Economic Effects of Prolonged Clopidogrel Therapy After Percutaneous Coronary Intervention

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OBJECTIVES	This study examined the incremental cost-effectiveness of extending clopidogrel therapy from one month to one year after percutaneous coronary intervention (PCI) in an unselected, heterogeneous patient population.
BACKGROUND	Clinical trials suggest that prolonging clopidogrel therapy for up to one year after PCI reduces downstream cardiac events. However, clopidogrel therapy is costly and may increase bleeding risk.
METHODS	Using decision analysis, we compared the outcomes and cost of prolonging clopidogrel treatment from one month to one year after PCI with the alternative strategy of discontinuing therapy one month after the procedure. Event rates were based on 3,976 PCI patients who were treated between January 1999 and December 2001 at the Duke Medical Center and received no more than one month of clopidogrel after the procedure. Baseline characteristics and event rates were obtained from Duke clinical information systems. The effect of prolonged clopidogrel therapy on event rates was based on the Clopidogrel for the Reduction of Events During Observation (CREDO) trial per-protocol data. Unit costs and the effect of myocardial infarction (MI) on life expectancy were based on published sources.
RESULTS	Extending clopidogrel therapy from one month to one year after PCI cost $879 per patient and reduced the risk of MI by 2.6%. Assuming MI decreases life expectancy by two years, prolonged therapy would cost $15,696 per year of life saved. Economic attractiveness of therapy varied with baseline risk, the effect of prolonged therapy on MI risk, and the price of clopidogrel.
CONCLUSIONS	Prolonging clopidogrel therapy for one year after PCI is economically attractive, particularly in high-risk patients. (J Am Coll Cardiol 2005;45:369–76) © 2005 by the American College of Cardiology Foundation

Over 500,000 percutaneous coronary interventions (PCIs) with stent implantation are performed annually in the U.S. (1). In these patients, the combination oral antiplatelet therapy of aspirin and clopidogrel for one month after PCI reduces thrombotic complications relative to aspirin therapy alone (2,3). However, there remains considerable debate as to how long clopidogrel therapy should be maintained (4,5).

Although two recent trials suggest that prolonging therapy for up to one year after PCI reduces downstream cardiac events, patients treated with clopidogrel may have an increased risk of bleeds (8.8% vs. 6.7%, p = 0.07) (6,7). In addition, clopidogrel therapy is costly (~$100 per month). To date, there have been no published analyses of the incremental cost-effectiveness of prolonged clopidogrel treatment after PCI (one month to one year) versus the previous standard of one month of therapy. In this study, we assessed the value of prolonged clopidogrel therapy in an unselected, heterogeneous population of patients treated in the era of bare-metal stents. First, we determined the rate of

cardiac events during the year after PCI among patients receiving one month of treatment. We then examined the incremental benefits and cost-effectiveness of extending clopidogrel therapy from one month to one year after PCI in this population. Finally, we explored the effect of patient risk on the cost-effectiveness of prolonged clopidogrel therapy.

METHODS

Patient population. The study sample included patients undergoing PCI at Duke University Medical Center between January 1, 1999, and December 31, 2001. During this time, which corresponds to the study periods of the two major clopidogrel trials, the standard of care at Duke was to treat patients with one month of clopidogrel after bare-metal stent implantation (6,7). Patients were included in the sample if they: 1) were over 21 years of age; 2) did not have significant left main coronary artery disease; 3) did not undergo percutaneous revascularization in the two weeks before the index PCI; 4) did not have a "staged procedure" (two planned procedures in the same admission); 5) did not receive intracoronary radiation therapy for in-stent restenosis; and 5) were treated with no more than one month of clopidogrel after the procedure.

Model. A decision model was developed to compare the outcomes and costs of prolonging clopidogrel therapy from one month to one year after PCI with the alternative strategy of discontinuing therapy after one month of

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CREDO = Clopidogrel for the Reduction of Events
  During Observation trial
DISCC = Duke Information System for
  Cardiovascular Care
DRG = diagnosis-related group
EPILOG = Evaluation in PTCA to Improve Long-term
  Outcome with abciximab GP IIb/IIIa
  blockade trial
GP = glycoprotein
MI = myocardial infarction
PCI = percutaneous coronary intervention

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periprocedural clopidogrel (DATA 3.5; TreeAge Software Inc., Williamstown, Massachusetts) (Fig. 1). In each treatment arm, the model included myocardial infarction (MI), revascularization (coronary artery bypass grafting [CABG] vs. PCI), major bleeding, and death (Fig. 1). Events that were rare or had minimal economic consequences (e.g., stroke, minor bleeds) were excluded, as their effect on results was negligible.

