness measurements: a review. *Stroke*. 1997;28:665-671.

Riley WA, Barnes RW, Applegate WB, et al. Reproducibility of noninvasive ultrasonic measurement of carotid atherosclerosis: the asymptomatic carotid artery plaque study. *Stroke*. 1992;23:1062-1068.

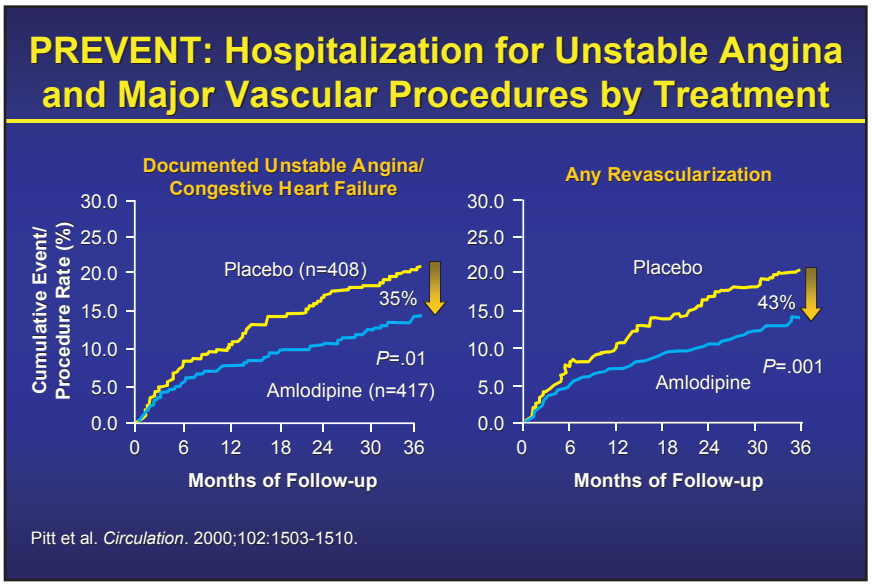


slide 49

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).

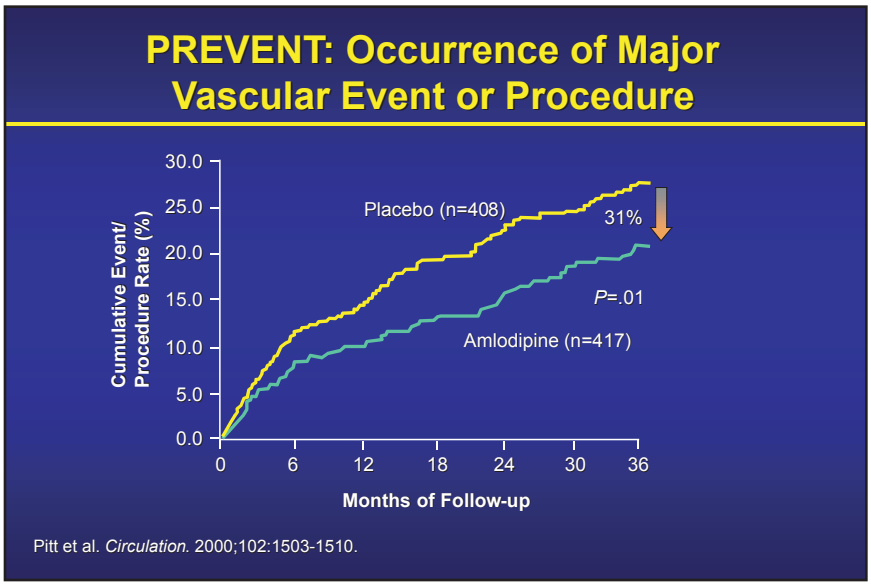
Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.



slide 50

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.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.



