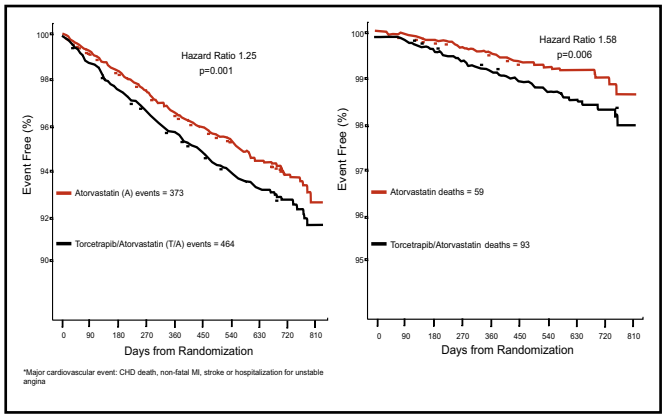
Sydney, Australia, explained that torcetrapib is a CETP inhibitor that has been shown to increase high-density lipoproteins (HDLs) in humans and to protect against atherosclerosis in rabbits. The study hypothesis was that torcetrapib would increase HDL and thus protect against cardiovascular disease.

Dr. Barter noted that the HDL and LDL levels in the study indicated that torcetrapib performed as predicted: compared with atorvastatin alone, at 12 months, torcetrapib and atorvastatin increased HDL by 72% (vs 1.8% for atorvastatin alone; p<0.001) and decreased LDL by 25% (vs an increase of 3.0% for atorvastatin alone; p<0.001). However, the drug was associated with a significantly higher number of major cardiovascular events (464 vs 373; p=0.001) and a significantly higher number of deaths (93 vs 59; p=0.006; Figures 1A and 1B). Of note among the deaths, said Dr. Barter, were more deaths in the combination arm related to infection (9 vs 0), cancer (24 vs 14), and stroke (6 vs 0).

Figures 1A and 1B. Kaplan-Meier Curves for Death from Any Cause and for the Primary Composite Outcome.



Torcetrapib was associated with several off-target pharmacologic effects unrelated to CETP inhibition, said Dr. Barter, such as significant increases in blood pressure, significant changes in serum electrolyte levels, and significant increases in the serum aldosterone level. The higher blood pressure associated with torcetrapib was thought to be related to the greater morbidity and mortality, but post hoc analysis indicated that this was unlikely to be the only explanation, as a greater increase in systolic blood pressure was associated with a lower rate of cardiovascular events. An increase in systolic pressure of more than 2.5 mm Hg was associated with a 5.9% rate of cardiovascular events, whereas an increase of 2.5 mm Hg or less was associated with a 6.3% increase.

Another interesting finding, said Dr. Barter was that in the torcetrapib group, the rate of cardiovascular events was lower in patients who had an increase in HDL-cholesterol (HDL-C) that was greater than the median. At 1 month, the rate of cardiovascular events was 5.9% among the patients who had an increase in HDL-C of more than 22 mg/dL and was 6.4% among patients who had an increase of 22 mg/dL or less. The hazard ratios for cardiovascular-related death or nonfatal myocardial infarction were lower for HDL-C levels that were greater than 60 mg/dL than for a level less than 60 mg/dL. The lowest hazard ratio (0.43; p<0.05) was associated with an HDL-C of more than 93 mg/DL at 3 months.

Dr. Barter emphasized that these post hoc observations are only suggestive and do not rule out HDL dysfunctionality nor the possibility that other unknown effects of CETP inhibition may have contributed to a mechanism-related adverse outcome.

"This study neither validates nor invalidates the hypothesis that raising HDL-cholesterol by inhibiting CETP may be cardioprotective," said Dr. Barter. "The adverse clinical outcome associated with use of torcetrapib may have been the consequence of an off-target pharmacology but the possibility of an adverse effect of CETP inhibition cannot be excluded by the results of this randomized trial," he added.

The study findings have been published: [Barter et al. NEJM 2007;357:2109-2122].

Diagnostic Accuracy of 64-Row MDCTA

Multidetector computed tomography angiography (MDCTA) may offer a noninvasive alternative for evaluating coronary artery anatomy in patients with suspected coronary artery disease (CAD). This imaging modality has good diagnostic accuracy for determining the presence of significant coronary artery stenosis in symptomatic patients and also identified those who were likely to be referred for a revascularization procedure (angioplasty or coronary bypass surgery).

