

# West Suburban Cardiologists

## Welcome To Our Inaugural Newsletter!

Highlights from ACC 2005

*In this issue, Dr. Dan Krauss reports on several key announcements and presentations from this year's meeting of the American College of Cardiology held in Orlando, Florida. For more information, please visit our website at [www.westsubcardiology.com](http://www.westsubcardiology.com).*

### Hypertension

#### Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA)

Generational differences in anti-hypertensive therapy were explored in the **ASCOT-BPLA** Trial, in which a traditional regimen of beta blockers and diuretics was pitted against newer agents from the ACE inhibitor and calcium channel blocker classes in patients with hypertension and multiple cardiac risk factors to look for possible reduction in subsequent coronary heart disease events.

**ASCOT-BPLA** enrolled patients ages 40-79 with a baseline untreated BP  $\geq 160/100$  or treated BP  $\geq 140/90$  and 3 or more risk factors for a future cardiovascular event, but no history of documented CHD. 9618 patients were randomized to treatment with atenolol 50-100mg with addition of bendroflumethiazide-K 1.25-2.5mg as necessary, while 9639 patients were randomized to amlodipine 5-10mg with ad-

dition of perindopril 4-8mg as needed. The target BP was  $< 140/90$  ( $< 130/80$  in diabetics). Doxazosin GITS 4-8mg could be used as a third agent in both groups if needed. In October 2004 the Data Safety Monitoring Board prematurely stopped the trial due to disadvantage in the beta blocker-diuretic arm after average follow-up of 5.4 years

Overall BP was lowered by 28/16 mmHg on therapy, slightly more in the calcium blocker/ACE inhibitor arm (by 3/2 mmHg). Compared with atenolol-thiazide treated patients, those treated with amlodipine/perindopril experienced a 14% reduction in all-cause mortality ( $p \leq 0.005$ ), 24% reduction in CV mortality ( $p \leq 0.005$ ), 14% reduction in all coronary events ( $p \leq 0.005$ ), 23% reduction in fatal or nonfatal stroke ( $p \leq 0.001$ ), 16% reduction for all CV events and procedures ( $p \leq 0.001$ ), and a 32% reduction in new diabetes ( $p \leq 0.001$ ). For the primary endpoint of nonfatal MI and fatal CHD, there was a nonsignificant 10% reduction in the calcium blocker/ACE inhibitor arm.

**Comment:** This trial has major implications for antihypertensive therapy. JNC 7 guidelines adopted in 2003 advocate thiazide diuretic use as initial therapy for most patients with hypertension, either alone or in combination. ASCOT-BPLA, however, suggests that newer agents have the potential to significantly reduce the burden of CHD events in hypertensive patients and may be preferable first-line drugs. The mechanism of this advantage is unclear; the modest blood pressure advantage in favor of amlodipine-perindopril seen in ASCOT-BPLA may explain its advantage. Alternatively, independent beneficial effects of these agents and/or deleterious effects of atenolol-thiazide could be involved.

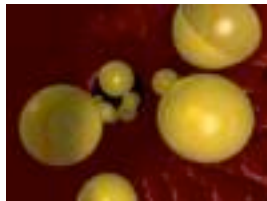


## Lipid Lowering

### Treating to New Targets Trial (TNT)

**TNT** was a 5 year study testing the hypothesis that aggressive LDL cholesterol lowering well below accepted optimal levels in patients with stable coronary heart disease (CHD) would further reduce the risk of major cardiovascular events beyond that achieved with standard moderate statin therapy.

