Best of the AHA Scientific Sessions 2008

Highlights From the American Heart Association Scientific Sessions, November 8-12, 2008, New Orleans, LA

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Key words: Acute coronary syndrome • Coronary heart disease • High-sensitivity C-reactive protein • International normalized ratio testing • Revascularization • Rosuvastatin • Vitamin C • Vitamin E

Studies presented at the American Heart Association Scientific Sessions contained important data of interest to the practicing cardiologist. Here we discuss key trials on the use of statins to prevent heart disease, timing of treatment in patients with acute coronary syndromes (ACS), the use of vitamin supplementation to reduce cardiovascular events, the effect of the angiotensin-receptor blocker irbesartan on cardiovascular outcomes, the use of home international normalized ratio (INR) testing in patients requiring anticoagulation, the use of rosiglitazone compared with glipizide among patients with diabetes undergoing coronary angiography, and how to optimize the dose of rivaroxaban for patients with ACS.

Reviewed by Karol E. Watson, MD, PhD, FACC, The David Geffen School of Medicine at UCLA, Los Angeles, CA; Alice K. Jacobs, MD, FACC, FAHA, Boston University School of Medicine, Boston University Medical Center, Boston, MA; and Norman E. Lepor, MD, FACC, FAHA, FSCAI, The David Geffen School of Medicine at UCLA, Cedars-Sinai Medical Center, Los Angeles, CA.

The JUPITER Trial

One of the most effective strategies for the prevention of coronary heart disease has been lipid-lowering therapy with statins. This therapy is currently administered to patients with elevated low-density lipoprotein cholesterol (LDL-C), depending on their calculated risk status. Currently, risk stratification involves simply counting major cardiovascular risk factors or utilizing risk algorithms that are based upon these factors. Although this paradigm of risk stratification has been very beneficial in targeting preventive therapies, some higher risk patients are not captured in the current schema. In an effort to improve cardiovascular risk stratification, significant attention has focused on additional potential risk markers, and high-sensitivity C-reactive protein (hsCRP) has received much attention.[1]

Design

The primary objective of Justification for the Use of Statins in Primary Prevention: An Intervention Trial

Evaluating Rosuvastatin (JUPITER)[2] was to determine whether treatment with rosuvastatin would reduce the rate of first major cardiovascular events (defined as the combined endpoint of cardiovascular death, stroke, myocardial infarction [MI], hospitalization for unstable angina, or arterial revascularization) among apparently healthy individuals with LDL-C levels less than 130 mg/dL, but with hsCRP levels at or greater than 2 mg/L. JUPITER randomized 17,802 healthy men and women to rosuvastatin 20 mg/d or placebo. Healthy men ages 50 years or older and healthy women ages 60 years or older were eligible for the trial if at the initial screening visit they had an LDL-C level of less than 130 mg/dL and an hsCRP level of 2.0 mg/L or more. The researchers screened 89,890 participants to enroll the 17,802.

Among the study subjects, 38.5% were women, and a significant number (25%) were African American or Hispanic. The median body mass index was 28.3, and the median blood pressure was 134/80 mm Hg. The metabolic syndrome, as defined by National Cholesterol Education Program Adult Treatment III (NCEP ATP III) criteria, was identified in 41% of study participants. Median LDL-C was 108 mg/dL, median high-density lipoprotein cholesterol (HDL-C) was 49 mg/dL, and median hsCRP was 4.3 mg/L.

Results

At an interim meeting of the trial's independent data safety and monitoring board, subjects in the rosuvastatin arm were found to have significant benefit, and therefore the trial was prematurely terminated at a mean follow-up of 1.9 years. Rosuvastatin therapy significantly reduced the primary composite endpoint by 44% as compared with placebo. This reduction was observed across the range of the individual endpoints that comprised the composite. It included a 55% reduction in nonfatal MI, a 48% reduction in nonfatal stroke, a 46% reduction in revascularizations, and a 47% reduction in the risk of hard cardiac events (a composite of MI, stroke, and death from cardiovascular causes) (Table 1).

Implications

Current treatment guidelines would likely not recommend statin therapy for the patients who were enrolled in the JUPITER trial. In this population, however, treatment with rosuvastatin yielded very significant benefits, despite LDL levels that might be considered adequate. This trial has the potential to change clinical practice, yet several clinical questions remain. How widely should hsCRP testing be applied? How low should LDL levels be targeted? How should risk stratification change? These questions, and many more, have been raised by the provocative findings of the JUPITER trial.

