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 as survivors without coronary disease and leave the population, to estimate the incremental cost effectiveness of the long-term use of aspirin, clopidogrel, or both for secondary prevention in patients with known coronary disease.

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.


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coronary disease develops in a person, the model classifies the pres- 288 tence of acute cardiac arrest, acute myocardial infarction, or angina, 289 and it includes deaths and health care costs during the first 30 days. 290 Then, the model tracks patients who survive the first month with 291 coronary disease and categorizes them according to whether they 292 are in their first or subsequent year after the initial event and 293 whether their history includes one or more cardiac arrests, myocar- 294 dial infarctions, or coronary-revascularization procedures. Each year, 295 patients with coronary disease have a defined risk of cardiac arrest, 296 acute myocardial infarction, or coronary revascularization (or any 297 combination of these events). Each event has a specific case fatal- 298 ity rate tailored to the condition in which the person started that 299 year. Each patient is assigned an annual cost on the basis of his or 300 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 litera- 301 ture, the National Vital Statistics reports, the National Hospi- 302 tal Discharge Survey, the National Health Interview Survey, the sec- 303 ond and third Health and Nutrition Examination Surveys, the Framingham Heart Study, and a variety of clinical trials and observ- 304 ational studies.16,19 The model has been updated with more re- 305 vised or newly estimated variables.20–23 The model is based on 306 the Framingham Heart Study, which has been shown to predict the 307 benefits found in cholesterol-lowering trials.24 Using the choles- 308 terol changes in the Scandinavian Simvastatin Survival Study,25 our 309 model nearly perfectly reproduces the observed reduction in 310 the rates of coronary events in that trial and provides cost-effec- 311 tiveness ratios in the same general range as those estimated for 312 that trial26 and for the Cholesterol and Recurrent Events Study.27 313 Health-related quality-of-life weights for coronary disease are 314 based on whether patients have angina, heart failure, or both.28 315 Noncoronary health-related quality-of-life weights are based on 316 observational data.29

Interventions

Our principal simulations modeled U.S. patients, 35 to 84 years 317 of age, in whom coronary disease developed during or before 3003 318 to 2027 and who survived their first month with it. Their currently 319 expected (no intervention) costs and quality-adjusted years of life 320 over this 25-year period were calculated and compared with what 321 would be expected with four strategies based on pooled data from 322 randomized trials for secondary prevention of coronary events in 323 patients with prior coronary disease.16,17,27,29: aspirin for all eligible 324 patients, aspirin for all eligible patients plus clopidogrel for patients 325 ineligible for aspirin, clopidogrel alone for all patients, and the 326 combination of aspirin for all eligible patients plus clopidogrel for 327 all patients.

For aspirin, the 31 percent reduction in the odds of nonfatal my- 328 ocardial infarction reported in the pooled trials1 was applied to my- 329 ocardial infarction, cardiac arrest, and death from chronic coronary 330 disease (Table 1). The 19 percent reduction in fatal stroke1 was used 331 to derive a 2.8 percent reduction for the rate of death from non- 332 coronary causes in the model. To model the effects of clopidogrel, 333 additional relative reductions were assumed for the rates of coro- 334 nary events (8.7 percent) and deaths from noncoronary causes (5.0 335 percent) on the basis of randomized data that directly compared aspirin with clopidogrel.16 Combination treatment with aspirin and 336 clopidogrel was assumed to yield a 20 percent relative reduction in 337 the rates of coronary events as compared with aspirin alone.30 338 In our base-line analysis, we assumed aspirin is used in 85 per- 339 cent of patients with coronary heart disease in 2003 on the basis 340 of data on patients discharged after acute infarctions.13 Our simu- 341 lations assumed that 94.3 percent of patients are eligible for treat- 342 ment with aspirin,31 and 100 percent are eligible for clopidogrel. 343 Compliance was not modeled because percent reductions in odds 344 in pooled trials were based on intent-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 clo- 345 pidogrel was assumed to be the sum of the two costs.

We assumed the incidence of gastrointestinal adverse effects 346 and rash to be as reported for aspirin and clopidogrel.31 In 1989, 347 the cost of one major episode of gastrointestinal bleeding and the cost of one minor episode of gastrointestinal bleeding were esti- 348 mated as $6,866 and $733, respectively.32 The yearly incidence of 349 the other, less serious complications was multiplied by the cost of 350 one office visit at $44.20, as in a prior analysis.14

In the 14 secondary-prevention trials involving high-risk pa- 351 tients, there was a 24 percent decrease in fatal or disabling strokes (P<0.01) and a 17 percent decrease in nondisabling strokes (P< 352 0.09) for patients receiving aspirin. The incidence of stroke in the 353 population with coronary disease was assumed to be the inci- 354 dence reported in pooled secondary statin trials,39 with the relative 355 distribution according to age group derived from studies conduct- 356 ed in Rochester, Minnesota, from 1980 to 1984.40 The in-hospital 357 mortality from stroke (18 percent), the percentage of hospital sur- 358 viors who went directly to a nursing home (15 percent), and the 359 percentage of patients transferred to a nursing home after a reha- 360 bilitation center (8 percent) were derived from Dobbins,35 whereas 361 the percentage of survivors discharged to a rehabilitation center 362 from acute-care hospitals (6.8 percent) was derived from Oster et 363 al.41 The cost of acute care for stroke (hospital costs plus physi- 364 cians’ fees) was reported to be $70,026 in 1991.42 From work of 365 the same authors, we derived the costs for one stay in a rehabili- 366 tation 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 dis- 367 ease, 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 3003 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 Tri- 372 alists’ reported standard deviation.1 For clopidogrel as compared 373 with aspirin and the combination of the two, we used the 95 per- 374 cent confidence intervals of the relative reductions.16,17

