Late-Breaking Trials
ACC '03

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This *Heartbeat* will summarize some of the results from late- breaking trials presented at the American College of Cardiology (ACC) meetings in Chicago from March 30th to April 2nd that should have some impact on your future practice.

SPORTIF III: Ximelagatran not inferior to warfarin in stroke…and easier to manage

In high-risk patients with atrial fibrillation, warfarin reduces stroke by 60% compared to a 20% reduction with aspirin. According to the results of the **S**troke **P**revention using an **OR**al **T**hrombin **I**nhibitor in atrial **F**ibrillation (**SPORTIF III**) trial, ximelagatran (Exantra; Astra Zeneca) is as effective as standard warfarin therapy in preventing stroke and systemic embolic events in patients with atrial fibrillation (AF), with less overall bleeding. The open-label study randomized 3407 patients from 23 countries with nonvalvular AF to a fixed dose of ximelagatran (36 mg bid) or adjusted-dose warfarin with a target INR of 2 to 3 based on monthly measurements. There was no significant difference in intracranial hemorrhage or rates of fatal or major bleeding. All-cause mortality was the same for both groups.

Because warfarin has established efficacy in preventing strokes, a placebo-controlled study was unethical. The goal was to see if ximelagatran was at least as effective as warfarin. The advantage of ximelagatran is the convenience and safety of fixed oral dosing. Routine coagulation monitoring and dose adjustment are not necessary, as they are with warfarin, and there is a low potential for food and drug interactions.

However, use of the new drug was associated with higher levels of transaminase liver enzymes - above 3 times the upper limit of normal - seen in 6.5% of patients in the ximelagatran group compared to 0.7% of patients on warfarin (p=0.001). The hope is that these elevations are not serious. There were no cases of liver failure or any systemic symptoms. Elevated liver enzymes returned to baseline spontaneously, or upon withdrawal of ximelagatran.

Implication: *Ximelagatran has the potential to extend treatment across the population at risk, preventing many more strokes in the atrial fibrillation population. Stoke prevention treatment will be easier both for the patient and for the physician.*

COMPANION: Synchronous pacemaker-defibrillator combination reduces all-cause mortality…and improves quality

Results of the 1,634-patient Comparison of Medical Therapy, Pacing and Defibrillation in the Chronic Heart Failure (**COMPANION**) study show that implanting a combination resynchronization-defibrillator device in Class III/IV heart failure (HF) patients, already on optimal medical therapy, reduced all-cause mortality by 43%.

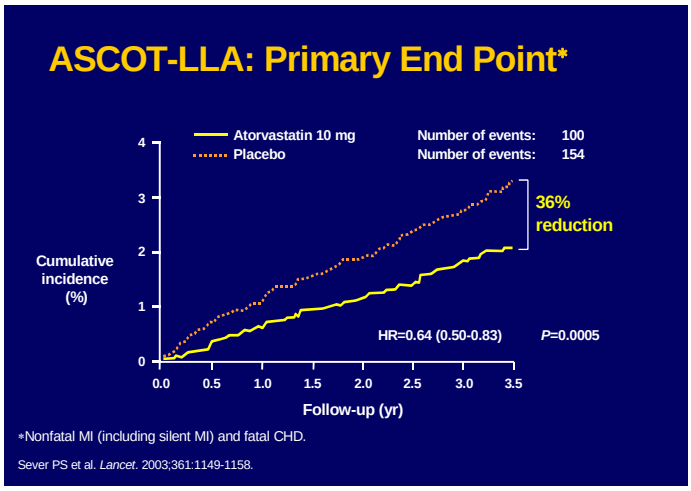
In addition to that 43% reduction of mortality on top of what is achieved with the best medical therapy (beta-blockers, ACE-inhibitors and spironolactone), patients who received either cardiac resynchronization therapy (CRT)–a synchronous right and left ventricular pacemaker—or a combination of CRT and defibrillator device CRT-D had 35% fewer hospitalizations for any cause and 39% fewer hospitalizations for HF. The benefits are impressive.

