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

PREVENT and the Role of NORVASC®

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

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

- Cardiovascular disease: a worldwide problem
- Progression of atherosclerosis
- Atherosclerosis and clinical events
- Approach to managing patients at risk
- Overview of CCBs and amlodipine in CAD
- Expanding the spectrum of therapy for CAD: PREVENT design and results
- Future directions

This lecture kit will cover the following points related to atherosclerosis and coronary artery disease (CAD):

- Cardiovascular disease: a worldwide problem
- Progression of atherosclerosis
- Atherosclerosis and clinical events
- Approach to managing patients at risk
- Overview of CCBs and amlodipine in CAD
- Expanding the spectrum of therapy for CAD: PREVENT design and results
- Future directions
In the past few years, research has revealed a great deal about the pathophysiology and treatment of CAD. Atherosclerosis, the central component of the pathophysiologic process underlying CAD, is now receiving more attention than ever before. There is now renewed emphasis on atherosclerosis as a systemic disease implicated in peripheral vascular disease (PVD) and stroke as well as CAD.

As a consequence of these shifts, the treatment paradigms are changing to focus on systemic therapy and risk factor management. The changing knowledge of how events happen is leading to scrutiny of the role of plaque stability and early lesions in the process and investigations of new therapeutic strategies in addition to lipid lowering.


Circulatory diseases—including hypertension, CAD, cerebrovascular disease, and cardiomyopathies—are the number 1 cause of death worldwide. In 1996, for example, CAD alone accounted for about 7.2 million deaths worldwide, while stroke accounted for about 4.6 million. Hypertension is the most common cardiovascular disorder, affecting about 690 million people, or about 20% of the world adult population.

Cardiovascular diseases, while still a concern to industrialized countries, now represent a growing threat to developing countries as risk factors become more widespread. Cardiovascular deaths are increasing at a faster rate in developing countries than in industrialized nations. For example, the 1990 rate of 398 cardiovascular deaths per 100,000 population in developed countries is projected to reach 405 per 100,000 by 2020 or a 1.8% increase. On the other hand, the 1990 rate of 220 cardiovascular deaths per 100,000 population in developing countries is expected to increase by 28% to 282 per 100,000 during the same period.


The economic burden of cardiovascular disease is enormous in countries where it is reported. The direct costs of circulatory diseases have been estimated to account for 10% of all direct healthcare costs in developed countries, or about 0.5% to 1.0% of their gross national products.

This slide shows available data on the total costs (direct and indirect) of CAD in selected countries. (Such data are generally not available from developing countries.) Note that these data are simple aggregates; they have not been adjusted for population, differences in disease prevalence, or inflation.

Atherosclerosis, the underlying pathology in the majority of cardiovascular diseases, is a progressive disease the stages of which have been well characterized in histologic studies and are represented schematically in these cross-sections. Adaptive intimal thickening, present from birth, especially at bifurcations, is considered histologically normal. However, these thickened intimal segments may identify lesion-prone locations.

- Type I lesions (not shown) are characterized by the presence of isolated macrophage foam cells. A type II (or fatty streak) lesion is defined primarily by the presence of macrophage foam cells and lipid-laden smooth muscle cells.
- Type III (preatheroma) lesions may develop soon after puberty. They contain scattered collections of extracellular lipid droplets and particles that disrupt the coherence of intimal smooth muscle cells. Types I to III lesions do not significantly thicken the arterial wall or narrow the lumen.
- Types IV, V, and VI are considered advanced lesions, because they disrupt the intimal structure. Arterial narrowing with encroachment on the lumen diameter is generally seen more with type V than with type IV lesions.
- Type IV through VI lesions may be associated with clinical syndromes. However, most CAD morbidity and mortality result from type VI lesions with lesion surface disruptions, such as fissure, ulceration, hematoma, hemorrhage, or thrombotic deposits.


It is now well recognized that atherosclerosis is a systemic disease whose pathophysiology underlies a broad range of cardiovascular disorders. For example, Aronow and colleagues performed a prospective trial studying the coexistence of CAD, peripheral arterial disease (PAD), and stroke (atherothrombotic brain infarction [ABI]) in 1886 patients 62 years of age or older in a long-term healthcare facility. As shown in this slide, a high percentage of patients with one of these vascular conditions also had clinically significant evidence of the other two. The recognition of the widespread systemic nature of atherosclerotic disease is one of the factors stimulating research into treatments that affect the atherosclerotic process itself.

