The rate for revascularization at 1 year was 2.0% for CABG versus 9.9% for PCI (OR=5.31, 95% CI, 2.00-14.11; p=0.001).

The rate of death at 1 year was 3.3% for CABG versus 3.2% for PCI (OR=0.98, 95% CI, 0.36-2.64; p=0.83). The rate of nonfatal MI was 5.7% for CABG versus 8.4% for PCI (OR=1.51, 95% CI, 0.75-3.03; p=0.25). The rate of nonfatal stroke was 2.5% for CABG versus 0.4% for PCI (OR=0.16, 95% CI, 0.02-1.33; p=0.09). The composite outcome of death, MI, stroke, and repeat revascularization was 11% for CABG versus 17.5% for PCI (OR=1.72, 95% CI, 1.02-2.87; p=0.04).

For CABG (n=245) versus the PCI-DES (n=179; 71% of total) subgroup, the primary composite outcome of death, nonfatal MI, and nonfatal stroke at 1 year was 10.2% for CABG versus 10.1% for PCI-DES (p=0.98). The rate for revascularization at 1 year was 2.0% for CABG versus 7.3% for PCI-DES (p=0.013). The rate of death at 1 year was 3.3% for CABG versus 3.9% for PCI-DES (p=0.723). The rate of nonfatal MI was 5.7% for CABG versus 6.2% for PCI-DES (p=0.852). The rate of nonfatal stroke was 2.5% for CABG versus 0% for PCI-DES (p=0.041). The composite outcome of death, nonfatal MI, nonfatal stroke, and repeat revascularization at 1 year was 11% for CABG versus 15.1% for PCI-DES (p=0.217).

Dr. Kapur noted that the findings are preliminary and that several clinical events still need to be adjudicated.

Biodegradable Biolimus Stent Appears Safe and Effective in PCI

A new generation of drug-eluting stent that is coated with biolimus and released from a biodegradable polymer demonstrated similar safety and efficacy through 9 months as compared with stents releasing sirolimus from a durable polymer in patients who were undergoing percutaneous coronary intervention (PCI), according to findings from the LEADERS (Limus Eluted from A Durable versus ERodable Stent) trial. The biolimus stent may have the potential to minimize late complications related to the polymer component.

Stephan Windecker, MD, Inselspital University Hospital, Bern, Switzerland, reported initial findings from the LEADERS trial, which were simultaneously published online in *The Lancet* [Windecker S et al. *Lancet* 2008].

Biolimus is a highly lipophilic, semi-synthetic sirolimus analog that is immersed in a biodegradable polymer and applied only to the abluminal vessel side of the stent, thereby reducing the amount of drug that is released into the circulation. By 6 to 9 months following PCI, the polymer completely dissolves into carbon dioxide and water, leaving only the stainless steel stent in the affected vessel. This novel design escapes the durable polymer surface coatings of current drug-eluting stents, which have been implicated in delayed healing and late stent thrombosis.

A "Real-World" Trial

In the LEADERS trial (NCT00389220), 1707 patients who were undergoing PCI were randomly assigned to receive a biolimus stent (n=857) or sirolimus stent (n=850). In a factorial design, 1 in 4 patients also was randomly selected for angiographic follow-up at 9 months.

In an attempt to reflect routine clinical practice, the study design employed broad inclusion criteria and few exclusion criteria. Patients with stable coronary artery disease (CAD) or acute coronary syndrome (ACS) that presented as unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or STEMI were enrolled. Patients had to have at least one lesion that had at least 50% diameter stenosis, but there were no limits on the lesion length or number of lesions or diseased vessels. Major exclusions included known allergy to standard antithrombotic agents, contrast, or stent material that was used in the study; elective surgery that required interruption of antiplatelet therapy; pregnancy; or participation in another trial.

"LEADERS is the first all-comers study of PCI comparing two drug-eluting stents," said Laura Mauri, MD, MSc, Brigham and Women's Hospital, Boston, MA. With predominantly off-label and high-risk characteristics, the complex patient population includes diabetes mellitus in 24% of patients, multivessel stenting in 23%, and acute myocardial infarction (MI) in 34%. "This reflects the breadth of practice we see today and [permitted evaluation of] safety and efficacy across a broad population," Dr. Mauri said.

The primary endpoint was the composite of cardiac death, MI, or clinically indicated target vessel revascularization (TVR) at 9 months. In those who were selected for angiographic evaluation (n=427), the primary endpoint was in-stent percent diameter stenosis as assessed by a blinded core laboratory.

