

Special Article

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

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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 four 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 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 \$31,000 per quality-adjusted year of life gained. Clopidogrel alone in all patients or in routine combination with aspirin had an incremental cost of more than \$130,000 per quality-adjusted year of life gained and remained financially unattractive across a wide range of assumptions. However, clopidogrel alone or in combination with aspirin would cost less than \$50,000 per quality-adjusted year of life gained if its price were reduced by 70 to 82 percent, to \$1.00 and \$0.60 per day, respectively.

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.)

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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 Model¹⁸⁻²⁷ 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

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coronary disease develops in a person, the model classifies the presentation 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 four 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, and the combination of aspirin for all eligible patients plus clopidogrel for all patients.

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 Combination treatment with aspirin and clopidogrel was assumed to yield a 20 percent relative reduction in the rates of coronary events as compared with aspirin alone.¹⁷

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}

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 \$8 billion in overall costs from 2003 to 2027 in patients 35 to 84 years of age (Table 2). The benefits, however, would be substan-

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	33.7	0.3–16.5 relative to aspirin	CAPRIE Steering Committee ¹⁶
Combination	37.2	10–28 relative to aspirin	CURE Investigators ¹⁷
Reduction in mortality from noncoronary causes (%)			
Aspirin	2.8		Antiplatelet Trialists' Collaboration ¹
Clopidogrel	2.9		Hebert et al. ²⁹
Combination	2.9		CAPRIE Steering Committee ¹⁶
Reduction in the rate of revascularization	None	Same as reduction in event rate	
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	\$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.

tial, with the avoidance of about 155,000 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 about 1.75 times 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 two thirds 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 150,000 myocardial infarctions and saving about 630,000 quality-adjusted years of life. However, the estimated incremental cost of this strategy of about \$155 billion would be nearly 20 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 only about 93 percent of 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 \$31,000 per quality-adjusted year of life saved. By comparison, either the strategy of routine use of clopidogrel alone in all patients or the strategy of combined aspirin plus clopidogrel in patients who are eligible for aspirin and clopidogrel alone in patients who are ineligible for aspirin would be associated with cost-effectiveness ratios of well 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.

With aspirin therapy, the costs of coronary heart 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

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§
Costs (millions of dollars)						
Drugs	0	1,730	1,919	11,438	167,003	170,032
Health care costs for coronary heart disease and noncoronary heart disease	1,797,000	1,865,000	1,872,000	1,877,000	1,878,000	1,901,000
Total costs	1,797,000	1,867,000	1,874,000	1,888,000	2,045,000	2,071,000
Incremental costs¶	—	69,000	8,000	14,000	156,000	182,000¶
Effectiveness (no.)						
Deaths from coronary heart disease	11,079,000	9,570,000	9,405,000	9,294,000	9,132,000	8,916,000
Deaths from noncoronary heart disease	4,019,000	4,268,000	4,295,000	4,314,000	4,343,000	4,389,000
Myocardial infarctions	16,508,000	15,075,000	14,919,000	14,813,000	14,664,000	14,466,000
Quality-adjusted years of life gained	115,535,000	121,768,000	122,450,000	122,906,000	123,538,000	124,343,000
Incremental quality-adjusted years of life gained¶	—	6,233,000	682,000	456,000	632,000	1,437,000¶
Cost effectiveness (dollars)						
Incremental cost per quality-adjusted year of life gained¶	—	11,000	11,000	31,000	250,000	130,000¶

*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 33.7 percent.

§The combined reduction in the rate of events is 37.2 percent.

¶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), which are compared with the values in the fifth column (aspirin for all eligible patients and clopidogrel for the remaining 5.7 percent).

