

Special Article

COST EFFECTIVENESS OF ASPIRIN, CLOPIDOGREL, OR BOTH FOR SECONDARY PREVENTION OF CORONARY HEART DISEASE

JEAN-MICHEL GASPOZ, M.D., PAMELA G. COXSON, PH.D., PAULA A. GOLDMAN, M.P.H.,
LAWRENCE W. WILLIAMS, M.SC., KAREN M. KUNTZ, SC.D., M.G. MYRIAM HUNINK, M.D., PH.D.,
AND LEE GOLDMAN, M.D., M.P.H.

ABSTRACT

Background Both aspirin and clopidogrel reduce the rate of cardiovascular events in patients with coronary heart disease. We estimated the cost effectiveness of the increased use of aspirin, clopidogrel, or both for secondary prevention in patients with coronary heart disease.

Methods We used the Coronary Heart Disease Policy Model, a computer simulation of the U.S. population, to estimate the incremental cost effectiveness (in dollars per quality-adjusted years of life gained) of five strategies in patients over 35 years of age with coronary disease from 2003 to 2027: aspirin for all eligible patients (i.e., those who were not allergic to or intolerant of aspirin), aspirin for all eligible patients plus clopidogrel for patients who were ineligible for aspirin, clopidogrel for all patients, and two options for the combination of aspirin for all eligible patients plus clopidogrel for all patients.

Results The extension of aspirin therapy from the current levels of use to all eligible patients for 25 years would have an estimated cost-effectiveness ratio of about \$11,000 per quality-adjusted year of life gained. The addition of clopidogrel for the 5 percent of patients who are ineligible for aspirin would cost about \$29,000 per quality-adjusted year of life gained. Clopidogrel alone in all patients or in combination with aspirin would have an incremental cost of more than \$100,000 per quality-adjusted year of life gained and would remain financially unattractive except in the highest-risk patients unless, contrary to the actual data, its early benefits in a one-year study were assumed to apply to all coronary and cerebrovascular events during sustained use. In patients who can tolerate aspirin, our best estimate is that clopidogrel would cost less than \$50,000 per quality-adjusted year of life gained if its price were reduced by about 60 percent.

Conclusions Increased prescription of aspirin for secondary prevention of coronary heart disease is attractive from a cost-effectiveness perspective. Because clopidogrel is more costly, its incremental cost effectiveness is currently unattractive, unless its use is restricted to patients who are ineligible for aspirin. (N Engl J Med 2002;346:1800-6.)

Copyright © 2002 Massachusetts Medical Society.

FOR patients with prior myocardial infarction, prior stroke, or other high-risk vascular conditions, antiplatelet therapy reduces the rate of myocardial infarction, stroke, or death from vascular causes by about 30 percent.¹ Despite abundant data and numerous recommendations, the use of aspirin for patients with coronary heart disease has lagged, although its use increased to about 85 percent of patients discharged after acute myocardial infarction by 1999.²⁻¹⁵

Clopidogrel, a thienopyridine derivative, was shown to reduce the relative risk of ischemic stroke, myocardial infarction, or death from vascular causes in patients with prior cardiovascular disease by 8.7 percent as compared with aspirin,¹⁶ and the addition of clopidogrel to aspirin for patients with acute coronary syndromes reduced the risk of death from cardiovascular causes, reinfarction, and stroke by 20 percent as compared with aspirin alone.¹⁷ The purpose of the present study was to perform an incremental cost-effectiveness analysis of the long-term use of aspirin, clopidogrel, or both for secondary prevention in patients with known coronary disease.

METHODS

The Coronary Heart Disease Policy Model¹⁸⁻²³ is a state-transition computer simulation that predicts the incidence of coronary disease and mortality from noncoronary causes among subjects without coronary disease, stratified according to age, sex, smoking status, diastolic blood pressure, serum cholesterol level, and high-density lipoprotein level. Each year, persons without coronary disease may die of noncoronary causes, they may reach 85 years of age as survivors without coronary disease and leave the model, they may remain alive and younger than 85 years of age without coronary disease, or coronary disease may develop. When coronary disease develops in a person, the model classifies the pres-

From the Clinique de Médecine II and the Division of Cardiology, Hôpitaux Universitaires, Geneva (J.-M.G.); the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco (P.G.C., L.G.); the Department of Health Policy and Management, Harvard School of Public Health, Boston (P.A.G., L.W.W., K.M.K., M.G.M.H.); and the Department of Epidemiology and Biostatistics and the Department of Radiology, Erasmus University Medical School, Rotterdam, the Netherlands (M.G.M.H.). Address reprint requests to Dr. Gaspoz at the Clinique de Médecine II, Department of Medicine, Hôpitaux Universitaires, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland, or at jean-michel.gaspoz@hcuge.ch.

