Aggressive treatment of atherosclerosis: The time is now

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ABSTRACT

In patients with known cardiovascular disease and those at high risk for it, physicians must begin to treat atherosclerosis earlier, with combination therapy of statins, aspirin, angiotensin-converting enzyme inhibitors, and beta-blockers. In those hospitalized with a cardiovascular event, a statin should be started in the hospital, regardless of lipid levels. Patients with diabetes should be treated as if they have preexisting cardiovascular disease.

OUR TRADITIONAL APPROACH to treating cardiovascular disease has largely failed. Too often, physicians treat only the ischemia and ignore the underlying disease process itself—atherosclerosis.

Many studies have shown that statins attack atherosclerosis not only by lowering lipid levels, but also through anti-inflammatory activity. Despite this evidence, these medications are markedly underutilized, even for patients with documented coronary artery disease and hyperlipidemia.

In patients hospitalized for a coronary event, we must do more than treat the ischemia. We must begin to aggressively treat the damaged vascular bed with combination medical therapy, including a statin (regardless of lipid levels), aspirin, a beta-blocker, and an angiotensin-converting enzyme (ACE) inhibitor. This therapy should be started before hospital discharge.

In addition, all patients with known atherosclerotic cardiovascular disease, regardless of how it was diagnosed, should receive appropriate combination therapy. And those patients at high risk, such as people with diabetes and those who score high on the Framingham risk model, should also be treated aggressively.

THE TRADITIONAL APPROACH: TREATING THE SYMPTOMS

Atherosclerosis is a sneaky disease. It begins silently: the patient is not aware of it and often neither is the physician. Then suddenly it strikes—the patient presents with unstable angina, acute myocardial infarction, or sudden death.

For patients fortunate enough to survive the initial presentation, we have systems in our hospitals to diagnose infarction, stabilize the patients, and get them revascularized. As they near the end of their hospitalization, many patients are again free of symptoms (or manifest stable angina). Often patients view themselves as no longer at risk.

But atherosclerosis is not just sneaky, it is ruthless: 80% to 90% of patients who manifest atherosclerosis eventually die of it. Once patients present with atherosclerosis, they are never "no longer at risk."

But often patients never receive the therapy they need to treat the underlying disease. When we looked at a group of patients with known coronary artery disease and documented hyperlipidemia referred to our catheteriza-

Any patient who presents with atherosclerosis is never 'no longer at risk'

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tion laboratory in 1992 and 1993, we were shocked to find that fewer than 5% of them were receiving lipid-lowering therapy.[1]

Those dismal statistics still hold. Recent data from the National Registry of Myocardial Infarction[1] show that the country is not yet achieving desired levels. For the more than 100,000 patients discharged after a myocardial infarction, 1 in 5 went home without aspirin, 1 in 3 without beta-blockers, more than half without ACE inhibitors, and two thirds without statins.

One survey asked practicing doctors if they were aware of the National Cholesterol Education Project guidelines for treating patients with known coronary artery disease to a low-density lipoprotein (LDL) cholesterol level below 100 mg/dL. While 95% of the doctors claimed they were treating according to these guidelines, in fact only 18% of patients were at goal levels.[2] Provider awareness alone does not equal successful implementation.

We asked cardiologists and primary care physicians why their patients were not receiving lipid-lowering therapy. Here are some of their responses:

- "They must be on treatment, I treat all my patients." (Even though clearly the majority of the patients were not on therapy.)
- "They are on a low-cholesterol diet." (Even though their lipid levels had not responded.)
- "There are lots of side effects to the medications. Patients don't like it. It's too expensive."

Mortality-reducing therapies are still underused, despite evidence and guidelines

A cardiologist responded, "You know, that's really the primary care physician's responsibility. Why are you asking me?" A primary care physician said, "Well, the cardiologist didn't think the patient needed any treatment," while another said, "It was the patient's fault; [the patient was] to be treated but got lost to follow-up."

