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Long-Term Cost Effectiveness of Early and Sustained Dual Oral Antiplatelet Therapy With Clopidogrel Given for Up to One Year After Percutaneous Coronary Intervention

Results From the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial

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OBJECTIVES This study sought to evaluate the long-term cost effectiveness of a clopidogrel loading strategy before percutaneous coronary intervention (PCI) followed by continued treatment for one year.

BACKGROUND The Clopidogrel for the Reduction of Events During Observation (CREDO) trial, a randomized trial of 2,116 patients, showed the effectiveness of antiplatelet therapy with clopidogrel 300 mg before PCI and 75 mg daily for one year afterward compared with placebo load and placebo days 29 to 365 in reducing the combined risk of death, myocardial infarction, and stroke. All patients received clopidogrel on days 1 to 28 and aspirin on days 1 to 365.

METHODS All hospitalizations were assigned a diagnosis-related group. Associated costs were estimated three ways (including professional costs): 1) Medicare costs, 2) MEDSTAT costs, and 3) blend with Medicare for those age ≥65 years and MEDSTAT for those age <65 years. Clopidogrel 75 mg cost $3.22. Life expectancy in trial survivors was estimated using external data. Confidence intervals were assessed by bootstrap.

RESULTS The primary composite end point occurred in 89 (8.45%) clopidogrel patients and in 122 (11.48%) placebo patients (relative risk reduction [RRR] 26.9%; 95% confidence interval [CI] 3.9% to 44.4%). The number of life-years gained (LYG) with clopidogrel was 0.1526 (95% CI 0.0263 to 0.2838) using Framingham data and 0.1920 (95% CI 0.054 to 0.337) using Saskatchewan data. Average total costs were $664 higher for the clopidogrel arm (95% CI −$461 to $1,784). The incremental cost-effectiveness ratios (ICERs) based on Framingham data ranged from $3,685/LYG to $4,353/LYG, with over 97% of bootstrap-derived ICER estimates below $50,000/LYG. The ICERs based on Saskatchewan data were $2,929/LYG to $3,460/LYG, with over 98% of estimates below $50,000/LYG.

CONCLUSIONS Platelet inhibition with clopidogrel loading before PCI followed by therapy for one year is highly cost effective. (J Am Coll Cardiol 2005;46:761–9) © 2005 by the American College of Cardiology Foundation

Use of aspirin in conjunction with an adenosine receptor antagonist (clopidogrel or ticlopidine) provides protection from thrombotic complications after percutaneous coronary intervention (PCI) (1–4). Although the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial (5) showed a significant reduction in death, stroke, and myocardial infarction (MI) among patients who had acute coronary syndromes and who were receiving clopidogrel versus placebo, the optimal timing for initiation and duration of treatment with clopidogrel was unknown. The recently published Clopidogrel for the Reduction of Events During Observation (CREDO) trial (6) showed that a loading strategy and continuous use of clopidogrel for one year after PCI led to a significant reduction in death, stroke, and MI rates compared with patients receiving clopidogrel for one month after PCI. These results support the early initiation and one-year treatment with clopidogrel for all patients (with and without acute coronary syndromes [ACS]) undergoing PCI.

Because over 600,000 PCI procedures are performed annually in the U.S. (7), treatment with clopidogrel as in the CREDO trial would require significant resource use. The cost and cost effectiveness of such a strategy, therefore, would provide insight regarding its impact on the health

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CI = confidence interval
CREDO = Clopidogrel for the Reduction of Events During Observation trial
CURE = Clopidogrel in Unstable angina to prevent Recurrent Events trial
DRG = diagnosis-related group
ICER = incremental cost-effectiveness ratio
LYG = life-year gained
MI = myocardial infarction
PCI = percutaneous coronary intervention
QALY = quality-adjusted life-year
RRR = relative risk reduction

care system. A recent study found clopidogrel use cost effective in patients with ACS (the CURE trial) and patients with ACS undergoing PCI (the PCI-CURE trial) (8,9). However, no study has evaluated the cost effectiveness in the setting of all patients receiving PCI with an optimal loading and post-procedure clopidogrel treatment strategy. The objective of this study is to evaluate the long-term cost effectiveness of clopidogrel in patients receiving PCI using clinical efficacy data and resource use from the CREDO trial and external data sources to estimate long-term survival. By translating the reduction in primary fatal and non-fatal events observed with clopidogrel in the CREDO trial into estimates of gains in life expectancy, an estimate of the incremental cost per life-year gained (LYG) may be calculated.

