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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

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 communication, 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

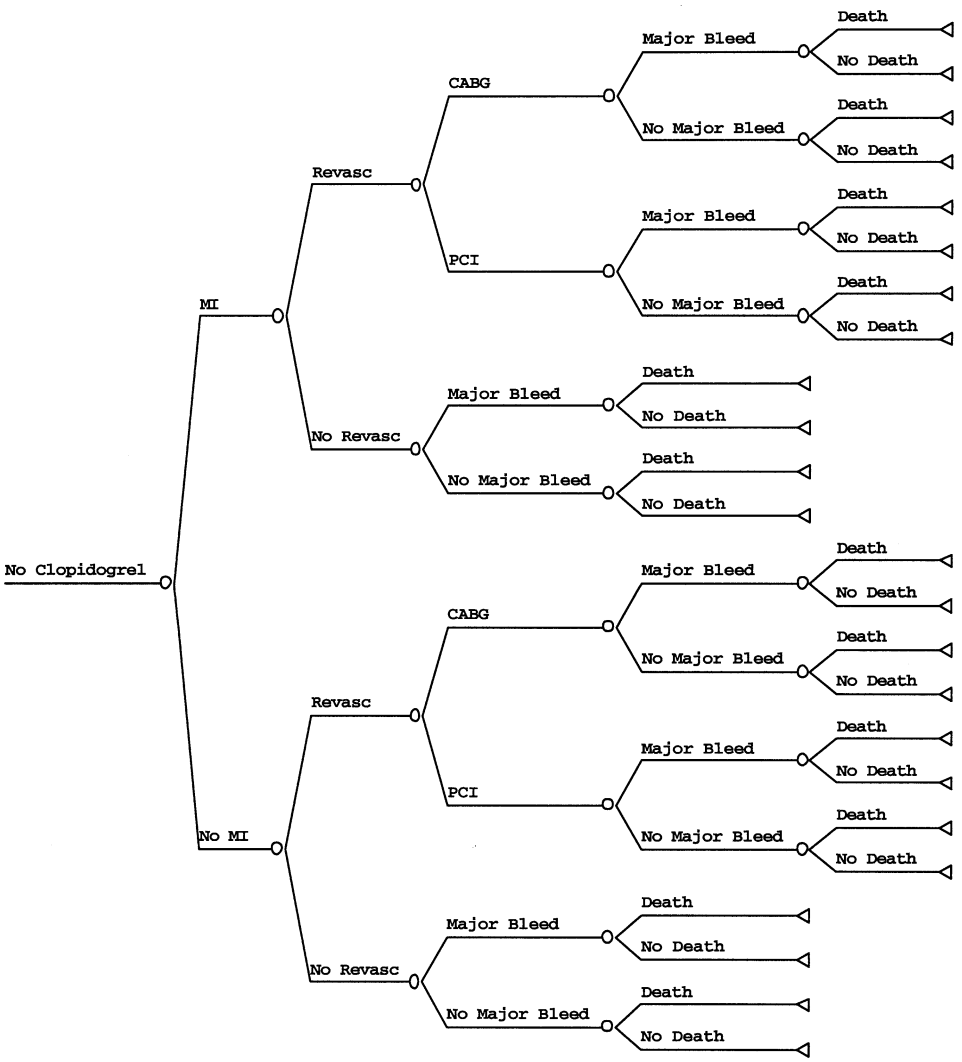

Figure 1. Decision model subtree for no clopidogrel arm. A parallel subtree exists for the treatment arm. **Circles** = chance nodes; **arrowheads** = terminal nodes. Revasc = revascularization.

subgroups to determine the extent to which the economic attractiveness of long-term clopidogrel varies with patient characteristics. First, we identified clinical factors associated with higher rates of MI in follow-up using a logistic regression model. A high-risk subgroup was then empirically defined as patients having diabetes, multivessel intervention, or MI within 24 h preceding their procedure. Patients not classified as higher risk comprised the lower risk subgroup.

RESULTS

Patient characteristics. A total of 4,037 Duke patients met the inclusion criteria and were included in the Duke PCI sample. Study patients were similar in age to patients enrolled in CREDO (Table 2) (6). However, Duke patients were more likely to be female and non-white and have diabetes, a history of MI, and a recent MI as the indication for their index PCI. In addition, the use of glycoprotein (GP) IIb/IIIa inhibitors was almost twice as common in the Duke sample.

