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Cost-Effectiveness of Clopidogrel plus Aspirin versus Aspirin Alone for Secondary Prevention of Cardiovascular Events: Results from the CHARISMA Trial

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ABSTRACT

Objective: To determine the incremental cost-effectiveness of clopidogrel plus aspirin (C + A) compared with aspirin (A) alone during the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial from a US payer perspective.
Background: Although the CHARISMA trial did not find a benefit of adding clopidogrel to aspirin in its overall study cohort, a benefit was suggested in a prespecified subgroup of patients with established cardiovascular (CV) disease. The cost-effectiveness of dual antiplatelet therapy in this population is unknown.
Methods: Medical resource utilization was assessed prospectively, and costs for hospitalizations, physician services, outpatient care, and medications were assigned using 2007 US dollars. Life expectancy was estimated contingent on fatal and nonfatal CV events using statistical models of long-term survival from the Saskatchewan Health database.
Results: C + A was associated with a 12.5% relative reduction in CV death, myocardial infarction, or stroke compared with A alone (6.9% vs. 7.9%, $P = 0.048$) over a median 28 months of follow-up. Severe or moderate bleeding events were higher in patients receiving C + A versus A alone (3.6% vs. 2.5%, $P < 0.001$). Mean cost/patient was $2607 higher for C + A, while projected life expectancy increased by an average of 0.072 years due to fewer in-trial events. The resulting incremental cost-effectiveness ratio (ICER) for C + A was $36,343/year of life gained. Findings were insensitive to discount rate, life expectancy projections, post-event costs, and indirect costs from lost productivity; the ICER was most sensitive to the cost of clopidogrel. Bootstrap analysis demonstrated that the ICER for C + A remained <$50,000/life-year gained in 70.6% of bootstrap replicates and <$100,000/life-year gained in 87.4%.
Conclusions: Among patients with established CV disease, adding clopidogrel to aspirin appears to increase life expectancy modestly at a cost generally considered acceptable within the US health-care system.
Keywords: aspirin, cardiovascular disease, clopidogrel, cost-effectiveness analysis, secondary prevention.

Introduction

Although previous studies have established the benefits of dual antiplatelet therapy for short- and intermediate-term administration in the setting of acute coronary syndrome (ACS) and after percutaneous coronary intervention (PCI) [1–3], the value of treating a population with chronic cardiovascular (CV) disease at high risk for new or recurrent events is less certain. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial examined this issue by evaluating the efficacy of clopidogrel plus low-dose aspirin compared with aspirin alone in a cohort of patients with established CV disease or multiple risk factors for CV events. Although the trial failed to demonstrate a benefit of clopidogrel for the primary composite end point of CV death, myocardial infarction (MI), or stroke in the overall population, a benefit was found in the prespecified subgroup of patients with established CV disease [4]. A recent subgroup analysis of CHARISMA limited to subjects with prior MI, ischemic stroke, or symptomatic peripheral arterial disease (PAD) also demonstrated a significant reduction in the primary trial end point [5]. Given these findings, dual antiplatelet therapy is often considered in patients with a high risk of atherothrombotic events—particularly those with extensive CV disease [6].

Whether dual antiplatelet therapy should be prescribed routinely to such high-risk patient cohorts requires a complete understanding of the long-term consequences of such therapy. In particular, for an individual patient, this decision must consider the trade-off between the potential benefits of preventing ischemic events weighed against the risk of bleeding complications. From a population perspective, the decision is further complicated by the fact that clopidogrel is a costly drug, particularly when given over an extended period.

During the design of CHARISMA, it was recognized that economic considerations would play an important role in determining the appropriate role of dual antiplatelet therapy for long-term prevention of atherothrombotic events and a prospective economic evaluation was therefore developed alongside the CHARISMA trial. Although the economic study was originally designed to incorporate the full trial population, given the trial's results (in particular, the finding of overt harm among the primary prevention subgroup), we felt that from both a clinical and policy perspective, the most informative analysis would be confined to the subgroup of 12,153 patients with established CV disease at the time of enrollment. The goal of the present study were thus to assess the cost-effectiveness of adding clopidogrel to

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aspirin for subjects with established CV disease based on empirical data from the CHARISMA trial.