[Karol E. Watson, MD, PhD, FACC]

Table 1
Results From the JUPITER Trial

	Rosuvastatin Group (n = 8901) n	Placebo Group (n = 8901) n	Hazard Ratio (95% CI)
Primary endpoint (cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization)	142	251	0.56 (0.46-0.69)
Nonfatal MI	22	62	0.35 (0.22-0.58)
Any MI	31	68	0.46 (0.30-0.70)
Nonfatal stroke	30	58	0.52 (0.33-0.80)
Any stroke	33	64	0.52 (0.34-0.79)
Revascularization	71	131	0.54 (0.41-0.72)
Hospitalization for unstable angina	16	27	0.59 (0.32-1.10)
Revascularization or hospitalization for unstable angina	76	143	0.53 (0.40-0.70)
MI, stroke, or death from cardiovascular causes	83	157	0.53 (0.40-0.69)
Total mortality	198	247	0.80 (0.67-0.97)

JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; CI, confidence interval; MI, myocardial infarction.
Data from Ridker PM et al.[2]

The TIMACS Study

It is well established that ST-segment elevation myocardial infarction (STEMI) represents a true medical emergency in which the relationship between time to treatment (reperfusion) and mortality is measured in minutes. For patients with unstable angina and non-STEMI ACS, the urgency of time to treatment (coronary angiography and revascularization) is less clear. Although multiple randomized clinical trials and meta-analyses in patients with ACS have shown that the "early" rather than the "selective" (for recurrent spontaneous or induced ischemia) invasive strategy improves outcomes (in men and high-risk women), the optimal timing (or the exact definition of "early") is unknown.

Accordingly, the Timing of Intervention in Patients with Acute Coronary Syndromes (TIMACS) study evaluated 3031 patients from 100 medical centers in 17 countries who had ACS suitable for revascularization.[3] Patients were randomly assigned to "early" (as soon as possible within 24 hours) versus "delayed" (more than 36 hours) coronary angiography followed by percutaneous coronary intervention or coronary artery bypass surgery. Risk stratification was performed using the Global Registry of Acute Cardiac Events (GRACE) score and categorized as low/intermediate or high. The primary endpoint of the trial was the combined rate of death, reinfarction, or stroke at 6 months. Secondary endpoints included a composite of death, new MI, or refractory ischemia; death, new MI, stroke, refractory ischemia, or repeat revascularization; and stroke.

Median times to angiography were 14 hours in the early group and 50 hours in the delayed group. Overall, there was no difference in the primary endpoint between the early and delayed strategies, although there was a significant reduction in events in high-risk patients (14.1%) versus low-risk patients (21.6%) (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.48-0.88; $P = .005$. Furthermore, secondary endpoints and refractory ischemia were significantly reduced in the group randomized to the early revascularization strategy (Table 2). The rates of major bleeding during the index hospitalization were similar between the early (3.1%) and late (3.5%) groups. The authors concluded that early invasive management for patients with ACS does not reduce the risk for death, new MI, or stroke overall.

Comments

This study is of interest because care for all ACS patients will likely be improved by the ongoing development of systems of care and regional networks established to provide patients with STEMI timely access to invasive therapies. Although the results suggest that most patients with ACS can be managed safely with an early or delayed invasive strategy, it will be important to obtain longer follow-up when a mortality benefit may be apparent. It will be helpful to assess the relative cost-effectiveness of the 2 approaches to care. The reduction in cost associated with a potential decrease in the length of the hospital stay will need to be balanced against the increase in cost of mobilizing the catheterization laboratory team off-hours. For now, it seems appropriate to risk stratify all patients with ACS

Table 2
Outcomes in the TIMACS Trial

	Early n = 1593 (%)	Delayed n = 1438 (%)	Hazard Ratio	95% Confidence Interval	*P* Value
Death, MI, stroke	9.7	11.4	0.85	0.68-1.06	0.53
Death, MI, refractory ischemia	9.6	13.1	0.72	0.58-0.89	.002
Death, MI, stroke, refractory ischemia plus repeat intervention	16.7	19.7	0.84	0.71-0.99	.039
Death	4.9	6.0	0.81	0.60-1.11	.19
MI	4.8	5.8	0.83	0.61-1.14	.25
Stroke	1.3	1.4	0.90	0.48-1.68	.74
Refractory ischemia	1.0	3.3	0.30	0.17-0.53	< .00001
Repeat intervention	8.8	8.6	1.04	0.82-1.34	.73

