A Cost-Effectiveness Analysis of Combination Antiplatelet Therapy for High-Risk Acute Coronary Syndromes: Clopidogrel plus Aspirin versus Aspirin Alone

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Background: **Although clopidogrel plus aspirin is more effective than aspirin alone in preventing subsequent vascular events in patients with unstable angina, the cost-effectiveness of this combination has yet to be examined in this high-risk population.**

Objective: **To determine the cost-effectiveness of clopidogrel plus aspirin compared with aspirin alone.**

Design: **Cost–utility analysis.**

Data Sources: **Published literature.**

Target Population: **Patients with unstable angina and electrocardiographic changes or non–Q-wave myocardial infarction.**

Time Horizon: **Lifetime.**

Perspective: **Societal.**

Interventions: **Combination therapy with clopidogrel, 75 mg/d, plus aspirin, 325 mg/d, for 1 year, followed by aspirin monotherapy, was compared with lifelong aspirin therapy, 325 mg/d.**

Outcome Measures: **Lifetime costs, life expectancy in quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio.**

Results of Base-Case Analysis: **Patients treated with aspirin alone lived 9.51 QALYs after their initial event and incurred expenses of $127 700; the addition of clopidogrel increased life expectancy to 9.61 QALYs and costs to $129 300. The incremental cost-effectiveness ratio for clopidogrel plus aspirin compared with aspirin alone was $15 400 per QALY.**

Results of Sensitivity Analyses: **The analysis of 1 year of therapy was robust to all sensitivity analyses. In the probabilistic sensitivity analysis, fewer than 3% of simulations resulted in cost-effectiveness ratios over $50 000 per QALY. The cost-effectiveness of longer combination therapy depends critically on the balance of thrombotic event rates, durable efficacy, and the increased bleeding rate in patients taking clopidogrel.**

Limitations: **This analysis may not apply to patients with severe heart failure, those undergoing long-term anticoagulant therapy, those recently managed with revascularization, or those undergoing short-term treatment with glycoprotein IIb/IIIa inhibitors.**

Conclusions: **In patients with high-risk acute coronary syndromes, 1 year of therapy with clopidogrel plus aspirin results in greater life expectancy than aspirin alone, at a cost within the traditional limits of cost-effectiveness. The durable efficacy of clopidogrel relative to the risk for hemorrhage should be further explored before more protracted therapy can be recommended.**

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The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated that clopidogrel plus aspirin was superior to aspirin alone in preventing the composite outcome of myocardial infarction, stroke, or cardiovascular death in the year following an acute coronary syndrome or non–Q-wave myocardial infarction (1). Although combination therapy is recommended for such patients for at least 1 month, the optimal duration is less clear (2). In addition, the cost of clopidogrel complicates the decision to combine it with aspirin. Adding clopidogrel to aspirin is "financially unattractive" if done in all patients with coronary disease (3) but may be cost-effective in high-risk patients, for whom clopidogrel offers more substantial absolute risk reduction. To assess the cost-effectiveness of clopidogrel plus aspirin relative to aspirin alone in high-risk patients with coronary artery disease and to explore the optimal duration of therapy, we constructed a decision analytic Markov model comparing these treatment strategies after an acute coronary syndrome as defined in CURE.

METHODS

We performed a cost-effectiveness analysis using a Markov model (4) (DATA 4.0, TreeAge Software, Inc., Williamstown, Massachusetts). We analyzed a reference case assuming a societal perspective (5) and a lifetime time horizon (6). Our analysis was based on the CURE trial, a randomized comparison of 3 to 12 months of therapy with clopidogrel plus aspirin or aspirin alone to prevent cardiovascular death, myocardial infarction, or stroke in 12 562 patients with an acute coronary syndrome (1). We discounted costs and utilities at 3% annually and determined lifetime costs, quality-adjusted life expectancy, and the incremental cost-effectiveness ratio. Sensitivity analyses included 1-way analyses on all data inputs; probabilistic sensitivity analysis; evaluation of varying duration of combination therapy, including potential loss of efficacy

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Context

In patients with unstable angina, combination therapy with clopidogrel plus aspirin has been shown to be more effective than aspirin alone in preventing myocardial infarction, stroke, or cardiovascular death, but the cost-effectiveness of such therapy has yet to be determined.

Contribution

When the authors used a societal perspective and lifetime time horizon, combination therapy increased quality-adjusted life span at a cost that was within the traditionally accepted limits of cost-effectiveness.

