Cost-effectiveness of New Antiplatelet Regimens Used as Secondary Prevention of Stroke or Transient Ischemic Attack

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Background: Compared with aspirin alone, use of the new antiplatelet regimens, including aspirin combined with dipyridamole and clopidogrel bisulfate, has been found to further reduce the risk of stroke and other vascular events in patients who have experienced stroke or transient ischemic attack. However, their cost-effectiveness ratios relative to aspirin alone have not been estimated.

Methods: We developed a Markov model to measure the clinical benefits and the economic consequences of the following strategies to treat high-risk patients aged 65 years or older: (1) aspirin, 325 mg/d; (2) aspirin, 50 mg/d, and dipyridamole, 400 mg/d; and (3) clopidogrel bisulfate, 75 mg/d. Input data were obtained by literature review. Outcomes were expressed as US dollars per quality-adjusted life-year (QALY).

Results: The use of aspirin combined with dipyridamole was more effective and less costly compared with the use of aspirin alone, providing a gain of 0.3 QALY for a 65-year-old patient. This regimen remained cost-effective despite wide sensitivity analyses. Clopidogrel was more effective and more costly compared with aspirin alone, yielding a gain of 0.2 QALY with a marginal cost-effectiveness ratio of $26580 per each additional QALY (patient aged 65 years). Sensitivity analyses demonstrated that the efficacy of clopidogrel and its cost were key factors in determining its cost-effectiveness ratio compared with aspirin, which exceeded $50000 when its efficacy decreased by half or its cost doubled.

Conclusion: To prevent stroke in high-risk patients, dipyridamole combined with aspirin was more effective and less costly than aspirin alone, and clopidogrel was cost-effective compared with current standards of medical practice, except in extreme scenarios.

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Many clinical trials1 have evaluated the benefit of long-term use of aspirin in reducing the risk of thrombotic events. Specifically, it reduces the relative risk of stroke and death from vascular events, such as myocardial infarction (MI), by about 25% compared with placebo. Recently, 2 other antiplatelet regimens, clopidogrel bisulfate, a thienopyridine derivative like ticlopidine hydrochloride, and a new formulation of dipyridamole combined with aspirin, were reported in large clinical trials2-3 to further reduce the risk of vascular events compared with aspirin. Both regimens were recently approved by the Food and Drug Administration for secondary prevention of stroke. However, despite their increased efficacy when compared with aspirin, both clopidogrel and, to a lesser extent, dipyridamole combined with aspirin are more expensive than aspirin alone. In 2 recent review articles4-5 on this topic, the authors thought that the new regimens were very expensive alternatives to aspirin for secondary prevention of stroke. However, a formal cost-effectiveness analysis is still lacking.

Whereas individual patients and physicians are mainly interested in one patient’s welfare, hospitals, health care policy agencies, or, more generally, society as a whole must also be concerned that health care resources spent for one strategy may limit the availability of resources for another one.8 Therefore, we used the techniques of decision analysis to assess the clinical benefit and the economic burden of different antiplatelet preventive therapies for patients who had experienced stroke or transient ischemic attack (TIA) secondary to atherosclerotic lesions that are not amenable to surgery either because they have no corresponding carotid lesions or because the patient’s general condition does not allow surgery. Specifically, we measured the cost-effectiveness ratios of clopidogrel and dipyridamole combined with aspirin relative to aspirin alone. We did not consider ticlopidine in this analysis because this compound is likely to be replaced by clopidogrel because of its better hematologic tolerance.
METHODS

SECONDARY PREVENTION STRATEGIES

For patients who experienced ischemic stroke or TIA and are not candidates for carotid surgery, we analyzed the choice between the following secondary prevention strategies: (1) aspirin, 325 mg/d; (2) clopidogrel bisulfate, 75 mg/d; and (3) dipyridamole, 400 mg/d, and aspirin, 50 mg/d.