METHODS

Design of the CREDO trial. The CREDO study, a large, multi-center randomized controlled trial, has previously been described in detail (6). Briefly, 2,116 patients were recruited from June 1999 to April 2001 at 99 centers in the U.S. and Canada. Patients with coronary artery disease undergoing planned or probable PCI were randomized to clopidogrel loading (300 mg) 3 to 24 h before PCI plus one year of therapy with clopidogrel (75 mg daily) (n = 1,053) versus placebo for loading and after day 28 (n = 1,063). All patients received clopidogrel (75 mg daily) on days 0 to 28 and aspirin (325 mg daily until day 28, then at the discretion of the investigator) throughout the study period. The primary end point at one year was a composite of cardiovascular death, nonfatal MI, or stroke.

Economic analysis plan and assessment of cost. The economic analytic plan was to compare the costs of the two treatment arms in the U.S. setting, and if the clopidogrel arm was more costly as well as more effective, to perform an incremental cost-effectiveness analysis. Costs included in the analysis are direct medical care costs for hospitalization and the cost of clopidogrel and aspirin (10,11). No data are available from the CREDO trial to calculate direct costs associated with outpatient visits and testing or indirect costs attributable to lost productivity. Costs and projected life expectancy differences were discounted 3% annually. Health care costs were calculated by applying unit costs to resource utilization reported over the course of the trial. The analysis uses costs in U.S. dollars for the year 2001, but utilizes resource use information and clinical outcomes for all 2,116 patients.

All major cardiovascular health care-related resources were collected prospectively in conjunction with clinical trial data. All revascularization procedures (including those occurring during subsequent hospitalizations) were reported, as well as medications taken in hospital and at home. Diagnostic tests, therapeutic procedures, and drugs taken during interim hospitalizations were also recorded. Ambulatory care and outpatient diagnostic testing (other than coronary angiography) were not recorded. Because the majority of resource-intensive procedures and tests are performed while patients are hospitalized, it is likely that most of the major components of health care resource use were collected. Possible exceptions would include same-day testing not requiring hospitalization, such as nuclear imaging studies or echocardiograms, in addition to rehabilitation and nursing home stays after stroke. Medication use other than study drug was not found to differ between the arms.

Using a pre-defined algorithm, the initial and subsequent hospitalizations were assigned, based on the most expensive procedure or adverse event during the admission, a diagnosis-related group (DRG) as developed by Medicare in the U.S. Non-cardiovascular events were also recorded and included in the analysis. Costs were estimated for each DRG based on average Medicare reimbursement rates from the Medicare Part A (MEDPAR) (12) and average private payer reimbursement rates from the MEDSTAT database (13). A blended cost estimate of the two fee schedules was generated allocating Medicare costs to the CREDO trial patients age 65 years and older and MEDSTAT costs to patients younger than age 65 years. Professional costs are included in MEDSTAT estimates and were calculated as a percentage (32%) of hospital costs by DRG for Medicare estimates (14). The Redbook average wholesale cost of $3.22 (2001 dollars) for 75 mg of clopidogrel and $0.04 for aspirin was used in the analysis.

Life expectancy estimation. Lifetime cost-effectiveness ratios in terms of cost per LYG were estimated based on in-trial estimates of incremental costs, event rates (death, MI, and stroke), and estimates of lost life expectancy associated with in-trial events (death, MI, and stroke) obtained from two sources: the Framingham Heart Study (15,16) and the Saskatchewan Health database (17–19). Life-years lost were calculated by subtracting the mean survival given the observed pattern of events in the trial from the survival expected with no events during the trial.

For the Saskatchewan Health database, survival data on qualifying patients, from among 50,734 men and women who were age 21 years or older at the time of a diagnosis that could have qualified them for the trial between January 1, 1990, and December 31, 1995, with follow-up through the end of 2000, were analyzed using published methods

(17). Briefly, mean survival beyond the end of the trial was estimated by integrating the survival curves, adjusted for various patient characteristics, including experience of specific subsequent ischemic events (17). Cox proportional hazards models for each time period were derived for patients with age, diabetes, previous MI, previous ischemic stroke, prior CABG, and lipid-lowering drug use as covariates (17,20–25). The cumulative survival functions over time were derived by applying the hazard functions in sufficiently brief intervals that the hazard can be assumed to be constant over the period.