Cautions

Data are not yet available to determine whether combination therapy for longer than 1 year remains cost-effective, due to the uncertainty of the relationship between long-term efficacy and risk for hemorrhage.

–The Editors

over time; and consideration of populations with varying risk.

Target Population

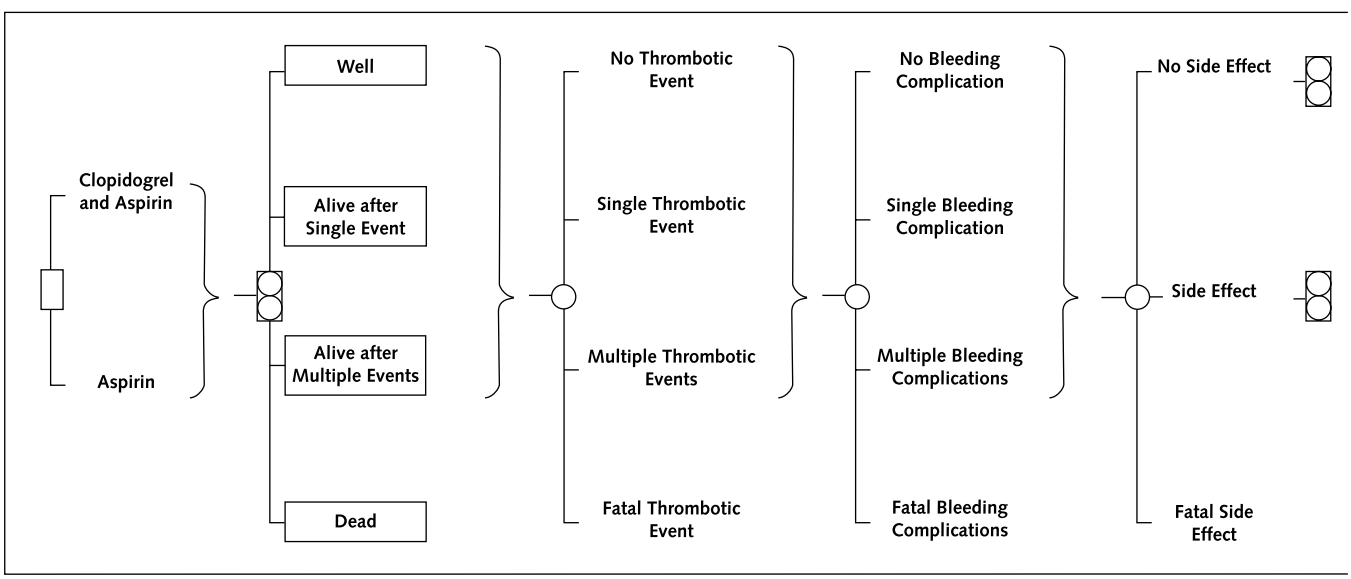
The target population was analogous to that of the CURE trial (1): patients with an acute coronary syndrome characterized by electrocardiographic changes or elevated serum cardiac markers in association with chest pain. Patients who had prolonged ST-segment elevation, who had undergone revascularization in the previous 3 months, who were at risk for severe bleeding or heart failure, or who had been treated with oral anticoagulants or glycoprotein IIb/IIIa inhibitors in the preceding 3 days were excluded. On the basis of the average age of CURE patients, we considered a 64-year-old as our base case and explored other ages in sensitivity analysis. We compared treatment costs and clinical outcomes for 2 types of antiplatelet therapy: 1) aspirin alone, 325 mg/d, and 2) clopidogrel, 75 mg/d, plus aspirin, 325 mg/d, for 1 year, followed by aspirin monotherapy.

Model Structure

In our model, we included vascular events: myocardial infarction, stroke, vascular death and revascularization, intracerebral and gastrointestinal hemorrhagic events, and clopidogrel-associated thrombotic thrombocytopenic purpura. We included age-related mortality, correcting for events explicitly included in the model. We did not directly include procedures or outcomes, such as congestive heart failure, that CURE did not specifically address (1). We indirectly accounted for the cost of such events by using age-adjusted annual health care costs (7). This assumes equal probability of such events in each arm of the analysis. We allowed for multiple events, including multiple events of a particular type, within a given monthly cycle.