Methods

Design and Principal Findings of the CHARISMA Trial

The design and findings of the CHARISMA trial have been reported previously [4,7]. Briefly, CHARISMA was a multicenter randomized controlled trial that examined whether clopidogrel plus low-dose aspirin would reduce CV events compared with low-dose aspirin alone among patients with either established coronary, cerebrovascular, or PAD or with multiple risk factors for CV events. Overall, 15,603 patients were recruited from 32 countries and 768 sites between October 1, 2002 and November 14, 2003 and were randomized to receive 75 mg of clopidogrel daily or placebo over a median follow-up period of 28 months. All patients received 75 to 162 mg of aspirin daily. Patients were excluded from CHARISMA if they were considered to require clopidogrel at the time of enrollment (e.g., due to recent PCI). Nevertheless, if enrolled patients underwent coronary stenting after randomization, they received open-label clopidogrel and subsequent costs were captured. The CHARISMA trial demonstrated a statistically significant benefit in the prespecified subgroup of patients with established CV disease, with a 12.5% relative reduction in the primary composite end point of CV death, MI, or stroke compared with aspirin alone (6.9% vs. 7.9%, $P = 0.048$) [4]. Subjects randomized to clopidogrel were also more likely to experience moderate-to-severe bleeding (3.6% vs. 2.5%, $P < 0.001$).

Economic Analysis

The goal of the economic analysis was to evaluate the incremental cost and cost-effectiveness of clopidogrel and aspirin versus aspirin alone in patients with established CV disease. The perspective of the economic analysis was that of the US health-care system (payer perspective). Although the analysis considered a lifetime horizon for each patient, the actual duration of treatment was assumed to mirror that provided in CHARISMA (a median of 28 months) because the precise effect of long-term therapy in this population is unknown.

Cost Estimation

The general approach to estimating costs was to multiply counts of resource utilization (hospitalizations, physician costs, procedures, post-acute care, medications) by price weights derived from comparable populations of US patients. The most recent national cost data available at the time of analysis were used and inflated to 2007 US dollars using the medical component of the Consumer Price Index. All unit costs were defined prospectively and applied in a blinded fashion to all patients.

Life Expectancy Estimation

As noted previously, the median duration of follow-up observed for an individual patient enrolled in CHARISMA was 28 months. Because the in-trial follow-up duration was relatively brief compared with overall life expectancy for the CHARISMA population, our analysis required the calculation of life expectancy estimates for the study population to determine the years of life lost due to both fatal and nonfatal events during the trial. These estimates were derived from an analysis of the Saskatchewan Health Database—a publicly available, comprehensive, longitudinal health-care utilization database containing the entire population of the Canadian province of Saskatchewan [8,9].

We identified a reference population with similar baseline characteristics to CHARISMA subgroup with established CV disease: a cohort of 53,983 men and women aged ≥45 years with hospital or clinic visit between 1990 and 1995 with diagnosis codes indicating coronary artery disease (angina, MI, PCI, or coronary artery bypass graft surgery), cerebrovascular disease (ischemic stroke or transient ischemic attack [10]), or PAD. Follow-up survival data for this cohort were available through 2002. Parametric regression models were developed to estimate piecewise hazard functions of death over time for patients who experienced nonfatal MI or stroke (or their combination), adjusting for age, sex, key CV risk factors, and prior events/procedures; and life expectancy for each study participant who survived to the end of the study was predicted contingent on occurrence of in-trial CV events [11]. Life expectancy projections were conditional on the occurrence of combinations of MI and stroke severity that were components of the primary composite end point of the study. These projections accounted for the number of days of survival already observed within the trial for each subject by incorporating a mean delay derived from the average time from the last qualifying event in the CHARISMA trial to the end of the follow-up for patients alive at the end of the study.

Analyses from the Saskatchewan database have demonstrated that such regression-based life expectancy predictions are comparable to and validated against results observed in other epidemiologic studies of coronary artery disease [12]. Analogous approaches have been used as a source for life expectancy projections for several previous trial-based economic analyses as well [13–16]. Because we assumed that clopidogrel treatment would be discontinued at the end of the trial, our base-case analysis assumed no further differences between the two groups in the rate of subsequent CV events beyond the end of the trial.

Statistical Analysis

Categorical data are reported as frequencies, and continuous data are reported as mean ± standard deviation. Categorical variables were compared using the Fisher's exact test, and continuous variables were compared using the two-sample *t* test for means. All statistical calculations were performed using SAS version 9 (SAS Institute, Cary, NC).

