Heart Affairs

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Cholesterol - Lower is better

What should be the cholesterol levels in a patient with heart disease? The lipid portion of PROVE IT/TIMI - 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 Investigators) studied about 4,000 patients with acute coronary syndrome to determine whether intensive low-density lipoprotein (LDL) cholesterol lowering with statin therapy will reduce coronary events and mortality.[1] The patients were randomized to either 40 mg/day of pravastatin or 80 mg/day of atorvastatin. At a mean follow-up of 24 months the LDL level attained on pravastatin 40 mg was 95 mg/dl, whereas the level attained on atorvastatin 80 mg was 62 mg/dl. The primary endpoint (all-cause mortality, myocardial infarction, unstable angina requiring hospitalization, revascularization, or stroke) was reached in 26.3% of pravastatin group and 22.4% of atorvastatin group (p = 0.005). Patients in whom statin therapy was associated with C-reactive protein levels of less than 2 mg/dl had better clinical outcomes regardless of the LDL level achieved with therapy. The Reversal of Atheroscelerosis with Aggressive Lipid Lowering study (REVERSAL) investigated the progression of coronary atherosclerosis (evaluated by intravascular ultrasound) in about 500 patients with angiographically documented coronary artery disease.[2] Intensive lipid-lowering therapy (80 mg of atorvastatin daily) showed significant reduction in both atherosclerotic progression and adverse clinical outcomes compared to moderate lipid-lowering therapy (40 mg of pravastatin daily). These benefits were associated with significantly greater concomitant reductions in C-reactive protein and atherogenic lipoproteins. Thus, there is now considerable evidence to suggest that in patients with documented atherosclerosis, diabetes or high Framingham risk score the goal of lipid-lowering therapy should be LDL of 70 or lower.[3]

1. Cannon CP. Pravastatin or atorvastatin evaluation and infection therapy - thrombolysis in myocardial infarction 22 investigators. intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J. Med 2004;350:1495-1504.
2. Nissen SE. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis; a randomized controlled trial. Reversal of atherosclerosis with aggressive lipid lowering (REVERSAL). JAMA 2004;291:1071-80.
3. Grundy SM. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. Circulation 2004;228:227-39.

Heart failure therapy - Moving from drugs to devices

Sudden death from ventricular arrhythmias remains a leading cause of death among patients with congestive heart failure (CHF). The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed that by implanting a defibrillator in patients with CHF significantly reduces mortality.[1] SCD-HeFT was a double-blind study of about 2,500 patients with NYHA class II or III CHF and a left ventricular ejection fraction (LVEF) of 35% or less, randomized to conventional therapy for CHF plus placebo (n = 847), conventional therapy plus amiodarone (n = 845), or conventional therapy plus implantable cardioverter defibrillator (ICD). The primary outcome was all-cause mortality. At a median follow-up of about 4 years, there were 244 deaths (29%) in the placebo group, 240 (28%) in the amiodarone group, and 182 deaths (22%) in the ICD group. The risk of death with amiodarone was not significantly different from that with placebo (hazard ratio [HR] 1.06; 97.5% confidence interval [CI], 0.86-1.30; p = 0.53). However, ICD therapy was associated with a 23% decreased risk of death compared with placebo (HR, 0.77; 97.5% CI, 0.62-0.96; p = 0.007), and a 7.2% absolute decrease in mortality after five years in the overall population.

The results of SCD-HeFT, COMPANION and CARE-HF have demonstrated that electrical therapy (with implantable defibrillators and cardiac resynchronization devices) improves morbidity and mortality in patients with CHF and is going to play an increasingly important role in future management of heart failure.[2,3]

1. Bardy GH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. sudden cardiac death in heart failure trial (SCD-HeFT). N Engl J Med 2005;352:225-37.
2. Bristow MR. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
3. Cleland JG. The effects of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.

Atrial Fibrillation - Importance of pulmonary veins

Over the last few years several investigators have contributed to our understanding of atrial fibrillation and its mechanism. It is now becoming clear that pulmonary veins play a very important role in the initiation of atrial fibrillation. The seminal observation by Haissaguerre et al that a

fibrillation. The seminal observation by Haissaguerre et al that a large proportion of patients with paroxysmal atrial fibrillation (AF) have ectopic foci located in the proximal pulmonary veins opened a new chapter on mechanisms of atrial arrhythmias.[1] Since then, multiple groups have demonstrated initiation of AF from pulmonary veins[2], which may be larger in diameter and be associated with larger left atria than in patients without AF.[3,4] Most foci responsible for AF appear to come from the upper pulmonary veins and are ostial in location.

The finding of pulmonary veins as the source of ectopic foci for initiation of AF, has naturally led to efforts at using radiofrequency ablation to eliminate these foci. Initial attempts were aimed at directly ablating the foci inside the pulmonary veins but resulted in unacceptable complication of pulmonary vein stenosis.[5] More recently two different approaches are being utilized. In one approach the electrical connections between the pulmonary veins and left atrium are ablated (segmental ostial ablation)[6], while in another approach developed by Pappone et al, long lesions are made encircling the pulmonary veins and isolating them from left atrium (circumferential left atrial ablation). The circumferential approach seems to be more effective with elimination of AF in approximately 85% of patients at 6 months as compared to 67% with ostial approach.[7] Radiofrequency catheter ablation of AF is an exciting and rapidly evolving field. It provides us with one more tool to manage a highly complex and prevalent disease.