Event rates. Of the total Duke sample, 3,976 Duke patients (98%) were alive one month after their index PCI and were included in the analyses. Among Duke patients surviving at least one month, the rates of MI and death in the subsequent 11 months were considerably higher than those in CREDO (Table 3). Compared with CREDO, the death rate among Duke patients was three times as high (4.2% vs. 1.4%) and the MI rate was almost twice as high (5.8% vs. 3.2%). Among high-risk patients, death and MI rates reached 5.1% and 8%, respectively. Even the lower risk patients treated at Duke had higher event rates than those observed in CREDO (death: 3.4% vs. 1.4%; MI: 3.7% vs. 3.2%).

Patients with MI had a greater risk of experiencing additional events relative to other patients. Of events explicitly included in the model, MI patients were at increased risk of revascularization (60% vs. 11.5%), CABG

Table 1. Unit Costs*

Variable	Amount
Hospitalization cost	
CABG	$26,918
PCI (no MI/MI)	$9,035/$11,309
MI (no death/death)	$5,580/$6,440
Death (no other event)	$4,465
Bleed (no other event)	$4,127
Incremental cost of death	$2,011
Incremental cost of major bleed	$3,592
Physician fees	
CABG admission (+/− MI, death)	$3,637–$4,427
MI admission (no death/death)	$502/$798
PCI admission (+/− MI, death)	$1,471–$2,058
Major bleed admission (no death/death)	$480/$815
Death only	$463
Incremental fee for bleed admission	$123
Clopidogrel cost	$3.22/day + $2.50/ month dispensing fee

*Costs in year 2000 U.S. dollars.
+/− = with or without; CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

(if revascularized) (29.7% vs. 26.7%), and death (11.6% vs. 1.6% if revascularized; 14.0% vs. 3.9% if not revascularized).

Effect of MI on expected survival. Based on age- and gender-specific life expectancies for Framingham heart disease patients, the expected survival of patients in the Duke sample was 13.2 years (undiscounted). The estimated reduction in life expectancy of patients surviving six months after acute MI was approximately two years (undiscounted) (17). Combining these estimates gave an estimated life expectancy for patients surviving an MI of 11.2 years (undiscounted).

Table 2. Baseline Patient Characteristics

	Duke Sample (n = 4,037)	CREDO (n = 2,116)
Age (yrs)	62 ± 12	62 ± 11
Gender (% female)	35	29
Race (% non-white)	26	11
Risk factors (%)		
Previous MI	52	34
Previous stroke	5	7
Diabetes	29	26
Peripheral vascular disease	10	10
Hyperlipidemia	60	75
Smoking (past year)	24	31
Indication for PCI (%)		
Recent MI	30	14
Unstable/worsening angina*	55	53
Other	15	33
Procedural characteristics†		
Stent(s) used (%)	92	89
Number of stents	1.6 ± 0.9	1.5 ± 0.8
GP IIb/IIIa inhibitor use (%)	86	45

*In Duke sample, defined as unstable or worsening; in CREDO, defined as unstable. †Per-protocol CREDO population. Data are presented as the mean ± SD or percentage of patients.
CREDO = Clopidogrel for the Reduction of Events During Observation; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Baseline analysis: total sample. Extending clopidogrel therapy from one month after PCI to one year after the procedure reduced inpatient costs by $236 due to the decreased incidence of MI (5.8% to 3.2%). These savings were more than offset by the additional cost of clopidogrel ($1,115), resulting in a net increase in total cost of $879 per patient (Table 4). Thus, the estimated cost of prolonged clopidogrel therapy per MI avoided between one month and one year after PCI was $34,336. Assuming life expectancy is reduced by about two years per MI (before discounting), the cost-effectiveness of continuing clopidogrel between one month and one year would be $15,696 per year of life saved (Table 4).

Baseline analysis: high- and low-risk subsets. In the high-risk subset, the incremental cost of prolonging clopidogrel therapy from one to 12 months after PCI was slightly lower than that in the total sample ($775 vs. $879) (Table 5). This, combined with a larger absolute reduction in the incidence of MI in the high-risk subgroup (8% to 4.5%), caused clopidogrel to have a lower incremental cost per MI avoided ($21,893). This translated into a cost-effectiveness ratio of $10,333 per year of life saved for high-risk patients.