ASSUMPTIONS

In formulating our model, we made several assumptions. We included the small increase in fatal hemorrhagic stroke secondary to antiplatelet therapy in the baseline stroke-related case fatality rate according to the outcome measured in major clinical trials.1 Adverse effects of treatment were categorized into (1) major gastrointestinal hemorrhage leading to permanent discontinuation of prophylactic therapy; (2) any other hemorrhagic complication leading to permanent discontinuation of prophylactic therapy; and (3) nonhemorrhagic adverse effects, including upper gastrointestinal symptoms, rash, diarrhea, constipation, and headache (in patients taking aspirin plus dipyridamole); all the latter complications led to treatment being withheld in some patients only. We assumed that treatment efficacy of preventing stroke as well as the risks of adverse effects related to therapy remained constant during therapy. Finally, we considered that treatment discontinuation was permanent (even despite the occurrence of a subsequent embolic event), thus increasing the long-term risk of subsequent stroke.

DECISION TREE

Using a decision analysis software program (Decision Maker 7.1; Pratt Medical Group, Boston, Mass), we did a computer simulation to estimate the likely clinical and economic outcomes in a hypothetical cohort of men and women aged 65 years who had experienced stroke or TIA and were followed up until death (Figure 1). The core of our decision tree was a model representing the natural history of patients who had experienced stroke or TIA. Over time, these patients may die of age-, sex-, or cardiovascular-related causes; have recurrent strokes; or have treatment-related complications. To simulate such clinical situations involving events that may occur more than once over time (eg, strokes) at different times we used a Markov model.7,8 In a Markov model, patients move between various health states depending on the chance events modeled in the decision tree and the probabilities of those events. States can be long-term (eg, long-term morbidity after stroke) or short-term (eg, short-term morbidity after major gastrointestinal hemorrhage). Patients may move from one state of health to another in each cycle, which is 1 month long. The simulation continues until all patients are dead and the average value (expected utility) of each strategy is calculated by tracking how much time is spent in each health state and the consequences of being in that state. The states of health are listed in Figure 1. At the beginning of the Markov model, all patients take 1 of the 3 optional prophylactic regimens and begin the simulation in the first state, healthy using prophylactic therapy, no stroke. Then, 4 groups of events are possible. First, patients face the risk of death from age or comorbidity-related causes, and those who survive face the risk of MI (fatal or not fatal). Patients recovering from MI and those without clinical ischemic heart disease are then subjected to the occurrence of hemorrhagic or nonhemorrhagic adverse effects of treatment, which can eventually lead to treatment interruption. In either case, patients face the risk of stroke that could result in death, permanent disability, or resolution. In each cycle, more than 1 event may occur, resulting in a new distribution across the health states.

OUTCOME MEASURES

We examined the outcomes of each strategy in terms of both costs and effectiveness. We represented costs as variable costs, and we gauged effectiveness by using quality-adjusted life-years (QALYs). This scale addresses both longevity and quality of life.9 As life expectancy is calculated by the Markov model, it is adjusted for the loss of quality of life experienced by the patient in each strategy. Quality of life is diminished by reduced functional capabilities in both the short and long term. In accordance with stan-

RESULTS

BASELINE ANALYSIS

Table 3 summarizes the baseline results of our analysis of a hypothetical cohort of 65-year-old patients. Clopidogrel is both more effective and more costly compared with aspirin alone, with a marginal cost-effectiveness ratio of $26,580 per each additional QALY. Prophylactic treatment with aspirin combined with dipyridamole is also more effective than aspirin alone, but it is less costly: thus, it saves both lives and costs and stands out as a dominant strategy.