The study subjects included 10,001 patients between 35 and 75 years of age with stable CHD, defined as prior MI, prior or current angina with objective evidence of coronary atherosclerotic disease, or prior coronary revascularization. Mean baseline LDL cholesterol levels ranged from 130-250 mg/dL. All patients were treated with atorvastatin 10mg/day during an 8 week open-label run-in period to a mean LDL cholesterol of 98 mg/dL; patients were then randomized in a double-blinded fashion to an intensive lipid-lowering regimen (atorvastatin 80mg/day) or to standard moderate statin therapy (atorvastatin 10mg/day). The primary endpoint was the occurrence of a major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related MI, resuscitation



from cardiac arrest, or fatal or nonfatal stroke. The groups were well matched at baseline, with an average age of 61 years old, 81% male, 94% white, and similar rates of hypertension (54%), diabetes (15%), current smoking (14%), and prior MI (58%).

Moderate statin therapy with atorvastatin 10 mg/day lowered the mean LDL cholesterol to 101 mg/dL, while intensive therapy with atorvastatin 80 mg/day lowered the mean LDL cholesterol to 77 mg/dL. Mean HDL cholesterol levels were comparable in both groups at 47 mg/dL.

The primary endpoint occurred in 8.7% of patients treated with atorvastatin 80 mg/day and 10.9% of patients receiving atorvastatin 10 mg/day, a 22% relative risk reduction ( $p < 0.001$ ). Rates of nonfatal MI and fatal or nonfatal stroke were also significantly reduced in the high dose atorvastatin group, 22% and 25%, respectively. Overall death rates were equal in both arms. Treatment was well tolerated in both groups, with myalgias reported in 5% of both arms, although the rate of elevation of liver function tests was greater in the atorvastatin 80 mg/day group (1.2% vs. 0.2%,  $p < 0.001$ )

*Comment:* This landmark trial lends further credence to the "lower is better" hypothesis regarding lipid management in CHD patients, and nicely complements results from the **Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE IT)**, in which 4162 ACS patients were randomized to "standard" statin therapy using pravastatin 40 mg/day vs. intensive therapy with atorvastatin 80 mg/day. High dose atorvastatin patients achieved a mean LDL cholesterol of 62 mg/dL, and gained a 16% risk reduction in the composite endpoint of death, MI, stroke, unstable angina requiring hospitalization, and revascularization > 30 days after randomization compared with the pravastatin arm (mean LDL 95 mg/dL). Importantly, however, **TNT** was not powered to detect mortality differences between the high- and low-dose atorvastatin treatment arms, and a trend towards higher non-cardiovascular mortality was seen with high-dose atorvastatin therapy.

## Women and Heart Disease

### A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women – The Women's Health Study

Aspirin's efficacy in the secondary prevention of MI is well documented, and an

evenly matched at baseline with an average age of 55 years old, 28% premenopausal, 26% hypertensive, 3% diabetic, and 13% current smokers. Major cardiovascular events, defined as nonfatal MI, nonfatal stroke, or death from CV causes, occurred in 477 women taking aspirin and 522 women receiving pla-

cardiovascular events ( $p=0.008$ ), 30% in ischemic stroke ( $p=0.05$ ), and 34% in MI ( $p=0.04$ ) compared with patients receiving placebo. The rate of transfusion-requiring hemorrhage was increased by 40% in women taking aspirin ( $p=0.02$ ).

*Comment:* This trial refines the role of aspirin for primary prevention of cardiovascular events in women. In women younger than 65 years old, no primary endpoint related to cardiac mortality or morbidity was decreased by aspirin, while both TIA and stroke risks were reduced, suggesting an important and biologically consistent protective effect. Aspirin for primary prevention in women over 65 years old is supported by the data, but given the increased risk of hemorrhage on aspirin therapy, recommendations should be made on an individual basis. Importantly, these data do not undermine the well-documented efficacy of aspirin therapy as secondary prevention in women who have had previous cardiac events.



abundance of evidence suggests that it is beneficial for primary prevention in men. Data on primary prevention in women, however, is limited. This question was addressed in the **Women's Health Study**, a randomized, prospective, double-blind, placebo-controlled trial of 39,876 healthy women followed for a mean of 10 years.