We created Markov states for conditions that changed quality of life, annual cost, or probability of future events. For events with temporary decrements in quality of life, we assessed a utility toll proportional to the duration of hospitalization required (8). We also modeled each combination of 2 events. When more than 2 events occurred, we

Figure 1. **Schematic representation of the decision model.**



The rectangular node depicts the treatment decision. Representative Markov states are outlined. The remaining 3 subtrees, 1 each for thrombotic events, hemorrhagic events, and side effect, make up the monthly cycle of the model. Multiple events, including multiple events within a subtree, are possible. At the completion of each cycle, patients return to the Markov state appropriate for both the Markov state in which they began the cycle and the events occurring during the cycle. Not shown is the risk for age-related mortality, present in each cycle.

used the Markov state that combined the 2 events with the lowest utility (**Figure 1**).

Model Inputs

Probabilities

We derived probabilities for vascular and hemorrhagic events over the first year of our analysis from the CURE trial (1). Rates of cardiovascular outcomes were highest in the month immediately following the acute coronary syndrome (1). To account for temporal variation in risk, we calculated probabilities for the first month separately from those for subsequent months. Beyond the time frame of the CURE trial, we empirically calculated declining probability functions for myocardial infarction, cardiovascular death, and revascularization on the basis of proportional decline in risk over time in survivors of non–Q-wave myocardial infarction (9).

We assumed that all bleeding events, other than intracerebral hemorrhage, were gastrointestinal. Because intracerebral hemorrhage was equally likely for the 2 treatment strategies (1), all of the excess bleeding in the clopidogrel plus aspirin arm was attributed to gastrointestinal causes. The rate of thrombotic thrombocytopenic purpura associated with clopidogrel was derived from an observational study (10, 11). We represented uncertainty in event rates through β distributions based on the number of events that occurred and the number of patient-years at risk. We obtained age-specific mortality from life tables (12) and corrected for death rates of events explicitly included in our model (**Table**).

Efficacy of Combination Therapy

Despite the variation in risk, the relative efficacy of clopidogrel plus aspirin did not vary between the first and subsequent months (1). In modeling beyond the time frame of the CURE trial, we assumed in our base case that efficacy remained constant, on the basis of data for clopidogrel monotherapy (13). We explored waning efficacy over time in sensitivity analysis. We used 3 variables to describe loss of efficacy, duration of constant efficacy (1 year to lifetime), duration of efficacy deterioration (1 to 10 years), and the extent of efficacy decline relative to aspirin monotherapy (none to complete loss).

Costs

We derived costs for each event and for chronic care of disabled patients from the literature. For medications, we used the average wholesale price in the United States as our base value (35) and considered prices negotiated by a large-volume purchaser in constructing the price range. Acute care costs for clinical events represent the direct costs of all medical care incurred during hospitalization. Chronic care costs represent direct expenditures for medications, procedures, and nursing care specific to the condition in question and were assessed for each month in the Markov state. For Markov states representing survival after either severe stroke or intracerebral hemorrhage and another event, we assumed 20% of the long-term cost of the additional condition to account for overlapping therapy. We accounted for other health care costs by using age-adjusted annual health expenditures (7). We updated costs to 2002 U.S. dollars with a gross domestic product deflator (44) and generated log-normal distributions for each estimate for use in sensitivity analyses (**Table**).

Utilities

We used published population-based utilities, representing either time-tradeoff or standard-gamble techniques. For Markov states representing 2 events, we combined utilities with multiplication (8). For events and procedures that did not result in durable changes in the health state of the individual, we used disutility tolls based on the average duration of hospitalization (8). We modeled uncertainty in utility estimates by calculating β distributions based on the range of utility estimates in the literature (**Table**).

Sensitivity Analyses

To assess the degree to which variation in any variable altered our results, we performed 1-way sensitivity analyses for each model input by analyzing the results at both extremes of its 95% CI. In evaluating patients of different ages, we adjusted both age-related mortality and estimates of annual health care cost accordingly. To better understand the distribution of the cost-effectiveness ratio for clopidogrel plus aspirin and the potential value of further research, we performed probabilistic sensitivity analysis using Monte Carlo simulation (45, 46). In each of 1000 simulations, the value for each model input was randomly selected from its distribution. We constructed a cost-effectiveness acceptability curve by calculating the average net monetary benefit for each strategy in each simulation over cost-effectiveness thresholds ranging from no additional expenditure for the least expensive therapy to $100 000 for each quality-adjusted life-year (QALY) gained. We then determined the proportion of simulations for which clopidogrel plus aspirin resulted in the greater net monetary benefit at each cost-effectiveness threshold. We also assessed varying the duration of clopidogrel therapy from 1 month to 1 year in monthly increments. We considered prolonged therapy, up to patient lifetime, in yearly increments, simultaneously assessing potential decline in the efficacy of clopidogrel.