Further evidence of the systemic nature of atherosclerosis was provided in a study by O’Leary et al. The association between the carotid artery intimal-medial thickness (IMT) and the incidence of new myocardial infarction (MI) or stroke (combined endpoint) was studied in 4476 subjects aged 65 years or older who had no clinical evidence of cardiovascular disease.

The carotid arteries were measured noninvasively by means of high-resolution B-mode ultrasonography. After a median follow-up period of 6.2 years, the study revealed that an increase of 1 standard deviation in combined IMT was associated with a relative risk of 1.36 for the combined endpoint of MI or stroke after adjustment for age, sex, and other major cardiovascular risk factors. As noted, the higher the IMT quintile, the lower the event-free survival.

The authors concluded that measurements of carotid artery IMT have strong predictive power regarding new cardiovascular events, even with adjustments for traditional risk factors. In fact, these measurements appear to be more powerful predictors of events than the conventional risk factors of smoking, high-fat diet, etc.

The early appearance of asymptomatic atherosclerosis was well documented in the Bogalusa Heart Study in which autopsy studies were performed on 204 young persons aged 2 to 39 years who died from various causes, principally trauma. The prevalence of raised fibrous plaque lesions in the aorta and coronary arteries increased with age. By age 26 to 39, 60% had lesions in the aorta and 69% had coronary artery lesions ($P = .001$). Fatty streaks in the aorta and coronary arteries were even more prevalent, also increasing with age. The extent of fatty streaks was associated with recognized cardiovascular risk factors.

The relation between atherosclerosis and CAD can be understood by examining the effect of traditional treatment consisting of lipid lowering with statin-class drugs. The evidence supporting this approach is convincing in primary prevention and secondary prevention populations with cholesterol levels ranging from mildly to moderately elevated through to severe hypercholesterolemia. In the primary prevention studies, West of Scotland Coronary Prevention Study (WOSCOPS) and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), statin therapy reduced low-density lipoprotein cholesterol (LDL-C) from 20% to 24% and was associated with reductions in coronary death and nonfatal MI ranging from 31% to 35%. In the Scandinavian Simvastatin Survival Study (4S), Cholesterol And Recurrent Events Trial (CARE), and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies in patients with previous coronary disease, statin therapy reduced LDL-C between 25% and 35% and resulted in event reductions ranging from 23% to 30%.


Lipid trials that have examined the effect on angiographic stenosis have provided insight into the relation between arterial changes and events. Active treatment with colestipol and nicotinic acid or lovastatin and colestipol in the Familial Atherosclerosis Treatment Study (FATS) and with diet and resin in the St Thomas’ Atherosclerosis Regression Study (STARS) produced significant event reductions from 70% to 80%. However, the change in percent stenosis was much smaller, ranging from 0.7% to 1.9%. These observations and the additional observation from FATS that lesions associated with events progressed abruptly from mild to moderate baseline severity to severe obstruction (reflecting plaque fissure and disruption) provided further support for the concept that acute events result from plaque disruption and thrombosis rather than from severity of the fixed stenosis.


Further clarification of the relation between atherosclerosis and acute events comes from studies of patients who underwent angiograms prior to an MI and subsequently presented with acute MIs. These studies have shown that the culprit lesion is not necessarily a significant obstruction and in fact is often a less severe stenosis. In a pooled analysis of 4 studies, most patients presenting with an acute MI were noted to have <70% stenosis in the culprit artery.

Coronary remodeling is an adaptive process by which the arterial wall changes in shape to maintain flow despite the encroachment of plaque. This process may explain why less severe luminal narrowing may still be associated with progressive atherosclerosis and CAD. As plaque accumulates, the arterial wall reacts by remodeling. As atherosclerosis progresses toward the more severe stages pictured on the right, the lumen remains relatively constant because of compensatory expansion of the arterial wall. Eventually, in more severe stages of the disease, the artery is unable to expand further and the lumen begins to narrow.

The same process may work in reverse with disease regression. That is, plaque can be removed from the arterial wall with little change in lumen size. Therefore, luminal measurement by quantitative coronary angiography (QCA) may be a less sensitive marker for the progression or regression of disease than direct evaluation of plaque thickness through the use of intravascular ultrasound.