For both Framingham and Saskatchewan data, estimates of life-years lost because of events were obtained by subtracting life expectancy estimates for individuals with a given event pattern from life expectancy estimates for individuals with no events (24). This assumes that non-fatal events in the trial had the same prognostic importance as events from the Framingham and Saskatchewan database. For patients who experienced multiple events of different types during the trial, lost life expectancy was estimated assuming a hierarchy of: 1) death, 2) stroke, and 3) MI (e.g., patients with both non-fatal MI and non-fatal stroke had their lost life expectancy based on estimates for patients with non-fatal stroke). It was assumed in performing these analyses that the clopidogrel would be stopped at the end of the trial and that there would be no further reduction (or increase) in non-fatal events between the two arms. The difference between treatment groups in average life-years lost because of events (placebo − clopidogrel) yields an estimate of the LYG with clopidogrel.

Estimation of cost effectiveness. A societal perspective was used for the cost-effectiveness analysis. The cost effectiveness of clopidogrel was expressed as the incremental cost-effectiveness ratio (ICER), the added cost in the clopidogrel arm divided by LYG. Bootstrap methods (5,000 iterations) were used to estimate the 95% confidence intervals (CIs) of the distribution of ICERs (26,27). Sensitivity analyses included reducing life expectancy gains by 50% and 80%, adding estimated costs associated with bleeding, calculating additional costs beyond the trial period, and quality adjusting survival. The impact of bleeding on cost could not be calculated directly because the costing was based on DRGs, which would not necessarily be affected by bleeding. Therefore, the impact of bleeding on hospital length of stay was estimated using CURE trial data (because length of stay was not available in the CREDO trial dataset), and the concomitant cost increase was estimated assuming an average cost of $2,000 per day. Statistical analyses were performed with SAS version 8.2 (SAS Institute Inc., Cary, North Carolina) and S-Plus version 6.0 (Mathsoft, Seattle, Washington).

RESULTS

Summary of the clinical data. There was no difference between the groups in age, gender, MI either at presentation or in previous history, diabetes, or hypertension (Table 1). After one year, patients pretreated with 300 mg clopidogrel before PCI and continued on therapy for one year had an 8.5% event rate compared with 11.5% in the placebo group

Table 1. Clinical Results Summary

	Clopidogrel (n = 1,053)	Placebo (n = 1,063)	p Value
Age, yrs (mean ± SD)	62 ± 11	62 ± 11	0.45
White race, no. (%)	929 (88.2)	951 (89.5)	0.92
Women, no. (%)	309 (29.3)	297 (27.9)	0.50
Risk factors, no. (%)			
Prior myocardial infarction	353 (33.5)	366 (34.4)	0.68
Diabetes	290 (27.5)	270 (25.4)	0.26
Hypertension	710 (67.4)	740 (69.6)	0.28
Peripheral vascular disease	102 (9.7)	109 (10.3)	0.72
Treatment after initial angiogram, no. (%)			
PCI	902 (85.6)	916 (86.2)	
Medical therapy	87 (8.3)	81 (7.6)	0.96
CABG	41 (3.9)	42 (4.0)	
Indication for PCI, no. (%)			
Recent MI	151 (14.3)	139 (13.1)	
Unstable angina	553 (52.5)	564 (53.1)	0.74
Stable angina and other	345 (32.8)	349 (32.8)	
One-year end points			
Death, MI, stroke	89 (8.5)	122 (11.5)	0.02
Death	18 (1.7)	24 (2.3)	0.45
MI	70 (6.6)	90 (8.5)	0.13
Stroke	9 (0.9)	12 (1.1)	0.68
Bleeding			
Major	93 (8.8)	71 (6.7)	0.07
Minor	56 (5.3)	59 (5.6)	0.84

CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

Table 2. Life-Years Lost Because of Cardiovascular Events

	Clopidogrel	Placebo	LYG in Clopidogrel Arm (Placebo-Clopidogrel)	95% CI of Δ
Framingham				
Death	0.1482	0.2268	0.0787	−0.0402, 0.1997
Myocardial infarction	0.0980	0.1476	0.0496	0.0054, 0.0952
Stroke	0.0214	0.0458	0.0243	−0.0063, 0.0558
Total	0.2676	0.4202	0.1526	0.0263, 0.2838
Saskatchewan				
Death	0.1353	0.2108	0.0755	−0.0369, 0.1909
Myocardial infarction	0.2095	0.3105	0.1010	0.0163, 0.1834
Stroke	0.0263	0.0470	0.0207	−0.0107, 0.0540
Total	0.3763	0.5683	0.1920	0.0539, 0.3369

CI = confidence interval; LVG = life-year gained.

of the composite end point of death, MI, or stroke (relative risk reduction [RRR] 26.9% [p = 0.02; 95% CI 3.9% to 44.4%]). The degree of benefit was consistent across all subgroups and within individual components of the end point. There was a trend toward more major bleeding in the clopidogrel arm that did not reach statistical significance. The placebo event rate was similar to that in the Saskatchewan database.

Estimation of LYG. Both Framingham and Saskatchewan estimates showed that patients in the placebo group had greater lost life expectancy because of MI than those receiving clopidogrel: 0.050 life-years lost (95% CI 0.005 to 0.095) using Framingham and 0.101 life-years lost (95% CI 0.016 to 0.183) using Saskatchewan models (Table 2). In addition, there were trends toward greater lost life expectancy because of death and stroke for the placebo group using both estimates. Based on the Framingham model, patients in the clopidogrel arm were estimated to have gained, on average, 0.1526 life-years (95% CI 0.0263 to 0.2838) over patients in the placebo arm. The Saskatchewan model showed an overall life expectancy gain of 0.1920 life-years (95% CI 0.0539 to 0.3369) for the clopidogrel group over the placebo group.

In-trial costs. The most common DRGs, and their costs, assigned to hospitalizations included angioplasty with stent, angioplasty without stent, and other cardiovascular diagnoses (Table 3). The most common noncardiac DRG was pneumonia. Costs are presented in Table 4. One-year costs were higher for the clopidogrel arm using all three costing methods: $563 (95% CI −$483 to $1,642) for Medicare, $573 (95% CI −$633 to $1,765) for MEDSTAT, and $664 (95% CI −$461 to $1,765) for the blend. None of the cost differences reached statistical significance. Total one-year costs for patients in the clopidogrel arm were $19,994 based on Medicare estimates, $23,394 based on MEDSTAT estimates, and $21,974 based on Medicare/MEDSTAT blend estimates, compared with placebo estimates of $19,431, $22,821, and $21,310 for Medicare, MEDSTAT, and blend, respectively.

Cost effectiveness. Results of the cost effectiveness analysis are presented in Table 5. Using Framingham-based estimates, not including costs beyond the trial period, the ICERs ranged from $3,684 with MEDSTAT to $4,353 with blend. Over 97% of the bootstrap estimates were below $50,000/LYG. Similarly, using Saskatchewan-based estimates, ICERs ranged from $2,929 with MEDSTAT to $3,460 with blend, with over 98% of bootstrap estimates below $50,000/LYG. A plot of the bootstrap-derived joint distribution of cost and effectiveness differences based on blended costing both effectiveness estimates is shown in Figure 1, and the associated cost-effectiveness acceptability curve based on blended costing is plotted in Figure 2. The

Table 3. Top 10 Hospitalization Diagnostic-Related Groups (DRGs) in CREDO

DRG	Description	Number of Hospitalizations		Hospitalization + Physician Cost (MEDSTAT)	Hospitalization + Physician Cost (Medicare)
		Clopidogrel	Placebo		
116	Other permanent cardiac pacemaker or PTCA with coronary artery stent implant	822	823	$17,769	$14,182
112	Percutaneous cardiovascular procedures	221	234	$10,688	$12,415
140	Angina pectoris	125	118	$4,136	$3,114
143	Chest pain	102	109	$3,663	$3,213
107	Coronary bypass with cardiac catheter	89	88	$41,764	$35,881
133	Atherosclerosis	12	21	$7,921	$3,608
127	Heart failure and shock	20	12	$7,208	$6,085
90	Simple pneumonia and pleurisy age >17 yrs	8	12	$4,801	$3,427
106	Coronary bypass with PTCA circulatory disorders with	7	12	$43,903	$49,543
122	AMI without major complication discharged alive	8	9	$11,047.59	$6,084.76

