Cost-Effectiveness of Clopidogrel in Patients with Acute Coronary Syndrome

Speaker: William S. Weintraub, MD, Professor of Medicine, Division of Cardiology, Department of Medicine and Chief, Emory Center for Outcomes Research, Emory University School of Medicine, Atlanta, Georgia.

Clopidogrel (Plavix®, Sanofi-Synthelabo/Bristol-Myers Squibb) has been found to be both efficacious and cost-effective over the long term in patients who have undergone percutaneous coronary intervention (PCI) early after non-ST-segment elevation acute coronary syndrome (ACS).

Results from the Percutaneous Coronary Intervention–Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (PCI–CURE) study demonstrated the benefits of clopidogrel, when added to aspirin, up to one year after PCI following ACS. An analysis was carried out to evaluate the cost-effectiveness of clopidogrel in platelet inhibition for up to one year after PCI, during the initial hospitalization in the PCI–CURE trial. After PCI, more than 80% of the patients received the open-label, adenosine diphosphate (ADP)–receptor antagonist for four weeks, followed by the study drug for up to one year.

This PCI–CURE subgroup characterizes PCI practice patterns in the U.S. The composite of cardiovascular death, stroke, or myocardial infarction (MI) occurred in 9.3% of patients (76) receiving clopidogrel and in 12.8% of patients (116) receiving placebo, resulting in a 27% reduction in risk that favored clopidogrel.

Hospitalized patients were assigned to a Diagnosis-Related Group (DRG). Costs were estimated from Medicare’s average reimbursement, MEDSTAT private insurance, and a blend of MEDSTAT for those younger than 65 years of age and Medicare for those older than age 65. Clopidogrel was assigned an average wholesale cost of $3.22 per day. Life expectancy losses associated with death, nonfatal MI, and nonfatal stroke were estimated from published data from the Framingham study, which were discounted 3%, and from the Saskatchewan Health Database.

The incremental cost-effectiveness ratio was $935 per life-year gained with clopidogrel in the PCI–CURE study. This compared with other reported cost-effectiveness ratios or cardiovascular interventions, for example:

- $220 per life-year gained for smoking cessation after an MI
- $2,080 per life-year gained for treatment with the angiotensin-converting enzyme (ACE)–inhibitor lisinopril (Prinivil®, Merck) after an MI
- $21,200 per life-year gained for thrombolytic therapy in the elderly
- $5,400–$32,000 per life-year gained for treatment with statins

In conclusion, the results for clopidogrel are robust, as confirmed by various costing strategies and estimates of the effects of events on long-term survival.

Intensive Statin Therapy After Acute Coronary Syndrome

Speaker: Christopher P. Cannon, MD, Associate Professor of Medicine, Harvard Medical School, and Thrombolysis in Myocardial Infarction (TIMI) Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts.

Patients with a recent episode of ACS derived greater protection against death or major cardiovascular events when they received an early, continuous, intensive lipid-lowering statin regimen instead of standard-dose statin therapy.

These landmark results came from the Pravastatin or Atorvastatin Evaluation and Infarction Therapy–Thrombolysis in Myocardial Infarction 22 trial (PROVE IT–TIMI 22). This large-scale, international study included 4,162 patients who had been hospitalized because of an ACS within the preceding 10 days. The patients had a total cholesterol count of 240 mg/dl or less upon hospital entry or up to six months earlier.
The patients were enrolled at 349 hospital sites in eight countries. Of these patients, 2,099 were randomly assigned to receive intensive therapy with atorvastatin (Lipitor®, Pfizer) 80 mg daily; 2,063 received standard statin therapy with pravastatin (Pravachol®, Bristol-Myers Squibb) 40 mg daily, along with standard medical and interventional treatment for ACS, including aspirin 75–325 mg daily with or without clopidogrel (Plavix®) or warfarin (Coumadin®, DuPont). Patients were observed at 30 days, at four months, and every four months thereafter for 18 to 36 months. Follow-up observation lasted for approximately 24 months. The primary endpoint of the study was the composite of all-cause mortality, MI, and documented unstable angina requiring rehospitalization, revascularization, or stroke.