Because the median follow-up time in the secondary-preven- 375 tion trials for high-risk patients was three years,1 we modeled in- 376 terventions 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 accord- 377 ing to age and clinical characteristics, and we assessed the cost ef- 378 fectiveness of the interventions, assuming that they might have as 379 great an effect on reducing coronary revascularization procedures 380 as on reducing other coronary events.

We varied the health care costs of noncoronary disease by up 381 to 100 percent and assessed the effect of excluding them from our 382 analysis. We simulated a higher annual discount rate of 5 percent. 383 Total costs were calculated as the sum of costs of coronary dis- 384 ease, costs of noncoronary disease (an annual estimate based on 385 data from the National Medical Expenditure Survey), and the costs 386 of the specific intervention being studied, and were summed from 387 2003 to 2027 with the use of a discount rate of 3 percent per year. 388 All costs were converted to year-2000 U.S. dollars with the use of 389 the medical care component of the Consumer Price Index.

RESULTS

As compared with the estimated current utilization of aspirin, extension of aspirin therapy to all el- 390 igible patients would result in an additional $189 million in drug costs and $8 billion in overall costs 391 from 2003 to 2027 in patients 35 to 84 years of age (Table 2). The benefits, however, would be substan-
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 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

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**Table 1. Summary of Variables.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>BASE-LINE ESTIMATE USED IN ANALYSIS</th>
<th>RANGE USED IN SENSITIVITY ANALYSES</th>
<th>SOURCE OF DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in the rate of coronary heart disease events* (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>31.0</td>
<td>21–41</td>
<td>Antiplatelet Trialists’ Collaboration¹</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>33.7</td>
<td>0.3–16.5 relative to aspirin</td>
<td>CAPRIE Steering Committee²⁶</td>
</tr>
<tr>
<td>Combination</td>
<td>37.2</td>
<td>10–28 relative to aspirin</td>
<td>CURE Investigators²⁷</td>
</tr>
<tr>
<td>Reduction in mortality from noncoronary causes (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2.8</td>
<td></td>
<td>Antiplatelet Trialists’ Collaboration¹</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>2.9</td>
<td></td>
<td>Hebert et al.²⁹</td>
</tr>
<tr>
<td>Combination</td>
<td>2.9</td>
<td></td>
<td>CAPRIE Steering Committee²⁶</td>
</tr>
<tr>
<td>Reduction in the rate of revascularization</td>
<td>None</td>
<td>Same as reduction in event rate</td>
<td></td>
</tr>
<tr>
<td>Current rate of use of aspirin (%)</td>
<td>85</td>
<td>42–85</td>
<td>Jencks et al.¹³</td>
</tr>
<tr>
<td>Cost of medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>$0.04/tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>$3.22/day</td>
<td>$0–$3.22/day</td>
<td>Medical Economics Staff³⁰</td>
</tr>
<tr>
<td>Combination</td>
<td>$3.26/day</td>
<td>$0.04–$3.26/day</td>
<td></td>
</tr>
<tr>
<td>Annual cost of noncoronary heart disease according to age range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–44 yr</td>
<td>$1,994/yr</td>
<td>$0–$4,000/yr</td>
<td>Stinnett et al.³¹</td>
</tr>
<tr>
<td>45–64 yr</td>
<td>$3,794/yr</td>
<td>$0–$7,600/yr</td>
<td></td>
</tr>
<tr>
<td>65–84 yr</td>
<td>$7,796/yr</td>
<td>$0–$16,000/yr</td>
<td></td>
</tr>
<tr>
<td>Mean annual cost of coronary heart disease</td>
<td>$6,200</td>
<td></td>
<td>Weinstein et al.³⁸</td>
</tr>
<tr>
<td>Discount rate (%)</td>
<td>3</td>
<td>3–5</td>
<td>Scandinavian Simvastatin Survival Study³⁵</td>
</tr>
<tr>
<td>Annual incidence of stroke per 100,000 persons</td>
<td>135</td>
<td></td>
<td>Hebert et al.²⁹</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Cost (millions of dollars)</th>
<th>Current Use of Aspirin (85%)</th>
<th>Aspirin for All Eligible Patients†</th>
<th>Aspirin for All Eligible Patients and Clopidogrel for the Remaining 5.7 Percent</th>
<th>Clopidogrel for All Patients‡</th>
<th>Combination of Clopidogrel for All Patients Plus Aspirin for Eligible Patients§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>0</td>
<td>1,730</td>
<td>1,819</td>
<td>11,438</td>
<td>167,003</td>
</tr>
<tr>
<td>Health care costs for coronary heart disease and noncoronary heart disease</td>
<td>1,797,000</td>
<td>1,867,000</td>
<td>1,874,000</td>
<td>1,888,000</td>
<td>2,045,000</td>
</tr>
<tr>
<td>Incremental costs¶</td>
<td>—</td>
<td>69,000</td>
<td>8,000</td>
<td>14,000</td>
<td>156,000</td>
</tr>
<tr>
<td>Effectiveness (no.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths from coronary heart disease</td>
<td>10,079,000</td>
<td>9,570,000</td>
<td>9,405,000</td>
<td>9,294,000</td>
<td>9,294,000</td>
</tr>
<tr>
<td>Deaths from noncoronary heart disease</td>
<td>4,019,000</td>
<td>4,268,000</td>
<td>4,295,000</td>
<td>4,314,000</td>
<td>4,343,000</td>
</tr>
<tr>
<td>Myocardial infarctions</td>
<td>16,308,000</td>
<td>15,075,000</td>
<td>14,919,000</td>
<td>14,875,000</td>
<td>14,664,000</td>
</tr>
<tr>
<td>Quality-adjusted years of life gained</td>
<td>125,535,000</td>
<td>121,768,000</td>
<td>122,450,000</td>
<td>122,906,000</td>
<td>123,538,000</td>
</tr>
<tr>
<td>Incremental quality-adjusted years of life gained¶</td>
<td>—</td>
<td>6,233,000</td>
<td>682,000</td>
<td>650,000</td>
<td>622,000</td>
</tr>
</tbody>
</table>