Cost-Effectiveness Analysis

The incremental cost-effectiveness ratio (ICER) of clopidogrel + aspirin versus aspirin alone was calculated by dividing the net cost associated with clopidogrel treatment by the difference in lost life expectancy between the two treatment groups, where lost life expectancy represents the difference between an individual's life expectancy based on the observed in-trial outcomes and his or her life expectancy in the absence of primary outcome events. For a patient who died during the study, lost life expectancy was the difference between predicted life expectancy at the beginning of the study and observed survival duration. For a patient who experienced no adverse events during the trial, lost life expectancy was zero. We used lost life expectancy (rather than differences in life expectancy) as the basis for our cost-effectiveness analysis to minimize the chance that minor imbalances in the baseline distribution of patient characteristics between treatment groups would produce spurious results.

We used bootstrap resampling (1000 replicates) to calculate bias-corrected 95% confidence intervals for all costs and cost differences. The probability that clopidogrel treatment would be

Table 1 Baseline clinical characteristics and outcomes

	Clopidogrel + Aspirin (N = 6062)	Aspirin alone (N = 6091)	*P*-value
Age (years, standard deviation)	64.0 ± 9.6	64.1 ± 9.6	0.494
Female (%)	27.4	27.0	0.639
Diabetes (%)	31.1	31.0	0.875
Hypertension	69.0	70.3	0.124
Current smoker (%)	19.7	20.1	0.570
Prior myocardial infarction (%)	40.7	41.9	0.191
Prior stroke (%)	30.2	29.3	0.331
History of peripheral arterial disease (%)	26.3	26.4	0.902
Hypercholesterolemia (%)	71.3	71.7	0.574
Prior percutaneous coronary intervention (%)	26.5	27.0	0.525
Prior coronary artery bypass surgery (%)	22.3	22.7	0.664
Prior carotid endarterectomy (%)	5.6	5.2	0.355
Prior peripheral revascularization (%)	14.1	13.6	0.431
Primary efficacy end point (cardiovascular death, MI, or stroke) (%)	6.9	7.9	0.048
Death from any cause (%)	4.6	5.0	0.27
Cardiovascular death (%)	2.8	3.1	0.34
MI—fatal and nonfatal (%)	2.4	2.7	0.28
Stroke—fatal and nonfatal (%)	2.8	3.3	0.09
Ischemic stroke (%)	2.4	2.8	0.14
Intracranial hemorrhage (%)	0.3	0.3	0.87
Severe or moderate bleeding (%)	3.6	2.5	<0.001

CV, cardiovascular; MI, myocardial infarction.

economically attractive over a range of willingness-to-pay thresholds was displayed in the form of a cost-effectiveness acceptability curve [17]. Consistent with current guidelines, both costs and life expectancy in the base-case were discounted 3% annually. Sensitivity analyses were performed, varying each of the key analytic assumptions, including the cost of clopidogrel, discount rate, post-acute care costs, and estimates of lost life-years (LYs).

Indirect Cost Analysis

Although indirect costs were excluded from the primary economic analysis, we conducted secondary analyses examining the impact of indirect costs due to lost productivity on the cost-effectiveness. Estimates of indirect costs and the proportion of patients working were obtained from a 1-year follow-up data from the Reduction of Atherothrombosis for Continued Health Registry [6], pertaining to a cohort of patients similar to those with established CV disease in CHARISMA. We estimated the proportion of working individuals within risk groups defined according to patient history and the associated average number of missed days of work associated with specific CV events (MI, stroke, and combinations of MI and stroke). The costs associated with lost productivity were then estimated by multiplying the proportion of CHARISMA-eligible patients who were employed (by age and sex) by the median daily wage for the United States in 2004 [18] inflated to 2007 dollars ($139), and multiplied by the mean number of missed work days associated with the specific event. A similar approach was used for days of work lost due to a fatal event, except that a "friction cost" approach [19] was used which capped duration of lost work at 96 days, beyond which we assumed that a replacement for the deceased worker would be found.

Role of the Sponsor

The CHARISMA trial and the associated economic evaluation were funded by grants from Sanofi-Aventis (Paris, France) and Bristol-Myers Squibb (New York, NY). Although the analysis plan was developed prospectively in conjunction with the CHARISMA investigators and sponsors, the authors had free access to the complete study data and performed all of the analyses independently.