Prolonged clopidogrel therapy was less economically attractive among patients lacking high-risk features (Table 5). The lower incidence of MI in this subgroup (3.7%) resulted in smaller absolute reductions in MIs (−1.6%) and associated inpatient costs (−$132) per patient. The cost-effectiveness ratios were almost triple those for the high-risk subset ($59,939 per MI avoided and $26,568 per year of life saved).

Sensitivity analyses. RELATIVE RISK OF MI. The economic attractiveness of clopidogrel therapy was relatively robust to moderate reductions in the effect of clopidogrel on the rate of MI. An absolute increase of 10% in the relative risk for MI with clopidogrel from the baseline value of 0.56 would not change the cost-effectiveness substantially (Fig. 2). However, if the relative risk for MI associated with long-term clopidogrel therapy increased above 85%, which is within the confidence interval of the estimate (0.3–1.0), the cost-effectiveness ratio would increase sharply and exceed $50,000 for the total sample.

MEDICATION COST AND COMPLIANCE WITH THERAPY. The economic attractiveness of the clopidogrel strategy was sensitive to variation in the price of the drug (Fig. 3). A decrease of one-third in the price of clopidogrel from $3.22 to $2.15 daily would reduce the incremental cost of the clopidogrel strategy by $361 (from $879 to $518), resulting in a cost per year of life saved of only $9,250. In the high-risk subset, a 33% price reduction would result in a cost per year of life saved of $5,520 (Fig. 3).

Compliance with therapy in CREDO was fairly low in both the treatment and control groups (63% and 61%, respectively). If all patients were compliant with drug therapy and the effectiveness of clopidogrel increased in proportion to the improvement in compliance (improving

Table 3. Event Rates Between One and 12 Months After Percutaneous Coronary Intervention

Patient Population	Sample Size	No Clopidogrel (%)				Clopidogrel (%)	
		Death	MI	Revasc	Major Bleed	MI*	Absolute Risk Reduction (MI)*
CREDO	910	1.4	3.2	15.2	3.0	1.8	1.4
Duke							
Total	3,976	4.2	5.8	14.3	n/a†	3.2	2.6
High risk	1,919	5.1	8.0	16.5	n/a†	4.5	3.5
Low risk	2,057	3.4	3.7	12.3	n/a†	2.1	1.6

*Assumes relative risk for MI with clopidogrel treatment from CREDO (0.56). †Not available for Duke sample; used CREDO rate in model.

CREDO = Clopidogrel for the Reduction of Events During Observation trial; MI = myocardial infarction; Revasc = revascularization.

the relative risk of MI from 0.56 to 0.42), the cost per year of life saved would improve to $10,622 (incremental cost of $786; years of life saved of 0.074).

COST OF MI. As the cost of hospitalization for MI increased, the financial attractiveness of clopidogrel therapy improved because savings from avoided hospitalizations increased. Due to the low frequency of MIs, relatively large changes in the cost of MI had only a moderate effect on the expected cost and cost-effectiveness of the clopidogrel strategy. For example, in the total sample, even if the inpatient costs associated with MI tripled, the cost per patient of extended clopidogrel therapy would still exceed the no treatment strategy by $713, leaving a cost-effectiveness ratio of $12,732 per year of life saved.

COST AND RELATIVE RISK OF MAJOR BLEEDS. Results were relatively insensitive to variations in the effect of clopidogrel on the incidence of major bleeds and in the cost of bleeds, due to the low baseline risk of major bleeding (3%). Even if the cost of treating major bleeds increased by 30% and the relative risk for major bleeding increased from 1.4 to 2, the cost per year of life saved in the total sample would increase to only $17,589. Similarly, the cost-effectiveness would improve only marginally from $15,696 to $14,589 per year of life saved if excess bleeds with clopidogrel were eliminated.

