Conducted in partnership with the National Cancer Institute, the Cross Trial Safety Analysis was designed to characterize the long-term CV risk associated with celecoxib, a cyclooxygenase-2 (COX-2) inhibitor. Results of the analysis were published immediately following the late breaking trials session in an online version of the journal *Circulation* [Solomon et al. *Circulation* 2008].

Together, the 6 participating trials enrolled 7950 patients and provided the equivalent of 16,070 years of patient follow-up for analysis. Patients with no CV risk factors at baseline were described as low-risk for future cardiac events. Moderate-risk patients had at least one of the following risk factors: age >75 years, hypertension, hyperlipidemia, current tobacco use, or concurrent use of low-dose aspirin. Patients with 2 or more risk factors, and those with diabetes or previous CV disease, were classified as high-risk.

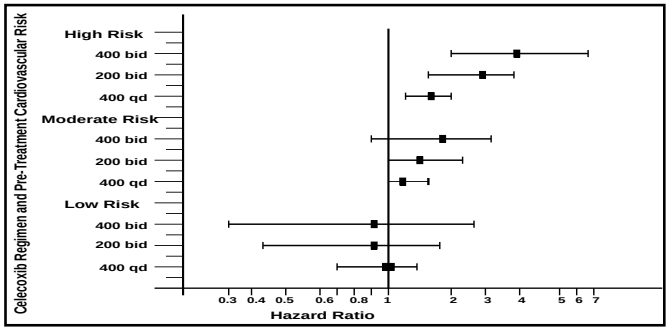
Across all patient groups (median follow-up of 31 months) and dosing regimens, the risk of CV events was elevated with celecoxib use compared with placebo [HR 1.6; 95% CI, 1.1-2.3; p=0.034].

The risk of CV events varied across the different dosing regimens that were evaluated in the trial (p value for dose regimen effect = 0.0005). Hazard ratios for the primary endpoint—a composite of CV death, myocardial infarction, stroke, heart failure, or thromboembolic event—were 1.1, 95% CI, 0.6-2.0 for the once-daily 400 mg dose, 1.8, 95% CI, 1.1-3.1 for the 200 mg dose given twice a day, and 3.1, 95% CI, 1.5-6.1 for the twice-daily 400 mg dose.

Dr. Solomon and colleagues also observed an interaction between baseline CV risk and celecoxib regimen (interaction p=0.034). For patients with the lowest baseline CV risk, the risks associated with the 400 mg once daily, 200 mg twice daily, and 400 mg twice daily regimens were roughly equivalent, with hazard ratios of 1.0, 0.9, and 0.9, respectively. However, for patients with the highest baseline CV risk, the differences across doses were pronounced. The hazard ratios for the primary endpoint were 1.5, 95% CI, 1.2-1.9, 2.3, 95% CI, 1.5-3.4, and 3.5, 95% CI, 1.9-6.4, respectively (Figure 1).

Dr. Solomon noted that the Celecoxib Cross Trial Safety Analysis findings support the American Heart Association position on celecoxib prescribing, which states that the lowest possible doses of celecoxib should be prescribed, especially in patients who are at highest risk of developing CV disease.

Figure 1. Risk of Celecoxib-Related CV Events by Celecoxib Dose and Baseline CV Risk.



Two Drugs Have Potential to Slow Progression of Atherosclerosis

Two trials explored the potential for pharmacologic therapy to slow the progression of atherosclerosis or even cause plaque regression in patients with coronary artery disease (CAD). The studies involved different classes of drugs and different imaging modalities to evaluate the change in the degree of stenosis caused by the atherosclerotic plaque.

In the ASTEROID trial, 507 patients with angiographic evidence of CAD were treated with rosuvastatin 40 mg/day for 24 months in an uncontrolled observational study. The initial results, first presented in 2006, demonstrated that the drug reduced plaque volume, as measured by intravascular ultrasound (IVUS), in arteries with less than 50% stenosis. Rosuvastatin 40 mg was well tolerated, with low rates of elevated ALT (1.8%) and CK (1.2%) observed, and only 12% of patients discontinuing due to adverse events. The current analysis was performed to evaluate changes in vascular lumen by quantitative coronary angiography (QCA) in arteries with more than 25% stenosis.

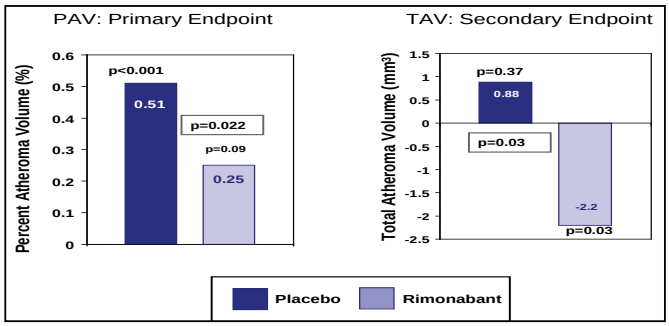
Christie Ballantyne, MD, Baylor College of Medicine, Houston, TX, reported that the coronary angiograms of 292 patients were evaluated at baseline and at 24 months. QCA showed that treatment with rosuvastatin led to an increase in the mean minimal lumen diameter from 1.65 ± 0.36 mm to 1.68 ± 0.38 mm (p<0.001) and a decrease in the mean percentage diameter stenosis from 37.3 ± 8.4% to 36.0± 10.1% (p<0.001).