Results

Clinical Outcomes

Of the 12,153 subjects with established CV disease enrolled in CHARISMA, 6062 were randomized to clopidogrel + aspirin, and 6091 were randomized to aspirin alone. There were no significant differences in the baseline clinical characteristics between the two groups (Table 1). Among the subgroup with established CV disease, clopidogrel + aspirin was associated with a reduction in the incidence of the primary composite end point of CV death, MI, or stroke compared with aspirin alone (6.9% vs. 7.9%, $P = 0.048$) [4]. Dual antiplatelet therapy was associated with trends toward lower risk for CV death, MI, and stroke when examined individually—although none of these differences reached statistical significance (Table 1). Severe or moderate bleeding events were higher in patients receiving clopidogrel + aspirin compared with aspirin alone (3.6% vs. 2.5%, $P < 0.001$).

Medical Resource Utilization and Costs

Overall, there were no significant differences in the incidence of hospitalization during the 28-month follow-up period of patients randomized to clopidogrel + aspirin compared with aspirin alone (Table 2). Although the hospitalization rate for stroke or intracranial hemorrhage was significantly lower with clopidogrel (2.5 vs. 3.4 per 100 patients, $P = 0.01$), this was counterbalanced by an increase in the rate of hospitalization for bleeding (2.7 vs. 1.5 per 100 patients, $P < 0.001$). The rates of hospitalization for MI or other CV reasons were not significantly different between the two treatment groups. No significant differences in the rates of coronary, cerebrovascular, or peripheral arterial revascularization procedures were noted between the clopidogrel + aspirin and aspirin alone groups.

Overall, medical care costs were $2607/patient higher for the clopidogrel + aspirin group compared with the aspirin alone

Table 2 Medical resource utilization and costs in the CHARISMA trial

	Clopidogrel + Aspirin	Aspirin alone	Absolute difference (95% CI)	*P*-value
Hospitalizations (N per 100 patients)				
Total admissions	36.37	37.60	−1.22 (−4.21, 1.76)	0.42
MI admissions	2.54	2.89	−0.35 (−1.04, 0.34)	0.32
Stroke/ICH admissions	2.51	3.41	−0.91 (−1.58, −0.23)	0.01
Severe or moderate bleeding	2.74	1.46	1.28 (0.69, 1.86)	<0.001
Other cardiovascular-related admissions*	28.59	29.83	−1.24 (−3.88, 1.39)	0.36
Total length of stay (days)	3.57	3.49	0.08 (−0.43, 0.58)	0.76
Cardiovascular resource use (N per 100 patients)				
Coronary angiography	7.16	7.09	0.07 (−0.94, 1.07)	0.90
Balloon angioplasty	2.87	3.02	−0.15 (−0.81, 0.51)	0.65
PCI	4.32	4.76	−0.44 (−1.25, 0.38)	0.29
CABG	1.63	1.66	−0.03 (−0.48, 0.43)	0.91
Carotid endarterectomy	0.82	0.85	−0.03 (−0.36, 0.31)	0.87
Peripheral artery bypass	7.16	7.09	0.07 (−0.94, 1.07)	0.90
Mean cost per patient†				
Hospitalizations	$4,109	$4,266	−$157 (−534, 212)	0.42
Inpatient physician costs	$1,329	$1,363	−$35 (−149, 76)	0.56
Clopidogrel	$3,062	$169	$2,894 (2,861, 2,927)	<0.001
Other medications	$4,822	$4,837	−$16 (−117, 82)	0.77
Outpatient care	$421	$501	−$80 (−173, 11)	0.08
Total	$13,743	$11,136	$2,607 (2,068, 3,146)	<0.001

*Includes unstable angina, transient ischemic attack or coronary revascularization.
†Reported costs are discounted by 3%. Confidence intervals for costs estimated from bootstrap analysis of 1,000 replicates. The confidence interval suggests that the parameter of interest is within the stated range in 95% of replicates. Confidence intervals that exclude zero suggest less than a 5% statistical significance due to chance alone.
CABG, coronary artery bypass graft surgery; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; ICH, intracranial hemorrhage; MI, myocardial infarction; PCI, percutaneous coronary intervention.

group ($13,743 vs. $11,136, $P < 0.001$; Table 3). Higher medication costs over the study period explained virtually all of this difference, with additional costs of $2894/patient for clopidogrel + aspirin treatment compared with aspirin alone ($3062 vs. $169, $P < 0.001$). Other costs including hospitalizations, physician services, and outpatient/chronic care tended to be less among the clopidogrel group, but these differences were not statistically significant.