To better characterize the role of risk in determining the cost-effectiveness of clopidogrel with aspirin, we conducted a 2-way sensitivity analysis on the annual probability of vascular events and the proportion of events that were cerebrovascular. We based this analysis on steady-state event rates from the CURE trial, excluding those events in the first month, and on the durable efficacy of clopidogrel. To determine the aggregate effect of adding clopidogrel to aspirin after an acute coronary syndrome, we

Table. **Model Inputs***

Definition	Base-Case Value (Range)	Reference
Event probabilities for patients treated with aspirin (first month)		
Fatal myocardial infarction	0.0079 (0.0059 to 0.014)	1
Nonfatal myocardial infarction	0.024 (0.020 to 0.028)	1
Revascularization	0.227 (0.217 to 0.237)	1
Vascular death	0.016 (0.013 to 0.019)	1
Bleeding	0.015 (0.012 to 0.018)	1
Event probabilities for patients treated with aspirin (months 2 to 12)		
Fatal myocardial infarction	0.0011 (0.00081 to 0.0014)	1
Nonfatal myocardial infarction	0.0036 (0.0031 to 0.0041)	1
Revascularization	0.018 (0.017 to 0.019)	1
Vascular death	0.0023 (0.0019 to 0.0027)	1
Bleeding	0.011 (0.009 to 0.014)	1
Event probabilities for all patients treated with aspirin (monthly)		
Fatal stroke	0.00049 (0.00033 to 0.00069)	1
Nonfatal stroke	0.0010 (0.00079 to 0.0013)	1
Fatal intracerebral hemorrhage	0.0001 (0.00089 to 0.0018)	13
Nonfatal intracerebral hemorrhage	0.0001 (0.00094 to 0.0018)	13
Event probabilities for all patients treated with clopidogrel		
Fatal thrombotic thrombocytopenic purpura		
First month on therapy (monthly)	0.000001	10, 11
After first month (annual)	0.000001	10, 11
Nonfatal thrombotic thrombocytopenic purpura		
First month on therapy (monthly)	0.000006	10, 11
After first month (annual)	0.000007	10, 11
Efficacy of clopidogrel with aspirin (relative risk reduction), %		
Thrombosis prevention	20 (10 to 28)	1
Bleeding	−38 (−67 to 0)	1
Revascularization (first month)	9 (0 to 18)	1
Costs, $		
Fatal stroke	16 061 (5000 to 39 000)	14, 15
Severe stroke	16 295 (5000 to 40 000)	14, 16–23
Moderate stroke	11 760 (2500 to 35 000)	14, 16, 19, 21, 24
Mild stroke	5865 (1500 to 16 000)	14, 16, 19, 21–23, 25
Fatal myocardial infarction	19 689 (5000 to 54 000)	14, 16, 26
Nonfatal myocardial infarction	17 452 (5000 to 45 000)	14, 16, 26
Coronary angioplasty	12 485 (5000 to 26 000)	27–29
Coronary artery bypass surgery	28 100 (15 000 to 48 000)	27–30
Fatal intracerebral hemorrhage	21 358 (9000 to 43 000)	15
Nonfatal intracerebral hemorrhage	27 106 (7500 to 71 000)	15, 22, 31
Gastrointestinal bleeding	5731 (1500 to 15 000)	14, 32
Thrombotic thrombocytopenic purpura	35 542 (5000 to 128 000)	33
Vascular death	7500 (1000 to 28 000)	Assumed
Other death	5000 (1000 to 15 000)	Assumed
Annual care after severe stroke	33 687 (10 000 to 84 000)	19, 21, 34
Annual care after moderate stroke	20 214 (5000 to 56 000)	19
Annual care after mild stroke	5615 (0 to 36 000)	19
Annual care for coronary disease	1180 (0 to 7600)	16, 26
Annual care after intracerebral hemorrhage	18 543 (5000 to 49 000)	22, 31, 34
Annual care, age 50 y	2330 (1500 to 3100)	7
Annual care, age 65 y	3040 (2160 to 3920)	7
Annual care, age 80 y	3750 (2760 to 4740)	7
Daily cost of clopidogrel	3.80 (1.80 to 7.10)	35, VA pharmacy
Daily cost of aspirin	0.02 (0.01 to 0.04)	35, VA pharmacy
Utilities		
Severe stroke	0.11 (0 to 0.35)	36–40
Moderate stroke	0.39 (0.25 to 0.55)	36–38, 40
Mild stroke	0.76 (0.55 to 0.95)	36–38, 40, 41
Coronary artery disease	0.87 (0.80 to 0.95)	42
Intracerebral hemorrhage	0.30 (0 to 0.60)	40, 43
Disutility tolls, *QALY*		
Gastrointestinal bleeding	0.005 (0 to 0.01)	Assumed
Thrombotic thrombocytopenic purpura	0.027 (0 to 0.055)	Assumed
Other input		
Discount rate, %	3 (0 to 5)	6

