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

group had a significant 59% reduction in Lp-PLA$_2$ activity compared with those in the placebo group (62 vs 153 µmol/min^{-1}/L^{-1}; p<0.001). Other inflammatory biomarkers, including oxidized phospholipid/apolipoprotein B, did not change significantly. However, in a post hoc analysis, a higher proportion of patients in the darapladib group achieved hsCRP levels <1 mg/L compared with placebo (62% vs 45%; p=0.008).

The IBIS-2 trial was not powered to evaluate the effects of darapladib on cardiovascular outcomes, and no differences were observed. A safety analysis showed no differences in serious adverse events or clinical outcomes between the treatment groups, although there was a slightly higher systolic blood pressure, measured noninvasively (+3.0 mm Hg. 95% CI +0.3 to +5.7 mm Hg; p=0.031), in patients who were treated with darapladib.

In summary, IBIS-2 failed to show that Lp-PLA$_2$ inhibition improves plaque stability, as measured by IVUS palpography. However, analyses of the IBIS-2 secondary endpoints suggest that necrotic core expansion occurs despite optimal medical therapy, even in the absence of an overall change in plaque size. In addition, treatment with darapladib appears to halt this process in patients with established coronary disease. This trial was relatively small, and patients were followed for only 12 months; thus, future clinical trials will be required to evaluate whether Lp-PLA$_2$ inhibition, by stopping expansion of the necrotic core, can prevent recurrent cardiovascular events in high-risk patients.

Promise and Problems Emerge for Oral Investigative Factor Xa Drug in Treating Acute Coronary Syndrome

Treatment with investigative apixaban, an oral factor Xa inhibitor, shows promise as add-on protection against recurrent ischemic cardiovascular (CV) events among acute coronary syndrome (ACS) patients who already are on standard antiplatelet therapy, including aspirin and clopidogrel. But dose-dependent bleeding remains an unresolved problem.

Investigators from the APPRAISE-1 (A Phase 2, Placebo-Controlled, Randomized, Double-Blind, Parallel Arm, Dose-Ranging Study to Evaluate Safety and Efficacy of Apixaban in Patients with a Recent Acute Coronary Syndrome; NCT00313300) trial reported their findings in Munich at the European Society of Cardiology Congress 2008.

"The addition of apixaban to standard antiplatelet therapy for 6 months after onset of ACS resulted both in dose-dependent increases in bleeding and in a trend toward a reduction in clinically important ischemic events," said principal investigator John Alexander, MD, Duke Clinical Research Institute and Duke Heart Center, Durham, NC.

Dr. Alexander noted that one of the most challenging problems in treating ACS patients is finding a drug combination that inhibits clot formation without increasing the risk of serious bleeding. APPRAISE-1 is the first trial of an oral drug that targets factor Xa, a key enzyme in blood coagulation.

APPRAISE-1 was a phase 2 study that aimed at defining the optimal dose of apixaban regarding safety and efficacy in patients with a recent onset ACS. The study took place in 2 phases.

Phase A enrolled 547 patients who manifested ACS within the prior 7 days. Subjects were randomized to placebo (n=184), apixaban 2.5 mg BID (n=179), or apixaban 10 mg QD (n=184). Following the safety review of phase A, the enrollment was continued in phase B, reaching a study total of 1715 subjects. Those who were enrolled after the safety review were randomized to placebo (n=427), apixaban 2.5 mg BID (n=138), apixaban 10 mg QD (n=134), apixaban 10 mg BID (n=248), and apixaban 20 mg QD (n=221).

The primary safety outcome was major bleeding, as measured with the International Society of Thrombosis and Hemostasis (ISTH) scale, or clinically relevant non-major (CRNM) bleeding. The secondary efficacy outcome was a composite of CV death, myocardial infarction (MI), severe recurrent ischemia, and ischemic stroke.

During phase B of the trial, the higher apixaban dosing groups (10 mg BID and 20 mg QD) were discontinued due to unacceptably increased rates of total bleeding.

The index event was ST-elevation MI in 67% of patients. Investigators reported that the incidence of major or CRNM bleeding was 5.7% for apixaban 2.5 mg BID (n=315), 7.9% for apixaban 10 mg QD (n=315), and 3.0% for placebo (n=599). Bleeding at both apixaban dosages was higher compared with placebo (2.5 mg BID: HR 1.78; 95% CI, 0.91 to 3.48; p=0.09; and 10 mg QD: HR 2.45; 95% CI, 1.31 to 4.61; p=0.005; Figure 1). The absolute rates of bleeding were higher in patients on clopidogrel (7.0% for apixaban 2.5 mg BID, 9.1% for apixaban 10 mg QD, and 3.1% for placebo) compared with aspirin (2.4% for apixaban 2.5 mg BID, 4.1% for apixaban 10 mg QD, and 2.7% for placebo).

For the combined secondary efficacy endpoint outcome of CV death, MI, severe recurrent ischemia, or ischemic stroke, investigators reported incidence rates of 7.6% for apixaban 2.5 mg BID (n=317), 8.7% for apixaban 10 mg QD