REDUCTION IN LIFE EXPECTANCY DUE TO MI. There is considerable uncertainty regarding the effect of MI on life expectancy. If the baseline estimate of years of life lost over a lifetime due to an MI (two years) were reduced by 50%, the cost-effectiveness ratio for the total sample would increase from $15,696 to $21,975. Similar reductions in the effect of MI on long-term survival would increase the cost per year of life saved to $14,706 for high-risk patients and over $36,000 in the low-risk subgroup (Fig. 4).

DISCUSSION

Although there is growing evidence supporting the effectiveness of prolonged clopidogrel therapy, some clinicians have expressed concern about its broad application, given the cost of treatment (4). Our study suggests that continuing clopidogrel therapy after PCI beyond one month and out to at least one year in a tertiary care practice setting is economically attractive relative to currently accepted treatments (19). The value of prolonged therapy varies with patient characteristics and is greatest for patients at high risk of MI. The cost-effectiveness of prolonged therapy is similar to that estimated for statin therapy in secondary prevention (20,21).

Importance of relative risk for MI with clopidogrel. Our results hinge on the ability of clopidogrel to reduce the

Table 4. Modeled Outcomes and Cost-Effectiveness: Total Sample

Variable	Clopidogrel	No Clopidogrel	Difference (Clopidogrel vs. None)
Cost*			
Hospital	$2,252	$2,459	−$207
Physician	$317	$346	−$29
Medications	$1,115	$0	$1,115
Total	$3,715	$2,819	$896
Outcomes			
Death (1 month to 1 yr)	3.92%	4.15%	−0.23%
MI (1 month to 1 yr)	3.24%	5.80%	−2.56%
Life expectancy (discounted yrs)†	10.43	10.37	0.056
Cost-effectiveness			
$/MI avoided		$34,336	
$/yr of life saved		$15,696	

*Between 1 and 12 months following after percutaneous coronary intervention. †Years of life discounted at 3% per year.

MI = myocardial infarction.

Table 5. Modeled Outcomes and Cost-Effectiveness: High- and Low-Risk Subsets

Variable	High-Risk Subset			Low-Risk Subset		
	Clopidogrel	No Clopidogrel	Difference (Clopidogrel vs. None)	Clopidogrel	No Clopidogrel	Difference (Clopidogrel vs. None)
Cost*						
Hospital	$2,602	$2,900	−$298	$1,925	$2,040	−$115
Physician	$365	$407	−$42	$271	$288	−$17
Clopidogrel	$1,115	0	+$1,115	$1,115	0	+$1,115
Total	$4,082	$3,307	+$775	$3,311	$2,328	+$983
Outcomes						
Death (1 month to 1 yr)	4.72%	5.01%	−0.29%	3.21%	3.37%	−0.16%
MI (1 month to 1 yr)	4.46%	8.0%	−3.54%	2.06%	3.70%	−1.64%
Life expectancy (discounted yrs)†	10.33	10.26	+0.075	10.53	10.49	+.037
Cost-effectiveness						
$/MI avoided		$21,893			$59,939	
$/yr of life saved		$10,333			$26,568	

*Between 1 and 12 months after percutaneous coronary intervention. †Years of life discounted at 3% per year.
MI = myocardial infarction.

incidence of MI beyond one month after PCI. Fewer MIs result in savings from less frequent hospitalizations and longer expected survival. A moderate reduction in the effectiveness of clopidogrel in preventing MIs would not affect the results substantially. However, if the relative risk for MI with clopidogrel rose above 0.85 (from 0.56), which is within the confidence interval for the estimate (0.3 to 1.0), the cost per year of life saved with prolonged therapy would become much less attractive and would be prohibitive in the low-risk group. Because high-risk patients have an increased risk of MI, clopidogrel therapy is most economically attractive in this group.

Sensitivity of results to other factors. The cost-effectiveness of therapy was directly related to the price of clopidogrel. Although this analysis was conducted from a societal perspective, it is worth noting that without comprehensive prescription drug coverage, the financial burden of clopidogrel therapy would fall primarily on patients. The additional burden may be particularly problematic in this population of patients, which is typically prescribed multiple long-term medications for heart disease, costing several hundred dollars per month. Third-party coverage of outpatient medications or a decrease in medication cost would reduce the burden to patients and improve the cost-effectiveness of prolonged therapy considerably. In the absence of coverage, physicians and patients may have to contemplate the value of clopidogrel relative to other medications currently prescribed, in light of each patient's specific risk profile.