TIMACS, Timing of Intervention in Patients with Acute Coronary Syndromes; MI, myocardial infarction.
Data from Mehta SR.[3]

to determine the optimal timing of coronary angiography and potential revascularization, moving forward with the early strategy in high-risk patients and in all patients when the resources are available, given the absence of harm in doing so.
[Alice K. Jacobs, MD, FACC, FAHA]

Physicians Health Study II

The Physicians Health Study II (PHS II) trial was designed to assess the role of vitamin C and E supplementation in the prevention of cardiovascular events in low-risk male physicians.[4] Patients were randomized in a 2 × 2 × 2 × 2 factorial trial to either vitamin E (400 IU synthetic α-tocopherol) or placebo every other day, to vitamin C (500 mg synthetic ascorbic acid) or placebo daily, to a multivitamin (Centrum Silver) or placebo, or to beta-carotene (50 mg of Lurotin) or placebo every other day. A total of 14,641 healthy men were randomized. The primary endpoint was a composite of nonfatal MI, nonfatal stroke, and cardiovascular mortality. Secondary endpoints included nonfatal MI, nonfatal stroke, cardiovascular mortality, congestive heart failure, angina pectoris, and revascularization.

There was no difference between patients receiving vitamin E or placebo in the incidence of major cardiovascular events (8.5% vs 8.5%; HR, 1.01; 95% CI, 0.90-1.13; $P = .86$). There was also no difference in the incidence of MI, stroke, congestive heart failure, or all-cause mortality. There was, however, a significant increase in the risk of hemorrhagic stroke in the vitamin E arm as compared with the placebo arm (0.53% vs 0.31%; HR, 1.74; $P = .04$). There was no difference between patients receiving vitamin C or placebo in the incidence of major cardiovascular events, MI, stroke, or all-cause mortality (Figure 1).

The results of the PHS II trial indicated that neither vitamin C nor vitamin E supplementation was associated with a reduction in major cardiovascular outcomes in men as compared with placebo. Vitamin E may be associated with a slightly higher incidence of hemorrhagic stroke compared with placebo.

The I-PRESERVE Study

The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) study evaluated the effect of the angiotensin-receptor blocker irbesartan on cardiovascular outcomes in patients with heart failure and normal left ventricular ejection fraction (LVEF).[5] Patients were started on irbesartan 75 mg/d or placebo, with a forced titration (a doubling to 150 mg/d after 1-2 weeks, and then again to 300 mg/d after another 1-2 weeks). Patients continued to take their other heart failure treatments, including diuretics (83%), spironolactone (15%), β-blockers (59%), oral anticoagulants (19%), antiplatelet therapies (59%), angiotensin-converting enzyme (ACE) inhibitors (26%), digoxin (14%), and lipid-lowering agents (31%).

The 4128 study subjects were randomized to irbesartan (2067) or placebo (2061). Baseline characteristics were fairly similar between the groups. At baseline, LVEF was 60%, and 44% of patients had been hospitalized for heart failure within the preceding 6 months. Median baseline N-terminal B-type natriuretic peptide (NT-proBNP) levels were approximately 340 pg/mL. There was a mean decrease in systolic and diastolic blood pressure by 3.8/2.1 mm Hg in the irbesartan group, as compared with 0.2/0.2 mm Hg in the placebo group. There was no difference between the irbesartan and placebo groups in the incidence of the primary outcome of all-cause mortality or hospitalization for cardiovascular causes (36% vs 37%; $P = .35$) (Figure 2). There was no observed difference between the 2 groups in the incidence of mortality, cardiovascular hospitalizations, worsening heart failure, or ventricular arrhythmias. Measures of quality of life or changes in NT-proBNP were not significantly different between the 2 groups. There was no difference in the mean levels of serum creatinine between the 2 groups at the end of the study, although a doubling of serum creatinine occurred more frequently with irbesartan than with placebo (6% vs 4%; $P > .0001$).