These responses highlight some of the barriers that exist to effectively translating evidence-based guideline recommendations into routine clinical practice. Despite overwhelming clinical trial evidence, expert opinion, national guidelines, and a vast array of educational conferences, evidence-based, mortality-reducing therapies continue to be underutilized. New approaches to improving the use of proven, guideline-recommended therapies are clearly needed.

DISPELLING HEART DISEASE MYTHS

Justification for traditional treatment of heart disease, ie, treating the ischemia while placing a lower priority on risk reduction, is based on several false beliefs:

Myth 1: Most clinical events are caused by major stenosis

The traditional view is that most clinical events are caused by 70% flow-limiting stenosis. But in fact such situations account for only about 15% of clinical events. The vast majority of myocardial infarctions occur with stenosis of less than 50%, caused by lesions previously regarded as mild plaques.[3] Many patients with such "nonobstructive" lesions seen on angiography are sent home and erroneously told they have mild disease with little to worry about.

Myth 2: Patients with ischemia are at higher risk

A National Heart, Lung, and Blood Institute (NHLBI) study followed patients with comparable disease defined by angiography, but some had detectable ischemia on stress testing and some did not. Subsequent rates of myocardial infarction and cardiac death were the same. While ischemia was not a predictor of outcome, more extensive atherosclerosis was: patients with two-vessel disease had greater risk than those with one-vessel involvement.[4]

Myth 3: Reducing ischemia improves survival

It is well documented that angioplasty is more effective than medical treatment in reducing angina and ischemia. However, in the Randomized Intervention Treatment of Angina (RITA-2) trial,[5] in which patients with coronary artery disease were randomized to angioplasty vs medical treatment, long-term rates of myocardial infarction and cardiac death were similar.

A NEW MODEL OF ATHEROSCLEROSIS: TARGET THE DISEASE, NOT THE LUMEN

Many of the myths about cardiovascular disease came about because the process of atherosclerosis was thought to result in a gradual nar-

rowing of the artery, leading to ischemia, then to an event. But a better model is *outward remodeling*, in which plaque begins within the artery wall and the artery responds by expanding outward rather than into the lumen. Thus, an extensive plaque may form without significantly compromising blood flow or causing ischemia on a stress test. When a trigger ruptures the plaque, the patient acutely goes from being asymptomatic to having an event. The risk depends on how vulnerable the plaque is to rupture, rather than how narrow the artery is. A plaque becomes vulnerable to rupture if the lipid core is large, if the overlying fibrous cap is thin, and if there is inflammation in the lesion.[3]

With this new model, it is apparent that we need to target the underlying atherosclerotic vascular disease process instead of addressing the size of the lumen. Most patients with coronary artery disease live longer if treated with cardiovascular protective drugs, making a strong case for treatment of atherosclerosis regardless of where in the body it occurs. By giving drugs that combat atherosclerosis, we have the advantage of not needing to know exactly where the next at-risk lesion is. Instead, we are treating the entire vascular bed. The rapid reduction in inflammatory markers and the role inflammation plays in plaque rupture provide the rationale for starting therapy immediately upon presentation.

Statins reduce morbidity and mortality. The Scandinavian Simvastatin Survival Study (4S)[6] of patients with known coronary artery disease showed fewer fatal and nonfatal events after only 6 months on statins compared with controls. Over 6 years, the benefits were dramatic: a 42% reduction in cardiovascular mortality and a 34% reduction in major events. Benefits extended to both men and women, patients older and younger than 65 years, smokers and nonsmokers, and patients with or without hypertension or diabetes.

STATINS: MORE THAN LIPID CONTROL

Statins lower total and serum LDL cholesterol levels by two mechanisms. In the short term, they decrease cholesterol and LDL synthesis. But, over time, synthesis increases to baseline levels. Still, despite this increase in synthesis, serum LDL levels remain low. We believe this is because long-term statin use results in upregulation of LDL receptors to more than double the normal LDL receptor density. This results in increased LDL clearance that more than offsets the increase in synthesis.