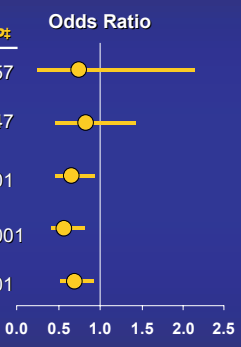
slide 51

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.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*. 2000;102:1503-1510.

PREVENT: Effects of Amlodipine Besylate on Cardiovascular Morbidity and Mortality

	Amlo*	Pl†	RRR %	HR‡	95% CI‡	P‡
All-cause mortality	6	8	26	.74	0.26-2.12	.57
Major vascular event	23	28	18	.82	0.47-1.42	.47
Other documented nonfatal vascular events (CHF, unstable angina)	61	88	35	.65	0.47-0.91	.01
Major vascular procedures§	53	86	43	.57	0.41-0.81	.001
Any major/documented vascular event or procedure	86	116	31	.69	0.52-0.92	.01

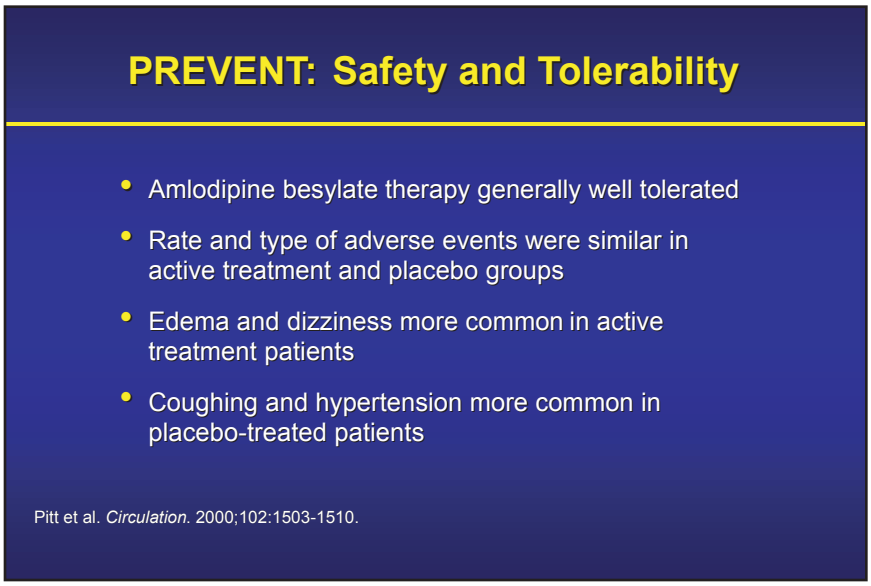


*Amlo =Amlodipine, n=417; † Pl=Placebo, n=408; ‡ From proportional hazards models; *P* values presented only for prespecified composite event outcomes; § Includes angioplasties, stents, and atherectomies.
Pitt et al. *Circulation.* 2000;102:1503-1510.

slide 52

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).

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.



slide 53

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.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*. 2000;102:1503-1510.

PREVENT: Amlodipine Reduced Cost of Inpatient Care Associated With CAD

- 27.9 clinical events averted per 100 patients treated with amlodipine over 3 years
- Total net savings in inpatient care: $426,462* over 3 years
- Average net savings per patient per year: $628*

* 1997 US dollars.
Chen et al. *J Am Coll Cardiol.* 2000;35(suppl A):555. Abstract 1171-14.

slide 54

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.

Chen GJ, Byington RP, Moran W. Amlodipine reduces cost of inpatient care associated with treatment of cardiovascular diseases in patients with clinical coronary artery disease. *J Am Coll Cardiol.* 2000;35(suppl A):555. Abstract 1171-14.