Results were relatively robust to variation in the estimate of the effect of MI on life expectancy, but prolonged clopidogrel therapy became increasingly less attractive as the survival advantage gained by avoiding an MI fell below one year. Variation in the cost of MI, cost of bleeds, and effect

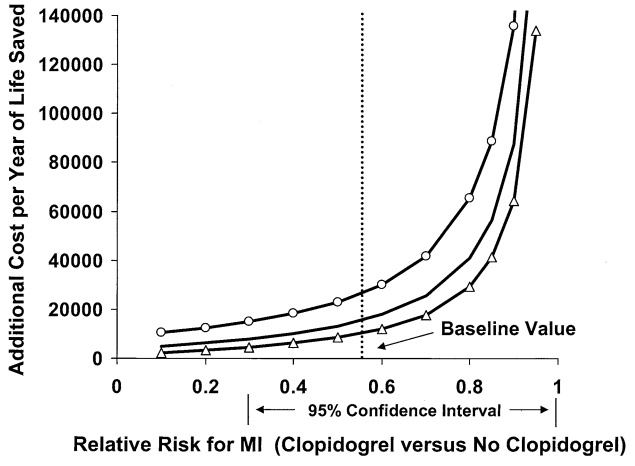

Figure 2. Cost-effectiveness of prolonged clopidogrel therapy: sensitivity to variation in relative risk for myocardial infarction (MI). The cost per year of life saved is shown for values of relative risk for MI between 0 and 1. **Solid line without symbols** = all patients; **line with triangles** = high-risk patients; **line with circles** = low-risk patients. Baseline value of relative risk for MI is indicated by the **vertical dotted line**.

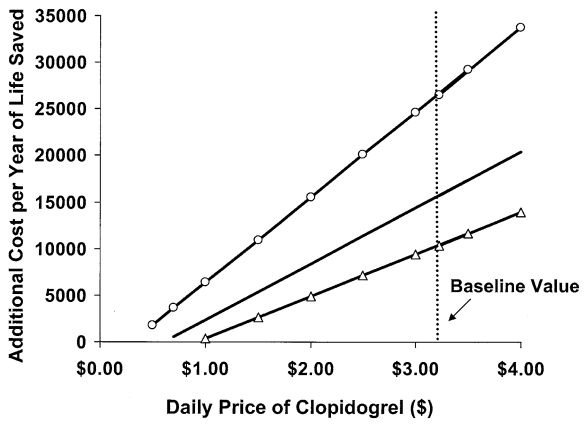

Figure 3. Cost-effectiveness of prolonged clopidogrel therapy: sensitivity to variation in price of clopidogrel. The cost per year of life saved is shown for clopidogrel prices between $0 and $4 per day. **Solid line without symbols** = all patients; **line with triangles** = high-risk patients; **line with circles** = low-risk patients. Baseline value for daily price of clopidogrel is indicated by the **vertical dotted line**.

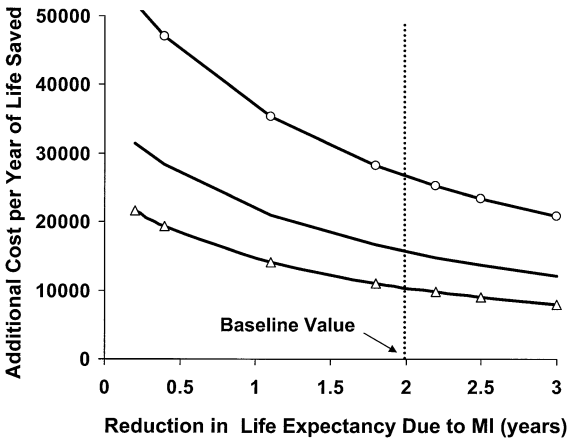

Figure 4. Cost-effectiveness of prolonged clopidogrel therapy: sensitivity to variation in estimate of the reduction in life expectancy associated with myocardial infarction (MI). The cost per year of life saved is shown for a range of values of reduction in life expectancy subsequent to MI. **Solid line without symbols** = all patients; **line with triangles** = high-risk patients; **line with circles** = low-risk patients. Baseline value for reduction in life expectancy due to MI is indicated by the **vertical dotted line**.

of clopidogrel on bleeding had relatively little impact on the cost-effectiveness of prolonged therapy.