Life Expectancy

Table 4 presents age and sex-specific life expectancy and lost life expectancy values projected for prototypical CHARISMA participants based on the Saskatchewan Health Database. For example, for a 65-year-old man alive at the end of the trial, the observed lost life expectancy due to a nonfatal MI was 4.7 years and ranged from 6.2 to 8.7 years for a nonfatal stroke depending on severity. As expected, younger patients had greater life expectancy losses associated with in-trial events because of their longer life spans compared with older patients. Women had greater lost life expectancies than men for comparable event patterns.

Table 3 Projected life expectancy and lost life expectancy associated with nonfatal in-trial events based on Saskatchewan data

	Life expectancy without in-trial events (years)	Unadjusted lost life expectancy associated with specific in-trial events (years)*		
		MI	Stroke (mild)	Stroke (moderate-severe)
Sex/Age				
Male, age 55	15.04	5.74	8.72	11.79
Male, age 65	11.63	4.69	6.23	8.71
Male, age 75	8.28	3.31	4.03	5.9
Female, age 55	16.49	6.97	9.95	13.34
Female, age 65	13.17	5.93	7.53	10.34
Female, age 75	9.77	4.47	5.27	7.46

*Lost life expectancy represents the difference between an individual's life expectancy without events and his/her life expectancy conditional on experiencing an event of interest during the trial period.
MI, myocardial infarction.

Cost-effectiveness analysis: base-case. Under our baseline assumptions, treatment with clopidogrel + aspirin over a median of 28 months was projected to increase life expectancy by 0.072 years/patient compared with aspirin alone while increasing medical care costs by $2607/patient. The resulting ICER for clopidogrel was $36,343 per LY gained (Table 5). The clopidogrel strategy was more costly in 100% of trial replicates and economically dominated (i.e., more costly and less effective) in 5.4%. Under our base-case assumptions, the ICER for the addition of clopidogrel to aspirin was <$50,000 per LY gained in 70.6% of simulations and <$100,000 per LY gained in 87.4% (Fig. 1).

Subgroup Analyses

In general, there was little variation in the incremental cost of clopidogrel therapy across the subgroups examined. Female patients had higher incremental costs associated with a dual antiplatelet strategy ($3284) compared with men ($2360) leading to a higher ICER ($54,817 vs. $31,024/LY gained). Projected gains in life expectancy among patient subgroups ranged from a low of 0.040 years among patients aged ≥65 years to a high of 0.133 years among patients with symptomatic PAD (Table 4). As a result, the ICER for clopidogrel treatment was <$25,000/LY gained among patients with previous CV events or PAD, and substantially higher among patients without these conditions. The cost-effectiveness of clopidogrel was also less favorable among patients aged ≥65 years and diabetic patients, primarily because of smaller predicted gains in life expectancy compared with younger and nondiabetic patients.

Sensitivity Analyses

Clopidogrel remained economically attractive over a broad range of assumptions regarding post-event costs, the prognostic impact of nonfatal events, and discount rates (Table 6). Because the majority of the cost difference between the two treatment arms

Table 4 Cost-effectiveness among selected patient subgroups

	Clopidogrel + Aspirin (N)	Aspirin alone (N)	Cost difference	Additional life-years with clopidogrel	Incremental C/E ratio ($/life-years gained)
Overall population	6,062	6,091	$2,607	0.072	$36,343
Age <65	3,188	3,173	2,777	0.099	$28,144
Age ≥65	2,874	2,918	2,430	0.040	$61,213
Male	4,400	4,445	$2,360	0.076	$31,024
Female	1,662	1,646	$3,284	0.060	$54,817
Caucasian	5,533	5,567	$2,692	0.075	$36,139
Non-Caucasian	529	524	$1,721	0.043	$39,745
Diabetes mellitus	1,886	1,887	$2,428	0.057	$42,303
Without diabetes	4,176	4,204	$2,681	0.079	$34,024
Prior MI*	2,470	2,553	$2,662	0.130	$20,413
Prior stroke*	1,828	1,787	$2,558	0.121	$21,163
Documented PAD*	1,594	1,608	$1,450	0.133	$10,910
No prior MI, stroke, or PAD†	959	946	$3,570	0.079	$45,088

*Patients may have had more than one type of prior event.
†Includes patients with angina, percutaneous coronary intervention, coronary artery bypass grafting, or transient ischemic attack.
C/E, cost-effectiveness; MI, myocardial infarction; PAD, peripheral arterial disease.

was due to the cost of clopidogrel itself, the cost-effectiveness of clopidogrel was particularly sensitive to its acquisition cost: a 50% decrease in the daily cost of clopidogrel resulted in an ICER of $16,176/LY, whereas a 50% increase in cost resulted in an ICER of $56,520/LY.

