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Economic Assessment of the Secondary Prevention of Ischaemic Stroke with Dipyridamole plus Aspirin (Aggrenox®/Asasantin®) in France

Jean-Pierre Marissal and *Bernard Selke*

CRESGE-LABORES (URA-CNRS 362), Lille, France

Abstract

Objective: To assess the cost effectiveness of aspirin 25mg plus dipyridamole 200mg twice daily in the secondary prevention of ischaemic stroke, according to the French social security perspective, using efficacy data from the second European Stroke Prevention Study (ESPS-2). The ESPS-2 was a double-blind, placebo-controlled clinical trial which assessed the efficacy of four secondary prevention strategies: (i) placebo; (ii) aspirin (acetylsalicylic acid) 25mg twice daily; (iii) dipyridamole 200mg twice daily; and (iv) aspirin 25mg plus dipyridamole 200mg twice daily.

Method: We performed a cost-effectiveness analysis with Monte Carlo simulations to compute confidence intervals. We combined data from various sources including the Dijon Stroke Registry, Institut National de la Statistique et des Etudes Economiques, Etude du Coût de l'Infarctus Cérébral (Study of the Cost of Cerebral Infarction [ECIC]) study and the ESPS-2 trial.

Results: According to our findings, a preventive strategy with aspirin 25mg plus dipyridamole 200mg twice daily is associated with net benefits per avoided stroke recurrence amounting to $US23 932 (95% CI −$US32 609, $US35 772) compared with aspirin 25mg twice daily alone, and $US31 555 (95% CI $US4921, $US74 515) compared with dipyridamole alone (1997 values). Sensitivity analysis demonstrated that dipyridamole plus aspirin was still cost effective when the average cost of adverse effects per episode (ignored in the original estimation of the cost-effectiveness ratios due to a lack of data) was assumed to be $US8600 (50 000 French francs); this cost is unlikely as most of the adverse effects associated with aspirin plus dipyridamole are only slight to moderate in severity.

Conclusions: In the secondary prevention of stroke in France, this study suggests, given its underlying assumptions and data, that aspirin 25mg plus dipyridamole 200mg twice daily is likely to be a cost-effective strategy from the social security perspective, when compared with other relevant strategies that were evaluated in the ESPS-2 trial.

There is increasing interest in the literature regarding the economic impact of using antiplatelet agents in the secondary prevention of cardiovascular and cerebrovascular diseases. Van Bergen et al.[1] showed that the extra costs associated with long-term oral anticoagulant treatment are outweighed by a decrease in the hospital costs in patients with prior myocardial infarction. Scott and Scott,[2] using data from the second European Stroke Prevention Study (ESPS-2) on the secondary prevention of stroke in patients with a prior history of ischaemic stroke, showed that treatment either with a combination of dipyridamole and aspirin (acetylsalicylic acid) or with aspirin alone led to savings compared with placebo (923.39 New Zealand dollars ($NZ) and $NZ905.16 [1996 values] per patient, respectively). Similar results were found by Chambers et al.[3] and Sarasin et al. [4] based on a Markov model in the same population. Results of the latter study suggested that combined treatment with aspirin 25mg and dipyridamole 200mg twice daily in patients aged 65 years and older may be more effective and a less costly strategy than aspirin 325mg per day alone, and that clopidogrel was associated with an inconclusive cost-effectiveness ratio compared with aspirin, due to a high daily treatment cost. Finally, Marissal et al.[5] highlighted the cost effectiveness of aspirin or lysine acetylsalicylate in the prevention of myocardial infarction and ischaemic stroke in patients with a high cardiovascular and cerebrovascular risk (history of myocardial infarction, ischaemic stroke, stable and unstable angina).

Although the cost-effectiveness analysis of aspirin plus dipyridamole, as a combined treatment, is well documented, there is still a lack of published data on the cost of stroke recurrence and some weaknesses in the statistical frameworks used in analyses conducted to date. These have led to inconclusiveness in the final results of economic evaluations.

The purpose of this paper is to assess the cost effectiveness, from the social security perspective, of using aspirin plus dipyridamole (Aggrenox®/Asasantin®[1])for the secondary prevention of stroke in France compared with aspirin or dipyridamole alone. Efficacy data were derived from the ESPS-2 trial. We used new cost data to capture the effect of dipyridamole 200mg plus aspirin 25mg twice daily on the severity of the stroke recurrence and performed Monte Carlo simulations to test for the statistical significance of the cost-effectiveness ratios.

Methodology

Data Sources

Epidemiological Data

Using the following data sources, we defined a hypothetical cohort of patients who were eligible for the secondary prevention of ischaemic stroke.