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-effectiveness 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 and the use of clopidogrel in patients who are intolerant of aspirin would save money as well as lives if these strategies reduce the rate of revascularization as much as they reduce the rate of myocardial infarction. Results were similar according

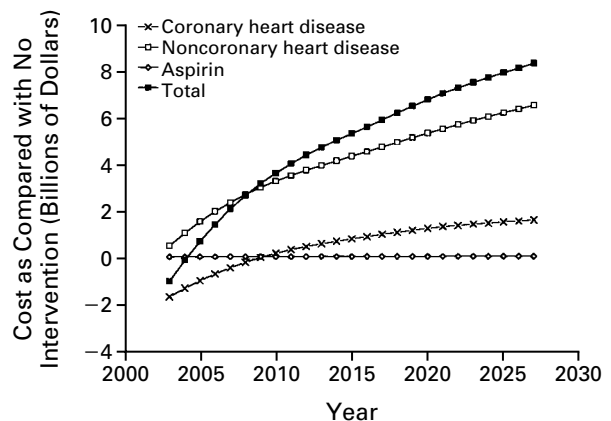


Figure 1. Annual Net Costs of Aspirin, Coronary Heart Disease, and Noncoronary Heart Disease with Routine Aspirin Use for Secondary Prevention in Patients 35 to 84 Years of Age.

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 AND CLOPIDOGREL FOR THE REMAINING 5.7 PERCENT VS. ASPIRIN ALONE FOR ALL ELIGIBLE PATIENTS	CLOPIDOGREL FOR ALL PATIENTS VS. ASPIRIN FOR ALL ELIGIBLE PATIENTS AND CLOPIDOGREL FOR THE REMAINING 5.7 PERCENT	COMBINATION OF CLOPIDOGREL FOR ALL PATIENTS PLUS ASPIRIN FOR ELIGIBLE PATIENTS VS. ASPIRIN FOR ALL ELIGIBLE PATIENTS AND CLOPIDOGREL FOR THE REMAINING 5.7 PERCENT	ASPIRIN FOR ALL ELIGIBLE PATIENTS
dollars/quality-adjusted year of life gained						
Principal simulation			11,000	31,000	250,000	130,000
Rate of aspirin use in 2003 in eligible patients	85%	42%	11,000	31,000	250,000	130,000
Benefit of aspirin for coronary heart disease	31%	25% (21%–41%)*	12,000	41,000	380,000	180,000
			12,000	36,000	310,000	160,000
			11,000	26,000	190,000	97,000
Relative benefit of clopidogrel over aspirin for coronary heart disease	8.7%	0.3%–16.5%*	11,000	33,000	6,600,000	130,000
			11,000	30,000	140,000	130,000
Relative benefit of the combined therapy over aspirin alone	20%	10%–28%*	11,000	31,000	250,000	240,000
			11,000	31,000	250,000	93,000
Health care cost of noncoronary heart disease	Table 1	0	3,000	23,000	240,000	120,000
		+10%	12,000	32,000	250,000	130,000
		+100%	19,000	39,000	260,000	130,000
Age range treated	35–84 yr	75–84 yr	8,000	25,000	210,000	110,000
		65–84 yr	10,000	27,000	210,000	110,000
		55–84 yr	11,000	29,000	230,000	120,000
		45–84 yr	11,000	30,000	240,000	120,000
		35–84 yr	11,000	31,000	250,000	130,000
Duration of benefit for coronary heart disease	25 yr	3 yr (drug costs continued)	23,000	130,000	1,400,000	680,000
Duration of benefit for coronary heart disease	25 yr	3 yr (drug costs stopped)	12,000	28,000	210,000	120,000
Price of clopidogrel	\$3.22	20% less	11,000	27,000	200,000	100,000
		20% more	11,000	35,000	300,000	150,000
Population	All patients with coronary heart disease	History of myocardial infarction only†	11,000	27,000	200,000	100,000
		Three times base-line event rates	10,000	20,000	110,000	59,000
Benefit of revascularization	None	Same as event rates	Save costs and lives	Save costs and lives	230,000	110,000

*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.

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.

The combination of aspirin plus clopidogrel was unattractive from a cost-effectiveness perspective except in the patients at highest risk. For example, the ratio fell below \$64,000 per quality-adjusted year of life gained only in patients with annual risks that were three times as high as that of the average patient with coronary disease. For the use of clopidogrel instead

of aspirin in patients who were eligible for aspirin, the ratio never fell below \$100,000 per quality-adjusted year of life gained.