entation as cardiac arrest, acute myocardial infarction, or angina, and it includes deaths and health care costs during the first 30 days. Then, the model tracks patients who survive the first month with coronary disease and categorizes them according to whether they are in their first or subsequent year after the initial event and whether their history includes one or more cardiac arrests, myocardial infarctions, or coronary-revascularization procedures. Each year, patients with coronary disease have a defined risk of cardiac arrest, acute myocardial infarction, or coronary revascularization (or any combination of these events). Each event has a specific case fatality rate tailored to the condition in which the person started that year. Each patient is assigned an annual cost on the basis of his or her history and on additional costs related to any new events.

Sources of Data and Calibration of the Model

Data for the initial model were obtained from a review of the literature, the National Vital Statistics reports, the National Hospital Discharge Survey, the National Health Interview Survey, the second and third Health and Nutrition Examination Surveys, the Framingham Heart Study, and a variety of clinical trials and observational studies.^{18,19} The model has been updated with many revised or newly estimated variables.²⁰⁻²³ The model is based on the Framingham Heart Study, which has been shown to predict the benefits found in cholesterol-lowering trials.²⁴ Using the cholesterol changes in the Scandinavian Simvastatin Survival Study,²⁵ our model nearly perfectly reproduces the observed reduction in the rates of coronary events in that trial and provides cost-effectiveness ratios in the same general range as those estimated for that trial²⁶ and for the Cholesterol and Recurrent Events study.²⁷

Health-related quality-of-life weights for coronary disease are based on whether patients have angina, heart failure, or both.²⁴ Noncoronary health-related quality-of-life weights are based on observational data.²⁸

Interventions

Our principal simulations modeled U.S. patients, 35 to 84 years of age, in whom coronary disease developed during or before 2003 to 2027 and who survived their first month with it. Their currently expected (no-intervention) costs and quality-adjusted years of life over this 25-year period were calculated and compared with what would be expected with five strategies based on pooled data from randomized trials for secondary prevention of coronary events in patients with prior coronary disease^{1,16,17,29}: aspirin for all eligible patients, aspirin for all eligible patients plus clopidogrel for patients ineligible for aspirin, clopidogrel alone for all patients, the combination of aspirin for all eligible patients plus clopidogrel for all patients for 25 years, and a scenario that reproduced the actual outcome data reported for one year of combination therapy.¹⁷

For aspirin, the 31 percent reduction in the odds of nonfatal myocardial infarction reported in the pooled trials¹ was applied to myocardial infarction, cardiac arrest, and death from chronic coronary disease (Table 1). The 19 percent reduction in fatal stroke¹ was used to derive a 2.8 percent reduction for the rate of death from noncoronary causes in the model. To model the effects of clopidogrel, additional relative reductions were assumed for the rates of coronary events (8.7 percent) and deaths from noncoronary causes (5.0 percent) on the basis of randomized data that directly compared aspirin with clopidogrel.¹⁶ For the combination of aspirin and clopidogrel, the most favorable assumption was a 20 percent relative reduction in the rates of coronary events as compared with aspirin alone.¹⁷ However, since the randomized trial of combination therapy included only 1 year of follow-up, we also modeled the 25-year effects of 1 year of therapy based on the actual outcome data in the trial.

In our base-line analysis, we assumed aspirin is used in 85 percent of patients with coronary heart disease in 2003 on the basis of data on patients discharged after acute infarctions.¹³ Our simulations assumed that 94.3 percent of patients are eligible for treatment with aspirin,³² and 100 percent are eligible for clopidogrel. Compliance was not modeled because percent reductions in odds in pooled trials were based on intention-to-treat analyses.¹

Drug costs were estimated to be \$0.04 for one 325-mg tablet of enteric-coated aspirin per day and \$3.22 for one 75-mg tablet of clopidogrel.³⁰ The cost of the combination of aspirin and clopidogrel was assumed to be the sum of the two costs.

