Pharmacoeconomic Analysis of Clopidogrel in Secondary Prevention of Coronary Artery Disease

Judy W. Cheng, PharmD, MPH

ABSTRACT

BACKGROUND: When used as an alternative to or in addition to aspirin, clopidogrel has been demonstrated by some but not all randomized controlled trials to be effective in secondary prevention of cardiovascular (CV) events in patients with (1) coronary artery disease (CAD), (2) acute coronary syndrome (ACS), and (3) coronary stent placement. However, a drawback to clopidogrel therapy is the cost to patients and the health care system. Clinical studies have also demonstrated that when clopidogrel is used in addition to aspirin, the combination has an increased bleeding risk compared with aspirin alone. Cost-effectiveness analysis may aid in developing strategies for optimal use of clopidogrel.

OBJECTIVE: To review and evaluate published pharmacoeconomic analyses on the use of clopidogrel in secondary prevention of CV events in patients who have known CAD, have ACS, or are undergoing percutaneous coronary interventions (PCIs).

METHODS: English-language peer-reviewed articles or abstracts were identified from MEDLINE and the Current Contents database (both from 1966 to August 15, 2006) using the search terms *clopidogrel and pharmacoeconomics* or *clopidogrel and cost analyses*. Citations from available articles were also reviewed for additional references.

RESULTS: Multiple cost-effectiveness analyses of clopidogrel were available for review. These pharmacoeconomic studies were performed using different clinical databases from randomized controlled trials as well as observational databases. Cost was from the perspective of different health care systems and society; it was expressed in varying cost-effectiveness terms (life-year gained vs. per quality-adjusted life-year [QALY]). Although direct comparison among studies was difficult, clopidogrel appeared to be cost effective when used for up to 12 months in combination with aspirin (compared with aspirin alone) in patients with ACS or in those undergoing PCIs, using different societal perspectives (both in the United States [average U.S.$15,000 per QALY among U.S. studies reporting per QALY] and in European countries [United Kingdom reported £18,888 (average U.S.$28,300) per QALY]). In contrast, when used as an alternative to aspirin for secondary prevention of CAD, clopidogrel had mixed results in cost-effectiveness analyses (results varied from U.S.$25,000 to $114,000 per QALY). A major limitation of the models cited is the extrapolation of outcomes far beyond the duration used in the clinical trial database.

CONCLUSION: On the basis of current cost-effectiveness data, clopidogrel should be used in addition to aspirin therapy for up to 12 months in all patients with non-ST elevation ACS as well as in those who received coronary stents. For secondary prevention of CAD, clopidogrel should be used only in those who cannot tolerate aspirin therapy.

KEYWORDS: Clopidogrel, Cost-effectiveness, Pharmacoeconomics, Coronary artery disease, Acute coronary syndrome

J Manag Care Pharm. 2007;13(X):326-36

What is already known about this subject

- Clopidogrel has shown statistical efficacy in secondary prevention of CAD. Optimal duration of therapy, patient subgroup selection, and cost-effectiveness are unsettled.

What this study adds

- Clopidogrel for 9-12 months in addition to aspirin therapy is likely cost effective for secondary prevention in patients who have ACS and who have received PCI.

- Clopidogrel has not been proven cost effective in patients with CAD and actually increases cardiovascular mortality in patients who have multiple cardiac risk factors. In these groups, clopidogrel should be reserved for the approximately 5% of patients who are aspirin intolerant.

Since publication of the results of the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trials, clopidogrel (Plavix) has established a role in the management of coronary artery disease (CAD) and acute coronary syndrome (ACS).[1,2] These studies, together with many other pivotal clinical trials, have demonstrated that clopidogrel in addition to aspirin can reduce cardiovascular (CV) events in patients with a broad spectrum of CAD and ACS, as well as in patients undergoing percutaneous coronary interventions (PCIs), specifically those who received coronary stents. Tables 1 and 2 summarize the results of these studies.[1-14] More recently, the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) clinical trial have called into question the value of PCI in high-risk patients with confirmed CAD. This large, 50-center trial with 4.6 years of median follow-up per patient may result in a reduced use of coronary stents for secondary prevention, one of the major indications for the use of clopidogrel.[6]

The combined use of aspirin and clopidogrel, however, has been demonstrated in many studies to increase the risk of bleeding (Tables 1 and 2).[1-14] In addition, because clopidogrel requires a fairly long time to achieve peak response (3 to 7 days),[15] more recent studies have continued to evaluate the increase in loading doses of clopidogrel, from 300 mg to 600 mg to 900 mg, in an attempt to achieve maximal effects faster.[13,16,17] However, the increased loading doses also increase the risk of bleeding.[13,16,17] The duration of clopidogrel plus aspirin therapy used in clinical studies varied from 1 month to 1 year, and data

TABLE 1	Clinical Trials of Clopidogrel for Medical Management of Coronary Artery Disease and Acute Coronary Syndrome						
				Outcomes (%)		Bleeding (%)	
Study	Patients	Regimen and Follow-up Period	Primary Endpoints	Treatment	Control	Treatment	Control
CAPRIE[1]	19,143 patients with ischemia, stroke, MI, and PVD subgroups	Clopidogrel 75 mg daily (n=9,577) vs. aspirin 325 mg daily (n=9,566) for 1-3 years	New fatal and nonfatal ischemic stroke, MI, and other vascular death	9.78*	10.64	0.85 (total)	1.19 (total)
CURE[2]	12,562 patients with ACS	Clopidogrel 300 mg loading dose followed by 75 mg daily (n=6,259) vs. placebo (n=6,303) (all received aspirin) for an average of 9 months	Death from CV causes, nonfatal MI, or stroke	9.3*	11.4	3.7* (major) 5.1* (minor)	2.7 (major) 2.4 (minor)
CLARITY[3]	3,491 patients with STEMI	Clopidogrel 300 mg loading dose followed by 75 mg daily (n=1,752) vs. placebo (n=1,739) (all received aspirin) for 30 days	Composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography	15*	21.7	1.9 (major) 1.6 (minor)	1.7 (major) 0.9 (minor)
CHARISMA[4]	15,603 patients with either clinically evident CV disease or multiple risk factors	Clopidogrel (75 mg per day) (n=7,802) or placebo (n=7,801) (all received aspirin) for a median of 28 months	Composite of MI, stroke, or death from CV causes	6.8 Rate of death: 3.9*	7.3 Rate of death: 2.2	1.7 (severe)	1.3 (severe)
COMMIT[5]	45,852 patients with STEMI	Clopidogrel (75 mg per day) (n=22,961) or placebo (n=22,861) (all received aspirin) for an average of 16 days	Death, reinfarction, and stroke prior to hospital discharge (up to 4 weeks)	9.3* (combined endpoint) 8.1* (death)	10.1 (combined endpoint) 7.5 (death)	0.58 (major)	0.54 (major)