The results of the I-PRESERVE trial indicate that angiotensin-receptor

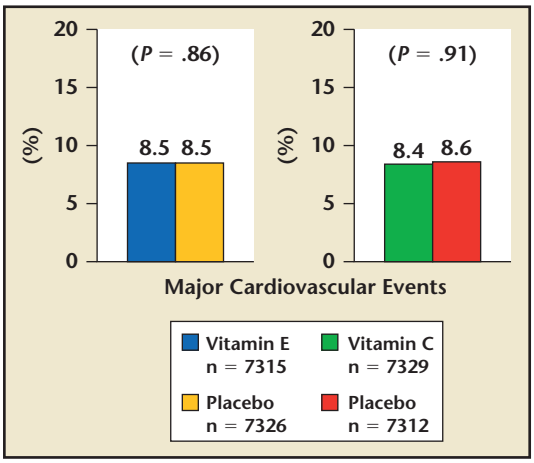

Figure 1. *The Physicians Health Study II (PHS II) trial was designed to assess the role of vitamin C and E supplementation in the prevention of cardiovascular events in low-risk male physicians. The results indicated that neither vitamin C supplementation nor vitamin E supplementation were associated with a reduction in major cardiovascular outcomes. Data from Sesso HD et al.[4] Adapted with permission from Cardiosource.*

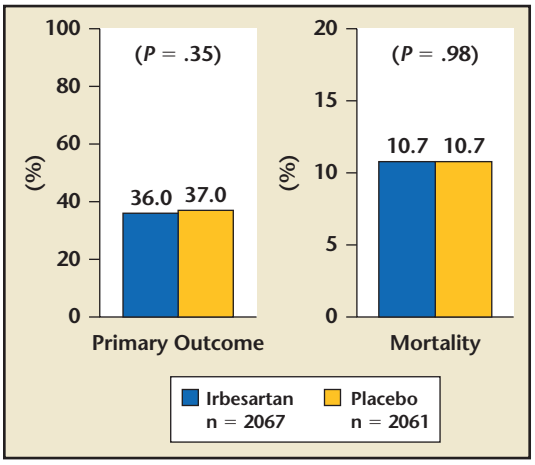

Figure 2. *The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) study evaluated the effect of the angiotensin-receptor blocker irbesartan on cardiovascular outcomes in patients with heart failure and normal left ventricular ejection fraction. There was no difference between the irbesartan and placebo groups in the incidence of the primary outcome of all-cause mortality or hospitalization for cardiovascular causes. Mortality was also similar. Data from Massie BM et al.[5] Adapted with permission from Cardiosource.*

blockade with irbesartan is not associated with a reduction in cardiovascular mortality and morbidity in patients with heart failure and normal ejection fraction over and above that seen with the patients' conventional treatments, including β-blockers, ACE inhibitors, and aldosterone blockers.

The Search Trial

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) was a 2 × 2 trial designed to evaluate the safety and efficacy of aggressive statin therapy and homocysteine reduction with folic acid plus vitamin B_{12} in patients who had recently suffered an MI.[6] Patients were randomized to receive either 20 mg/d of simvastatin or 80 mg/d of simvastatin, and folic acid plus vitamin B_{12} or placebo.

During the duration of the study, there was only a 14% reduction in LDL-C in the high-dose simvastatin arm compared with the low-dose arm, secondary to many drops in the low-dose arm. There was no difference between the high-dose and low-dose simvastatin arms in the incidence of major vascular events (24.5% vs 25.7%; HR, 0.86; 95% CI, 0.68-1.09; $P > .05$), all-cause mortality, cardiac mortality, or stroke (Figure 3). There was a significantly higher risk of myopathy in the high-dose simvastatin arm compared with the low-dose arm (0.88% vs 0.05%; $P < .05$). Of interest was the observation that patients taking high-dose simvastatin had a nearly 10-fold increase in myopathy than patients taking the low dose.