We assumed the incidence of gastrointestinal adverse effects and rash to be as reported for aspirin and clopidogrel.¹⁶ In 1989, the cost of one major episode of gastrointestinal bleeding and the cost of one minor episode of gastrointestinal bleeding were estimated as \$6,866 and \$733, respectively.³³ The yearly incidence of the other, less serious complications was multiplied by the cost of one office visit at \$44.20, as in a prior analysis.³⁴

In the 14 secondary-prevention trials involving high-risk patients, there was a 24 percent decrease in fatal or disabling strokes ($P < 0.01$) and a 17 percent decrease in nondisabling strokes ($P < 0.09$) for patients receiving aspirin. The incidence of stroke in the population with coronary disease was assumed to be the incidence reported in pooled secondary statin trials,²⁹ with the relative distribution according to age group derived from studies conducted in Rochester, Minnesota, from 1980 to 1984.³¹ The in-hospital mortality from stroke (18 percent), the percentage of hospital survivors who went directly to a nursing home (15 percent), and the percentage of patients transferred to a nursing home after a rehabilitation center (8 percent) were derived from Dobkin,³⁵ whereas the percentage of survivors discharged to a rehabilitation center from acute-care hospitals (6.8 percent) was derived from Oster et al.³⁴ The cost of acute care for stroke (hospital costs plus physicians' fees) was reported to be \$7,026 in 1991.³⁴ From work of the same authors, we derived the costs for one stay in a rehabilitation service (\$40,793), the cost for one year in a nursing home (\$26,620), the yearly costs for outpatient services and home care (\$1,212), and the yearly costs for recurrent strokes (\$624).

Total costs were calculated as the sum of costs of coronary disease, costs of noncoronary disease (an annual estimate based on data from the National Medical Expenditure Survey), and the costs of the specific intervention being studied, and were summed from 2003 to 2027 with the use of a discount rate of 3 percent per year. All costs were converted to year-2000 U.S. dollars with the use of the medical care component of the Consumer Price Index.

Sensitivity Analyses

Lower and upper bounds of the percent reductions in the odds of coronary events with aspirin were based on the Antiplatelet Trialists' reported standard deviation.¹ For clopidogrel as compared with aspirin and the combination of the two, we used the 95 percent confidence intervals of the relative reductions.^{16,17} For combination therapy, we performed sensitivity analyses in which the effects of therapy after the first year were assumed to be similar to the effects during months 9 to 12 of treatment.

Because the median follow-up time in the secondary-prevention trials for high-risk patients was three years,¹ we modeled interventions with benefits limited to three years, whereas drug-related complications and costs continued for 25 years or just 3 years. We examined cost effectiveness in subgroups of differing risk according to age and clinical characteristics, and we assessed the cost effectiveness of the interventions, assuming that they might have as great an effect on reducing coronary revascularization procedures as on reducing other coronary events.

We varied the health care costs of noncoronary disease by up to 100 percent and assessed the effect of excluding them from our analysis. We simulated a higher annual discount rate of 5 percent. The cost effectiveness of clopidogrel as compared with aspirin was assessed for a wide range of drug costs.

RESULTS

As compared with the estimated current utilization of aspirin, extension of aspirin therapy to all eligible patients would result in an additional \$189 million in drug costs and \$7 billion in overall costs from

TABLE 1. SUMMARY OF VARIABLES.

VARIABLE	BASE-LINE ESTIMATE USED IN ANALYSIS	RANGE USED IN SENSITIVITY ANALYSES	SOURCE OF DATA
Reduction in the rate of coronary heart disease events* (%)			
Aspirin	31.0	21–41	Antiplatelet Trialists' Collaboration ¹
Clopidogrel	37.0	0.3–16.5 relative to aspirin	CAPRIE Steering Committee ¹⁶
Combination, optimistic	44.8	10–28 relative to aspirin	CURE Investigators ¹⁷
Combination, actual	47.0†, 36.0‡		CURE Investigators ¹⁷
Reduction in mortality from noncoronary causes (%)			
Aspirin	2.8		Antiplatelet Trialists' Collaboration ¹
Clopidogrel	3.4		Hebert et al. ²⁹
Combination, optimistic	3.4		CAPRIE Steering Committee ¹⁶
Combination, actual	0		CURE Investigators ¹⁷
Reduction in the rate of revascularization (%)		Same as reduction in event rate	Antiplatelet Trialists' Collaboration ¹
Aspirin	0		Hebert et al. ²⁹
Clopidogrel	0		CAPRIE Steering Committee ¹⁶
Combination, optimistic	0		CURE Investigators ¹⁷
Combination, actual	8		
Current rate of use of aspirin (%)	85	42–85	Jencks et al. ¹³
Cost of medication			
Aspirin	\$0.04/tablet		
Clopidogrel	\$3.22/day	\$0–\$3.22/day	Medical Economics Staff ³⁰
Combination, optimistic	\$3.26/day	\$0.04–\$3.26/day	
Combination, actual	\$3.26/day	\$0.04–\$3.26/day	
Annual cost of noncoronary heart disease according to age range			
35–44 yr	\$1,994/yr	\$0–\$4,000/yr	
45–64 yr	\$3,794/yr	\$0–\$7,600/yr	Stinnett et al. ²¹
65–84 yr	\$7,796/yr	\$0–\$16,000/yr	
Mean annual cost of coronary heart disease	\$6,200		Weinstein et al., ¹⁸ Scandinavian Simvastatin Survival Study ²⁵
Discount rate (%)	3	3–5	
Annual incidence of stroke per 100,000 persons	135		Hebert et al., ²⁹ Broderick et al. ³¹

*Coronary heart disease events included myocardial infarction, cardiac arrest, and death from chronic coronary heart disease.

