potent oral direct inhibitor of Factor Xa that works at the intersection of the intrinsic and extrinsic pathways of the coagulation cascade, thus blocking initiation of the final common pathway of coagulation.

This multicenter trial enrolled 3491 patients who were in stable condition 1-7 days after an ACS event. The study population was categorized into 2 strata according to the treating physician's decision on antiplatelet therapy: Stratum 1 included 761 patients who were treated with aspirin (75-100 mg) alone, and Stratum 2 included 2730 patients who were treated with aspirin and clopidogrel. Dr. Gibson noted that these 2 study populations differed substantially from each other in terms of age, comorbidities, and, especially, with regard to ACS treatment. PCI was performed in only 8% of patients in Stratum 1 but was performed in 79% of patients in Stratum 2.

The patients in each stratum were randomly assigned to receive 6 months of placebo or once-daily or twice-daily rivaroxaban, wherein 3 total daily doses (5, 10, and 20 mg) were evaluated in Stratum 1 and 4 total daily doses (5, 10, 15, and 20 mg) were evaluated in Stratum 2.

The primary safety endpoint of the study was clinically significant bleeding, defined as a composite of thrombolysis in myocardial infarction (TIMI) major and minor bleeding and any bleeding that required medical attention. The study also explored the efficacy of rivaroxaban to reduce ischemic complications (primary composite=death from cardiovascular casuses, myocardial infarction (MI), stroke, and revascularization; secondary composite=risk of death, MI, or stroke).

Dr. Gibson reported that the incidence of bleeding followed a dose-response pattern, with higher bleeding rates as the dose of rivaroxaban increased (3.3% for placebo, 6.1% for 5 mg rivaroxaban, 10.9% for 10 mg, and 15.3% for 20 mg). The majority of bleeding events was categorized as bleeding that required medical attention (Table 1).

Rivaroxaban did not significantly reduce the risk of the primary composite endpoint (7.0% for placebo compared with 5.6% for the combined rivaroxaban groups (HR, 0.79; 95% CI, 0.60 to 1.05; p=0.1) in an analysis that combined the data across both strata among patients who received placebo compared with all doses of rivaroxaban combined. There was, however, a decrease in the secondary composite of death, MI, or stroke (5.5% vs 3.9%; HR, 0.69; 95% CI, 0.50 to 0.96; p=0.028), yielding a number that was needed to treat to prevent 1 event of 63.

Dr. Gibson announced that doses of 2.5 mg and 5 mg twice daily will be evaluated next in a phase 3 trial. In ATLAS ACS-TIMI 46, those doses led to a rate of the secondary efficacy endpoint of 6.6% in Stratum 1 (compared with 11.9% for placebo; HR, 054; p=0.08) and of 2.0% in Stratum 2 (compared with 3.8% for placebo; HR, 0.55; p=0.09), with a tradeoff of increased bleeding rates of 1.2% (p=0.17) and 1.0% (p=0.03), respectively. The phase 3 trial (ATLAS II – TIMI 51) is expected to enroll 13,500-16,000 patients and will begin in December 2008.

Table 1. Type of Bleeding According to Dose of Rivaroxaban.

	Bleeding Rate (%)		
	TIMI Major	TIMI Minor	Requiring Medical Attention
Stratum 1			
Placebo	0	0.4	1.6
5 mg	0	0	2.0
10 mg	2.1	0	4.1
20 mg	0	0.6	9.6
Stratum 2			
Placebo	0.2	0.2	3.5
5 mg	0.7	0.7	10.0
10 mg	1.5	0.7	9.8
15 mg	1.7	1.1	10.1
20 mg	2.0	0.9	14.5

Drug-Eluting Stents Prevent Death, MI, and Revascularization in Patients with Diabetes

For patients with diabetes who undergo percutaneous coronary intervention (PCI), drug-eluting stents (DES) reduce the risk of mortality, acute myocardial infarction (MI), and repeat revascularization compared with bare-metal stents (BMS). These 3-year findings from the Massachusetts Data Analysis Center Registry (Mass-DAC), which requires mandatory reporting and follow-up, reflect achievable treatment outcomes in the real-world clinical setting, researchers reported.

Findings from Mass-DAC are important because patients with diabetes have a higher prevalence of ischemic heart disease than the general population and account for approximately one-third of all patients who undergo PCI, said Laura Mauri, MD, MSc, Brigham and Women's

Hospital, Boston, MA. In addition, PCI is associated with unique limitations in the diabetic population, such as a higher risk of restenosis, MI, and cardiac mortality.