The median baseline low-density lipoprotein-cholesterol (LDL-C) level in both treatment groups was 106 mg/dl. During follow-up, the group receiving the standard dose of pravastatin achieved LDL-C levels of 95 mg/dl; the group receiving the intensive dose of atorvastatin achieved levels of 62 mg/dl. Among the 75% of patients who had not previously received statin therapy within 30 days, the median LDL-C levels had fallen by 22% in the pravastatin group and by 51% in the atorvastatin group.

The more intensive atorvastatin therapy was associated with a 16% reduction in the risk of all-cause mortality or major cardiovascular events, compared with the present standard treatment with regular-dose pravastatin. After two years, the incidence of cardiovascular events was 26.3% for the standard-dose pravastatin group and 22.4% for the high-dose atorvastatin group. The relative risk reduction of all-cause mortality alone was even greater (28%) with intensive statin therapy, the advantages of which began as early as 30 days after initiation and continued for two years.

**Following Treatment Guidelines in Potential Heart Attacks**

**Speaker:** Eric D. Peterson, MD, Associate Professor of Medicine, Division of Cardiology, Department of Medicine, Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina.

Results from the database of a national quality improvement initiative showed that hospitals with the highest adherence to national guidelines for treating patients with acute coronary syndrome (ACS) had significantly better patient outcomes, with more lives saved, than did hospitals that were less adherent. These findings are important, because although many studies have proved the effectiveness of individual treatment modalities in improving outcomes for patients with ACS, few have correlated individual hospitals’ use of these different therapies with actual patient outcomes.

Data from the an initiative called Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) were assessed to determine how hospitals adhered to nine American College of Cardiology/American Heart Association class I care indicators of in-hospital and discharge care. The trial encompassed 64,775 patients at more than 400 hospitals in the U.S. Hospitals that were in the top 25 percentile of adherence were rated as “leading”; those in the bottom 25 percentile were rated as “lagging.”

In each of the nine performance measures, significant performance gaps existed between the two types of hospitals. For example, there was a narrow gap in the rate of initial aspirin use (96% for the leading hospitals versus 85% for the lagging hospitals) and a wide gap in the use of glycoprotein (GP) IIb/IIIa inhibitors (50% for the leading hospitals versus 17% for the lagging hospitals).

The leading hospitals tended to be larger, with an average of 388 beds; the lagging hospitals had 321 beds. The leading hospitals were more often academic institutions (34% versus 21%, respectively). Finally, the leading hospitals were more likely to have the capability of performing coronary artery bypass graft surgery (81%) and percutaneous coronary interventions (59%).

**Fasudil in Patients with Stable Angina**

**Speaker:** Ralph M. Vicari, MD, Director, Mina Century Research, Melbourne, Florida.

Fasudil, a novel investigational oral vasodilator manufactured by Berlex, acts by inhibiting rho-kinase. It appears to be of particular value in patients with stable angina. It offers potential relief by a unique method of action and does not interact with beta blockers or calcium antagonists.

A phase 2 study was carried out to evaluate the effects of fasudil on total exercise duration and time to onset of myocardial ischemia in patients with stable angina. The patients were also taking antianginal therapy, either a beta blocker or a calcium antagonist and nitroglycerin as needed, as well as cardiovascular medications, including aspirin, statins, and ACE-inhibitors. Of 206 patients screened, 84 patients met the inclusion and exclusion criteria.

After a three-week washout period, fasudil or matching placebo was given three times daily for eight weeks. The active drug was force-titrated from 20 mg three times daily to 80 mg three times daily, at 290 mg every two weeks. The efficacy of the regimen was assessed by exercise testing in which symptoms of angina were decreased after eight weeks of therapy.