### 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.*

*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).

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**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.
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

### Table 3. Incremental Cost-Effectiveness Ratios in Key Sensitivity Analyses.

<table>
<thead>
<tr>
<th>Subject of Sensitivity Analysis</th>
<th>Base-Line Estimate</th>
<th>Estimates Used for Sensitivity Analysis</th>
<th>Intervention Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspirin for all eligible patients</td>
</tr>
<tr>
<td>Principal simulation</td>
<td>11,000</td>
<td>31,000</td>
<td>250,000</td>
</tr>
<tr>
<td>Rate of aspirin use in 2003 in eligible patients</td>
<td>85%</td>
<td>42%</td>
<td>12,000</td>
</tr>
<tr>
<td>Benefit of aspirin for coronary heart disease</td>
<td>31%</td>
<td>25% (21%–41%)*</td>
<td>12,000</td>
</tr>
<tr>
<td>Relative benefit of clopidogrel over aspirin for coronary heart disease</td>
<td>8.7%</td>
<td>0.3%–16.5%*</td>
<td>11,000</td>
</tr>
<tr>
<td>Relative benefit of the combined therapy over aspirin alone</td>
<td>20%</td>
<td>10%–28%*</td>
<td>11,000</td>
</tr>
<tr>
<td>Health care cost of noncoronary heart disease</td>
<td>Table 1</td>
<td>3,000</td>
<td>12,000</td>
</tr>
<tr>
<td>Age range treated</td>
<td>35–84 yr</td>
<td>75–84 yr</td>
<td>11,000</td>
</tr>
<tr>
<td>Duration of benefit for coronary heart disease</td>
<td>25 yr</td>
<td>3 yr (drug costs continued)</td>
<td>23,000</td>
</tr>
<tr>
<td>Duration of benefit for coronary heart disease</td>
<td>25 yr</td>
<td>3 yr (drug costs stopped)</td>
<td>12,000</td>
</tr>
<tr>
<td>Price of clopidogrel</td>
<td>$3.22</td>
<td>20% less</td>
<td>11,000</td>
</tr>
<tr>
<td>Population</td>
<td>All patients with coronary heart disease</td>
<td>History of myocardial infarction only</td>
<td>11,000</td>
</tr>
<tr>
<td>Benefit of revascularization</td>
<td>None</td>
<td>Same as event rates</td>
<td>Save costs and lives</td>
</tr>
</tbody>
</table>

*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.
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 syndromes were maintained in the long term. To date, available data have not clearly demonstrated an increased risk of thrombotic thrombocytopenic purpura with clopidogrel treatment. 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., 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 trials 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. Data also suggest that the long-term benefits of aspirin, when administered with thrombolysis, may be substantially greater than previously reported. 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. 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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**REFERENCES**


CORRECTION

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

To the Editor: Gaspoz et al. (June 6 issue) 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. 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. 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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References


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-analysis 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.

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 $RRR_{combined} = 1 - ([1 - RRR_{aspirin}] \times [1 - RRR_{clopidogrel}]),$ where $RRR$ is the relative risk reduction; the formula used by Gaspoz et al. was $RRR_{combined} = RRR_{aspirin} + (RRR_{aspirin} \times RRR_{clopidogrel}).$

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. 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.

References


3. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in

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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References


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.

References


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 infarction and the 32 percent reduction in the odds of vascular events among patients receiving moderate doses of aspirin 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. 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 therapy 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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References


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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