1. Haissaguerre M. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. E Engl J Med 1998;339:659-66.
2. Jais P. Distinctive electrophysiological properties of pulmonary veins in patients with atrial fibrillation. Circulation 2002;106:2479-85.
3. Kato R. Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation; lessons learned by use of magnetic resonance imaging. Circulation 2003;107:2004-10.
4. Schwartzman D. Characterization of left atrium and distal pulmonary vein morphology using multidimensional computed tomography. J Am Coll Cardiol 2003;41:1349-57.
5. Morady F. Catheter ablation of supraventricular arrhythmias: state of art. Pacing Clin Electrophysiol 2004;27:125-42.
6. Pappone C. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 2003;42:185-97.
7. Oral H. Catheter ablation for proxysmal atrial fibrillation: segmental pulmonary ostial ablation versus left atrial ablation. Circulation 2003;108:2355-60.

A Novel Breakthrough In The Management of Migraine: Addressing the "Heart" of the Problem

Migraine is present in 12% adults contributing significantly to the health care burden.[1] Recently a large body of evidence has accumulated that suggests a possible link between migraine and right to left heart shunts (RLS).[2] A recent interventional trial (n=162) of transcatheter patent foramen ovale (PFO) closure showed that before the intervention, 35% patients had migraine and 68% of those had migraine with aura (MA) (3). One year follow-up post-procedure showed complete resolution of migraine symptoms in 56% patients while 14% reported a significant (>or=50%) reduction in migraine frequency.[3] Azarbal et al studied 89 adult patients - 66 PFO/23 atrial septal defect (ASD), who underwent transcatheter closure of an interatrial communication.[4] Before the procedure, MA was present in 42% patients (45% patients with PFO and 30% patients with ASD). At three months after the procedure, migraine disappeared completely in 75% patients with MA and in 31% patients with migraine without aura. Of the remaining patients, 40% had significant improvement (>or=2 grades by the Migraine Disability Assessment Questionnaire).[4]

Interatrial communications may play a role in the etiology of migraine either through paradoxic embolism to the brain, which precipitates a spreading wave of depolarization that is recognized as migraine or humoral factors that escape degradation in bypassing the pulmonary circulation. These findings also lend shoulder to the hypothesis that the "migraine stroke" or hemiplegic migraine may not be caused by intense vasospasm but may be a manifestation of a paradoxical embolus through a RLS. A randomized trial is needed to determine whether transcatheter closure of interatrial shunts is an effective treatment for migraine.

1. Lipton Rb, Stewart WF, Kolodner K, Liberman J, Steiner TJ, Stewart WF migraine in the United States; epidemiology and patterns of health care use. Neurology 2002; 58:885-94
2. Del Sette M, Angeli S, Leandri M, Ferriero G, Bruzzone GL, Finocchi C,Gandolfo C. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis. 1998;8:327-30.
3. Reisman M, Christofferson RD, Jesurum J, Olsen JV, Spencer MP, Krabill KA, Diehl L, Aurora S, Gray WA. Migraine headache relief after transcatheter closure of patent foramen ovale. J Am Coll Cardiol. 2005;45:493-5.
4. Azarbal B, Tobis J, Suh W, Chan V, Dao C, Gaster R. Association of interatrial shunts and migraine headaches: impact of transcatheter closure. J Am Coll Cardiol. 2005;45:489-92.

Aspirin Prevention: Gender Differences

Low dose aspirin (100mg) trial in about 40,000 healthy women for cardiovascular disease (CVD) prevention highlighted gender differences in CVD biology.[1] This randomized trial involved women with a mean age about 55 years given either low dose aspirin every other day or placebo and followed for major clinical events (non-fatal myocardial infractions, non-fatal cardiovascular mortality). There were 477 events in the aspirin group and 522 events in the placebo group (P= 0.13). There was a 24% reduction in the incidence of ischemic stroke (P = 0.0008; relative risk= 0.7), and a non-significant increase in the risk of hem-

in the incidence of ischemic stroke (P = 0.0008; relative risk= 0.7), and a non-significant increase in the risk of hemorrhagic stroke (51% vs. 41%; P= 0.83). A total of 198 myocardial infarctions occurred in the aspirin group and 193 in the placebo group (P=0.89). Similarly coronary revascularization procedure was required in 89 women in the aspirin group whereas 37 required it in the placebo group (P=0.61). However death from any cause showed a non-significant reduction (P=0.32). Thus ischemic stroke and transient ischemic attacks were the only significant benefits of aspirin therapy in this relatively low risk population of women[1], which is in sharp contrast to an earlier study involving male doctors which showed a significant reduction in myocardial infarction but no effect on stroke or death rates.[2]

1. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352:1293-304.
2. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.