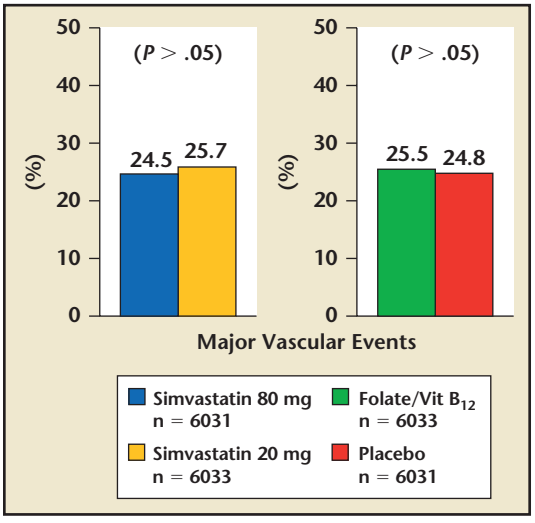

Figure 3. *The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the use of high-dose simvastatin versus low-dose simvastatin in patients who had recently suffered a myocardial infarction. Researchers also examined the use of folic acid plus vitamin (Vit) B_{12}. Results showed that the higher dose of simvastatin was no more effective than the lower dose. In addition, the use of folic acid plus Vit B_{12} did not reduce the incidence of major vascular events. Data from Collins R.[6] Adapted with permission from Cardiosource.*

The results of the SEARCH trial indicate that simvastatin 80 mg/d was no more effective than simvastatin 20 mg/d in the secondary prevention of adverse cardiovascular events in post-MI patients. The higher dose statin therapy was associated with a significantly higher incidence of myopathy. Investigators also found that 2 mg of folic acid and 1 mg of vitamin B_{12} a day failed to show any reduction in the primary outcome of major vascular events (nonfatal heart attack, coronary death, stroke, or arterial revascularization) compared with placebo. These data confirm the results of other recent clinical trial experiences showing no beneficial effect of folic acid and vitamin B_{12} on cardiovascular events.

The THINRS Trial

The Home INR Study (THINRS) evaluated the impact of home INR testing as compared with conventional testing in patients requiring anticoagulation.[7] The study subjects were patients with atrial fibrillation or a mechanical heart valve treated with warfarin who were capable of performing self-INR testing. Patients were randomized to self-INR testing (n = 1465) or conventional monthly INR testing (n = 1457). The indication for anticoagulation was atrial fibrillation in 83% of the study patients.

The primary outcome of time to death, stroke, or major bleeding in the self-testing group was 7.9% per patient-year versus 8.9% per patient-year in the conventional testing group ($P = .1$). The time in the target anticoagulation range was not

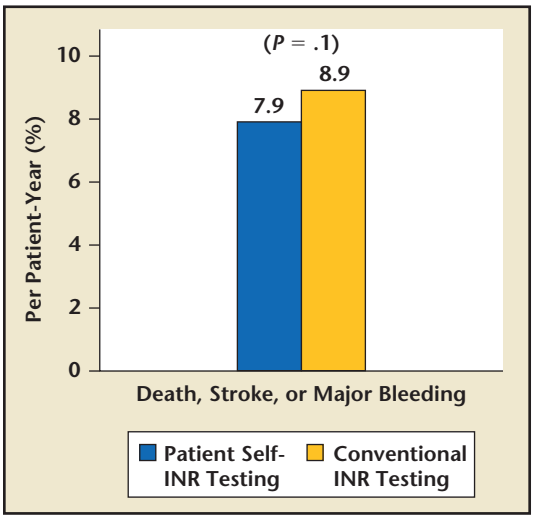

Figure 4. *The Home INR Study (THINRS) compared home international normalized ratio (INR) testing with conventional testing in patients requiring anticoagulation. Patient self-testing for INR monitoring did not reduce the composite outcome of death, stroke, or major bleeding. Data from Jacobson AK.[7] Adapted with permission from Cardiosource.*

significantly different between the groups (67% for self-testing vs 62% for conventional testing; $P < .05$). Patient self-testing for INR monitoring did not reduce the composite outcome of death, stroke, or major bleeding (Figure 4), nor was there any evidence of safety issues indicating that self-testing might be a safe alternative to conventional testing with ProTime® (Quality Assured Services, Inc, Orlando, FL).

The APPROACH Trial

The Assessment on the Prevention by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History (APPROACH) trial evaluated treatment with rosiglitazone compared with glipizide among patients with diabetes undergoing coronary angiography to determine if there is an effect on the progression of coronary atherosclerosis.[8] Patients with type 2 diabetes undergoing coronary angiography with a 10% to 50% stenosis in a nonintervened segment were included in this intravascular ultrasound study. The primary endpoint was a change in percent atheroma volume, with secondary endpoints including change in normalized total atheroma volume and change in atheroma volume in the most diseased 10-mm segment. Patients were excluded if they had prior coronary artery bypass grafting, valvular heart disease, an LVEF less than 40%, congestive heart failure, renal or liver dysfunction, or uncontrolled hypertension.