The measurement of atherosclerosis progression or regression by angiography may be confounded by the presence of diffuse disease in an artery. Progression of atheromatous change in mildly to moderately diseased vessels may occur in a diffuse manner involving only the “normal” diameter used for comparison to calculate severity of stenosis. This may result in a calculated less-severe lesion suggesting regression that actually should be regarded as pseudoregression. Or this may have no effect on percent stenosis severity, suggesting no progression of disease, when in actuality progression has occurred. As shown here, measurement changes on QCA, including percent diameter stenosis, minimum lumen diameter (MLD), and plaque area suggest regression of the lesion severity. In fact, what has happened is progression of diffuse disease, which is masked.

The Tight Stenosis Is Not the Active Lesion

Intravascular ultrasound (IVUS) imaging documents the thickness and composition of plaque in the arterial wall, and will show diffuse disease. In these views, IVUS is compared with angiography to show that tight stenosis is not necessarily the site of an active plaque. The small lumen seen at A on the angiogram represents a stenosis that is significant but without rupture. However, the hazy area at B on the angiogram contains a ruptured plaque with an exposed lipid core, as seen on the corresponding IVUS image.
Disruption of an atherosclerotic plaque is a complex pathophysiologic process central to the initiation of the acute coronary syndromes (ACS). A mature plaque is made up of 2 main components: a lipid-rich core and extracellular matrix proteins forming a fibrous cap. The presence of large, eccentric lipid pools and the infiltration of foam cells are features most often associated with plaque rupture or fissure, which usually occurs at the sites of the greatest mechanical stress. Fissures that occur at weak cap sites not under great mechanical stress are thought to be initiated by enzymatic degradation of the cap. Local thrombosis following plaque disruption results from interactions between the lipid core and blood.

Numerous factors probably trigger the rupture of a vulnerable plaque. Rupture exposes tissue factor in the lipid core, which precipitates platelet activation, adhesion, and aggregation, resulting in the formation of an occlusive thrombus. If the process leads to complete occlusion of the artery, an acute MI results. Alternatively, if occlusion is incomplete, unstable angina or non-Q-wave MI may develop. Spontaneous or pharmacologic lysis of thrombus, or pharmacologic interruption of platelet aggregation, may lead to resolution of the syndrome.
The acute transition from atherosclerosis to clinical CAD may be sudden and drastic. Analysis of subjects enrolled in the Framingham Heart Study shows that CAD frequently presents first as MI or sudden death.

Murabito et al studied 5144 subjects in the Framingham Heart Study in whom clinically overt CAD developed during biennial examinations during the period 1951 to 1986, and followed them through examinations that took place from 1986 to 1988.

Of these subjects, 1569 (895 men, 674 women) experienced a new coronary heart event. In men, sudden cardiac death accounted for 16% of the initial presentations, recognized MI 30%, and unrecognized MI 16%, for a total of 62%. In women, sudden cardiac death accounted for 14% of the initial presentations, recognized MI 18%, and unrecognized MI 14%, for a total of 46%.

One important risk factor for CAD is hypertension. Studies have shown that in particular older persons with hypertension, African Americans with hypertension, and hypertensive persons with diabetes have an elevated risk for CAD. The risk of CAD more than doubles from ages 35 to 64 to ages 65 to 94. In African Americans with hypertension, there is a 50% greater mortality from CAD than seen in the general population. Hypertensive patients with diabetes have a 2 to 4 times greater likelihood of having CAD than do patients without diabetes.


Patients who have established CAD are clearly at high risk for subsequent coronary events and CAD death and need extra protection. This is clear in statistics available from the American Heart Association, which show that 25% of men and 38% of women die within 1 year of having an MI.

In addition, about 10% of patients with acute ischemic heart disease experience nonfatal recurrent MI or death within the first 60 days of presentation, and about 40% of patients undergoing angioplasty require a repeat procedure within 6 months.

Patients With Established CAD Are a High-Risk Group

<table>
<thead>
<tr>
<th>Myocardial infarction (MI)</th>
<th>• 25% of men and 38% of women die within 1 year of a recognized MI</th>
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<tr>
<td>Acute ischemic heart disease</td>
<td>• One in 10 patients experiences nonfatal recurrent MI or death within 2 months of presentation</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>• 40% of patients may require a repeat procedure within 6 months</td>
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Systolic (SBP) and diastolic (DBP) blood pressures have been shown to correlate strongly with CAD mortality. The combined effect of systolic and diastolic blood pressure on age-adjusted CAD mortality is shown in this slide. These data, from a cohort of more than 300,000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT) and followed for an average of 12 years, show that SBP is actually a stronger predictor of death from CAD than DBP.