Secondary Analyses

Indirect costs associated with lost work productivity were estimated to be $96 and $110 for the clopidogrel + aspirin and aspirin alone groups, respectively. When these costs were included in the analysis, the ICER for clopidogrel was $36,148/LY gained. When we repeated our analysis using the entire CHARISMA population (including patients with multiple risk factors but no known CV disease at enrollment), the cost-effectiveness ratio increased to $84,657/LY gained (incremental cost = $2607; incremental life expectancy = 0.031 years).

Discussion

Although several studies have examined the cost-effectiveness of clopidogrel for short-term administration after ACS or PCI [15,20,21], this is the first prospectively designed economic evaluation of the addition of clopidogrel to contemporary medical therapy (including aspirin) for secondary prevention among patients with established CV disease. Based on the CHARISMA results, treatment with clopidogrel over a median of 28 months was associated with an absolute 1% lower risk of CV death, MI, or stroke at a net cost of $2607/patient. When extended over a lifetime horizon, these clinical benefits were projected to increase average life expectancy by 0.072 years with a resulting ICER of $36,343/LY gained—a value generally considered acceptable within the US health-care system. [22] Our results were sensitive to the cost of clopidogrel but relatively insensitive to most other analytic parameters including the discount rate, the cost of inpatient and outpatient care, the cost of bleeding events, and the prognostic impact of nonfatal events.

Although the overall CHARISMA trial enrolled patients with both established CV disease and high-risk patients with multiple risk factors, we restricted our economic analysis to the large subgroup (>80% of the overall study population) with established CV disease at enrollment—a population found to benefit from adjunctive clopidogrel [4]. There are several reasons for this approach. First, this subgroup was prespecified in the analytic plan, prospectively identified at the time of enrollment, and differed both qualitatively and quantitatively in its response to

Table 5 Sensitivity analyses

	Additional cost with clopidogrel	Additional life-years with clopidogrel	Incremental C/E ratio ($/life-years gained)
0% annual discount rate	$2,661	0.106	$25,139
5% annual discount rate	$2,572	0.057	$44,891
Lost life-years due to in-trial cardiovascular deaths only*	$2,607	0.051	$51,033
Lost life-years due to nonfatal events 50% above Saskatchewan estimates	$2,607	0.082	$31,771
Lost life-years due to nonfatal events 50% below Saskatchewan estimates	$2,607	0.061	$42,453
Clopidogrel costs 50% below average wholesale price	$1,160	0.072	$16,176
Clopidogrel costs 50% above average wholesale price	$4,054	0.072	$56,520
Cost of bleeding events 50% below base-case	$2,549	0.072	$35,546
Cost of bleeding events 50% above base-case	$2,661	0.072	$37,099
Hospitalization costs 50% below base-case	$2,703	0.072	$37,680
Hospitalization costs 50% above base-case	$2,511	0.072	$35,006
Post-acute care costs 50% below base-case	$2,646	0.072	$36,899
Post-acute care costs 50% above base-case	$2,567	0.072	$35,788
Including indirect costs from lost work productivity	$2,593	0.072	$36,148
Including indirect costs from lost work productivity 50% below base-case	$2,600	0.072	$36,246
Including indirect costs from lost work productivity 50% above base-case	$2,586	0.072	$36,051

*Calculated for both clopidogrel + aspirin and aspirin alone patients.
C/E, cost-effectiveness.

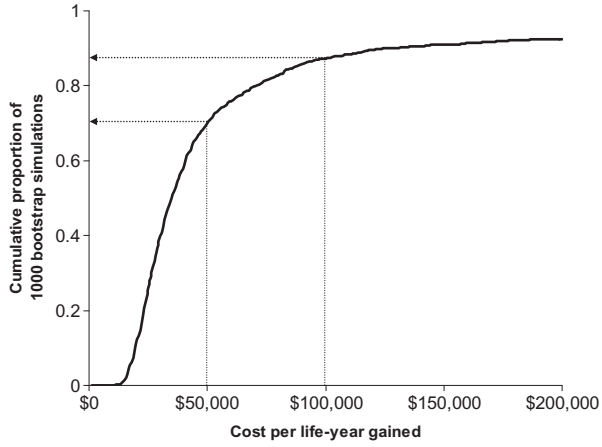

Figure 1 Cumulative distribution plot of the incremental cost-effectiveness ratio for clopidogrel + aspirin versus aspirin alone based on bootstrap analysis of primary Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance results. As indicated by the dashed lines, 70.6% of bootstrapped cost-effectiveness ratios were <$50,000 per life-year gained and 87.4% were <$100,000 per life-year gained.