Patients were randomized to rosiglitazone titrated to 8 mg/d or glipizide titrated to 15 mg/d. Insulin or metformin could be added after 3 months to achieve a glycated hemoglobin of less than 7.0%. Patients had baseline and repeat intravascular ultrasound at 18 months. The median duration of diabetes was 4.8 years, with a mean glycated hemoglobin of 7.2%.

The primary endpoint, change in percent atheroma volume, was −0.21% in the rosiglitazone group versus 0.43% in the glipizide group ($P = .12$ between groups) (Figure 5). The change in total atheroma volume was −3.9 mm^3 in the rosiglitazone group versus 1.2 mm^3 in the glipizide group ($P = .04$), and the change in atheroma volume in the most diseased 10-mm segment was −5.3 mm^3 in the rosiglitazone group versus −3.6 mm^3 ($P = .13$) in the glipizide group. There were no differences in cardiovascular outcomes, including death, MI, stroke, congestive heart failure, and coronary revascularization. Adverse events, including bone fracture, mean weight gain, and hemoglobin decrease of more than 3 g/dL, were more common with rosiglitazone, but hypoglycemia was more common with glipizide (8% vs 28%; $P < .0001$). Rosiglitazone was associated with a greater percent change in hsCRP and a greater increase in HDL-C than glipizide, but also with a small increase in LDL-C.

In patients with type 2 diabetes, the use of rosiglitazone did not reduce percent atheroma volume compared with glipizide but was associated with a reduction in total

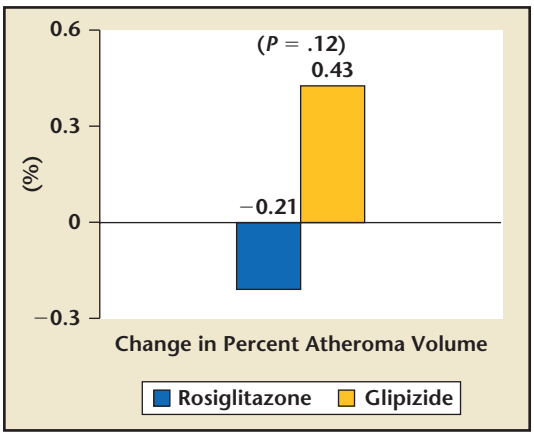

Figure 5. *The Assessment on the Prevention by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History (APPROACH) trial evaluated treatment with rosiglitazone compared with glipizide among patients with diabetes undergoing coronary angiography to determine if there was an effect on the progression of coronary atherosclerosis. The use of rosiglitazone did not reduce percent atheroma volume as compared with glipizide, but it was associated with a reduction in total atheroma volume. Data from Nesto RW.[8] Adapted with permission from Cardiosource.*

atheroma volume. Cardiovascular outcomes were similar between the groups, with rosiglitazone associated with more weight gain and more decline in hemoglobin and, importantly, with less hypoglycemia.

The ATLAS ACS TIMI 46 Trial

The Randomized Comparison of Rivaroxaban, an Oral Direct Factor Xa Inhibitor, with Placebo in Patients with Acute Coronary Syndromes (ATLAS ACS TIMI 46) trial was designed to identify tolerable doses of rivaroxaban, an oral direct factor Xa inhibitor, in the treatment of patients with ACS.[9] The patients included in the study had ACS symptoms exceeding 10 minutes at rest within 7 days of randomization, STEMI, or non-STEMI/unstable angina with at least 1 of the following: elevated cardiac biomarkers, ST-segment deviation of 1 mm or more, or Thrombolysis In Myocardial Infarction (TIMI) risk score of 3 or more. Patients were excluded if they had an increased bleeding risk; a gastrointestinal bleed within the previous 6 months; an indication for warfarin; history of hemorrhagic stroke, ischemic stroke, or transient ischemic attack within the previous 30 days; abciximab treatment within the previous 8 hours; or eptifibatide or tirofiban treatment within the previous 2 hours. The primary efficacy endpoint was a composite of death, MI, stroke, or severe ischemia requiring revascularization. Safety endpoints included clinically significant bleeding (TIMI major, TIMI minor, or bleeding requiring medical attention).