SENSITIVITY ANALYSES

The earlier results largely depended on the baseline values used in the model, but estimates of these parameters vary in the published literature. Therefore, we examined the effect of changing the values of each parameter through sensitivity analyses. Results of selected 1-way sensitivity analyses comparing clopidogrel and aspirin alone are shown in Figure 2. The results were most sensitive to the efficacy and costs of clopidogrel. When we varied the incremental efficacy of clopidogel in preventing both stroke and MI from 12% and 20% (respective upper range) to 4% and 3% (respective lower range), the cost-effectiveness ratio for clopidogrel changed from $16068 per QALY to $69888 per QALY. Threshold efficacies in preventing stroke and MI below which the cost-effectiveness ratio exceeded $50,000 per QALY were 5.1% and 8%, respectively. When the costs of clopidogrel were divided or multiplied by a factor of 2, its cost-effectiveness ratio changed from $132000 per QALY (daily cost, $1.20) to $63924 per QALY (daily cost, $4.80). The threshold daily cost of clopidogrel above which the cost-effectiveness ratio exceeded $50,000 per QALY was $3.80.
standard principles of economic analyses, we discounted both future costs and QALYs by 3% per year to reflect the higher value of spending a dollar now as opposed to a year from now.10

DATA SOURCES
Probabilities were drawn from a MEDLINE search and examination of the bibliographies of all identified articles. Estimates on (1) the incidence of treatment-related adverse effects, (2) the risks of MI, and (3) the reduction in adverse vascular events (stroke and MI) associated with the use of aspirin with or without dipyridamole and with the use of clopidogrel were based on the number of those events reported in the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial,2 and the second European Stroke Prevention Study (ESPSP-2).3 For the CAPRIE trial, calculations were based only on patients recruited after the occurrence of a cerebrovascular event. Based on published analyses, we estimated the incidence of recurrent stroke in our population by multiplying the age-specific annual risk of stroke in the general population by the relative risk of stroke in high-risk subgroups of patients, such as those with TIA or nondisabling stroke.5,12

These estimates on stroke risk were comparable with estimates of the frequency of ipsilateral and contralateral stroke without surgery in published studies13-16 of high-risk patients. The stroke-related case-fatality rate and the proportion of individuals who experienced nonfatal stroke with long-term disability that required inpatient rehabilitation were obtained from epidemiological surveys.12,17,18 The choice of the quality-adjustment factors was based on existing studies that considered these issues and on previous decision analysis studies.19-22 Table 1 depicts the baseline probabilities, rates, and quality-adjustment factors used in the analysis and the ranges tested in sensitivity analyses.

Our analysis included all health-related costs (in US dollars) associated with each strategy, which were assessed from a societal perspective and discounted at 3% per year (Table 2).24 All costs were inflated to 1998 US dollars. Medical care costs associated with each therapy included the following: (1) daily costs for each antiplatelet regimen; (2) costs of the adverse effects of treatment; (3) costs of stroke and MI for both the short and long term. The costs of aspirin with or without dipyridamole were based on current market prices. The costs of clopidogrel were estimated using the prices of ticlopidine as an anchor point. In some US health plans, the cost of clopidogrel was 20% less to 20% more than that of ticlopidine, whereas in Switzerland and Germany, the cost of clopidogrel exceeded that of ticlopidine by 20% and 30%, respectively. Hospital costs for treatment-related hemorrhagic and nonhemorrhagic adverse effects were based on published estimates from US hospitals. These costs reflected average Medicare reimbursements for the diagnosis related group linked to major gastrointestinal hemorrhage and outpatient costs for the less severe complications.15,23

The costs of stroke included the hospital costs of the acute initial event (all patients), the costs of inpatient rehabilitation for the proportion of patients with severe disability, and the costs for ongoing treatment for all stroke survivors during the remainder of their lives. The costs of hospital care for acute stroke were obtained from average Medicare reimbursements for the diagnosis related group linked to cerebrovascular disorder, in addition to the costs of professional services.12

