Aggressive Treatment: The Time is Now

Number 80 June, 2003

Atherothrombosis (a combination of atherosclerosis that is compounded and extended by thrombus formation) is a sneaky disease. It begins silently (atherosclerosis). Neither patients nor physicians are aware of it. Then suddenly it strikes (plaque rupture and thrombosis)—the patient presents with unstable angina, an acute myocardial infarction, an acute cerebral vascular accident (CVA) or sudden cardiac death. But atherothrombosis, which can attack the coronary, cerebral or peripheral arterial vessels, is not just sneaky; it is ruthless. Assuming they were fortunate enough to survive the initial presentation, 80% to 90% of patients who have it die of it.

Prevention of primary events or recurrent events is the most aggressive treatment and is mandatory for improved outcomes. In patients with known cardiovascular disease and those at high-risk for it, physicians must begin to treat atherothrombosis earlier, with combination therapy of statins—regardless of baseline lipid levels—aspirin, ACE inhibitors, and beta-blockers. If a combination of these four CV medications is used in all patients with CVD who have no contraindication 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 CV event is only 7.

These mortality-reducing therapies in coronary artery disease (CAD) patients are still underused despite overwhelming clinical evidence, expert opinion and evidence-based guidelines. This is even more true in cerebral vascular disease and peripheral vascular disease patients.

In addition to the traditional approach of treating the acute ischemic problem with revascularization, the underlying disease process, atherothrombosis, a damaged vascular bed, must be treated. Target "*the systemic disease*", not the lumen!

Global Risk Reduction

Most patients with CAD live longer if treated with CVD protective drugs, making a strong case for treatment of atherothrombosis regardless of where in the body it occurs. Shot-gun therapy (good in this case)—treating the entire vascular bed—gives us the advantage of not having to know exactly where the next at-risk lesion is. The rapid reduction in inflammatory markers (hs-CRP), especially with statins, and the role inflammation plays in plaque rupture provide the rational for starting therapy at presentation regardless of baseline lipid values.

Additionally we are taking advantage of this early window of opportunity in the hospital, when patients are more amenable to treatment. Patients and physicians are more apt to view this treatment as essential and compliance is proven to be significantly better. Starting treatment as an outpatient in patients without symptoms can be a difficult barrier for both physician and patient to cross.

Starting Aggressive Therapy Before an Event

New guidelines and recent studies support the aggressive treatment of patients with known atherothrombosis whether they have coronary, peripheral, carotid or cerebral vascular disease. It doesn't matter how the diagnosis was made, whether the patients have symptoms, or whether they have undergone revascularization. But we don't have to wait until patients have an event before we start treatment. Preventative therapy with aspirin, statins, beta-blockers, and ACE inhibitors can be started once we have identified a high-risk patient with sub-clinical disease. It is proven that this slows disease progression. ***Patients with diabetes have subclinical disease*** and the same risk as a patient with known CAD.

Diabetics should be treated aggressively with combination medical therapy. Atherothrombosis accounts for most deaths among diabetics. Angiotensin II blockers (ACE inhibitors and angiotensin receptor blockers [ARBs]) have also been shown to decrease the progression of renal disease in diabetics. Recent information would suggest that the combination of both angiotensin II blockers would offer even more renal protection.

In patients with 2 or more major cardiac risk factors, the Framingham risk model can be used to identify high and moderate risk patients. Aggressiveness of treatment with statins is determined by the calculation. If 10- year risk is greater than 20%, we treat with statins to goal LDL-C of 100mg/dL and aspirin. If 10-year risk is between 10% and 20%, we start therapeutic lifestyle changes (TLC) and aspirin, then go to statins if that approach is unsuccessful.

Identification of the metabolic syndrome, which affects millions of pre-diabetic persons in the US, is important because it is associated with a 2-fold increased risk for CAD. Features include, abdominal (also known as central) obesity, which is becoming increasing prevalent; insulin resistance, leading to hyperinsulinemia; hypertryglyceridemia; low HDL-C levels; hypertension and a pro-coagulant state. Treatment centers on TLC, as diet and exercise are proven to prevent progression to diabetes. Aspirin and medical treatment of hypertension are obviously indicated along with correction of lipid abnormalities.

Now is the time to ensure that each and every patient with atherothrombosis or at high-risk for its development is being treated with proven, guideline recommended, life-saving therapies. TLC should be part of all of these therapeutic programs.

New Aggressive Hypertension Guidelines

May was National High Blood Pressure Education Month, so we have to give some space to the just released new national guidelines, the seventh report of the Joint National Committee (JNC 7). They recommend a more aggressive approach to detecting and treating hypertension, including a new "pre-hypertension" classification, which covers about 22% of American adults or about 45 million persons. They also emphasize the need for clinicians to pay more attention to systolic hypertension in patients older than 50. It is a more important CV risk factor, much more common and harder to control.