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 as compared with aspirin would fall to \$50,000 per quality-adjusted year of life gained if the cost of clopidogrel were reduced by 82 percent, from \$3.22 daily to \$0.60 daily. For the

combination of aspirin plus clopidogrel, the daily price of clopidogrel would have to fall by 70 percent, to about \$1 daily, for a cost-effectiveness ratio of \$50,000 per quality-adjusted year of life gained.

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 clopidogrel as compared with 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 reached favorable cost-effectiveness ratios only when its costs were reduced to about \$0.60 per day. Clopidogrel used in combination with aspirin for all patients who were eligible for aspirin also had unattractive cost-effectiveness ratios, even if the health benefits described for patients with acute coronary syndromes¹⁷ were maintained in the long term. 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. The gap between proven effectiveness and unattractive projected cost effectiveness could be eliminated by reductions in the price of clopidogrel.

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CORRECTION

Aspirin, Clopidogrel, or Both for Secondary Prevention of Coronary Disease

To the Editor: Gaspoz et al. (June 6 issue)¹ present an interesting perspective on the problem of escalating health care costs. Their comparison between the cost effectiveness of aspirin and that of clopidogrel is commendable, given the increasing focus by the public on the costs of newer drugs. In their analysis, the authors' assumptions about the costs of the drugs do not take into consideration future costs that would be expected to be lower for both brand-name and generic versions of clopidogrel.

Estimates of the cost of developing a new drug vary, with some figures as high as \$800 million.² The need to recoup these expenses is one of many reasons for the price of new drugs. Without the marketing of new drugs, it is doubtful whether lower-priced generic versions would become available once the patents had expired; if they did not, the public would be deprived of therapeutically superior medications. Clopidogrel has been shown to be more effective than aspirin alone in reducing the incidence of cardiovascular events.³ The authors' conclusion that the use of clopidogrel is financially unattractive appears to sound a death knell for therapeutic innovation and to mark the beginning of a managed-care era for the pharmaceutical industry.

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To the Editor: We believe that the estimates of incremental effectiveness used by Gaspoz et al. are incorrect for each of the strategies evaluated. First, the 31 percent relative risk reduction associated with aspirin therapy is based on a meta-analysis¹ of trials performed before statins, angiotensin-converting-enzyme inhibitors, glycoprotein IIb/IIIa inhibitors, and coronary stents were used routinely after acute coronary syndromes. A more recent report from the same group suggests that there was a 27.7 percent relative risk reduction for nonfatal

myocardial infarction and only a 21 percent relative risk reduction for major cardiovascular events.²

Second, it appears that the incremental effects of clopidogrel and of clopidogrel plus aspirin were underestimated. Assuming a 31 percent relative risk reduction from aspirin, an incremental 20 percent relative risk reduction associated with the addition of clopidogrel should yield a net 44.8 percent relative risk reduction, as opposed to the 37.2 percent used by Gaspoz et al. Similarly, the relative risk reduction with clopidogrel alone should be 37 percent, rather than the 33.7 percent reported. The correct formula is $RRR_{combined} = 1 - [(1 - RRR_{aspirin}) \times (1 - RRR_{aspirin+clopidogrel})]$, where RRR is the relative risk reduction; the formula used by Gaspoz et al. was $RRR_{combined} = RRR_{aspirin} + (RRR_{aspirin} \times RRR_{aspirin+clopidogrel})$.

The assumptions of efficacy and safety used in this model are taken from a short-term study involving patients treated early after the onset of an acute coronary syndrome, for a maximum of 12 months.³ The extrapolation of such results to long-term therapy is inherently flawed. The rate of adverse ischemic events is highest during the period immediately after an acute coronary syndrome and decreases thereafter. Episodes of bleeding, on the other hand, would probably follow a more "linear" time course. Because the risks and benefits of 25 years of treatment with the combination of clopidogrel and aspirin have not been established, the cost effectiveness of this strategy is irrelevant.