Hypertension is frequently associated with additional risk factors. Observations in Framingham offspring indicate that in more than 80% of cases, elevated blood pressure tends to cluster with 1 or more other major risk factors, such as obesity, elevated blood lipids, glucose intolerance, and left ventricular hypertrophy (LVH). A cluster of 2 or more additional risk factors occurs in about half of all those with high blood pressure, a frequency twice that expected by chance, and clusters of 3 or more risk factors occur at 4 times the expected rate. A slightly higher proportion of Framingham male offspring had clusters of 2 or 3 risk factors; however, 12% of women, compared with 8% of men, had a cluster of 4 or more risk factors. Risk factor clustering enables physicians to estimate the probability for development of CAD in patients who have hypertension and additional risk factors.

The risk of having a CAD event increases according to the burden of associated risk factors. These data, from men in the Framingham study who were 45 years of age and had mild hypertension, show that systolic hypertension constitutes an important independent risk factor for CAD, and that the risk increases in proportion to the number and severity of the associated risk factors, including elevated total cholesterol, low levels of high-density lipoprotein cholesterol (HDL-C), the presence of diabetes mellitus, cigarette smoking, and electrocardiographic (ECG) evidence of LVH.

The authors of the ACC/AHA/ACP-ASIM guidelines on chronic stable angina noted the importance of risk factor management as a means of impacting disease progression and outcomes. They advocated the following system to categorize management of CAD risk factors:

- **Category I**: risk factors clearly associated with an increase in coronary disease risk for which interventions have been shown to reduce the incidence of coronary disease events
- **Category II**: risk factors clearly associated with an increase in risk for which interventions are likely to reduce the incidence of coronary disease events
- **Category III**: risk factors clearly associated with an increase in risk for which interventions might reduce the incidence of coronary disease events
- **Category IV**: risk factors associated with an increase in risk that cannot be modified or, if modifiable, would be unlikely to reduce the incidence of coronary disease events

Interventions in Category I include:

- Complete cessation of cigarette smoking
- Diet modifications and, if necessary, drug therapy to achieve an LDL-C level of ≤100 mg/dL
- Lifestyle modifications and, if necessary, drug therapy to achieve BP <140/90 mm Hg; if diabetes, renal failure, or heart failure, goal is ≤130/85 mm Hg
- Treatment to effect regression
- Aspirin, 80 mg to 325 mg/day— or if aspirin is contraindicated, clopidogrel—if thrombogenic factors have been identified.

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Category II interventions likely to reduce the incidence of coronary disease events include:

- Treatment to achieve a fasting blood sugar level of <126 mg/dL.
- Lifestyle modification (weight management, physical activity, smoking cessation) to achieve an HDL-C level of >35 mg/dL; if drug therapy is needed to achieve LDL-C goals, consider prescribing niacin, a statin, or fibrate to also increase the HDL-C level.
- Intensive diet and appropriate physical activity to achieve a weight <120% of the ideal for height.
- A minimum of 30 to 60 minutes of moderate-intensity exercise 3 or 4 times a week, along with an increase in the exercise level of daily lifestyle activities; for moderate- to high-risk patients, recommend medically supervised exercise.

Category III interventions which might reduce the incidence of coronary disease events include:

- Management directed at stress reduction and enhancement of psychological well-being; this may include management of depression or anxiety.
- Nonpharmacologic and pharmacologic management of high triglyceride levels.
- High-dose niacin to reduce elevated levels of lipoprotein(a).
- Dietary supplementation with vitamins B6 and B12 and folic acid to lower elevated homocysteine levels.
- Increased dietary intake of foods rich in antioxidants (vitamin C, vitamin E, and beta carotene), dietary supplementation with these antioxidants, or use of probucol to counter the oxidation of LDL-C.
- Interventions to decrease excessive alcohol consumption.
- Category IV includes nonmodifiable risk factors, such as advancing age, male sex, and a family history of premature CAD.

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Reduction of total blood cholesterol and the achievement of a favorable lipid balance, the conventional first step toward CAD prevention, is a proven approach that can result in a reduction of approximately 30% in predicted fatal and nonfatal cardiovascular events. However, it may take up to a year to see an effect on events. Investigators continue to explore preventive strategies involving other risk factors, control of which may eventually permit a similar and complementary effect to that of lipid therapy.