†Myocardial infarction only.

‡Cardiovascular death only.

2003 to 2027 in patients 35 to 84 years of age (Table 2). The benefits, however, would be substantial, with the avoidance of about 156,000 myocardial infarctions and a gain of an additional 682,000 quality-adjusted years of life over the same period. As compared with no aspirin, the use of aspirin in all eligible patients would save an estimated 6.9 million quality-adjusted years between 2003 and 2027.

The use of clopidogrel for the 5.7 percent of patients ineligible for aspirin (Table 2, column 5 minus column 4) would cost almost twice as much as the extension of aspirin from its current 85 percent rate of use to use in all eligible patients (Table 2, column 4 minus column 3) and would yield only about 75 percent of the incremental effectiveness. The strategy of substituting clopidogrel for aspirin in all patients who are eligible for aspirin would generate additional benefits beyond the strategy of using aspirin in patients who are eligible for aspirin and clopidogrel only

in patients who are ineligible for aspirin (Table 2, column 6 minus column 5), preventing about 334,000 myocardial infarctions and saving about 1,450,000 quality-adjusted years of life. However, the estimated incremental cost of this strategy of about \$165 billion would be nearly 24 times the incremental cost of the strategy of extending aspirin therapy from its current 85 percent rate of use to use in all eligible patients (Table 2, column 4 minus column 3) and would yield about twice the incremental effectiveness of the latter strategy.

According to these projections, the estimated cost effectiveness of extending aspirin therapy to all eligible patients is favorable by any measure: with our base-line estimates, the ratio would be about \$11,000 per quality-adjusted year of life saved. The addition of clopidogrel for the estimated 5.7 percent of patients who are ineligible for aspirin is also associated with a reasonable cost-effectiveness ratio of about \$29,000 per

ANTIPLATELET AGENTS FOR SECONDARY PREVENTION OF CORONARY EVENTS

TABLE 2. COSTS, EFFECTIVENESS, AND COST EFFECTIVENESS OF VARIOUS ASPIRIN AND CLOPIDOGREL SECONDARY PREVENTION STRATEGIES FROM 2003 TO 2027 IN PATIENTS 35 TO 84 YEARS OF AGE.*

VARIABLE	ZERO UTILIZATION	CURRENT USE OF ASPIRIN (85%)	ASPIRIN FOR ALL ELIGIBLE PATIENTS†	ASPIRIN FOR ALL ELIGIBLE PATIENTS AND CLOPIDOGREL FOR THE REMAINING 5.7 PERCENT	CLOPIDOGREL FOR ALL PATIENTS‡	COMBINATION OF CLOPIDOGREL FOR ALL PATIENTS PLUS ASPIRIN FOR ELIGIBLE PATIENTS (MOST OPTIMISTIC)§	CLOPIDOGREL FOR ALL PATIENTS IN 1ST YEAR OF CORONARY HEART DISEASE, PLUS ASPIRIN FOR ELIGIBLE PATIENTS¶
Costs (millions of dollars)							
Drugs	0	1,730	1,919	11,505	168,174	172,619	23,063
Health care costs for coronary heart disease and noncoronary heart disease	1,797,000	1,865,000	1,872,000	1,877,000	1,886,000	1,918,000	1,875,000
Total costs	1,797,000	1,867,000	1,874,000	1,888,000	2,054,000	2,090,000	1,898,000
Incremental costs	—	69,000	8,000	15,000	165,000	202,000	9,000
Effectiveness (no.)							
Deaths from coronary heart disease	11,079,000	9,570,000	9,405,000	9,282,000	8,920,000	8,423,000	9,268,000
Deaths from noncoronary heart disease	4,019,000	4,268,000	4,295,000	4,315,000	4,370,000	4,473,000	4,318,000
Myocardial infarctions	16,508,000	15,075,000	14,919,000	14,802,000	14,468,000	14,016,000	14,706,000
Quality-adjusted years of life gained	115,535,000	121,768,000	122,450,000	122,956,000	124,406,000	126,238,000	123,009,000
Incremental quality-adjusted years of life gained	—	6,233,000	682,000	506,000	1,450,000	3,283,000	54,000
Cost effectiveness (dollars)							
Incremental cost per quality-adjusted year of life gained	—	11,000	11,000	29,000	114,000	61,000	177,000

*At the start of the simulation, about 6.8 million people are estimated to have coronary heart disease, and each year about 700,000 to 900,000 new cases are estimated to occur.

