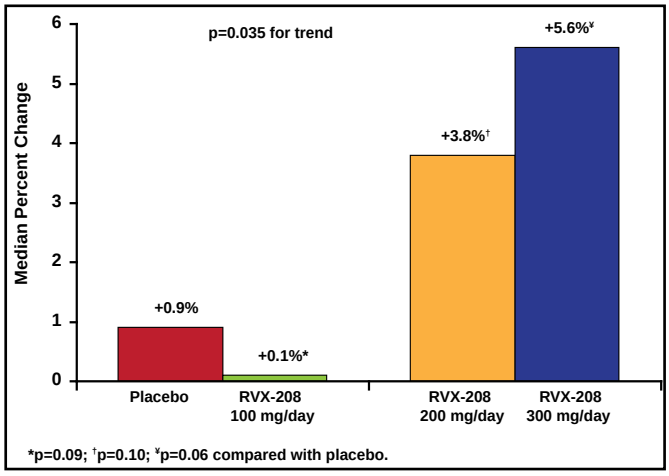
compared with placebo (+5.6% in the 300 mg/day group [p=0.06]; +3.8% in the 200 mg/day group [p=0.10]; and +0.1% in the 100 mg/day group [p=0.09]; Figure 1). However, a dose-dependent increase in apoA1 levels was observed across the dosing range [p=0.035]. RVX-208 produced significantly increased HDL-C levels at the two higher dose levels (+6.3% at the 200-mg/day dose [p<0.05] and +8.3% at 300 mg/day [p<0.01]) but not at the 100-mg/day dose. Although there was no increase in the number of HDL particles, the size of the particles appeared to change, with a preferential increase in the larger HDL particles by up to 21% at the highest dose (p<0.001 versus placebo). There was also a significant (p<0.05) increase in the amount of α1 HDL at the higher doses. There was no change in LDL-C, triglycerides, apoB, or hsCRP.

Figure 1. Median Change in ApoA-1 From Baseline.



Reproduced with permission from S. Nicholls, MD.

Rates of increased ALT/AST levels were higher for each dose of RVX-208 compared with placebo, with 3 patients in the 100 mg/day group, 8 patients in the 200 mg group, and 7 patients in the 300 mg group having ALT/AST >3 xULN (p=0.009). A total of 8 patients had ALT/AST >8 xULN. The liver enzyme increases were reversible, and there was no evidence of liver damage.

"The changes in apoA1, HDL-C, and large HDL particles are consistent with enhanced mobilization of lipids into functional HDL particles and reversible transaminase elevations," Dr. Nicholls said, thus establishing proof of concept. He also noted that most of the benefits of RVX-208 were seen during Weeks 8 to 12, indicating that longer treatment may have provided an increased benefit. However, the increases in AST/ALT that were seen in this study deserve careful prospective evaluation in future longer-term studies and could limit the clinical utility of this compound.

BASKET-PROVE: DES Just as Safe as BMS in Large Coronary Vessels

Drug-eluting stents (DES) confer no additional late cardiovascular risk in patients with stenting of large coronary arteries when compared with bare-metal stents (BMS), reported Christoph Kaiser, MD, University Hospital, Basel, Switzerland. Prof. Kaiser presented the results of the 24-month Basel Stent Cost-effectiveness Trial-PROspective Evaluation Examination (BASKET-PROVE; ISRCTN72444640).

The trial was designed to test the hypothesis that in large coronary arteries, first-generation DES provide only a small reduction in target vessel revascularization (TVR) and may increase late cardiac death/myocardial infarction (MI). This study was designed after a retrospective analysis of the single-center BASKET—Late Thrombotic Events (BASKET-LATE) trial, which examined the difference between first-generation DES and BMS among 826 patients, demonstrated that DES were associated with an increase in cardiac-related deaths or non-fatal MI after 6 months in patients with stenting of *large* vessels. Of note, no such association was found in patients with *small* vessels, however (Pfisterer M et al. *Eur Heart J* 2009), for which DES remain the stent of choice. A secondary aim of BASKET-PROVE was to determine whether a similar risk-benefit relationship would also be found for second-generation DES.

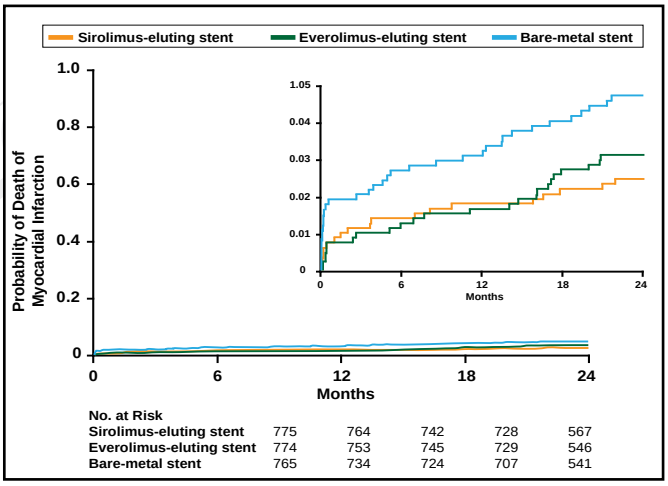
The study enrolled 2314 patients with vessels 3 mm in diameter and divided them into 3 groups: sirolimus-eluting (first-generation; SES) DES (n=775), everolimus-eluting (second-generation; EES) DES (n=774), and BMS (n=765). The mean patient age was 66 years, and 18% were diabetic. Patients represented a typical population that required stenting, with two-thirds presenting with acute coronary syndromes (34% with STEMI) and the remainder with stable chronic coronary artery disease. Patients were placed on aspirin therapy (75-100 mg daily) indefinitely and on clopidogrel 75 mg daily for a minimum of 1 year.