Patients were randomized in a 1:1:1 fashion to either placebo, rivaroxaban once daily, or rivaroxaban twice daily. The 3491 study subjects were first randomized to either aspirin alone (761) or aspirin plus clopidogrel (2730). Both of these groups were then assigned to receive rivaroxaban at total daily doses of 5 mg, 10 mg, 15 mg, or 20 mg, administered as either once-daily or twice-daily doses, or placebo. There were 1166 patients in the once-daily rivaroxaban group, 1156 in the twice-daily rivaroxaban group, and 1160 patients in the placebo group.

The primary efficacy endpoint of death, MI, stroke, or severe ischemia requiring revascularization occurred less frequently in the rivaroxaban arm compared with the placebo arm, although this difference did not reach statistical significance (5.6% vs 7.0%; $P = .10$) (Figure 6). There was

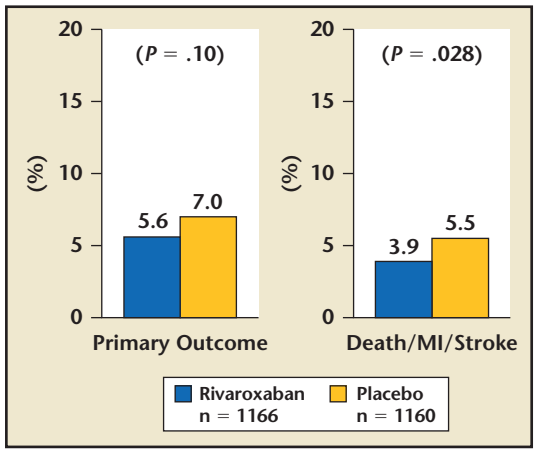

Figure 6. *The Randomized Comparison of Rivaroxaban, an Oral Direct Factor Xa Inhibitor, with Placebo in Patients with Acute Coronary Syndromes (ATLAS ACS TIMI 46) trial examined the use of various doses of rivaroxaban, an oral direct factor Xa inhibitor, in the treatment of patients with acute coronary syndromes. The results indicated that rivaroxaban was associated with improved efficacy compared with placebo. There was a dose-response curve with respect to the primary safety endpoint of clinically significant bleeding. MI, myocardial infarction. Data from Gibson CM.[9] Adapted with permission from Cardiosource.*

Main Points

- Treatment with rosuvastatin yielded very significant benefits in apparently healthy study subjects with LDL-C levels less than 130 mg/dL and hsCRP levels at or greater than 2 mg/L.
- New data suggest that most patients with ACS can be managed safely with an early or delayed invasive strategy, although longer follow-up is needed to determine any mortality benefit.
- The angiotensin-receptor blockade with irbesartan was not associated with a reduction in cardiovascular mortality and morbidity in patients with heart failure and normal ejection fraction over and above that seen with the patients' conventional treatments.
- A higher dose of simvastatin (80 mg/d) was no more effective than a lower dose (20 mg/d) in the secondary prevention of adverse cardiovascular events in post-MI patients.
- In patients with type 2 diabetes, the use of rosiglitazone did not reduce percent atheroma volume compared with glipizide, although it was associated with a reduction in total atheroma volume.
- Rivaroxaban was associated with improved efficacy compared with placebo in ACS patients also receiving oral antiplatelet therapy, but with a higher risk of clinically significant bleeding—particularly at higher doses.

a statistically significant reduction in the secondary endpoint of death, MI, or stroke in the rivaroxaban arm compared with the placebo arm (3.9% vs 5.5%; $P = .028$). There was a dose-response curve with respect to the primary safety endpoint of clinically significant bleeding. Bleeding rates were 15.3%, 12.7%, 10.9%, 6.1%, and 3.3% ($P < .001$) for rivaroxaban doses of 20 mg, 15 mg, 10 mg, 5 mg, and placebo, respectively. Bleeding was higher in those patients receiving dual antiplatelet therapy compared with aspirin alone. Liver test abnormalities were equally frequent in the rivaroxaban and placebo arms.

The results of the ATLAS ACS TIMI 46 trial indicate that rivaroxaban was associated with improved efficacy compared with placebo in ACS patients also receiving oral antiplatelet therapy, with a higher risk of clinically significant bleeding—particularly at higher doses. A larger randomized trial will assess the efficacy and safety of rivaroxaban based on the results of this phase II, dose-finding study. ■

[Norman E. Lepor, MD, FACC, FAHA, FSCAI]

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