The analysis was conducted from the perspective of society (8,9). Primary outcomes included the incremental cost and the incremental cost per MI prevented with clopidogrel therapy between one and 12 months after the index PCI. Using secondary data sources, we also extrapolated beyond the trial period to estimate the incremental cost per year of life saved associated with prolonging clopidogrel therapy from one month to one year after PCI.

Data sources. BASELINE CHARACTERISTICS AND EVENT RATES. Baseline demographics, clinical characteristics, treatments, discharge medications, and rates of major events (MI, death, repeat revascularization) after PCI (given one month of therapy) were obtained from the Duke Information System for Cardiovascular Care (DISCC). The DISCC events are obtained through annual mail and telephone follow-up of patients, supplemented by searches of Duke claims data and the National Death Index. The MIs were confirmed by discharge summaries. The DISCC follow-up was 96% complete in our time frame. Conditional event rates were derived as needed (probability of revascularization conditional on MI; probability of CABG conditional on revascularization and MI; probability of death conditional on MI and revascularization). Rates of major bleeding were based on Clopidogrel for the Reduction of Events During Observation (CREDO) trial data for per-protocol patients (those who underwent percutaneous revascularization), because bleeding complications are not systematically recorded in DISCC (Dr. S. Steinhubl, personal communication, June 20, 2003).

The effect of prolonged clopidogrel therapy on rates of MI (relative risk 0.56), major bleeding (relative risk 1.46), repeat revascularization (relative risk 1.0), and death (relative risk 1.0) during the 1- to 12-month follow-up period was based on CREDO per-protocol data (Dr. S. Steinhubl, personal com-

munication, June 20, 2003). The relative risk reduction associated with clopidogrel treatment was assumed to be constant across all patient subgroups, as was found in CREDO (6).

UNIT COSTS. Hospitalization costs were based on average Medicare reimbursement for diagnosis-related group (DRG) categories for major clinical events and event combinations in the decision model (MI with/without death, PCI with/without MI, gastrointestinal bleed, cardiac arrest) and on average Medicare payments for CABG procedures (Table 1) (10,11). The incremental cost of death (in addition to events other than MI and CABG) was based on the difference in DRG payments for MI with and without death. An estimate of the incremental cost of bleeds was obtained from the Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) economic substudy (12). Physician fees were calculated using Medicare fee schedules for procedures and inpatient management, assuming average lengths of stay reported for DRGs (10,13). The cost of clopidogrel was based on the average wholesale price plus a monthly dispensing fee (14). Costs were adjusted to $2,000 (U.S.) using the average annual Producer Price Index for general medical and surgical hospitals (15).

LIFE EXPECTANCY. Estimates of life expectancy were based on two previous analyses of longitudinal data. Age- and gender-specific estimated life expectancies for patients with a history of coronary heart disease were obtained from an analysis of Framingham Heart Study data and applied to the Duke sample to obtain overall life expectancy for the model (16). The post-acute reduction in this life expectancy associated with a nonfatal MI was obtained from previous analyses of longitudinal DISCC data (17). Alternative estimates of the reduction in life expectancy attributable to MI were examined in sensitivity analyses.

Analysis. The baseline analysis was based on event rates in the Duke sample and incorporated assumptions in Table 1. The expected cost and event rates for the period between one month and one year after PCI were compared between treatment strategies. The incremental cost per MI avoided with prolonged therapy was then calculated for the 11-month follow-up period. The denominator in this ratio reflects only the clinical consequences of MI, because any costs associated with MI are included in the numerator. The cost per year of life saved over a patient's lifetime with prolonged therapy was also calculated using the external estimates of the effect of MI on life expectancy described earlier. In the analysis, years of life gained in the future were discounted at the standard annual rate of 3% (18).

Single and multiway sensitivity analyses were performed to assess the robustness of results to reasonable variations in clinical and economic factors. Variables examined included the relative risk reduction for MI, cost of MI, rate and cost of major bleeds, price of clopidogrel, medication compliance, and reduction in life expectancy due to MI.

The analyses were repeated for high- and low-risk patient