* Probabilities are monthly unless otherwise specified. When disabilities coexisted, we combined utilities by multiplication. Costs are expressed in 2002 U.S. dollars and represent one-time charges for acute events, annual costs of chronic care for the specified condition, and daily costs of clopidogrel and aspirin. QALY = quality-adjusted life-year; VA = Veterans Affairs.

first estimated the number of people in the United States who would meet the inclusion and exclusion criteria on an annual basis (47). We projected the lifetime mean health and economic outcomes for this cohort.

RESULTS

Base-Case Analysis

Patients treated with aspirin lived an average of 9.51 QALYs after their initial event, incurring costs of $127 700. Those treated with clopidogrel plus aspirin lived an average of 9.61 QALYs (that is, an additional 0.10 QALY), with a lifetime cost of $129 300, or $1600 more. The incremental cost-effectiveness ratio for clopidogrel plus aspirin relative to aspirin alone was $15 400 per QALY.

Sensitivity Analyses

One-Way Analyses

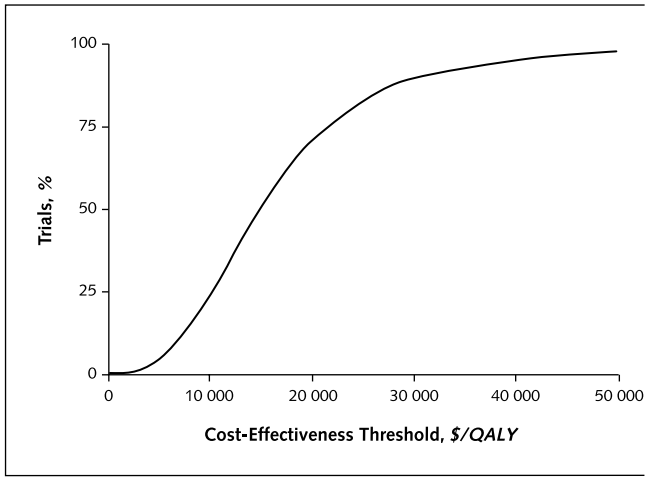
Our evaluation was robust to all one-way analyses. At the lowest efficacy estimate for clopidogrel plus aspirin, a 10% relative risk reduction, the incremental cost-effectiveness ratio was $45 900 per QALY. At a relative risk reduction of 28%, the cost-effectiveness ratio decreased to $9800 per QALY compared with aspirin alone. The cost of clopidogrel was less important. The average discounted lifetime cost for combination therapy increased by $1100 when clopidogrel cost $7.10 per day, resulting in an incremental cost-effectiveness ratio of $26 000 per QALY. At a daily cost of $1.80, this decreased to $8900 per QALY.

Variation in the probability of hemorrhage altered both the effectiveness, in quality-adjusted life expectancy, and the cost-effectiveness of adding clopidogrel to aspirin. The 38% increase in the relative risk for hemorrhage in the base case decreased average life expectancy by 0.032 QALY and decreased costs by $100. When the relative risk for hemorrhage was 67% greater with clopidogrel plus aspirin than with aspirin alone, the addition of clopidogrel to aspirin cost $18 800 for each QALY gained. When the increase in the bleeding risk was only 13%, the cost-effectiveness ratio decreased to $13 400 per QALY compared with aspirin.

Probabilistic Analysis

At a cost-effectiveness threshold of zero, the less expensive therapy was selected regardless of efficacy. Aspirin alone was less expensive in 99.7% of the simulations. As we increased the cost-effectiveness threshold, that is, society's willingness to pay for improved quantity or quality of life, the combination of clopidogrel and aspirin became progressively more attractive. At a cost-effectiveness threshold of $14 600 per QALY, clopidogrel with aspirin was optimal in 50% of simulations. Combination therapy was optimal in 97.2% of simulations at a threshold of $50 000 per QALY (**Figure 2**).