AMI = acute myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Table 4. Cost in U.S. Dollars

	Clopidogrel	Placebo	Δ	95% CI of Δ
Initial hospitalization				
Medicare	$13,886	$14,094	−$208	−$736, $359
MEDSTAT	$16,834	$17,002	−$168	−$749, $422
Blend	$15,614	$15,744	−$130	−$706, $461
Follow-up hospitalization costs				
Medicare	$5,205	$5,235	−$29	−$971, $887
MEDSTAT	$5,658	$5,717	−$58	−$1,159, $978
Blend	$5,459	$5,464	−$5	−$999, $977
Clopidogrel and ASA costs (1 yr)	$902	$102	$800	$774, $825
1-yr total cost				
Medicare	$19,994	$19,431	$563	−$483, $1,642
MEDSTAT	$23,394	$22,821	$573	−$633, $1,765
Blend	$21,974	$21,310	$664	−$461, $1,784

ASA = aspirin; CI = confidence interval.

three costing approaches yielded similar results, with over 90% of bootstrap-derived cost-effectiveness estimates below $18,000.

Sensitivity analyses. These analyses required the use of external databases to project life expectancy beyond the end of the trial. The life expectancy gain with clopidogrel may be either smaller or larger than projected. If the estimated gain in life expectancy is only half of that projected, using the blended costing approach and Framingham life expectancy estimates, the ICER would be $8,706, with 95.7% of bootstrap samples below $50,000/LYG; based on Saskatchewan the ICER would be $6,921, with 97.9% of bootstrap samples below $50,000/LYG. If the life expectancy gain is just 20% of that projected, the ICER would be $21,766, with 82.7% below $50,000/LYG based on the Framingham model, and $17,302, with 89.3% below $50,000/LYG based on the Saskatchewan model.

Based on the CURE trial data, the length of stay increased 5.94 days for hospitalizations in which a minor bleed occurred and 9.91 days in hospitalizations in which a life-threatening bleed occurred. Combining the length of stay data with the bleeding incidence from Table 1 adds an incremental average 0.9916 days to the length of stay. If an additional day in the hospital, independent of the DRG assignment, costs $2,000 per day, then incremental bleeding caused by clopidogrel adds $399 to the average cost per patient. This would increase the Framingham-derived ICER using blend costing from $4,353 to $6,966.

Because patients who survive will incur additional health care costs, we estimated costs beyond the trial period at $4,370 per year based on Medicare estimates, and then discounted this cost at 3% per year (28). Patients who die or have reduced life expectancy will have forgone costs for those lost life-years. Forgone costs will be higher in the placebo group because of a shorter life expectancy. With forgone costs accounted for in the analysis, the ICERs nearly doubled (Table 6).

Utility was not measured in the CREDO trial, and thus we could not calculate quality-adjusted life-years (QALYs) directly using patient-level data. Because there were more non-fatal events in the placebo arm, it might be reasonable to expect utility to be higher in the clopidogrel arm, rendering results described above conservative. However, if utility is <1.0 but equal for both arms, the ICER in terms of cost per QALY gained would be higher than the cost per LYG estimate. If utility was 0.80 in both arms (29), then the ICER using Framingham life expectancy and blended costs would be $5,441/QALY gained. If costs in added years of life were also included, the ICER would be $10,568/QALY gained.

DISCUSSION

The results from this study show that a loading strategy followed by one year of anti-platelet therapy with clopidogrel is cost effective for patients undergoing PCI. Al-

Table 5. Long-Term Cost Effectiveness, In-Trial Costs Only

	Δ Cost	Δ Life-Years	ICER (Cost per LYG)	% Dominant	% Dominated	% <50,000/LYG
Framingham						
Medicare	$563	0.1526	$3,684	15.0%	1.0%	97.3%
MEDSTAT	$573	0.1526	$3,755	18.1%	0.8%	98.3%
Blend	$664	0.1526	$4,353	12.6%	0.7%	97.5%
Saskatchewan						
Medicare	$563	0.1920	$2,929	14.9%	0.4%	98.7%
MEDSTAT	$573	0.1920	$2,985	17.6%	0.4%	98.8%
Blend	$664	0.1920	$3,460	13.1%	0.2%	98.9%

ICER = incremental cost-effectiveness ratio; LYG = life-year gained.