Non-Inferior Efficacy and Safety

Nine months after PCI, a similar proportion of patients with biolimus-eluting stents and sirolimus-eluting stents reached the primary endpoint (9.2% vs 10.5%; RR=0.88; 95% CI, 0.64 to 1.19; p=0.003 for non-inferiority). Regarding individual safety and efficacy outcomes at 9 months, patients

in the biolimus and sirolimus groups had similar rates of death (2.6% vs 2.8%; p=0.74), cardiac death (1.6% vs 2.5%; p=0.22), MI (5.7% vs 4.6%; p=0.30), and clinically indicated TVR (4.4% vs 5.5%; p=0.29) (p values for superiority).

The cumulative rate of definite stent thrombosis (ST) at 9 months was 1.9% with biolimus versus 2.0% with sirolimus (RR=0.93; 95% CI, 0.47 to 1.85). The majority of ST events occurred during the first 30 days in both groups. A detailed analysis of definite, probable, and possible ST events over various time periods (0 to 30 days, 31 days to 9 months, 0 to 9 months) showed no differences between the stent groups.

In subgroup analyses, the primary endpoint results were consistent across a broad range of patient characteristics and angiographic findings, including patients with diabetes mellitus; presentation with ACS; and presence of multivessel disease, de novo lesions, and small-vessel disease. The only exception was in the subgroup of STEMI patients (interaction p=0.02) who showed a treatment effect that favored biolimus (RR=0.37; 95% CI, 0.16 to 0.84), while patients without STEMI had equivalent risk, regardless of stent type (RR=1.03; 95% CI, 0.74 to 1.44).

Comparable Angiographic Outcomes

Biolimus stents also achieved the criteria for non-inferiority in the angiographic substudy with an in-stent diameter stenosis rate of 20.9% compared with 23.3% in the sirolimus group (p=0.001 for non-inferiority). No coronary aneurysms occurred in either stent group. Other angiographic outcomes, including in-stent percentage diameter stenosis, late loss, and binary restenosis, showed no significant differences between biolimus-eluting and sirolimus-eluting stents on superiority testing.

The next question is whether biolimus-eluting stents can improve long-term safety. In the ongoing follow-up of the LEADERS trial, the secondary endpoints are scheduled for annual re-evaluation beginning at Year 1 and continuing through Year 5; however, a larger trial would be required to assess for superiority of the biolimus stent.

Darapladib May Slow Expansion of Atherosclerotic Plaques

Darapladib, a novel inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), may slow expansion of the necrotic core of atherosclerotic plaques in patients with acute coronary syndrome (ACS) or other symptomatic coronary diseases, according to mixed results from the Integrated Biomarker and Imaging Study-2 (IBIS-2; NCT00268996).

Lp-PLA_2, an enzyme that promotes inflammation and plaque formation, is highly expressed in the necrotic core of atherosclerotic lesions. By suppressing Lp-PLA_2, darapladib theoretically reduces endothelial inflammation and growth of the necrotic core.

In IBIS-2, 330 patients were randomly assigned to treatment with darapladib (n=175) or placebo (n=155) in addition to optimal medical therapy to evaluate the effects of Lp-PLA_2 inhibition on coronary plaque deformability, composition, and size. William Wijns, MD, PhD, OLV Hospital, Aalst, Belgium, reported findings from IBIS-2, which were simultaneously published online in *Circulation* [Serruys PW et al. *Circulation 2008*].

Neutral Primary Endpoint

Investigators used intravascular ultrasound (IVUS) to visualize several parameters of plaque stability, including the plaque's necrotic core, dense calcium areas, and fibrous tissue. Another technique, called IVUS palpography, was used to measure the levels of tissue strain along segments of the target vessel.

Dr. Wijns and colleagues also measured high-sensitivity C-reactive protein (hsCRP) levels as a marker of systemic inflammation. The co-primary endpoints in IBIS-2 were changes in IVUS palpography and hsCRP at 12 months compared with baseline.

After 1 year of treatment, the between-group difference in plaque deformability was not statistically significant (-0.08; p=0.22). In addition, although mean hsCRP levels declined in all patients, the mean hsCRP levels at 12 months in the placebo (1.0 mg/L) and darapladib (0.9 mg/L) groups were comparable (p=0.35).

Promising Secondary Endpoint Results

Although the IBIS-2 trial did not meet either of its co-primary endpoints, the comparison of secondary endpoints did suggest some benefit with darapladib. For example, while the volume of the necrotic core increased over 12 months in the placebo group (4.5± 17.9 mm^3; p=0.009), plaque growth appeared to arrest in the darapladib group (–0.5±13.9 mm^3; p=0.71), resulting in a significant difference between the 2 treatment groups of 5.2 mm^3, favoring darapladib (p=0.012).

Darapladib also had a beneficial effect on inflammatory biomarkers. As expected, patients in the darapladib