Figure 2. **Results of probabilistic sensitivity analysis.**



Shown are the results of a 1000-simulation Monte Carlo analysis comparing 1 year of therapy with clopidogrel plus aspirin followed by aspirin alone with aspirin monotherapy. The *y*-axis depicts the proportion of trials for which clopidogrel with aspirin resulted in a greater net monetary benefit than aspirin alone. QALY = quality-adjusted life-year.

Duration of Therapy

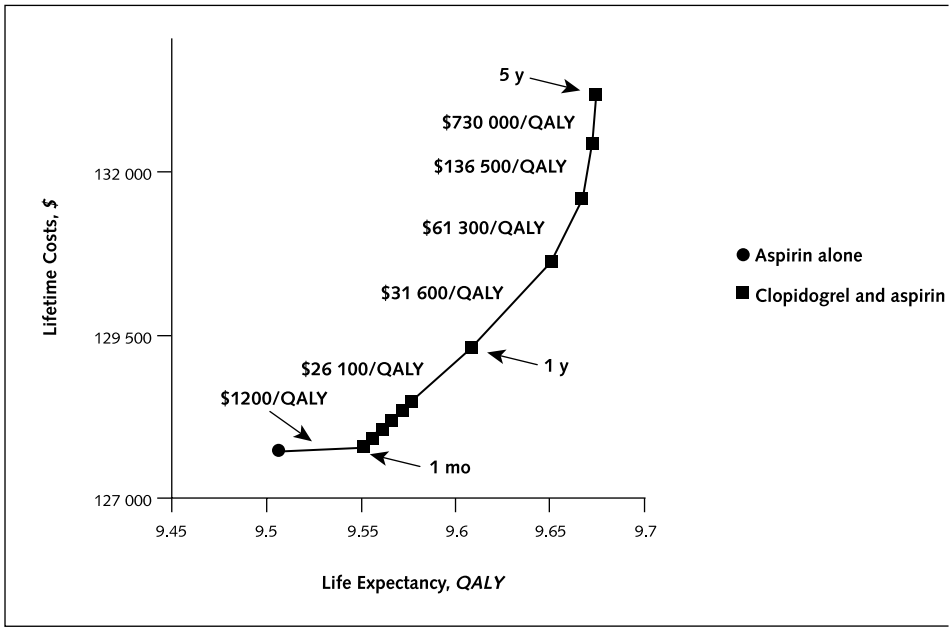
When clopidogrel was used only for the first month after the initial event, patients lived longer (9.55 vs. 9.51 QALYs) and incurred an additional $54 ($1200 per QALY) in lifetime costs compared with patients treated with aspirin alone. Each additional month of therapy added approximately 0.005 QALY in life expectancy, at an incremental cost of $140 ($26 100 per QALY) relative to the next shorter duration of therapy (**Figure 3**).

Treatment beyond 1 year was progressively less cost-effective. Five years of combination therapy yielded the greatest quality-adjusted life expectancy (9.67 QALYs), with the hemorrhagic risk of longer therapy outweighing the benefit. The marginal cost of the second year of therapy ($31 600 per QALY) was similar to that of the first, but the costs of the third, fourth, and fifth years of therapy ($61 300 per QALY, $136 500 per QALY, and $730 000 per QALY, respectively) were less financially attractive. The incremental cost-effectiveness ratio of the third year of therapy relative to the first 2 years was more than $100 000 per QALY in simulations in which the efficacy of clopidogrel decreased by more than 25% before the end of the third year.

Risk of the Population

Variation in the risk of the population, in conjunction with the proportion of events that were cerebrovascular, also determined the cost-effectiveness of adding clopidogrel to aspirin (**Figure 4**). In the base case, the cumulative annual probability of a vascular event was 10.1%. Strokes accounted for 18.2% of events. As the probability of any vascular event decreased, the proportion of stroke-related events required to maintain the same cost-effectiveness ratio increased. For populations with a low risk for vascular