†Utilization is assumed to be 94.3 percent; the reduction in the rate of events is 31 percent.

‡Utilization is assumed to be 100 percent; the reduction in the rate of events is 37 percent.

§The combined reduction in the rate of events is 44.8 percent.

¶Reductions in the rate of events as actually reported during one year of therapy¹⁷ (see Table 1).

||Each column is compared with the prior strategy (one column to its left), except for the incremental values for the seventh column (the combination of clopidogrel for all patients plus aspirin for eligible patients) and the eighth column (actual data on combination therapy), which are compared with the values in the fifth column (aspirin for all eligible patients and clopidogrel for the remaining 5.7 percent).

quality-adjusted year of life saved. The routine use of clopidogrel alone in all patients would be associated with cost-effectiveness ratios of over \$100,000 as compared with aspirin alone or with the routine use of aspirin complemented by the use of clopidogrel in patients who are ineligible for aspirin. The combination of clopidogrel for all patients plus aspirin for eligible patients (Table 2, column 7 minus column 5) would yield an incremental cost-effectiveness ratio of \$61,000 per quality-adjusted year of life saved in the unlikely event that the annual 20 percent benefit of the combination of the two drugs would continue for 25 years. If, however, the actual results of the one year of combination therapy reported in the randomized trial¹⁷ are considered (Table 2, column 8 minus column 5), the 25-year cost-effectiveness ratio would be \$177,000 per quality-adjusted year of life gained.

With aspirin therapy, the costs of coronary heart

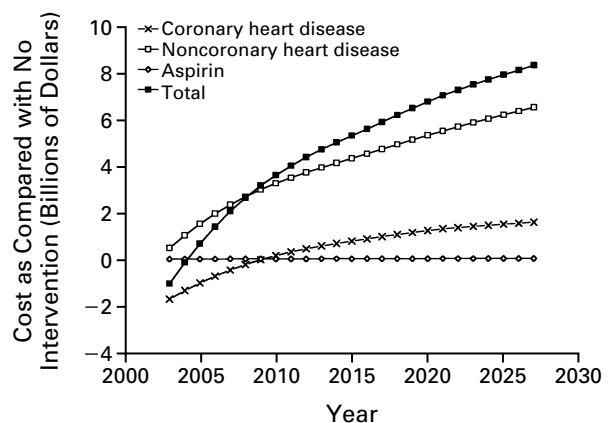


Figure 1. Annual Net Costs of Aspirin, Coronary Heart Disease, and Noncoronary Heart Disease with Routine Aspirin Use for Secondary Prevention in Patients 35 to 84 Years of Age.

TABLE 3. INCREMENTAL COST-EFFECTIVENESS RATIOS IN KEY SENSITIVITY ANALYSES.