therapy compared with the "multiple risk factor" (i.e., primary prevention) subgroup [4]. Moreover, the benefits of clopidogrel in this subgroup are consistent with previous studies demonstrating the incremental benefit of clopidogrel to aspirin in both acute and chronic treatment among patients with established CV disease including the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events, [23] Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) [1], and Clopidogrel for the Reduction of Events During Observation [3] trials. Finally, because CHARISMA demonstrated excess mortality among patients without documented CV disease, it is unlikely that such patients would be prescribed clopidogrel for primary prevention, making the issue of cost-effectiveness effectively moot in this population.

The clinical decision to initiate dual antiplatelet therapy requires an individualized assessment of potential benefit versus potential risk. Based on the results of CHARISMA, one can project that treatment of 1000 patients with established CV disease for 28 months would result in 10 fewer deaths, MIs, or strokes although producing 11 additional moderate-to-severe bleeding events. These values correspond to numbers needed to treat (NNT) of 100 and a number needed to harm of 91. Ultimately, the clinician must decide whether the relative importance of these events—in terms of both clinical and economic consequences—warrants the treatment for a given individual. If the potential harm exceeds the benefit for a particular patient, dual antiplatelet therapy would not be advised regardless of the cost-effectiveness. Our analysis—which uses quantitative approaches to valuing both sets of consequences—suggests that despite the additional risk, there may be sufficient value in avoiding serious CV events to justify both the additional risk and cost of clopidogrel for the study population.

Moreover, there may be specific patient subgroups where both the balance of risk and benefit as well as cost-effectiveness strongly favors extended dual antiplatelet therapy. For example, a recent subgroup analysis of CHARISMA limited to subjects with prior MI, ischemic stroke, or PAD demonstrated a 1.5% absolute (17% relative reduction) in the risk of CV death, MI, or stroke; this corresponds with an NNT of 67 to prevent an event [5]. In addition to our main results, our subgroup analyses demonstrate that adding clopidogrel to low-dose aspirin in these high-risk patients (e.g., prior ischemic stroke, prior MI, or PAD) was even more cost-effective than for overall cohort with established CV disease. These findings reflect the fact that in CHARISMA, such patients were at both higher risk of CV events and derived a greater benefit from dual antiplatelet therapy than other trial participants. The fact that the ICER for clopidogrel for these high-risk patient subgroups was <$22,000/LY gained in our analysis (Table 4) suggests that these individuals may be ideal populations for targeted application of dual antiplatelet therapy.

Comparison with Previous Studies

Overall, the cost-effectiveness of clopidogrel in the CHARISMA-established CV disease population appears less favorable than in prior studies of ACS and after PCI. For example, in the CURE trial, the ICER for ~9 months of adding clopidogrel to aspirin was ~$6000/LY in the ACS population and was even lower among patients undergoing early PCI [15,21]. Using a decision analytic model, investigators from Duke University found that the ICER of extending the duration of clopidogrel from 1 to 12 months after PCI was $15,696/LY, compared with aspirin alone [24]. The favorable cost-effectiveness of clopidogrel in ACS and post-PCI settings is likely due to the greater absolute benefit of clopidogrel in these high-risk patient subsets. Combined with the relatively brief administration of clopidogrel examined in these trials, it is not surprising that the cost-effectiveness of adding clopidogrel to aspirin would be more attractive under these conditions than in CHARIMSA.

Our findings also appear to differ somewhat from previous cost-effectiveness models that examined longer-term clopidogrel for secondary prevention. Using a state-transition computer

Table 6 Sensitivity analyses

	Additional cost with clopidogrel	Additional life-years with clopidogrel	Incremental C/E ratio ($/life-years gained)
0% annual discount rate	$2,699	0.106	$25,491
5% annual discount rate	$2,609	0.057	$45,535
Lost life-years for cardiovascular deaths only	$2,644	0.051	$51,758
Lost life-years (for nonfatal events) 50% above Saskatchewan estimates	$2,644	0.082	$32,223
Lost life-years (for nonfatal events) 50% below Saskatchewan estimates	$2,644	0.061	$43,057
Clopidogrel costs 50% below average wholesale price	$1,197	0.072	$16,687
Clopidogrel costs 50% above average wholesale price	$4,091	0.072	$57,042
Post-acute care costs 50% below base-case	$2,678	0.072	$37,344
Post-acute care costs 50% above base-case	$2,609	0.072	$36,376
Including indirect costs from lost work productivity	$2,631	0.072	$36,680