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Editor's note: Drs. de Lemos and McGuire report having received speaker's honorariums from Sanofi, which manufactures clopidogrel. Dr. de Lemos reports having received speaker's honorariums from Bristol-Myers Squibb, which markets clopidogrel.

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patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. [Erratum, *N Engl J Med* 2001;345:1506, 1716.]

To the Editor: I use the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study¹ to teach residents the importance of avoiding the use of relative risk reductions in describing treatment effects and instead using absolute risk reductions and numbers needed to treat. Treatment with clopidogrel resulted in an 8.7 percent relative risk reduction for the composite primary end point of ischemic stroke, myocardial infarction, or death from vascular causes, as compared with aspirin. At first glance, this reduction seems impressive, but closer scrutiny reveals an absolute risk reduction of only 0.9 percent and a number needed to treat of 115 (95 percent confidence interval, 58 to 8647). This huge 95 percent confidence interval, which ranges from a number needed to treat that would be worthwhile to one that would offer no advantage at all, calls into question whether clopidogrel is truly superior to aspirin. On the basis of the number needed to treat of 115, 114 patients would have to be treated for 730 days (2 years) at a cost of \$3.22 per tablet in order to prevent 1 patient from having an adverse event. The cost would be \$267,968 per adverse event prevented. A Cochrane review² that included the findings of the CAPRIE trial presented data for single outcomes rather than for a cluster of clinical outcomes. According to these analyses, the differences between clopidogrel and aspirin in terms of the outcomes of total strokes and total deaths are nonsignificant. For total myocardial infarctions, the absolute risk reduction is 0.7 percent, giving a number needed to treat of 143, and the cost per myocardial infarction prevented over a two-year period is a staggering \$333,785.

Coronary heart disease is a major killer of adults in the United States. An estimated 40 million Americans are uninsured, and those who are insured are paying more but getting less. In this context, I would replace the somewhat euphemistic term "unattractive" used by Gaspoz et al. with the term "prohibitive" in describing the cost effectiveness of routine use of clopidogrel for secondary prevention of coronary heart disease.

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To the Editor: In his commentary on the study by Gaspoz et al., Wood¹ states that he finds it "deeply troubling" that the authors interpret \$130,000 per quality-adjusted year of life for clopidogrel as an "unattractive" value for expenditure. He then cites the cost of drug development as reasonable justification for the price of the drug. Unfortunately, his link between drug pricing and drug-development costs — a link often made by pharmaceutical manufacturers — is spurious. The \$3.22 price of a 75-mg clopidogrel tablet has very little to do with the cost of developing the drug. Rather, it is what the managers at the companies that market clopidogrel (Bristol-Myers Squibb and Sanofi Pharmaceuticals) believe the market will bear for this product. What troubles me is that Wood appears to reject the fact that health value for expenditure should play any part in the argument, particularly when the quality-adjusted years of life are his. Public and private health insurance plans face budget constraints and severe pressure to curb future increases in health care expenditures. Those who make the difficult decisions for these organizations know that the incremental cost of adding clopidogrel to their formularies will force them to cut costs elsewhere, perhaps by restricting access to much more cost-effective therapies. Even if the lives saved by those treatments are not his, which ones would he choose?

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Editor's note: Dr. Ramsey reports having received a research grant from Bristol-Myers Squibb.

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To the Editor: Wood seems to be arguing that we should be willing to pay any increase in cost, no matter how large, in return for any increase in benefit, no matter how minuscule. Such an attitude would certainly cost more lives than it would save. Forty million Americans lack health insurance and therefore lack access to even basic health care. As medical costs continue to rise, more and more employers are forced to drop health care coverage. Nobody knows how many people die because lack of insurance causes them to delay seeking medical care until it is too late, but the number is certainly larger than the number of lives saved by adding clopidogrel to aspirin therapy.