Implication: *CRT or CRT-D treatment will result in a significant improvement in quality of life for HF patients as well as improved survival, when used with other indicated medical therapy—B-blockers, ACE inhibitors and spironolactone.*

ASCOT-LLA: Atorvastatin improves outcomes in hypertensives with normal or mildly elevated cholesterol

According to the results of the **L**ipid-**L**owering **A**rm of the **A**ngio-**S**candinavian **C**ardiac **O**utcomes **T**rial (**ASCOT-LLA**), hypertensive patients with normal or slightly elevated cholesterol who took atorvastatin had a 36% reduction in the primary end point of nonfatal MI (including silent MI) and fatal CHD compared with placebo (Figure 1).

Figure 1.



Planned follow-up was 5 years, but treatment was stopped after 3.3 years, when highly significant reductions in the primary end point had emerged. Overall, 100 primary end-point events occurred in the atorvastatin group compared with 154 events in the placebo group (hazard ratio 0.64 [95% CI 0.50-0.83], *P*=0.0005).

At the end of the study, mean TC concentration was reduced 19% (163 mg/dL atorvastatin vs. 201 mg/dL placebo), mean calculated LDL-C was reduced 29% (90 mg/dL vs. 126 mg/dL), and mean TG was reduced 14% (114 mg/dL vs. 132 mg/dL). HDL-C levels decreased, but these changes were minimal.

Blood pressure control throughout the trial was similar in both groups at the end of follow-up, with mean values of 138/80 mm Hg. The 10-mg dose of atorvastatin was not titrated up in ASCOT-LLA, although based on currently available evidence from clinical studies, higher doses would have produced greater reductions in TC and LDL-C concentrations, and this likely would have led to even larger reductions in cardiovascular events. In addition, the authors speculate that had the study continued for the planned 5 years, the reduction in fatal and nonfatal CHD events could have approached 50%.

Adverse events and rates of liver-enzyme abnormalities did not differ between the two groups. There was one nonfatal case of rhabdomyolysis reported in a man in the atorvastatin-treated group who had a high alcohol intake and a recent febrile illness (Sever PS et al. *Lancet.* April 5 2003;361: 1149-1158).

For high-risk patients usage of each of the available statins presently on the market have now been shown to be associated with improved outcomes. “A statin is a statin”….is a statin—at least for this drug class.

Implication: *Because the reductions of major CV events were large, given the short follow-up time, these findings may affect future lipid-lowering guidelines—extending their usage in primary prevention—to improve outcomes.*

Raising HDL-C: slows CAD progression and reduces mortality

The protective effect of HDL-C is well known, while decreasing LDL-C gets most of the press. Unfortunately, about half of MI victims have normal LDL-C levels. Two studies presented at the ACC’03 meeting support the concept that aggressively targeting low HDL-C and increasing it can slow the progression of atherosclerosis and reduce mortality. Treatment included fibrates, and/or niacin along with a cardiovascular (CV) workout program and a heart-healthy diet.

According to the **B**enafibrate **I**nfarction **P**revention (**BIP**) trial, patients who had the highest HDL increases in the fibrate group had a 40% less chance of dying compared to those in the placebo group.

Implications: *HDL-C has an important protective role. Statins are not the only way to treat dyslipidemia. Increasing HDL also improves outcomes. Prevention of heart disease does not always come in pill form.*

EPHESUS: Decreased mortality in HF patients with selective aldosterone blockade

In the Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial (**EPHESUS**), treatment with eplerenone (Inspra®, Pharmacia) in addition to optimal medical therapy early after MI in patients with LV dysfunction and HF reduced overall mortality in this population by 15%. Rates of death from cardiovascular causes and the combination of death from cardiovascular causes and hospitalization for cardiovascular events were also significantly reduced with eplerenone compared with placebo.