The costs for patients with severe disability who required inpatient rehabilitation were based on data from rehabilitation services.12,26 The costs for ongoing medical treatment for all stroke survivors, including readmissions to the hospital, physician, outpatient and long-term care (including rehabilitation), as well as prophylactic antiplatelet therapy, were based on Medicare data.12,26 Further analysis of Medicare data demonstrated substantial variation in the costs of stroke and ongoing medical treatment.29 For example, analysis of Medicare stroke costs revealed that in regions with greater use of resources, costs differed by approximately 30% from those in regions with less use of resources.30 In addition, a major cost not directly reflected in Medicare data (because it is generally not covered) is the cost of nursing home care. Thus, although the average cost per stroke is reported to be around $50000, the exact amount of resources consumed for this disorder is difficult to calculate. Coronary heart disease–related costs were extracted from the Coronary Heart Disease Policy Model.31

Results of sensitivity analyses comparing aspirin combined with dipyridamole with aspirin alone revealed that this former strategy remained more effective and less costly than aspirin alone for all variables in the model tested within the ranges depicted in Table 1, except treatment efficacy. When the incremental efficacy of aspirin combined with dipyridamole in preventing stroke and MI decreased to 8% and 3%, respectively (baseline values: 24% and 10%), this strategy became more costly than aspirin alone. However, the marginal cost-effectiveness ratio of the combination strategy remained low ($15804/QALY). When we varied the daily costs of aspirin combined with dipyridamole, its cost-effectiveness ratio changed from cost savings, with a daily cost of $0.30, to $3630 per QALY, with a daily cost of $1.20.

Figure 3 shows the marginal cost-effectiveness ratios of clopidogrel compared with aspirin as a function of the age at which secondary prevention is prescribed. Using the baseline values depicted in Table 1, the marginal cost-effectiveness ratio of clopidogrel came close to $50000 per QALY (exactly $47980) only when prevention was started in patients aged 80 years. However, the cost-effectiveness ratio of clopidogrel was greater than $50000 per QALY whatever the age of the initiation of therapy when the incremental efficacy of clopidogrel in preventing stroke and MI compared with that of aspirin (base case: 8% and 14%, respectively) was divided by a factor of 2 (to 4% and 7%, respectively). For all ages at which antiplatelet therapy was started, aspirin and dipyridamole remained more effective and less costly than aspirin alone, even if the incremental efficacy was divided by 2 (extended dominance).

Our results demonstrate that, compared with aspirin alone, aspirin combined with dipyridamole is both more effective and less costly. In other words, the incremental costs
incurred by this regimen are more than offset by the savings afforded through the avoidance of additional stroke-related costs. It is only when the additional efficacy of aspirin combined with dipyridamole in preventing both stroke and MI is diminished by more than half or when its costs are doubled that this strategy becomes more costly than aspirin; however, the marginal cost-effectiveness ratio remained below $5000 per additional QALY.

Compared with aspirin alone, our analyses showed that the additional costs incurred by clopidogrel are not offset by the savings afforded through its increased clinical benefit and that the cost-effectiveness ratio of clopidogrel is very sensitive to its efficacy in reducing the risks of stroke and MI and related costs. However, except in extreme clinical situations (ie, patients older than 80 years or a scenario in which the marginal efficacy of clopidogrel is reduced by a factor of 2 compared with that of aspirin), this regimen is cost-effective. Specifically, the cost-effectiveness of clopidogrel remains below $50000 per additional QALY in most clinical settings, a figure that compares favorably with those reported for other generally accepted medical interventions to prevent or treat cardiovascular diseases.\textsuperscript{32,33} Furthermore, for patients aged 65 or 70 years, the cost-effectiveness ratio of clopidogrel, which was around $30000 per QALY, may be widely considered appropriate. As the costs of clopidogrel may vary between countries or health care plans, these results should be interpreted in the perspective of costs faced by individual patients. Thus, if the daily cost of clopidogrel exceeds $3.80, then its cost-effectiveness ratio reaches $50000 per QALY.

An incremental cost-effectiveness analysis of clopidogrel compared with dipyridamole combined with aspirin was intentionally omitted because data on these 2 regimens were obtained only from trials without direct comparisons of them. Thus, in light of the literature published to date, we conclude that, compared with aspirin, both new antiplatelet regimens appear cost-effective or even cost saving for secondary prevention in patients who have recently experienced TIA or stroke. This conclusion is robust since it was not modified in sensitivity analyses performed on wide ranges for all critical variables.