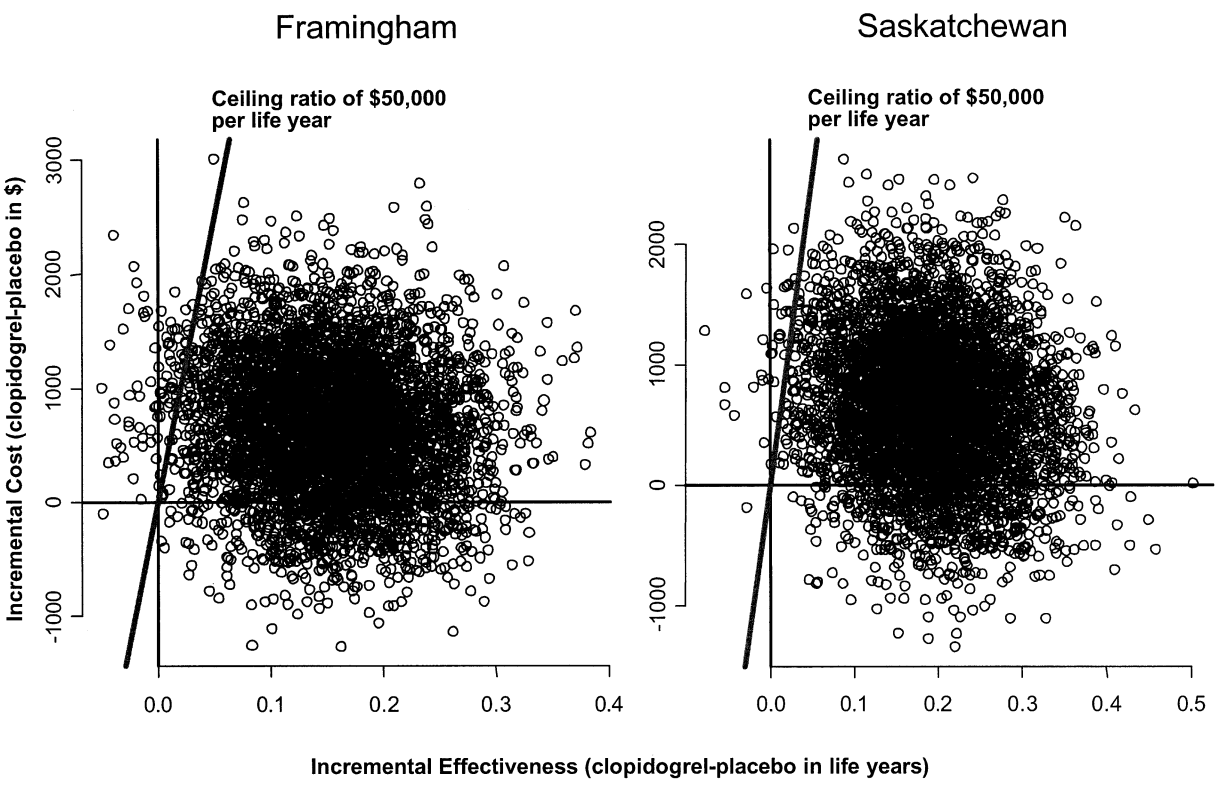

Figure 1. Scatterplot of the joint distribution of bootstrap estimates of cost and effectiveness differences based on Blended costs for Framingham **(left)** and Saskatchewan **(right)** life expectancy estimates. The line extending through the origin (0.0) is a hypothetical cost-effectiveness threshold of $50,000 per life-year gained.

though one-year average costs associated with clopidogrel use trended higher with clopidogrel using all three costing methods, after estimating LYG by preventing events, the CREDO trial clopidogrel strategy was highly cost effective,