CAPARES: Effect of Amlodipine on Restenosis and Clinical Outcomes in PTCA Patients

- Placebo-controlled, double-blind, randomized, multicenter trial of patients undergoing PTCA
- Pretreatment with
  - Amlodipine 10 mg (n=318)
  - Placebo (n=317)
- QCA endpoint: loss in minimal lumen diameter from post-PTCA to follow-up
- Clinical endpoints
  - Death
  - MI
  - CABG
  - Repeat PTCA

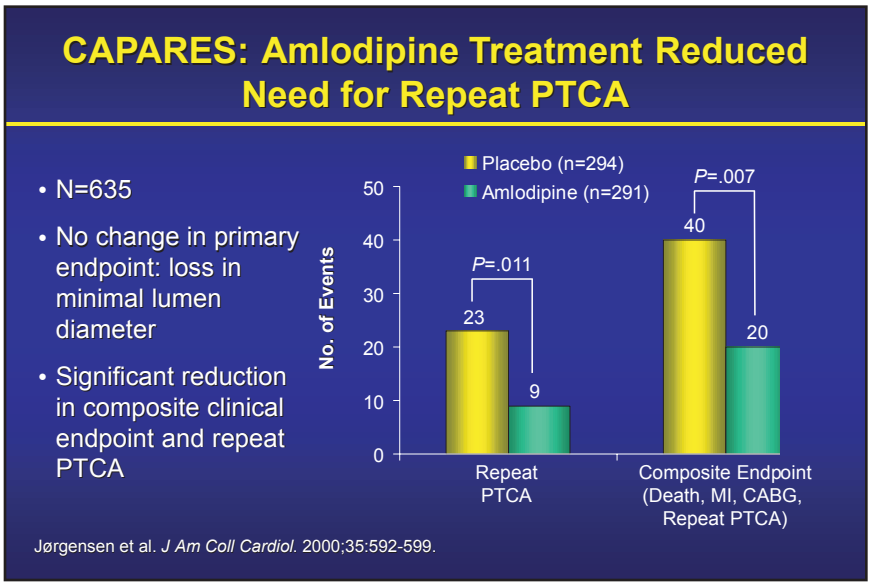
Jørgensen et al. *J Am Coll Cardiol.* 2000;35:592-599.

slide 55

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.

Jørgensen B, Simonsen S, Endresen K, et al. Restenosis and clinical outcome in patients treated with amlodipine after angioplasty: results from the Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES). *J Am Coll Cardiol.* 2000;35:592-599.



slide 56

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.

Jørgensen B, Simonsen S, Endresen K, et al. Restenosis and clinical outcome in patients treated with amlodipine after angioplasty: results from the Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES). *J Am Coll Cardiol.* 2000;35:592-599.

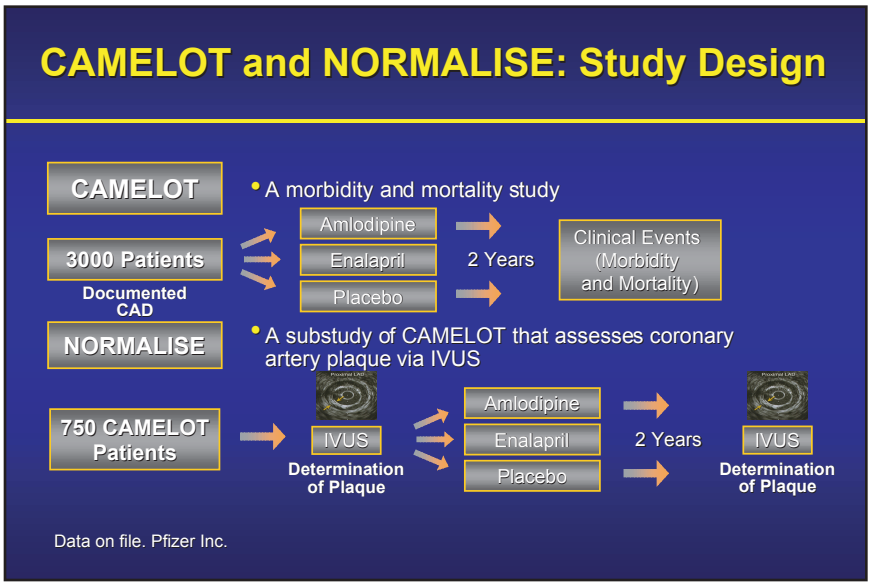
Effect of Amlodipine in CAD Trials and Future Directions