*P <0.05 compared with control.

ACS = acute coronary syndrome; CAPRIE = Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLARITY = Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT = Clopidogrel and Metropolis in Myocardial Infarct Trial; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV = cardiovascular; MI = myocardial infarction; NA = not available; PVD = peripheral vascular disease; STEMI = ST-segment elevation MI.

on the combination regimen beyond 1 year are not available.[1-14] Some clinicians recommend that patients use clopidogrel plus aspirin therapy for life to theoretically prevent the risk of future CV events. The risk versus benefit ratio of such prolonged use is unknown.

The 15,603 patients in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial who had either clinically evident CV disease or multiple risk factors were randomly assigned to low-dose aspirin (75 to 162 mg per day) plus either clopidogrel (75 mg per day) or placebo and were followed for a median time of 28 months.[4] Clopidogrel plus aspirin was not more effective than aspirin alone in reducing the rate of myocardial infarction (MI), stroke, or death from CV causes in patients at high risk of CV events in the group with CAD.

In the group with multiple cardiac risk factors, the rate of death from CV causes was higher with clopidogrel (3.9 percent) than with aspirin alone (2.2 percent [P=0.01]). Recently, reports from long-term follow-up of patients with drug-eluting stents indicated that after stopping clopidogrel therapy at 12 months after stent placement, patients continued to experience increased risk of late-stent rethrombosis.[18,19] More clinical studies are required to establish the optimal duration of clopidogrel plus aspirin therapy in this patient population.

Clopidogrel compared with other oral antiplatelet medications can be costly to patients and the health care system. The discount price of clopidogrel at an Internet pharmacy in 2006 is about $4 per 75 mg tablet, translating to a cost of $120 per month.[12] The conduct of cost-effectiveness analyses may help evaluate the risk versus benefit of clopidogrel therapy with its apparent role

TABLE 2 — *Clinical Trials of Clopidogrel in Preventing Rethrombosis After Percutaneous Coronary Interventions*

Study	Patients	Regimen and Follow-up Period	Primary Endpoints	Outcomes (%)		Bleeding (%)	
				Treatment	Control	Treatment	Control
Muller et al.[7]	700 patients receiving coronary stents	Clopidogrel 75 mg daily (n=345) or ticlopidine 250 mg twice daily (n=355) for 4 weeks (all received aspirin 100 mg daily)	Death from cardiac causes, urgent target vessel revascularization, angiographically evident stent occlusion, or nonfatal MI within 30 days	3.1	1.7	NA	NA
CLASSICS[8]	1,029 patients receiving coronary stents	Clopidogrel 300 mg loading, then 75 mg daily (n=345) vs. clopidogrel 75 mg daily (n=335) vs. ticlopidine 250 mg twice daily (n=340) for 1 month	Major bleeding complications, hematologic side effects, or drug discontinuation due to noncardiac adverse effects	2.9* (with loading dose) 6.3* (without loading dose)	9.1	1.5 (with loading dose) 1.2 (without loading dose)	1.2
PCI-CURE[9]	2,658 patients from CURE trial	Same as CURE ACS patients who underwent PCI (Yes)? Clopidogrel 300 mg loading, then 75 mg daily (n=1,313) vs. placebo (n=1,345) (all received aspirin) for an average of 9 months	MI, CV death, or urgent revascularization 30 days after PCI	4.6*	6.4	2.7 (major) 3.5* (minor)	2.5 (major) 2.1 (minor)
WRIST PLUS[10]	120 patients with in-stent restenosis	Clopidogrel 300 mg loading, then 75 mg daily for 6 months vs. 1 month for historical control (all received aspirin)	Late-stent thrombosis rate and the composite clinical events of death, MI, and target lesion revascularization at 6 months	23.3*	32	NA	NA
WRIST 12[11]	120 patients with in-stent restenosis	Clopidogrel 300 mg loading, then 75 mg daily for 6 months vs. 1 month for historical control from WRIST PLUS (all received aspirin)	Late-stent thrombosis rate and the composite clinical events of death, MI, and target lesion revascularization at 15 months	29*	36	5 (total)	5 (total)
CREDO[12]	2,116 patients undergoing elective PCI	Clopidogrel 300 mg loading, then 75 mg daily for 1 month (n=1,053) vs. 12 months (n=1,063) (all received aspirin)	Composite of death, MI, or stroke up to 1 year; only the composite endpoint was statistically significant; all individual conditions measured separately were not	8.5*	11.5	8.8 (major) 5.3 (minor)	6.7 (major) 5.6 (minor)
ARMYDA[13]	255 patients undergoing PCI	Clopidogrel 600 mg (n=126) vs. 300 mg (n=129) loading dose	30-day occurrence of death, MI, or target vessel revascularization	4*	12	0 (major) 1 patient (minor)	0 (major) 1 patient (minor)
PCI-CLARITY[14]	1,863 patients with STEMI	Clopidogrel 300 mg loading dose followed by 75 mg daily (n=933) vs. placebo (n=930) (all received aspirin) for 30 days	Composite of an occluded infarct-related artery on angiography, death, or recurrent MI before angiography	3.6*	6.2	0.5 (major) 1.4 (minor)	1.1 (major) 1.8 (minor)

*P <0.05 compared with control.