SUBJECT OF SENSITIVITY ANALYSIS	BASE-LINE ESTIMATE	ESTIMATES USED FOR SENSITIVITY ANALYSIS	INTERVENTION STRATEGY				
			ASPIRIN FOR ALL ELIGIBLE PATIENTS	ASPIRIN ALONE FOR ALL ELIGIBLE PATIENTS	CLOPIDOGREL FOR ALL PATIENTS VS. ASPIRIN FOR ALL ELIGIBLE PATIENTS AND CLOPIDOGREL FOR THE REMAINING 5.7 PERCENT VS. ASPIRIN FOR ALL ELIGIBLE PATIENTS	CLOPIDOGREL FOR ALL PATIENTS VS. ASPIRIN FOR ALL ELIGIBLE PATIENTS AND CLOPIDOGREL FOR THE REMAINING 5.7 PERCENT (MOST OPTIMISTIC ASSUMPTION)	COMBINATION OF CLOPIDOGREL FOR ALL PATIENTS PLUS ASPIRIN FOR ELIGIBLE PATIENTS VS. ASPIRIN FOR ALL ELIGIBLE PATIENTS AND CLOPIDOGREL FOR THE OTHER 5.7 PERCENT (ACTUAL DATA)
dollars/quality-adjusted year of life gained*							
Principal simulation			11,000	29,000	110,000	61,000	180,000
Rate of aspirin use in 2003 in eligible patients	85%	42%	11,000	29,000	110,000	61,000	180,000
Benefit of aspirin for coronary heart disease	31%	25% (21%–41%)†	12,000	32,000	110,000	58,000	170,000
			12,000	35,000	100,000	57,000	160,000
			11,000	25,000	130,000	69,000	200,000
Relative benefit of clopidogrel over aspirin for coronary heart disease	8.7%	0.3%–16.5%†	11,000	32,000	1,300,000	61,000	180,000
			11,000	27,000	66,000	61,000	180,000
Relative benefit of the combined therapy over aspirin alone	20%	10%–28%†	11,000	29,000	110,000	110,000	180,000
			11,000	29,000	110,000	47,000	180,000
Health care cost of noncoronary heart disease	Table 1	0 +10% +100%	3,000	21,000	110,000	53,000	170,000
			12,000	30,000	120,000	62,000	180,000
			19,000	37,000	120,000	70,000	190,000
Age range treated	35–84 yr	75–84 yr 65–84 yr 55–84 yr 45–84 yr 35–84 yr	8,000	23,000	96,000	52,000	140,000
			10,000	26,000	99,000	54,000	140,000
			11,000	28,000	110,000	58,000	150,000
			11,000	28,000	110,000	60,000	170,000
			11,000	29,000	110,000	61,000	180,000
Duration of benefit for coronary heart disease	25 yr	3 yr (drug costs continued)	23,000	120,000	640,000	300,000	Not applicable
Duration of benefit for coronary heart disease	25 yr	3 yr (drug costs stopped)	12,000	26,000	99,000	57,000	Not applicable
Price of clopidogrel	\$3.22	20% less 20% more	11,000	25,000	92,000	52,000	130,000
			11,000	33,000	140,000	71,000	220,000
Population	All patients with coronary heart disease	History of myocardial infarction only‡ Three times base-line event rates	11,000	25,000	91,000	50,000	120,000
			10,000	19,000	53,000	32,000	71,000
Benefit of revascularization	None	Same as event rates	Save costs and lives	7,000	90,000	39,000	150,000

*Values are rounded to two significant digits.

†Ranges are 95 percent confidence intervals.

‡This estimate is the cohort of all persons in the model with a history of myocardial infarction at the end of 2002.

disease would decline substantially in the first several years (Fig. 1). However, the costs of noncoronary disease and later costs related to coronary disease would increase, because more patients would be alive with coronary disease and susceptible to recurrent coronary events. In analyses that considered only patients with prevalent coronary disease in 2002 and did not

include patients with incident cases each year, the cost-effectiveness ratios over the 25-year simulation were very similar.

Sensitivity Analyses

If the rate of aspirin use in eligible patients were only 42 percent instead of 85 percent, all cost-effec-

tiveness ratios would remain the same, but the absolute benefits of current aspirin use would be about 50 percent of those reported in Table 2. Aspirin has a more favorable cost-effectiveness ratio (\$3,000 per quality-adjusted year of life gained) if the health care costs of noncoronary disease are not considered (Table 3). The use of aspirin would save money as well as lives if this strategy reduces the rate of revascularization as much as it reduces the rate of myocardial infarction. Results were similar according to sex and age, even if treatment continued beyond the age of 85. Conversely, if the benefits of therapy persisted for only 3 years even though therapy was continued for 25 years, all options would become much less attractive.

For the use of clopidogrel instead of aspirin in patients who were eligible for aspirin, the cost-effectiveness ratio never fell below \$50,000 per quality-adjusted year of life gained, but it approached this level for patients with annual risks that are three times as high as those of the average patient with coronary disease. The combination of aspirin plus clopidogrel had borderline or reasonable cost-effectiveness ratios in several sensitivity analyses if its 1 year benefits for all vascular events persisted for 25 years. However, if the benefit after the first year was similar to the benefit for vascular events in months 9 to 12 of the trial,¹⁷ the base-line cost-effectiveness ratio was \$120,000 per quality-adjusted year of life gained. Similarly, the 25-year benefits of 1 year of combination therapy based on actual data from the randomized trial were associated with unfavorable cost-effectiveness ratios and never fell below \$70,000 per quality-adjusted year of life gained, even in the highest-risk patients.

The substitution of clopidogrel for aspirin or the addition of clopidogrel to aspirin in patients who are eligible for aspirin would become attractive, however, if the cost of clopidogrel declined substantially. For example, in our base-line analysis, the cost-effectiveness ratio of clopidogrel instead of aspirin would fall to \$50,000 per quality-adjusted year of life gained if the cost of clopidogrel were reduced by about 60 percent, from \$3.22 daily to \$1.32 daily.