Compliance with dual antiplatelet therapy was high (82%) at 1 year. After 2 years, there was no significant difference in the primary endpoint of cardiac death or nonfatal MI between the groups (2.6% for SES, 3.2% for EES, and 4.8% for BMS; p=0.13 SES vs BMS and p=0.37 EES vs BMS).

Also, there were no significant differences in the secondary endpoints of total death, noncardiac death, or stent thrombosis. However, there was a statistically

significant difference in non-MI-related TVR between the DES patients and those who received the BMS (SES, p=0.007; EES, p=0.002), although there was no statistically significant difference between the two DES groups. This resulted in a significant difference in the composite of cardiac death, nonfatal MI, and TVR (MACE), which was significantly reduced by both of the DES (SES, p=0.009; EES, p=0.005) . Limitations of the study include low overall number of events, resulting in reduced power to detect differences between groups (the 2.2% absolute difference in the primary endpoint between SES and BMS was not statistically different despite representing an ~85% relative increase), and unblinded adjudication of approximately one-third of reported events.

Figure 1. Kaplan-Meier Estimates of Composite Primary Endpoint at 24 Months.



"In contemporaneous stenting of large coronary arteries, late safety problems with drug-eluting stents could not be confirmed, and there was even a trend in the opposite direction," said Dr. Kaiser. The findings, he noted, should influence medical practice.

Results of this study were published simultaneously in *The New England Journal of Medicine*. Kaiser C et al. *N Eng J Med* 2010.

ACT Trial Results Should Change Clinical Practice

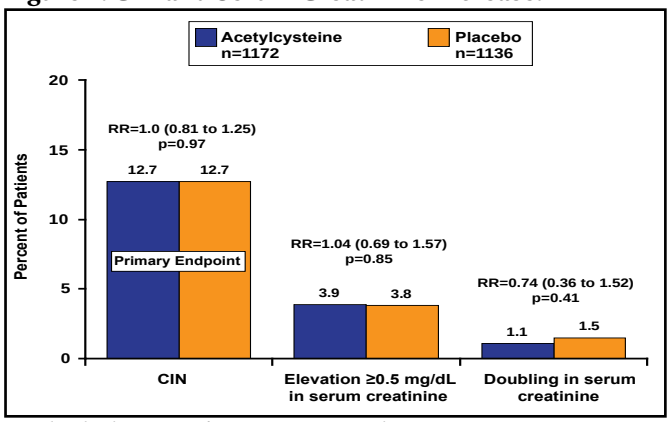
Based on the results of the Acetylcysteine for the prevention of Contrast-Induced nephropathy (ACT; NCT00736866) trial, there is no evidence that the antioxidant N-acetylcysteine (NAC) reduces the risk of contrast-induced nephropathy (CIN) in patients who are undergoing coronary and vascular angiography. That was the message from Otavio Berwanger, MD, PhD, Hospital do Coração, São Paulo, Brazil, after he presented the main results of the ACT trial.

The study was designed to test the hypothesis that using NAC could reduce the risk of CIN (defined as a ≥25% elevation in serum creatinine above baseline 48 to 96 hours postangiography) in patients who were undergoing coronary and vascular angiography. Secondary outcomes included mortality, the need for dialysis, cardiovascular mortality, side effects, and doubling of serum creatinine. CIN occurs in between 9% and 38% of patients with risk factors, such as renal failure, diabetes, and age >70 years [McCullough PA et al. *Am J Card* 2006]. Although there have been no large, randomized, placebo-controlled trials that have been designed to test the benefit of NAC on CIN risk, its use has become widespread.

ACT enrolled 2308 patients with at least one risk factor for CIN (ie, age >70 years, chronic renal failure, diabetes, heart failure or left ventricular ejection fraction <45, shock). The patients were randomized to receive NAC 1200 mg twice daily (2 doses pre- and 2 doses postprocedure) or placebo and underwent intravascular angiography at 46 centers in Brazil. The mean patient age was 68 years, 61% were diabetic, and the mean volume of contrast that was delivered was 100 cc.

The incidence of CIN was 12.7% in both the NAC and placebo groups (RR, 1.00; 0.81 to 1.25; p=0.97; Figure 1), with nearly identical rates of mortality or the need for dialysis (2.2% vs 2.3%; p=0.91), total mortality (2% vs 2.1%; p=0.80), need for dialysis (0.3% for both; p=0.97), and cardiovascular mortality (1.5% vs 1.6%; p=0.93). The findings were consistent regardless of the type of contrast that was used for the procedure or the procedure itself (67% coronary diagnostic angiographies, 29% percutaneous interventions, 4% vascular procedures).

Figure 1. CIN and Serum Creatinine Increase.



Reproduced with permission from O. Berwanger, MD, PhD.