"Our interpretation of this analysis is that multidetector CT will become an integral part of the diagnostic algorithm in patients with coronary artery disease," said Julie Miller, MD, Johns Hopkins University, Baltimore, MD, who reported on the study.

The international, multicenter, trial (CORE-64) was the first prospective study to compare 64-row 0.5 mm MDCTA with – quantitative coronary angiography

(QCA). The final analysis was done on data for 291 patients (868 vessels; 3,782 segments) who were a median of 59 years old and had an Agatston calcium score ≤600 (a score of >400 indicates a high likelihood of at least one stenosis). The patients had ECG-gated contrast-enhanced 64-slice MDCT (0.5 mm slice thickness) within 30 days before scheduled QCA and were followed up for clinical events at 30 days and 6 months.

The study differed from other studies in that the entire coronary tree was analyzed, said Dr. Miller; all nonstented segments of at least 1.5 mm were evaluated by both methods. Significant stenosis by QCA was defined as more than 50% stenosis. The diagnostic accuracy (sensitivity and specificity) of MDCTA for identifying significant stenosis (compared with QCA) was the primary endpoint.

The diagnostic performance of MDCTA was better on a per patient basis than on a per vessel basis. On a per patient basis, MDCTA had a sensitivity of 85% and a specificity of 90% (Table 1). In contrast, the sensitivity and specificity were 76% and 93%, respectively, on a per vessel basis. Dr. Miller noted that MDCTA was highly diagnostic based on receiver operating characteristics (ROC) analysis of the data – the ROC area was 93% on a per patient basis, and 91% on a per vessel basis. The ability of MDCTA to predict the need for revascularization was similar to that of QCA; the ROC area for MDCTA was 0.84 compared with 0.82 for QCA (p=0.36) on a per patient basis and 0.84 and 0.89, respectively, on a per vessel basis.

Table 1. Comparison of Diagnostic Accuracy of 64-Row MDCTA (Compared with QCA) on Per Patient and Per Vessel Basis.

	Detection of Significant Stenosis (%)*	
	Per Patient	Per Vessel
Sensitivity	85	76
Specificity	90	93
Positive predictive value	91	82
Negative predictive value	83	89
ROC area	93	91

*Significant stenosis was defined as more than 50% stenosis.

ROC=receiver operating characteristics.

Previous studies have shown highly variable results for the diagnostic accuracy of MDCTA, but Dr. Miller pointed out that those studies were single-center studies and did not compare MDCTA with QCA in predicting revascularization.

Rhythm Control Has No Impact on Mortality: Results of the AF-CHF Trial

The results of the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial were presented by Denis Roy, MD, Montreal Heart Institute, Montreal, Canada. The study was funded by the Canadian Institutes of Health Research and was conducted from May 2001 through June 2007 in the US, Canada, Europe, Argentina, Brazil, and Israel. The objective of the trial was to determine if the restoration and maintenance of sinus rhythm would result in a reduction of cardiovascular mortality compared with simple rate control in patients with both CHF and AF. Eligibility criteria were as follows:

- CHF:
  - New York Heart Association (NYHA) Class II-IV with a left ventricular ejection fraction (LVEF) ≤35%, or
  - NYHA I with a prior hospitalization for CHF, or
  - LVEF ≤25%.
- AF:
  - one episode of AF ≥ 6 hours in the last 6 months, or
  - one episode of shorter duration AF within the last 6 months and prior D/C shock.

Patients were randomized to one of two treatment groups. The first group was treated with rhythm control using antiarrhythmic drugs (amiodarone, sotalol, or dofetilide) or non-pharmacologic methods, including cardioversion. Patients randomized to the other treatment arm underwent rate control using beta-blockers and/or digoxin, pacemaker therapy, and AV nodal ablation when necessary. Target heart rates were <80 bpm during resting ECG and <110 bpm during the 6-minute walk. Patients in both groups were given optimal treatment for their CHF and were followed for at least 2 years. The study had 80% power to detect a 25% decrease in cardiovascular (CV) mortality.

A total of 1,376 patients were randomized—682 to rhythm control and 694 to rate control. Patient baseline demographic characteristics were similar, with the majority of the patients being men (78% in rhythm and 85% in rate control). There were 217 (31.8%) deaths in the rhythm control group and 228 (32.9%) in the rate control group; 80% of the deaths were CV-related. The study did not meet its primary objective of reducing CV mortality by 25% using rhythm control (HR 1.06; p=0.59), nor were there any statistically significant differences