ACS=acute coronary syndrome; ARMYDA=Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty; CLASSICS=Clopidogrel Aspirin Stent International Cooperative Study; CREDO=Clopidogrel for the Reduction of Events During Observation; CV=cardiovascular; MI=myocardial infarction; NA=not available; PCI=percutaneous coronary intervention; PCI-CLARITY=Pretreatment With Clopidogrel–Clopidogrel as Adjunctive Reperfusion Therapy; PCI-CURE=Pretreatment With Clopidogrel and Aspirin Followed by Long-term Therapy in Patients Undergoing Percutaneous Coronary Intervention; STEMI=ST-segment elevation MI; WRIST=Washington Radiation for In-Stent Restenosis Trial; WRIST PLUS=Washington Radiation for In-Stent Restenosis Trial Plus 6 Months of Clopidogrel.

in reducing CV events in patients with certain CV conditions, the potential increased risk of bleeding when used in combination with aspirin, and its high direct drug cost. Cost-effectiveness analyses can also potentially help us to decide which patient populations may benefit the most from combination therapy.

The availability of numerous large, randomized, controlled studies of clopidogrel efficacy allows pharmacoeconomic evaluations to be performed in different patient populations, using the data from health care resources consumed (e.g., number of hospitalizations, amount of outpatient care consumed, and medication cost).[20-37] This article reviews previously published pharmacoeconomic analyses on the use of clopidogrel in patients with known CAD. These analyses include the use of clopidogrel for secondary prevention of CV events in patients with ACS and in those undergoing PCI.

■ Methods

English-language peer-reviewed articles or abstracts were identified from MEDLINE and the Current Content database (both from 1966 to August 15, 2006) using the search terms *clopidogrel, pharmacoeconomics,* and *cost analyses.* No exclusion criteria were used. Citations from available articles were also reviewed for additional references. The author critically evaluated all identified references regarding study methodology, the database used for analysis, assumptions, different societal perspectives, and the time horizon for extrapolation of the results.

■ Results

Fourteen pharmacoeconomic analyses were identified on the use of clopidogrel in the management of CAD and ACS. Among the large-scale, [multicenter] randomized controlled studies, the CAPRIE, CURE, Percutaneous Coronary Intervention-CURE (PCI-CURE), and Clopidogrel for the Reduction of Events During Observation (CREDO) trial databases have been used for pharmacoeconomic analyses (Table 3).[1,2,9,12]

Pharmacoeconomic Analyses Using Clinical Trial Database

Shleinitz et al. performed a cost-utility analysis of clopidogrel and aspirin for secondary prevention of CV events in patients with prior MI, stroke, or peripheral arterial disease (PAD).[20] On the basis of event probabilities derived from the CAPRIE database,[1] a Markov model was constructed using a base case of a 63-year-old patient on lifetime treatment, assuming a societal perspective and discounting costs and utilities at an annual rate of 3%. Outcome measures included costs, life expectancy in quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and events averted. A base case of a 50- and 75-year-old patient was used in the sensitivity analysis. Costs for type of event and for chronic care of disabled patients were derived from the Medicare diagnostic-related group reimbursement data. Costs for medications used were the U.S. average wholesale prices. All costs were reported in 2002 values.

Regarding secondary prevention of CAD, aspirin was both less expensive and more effective than clopidogrel in post-MI patients. The authors concluded that the CAPRIE data do not support use of clopidogrel in patients post-MI. It is important to note that the CAPRIE study provided patient outcome data up to approximately 2 years (not lifetime) after use of clopidogrel. Therefore, the assumption made by the investigators regarding lifetime CV events may not be correct in this group of patients. This assumption may affect the ultimate cost-effectiveness of clopidogrel.

Latour-Perez et al. performed a cost-utility analysis of clopidogrel in preventing long-term CV events.[21] Based on event probabilities derived from the CURE database, the Framingham study, and the Spanish National Statistics,[2,22,23] Markov models were constructed assuming a payer's perspective, using a base case of a 64-year-old patient on lifetime treatment. All costs were reported in 1999 euros (with 1 euro equaling slightly more than US $1 throughout 1999). The cost of the drug was calculated from the retail sales cost in Spain. A discount rate of 3% yearly was applied for calculating both costs and utilities. Sensitivity analysis was performed for each of the variables included in the model. The most decisive determinants from the one-way sensitivity analysis were assessed in the best and worst possible situations.

The average cost per QALY saved owing to clopidogrel was 2,000 euros. The cost-effectiveness ratio was very sensitive to the age of the patient, the base risk of CV events, and the precision of the estimated effectiveness of clopidogrel. The cost per QALY ranged from 5,000 euros for a high-risk 40-year-old patient to 30,000 euros for a low-risk, 80-year-old patient. According to the cost-effectiveness threshold in Spain (26,710 euros per QALY), the probability that clopidogrel was cost-effective by Monte Carlo simulation in the base analysis case was 85.3%. Similar to the CAPRIE data used in the study performed by Schleinitz et al., CURE study data followed patient outcomes for a limited time—in this case, only 9 months. The assumption of lifetime events based on the Framingham study and the Spanish National Statistics data may or may not be correct for the patients enrolled in the CURE study. Therefore, the cost-effectiveness model results may be affected.