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The authors reply: We disagree with Dr. Akinlade. Pharmaceutical companies should be able to achieve profits at reasonable cost-effectiveness ratios so that beneficial drugs are affordable. Future

drug prices are unpredictable, and the patents on clopidogrel run until 2019.

Dr. Armstrong calculates the costs per event avoided to reach conclusions that are stronger than ours. We prefer the term "unattractive" but understand his preference for "prohibitive."

Drs. de Lemos and McGuire raise three issues. First, our estimated 31 percent reduction in the risk of cardiovascular events with aspirin is consistent with the 30 percent reduction in the odds of nonfatal myocardial infarction among patients with previous infarction¹ and the 32 percent reduction in the odds of vascular events among patients receiving moderate doses of aspirin² in the most recent overview.

Second, we appreciate their carefulness in detecting our mathematical error and apologize for it. A corrected version of our article is now available at <http://www.nejm.org>. With the correction of this error and a similar error in estimating the benefits in reducing the risk of stroke, the use of clopidogrel alone instead of aspirin is associated with a cost-effectiveness ratio of \$110,000 per quality-adjusted year of life saved and remains unattractive except for patients with the highest risk. For the combination of clopidogrel and aspirin, the cost-effectiveness ratio changed from \$130,000 to \$61,000 per quality-adjusted year of life saved, on the basis of our original assumptions that had been purposely tilted to favor clopidogrel in order to ensure the robustness of our conclusion that clopidogrel was unattractive from the perspective of cost effectiveness despite the most favorable set of estimates. These assumptions, which were unlikely to be accurate, were that the 20 percent benefit of combination therapy for the prevention of nonfatal myocardial infarction that was found during the first year in patients with acute coronary syndromes would be maintained for 25 years and that the same benefit would apply to all cardiovascular events. However, the observed relative benefits of combination therapy declined by about 50 percent during months 9 through 12 of the trial, and the reductions in the rates of stroke, fatal myocardial infarction, and death from cardiovascular causes were much lower than 20 percent, even during the first year.³ If the relative benefit of combination therapy in terms of all events after the first year were similar to what was seen during months 9 through 12, the cost-effectiveness ratio would be about \$120,000 per quality-adjusted year of life saved — nearly identical to the \$130,000 we estimated.

Third, when the actual event-specific results reported for 12 months of combination therapy³ were applied to our original question, which was about the cost effectiveness of therapy beginning 30 days after the onset of symptomatic coronary disease, the 25-year cost-effectiveness ratio for 1 year of combination treatment was \$180,000 per quality-adjusted year of life gained. As a result, we stand by our original conclusion that the long-term use of clopidogrel, despite its apparent effectiveness, is financially unattractive for patients who can tolerate aspirin, unless its price is reduced substantially.

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Dr. Wood replies: Gaspoz et al. demonstrated that the addition of clopidogrel to aspirin therapy would produce a benefit of 1,437,000 quality-adjusted years of life over a 25-year period as compared with aspirin therapy alone — hardly a "minuscule" benefit, as Dr. Yaes suggests. The cost of these years of life will fall with the price of clopidogrel, as the authors acknowledged. Dr. Ramsey takes issue with the ways in which drugs are priced. Although the pricing of drugs and the fact that 40 million Americans lack health insurance are serious issues, the fundamental issue is whether we should ration care, and if so, how that rationing should be carried out. I would argue that our expenditures for health care, which, as a fraction of the gross domestic product, are higher than those of any other developed country, could certainly support therapies that have been proved to result in substantial reductions in mortality in well-controlled clinical trials. Surely, the first therapies to be eliminated should be those that we know to be ineffective or those that have not been demonstrated to be effective. Too many such therapies are still in widespread use. If society deems it appropriate to restrict care further, it will be critical for physicians to be explicit about such restrictions in talking to their patients, who might choose to deploy their economic resources differently. Patients expect us to be frank and open about the options we recommend to them. To deny patients potentially lifesaving therapy without offering them the option of receiving it (even if it must be at their own expense) seems unethical. Reasonable people can differ in their judgments of economic value; if you doubt it, look at the variety of cars in any large parking lot.

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