The 80 mg/day simvastatin regimen was associated with a higher incidence of myopathy (53 cases vs 3 in the 20 mg dose group), 25 of which occurred in the first year.

A second objective of the SEARCH study was to evaluate the effect of folic acid on MVE. In a 2 X 2 factorial design, participants in SEARCH (none of whom had a clear indication for folic acid) also were randomly assigned to receive either 2 mg of folic acid + 1 mg of vitamin B_{12} daily (n=6033) or placebo (n=6031). The average homocysteine level at baseline was 13.5 µmol/L. After an average of 6.7 years of follow-up, although homocysteine levels were 3 to 4 µmol/L lower in patients who received the folic acid/vitamin combination, the reduction was not associated with a reduction in MVE (25.5% vs 24.8%; HR, 1.04; 95% CI, 0.95-1.14; p>0.05). Long-term supplementation with these vitamins was shown to be safe, however, with no significant excess of any major adverse events, including cancer.

Additional information on SEARCH can be found at http://www.searchinfo.org.

Vitamin E and C Supplements Do Not Reduce Long-Term Cardiovascular Risk

After 8 years of treatment, the antioxidant vitamins E and C do not help prevent myocardial infarction (MI), stroke, or cardiovascular (CV) death in low-risk men, according to findings from the Physicians' Health Study II (NCT00270647). These findings refute the belief that long-term treatment with these antioxidant vitamins are cardioprotective, researchers reported.

"Available trial data do not support the use of vitamin E and vitamin C supplements as part of a comprehensive cardiovascular disease prevention strategy," said J. Michael Gaziano, MD, Brigham and Women's Hospital and VA Medical Center, Boston, MA. Dr. Gaziano presented results of the Physicians' Health Study II, which were simultaneously published online in the *Journal of the American Medical Association* [Sesso HD et al. *JAMA* 2008].

In the Physicians' Health Study II, 14,641 male doctors were randomly assigned to receive vitamin E (400 IU every other day) or placebo, and also assigned to receive an additional vitamin C supplement (500 mg/day) or placebo. The participants were relatively healthy when they enrolled in the study, of whom just 5.1% had cardiovascular disease at baseline. The mean age of participants was 64 years at the start of the study, which began in 1997. The primary endpoint was major CV events, which was a composite of nonfatal MI, nonfatal stroke, and CV mortality.

After 8 years of follow-up, there were 1245 confirmed major CV events. A similar number of events were reported in the groups that received vitamin E versus placebo (620 vs 625 events; HR, 1.01; 95% CI, 0.90 to 1.13; p=0.96) and in the groups that received vitamin C versus placebo (619 vs 626 events; HR, 0.99; 95% CI, 0.89 to 1.11; p=0.84).

Treatment with vitamin E was associated with an increased risk of hemorrhagic stroke compared with placebo (39 vs 23 events; HR, 1.74; 95% CI, 1.04 to 2.91; p=0.04). By comparison, vitamin C had no effect on the risk of hemorrhagic stroke (30 vs 32 events; HR, 0.95; 95% CI, 0.57 to 1.56).

Vitamins E and C, alone or in combination, had no effect on any of the other individual endpoints of nonfatal MI, ischemic stroke, CV death, or other CV outcomes. In particular, there was no interaction between vitamin E and congestive heart failure (CHF). The trial investigators designated CHF as a prespecified secondary endpoint, given the suggestion of a relationship between vitamin E and CHF in the HOPE trial.

Data on a third randomization, in which participants received either a daily multivitamin supplement or placebo, are still being evaluated. Researchers also collected information on cancer incidence and will report these findings at a later time, Dr. Gaziano said.

Phase 2 Trial Provides Safety and Outcomes Data on Novel Anticoagulant Agent

Despite the advent of dual antiplatelet therapy with aspirin and clopidogrel, rates of in-hospital and 1-year mortality and reinfarction after acute coronary syndrome (ACS) are approximately 10%. The results of the ATLAS ACS-TIMI 46 (NCT00402597) trial represent an important step toward meeting a need for more effective antithrombotic therapy after ACS.

ATLAS ACS-TIMI 46 was a phase 2 dose-finding trial of rivaroxaban that was added to standard antiplatelet therapy with either aspirin alone or aspirin plus clopidogrel. C. Michael Gibson, MD, the TIMI Study Group, Boston, MA, lead author of the trial, explained that rivaroxaban is a

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