Lindgren et al. performed a cost-utility study of clopidogrel based on the CURE database, the Swedish Hospital Discharge Registry, and the Swedish Causes of Death Registry.[2,24] A Markov model was constructed assuming a societal perspective, using the base case of a patient similar to those enrolled in the CURE study and of another patient similar to those in the Swedish registries, to estimate the ICER, or cost per additional event avoided, of clopidogrel plus aspirin therapy. All costs were in year 2000 values (with a discount rate between 0% and 5% for cost calculation and sensitivity analysis). Costs were obtained from studies performed by Zethraeus et al.[25] and Johannesson

TABLE 3 Cost-effectiveness Analysis of Clopidogrel for Coronary Artery Disease

Study	Country of Analysis	Analysis Time Period	Source of Clinical Data	Cost Perspective	Sensitivity Analysis	Cost-effectiveness of Clopidogrel
Schleinitz et al. (2004)[20]	U.S.	Lifetime of a 63-year-old patient	CAPRIE (clopidogrel vs. aspirin)	Societal	Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)	MI: aspirin less expensive and more effective
Latour-Perez et al. (2004)[21]	Spain	12 months	CURE (clopidogrel + aspirin vs. aspirin)	Societal	Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)	12,000 euros/QALY
Lindgren et al. (2004)[24]	Sweden	12 months	CURE (clopidogrel + aspirin vs. aspirin)	Societal	Outer limits of 95% CI of the relative risk of events	1,009-1,365 euros per life-year gained
Lamy et al. (2004)[27]	U.S., U.K., Sweden, France, Canada	9 months	CURE (clopidogrel + aspirin vs. aspirin)	Societal	Bootstrap analysis	U.S.: 25,437 euros per prevented life-threatening event U.K.: 16,847 euros per prevented life-threatening event Sweden: 13,857 euros per prevented life-threatening event France: 16,186 euros per prevented life-threatening event Canada: 5,585 euros per prevented life-threatening event
Weintraub et al. (2005)[28]	U.S.	9 months	CURE (clopidogrel + aspirin vs. aspirin)	Payer	Bootstrap methods (5,000 replicates)	$6,318 per life-year gained
Schleinitz et al. (2005)[29]	U.S.	Lifetime	CURE (clopidogrel + aspirin vs. aspirin)	Societal	Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)	$15,400/QALY
Badia et al. (2005)[30]	Spain	12 months and lifetime	CURE (clopidogrel + aspirin vs. aspirin)		Outer limits of 95% CI of the relative risk of events	12 months: 17,190 euros per life-year gained Lifetime: 30,000 euros per life-year gained
Lindgren et al. (2005)[31]	Sweden	12 months	PCI-CURE (clopidogrel + aspirin vs. aspirin)	Payer and Societal	Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)	Payer: 10,993 euros per life-year gained Societal: 8,127 euros per life-year gained

(continued on next page)

et al.[26] Sensitivity analysis was performed using varying event rates from 50% of those observed to 10% more than those observed in the CURE study. The analysis demonstrated an ICER of 1,365 euros per QALY from a payer perspective and cost saving from a societal perspective. The analysis based on the registries demonstrated an ICER of 1,009 euros per QALY from both a payer and a societal perspective.

The investigators concluded that clopidogrel was cost-effective. Similar to other models created, the Markov model used the Swedish Hospital Discharge Registry and the Swedish Causes of Death Registry for information regarding the incidence of CV events beyond 9 months, which was the duration of follow-up in CURE. Extrapolating results beyond 9 months may or may not represent the events experienced by the patients enrolled in the CURE study. Therefore, the cost-effectiveness results may be affected.

TABLE 3 Cost-effectiveness Analysis of Clopidogrel for Coronary Artery Disease (continued)

Study	Country of Analysis	Analysis Time Period	Source of Clinical Data	Cost Perspective	Sensitivity Analysis	Cost-effectiveness of Clopidogrel
Mahoney et al. (2006)[32]	U.S.	12 months	PCI-CURE (clopidogrel + aspirin vs. aspirin)	Societal	Considering the impact of clopidogrel on risk of fatal MI only, fatal and nonfatal MI only, as well as all death	Overall: $2,856-$4,885 per life-year gained Early PCI subgroup: $935 per life-year gained
Ringborg et al. (2005)[33]	Sweden	12 months	CREDO (aspirin + clopidogrel 1 month vs. aspirin + clopidogrel 12 months)	Societal	Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)	3,022 euros per life-year gained
Beinart et al. (2005)[34]	U.S.	12 months	CREDO (aspirin + clopidogrel 1 month vs. aspirin + clopidogrel 12 months)	Societal	Bootstrap method (5,000 iterations)	Based on Framingham life-expectancy estimation: $3,685-$4,353/life-year gained Based on Saskatchewan life-expectancy estimation: $2,929-$3,460/life-year gained
Cowper et al. (2005)[35]	U.S.	12 months	Patients undergoing PCI at Duke University Medical Center from January 1999 to December 2001	Societal	Single and multiway sensitivity analysis	$15,696 per life-year gained
Gaspoz et al. (2002)[36]	U.S.	25 years	Coronary Heart Disease Model (clopidogrel vs. aspirin)	Payer	Outer limits of 95% CI of the relative risk of events based on the Antiplatelet Trial List	$11,400/QALY
Karnon et al. (2005)[37]	U.K.	Lifetime	U.K. observation study (clopidogrel vs. aspirin)	Payer	Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)	Clopidogrel: £18,888/QALY Aspirin: £21,488/QALY

CAPRIE = Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CI = confidence interval; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; MI = myocardial infarction; PCI = percutaneous coronary interventions; PCI-CURE = Pretreatment With Clopidogrel and Aspirin Followed by Long-term Therapy in Patients Undergoing Percutaneous Coronary Intervention; QALY = quality-adjusted life-year.

