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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