All groups were able to increase their duration of exercise over their baseline values, the fasudil group by 1.97 minutes and the placebo group by 1.43 minutes. At eight weeks, the fasudil patients experienced a significantly delayed time to myocardial ischemia (2.83 minutes), compared with those taking placebo.

No significant differences in the incidence of adverse drug events (ADEs) or in heart rate, systolic blood pressure, diastolic blood pressure, or the product of heart rate and systolic blood pressure were observed between these two groups.

**Ezetimibe Plus Simvastatin for Hypercholesterolemia**

**Speaker:** Christie Ballantyne, MD, Director of the Center for Cardiovascular Disease Prevention, and Professor of Medicine, Baylor College of Medicine and The Methodist DeBakey Heart Center, Houston, Texas.

In patients with high cholesterol levels, ezetimibe (EZE)
(Zetia®) plus simvastatin (Zocor®) (both manufactured by Merck/Schering Plough), were given. These two agents, which inhibit both cholesterol synthesis and intestinal absorption, provided significantly greater reductions in LDL-C for a range of doses, compared with atorvastatin (Lipitor®) monotherapy in all dosing ranges.

A total of 788 patients underwent a four-week diet/placebo run-in period. They were then randomly assigned to three treatment groups. Each group underwent four sequential, six-week treatment periods:

- atorvastatin 10 mg in period 1, titrated to 20, 40, and 80 mg in periods 2 to 4
- EZE 10 mg with simvastatin 10 mg in period 1, titrated to EZE 10 mg with simvastatin 20 mg, to EZE 10 mg with simvastatin 40 mg, and to EZE 10 mg with simvastatin 80 mg from periods 2 to 4
- EZE 10 mg with simvastatin 20 mg in period 1, titrated to EZE 10 mg with simvastatin 40 mg for periods 2 and 3
- EZE 10 mg with simvastatin 80 mg in period 4

The primary endpoint of this study was the mean percent change in LDL-C from the baseline to the end of period 1 with key secondary endpoints, including mean percent change in LDL-C from the baseline to the end of periods 2, 3, and 4 and the percent change in high-density lipoprotein-cholesterol (HDL-C) from the baseline to the end of period 4.

Other efficacy measures included percent changes across dose ranges in all treatment groups in apolipoprotein B (apo B), cholesterol, apo A cholesterol, non–HDL-C, and triglycerides. The average LDL-C levels at the baseline across the treatment groups ranged from 179 to 181 mg/dl.

After six weeks of therapy, the patients taking EZE 10 mg plus simvastatin 10 mg and EZE 10 mg plus simvastatin 20 mg experienced LDL-C reductions of 46% and 50%, respectively, compared with the significantly lower reduction in HDL-C levels with atorvastatin alone (37%).

The investigators also doubled the respective statin doses up to a maximum of 80 mg for each treatment group. EZE plus simvastatin consistently provided greater reductions of LDL-C than did atorvastatin at all points in the treatment period. Furthermore, the EZE/simvastatin combination further improved the other lipid and lipoprotein parameters studied.

**Ximeligantran for Stroke Prevention in Nonvalvular Atrial Fibrillation**

**Speaker:** Jonathan L. Halperin, MD, Professor of Medicine and Director of Cardiology Clinical Services, The Zena and Michael A. Wiener Cardiovascular Institute and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, New York.

Pooled data from two phase III stroke-prevention trials demonstrated that ximeligantran (Exantra®, AstraZeneca), an oral direct thrombin inhibitor, administered without coagulation monitoring or dose adjustments, was at least as effective as warfarin (Coumadin®) for preventing stroke and systemic embolic events. It was also associated with less bleeding than the current treatment with adequately controlled warfarin in both men and women with nonvalvular atrial fibrillation.

Although nonvalvular atrial fibrillation affects women less often than men, the risk of stroke is greater among women. This analysis of the Stroke Prevention by Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and IV non-inferiority trials compared the efficacy and safety of 5,075 men and 2,257 women with atrial fibrillation. These patients received either a fixed dose of ximeligantran at 36 mg twice daily or an adjusted dose of warfarin, with a target International Normalized Ratio (INR) of 2.0–3.0.