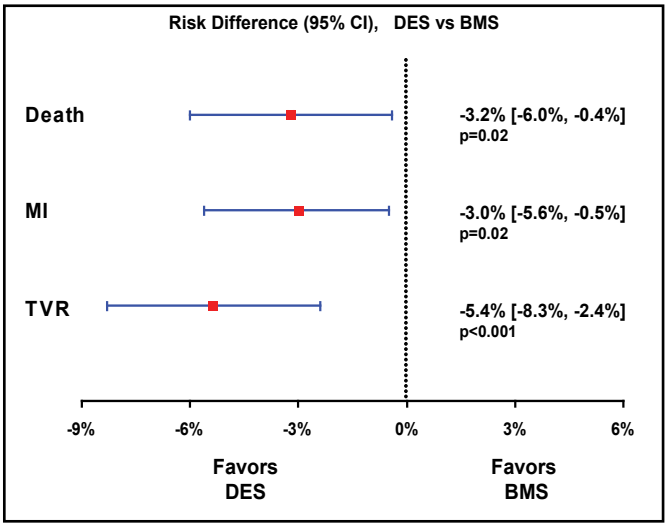
Dr. Mauri presented results of the Mass-DAC trial, which were simultaneously published online in *Circulation* [Garg P et al. *Circulation* 2008].

The Mass-DAC analysis included data from all adults who underwent PCI in Massachusetts from April 1, 2003 through Sept. 30, 2004 and completed a 3-year follow-up (n=21,045). Of the 5051 patients with diabetes, 3341 received a DES and 1710 received a BMS. Patients who received both types of stent were excluded from the analysis.

Because Mass-DAC was an observational study in which patients were not randomly assigned to different treatment groups, several baseline characteristics differed in the 2 groups. Therefore, propensity score matching using 67 clinical variables was used to compare outcomes in the DES and BMS groups. The primary endpoints were mortality, MI, and target vessel revascularization after 3 years.

The unadjusted mortality rate was 14.4% for patients who received DES and 22.2% for those who received BMS. According to propensity score analysis, DES were associated with a 3.2% absolute reduction in the risk of death compared with BMS (17.5% vs 20.7%; p=0.02), a 3% absolute reduction in the risk of MI (13.8% vs 16.9%; p=0.02), and a 5.4% absolute reduction in the risk of target vessel revascularization (18.4% vs 23.7%; p<0.001; Figure 1).

Figure 1. Drug-Eluting and Bare-Metal Stenting for Diabetes Mellitus - Matched Risk Differences at 3 Years.



Dr. Mauri noted that the mortality curves for the DES and BMS groups stayed roughly parallel from 6 months through 3 years. The durability of the restenosis benefit with the small but persistent survival benefit that was associated with DES suggests that they should be the preferred therapy in patients with diabetes, she concluded.

Early Invasive Management Beneficial for High-Risk NSTEMI Patients

An early invasive strategy is as safe as delayed invasive management in patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI), according to findings from the TIMACS (Timing of Intervention in Patients with Acute Coronary Syndromes; NCT00552513) trial. However, early invasive care does not significantly reduce the risk of death, new myocardial infarction (MI), or stroke compared with a delayed invasive strategy in most patients, except for those who are at the highest risk for adverse events.

The TIMACS trial included 3031 patients who were randomly assigned to an early invasive strategy that included coronary angiography within 24 hours followed by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) as needed (n=1593), or to a delayed strategy in which patients received angiography, PCI, or CABG 36 hours or more after the onset of symptoms (n=1438). The median times to angiography in the early and delayed groups were 14 and 50 hours, respectively.

Patients in the early and delayed management groups had similar rates of the primary composite endpoint of death, MI, or stroke within 6 months (9.7% vs 11.4%, HR, 0.85; 95% CI, 0.68 to 1.06; p=0.15; Figure 1). In a secondary endpoint analysis, early invasive management reduced the risk of refractory ischemia compared with delayed management (1.0% vs 3.3%; HR, 0.30; 95% CI, 0.17 to 0.53; p<0.00001), without increasing the risk of major bleeding during the index hospitalization (3.1% vs 3.5%; p=0.53).

Early management also reduced the risk of death or cardiovascular events among patients who were at high risk for adverse events, as determined by GRACE (Global Registry of Acute Coronary Events) scores ≥140. For patients with low or intermediate risk according to GRACE scoring, the 6-month risk of death, MI, or stroke was similar in the early and delayed management groups (7.7% vs 6.7%; p=0.43). However, among patients in the