Lamy et al. also performed a cost-effectiveness study from a third-party payer perspective based on the CURE database.[27] Unit cost of all resources was obtained for each country that participated in the CURE study (United Kingdom, United States, Sweden, France, and Canada) and was reported in local currency in 2001 values. A bootstrap analysis was used to calculate standard errors and 95% confidence intervals (CIs) for the difference in average costs in different countries between clopidogrel plus aspirin therapy and aspirin alone. The average cost per patient was higher in the clopidogrel plus aspirin group than in the aspirin alone group in all countries (difference in

costs for a 9-month period: £208 in the United Kingdom, $451 in the United States, SkR 2,571 in Sweden, 325 euros in France, Can$161 in Canada). This equated to an ICER of £10,366 in the United Kingdom, $22,484 in the United States, SkR 127,951 in Sweden, 16,186 euros in France, Can$7,973 in Canada per primary event avoided. The investigators concluded that the ICER for clopidogrel was similar to that of other therapies (such as low-molecular-weight heparin and glycoprotein IIb/IIIa receptor antagonists) used for ACS management. In clinical practice, however, clopidogrel, low-molecular-weight heparin, and glycoprotein IIb/IIIa receptor antagonists are often

used together during ACS. The ICER reported in this study already took into account low-molecular-weight heparin and glycoprotein IIb/IIIa receptor antagonists as background therapy. Therefore, the conclusion that the ICER of clopidogrel is similar to other ACS therapy may not be accurate.

The same group of investigators performed another cost-effectiveness analysis based on the CURE database, but focused on a U.S. perspective. Costs were derived from average wholesale drug cost in the United States and from Medicare reimbursement.[28] The ICER reported in this analysis was $6,318 per life-year gained with clopidogrel, with 94% of bootstrap-derived ICER estimates of <$50,000 (the U.S. threshold of cost-effectiveness) per life-year gained. It is, however, important to realize that there were only 500 patients from the United States out of approximately 12,000 patients enrolled in CURE. Most patients in CURE received medical management for ACS. For those who received PCI, the average time to PCI was 6 days. That does not reflect the usual management of ACS in the United States, where patients are referred to PCI much sooner after an ACS event.

Schleinitz and Heidenreich also performed a cost-effectiveness analysis using a Markov model assuming a societal perspective, using a base case of a 64-year-old patient on lifetime treatment.[29] Information on incidence of CV events was obtained from the CURE trial. All costs were reported as 2002 U.S. dollars. The costs of drugs were U.S. average wholesale price. Health care costs were derived from published literature. A one-way sensitivity analysis was performed for each of the variables included in the model. The ICER of clopidogrel plus aspirin therapy compared with aspirin alone was $15,400 per QALY. The authors concluded that clopidogrel plus aspirin therapy for 1 year in patients with high-risk ACS is cost effective within traditional limits (i.e., <$50,000 per QALY).

Similar to other cost-effectiveness analyses, the CURE study provides information on patient events up to 9 months only. The assumption made by the authors regarding lifetime CV events therefore may or may not represent the experiences of the patients enrolled in the CURE study. Similar to the study performed by Lamy et al., the Schleinitz and Heidenreich study had only 500 patients from the United States out of approximately 12,000 patients enrolled in CURE. Therefore, the results do not reflect the usual management of ACS in the United States.

Badia et al. performed a cost-effectiveness analysis based on the CURE study database.[30] A Markov model covering 6 states of health reflecting the clinical progress of patients with non-ST elevation ACS was adapted to the Spanish setting. A discount rate of 3% yearly was allowed for all costs and health benefits. The unit cost of the direct health resources was obtained from a Spanish setting costs database. Univariate sensitivity analysis was performed. In the short-term analysis (1 year), the incremental cost per event avoided with the addition of clopidogrel was 17,190 euros (with 1 euro in 2005 ranging from U.S.$1.18 to $1.31). In the long-term analysis (>1 year), the incremental cost

per life-year gained was 8,132 euros. These costs were below the cost-effectiveness threshold (30,000 euro per life-year gained) in Spain. Therefore, clopidogrel was considered cost effective. Once again, the long-term analysis using CV events experienced by a Spanish population may or may not represent those experienced by the CURE population.

Lindgren et al. performed a cost-effectiveness study based on the PCI-CURE database, the Swedish Hospital Discharge Registry, and the Swedish Causes of Death Registry.[31] A Markov model was constructed assuming a third-party payer and a societal perspective, using the base case of a patient similar to patients in the Swedish registries, to estimate the ICER of clopidogrel plus aspirin therapy compared with aspirin alone. All costs were in year 2004 values (with 1 euro ranging from U.S.$1.19 to $1.34). Costs were obtained from published sources (discount rate of 3% yearly). The analysis demonstrated an ICER of 8,127 euros per QALY from a payer perspective and 10,933 euros per QALY from a societal perspective. The investigators concluded that clopidogrel used in a setting similar to that of the PCI-CURE study was cost effective. The long-term analysis performed using CV events documented by the Swedish Hospital Discharge Registry and the Swedish Causes of Death Registry beyond the 9-month follow-up period of PCI-CURE may or may not represent the actual CV events experienced by the PCI-CURE population if they had been followed beyond 9 months.

Mahoney et al. performed a cost-effectiveness study from a third-party payer perspective based on the PCI-CURE database.[32] Unit cost of resources used were derived from the U.S. Medicare diagnosis-related group reimbursement. Costs of medication were U.S. average wholesale prices. Discounting of costs was not performed, since the duration of follow-up of PCI-CURE was only 1 year. Since patients in the clopidogrel and the placebo groups received similar background therapy, the costs of the background therapy were not taken into account during the cost-effectiveness analysis. The incremental cost per life-year gained with clopidogrel ranged from $2,856 to $4,885 overall (from dominant to $935 for the early PCI group). The investigators concluded that clopidogrel was highly cost effective when used in this patient population. Similar to other studies evaluating the cost-effectiveness of clopidogrel use in the United States based on the PCI-CURE study, in PCI-CURE, the average time to PCI was 6 days. That does not reflect the usual management of ACS in the United States, where patients are referred to PCI much sooner after an ACS event.