Figure 3. **Sensitivity analysis on duration of therapy.**



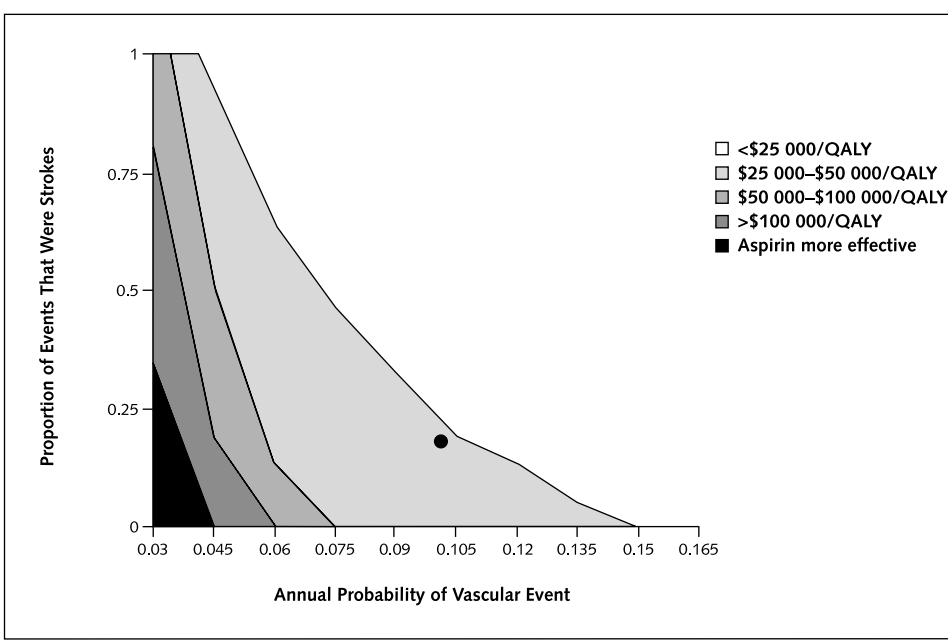
Shown are the results of lifetime treatment with aspirin and the results of varying duration of combination therapy with clopidogrel plus aspirin followed by aspirin alone. Lines depict the incremental cost-effectiveness ratio for the next longer duration. Quality-adjusted life expectancy was greatest with 5 years of combination therapy. QALY = quality-adjusted life-year.

events, particularly if the majority of that risk was attributable to coronary events, treatment with aspirin alone resulted in greater quality-adjusted life expectancy.

Aggregate Results

We estimated that 250 000 people in the United States would meet the inclusion and exclusion criteria of the CURE trial annually. Adding clopidogrel to aspirin therapy for 1 year in this cohort resulted in a societal gain of 25 500 QALYs at a cost of $392 million over the cohort's lifetime. The first month of combination therapy provided 11 000 additional QALYs at a cost of $13.5 million. Each additional month added 1300 QALYs and cost $35 million.

Figure 4. **Two-way sensitivity analysis on annual event rate and the proportion of events attributable to cerebrovascular accidents.**



The black circle indicates the base case. QALY = quality-adjusted life-year.

DISCUSSION

For patients with high-risk acute coronary syndromes, adding clopidogrel to aspirin for 1 month increased life expectancy by 0.04 QALY, more than 2 weeks of perfect health, at excellent value. One year of combination therapy added more than 1 month to quality-adjusted life expectancy and cost $15 400 for each QALY gained relative to aspirin, or $26 100 per QALY relative to 1 month of combination treatment. Our analysis was robust to all sensitivity analyses. In probabilistic sensitivity analysis, fewer than 3% of simulations favored aspirin monotherapy at a cost-effectiveness threshold of $50 000 per QALY, indicating that further trials of combination therapy for this indication and duration would provide little value (46). The incremental benefit and value of 1 year of combined therapy with clopidogrel and aspirin are almost identical to those of therapy with glycoprotein IIb/IIIa inhibitors for a similar population receiving a coronary stent (48) and represent better value than implantation of a cardioverter defibrillator in patients with ventricular arrhythmias (49).

Longer courses of combination treatment after an acute coronary syndrome, particularly beyond 2 years, are less likely to be cost-effective. This finding is critically dependent on 3 variables: the ongoing risk of the treated population, the durable efficacy of clopidogrel added to aspirin, and the bleeding risk conferred by adding clopidogrel. For persons who have an annual risk for a vascular event of less than 4% and a low risk for stroke, aspirin alone is more effective than combined clopidogrel and aspirin (**Figure 3**). For such patients, the benefit of fewer vascular events is outweighed by the increased risk for bleeding. The progressive decrease in risk explains why the cost-effectiveness of combination therapy wanes over time.