Aspirin 100mg every other day was given to 19,934 women aged 45 or older who were without CHD, cerebrovascular disease, or other major medical problems. The groups were

cebo, a nonsignificant 9% risk reduction. Aspirin therapy did not significantly reduce the overall risk of MI, or the risks of fatal MI, nonfatal MI, coronary revascularization, cardiovascular death, or death from any cause. A 24% reduction in the risk of ischemic stroke ( $p=0.009$ ) and a 22% reduction in the risk of TIA ( $p=0.01$ ) were noted in aspirin treated patients without a significant increase in hemorrhagic stroke rate. Aspirin's greatest benefits were seen in women at least 65 years old on study entry; this group gained risk reductions of 26% in major

## Antithrombotic Therapy in Acute MI

The addition of clopidogrel to standard antithrombotic therapy was studied in two trials released at the ACC in 2005.

**COMMIT/CCS-2 (Clopidogrel & Metoprolol in Myocardial Infarction Trial)** was a Chinese study of 45,852 patients with suspected acute MI randomized to clopidogrel 75mg daily vs. placebo. Patients were randomized concurrently in a factorial design to treatment with metoprolol or placebo. All patients received aspirin 162mg daily; patients undergoing primary PCI or deemed to be at high risk of bleeding were excluded. Primary endpoints were all-cause mortality and a composite of death, reinfarction, or stroke at hospital discharge, with mean follow-up of 16 days. Fifty percent of patients in each group received fibrinolytic therapy, 2/3 for ST segment elevation MI presenting within 12 hours of onset. The groups were evenly matched for use of anti-coagulants (75%), ACE inhibitors (68%), and nitrates (94%).

Mortality was reduced by 7% in patients receiving clopidogrel compared with placebo (7.5% vs. 8.1%,  $p=0.03$ ). The combined endpoint of death, reinfarction, or stroke was reduced by 9% with clopidogrel therapy (9.3% vs. 10.1%,  $p=0.002$ ). Reinfarction was

lower in the clopidogrel group (2.1% vs. 2.4%,  $p=0.02$ ), but stroke rates did not differ by treatment. The benefits of clopidogrel treatment in the composite endpoint were seen in all prespecified subgroups including gender, age, time from symptom onset, and fibrinolytic use. There was no excess in major bleeding or hemorrhagic stroke with dual anti-platelet therapy.

**CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28)**. This study evaluated 3491 patients with ST segment elevation MI within 12 hours of onset. All patients received fibrinolytic therapy, aspirin, and, when appropriate, heparin; they were then



randomized to a clopidogrel 300mg loading dose followed by 75 mg daily, or placebo. Angiography was performed 2-8 days later. The primary endpoint was occlusion of the infarct-related artery, death or reinfarction by the time of angiography. Baseline clinical characteristics were similar in the two groups, as were usage of beta blockers (89%), statins (80%), and ACE inhibitors/ARBs (73%).

Clopidogrel treatment conveyed a 36% reduction in the primary endpoint (15% vs. 21%,  $p=0.00000036$ ). Benefit was seen regardless of age, gender, infarct location, or type of fibrinolytic agent or heparin used. This powerful risk reduction was primarily driven by improved patency of the infarct-related artery in patients treated with clopidogrel (*TIMI flow grade 0/1* 11.7% vs. 18.1% in the placebo arm,  $p<0.001$ ). The 30 day composite endpoint of cardiovascular death, reinfarction, or recurrent ischemia requiring urgent revascularization was also reduced by 20% with clopidogrel therapy (11.6% vs. 14.1%,  $p=0.03$ ). There was no significant difference in bleeding rates between the two groups, even in those patients who underwent CABG.

**Comment:** Taken together, these trials represent almost 50,000 patients with acute MI in whom the addition of clopidogrel to standard anti-thrombotic therapy, including fibrinolysis, resulted in significant reductions in short-term mortality, reinfarction, and recurrent ischemia. No significant excess in hemorrhage was noted. These trials did not include patients referred for direct angioplasty, which limits the generalizability of clopidogrel pretreatment in this subset of patients.

Thomas Levin MD April 2005