- Effect of amlodipine in CAD Trials
  - Reduced rate of atherosclerosis progression measured by carotid IMT—PREVENT
  - Reduced hospitalizations for unstable angina—PREVENT
  - Reduced revascularizations—PREVENT and CAPARES
  - Reduced composite cardiovascular endpoint—PREVENT and CAPARES
- Future directions: CAMELOT and NORMALISE
  - Further characterize effect on atherosclerotic lesions and clinical events
  - Identify effect of blood pressure changes on CAD
  - Correlate lesion progression/regression and events

slide 57

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.



slide 58

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.

NORVASC: Dose-Related Side Effects

Adverse Event	NORVASC 5 mg (%, n=296)	NORVASC 10 mg (%, n=268)	Placebo (%, n=520)
Edema	3.0	10.8	0.6
Dizziness	3.4	3.4	1.5
Flushing	1.4	2.6	0.0
Palpitation	1.4	4.5	0.6

Physicians' Desk Reference®, 2000:2539.

slide 59

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.

Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics Company, Inc; 2000:2539.

Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study (TOMHS) Research Group. Treatment of Mild Hypertension Study: final results. *JAMA*. 1993;270:713-724.

NORVASC: Expanding the Spectrum of Efficacy

- Efficacy in hypertension and angina
  - With NORVASC 4 of 5 patients reach systolic and diastolic blood pressure goals in clinical trials
  - NORVASC lowers blood pressure gradually, maintains efficacy for 24 hours
  - NORVASC provides effective control of stable and vasospastic angina
- Efficacy in reducing risk of complications of CAD
  - In PREVENT, NORVASC reduced procedures and hospitalization for unstable angina
  - NORVASC slowed progression of carotid atherosclerosis
  - NORVASC reduced healthcare costs of CAD treatment

Pitt et al. *Circulation.* 2000;102:1503-1510.
Neaton et al. *JAMA.* 1993;270:713-724.

slide 60

In clinical trials, NORVASC has proven efficacy for reducing blood pressure and controlling angina. With NORVASC once daily, 4 out of 5 patients have been able to achieve and maintain a goal blood pressure, with excellent tolerability. In TOMHS, for example, 83% of patients maintained antihypertensive control with NORVASC monotherapy after 4 years. NORVASC reduces blood pressure gently and gradually, maintaining antihypertensive effect throughout a full 24 hours with a minimum of side effects.

NORVASC 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 NORVASC in PREVENT is its efficacy for reducing the complications of CAD. In PREVENT, NORVASC reduced the rate of major vascular procedures (CABG, PTCA) by 43% and of hospitalizations for unstable angina and CHF by 35%.

Over a 36-month treatment period, NORVASC significantly reduced the progression of carotid atherosclerosis (the presence of carotid plaque has been directly associated with the presence of CAD as measured by IMT).

When the reductions in events and procedures seen in PREVENT were evaluated against the cost of treatment, NORVASC showed a net savings in CAD-derived healthcare costs of $628 per patient per year (calculated in 1997 US dollars). From the cost analysis, the investigators concluded that NORVASC "appears to be a cost-saving agent in treatment of patients with angiographic evidence of coronary artery disease."

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503-1510.

Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study (TOMHS) Research Group. Treatment of Mild Hypertension Study: final results. *JAMA.* 1993;270:713-724.

REFERENCES

American Heart Association. *2000 Heart and Stroke Statistical Update*. Dallas, Tex.: American Heart Association; 1999.

Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women ≥62 years of age. *Am J Cardiol*. 1994;74:64-65.

Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N Engl J Med*. 1998;338:1650-1656.

Borhani NO, Mercuri M, Borhani PA. Final outcome results of the multicenter isradipine diuretic atherosclerosis study (MIDAS): a randomized controlled trial. *JAMA*. 1996;276:785-791.

Brown BG, Zhao X-Q, Sacco DE, Albers JJ. Lipid lowering and plaque regression: new insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation*. 1993;87:1781-1791.

Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1285-1298.

Byington RP, Miller ME, Herrington D, et al, for the PREVENT Investigators. Rationale, design, and baseline characteristics of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Am J Cardiol*. 1997;80:1087-1090.

Chen GJ, Byington RP, Moran W. Amlodipine reduces cost of inpatient care associated with treatment of cardiovascular diseases in patients with clinical coronary artery disease. *J Am Coll Cardiol*. 2000;35(suppl A):555. Abstract 1171-14.

Data on file. Pfizer Inc.

Davies MJ. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. *Circulation*. 1996;94:2013-2020.

de Feyter PJ, Serruys PW, Davies MJ, et al. Quantitative coronary angiography to measure progression and regression of coronary atherosclerosis: value, limitations, and implications for clinical trials. *Circulation*. 1991;84:412-423.

DiBianco R, Schoomaker FW, Singh JG, et al. Amlodipine combined with beta blockade for chronic angina: results of a multicenter, placebo-controlled, randomized double-blind study. *Clin Cardiol*. 1992;15:519-524.

Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279:1615-1622.

Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM 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 (Committee on the Management of Patients With Chronic Stable Angina.) *J Am Coll Cardiol*. 1999;33:2092-2197.

Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316:1371-1375.

Heart and Stroke Foundation of Canada. *The Changing Face of Heart Disease and Stroke in Canada 2000*. Ottawa, Canada; 1999.

Help for Health Trusts' NHS A^{TO}Z HELP-DIRECT Web site. Available at: http://www.nhsatoz.org./nhsd. Accessed May 10, 2000.

Jørgensen B, Simonsen S, Endresen K, et al. Restenosis and clinical outcome in patients treated with amlodipine after angioplasty: results from the Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES). *J Am Coll Cardiol*. 2000;35:592-599.

Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens*. 2000;13:3S-10S.

Kanters SDJM, Algra A, van Leeuwen MS, Banga J-D. Reproducibility of in vivo carotid intima-media thickness measurements: a review. *Stroke*. 1997;28:665-671.

Klever-Deichert G, Hinzpeter B, Hunsche E, Lauterbach KW. Costs of coronary heart diseases over the remaining life time in coronary heart disease cases—an analysis of the current status of coronary heart disease cases in Germany from the social perspective. *Z Kardiol*. 1999;88:991-1000.

Lichtlen PR, Hugenholtz 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;4:1047-1068.

Mark DB, Braunwald E. Medical management of unstable angina. In: Fuster V, Ross R, Topol EJ, eds. *Atherosclerosis and Coronary Artery Disease*. Philadelphia, Pa: Lippincott-Raven Publishers; 1996.

Mason RP, Moisey DM, Shajenko L. Cholesterol alters the binding of Ca^{2+} channel blockers to the membrane lipid bilayer. *Mol Pharmacol*. 1992;41:315-321.

Mason RP, Walter MF, Trumbore MW, Olmstead EJ Jr, Mason PE. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. *J Mol Cell Cardiol*. 1999;31:275-281.

Mason RP. Cytoprotective properties of a long-acting calcium channel blocker: new mechanisms of action. *Am J Hypertens*. 1998;11:254A. Abstract.

Murabito JM, Evans JC, Larson MG, et al. Prognosis after the onset of coronary heart disease: an investigation of differences in outcome between the sexes according to initial coronary disease presentation. *Circulation*. 1993;88:2548-2555.

Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study (TOMHS) Research Group. Treatment of Mild Hypertension Study: final results. *JAMA*. 1993;270:713-724.

Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. *Arch Intern Med*. 1992;152:56-64.

O'Leary DH, Polak JF, Kronmal RA, et al, for the Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14-22.

Pedersen TR, Olsson AG, Faergeman O, et al, for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation*. 1998;97:1453-1460.

Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics Company, Inc; 2000:2539.

Pitt B, Byington RP, Furberg CD, et al, for the PREVENT Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*. 2000;102:1503-1510.

Riley WA, Barnes RW, Applegate WB, et al. Reproducibility of noninvasive ultrasonic measurement of carotid atherosclerosis: the asymptomatic carotid artery plaque study. *Stroke*. 1992;23:1062-1068.

Sacks FM, Moyé LA, Davis BR, et al. Relationship between plasma LDL concentration during treatment with pravastatin and recurrent coronary events in the Cholesterol And Recurrent Events Trial. *Circulation*. 1998;97:1446-1452.

Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.

Smith ER. Cardiovascular disease and the global village. *Can J Cardiol*. 2000;16:234-235.

Smith SC Jr. Risk-reduction therapy: the challenge to change. *Circulation*. 1996;93;2205-2211.

Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1995;92:1355-1374.

Stary HC. The histological classification of atherosclerotic lesions in human coronary arteries. In: Fuster V, Ross R, Topol EJ, eds. *Atherosclerosis and Coronary Artery Disease*. Philadelphia, Pa: Lippincott-Raven Publishers; 1996.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the National High Blood Pressure Education Program Coordination Committee. *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. NIH publication 98-4080, November 1997.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary artery disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339-1349-1357.

Tulenko TN, Stepp DW, Chen M, et al. Actions of the charged dihydropyridine amlodipine in a cell culture model of dietary atherosclerosis. *J Cardiovasc Pharmacol*. 1995;26(suppl A):S11-S17.

US Department of Health and Human Services (DHHS). National Center for Health Statistics. Third National Health and Nutrition Examination Survey. 1991-1994, NHANES III data files [CD-ROM].

USDHHS. *Managing Unstable Angina. Consumer Version Clinical Practice Guideline*. 1994. Available at: http:// text.nlm.nih.gov/tempfiles/is/tempD135270.html. Accessed May 12, 2000.

van Zwieten PA. Amlodipine: an overview of its pharmacodynamic and pharmacokinetic properties. *Clin Cardiol*. 1994; 17(suppl III):III-3-III-6.

Waters D, Lesperance J, Craven TE, Hudon G, Gillam LD. Advantages and limitations of serial coronary arteriography for the assessment of progression and regression of coronary atherosclerosis: implications for clinical trials. *Circulation*. 1993;87 (suppl II):II-38-II-47.

Waters D, Lesperance J, Francetich M, et al. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. *Circulation*. 1990;82:1940-1953.

Watts GF, Lewis B, Brunt JNH, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). *Lancet*. 1992;339:563-569.

Weinstein DB. The antiatherogenic potential of calcium channel antagonists. *J Cardiovasc Pharmacol*. 1988;12(suppl 6):S29-S35.

West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation*. 1998;97:1440-1445.

World Health Organization. *The World Health Report, 1997. Conquering Suffering, Enriching Humanity*. Geneva, Switzerland; 1997.

Yang M-C, Huang I-C. Establishing a cost estimation model for hypertension and its related diseases in Taiwan. *J Formos Med Assoc*. 1999;98:394-402.

Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable angina pectoris. *N Engl J Med*. 2000;342:101-114.

Zethraeus N, Molin T, Henriksson P, Jonsson B. Costs of coronary heart disease and stroke: the case of Sweden. *J Intern Med*. 1999;246:151-159.

Zhang X, Hintze TH. Amlodipine releases nitric oxide from canine coronary microvessels: an unexpected mechanism of a calcium channel-blocking agent. *Circulation*. 1998;97:576-580.