During 11,233 patient-years and exposure over a mean of 19 months, the results were as follows:

- Women receiving ximeligantran experienced 72 primary events at a rate of 2.2% per year; women taking warfarin showed a rate of 2.0% per year.
- Men taking ximeligantran experienced 112 primary events at a rate of 1.4% per year; men receiving warfarin experienced a rate of 1.5% per year.

Ximeligantran, however, was associated with a lower incidence of bleeding in both men and women compared with warfarin, but the overall combined rates of major and minor hemorrhages were greater among women. Results were as follows:

- In women taking ximeligantran, the incidence of major and minor bleeding was 35.4%; for men receiving ximeligantran, it was 30.1% per year.
- For women who were treated with warfarin, the rate of bleeding was 44.8%; for men taking warfarin, the incidence was 36.3% per year.

**Encapsulated Pravastatin for HIV Infection in Patients with Dyslipidemia**

**Speaker:** Matthew K. Ito, PharmD, Professor and Vice Chair, Pharmacy Practice Department, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, California.

Dyslipidemia is a common side effect of protease inhibitor therapy in HIV-infected patients. An encapsulated form of pravastatin (Pravachol®) appears to offer a new efficacious therapeutic approach for these patients. This form of the statin brings about significantly greater reductions in total cholesterol, LDL-C, and non–HDL-C levels compared with nonencapsulated pravastatin, and it has a similar safety profile.

Because lipid abnormalities are common in patients taking protease inhibitors and there is an ongoing concern about potential drug interactions with statins, an enteric-coated formulation of pravastatin was compared with nonencapsulated pravastatin in HIV patients to assess LDL-C reductions after four weeks of therapy. The secondary endpoint of the study was to assess the biotransformation of pravastatin in the acid environment of the stomach and duodenum to the relatively inactive metabolite SQ 31.906 in both formulations of pravastatin after four weeks of therapy. It was hypothesized that the

---

**Meeting Highlights: American College of Cardiology**
encapsulated formulation would offer better protection for the active drug and would result in enhanced bioavailability and greater efficacy.

A prospective, open-label, randomized crossover study enrolled 16 HIV-infected men who received a protease inhibitor and whose LDL-C levels exceeded the goals of the National Cholesterol Education Program. The patients were randomly assigned to receive standard pravastatin 10-mg tablets or encapsulated tablets (Capsule 00 Blue, Gallipot, Inc.; lactose monohydrate, Spectrum Chemical). They were instructed to take one tablet every evening for 28 days. After a 28-day washout period, the patients were switched to the alternative formulation.

Of the 16 patients who initially enrolled in the study, 12 completed the full courses of therapy. Encapsulated pravastatin produced significantly greater reductions in total cholesterol (–22%) than did the nonencapsulated type (–12%) and in LDL-C (–25% versus –13%, respectively).

The one-hour, post-dose ratio of plasma pravastatin to SQ 31.906 was higher with the encapsulated formulation (2.2 versus 1.1), demonstrating a reduction in the biotransformation of pravastatin to SQ 31.906.

Beta-Blocker Exchange in Stable Heart Failure

Speaker: Andrea DiLenarda, MD, Director, Heart Failure Clinic, Ospedale di Cattinara, Triesta, Italy.

A subgroup analysis of data from the Carvedilol or Metoprolol European Trial (COMET) suggests that (1) switching to a different beta blocker without downward dose titration is a practical, safe, and well-tolerated strategy for patients with clinically stable heart failure and (2) switching from metoprolol (Lopressor®, Novartis) to carvedilol (Coreg®, Glaxo-SmithKline) results in fewer serious and heart failure–related events than switching to metoprolol while maintaining the survival benefit advantage of carvedilol demonstrated in the original COMET study.