Although our analysis of 1 year of therapy was robust to variation in the efficacy estimate of clopidogrel plus aspirin, this was not true for longer treatment. Combination therapy must maintain a threshold of absolute risk reduction to overcome the risk for bleeding and the increased cost of adding clopidogrel to aspirin. Decreasing risk leads to smaller allowances in relative efficacy to maintain this threshold, meaning the precision of the efficacy estimate becomes more important as risk decreases.

Our analysis was less affected by the cost of clopidogrel. Even when clopidogrel was free, patients receiving 1 year of clopidogrel treatment incurred average lifetime costs that were $300 greater than those for patients treated with aspirin alone. These findings were due to the additional cost of medical care over a longer lifetime and to the cost of hemorrhages. Thus, medication cost was responsible for 80% of the incremental cost of combination therapy. Although increasing age commonly decreases the cost-effectiveness of preventive strategies, age was less important in identifying patients for whom the addition of clopidogrel would be effective. This is due to the immediate reduction in thrombotic event rates conferred by clopidogrel.

Our analysis shares the limitations of the CURE trial. Patients who were treated with glycoprotein IIb/IIIa inhibitors within the preceding 3 days or who had undergone revascularization within the preceding 3 months were excluded from CURE (1). In a randomized comparison of 1 year versus 1 month of combined clopidogrel and aspirin therapy in patients who underwent elective percutaneous coronary intervention (many of whom received glycoprotein IIb/IIIa inhibitors), relative and absolute risk reductions for cardiovascular outcomes, as well as risk for bleeding, were similar to those seen in the CURE trial (50). This suggests that combination therapy may be similarly cost-effective in such patients. Our analysis may not apply to patients receiving anticoagulants or those at risk for severe bleeding or heart failure, who were also excluded from CURE (1). We assumed that all excess bleeding events were gastrointestinal and were potentially more costly than procedural hemorrhage. Thus, the true incremental cost-effectiveness ratio for the addition of clopidogrel to aspirin may be lower than in our base case.

Our estimation of decline in the event rate over time is based on data from the Framingham Heart Study (9). Short-term prognosis for survivors of myocardial infarction has substantially improved over time, suggesting that we may have underestimated future events. This would bias our analysis against longer treatment with clopidogrel. It does not change the need for data on long-term therapy.

The applicability of this work to other groups of patients is not certain. Our results cannot be generalized to all patients with coronary disease. We and others have shown that clopidogrel, alone or in combination with aspirin, is less effective than aspirin or is financially unattractive in other groups with coronary disease (3, 51). Our current analysis not only confirms this but also suggests that the increased risk for hemorrhage relative to decreased thrombotic risk explains this finding. Our 2-way analysis of population risk and the proportion of events attributable to strokes suggests that the addition of clopidogrel to aspirin may be equally cost-effective in other high-risk populations, particularly patients with previous stroke. This extrapolation assumes that clopidogrel plus aspirin is equally effective in other populations, an assumption not supported in a trial of clopidogrel monotherapy (13). Furthermore, at least 2 strategies, clopidogrel monotherapy and aspirin plus dipyridamole, are more effective than, and cost-effective in comparison with, aspirin in patients with previous stroke (51, 52). This must be confirmed by current trials in patients with cerebrovascular disease (53) and must be compared with all available treatment strategies.

Because the decision about optimal therapy for acute coronary syndromes will involve many patients each year, the aggregate impact of the addition of clopidogrel may also be relevant. Assuming that our analysis applies to 250 000 patients per year in the United States, adding

clopidogrel to aspirin for 1 year increases lifetime costs by $392 million. The first month of therapy provides 43% of the potential gain (11 000 QALYs) but only 3.4% of the incremental costs ($13.5 million). Although prolonged therapy represents good value according to traditional limits of cost-effectiveness, the value of other potential medical or nonmedical uses of the $35 million required for each month of therapy must also be considered.

In patients with high-risk unstable angina or non–Q-wave myocardial infarction, the addition of 1 year of clopidogrel therapy to aspirin therapy increases quality-adjusted life expectancy by 4 weeks at a cost that is comparable to other accepted therapies. The balance between reduced risk for vascular events and increased risk for hemorrhage is critical in determining the relative efficacy, and ultimately the cost-effectiveness, of this strategy compared with aspirin therapy alone. Further assessment of the benefits and risks of combination therapy beyond 1 year is warranted before it can be recommended.

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