Key messages:

- After age 50, systolic BP >140 mm Hg is a much more important risk factor for CV disease than diastolic BP.
- The risk of CV disease begins at 115/75 mm Hg and doubles with each 20/10 mm Hg increment. Individuals who have normal BP at age 55 have a 90% lifetime risk for developing hypertension.
- Normal BP is less than 120/80. A systolic BP of 120-139 mm Hg or a diastolic BP of 80-89 mm Hg should be considered as pre-hypertensive and requires health-promoting lifestyle modifications to prevent CV disease.
- Most patients with hypertension will require 2 or more anti-hypertensive medications to achieve goal BP.
- Most patients with uncomplicated hypertension should receive a thiazide-type diuretic, either alone or combined with drugs from other classes.
- Certain high-risk conditions (CVD or DM) are compelling indications for the initial use of other anti-hypertensive drug classes including ACE inhibitors, angiotensin-receptor blockers, ß-blockers, or calcium channel blockers.
- If BP is >20/10 mm Hg above goal BP, consider initiating therapy with 2 anti-hypertensive agents, including a thiazide-type diuretic.

Chobanian AM et al. *JAMA 2003; 289(19): 2560-2572*

Updated Guidelines: http://www.nhlbi.nih.gov/hbp

In an accompanying editorial the authors write, "Lowering BP toward the new goal level of 120/80 mm Hg will decrease heart attacks, heart failure, stroke, kidney disease, and will save lives." (Kottke et al. *JAMA* 2003; 289: 2573-74)

The Debate Begins

Experts at these hypertension meetings raised several concerns about the guideline changes. They feared that changing the label from hi-normal blood pressure to pre-hypertension would cause undue patient concern. I believe that the new label more accurately describes the urgency of the situation and hope it will prompt people to take preventative action earlier.

They were also concerned that diuretics were named the drug of first choice. The committee emphasized

that they are not inflexible in this regard. All five classes of medication (diuretics, ACE inhibitors, ARBs, beta-blockers, and calcium blockers) can adequately assist with control of hypertension. They do emphasize however, that diuretics enhance the anti-hypertensive efficacy of multi-drug programs, are more affordable than other anti-hypertensive agents and are virtually unsurpassed in preventing the CV complications of hypertension. This is supported by multiple studies including ALLHAT. The only exception was the recent Second Australia National Blood Pressure trial, which reported slightly better outcomes with an ACE inhibitor. As a cardiologist I'm slightly prejudiced (HOPE etc) and still love the combination of ACE inhibitors married to a diuretic.

Control rates for hypertension are stagnant at 34%. The burden of hypertension can be reduced with more aggressive recognition and treatment in conjunction with therapeutic lifestyle changes (TLC)—diet and exercise. On a larger scale, public health approaches provide an opportunity to lower the BP of a population, including reducing calories, saturated fat, and salt in processed foods and increasing community and school-based opportunities for physical activity. These initiatives become especially critical as obesity reaches epidemic proportions in the US. Currently, 122 million adults are overweight or obese, contributing to the rise in BP and metabolic syndrome.

News Briefs:

What is the most effective beta-blocker in HF?

Results of the **C**arvedilol **O**r **M**etoprolol **E**uropean **T**rial (**COMET**) will be presented at the European Society of Cardiology in France later this month. Several large trials have shown the benefits of beta-blockers (including both carvedilol and metoprolol) in HF. Carvedilol has additional properties (beta-2 blockade, alpha-1 blockade—resulting in decreased systemic vascular resistance, increased insulin sensitivity, and anti-oxidant properties) which has led to speculation that it could be more beneficial than other beta-blockers. COMET was conducted to see if these differences translate into improved mortality.

This is the first head-to-head mortality study comparing two beta-blockers in patients with chronic HF. *There was a clear survival benefit with carvedilol when compared to metoprolol in chronic HF patients.* No further details are available.

Atkins Not So Crazy…maybe?

Two recent studies were published in the May 21st N Engl J Med involving the extremely popular but controversial Atkins diet—low carbohydrate, high protein, high fat program—compared to a more conventional low calorie, low fat, high carbohydrate program (Samaha FF et al. *N Engl J Med* 2003; 348; 2074-81 & Foster GD et al. *N Engl J Med* 2003; 348: 2082-90).

Atkins has promoted his approach without scientific data and the cardiology community has criticized this diet also without scientific data—therefore the studies. The *Atkins diet was associated with more weight loss*—though minimal a year out—*and* was also associated with a greater improvement in triglycerides and HDL-C levels as well as improved insulin sensitivity…i.e., *an improved cardiac risk profile.*

These findings should be interpreted with caution, given the short duration of the study. Future studies evaluating long-term cardiovascular outcomes are needed before a high-fat, carbohydrate-restricted diet can be endorsed. These results, however, certainly would make anyone think twice before dismissing the Atkins diet.

Ezetimibe "Turbocharges" Statin

The "one-two" punch of the co-administration of ezetimibe (Zetia 10 mg)—a cholesterol absorption inhibitor—and a statin—a cholesterol production blocker—are leaving investigators quite optimistic. The co-administration of atorvastatin (varying dosages) and ezetimibe significantly reduced LDL-C and triglycerides, increased HDL-C levels and reduced hs-CRP compared with those just receiving the statin. (Ballantyne CM et al. *Circulation* 2003; Electronic April 29 http://circ.ahajournals.org)

Mario L Maiese, DO, FACC, FACOI
Associate Professor of Medicine, UMDNJSOM

Heartbeats can be found @ www.sjhg.salu.net Patient Education—From Your Physician.
Mail to: maiese@dnamail.com