We know receptor density is important: patients with heterozygous familial hypercholesterolemia, who develop premature atherosclerosis in their 30s and 40s, have a genetic defect that causes them to have only half the normal number of LDL receptors.

But it is becoming clearer that a mechanism beyond lipid control is also at work. When similar lipid levels are achieved by diet and by statins, we see less inflammation, fewer calcifications, and less need for revascularization in those taking statins.

Animal studies have also shown that as early as 3 months after starting statins, there is only a minor reduction in lipid content and no real change in lesion size in the arteries. What is seen is an 80% reduction in inflammatory mononuclear cell infiltrate. Statins also cause a marked early fall in the C-reactive protein level and a long-term maintenance of this low level. Patients on dietary therapy without statins show a continual elevation of inflammatory marker over 5 years.

Too often, we treat the ischemia but ignore the atherosclerosis

Statins have a potent anti-inflammatory, antiatherogenic activity that explains their earlier and disproportionate benefits compared with other forms of lipid-lowering therapy.

In large studies in patients with angiographically proven coronary artery disease, statins clearly reduced cardiovascular events even if baseline lipids were already at target levels. No harm was evident, and benefits extended to a reduced risk for strokes and transient ischemic attacks.

TREATMENT DECISIONS

Whom should we treat?

Patients with known atherosclerosis should be treated, whether they have coronary, peripheral, or cerebral vascular disease. It does not matter how the diagnosis was made, whether the patients have symptoms, or whether they have undergone revascularization.

What should we treat with?

We have unequivocal evidence that the following therapies are of benefit:

- Antiplatelet therapy with aspirin, clopidogrel, or both[7]
- Neurohumoral inhibition with beta-blockers and ACE inhibitors in all patients without contraindications, including patients with normal blood pressure and normal ejection fraction[8]
- Antiatherogenic therapy with statins, regardless of LDL concentrations, in all patients with known cardiovascular disease.[9–12]

What doesn't work?

- Vitamin E and other antioxidants. Studies showed neither harm nor benefit from natural or synthetic products.[13]
- Antibiotic therapy. Azithromycin against chlamydial infection showed no substantial risk reduction in clinical events.[14]
- Hormone replacement therapy. For women with known coronary disease, risk of cardiovascular mortality increased despite improved lipid levels.[15] A major study of hormone replacement for primary prevention also showed increased rates of myocardial infarction and stroke.[16]

A statin should be started before hospital discharge

Can you pick and choose which therapies to use?

No. The 4S found that combination therapy is clearly beneficial.[6] Patients with known coronary artery disease on placebo had a 29% risk of an event in 5 years. Just being on statin therapy reduced the risk to 18.6%. Combining the statin with aspirin brought the risk down to 11.2%, and with a beta-blocker added on the risk was 8.6%, a 70% reduction of risk through this combination therapy. ACE inhibitors were not evaluated.

The Heart Outcomes Prevention Evaluation (HOPE) study, however, clearly demonstrated that ACE inhibitor benefits are additive to aspirin, beta-blocker, and statin therapy.[17] If the combination of these four simple cardiovascular medications is used in all patients with atherosclerotic disease who have no contraindications or intolerance, the cumulative risk reduction is 70%, the absolute risk reduction is 13.1%, and the number needed to treat to prevent a major cardiovascular event is only 7.

Should we try dietary therapy first?

Until recently, guidelines from the National Cholesterol Education Program (NCEP) recommended delaying prescribing statins after a clinical event until lipids were checked at the 6-week follow-up appointment and dietary interventions were subsequently attempted. With this practice, not only do we lose patients to follow-up, but both the patient and doctor view the need for statins as a failure on the patient's part. The goal becomes improving lifestyle so the patient does not need medications.