DISCUSSION

The prescription of aspirin until death or for 25 years has an attractive cost effectiveness in men and women with coronary disease across all age ranges and despite varying assumptions about the efficacy of treatment. For patients with contraindications to aspirin treatment, clopidogrel had a reasonably attractive cost-effectiveness ratio as compared with no antiplatelet treatment. By comparison, the incremental cost-effectiveness ratio of using clopidogrel instead of aspirin for patients who are eligible for aspirin was unattractive across a wide range of assumptions, because

of the higher daily costs of the drug itself. Clopidogrel used in combination with aspirin for all patients who were eligible for aspirin also had unattractive cost-effectiveness ratios, except when these assumptions were purposefully tilted to favor clopidogrel to an extent not suggested by the actual data from randomized trials.^{16,17} To date, available data have not clearly demonstrated an increased risk of thrombotic thrombocytopenic purpura with clopidogrel treatment.^{36,37} If such an association exists, clopidogrel would become even less attractive.

Though favorable, the annual overall cost effectiveness of aspirin therapy was not as favorable as might have been expected given the very low cost of aspirin itself. The main explanation is that the health care costs of noncoronary disease would be estimated to increase substantially, because patients whose cardiac events were prevented by aspirin would survive to have other medical costs. In the first several years of therapy, these other medical costs would be offset by the savings generated from the prevention of coronary events. Subsequently, however, costs related to coronary disease would also increase, because the prevalence of persons alive with coronary disease, and hence susceptible to coronary events, would be greatly increased because of deaths prevented by aspirin therapy.

Our findings are much less favorable for clopidogrel than those of Sarasin et al.,³⁸ who reported a cost-effectiveness ratio of about \$27,000 per quality-adjusted year of life gained for secondary prevention in patients with prior strokes or transient ischemic attacks. Those authors modeled clopidogrel use in highly selected patients who were 65 years of age and were not candidates for carotid surgery. They assumed an additional 14 percent reduction in vascular events with clopidogrel as compared with aspirin, a benefit that was 1.6 times as high as current data suggest. They did not consider downstream coronary costs, however, other than for myocardial infarction, or the costs of noncoronary disease, other than direct adverse effects of antiplatelet treatment. If we eliminated the costs considered in our study but not theirs, estimates of the cost effectiveness of clopidogrel in the two analyses would be similar.

Our findings represent a conservative assessment of the benefits of aspirin for secondary prevention of coronary disease. First, we modeled the effects of aspirin during long-term use when given to patients 30 days after they had survived an initial coronary event. Large, randomized trials³⁹ have also shown short-term benefits of aspirin for patients in the acute phase of myocardial infarction, in particular when combined with thrombolysis. The administration of aspirin in the acute phase of myocardial infarction has been estimated to cost \$2,800 per year of life

saved.⁴⁰ Data also suggest that the long-term benefits of aspirin, when administered with thrombolysis, may be substantially greater than previously reported.⁴¹ Second, we assumed that the daily dose of aspirin was 325 mg per day, because that regimen was the one most commonly used in the United States. There is good evidence that 100 mg per day could be as effective and safer.⁵ Third, we used the cost of the enteric-coated aspirin tablets, which may trigger fewer gastrointestinal complications, rather than other, less costly formulations.

Aspirin for secondary prevention of coronary disease is attractive from a cost-effectiveness perspective under a wide range of assumptions. Clopidogrel, as currently priced, has an attractive cost-effectiveness ratio for patients with contraindications to aspirin but not for patients who can tolerate aspirin, whether used alone or in combination with aspirin, unless assumptions about the relative benefits of clopidogrel are tilted beyond what is supported by actual data from the existing randomized trials.^{16,17} The gap between proven effectiveness and unattractive projected cost effectiveness could be eliminated by reductions in the price of clopidogrel.

Supported in part by grants from the Agency for Health Care Policy and Research (ROI HS06258) and the National Heart, Lung, and Blood Institute (ROI HL46315).