C/E, cost-effectiveness.

simulation model, Gaspoz et al. estimated an ICER of $61,000 to 120,000/QALY for lifetime dual antiplatelet therapy, depending on the baseline assumptions of benefit [25]. Schleinitz and Heidenreich reported an ICER of $15,400/QALY for clopidogrel added to aspirin for the first year after ACS and $31,600/QALY for the second year [26]. In a separate study, Schleinitz et al. found that the use of clopidogrel alone compared with aspirin alone appeared cost-effective after stroke ($31,200/QLY) and PAD ($25,100/QALY) but not after MI [27].

Some of these differences may be explained by different assumptions of benefit; earlier cost-effectiveness studies had to extrapolate the benefits of clopidogrel from relatively short-term ACS trials and apply them to longer-term therapy in a chronic CV disease population [26,28]. Another reason may be that in contrast to previous models [26,27], our study also accounted for long-term survival benefits associated with avoidance of nonfatal MI or stroke in the short term. The strength of our study is that it based the clinical outcomes of long-term clopidogrel obtained from a randomized clinical trial specifically designed to examine the population and treatment of interest, rather than estimated from observational data or studies of short-term administration. Although extrapolation beyond the trial duration was necessary to estimate life expectancy, these projections were also based on empirical observations from a large, relatively contemporary data set (i.e., Saskatchewan) that was both matched to the characteristics of the CHARISMA population and validated against external benchmarks [12]. Finally, it is possible that our findings are entirely consistent with previous models given the wide confidence limits of our results.

Implications for Treatment Duration

Although our study directly assessed the cost-effectiveness of clopidogrel therapy provided for a median of 28 months, it is important to recognize that our analysis assumed no further treatment costs or benefits beyond the time frame of the trial. This approach is commonly used when performing a trial-based economic analysis because the results of continued treatment beyond the trial time frame are unknown [15,29]. Whether our results can be readily extrapolated to more prolonged treatment (with its attendant costs, benefits, and side effects) depends on the extent to which the benefits observed in CHARISMA would be expected to continue with more prolonged therapy. Specifically, if the annual cost of therapy and absolute risk reduction beyond 28 months are similar to those observed in CHARISMA, the ICER for additional years of therapy should be similar as in during the trial. In CHARISMA, both the CV event rate in the aspirin alone group and the relative risk reduction associated with clopidogrel were nearly constant during the first 2 years of follow-up (event rate = 3.9% and 3.7%; relative risk reduction = 15.6% and 17.4%, respectively). The constant benefit associated with clopidogrel therapy over 2 years has also been observed in an observational study of patients who underwent PCI [30]. Although there are limited data on the benefits of clopidogrel after 28 months in patients with stable CV disease, the available data thus suggest that the assumption of a constant absolute risk reduction beyond the follow-up observed in the CHARISMA trial is reasonable.

Study Limitations

As with any randomized clinical trial, our results apply most directly to the trial population itself and should be extrapolated with caution to other populations at lower or higher risk than those enrolled in CHARISMA. In particular, extending our findings to patients at lower or higher risk of CV events than those studied in CHARISMA would require both disease-simulation modeling and additional assumptions. The approach of applying US-derived unit costs to resource utilization across a wide range of countries and health systems does not account for possible differences in treatment practices of other countries, such as different thresholds for hospitalization or use of procedures; 74% of patients in the CHARISMA trial with established CV disease were enrolled in 31 countries outside of the United States. Because there were only minimal cost offsets in the trial, however, there should be little if any bias introduced by this approach. Finally, the use of life expectancy projections derived from historical Saskatchewan data may not be perfectly applicable to current US practice and outcomes. To the extent that survival with coronary heart disease have improved after 1995 [31], however, it is likely that we have underestimated the life expectancy gains associated with clopidogrel and thus overestimated the resulting cost-effectiveness ratios.

Conclusions

For the prespecified subgroup of CHARISMA patients with established CV disease, adding clopidogrel to aspirin for secondary prevention over 28 months of therapy appears to increase life expectancy modestly at a cost commonly considered acceptable within the US health-care system.

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