If combination therapy is started in the hospital at the time of the event, patients and physicians are more apt to view the medications as essential treatment for the disease, and high compliance is likelier.

Starting lipid-lowering medications simultaneously with therapeutic lifestyle modifications (including dietary modification) is a substantially more effective means to get patients to goal and achieve cardiovascular risk reduction.

PRIMARY PREVENTION: STARTING THERAPY BEFORE AN EVENT

We do not need to wait until patients have had an event before starting treatment. For the preventive use of these therapies, we need to define who is at high enough risk to justify the cost of treatment.

People with diabetes are at great risk

People with diabetes run the risk of having a cardiac event similar to someone with known coronary artery disease. So recommendations[18] are to treat people with diabetes as if they have known coronary artery disease with this combination of cardioprotective therapy. The Heart Protection study[19] showed that, regardless of baseline LDL levels, people with diabetes with no known vascular disease reduced their risk with statin. Benefits have also been shown with aspirin, beta-blockers, and ACE inhibitors.

High and moderate risk according to the Framingham risk model

For others, we use the Framingham risk model. New NCEP guidelines say that an optimal LDL cholesterol level for everyone is below

FIGURE 1

100 mg/dL. If the patient has multiple risk factors, and the score adds up to a 20% risk or more over 10 years, we treat with statins. If the 10-year risk is between 10% and 20%, we would start with lifestyle changes, then go to statins if that approach is unsuccessful. Below that risk level, medications are not recommended.[18]

MAKING TREATMENT MORE AGGRESSIVE AND IMPROVING OUTCOMES

In 1994, the University of California Los Angeles instituted the Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP).[1] For all patients with any clinical event caused by atherosclerosis, no matter how defined, combination therapy is part of the fundamental treatment made before discharge. We give aspirin, beta-blockers, and ACE inhibitors unless contraindicated, and statins regardless of baseline lipid levels. We also refer patients to cardiac rehabilitation and dietary counseling, and we urge smoking cessation for the patient and family.[1]

We link the hospital phase of care to the outpatient phase, reinforcing achieving lipid goals and maintaining therapy. All instructions are kept simple, fitting on a single page,

and every physician who sees the patient is responsible for ensuring that therapy is maintained. We have tool kits to implement the focused algorithm (FIGURE 1), with preprinted admission sheets and discharge forms. We also deliver focused lectures, monitor treatment rates, and provide physicians with feedback based on chart review.

We went from a 6% treatment rate with statins to 86%—much higher than national rates.[20] And 1 year after discharge, 91% of patients were still on treatment. We have seen clinical improvement, as well. Before CHAMP, only 6% of patients with known coronary artery disease achieved an LDL level below 100 mg/dL. One year after the program was initiated, there was an almost 10-fold improvement to 58%. Most important, the need for repeat hospitalization was cut in half, and there was significant reduction in all causes of mortality.

The program was also found to be cost-effective, despite the expense of medications. On average, $1,000 was saved per patient in total medical costs over the first year because of the reduced need to rehospitalize patients for revascularization.

Other hospitals, both academic and nonacademic, urban and rural, have replicated our program successfully.

A NATIONWIDE EFFORT IS NEEDED

The results we achieved with CHAMP do not happen without a systematic effort. We need to have methods in place to ensure that lifesaving therapies are initiated and maintained.

New guidelines from the NCEP[18] and the American Heart Association and American College of Cardiology[21] both endorse in-hospital initiation of combination therapy for hospitalized patients with atherosclerosis. The American Heart Association has started a new program based on CHAMP called Get with the Guidelines, which provides volunteers who work with hospital-based teams in every acute care hospital to ensure implementation. They are also using an on-line data collection tool, so that as doctors are discharging patients, they can check their care relative to the national guidelines.

Now is the time to ensure that each and every patient with atherosclerosis is being treated with proven, guideline-recommended, lifesaving therapies.

Needed: Systematic programs to improve compliance with guidelines

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