Eplerenone, a selective aldosterone blocker that has been called a "cleaner and safer" version of spironolactone, is already approved by the FDA for treatment of hypertension. A total of 6632 patients with an ejection fraction $\leq$40% and rales were randomized to receive eplerenone in a starting dose of 25 mg, titrated to a maximum of 50 mg per day, or to placebo. Patients with diabetes required only an EF of $\leq$40%. Randomization took place an average of seven days after the MI (range 3 to14 days), and patients were followed until 1012 deaths had occurred. The mean dose of eplerenone reached was 43 mg/day. Over 16 months of follow-up, there were significantly fewer deaths and cardiovascular deaths in treated patients as well as a significant reduction in the end point of death from cardiovascular causes or hospitalization for cardiovascular events.

There was an increased incidence of hyperkalemia among patients treated with eplerenone, and the risk became statistically significant among patients with decreased creatinine clearance. This finding emphasizes the need to monitor serum potassium and adjust the dose of eplerenone accordingly. Risk is minimized by not using eplerenone in patients with decreased creatinine clearance (< 50 ml per minute), baseline serum potassium concentration of more than 5.0 mmol/L or a baseline serum creatinine concentration of more than 2.5 mg/dL. (Pitt B et al. *N Engl J Med* April 3 2003; 348: 1309-1321.)

Implication: *Eplerenone has the potential to reduce both overall mortality and that related to cardiovascular causes, as well as hospitalization for cardiovascular events, when given in addition to contemporary standard therapy in patients with acute MI complicated by LV dysfunction and heart failure. Meticulous attention to serum potassium and renal function is strongly recommended.*

Another Plus of Exercise: decreased *hs*-CRP

Hs-CRP, an inflammatory marker of high-risk CAD, is decreased with regular physical exercise. There was a progressive drop in hs-CRP levels with more intense exercise, even after adjusting for smoking, lipid levels and age. The decreases were greater for men compared to women, probably because men exercise more intensely.

Implication: *Physical activity may attenuate inflammation and modify cardiovascular risk without drug therapy.*

INVEST: Calcium channel blocker (CCB) regimen equal to beta-blockers and diuretics

According to the results of the 22,576 patient international Verapamil SR-Trandolapril (**INVEST**) study, verapamil as part of a multi-drug regimen was equally effective in controlling blood pressure, reducing mortality, myocardial infarctions (MIs), and strokes as combination therapy with beta-blockers and diuretics. The CCB-based strategy represents an alternative approach that will be important in patients who cannot tolerate so-called standard care, because it was demonstrated to be as beneficial in terms of preventing adverse outcomes and maybe even superior in terms of preventing new-onset diabetes, according to the presenters.

More than half of the patients were more than 65 years old, and all had documented hypertension and CVD. Patients in the verapamil arm also received an ACE inhibitor, trandolapril, and/or a diuretic to achieve target blood pressure. Trandolapril could be added to the other treatment arm as needed.

Implication: *Clinicians have another option when treating hypertension that results in equal blood pressure reduction and an equal reduction in adverse outcomes***.**

CREDO: Early and late benefits of early and prolonged usage of clopidogrel

The **C**lopidogrel for the **R**eduction of **E**vents **D**uring **O**bservation (**CREDO**) trial, a randomized, double-blind, placebo-controlled study, followed 2,116 patients who were to undergo elective percutaneous coronary intervention (PCI). Patients were loaded with 300 mg and then given 75 mg daily vs. placebo. Both groups received 325 mg of aspirin.

The continuation of clopidogrel and aspirin for one year showed a 26.9% relative reduction of irreversible atherothrombotic events compared to treatment for only 4 weeks. Administration of the loading dose more than 3 hours prior to the procedure did not affect peri-procedural events. However in a sub-group analysis, patients treated at least 6 hours prior to PCI had a significant reduction of peri-procedural major adverse cardiac events. (Steinhubl SR et al. *JAMA* Nov 2002; 288: 2411-20).

This information supports data from the CURE trail, in which the same treatment showed benefit over aspirin alone in acute coronary syndrome (ACS)—unstable angina patients—out to 9 months. Further details from CURE showed that the benefit of clopidogrel started to become evident within the first few hours of treatment. (Yusef S et al. *Circulation* February 25 2003; 107: 966-972)

Implication*: Both aspirin and clopidogrel should be initiated early and continued for the long term in ACS and pre PCI patients to lead to the greatest benefits for the largest number of patients.*

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