In the 1980s evidence started to emerge that calcium channel blockers (CCBs) might have antiatherosclerotic properties. Studies in cholesterol-fed rabbits showed that several CCBs (nifedipine, nicardipine, diltiazem, verapamil, isradipine) decreased the area of aortic atherosclerotic lesions from 31% to 64% and the cholesterol content from 29% to 75%. Furthermore, in vitro studies have demonstrated several mechanistic effects that may come into play in reversing atherosclerosis: in cell culture systems, CCBs were shown to inhibit migration and proliferation of smooth muscle cells and accumulation of extracellular matrix and lipid accumulation in “foam” cells. Interacted with lipoprotein metabolic pathways. As a result of these basic science studies, clinical investigators undertook trials of CCB agents to see whether they would regress atherosclerosis as measured by QCA or B-mode ultrasound.

Because experimental studies in cholesterol-fed rabbits demonstrated that CCB use retarded development of atherosclerosis, 2 investigative groups undertook clinical studies of the effects of short-acting CCBs on atherosclerosis in patients with CAD. Lichtlen et al conducted a prospective, double-blind, randomized, placebo-controlled study of high-dose nifedipine (80 mg) in patients with mild coronary disease to determine whether it would slow progression of atherosclerosis as measured by QCA. Patients (N=425) entered in the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT) were less than 65 years of age, preferably undergoing their first coronary angiogram, demonstrating early CAD, and not candidates for revascularization.

Endpoints were defined prior to the enrollment of patients and included both further development of existing stenoses and formation of new stenoses in previously “angiographically normal” segments. The angiographic results showed no differences between the placebo and nifedipine-treated groups with respect to progression or regression of lesions. After adjustment for the number of patients in each group, there were 0.80 new lesions per patient on placebo and 0.58 new lesions per patient on nifedipine (-27%, P = .031 between group difference). Clinical endpoint measures were not prospectively defined as a primary goal. The study showed no difference in MIs between the 2 groups, but a nonsignificant increase in cardiac deaths in the patients on nifedipine (8) versus those on placebo (2).

The Montreal Heart Study randomized 383 patients who were younger than 65 years and had 5% to 75% stenoses in at least 4 coronary artery segments to treatment with placebo or nicardipine (30 mg tid) for 2 years. When a second angiogram was done at 2 years, the results showed no difference between the treatment and placebo groups with respect to progression or regression of atherosclerosis. In a retrospective analysis among the 217 patients with 411 stenoses of 20% or less in the study, these minimal lesions progressed in only 15% of nicardipine patients versus 27% of placebo patients (P = .046). When lesions were examined, 16 of 178 minimal lesions in nicardipine patients versus 38 of 233 minimal lesions in placebo patients progressed (P = .038). There was no difference in cardiovascular deaths between the 2 treatment groups; there was a nonsignificant trend toward increased MIs in the nicardipine-treated patients (14) versus placebo (8).


Effects of CCBs on Vascular Changes and Clinical Events: Early Carotid IMT Study

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up</th>
<th>Vascular Changes</th>
<th>Vascular Events</th>
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<tbody>
<tr>
<td>MIDAS 1996</td>
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<td>Early (6 mo) slowing of IMT thickening with isradipine, but no difference between treatment groups in change in carotid IMT at 3 y</td>
<td>Trend toward ↑ major vascular events with isradipine</td>
</tr>
<tr>
<td>Isradipine (5-10 mg/day) vs hydrochlorothiazide (25-50 mg/day)</td>
<td>883</td>
<td>3 y</td>
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IMT = intimal-medial thickness.

A later clinical study evaluated the effects of the short-acting CCB isradipine compared with hydrochlorothiazide (HCTZ) on atherosclerosis in hypertensive patients with a carotid IMT of 1.3 to 3.5 mm. Quantitative B-mode ultrasound imaging is a noninvasive technique to measure the IMT of the carotid artery as a surrogate for assessing early atherosclerosis. Borhani et al used this technique over a 3-year follow-up to document changes in atherosclerosis in 883 patients randomized to either diuretic (HCTZ) or isradipine therapy. At the end of 3 years, there was no difference in the rate of progression of mean maximum IMT in 12 carotid focal points between the 2 treatment groups. However, at 6 months after randomization, the mean ± SD maximum IMT of the 12 focal points in the carotid arteries increased more in the HCTZ group than in the isradipine group, a difference that persisted but did not increase over the entire 3 years of the study. There was a trend toward increased vascular events in the patients receiving isradipine compared with placebo (25 vs 14, P = .07).

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.