In STRADIVARIUS, 839 abdominally obese patients with CAD were randomly assigned to treatment with either rimonabant 20 mg daily (422 patients) or placebo (417 patients). Rimonabant, a cannabanoid type 1 (CB1) receptor inhibitor, is an experimental agent that is not yet approved in

the United States but is available in some European countries. The percent atheroma volume (PAV) and normalized total atheroma volume (TAV) on IVUS were determined in all patients at the beginning of the study and again at 18 months in the 676 patients who completed the trial, regardless of whether they were still taking the study drug.

Steven E. Nissen, MD, Cleveland Clinic, Cleveland, OH, reported that rimonabant (compared with placebo) failed to reduce the primary endpoint of PAV (+0.25% change from baseline with rimonabant vs +0.51% with placebo; p=0.22; Figure 1). However, there was a significant difference between the two groups with respect to the secondary endpoint of change in TAV from baseline (-2.2 mm^3 rimonabant vs +0.88 mm^3 placebo; p=0.03).

Figure 1. Primary and Secondary IVUS Endpoints.



Of concern in the study was the higher frequency of psychiatric adverse events in the rimonabant arm (43.4% vs 28.4%; p<0.001). This difference was primarily driven by significant increases in anxiety (18.0% vs 11.8%; p=0.01) and depression (16.8% vs 11.3%; p=0.02). Dr. Nissen pointed out that approximately one-quarter of the patients in the study had a history of psychiatric disease at the start of the trial. The risk of psychiatric adverse events was a factor in the unanimous recommendation against approval of the drug by a U.S. Food and Drug Administration advisory panel in 2007.

The lipid-lowering benefits of both rosuvastatin and rimonabant were confirmed by these two studies. Rosuvastatin reduced low-density lipoprotein (LDL) levels by more than 50% and increased high-density lipoprotein (HDL) levels by 14%, while rimonabant increased HDL by 22% and reduced triglyceride levels by 21%. Dr. Ballantyne noted that it may be necessary to reduce LDL by >50% or set a target LDL near 60 mg/dL to induce plaque regression in coronary atherosclerosis.

The results of the QCA analysis from the ASTEROID trial were published online (*Circulation* 2008), and the primary results of STRADIVARIUS were published in *JAMA* 2008;299:1547-1560.

Cardiac Arrhythmias and Risk Stratification after MI

Patients who survive an acute myocardial infarction (MI) with diminished left ventricular (LV) function experience frequent and treatable arrhythmias, according to findings from the Cardiac Arrhythmias and Risk Stratification after Myocardial Infarction (CARISMA) observational study. Moreover, high-degree atrioventricular (AV) block appears to independently predict cardiac death in the post-MI patient population.

"The insertable ECG loop recorder is a diagnostic tool that should be considered to guide medical and device therapy in patients who survive myocardial infarction," said Poul Erik Bloch Thomsen, MD, Gentofte University Hospital, Copenhagen, Denmark, principal investigator of the CARISMA trial.

CARISMA is the first long-term observational study to examine implantable loop recorder data among post-MI patients. The study was designed to determine the risk of tachyarrhythmia and sudden death in patients who do not meet the criteria for an implantable cardioverter defibrillator (ICD) despite mild to moderate structural damage following an acute MI.

In CARISMA, investigators implanted insertable loop recorders in 297 patients an average of 11 days after MI. All patients had a low ejection fraction (EF<40%), and none had an ICD. During a 2-year follow-up, the loop recorders provided information every 4 months on the incidence of any arrhythmias: sinus bradycardia, sinus arrest, atrial fibrillation (AF), second or third degree AV block, ventricular tachycardia (VT), and fibrillation.

After a mean follow-up of 1.9 years, 137 patients (46%) had evidence of at least one of the pre-specified arrhythmias, of which only 14% was symptomatic.

New AF (≥125 bpm), the most frequent arrhythmia, was documented in 27% of patients. Sinus bradycardia (<30 bpm), AV block (<30 bpm), non-sustained VT (≥125 bpm, ≥16 beats), and sustained VT (≥125 bpm, ≥30 seconds) were each observed in approximately 17% of patients.

In a univariate analysis, AV block (HR 7.0; p=0.0004), sinus bradycardia (HR 5.8; p=0.004), and non-sustained VT (HR 3.4; p=0.025) appeared to predict cardiac death. However, by multivariate analysis, high-degree AV block remained the only independent predictor of cardiac death (HR 4.8; p<0.001).

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