Some limitations of our approach deserve comments. First, our analysis was based heavily on patient subgroups derived from a single trial for each regimen: the CAPRIE trial included 6431 patients who had experienced stroke and were followed up for as long as 3 years\textsuperscript{2}; and ESPS-2 examined the use of dipyridamole combined with aspirin in 3299 patients who had experienced TIA or stroke and were followed up for as long as 2 years.\textsuperscript{3} Indeed, the CAPRIE trial also included patients with other atherothrombotic complications (MI and peripheral arterial disease), and ESPS-2 randomized half its population to receive dipyridamole alone or placebo. These patients were excluded from our calculations, which resulted, in favor of clopidogrel, in a relative risk reduction of 8% and 14%, respectively, in preventing stroke and MI instead of the relative risk reduction of 5% and 19%, respectively, observed for the whole population of CAPRIE. However, we included these latter figures in our sensitivity analyses, as well as a scenario in which the incremental efficacy of clopidogrel in preventing stroke and MI would be similar (8.7%). These sensitivity analyses did not change our conclusions. However, it must be recognized that the results of ESPS-2 are at strong variance with the widespread view that dipyridamole use does not add anything to aspirin use.\textsuperscript{1} The very low dose of aspirin and the new galenic form and high dose of dipyridamole used in ESPS-2 might account for this discrepancy. Further trials, including the ESPRIT trial,\textsuperscript{35} should help to clarify this important point in the coming years.

Second, our estimates of the costs of stroke management are based on published Medicare data that do not include nursing home care. Thus, our baseline estimates were likely to underestimate the actual costs of stroke. However, higher stroke-related costs would further decrease the cost-effectiveness of the new antiplatelet therapies since these regimens prevent more strokes than aspirin. Third, we did not consider the potential influence of sex or ethnicity on the prognosis after TIA or stroke or on treatment efficacy.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{decision_tree.png}
\caption{The decision tree. The same prophylactic options are used for all decisions. Patients in the model start the simulation in the first state of health, healthy using prophylactic; no stroke. Three subtrees depict the events that patients face during each cycle of the simulation. LTM indicates long-term morbidity; STM, short-term morbidity; GI, gastrointestinal; and MI, myocardial infarction.}
\end{figure}
In conclusion, our analysis suggests that the use of these new antiplatelet regimens may replace the use of aspirin in patients who experienced TIA or stroke and are not candidates for carotid endarterectomy. A practical approach would be to start therapy with dipyridamole and aspirin, which is the dominant strategy because it saves QALYs and costs.

In the CAPRIE trial and ESPS-2, 64% and 58%, respectively, of the patients were men, but different results according to sex were not reported. Black and Hispanic subjects are likely to represent a minority in European trials. Fourth, the tested scenarios concerned patients aged 65 years, which corresponded exactly to the mean age of the patients in the 2 trials. In practice, many patients may be older than 65 years. However, sensitivity analyses as a function of age at which therapy is started revealed that the incremental cost-effectiveness ratio of clopidogrel compared with aspirin remained below $50 000 at least up to the age of 80 years.

In conclusion, our analysis suggests that the use of these new antiplatelet regimens may replace the use of aspirin in patients who experienced TIA or stroke and are not candidates for carotid endarterectomy. A practical approach would be to start therapy with dipyridamole and aspirin, which is the dominant strategy because it saves QALYs and costs.
in the initial treatment to give these patients a combina-
tion of dipyridamole and aspirin or clopidogrel if this com-
bination is contraindicated or not well tolerated. Finally, this
cclusion does not apply to other atherothrombotic condi-
tions, such as coronary artery disease or peripheral vas-
cular disease, in which the use of the combination of dipy-
iramole and aspirin has not been studied. However, given
the present results, it is certainly worth performing a spe-
cific cost-effectiveness analysis of clopidogrel vs aspirin in
these 2 indications.

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