Study sample compared with CREDO population. Event rates in our observational sample were considerably higher than those found in CREDO. This difference reflects the greater baseline risk in study patients relative to the CREDO population and is consistent with literature suggesting that patients treated in the community have a less favorable risk profile than those enrolled in randomized trials (22,23). Assuming the relative effectiveness of clopidogrel does not vary with patient risk, the greater baseline risk in the community increases the potential absolute benefit of prolonged clopidogrel treatment. The study sample also differed from the CREDO population in terms of GP IIb/IIIa inhibitor usage, with study patients being treated almost twice as often as CREDO patients. This difference is unlikely to have affected the results, because the study period did not include the first month after the procedure, during which time the benefits of GP IIb/IIIa inhibitors are realized (24).

Comparison with the CURE analysis. Although our study suggests that prolonging clopidogrel therapy may be worthwhile, particularly in high-risk patients, our results are considerably less favorable than the estimated cost per year of life saved of 1,365€ (approximately $1,650) in a recent cost-effectiveness analysis of CURE (25). Unlike our study, the CURE analysis combined the effects of initial therapy (one month of clopidogrel) with prolonged treatment. This approach overestimates the value of prolonged therapy, because treatment in the periprocedural period is more effective than in the subsequent months and costs a fraction of the expense associated with extended therapy. As in our study, the CURE analysis found that results were sensitive to the effectiveness of clopidogrel in preventing events and insensitive to the cost of bleeds.

Study limitations. There are several limitations to this study. First, the model was based on one year of data, and lifetime survival was extrapolated using available external estimates. Although these extrapolations are somewhat imprecise, they offer insight regarding the potential benefits of preventing downstream events and provide a metric with which to compare the treatment's value with that of other health care interventions. In this regard, contemporary long-term follow-up data are needed to better determine the survival benefits associated with preventing nonfatal MI. Second, this study addressed the issue of prolonging therapy until one year after the procedure. Unfortunately, the extent to which the relative benefits of clopidogrel continue to accrue beyond one year is unknown, limiting our ability to estimate the cost-effectiveness of extending therapy for more than one year. Similarly, based on current data, we could not estimate the incremental value of each additional month of therapy and determine whether the cost-effectiveness of treatment varies during the 11 months of prolonged treatment. More precise knowledge regarding the duration of clinical effectiveness would allow the most cost-effective regimen to be determined. Third, because of the design of CREDO, we could not rule out the possibility that the preprocedural loading dose contributed to the observed effect of prolonged treatment. However, reaching therapeutic levels earlier through loading reduces periprocedural events in the days after PCI, and a persistent loading effect beyond one month is unlikely. Fourth, unit costs were based on secondary sources. However, the results were robust to variations in the cost of care. Fifth, outpatient costs, non-health care costs of patients (e.g., travel, informal care), and productivity losses were not available and were excluded from the analysis. Because the primary effect of prolonged clopidogrel treatment was a reduction in MI and excluded costs associated with MI would be greater among patients not receiving prolonged treatment, exclusion of these societal costs made our analysis more conservative (i.e., biased against prolonged treatment). Although bleeding rates were slightly higher with prolonged treatment, the results were insensitive to variation in bleeding costs, and exclusion of any outpatient or non-health care patient costs associated with bleeds would not significantly affect results. Sixth, costs incurred during years of life gained due to the intervention were not included. The results did not change appreciably when estimates of these costs were included because of the relatively small survival difference involved and the effect of discounting on future costs. Finally, the study was based on data collected before the introduction of drug-eluting stents. With drug-eluting stents, clopidogrel therapy is typically recommended for three to six months after PCI (rather than for one month). This delays but does not avoid the issue of whether to extend clopidogrel therapy for one year.

Policy implications. Prolonging clopidogrel treatment for up to one year after PCI is as economically attractive from the societal perspective as many other health care interven-

tions currently provided. The therapy is most worthwhile in high-risk patients. However, without comprehensive medication coverage, the cost of the therapy would be borne primarily by patients already facing significant medication expenses. The financial burden would be alleviated substantially with a moderate reduction in the price of clopidogrel.

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