Ringborg et al. performed a cost-effectiveness study based on the CREDO database, the Swedish Hospital Discharge Registry, and the Swedish Causes of Death Registry.[33] A Markov model was developed on the assumption that a hypothetical cohort of patients in a post-PCI state had certain risks of suffering one of the event endpoints in the CREDO trial. Costs were obtained from studies performed by Zethraeus et al.[25] and Johannesson et al.[26] All costs were adjusted to 2004 values (with 1 euro

ranging from U.S.$1.19 to $1.34). First-order sensitivity analysis was performed. The model predicted an ICER of 3,022 euros. The authors concluded that the cost-effectiveness ratio of long-term treatment with clopidogrel in patients undergoing PCI was well below the threshold values currently considered cost effective in Sweden. Like most other cost-effectiveness analyses, the assumption of CV events experienced after 1 year using the 2 Swedish registries may not represent those experienced in the CREDO study, which followed patients for only 12 months.

Beinart et al. performed a similar cost-effectiveness analysis from the CREDO database, the Framingham Heart Study, and the Saskatchewan Health database.[34] Costs for each type of event and for chronic care of disabled patients were obtained from the Medicare diagnostic-related group reimbursement data. Costs for medications were the U.S. average wholesale price. The bootstrap method was used to estimate the 95% CIs of the distribution of ICER. Sensitivity analysis included reducing life-years gained by 50% and 80%, adding estimated costs associated with bleeding, and calculating additional costs beyond the trial period and quality-adjusted survival. The ICER based on the Framingham data ranged from $3,685 to $4,353 per life-year gained; more than 97% of bootstrap-derived ICER estimates were below $50,000 per life-year gained. The ICER based on Saskatchewan data was $2,929 to $3,460 per life-year gained; more than 98% of estimates were below $50,000 per life-year gained (the accepted threshold of cost-effectiveness in Canada).

The author therefore concluded that clopidogrel therapy when used for 1 year after PCI was cost effective in preventing lifetime CV events. Similar to most other cost-effectiveness analyses, the CREDO study followed patients for 12 months. The assumption of CV events experienced after 1 year using the Framingham and Saskatchewan Health databases may not represent those experienced in the CREDO study after 1 year.

Pharmacoeconomic Analyses Using Decision Modeling of Other Databases

Cowper et al. performed a cost-effectiveness analysis of clopidogrel plus aspirin therapy in patients undergoing PCI over a 3-year period at Duke University Medical Center.[35] The effect of prolonged clopidogrel therapy on event rates was based on the CREDO trial. Unit costs and the effect of MI on life expectancy were based on average Medicare reimbursement and the Framingham Heart Study, respectively. Single and multiway sensitivity analyses were performed for each variable in the model.

This study demonstrated that clopidogrel therapy cost $15,696 per year of life saved ($10,333 per year of life saved in the high-risk subset and $26,568 in the low-risk subset). Therefore, the use of clopidogrel for 1 year after PCI is economically attractive in the Duke University patient population. This major university medical center not only serves the population around its own community but is referred patients from other regions

in North Carolina. Therefore, the number of PCI procedures performed at Duke is likely to be higher than at most other medical centers in the United States, and the incidence of outcomes and adverse events may be different. Therefore, the applicability of these data to other populations beyond Duke University may be questionable.

Gaspoz et al. used the Coronary Heart Disease Policy Model, a computer simulation of the U.S. population, to evaluate the cost-effectiveness of using aspirin, clopidogrel, or both for secondary prevention of CAD.[36] Events data for the initial model were obtained from a review of the literature, the National Vital Statistics reports, the National Hospital Discharge Survey, the National Health Interview Survey, the second and third Health and Nutrition Examination Surveys, the Framingham Heart Study, and a variety of clinical trials and observational studies. The simulations modeled U.S. patients, 35 to 84 years old, in whom coronary disease developed during or before 2003 to 2007 and who survived their first month with it. Probability of events was based on pooled data from randomized trials for secondary prevention of coronary events in patients with prior coronary disease. Sensitivity analysis was performed by varying health care costs up to 100% and varying incidence of outcome events by using the 95% CI. The cost-effectiveness of aspirin in eligible patients for 25 years was calculated to be $11,000 per QALY, with a 31% absolute event rate reduction. The use of clopidogrel for the 5.7% of patients who were ineligible for aspirin therapy had an ICER of $31,000 per QALY, and reduced the absolute event rate by 33.7%. If clopidogrel and aspirin were used together in all patients, the ICER was $130,000 per QALY and remained financially unattractive across a broad range of financial assumptions; the combined reduction in absolute event rate was 37.2%. The investigators concluded that aspirin for secondary prevention of CAD is attractive from a cost-effectiveness perspective; clopidogrel alone was only cost effective when its price was reduced by at least 70% to U.S.$1.

Karnon et al. developed a health economic model from a third-party payer perspective to evaluate the cost-effectiveness of clopidogrel in secondary prevention of occlusive vascular disease.[37] Patients were assumed to receive treatment with either clopidogrel for 2 years followed by aspirin for their remaining lifespan or with aspirin alone for the whole lifespan. Data from United Kingdom observation studies were used to obtain vascular event rates. Costs were expressed in 2002 values (with 1 British pound in 2002 ranging from $1.42 to $1.58). Sensitivity analysis was performed by varying key parameters randomly at the same time. The ICER of aspirin was estimated to be £18,888 per life-year gained and £21,489 per QALY gained. Sensitivity analysis suggested the model was robust to a wide range of input. Therefore, 2 years of treatment with clopidogrel can be considered a cost-effective intervention in patients at risk of secondary occlusive vascular events. Currently, the official recommendation of duration of clopidogrel therapy in

combination with aspirin is 1 year.[38] Although 1 year may not be the optimal duration and future studies may suggest otherwise, the decision to use 2 years of clopidogrel therapy in this analysis is arbitrary and may make the results not applicable to current clinical practice.

■ Discussion

At least 13 randomized clinical trials published since 1996 have shown measurable statistical efficacy of (1) clopidogrel in secondary prevention of CAD compared with aspirin, (2) the efficacy of clopidogrel in combination with aspirin in ACS (including unstable angina, non-ST-segment elevation MI and ST-segment elevation MI), and (3) the prevention of rethrombosis after coronary stent placement compared with aspirin alone. The general pattern of results shows greater benefit for higher-acuity patients (ACS and PCI); patients who have multiple risk factors are actually harmed, as shown in the CHARISMA trial.