REFERENCES

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106. [Erratum, *BMJ* 1994;308:1540.]
2. *Idem*. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *Br Med J (Clin Res Ed)* 1998;296:320-31.
3. Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: a propensity analysis. *JAMA* 2001;286:1187-94.
4. Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med* 1994;330:1287-94.
5. Awtry EH, Loscalzo J. Aspirin. *Circulation* 2000;101:1206-18.
6. Aldhous P. A hearty endorsement for aspirin. *Science* 1994;263:24.
7. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1997;96:2751-3.
8. Cairns JA, Theroux P, Lewis HD Jr, Ezekowitz M, Meade TW, Sutton GC. Antithrombotic agents in coronary artery disease. *Chest* 1998;114:Suppl:611S-633S.
9. Ayanian JZ, Guadagnoli E, McNeil BJ, Cleary PD. Treatment and outcomes of acute myocardial infarction among patients of cardiologists and generalist physicians. *Arch Intern Med* 1997;157:2570-6.
10. Bratzler DW, de Leon AC Jr, Johnson MC, et al. The Cooperative Cardiovascular Project in Oklahoma. *J Okla State Med Assoc* 1997;90:219-27.
11. Krumholz HM, Radford MJ, Ellerbeck EF, et al. Aspirin for secondary prevention after acute myocardial infarction in the elderly: prescribed use and outcomes. *Ann Intern Med* 1996;124:292-8.
12. Krumholz HM, Radford MJ, Ellerbeck EF, et al. Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries: patterns of use and outcomes. *Circulation* 1995;92:2841-7.
13. Jencks SF, Cuedon T, Burwen DR, et al. Quality of medical care delivered to Medicare beneficiaries: a profile at state and national levels. *JAMA* 2000;284:1670-6.
14. Stafford RS. Aspirin use is low among United States outpatients with coronary artery disease. *Circulation* 2000;101:1097-101.
15. Rolka DB, Fagot-Campagna A, Narayan KM. Aspirin use among adults with diabetes: estimates from the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2001;24:197-201.
16. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
17. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. [Errata, *N Engl J Med* 2001;345:1506, 1716.]
18. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *Am J Public Health* 1987;77:1417-26.
19. Goldman L, Weinstein MC, Goldman PA, Williams LW. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA* 1991;265:1145-51.
20. Hunink MG, Goldman L, Tosteson AN, et al. The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. *JAMA* 1997;277:535-42.
21. Stinnett AA, Mittleman MA, Weinstein MC, et al. The cost-effectiveness of dietary and pharmacologic therapy for cholesterol reduction in adults. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in health and medicine*. New York: Oxford University Press, 1996:349-91.
22. Phillips KA, Shlipak MG, Coxson P, et al. Health and economic benefits of increased beta-blocker use following myocardial infarction. *JAMA* 2000;284:2748-54.
23. Goldman L, Phillips KA, Coxson P, et al. The effect of risk factor reductions between 1981 and 1990 on coronary heart disease incidence, prevalence, mortality and cost. *J Am Coll Cardiol* 2001;38:1012-7.
24. Morris S. A comparison of economic modeling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. *Health Econ* 1997;6:589-601.
25. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
26. Johannesson M, Jönsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. *N Engl J Med* 1997;336:332-6.
27. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *Am Heart J* 2001;141:727-34.
28. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making* 1993;13:89-102.
29. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. *JAMA* 1997;278:313-21.
30. Medical Economics Staff. *Drug topics red book*. Montvale, N.J.: Medical Economics, 2000.
31. Broderick JP, Phillips SJ, Whisnant JP, O'Fallon WM, Bergstralh EJ. Incidence rates of stroke in the eighties: the end of the decline in stroke? *Stroke* 1989;20:577-82.
32. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;28:717-22.
33. Edelson JT, Tosteson AN, Sax P. Cost-effectiveness of misoprostol for prophylaxis against nonsteroidal anti-inflammatory drug-induced gastrointestinal tract bleeding. *JAMA* 1990;264:41-7.
34. Oster G, Huse DM, Lacey MJ, Epstein AM. Cost-effectiveness of ticlopidine in preventing stroke in high-risk patients. *Stroke* 1994;25:1149-56.
35. Dobkin B. The economic impact of stroke. *Neurology* 1995;45:Suppl 1:S6-S9.
36. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000;342:1773-7.
37. Hankey GJ. Clopidogrel and thrombotic thrombocytopenic purpura. *Lancet* 2000;356:269-70.
38. Sarasin FP, Gaspoz JM, Bounameaux H. Cost-effectiveness of new antiplatelet regimens used as secondary prevention of stroke or transient ischemic attack. *Arch Intern Med* 2000;160:2773-8.
39. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
40. Hugenholtz PG. On jumbo and junkie trials: a fumbled affair, a jungle, or the ultimate solution? *Acta Med Port* 1991;4:Suppl 1:16S-18S.
41. Gorelick PB, Born GV, D'Agostino RB, Hanley DF Jr, Moye L, Pepine CJ. Therapeutic benefit: aspirin revisited in light of the introduction of clopidogrel. *Stroke* 1999;30:1716-21.