In the COMET study, a total of 3,029 patients with New York Heart Association class II–IV chronic heart failure were randomly selected to receive carvedilol, titrated to 25 mg daily, or metoprolol, titrated to 50 mg daily. The patients were monitored for 46 to 74 months. Carvedilol treatment produced a significant 17% reduction in cardiovascular mortality in patients with heart failure, compared with metoprolol.

Overall, 1,429 patients completed the COMET study on a regimen of the study’s beta blockers. Because the withdrawal of beta blockade may precipitate worsening heart failure and arrhythmias, all patients with stable heart failure who were taking the study medication in a blinded fashion were switched to open beta-blocker therapy. This was done without unblinding or downward dose titration at a dose equivalent to half the study dose of each patient. Thereafter, the investigators recommended titrating the dose upward to the maximum tolerated or to the targeted beta-blocker doses.

The physicians selected the beta blockers that they considered most appropriate. Of this group of patients, 92% were subsequently switched to a post-study beta blocker; 1,014 patients received carvedilol, 201 were given metoprolol, and 102 received bisoprolol (Zebeta®, Lederle); 108 patients received no post-study beta blockers.

The rates of serious ADEs were lowest in patients who continued with carvedilol (2.1%) or metoprolol (3.1%) or in patients who were switched from metoprolol to carvedilol therapy (3.1%). The rates were higher in patients who were switched from carvedilol to metoprolol (9.4%) or who discontinued beta blockers completely (11.1%). ADEs related to heart failure were more frequent in patients who switched from carvedilol to metoprolol (4.7%) than in those switching from metoprolol to carvedilol (2.3%).

Intravenous Nesiritide in Patients with Congestive Heart Failure and Pulmonary Hypertension

Speaker: Teresa DeMarco, MD, Professor of Medicine and Director of the Heart Failure and Pulmonary Hypertension Program, University of California–San Francisco, San Francisco, California.

Nesiritide (Natrecor®, Scios, Inc.), a recombinant human B-type natriuretic peptide, has been shown to be highly effective, safe, and well tolerated in relieving moderate to severe pulmonary hypertension (PH) in patients with acute heart failure.

At the time of the presentation, 13 patients had enrolled in this study; the goal was 20 patients. PH was characterized by a mean pulmonary artery pressure above 25 mm Hg and a right atrial pressure above 7 mm Hg. The patients were referred for catheterization of the right side of the heart.

Nine patients had postcapillary PH, with a pulmonary capillary wedge pressure (PCWP) exceeding 15 mm Hg. Four patients had precapillary PH, with a PCWP below 15 mm Hg. In the postcapillary PH group, the mean left ventricular ejection fraction (LVEF) was 27 ± 18%; in the precapillary PH group, the LVEF was 63.6 ± 6%.

After a baseline right-heart catheterization, nesiritide was administered at 2 mcg/kg as an IV bolus, followed by a 30-minute infusion of 0.01 mcg/kg per minute. Subsequent hemodynamic evaluation of the right side of the heart was performed at 15 and 30 minutes.

At the baseline examination, in the group with postcapillary PH, the mean right atrial pressure was 10 ± 1 mm Hg, the mean pulmonary artery pressure was 42 ± 7 mm Hg, and the PCWP was 25 ± 7 mm Hg. After the 30-minute infusion, nesiritide acutely and significantly decreased right atrial pressure by 52% and pulmonary artery pressure by 31%. The PCWP decreased by 46%, and pulmonary vascular resistance decreased by 33%.

There was also a significant decrease in arteriovenous oxygen difference (AVDO₂) of 26%, which reflected improved cardiac performance. Cardiac output increased by 33%.

For the few patients with precapillary PH at baseline, the mean right atrial pressure was 13 ± 6 mm Hg, the mean pulmonary artery pressure was 43 ± 6 mm Hg, and the PCWP was 10 ± 4 mm Hg. After the 30-minute infusion of nesiritide, reductions in systemic pressure and systemic vascular resistance were similar to that observed in the precapillary PH group; however, no acute changes in right-sided heart hemodynamics, pulmonary vascular resistance, or AVDO₂ were noted.