Compared with aspirin, which costs pennies per day, clopidogrel had a current cost in January 2007 of $4.11 per 75 mg tablet (for Plavix)[39] or of $3.67 per generic 75 mg tablet.[40] The high cost of clopidogrel combined with the clinical trials comparing clopidogrel with aspirin alone, and clopidogrel plus aspirin with aspirin alone beg for analysis of the cost-effectiveness of clopidogrel. Fourteen pharmacoeconomic analyses of clopidogrel were published through August 2006. Overall, from different societal perspectives (in the United States and in selected European countries), clopidogrel appears to be consistently cost effective when used in combination with aspirin (compared with aspirin alone) in patients with ACS or in those undergoing PCI. However, when used as an alternative to aspirin for secondary prevention of CAD, clopidogrel has mixed economic effectiveness. Schleinitz et al. demonstrated that clopidogrel is not cost effective post-MI for secondary prevention of CAD.[20] Gaspoz et al. also demonstrated that clopidogrel was not cost effective,[36] whereas Karnon et al. demonstrated otherwise.[38] The routine replacement of aspirin for clopidogrel for secondary prevention of CV events in patients with CAD is not warranted from an economic point of view. This conclusion is further justified by the results of the recent CHARISMA study in which clopidogrel, when used together with aspirin, was shown to increase adverse event outcomes in patients with CAD.[4]

Limitations

A significant limitation of the pharmacoeconomic models available for review is the decision to extrapolate data from short-term clinical trials and apply them to simulated patients for a "lifetime" of use. Assuming that the slope of the outcomes data can be merely extended in a continuous line is risky and open to error.

Another limitation of clinical modeling is the unsettled question of optimal duration of clopidogrel therapy after ACS or PCI. Most of the clinical effectiveness trials were performed based on 9 to 12 months of clopidogrel therapy. Whether this duration is optimal is not yet known. Whether extending therapy beyond 12 months in patients after ACS or PCI will extend any additional benefits clinically and economically cannot be determined in the available literature. Recent reports from long-term follow-up of patients with drug-eluting stents indicate that after stopping clopidogrel therapy at 12 months after stent placement, patients continued to experience increased risk of late-stent rethrombosis.[18,19] Whether these results indicate that drug-eluting stents should be avoided or clopidogrel use should be extended is not settled. Perhaps other conclusions will be drawn from this study.

Long-term use of clopidogrel plus aspirin not only potentially increases the risk of bleeding in patients but also poses other potential problems for clinical management of patients. For example, if during the lifetime of patients they require other forms of antiplatelet or anticoagulant therapy (e.g., warfarin), how should the clopidogrel plus aspirin therapy be modified? Furthermore, if the patients require surgery or invasive procedures, how is the clopidogrel plus aspirin therapy going to be managed? Current recommendations are that clopidogrel should be withheld for a minimum of 5 days before elective surgery.[38] The risk of stent rethrombosis if clopidogrel is withheld compared with the risk of major hemorrhage during surgery if clopidogrel is not withheld is unknown. On the other hand, for non–drug-eluting stents, the minimal duration of clopidogrel therapy that has been demonstrated effective as compared with placebo is 1 month, with 12-month clopidogrel therapy more effective clinically and economically.[12] However, the cost-effectiveness of duration of therapy between 1 and 12 months has not been evaluated. More clinical trials are underway to continue to explore the optimal duration of clopidogrel.

The majority of the cost-effectiveness analyses of clopidogrel used data from large-scale, multicenter, randomized controlled trials, whereas other analyses are from large local or national health databases. Although analyses performed based on data from large-scale clinical trials allow accurate capture of outcome events, the health care resources used in these studies may not truly reflect those in real-life clinical practice. Patients enrolled in clinical studies are monitored by specified protocols and usually received more intensive follow-up care. In real-life practice, the levels of follow-up and patient adherence to therapy may be different, thus affecting outcome events and resource use. On the other hand, cost-effectiveness analysis that used cohort population or a national/local health database may more accurately reflect real-life health care resource consumption. However, these databases were not intentionally developed for these kinds of analyses. The capture of information may be incomplete, patients may be lost to follow-up, and recall bias can never be completely ruled out, all of which affect the cost-effectiveness results.

Perspective on the Future

The role of clopidogrel in the management of CAD continues to evolve. Cost-effectiveness analyses of clopidogrel have been performed looking at clopidogrel as an alternative to aspirin for secondary prevention of CV events in patients with CAD, as well as in addition to aspirin, to reduce CV events in patients with ACS (unstable angina and non-ST-segment elevation MI) and in those undergoing PCI. Newer clinical studies have also demonstrated the efficacy of clopidogrel use in patients with ST-segment elevation MI. Cost-effectiveness of clopidogrel in this patient population should be evaluated to help justify the use of this agent. More clinical studies are also needed to establish the optimal duration of clopidogrel therapy. Finally, true generic clopidogrel is not yet available. When multiple generic manufacturers are able to market, the cost of the drug will decrease and thereby affect the cost-effectiveness analyses.

■■ Conclusions

Management of CAD entails the use of a variety of pharmacological agents with associated direct drug costs. This article comprehensively reviews the pharmacoeconomic analyses published to date, based on major clinical trials performed on clopidogrel in patients with CAD or ACS or in patients undergoing PCI. Clopidogrel is demonstrated to be cost effective from both a payer and a societal perspective in the United States, Canada, and selected European countries (United Kingdom, Spain, Sweden) when it is used in combination with aspirin (compared with aspirin alone) for 9-12 months in patients (1) who have unstable angina and non-ST-segment elevation MI and (2) who received coronary stent placement. The cost-effectiveness of clopidogrel when it is used as an alternative to aspirin for secondary prevention of CAD has not been shown, and clopidogrel should be reserved for patients who cannot tolerate aspirin. More clinical trials are underway to explore further the optimal duration of clopidogrel therapy. The results of these ongoing clinical trials will be opportunities to update the pharmacoeconomic analyses.