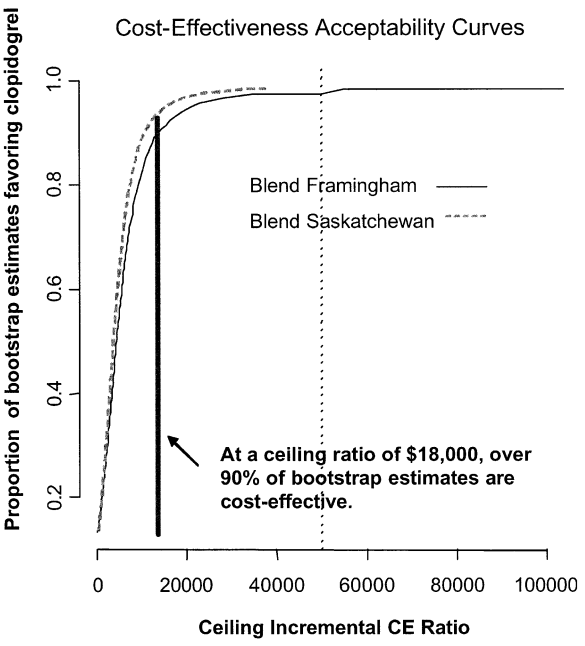

Figure 2. Cost-effectiveness acceptability curves based on Medicare/MEDSTAT costs for Framingham and Saskatchewan life expectancy estimates. CE = cost effectiveness.

with ICERs ranging from $3,684 to $4,353/LYG with Framingham estimates and $2,929 to $3,460/LYG with Saskatchewan estimates. These results were statistically robust and significant, with over 95% of bootstrap samples yielding estimates <$50,000 per LYG. These results were consistent for all three costing approaches and the two approaches to evaluating lost life expectancy. Although neither outpatient resource use nor indirect costs were included in these analyses, costs would be expected to be higher in the placebo arm because of the higher event rate, and cost-effectiveness estimates, therefore are likely conservative. The ICERs remained attractive in sensitivity analyses, including an analysis that included estimated costs beyond the trial period. All of these ICER estimates compare favorably with estimates of ICERs associated with other well-accepted cardiovascular therapies, such as statin therapy for patients with coronary heart disease (30,31) and thrombolytic therapy in elderly patients (32).

Platelet adenosine diphosphate blockers in conjunction with aspirin therapy have been shown to be beneficial in the treatment of vascular disease and in preventing thrombosis after PCI. In the CURE trial, clopidogrel therapy for up to one year prevented cardiovascular events in patients presenting with ACS (5). The subset of patients in the CURE trial who underwent PCI also derived significant benefit from clopidogrel therapy (33). The CREDO trial (6) showed that both ACS and non-ACS patients undergoing PCI had

Table 6. Long-Term Cost Effectiveness, Including Cost Beyond the Trial Period

	Δ Cost	Δ Life-Years	ICER (Cost per LYG)	% Dominant	% Dominated	% <50,000/LYG
Framingham						
Medicare	$1,188	0.1526	$7,786	2.0%	1.1%	96.9%
MEDSTAT	$1,199	0.1526	$7,857	2.2%	1.0%	97.9%
Blend	$1,290	0.1526	$8,454	1.8%	0.9%	97.1%
Saskatchewan						
Medicare	$1,247	0.1920	$6,492	1.3%	0.3%	98.6%
MEDSTAT	$1,257	0.1920	$6,548	1.9%	0.4%	98.6%
Blend	$1,348	0.1920	$7,023	1.1%	0.2%	98.8%

Abbreviations as in Table 5.

protection from major adverse events with clopidogrel treatment. In addition, the CREDO trial found that a loading strategy of clopidogrel followed by one year of therapy significantly reduced death and vascular events. Although clopidogrel has been extensively studied with positive clinical results, there has been concern over its cost.

This cost effectiveness of clopidogrel in patients with ACS has been reported in multiple studies (8,9,34). Clopidogrel use in ACS was cost effective in the short term from the perspective of multiple countries based on results from the CURE trial (19). In addition a Swedish report assessed the long-term cost effectiveness of clopidogrel on top of standard therapy (including aspirin) in patients with ACS and showed that clopidogrel is cost effective providing an incremental survival of 0.12 years and an ICER of €1365 (34). Two recent analyses using methodology similar to the current study found clopidogrel to be cost effective in the long term for the CURE and PCI-CURE trials (8,9). Early and sustained clopidogrel therapy for one year in patients with ACS who underwent PCI, compared with a strategy of no pretreatment and therapy for four weeks after PCI, had an ICER range from $2,856/LYG to $4,775/LYG overall and from dominant to $935/LYG for patients undergoing early PCI (8). All patients with ACS, regardless of PCI, had an ICER of $6,318 based on Framingham data and an ICER of $6,475 based on the Saskatchewan data.