Author

JUDY W. CHENG, PharmD, MPH, is an associate professor of pharmacy practice, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, New York, and a clinical pharmacy specialist in cardiology, Mount Sinai Medical Center, New York, New York.

AUTHOR CORRESPONDENCE: Judy W. Cheng, PharmD, MPH, Associate Professor of Pharmacy Practice, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, One Gustave L Levy Pl., Box 1211, New York, NY 10029. Tel: (212) 241-7718; Fax: (212) 987-0198; E-mail: judy.cheng@liu.edu

REFERENCES

1. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet.* 1996;348(9038):1329-39.

2. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;16;345(7):494-502.

3. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med.* 2005;352(12):1179-89.

4. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354 (16):1706-17.

5. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo controlled trial. *Lancet.* 2005;366(9497):1607-21.

6. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007;356(15):1503-16.

7. Muller C, Buttner HJ, Peterson J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after placement of coronary-artery stent. *Circulation.* 2000;101:590-93.

8. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting. *Circulation.* 2000;102:624-29.

9. Mehta ST, Yusuf S, Peter RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358:527-33.

10. Waksman R, Ajani AE, White RL, et al. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS). *Circulation.* 2001;103(19):2332-35.

11. Waksman T, Ajani AE, Pinnow E, et al. Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing gamma-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial (WRIST) 12 versus WRIST PLUS. *Circulation.* 2002;106(7):776-78.

12. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;288(19):2411-20.

13. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation.* 2005;111(16):2099-2106.

14. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA.* 2005;294(10):1224-32.

15. Plavix prescribing information. Available at: http://products.sanofi-aventis. us/plavix/plavix.html. Accessed July 17, 2006.

16. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA.* 2006;295(13):1531-38.

17. von Beckerath N, Taubert D, Pogatsa-Murray G, Schomig E, Kastrati A, Schomig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. *Circulation.* 2005;112(19): 2946-50.

18. Shuchman M. Debating the risk of drug-eluting stents. *N Engl J Med.* 2007;356:325-28.

19. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med.* 2007;356(10):989-97.

20. Schleinitz MD, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. *Am J Med.* 2004;116:797-806.

21. Latour-Perez J, Navarro-Ruiz A, Ridao-Lopez M, Cervera-Montes M. Using clopidogrel in non-ST segment elevation acute coronary syndrome patients: a cost-utility analysis in Spain. *Value Health.* 2004;7(1):52-60.

22. Guidry UC, Evans JC, Larson MG, et al. Temporal trends in event rates after Q-wave myocardial infarction. The Framingham Heart Study. *Circulation.* 1999;100:2054-59.

23. Instituto Nacional de Estadistica. INEbase. Madrid: Instituto Nacional de Estadistica. Available at: http://www.ine.es. Accessed July 21, 2006.

24. Lindgren P, Jonsson B, Yusuf S. Cost-effectiveness of clopidogrel in acute coronary syndromes in Sweden: a long-term model based on the CURE trial. *J Intern Med.* 2004;255:562-70.

25. Zethraeus N, Molin T, Henriksson P, et al. Cost of coronary heart disease and stroke: the case of Sweden. *J Intern Med.* 1999;246:151-59.

26. Johannesson M. At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? *Eur Heart J.* 2001;22:919-25.

27. Lamy A, Jonsson B, Weintraub S, et al. The cost-effectiveness of the use of clopidogrel in acute coronary syndromes in five countries based upon the CURE study. *Eur J Cardiovasc Prev Rehabil.* 2004;11:460-65.

28. Weintraub WS, Mahoney EM, Lamy A, et al. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. *J Am Coll Cardiol.* 2005;45:838-45.

29. Schleinitz MD, Heidenreich PA. A cost-effectiveness analysis of combination antiplatelet therapy for high-risk acute coronary syndromes: clopidogrel plus aspirin versus aspirin alone. *Ann Intern Med.* 2005;142:251-59.

30. Badia X, Bueno H, Juanatey JRG, Valentin V, Rubio M. Short- and long-term cost-effectiveness analysis of adding clopidogrel to standard therapy in acute coronary syndrome patients in Spain. *Rev Esp Cardiol.* 2005;58(12):1385-95.

31. Lindgren P, Stenestrand U, Malmberg K, Jonsson B. The long-term cost-effectiveness of clopidogrel plus aspirin in patients undergoing percutaneous coronary intervention in Sweden. *Clin Ther.* 2005;27:100-10.

32. Mahoney EM, Mehta S, Yuan Y, et al. Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation. *Am Heart J.* 2006;151:219-27.

33. Ringborg A, Lindgren P, Johsson B. The cost-effectiveness of dual oral antiplatelet therapy following percutaneous coronary intervention. *Eur J Health Econ.* 2005;6:354-62.

34. Beinart SC, Kolm P, Veledar E, et al. Long-term cost effectiveness of early and sustained dual oral antiplatelet therapy with clopidogrel given for up to one year after percutaneous coronary interventions. *J Am Coll Cardiol.* 2005;46:761-69.

35. Cowper PA, Udayakumar K, Sketch MH, Peterson ED. Economic effects of prolonged clopidogrel therapy after percutaneous coronary intervention. *J Am Coll Cardiol.* 2005;45:369-76.

36. Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med.* 2002;346:1800-06.

37. Karnon J, Brennan A, Pandor A, et al. Modeling the long term cost effectiveness of clopidogrel for the secondary prevention of occlusive vascular events in the UK. *Curr Med Res Opin.* 2006;21(1):101-12.

38. American College of Cardiology/American Heart Association. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002. *Circulation.* 2002;106: 1893-1900.

39. Plavix. Available at: http://www.drugstore.com/pharmacy/prices/drugprice. asp?ndc=63653117105&trx=1Z5006. Accessed July 17, 2006.

40. Clopidogrel. Available at: http://www.drugstore.com. Accessed January 6, 2007.