In contrast to these results, a study using decision analytic methodology suggested that lifetime therapy with clopidogrel would only be cost effective in aspirin-intolerant patients (35). However, this study was not performed with patient-level data, and it combined estimates of incidence and prevalence. This study considered therapy for life, which is difficult to model in cost-effectiveness studies (36). Our study is the first, to our knowledge, to present long-term cost effectiveness results for clopidogrel use in all patients undergoing PCI. A recent study (37) modeled the cost effectiveness of clopidogrel for one year versus one month after PCI on a registry population and found one-year treatment economically favorable. The event rates were higher in the registry patients than in the CREDO trial, suggesting a possible larger clinical effect of clopidogrel use in a non-trial setting.

A major strength of this analysis is that it was performed with patient-level data directly from the CREDO trial. Moreover, as a randomized comparison, the assessment of both effectiveness and cost reflect the actual exposure to treatments independently of selection bias. In the CREDO trial, concomitant medicine use reflected care consistent with American College of Cardiology/American Heart Association ACS guidelines; in particular, statin, angiotensin-converting enzyme inhibitor, and beta blocker use was encouraged. The CREDO trial, therefore, serves as a contemporary evaluation of the cost effectiveness of clopidogrel and aspirin versus aspirin and placebo in patients undergoing PCI.

Study limitations. Although this study was performed with resource use and clinical outcome data from a large clinical trial, it has potential limitations. The U.S. costs based on DRGs were applied to both American and Canadian patients and may not account for variation in resource use between these different health systems. Use of DRGs for costing could underestimate or overestimate the differences. For instance, if coronary artery bypass graft length of stay in Canada were longer than the U.S., resource utilization for Canadian patients would be underestimated if all patients were attributed the same U.S.-based DRG. Alternatively, a cost-accounting approach would allow for variability of costs within a DRG; however, these data were unavailable from the CREDO trial. Unless costs were higher in one treatment arm for the same DRG, this effect should have yielded unbiased overall cost estimates. This approach may also reduce the variability in assessment of cost differences attributable to treatment.

A societal perspective is ideally suited to a cost-effectiveness analysis. However, it is not feasible to measure any one cost from a societal perspective, thus proxies are used. The DRGs represent a payer cost perspective, widely applicable for macro hospital payments in the U.S. health care system, whereas cost-accounting systems represent a provider cost perspective. Therefore, although providers may not consider DRGs representative of their costs, it is perhaps a better measure of cost from a societal point of view. In addition, this study does not include all resource use, in particular rehabilitation after events and outpatient resource use. Indirect costs (lost wages or productivity) are also not included. These costs would most likely be higher in the placebo arm because there were more events that could lead to more resource consumption and more time

lost from work. As a result the cost effectiveness estimates in this analysis would be conservative. In addition, although inclusion of forgone costs as a result of early mortality increased the ICERs, the majority of bootstrap estimates were less than $50,000/LYG. An additional criticism may be our inability to assess the effect of drug-eluting stents on resource use. However, because drug-eluting stents do not seem to affect MI or survival rates, nor do they necessarily alter length of clopidogrel use, the current analysis is conservative.

There are also limitations to the use of external databases to estimate life expectancy. Improvements in medical care have prolonged survival in patients with vascular disease that may not be adequately reflected in the Framingham database. However, because there was more loss of life expectancy in the placebo arm, Framingham would have underestimated loss of life more in the placebo arm than in the clopidogrel arm, again making these results conservative. Saskatchewan Health, however, which was based on index hospitalizations occurring between 1990 and 1995, yielded similar life expectancy results as the placebo group in the CREDO trial. It is also worth noting that the uncertainty underlying the life expectancy estimates from Saskatchewan and Framingham models was not accounted for in this analysis. However, the two databases yielded consistent results, which suggest that the life expectancy estimates used in this analysis are reasonable. Although this analysis does assume that the impact of events noted in the CREDO trial have the same prognostic impact as events from the Framingham and Saskatchewan models, there is little doubt that events do predict future events (38,39). If the prognostic importance of events in the CREDO trial was one-half of that in the Framingham and Saskatchewan studies, then the ICERs would double but would still be reasonably low.

Over the last two decades, there have been vast improvements in the care of patients with vascular disease. Aspirin and other antiplatelet agents have proven efficacy when used appropriately in patients undergoing PCI. This study clearly shows that clopidogrel loading before PCI followed by one year of treatment is cost effective in the long term.

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