- The stroke registry of Dijon,[6] which provides an estimation of the annual incidence of first ever strokes in France according to sex, age group and aetiology (cerebral infarction, transient ischaemic attack, lacunes, subarachnoid haemorrhage, other haemorrhagic strokes) based on observed cases in Dijon, France. More recent papers have been published based on the Dijon Stroke Registry, providing new evidence on the increasing incidence of cerebral cortico-subcortical infarcts in France among people aged 75 years and older,[7] but the reference used in this paper has the advantage of providing precise data on the sex and age of patients with an incidence of first stroke, by type of ischaemia.
- Data provided by the Institut National de la Statistique et des Etudes Economiques on the employment status of workers in the French population, according to sex and age, in March 1998[8] and the unemployment rate in 1997[9] (table I). Combining the employment data with data on the incidence of first stroke enables the determination of the occupational status of the hypothetical cohort of patients eligible for secondary prevention at the time of the first event.
- Data from the Etude du Coût de l'Infarctus Cérébral (Study of the Cost of Cerebral Infarction [ECIC]) trial[10,11] (table II) on the occupational

1 The use of trade names is for product identification only and does not imply endorsement.

Table I. Employment status of the French population per sex and age group; data provided by the Institut National de la Statistique et des Etudes Economiques[8,9]

Age group (years)	Women (%)			Men (%)		
	on the labour work force	employed	unemployed	on the labour work force	employed	unemployed
15–24	25.0	17.4	7.6	32.1	24.7	7.4
25–49	78.7	68.5	10.2	95.1	86.0	9.1
50+	28.7	26.1	2.6	35.2	32.3	2.9

outcome (unemployment, long-term sick leave, short-term disability, return to the labour force) of 435 patients (63% male, average age at the time of stroke – 65.8 years) hospitalised for cerebral infarction and including 105 workers (24.1%). Comparing the occupational status of the patients at the time of the first stroke with data on the occupational outcome derived from the ECIC study allowed an estimation of the occupational status of the eligible hypothetical cohort of patients after the first stroke.

The extrapolation of the incidence data in Dijon to the French population gave an estimated number of incident cases of first ischaemic stroke (transient ischaemic attack, cerebral infarction, and lacunes) equal to 66 200, corresponding to an average annual incidence rate of first cases surviving to the acute phase of 113.0 cases per 100 000 inhabitants.[6] Using these data together with the data on occupational status of the French population[9] and the employment outcome of patients after an episode of cerebral infarction[10,11] gave an estimated number of patients in the labour force after the first event equal to 3450 patients (2250 men and 1200 women), which corresponded to a proportion of workers equal to 5.21% (95% CI 5.04%, 5.38%) in that population.

Efficacy Data

Efficacy data on the use of dipyridamole and aspirin in the secondary prevention of ischaemic stroke were derived from the ESPS-2 double-blind, placebo-controlled clinical trial[12] (table III). This double-blind, placebo-controlled trial in 6602 patients provided an assessment of the 24-month efficacy of four strategies in the secondary prevention of stroke: (i) placebo (n = 1649); (ii) aspirin 25mg twice daily (n = 1649); (iii) dipyridamole 200mg twice daily (n = 1654); and (iv) dipyridamole 200mg plus aspirin 25mg twice daily (n = 1650) [58% male, average age = 66.7 years, 76% with recent (not necessarily first) ischemic stroke, 24% with recent (not necessarily first) transient ischemic attack].

A comparison between the different treatments under evaluation showed that the combined treatment with dypiridamole plus aspirin was associated with a significant decrease in the risk of fatal and nonfatal stoke (primary endpoint) when compared with dypiridamole alone (RR = 0.72 [0.58–0.90]) and aspirin alone (RR = 0.74 [0.59–0.92]) although there was no statistical difference in terms of all cause death and in the combined stroke (fatal and nonfatal) and all cause death endpoint. A closer look at the results also showed a significant reduction in the risk of severe nonfatal stoke for combined treatment (see table III). For the purpose of the cost analysis, the rates of efficacy per level of severity of stoke recurrence were expressed as a 1-year rate by computing the square root of the 2-year rate of efficacy, to comply with the time structure of the cost data obtained from the ECIC study.

Table II. Employment outcome after an occurrence of cerebral infarction in 105 workers followed during an 18-month Etude du Coût de l'Infarctus Cérébral (Study of the Cost of Cerebral Infarction [ECIC]) trial[10]

Employment consequence	n	%
Back to previous work	33	31
Modifications in the work	30	29
Unemployment	2	2
Invalidity	18	17
Long-term sick leave	11	10
Retirement	9	9
Other withdrawals	2	2
Total	**105**	**100**

Table III. Efficacy of the different preventive strategies under evaluation in the Second European Stroke Prevention Study (ESPS-2)[12]

Endpoint	Placebo group			Aspirin (acetylsalicylic acid) 25mg twice daily			Dipyridamole 200mg twice daily			Aspirin 25mg plus dipyridamole 200mg twice daily			Between-groups difference test[a]
	n	%	SD (%)	n	%	SD (%)	n	%	SD (%)	n	%	SD (%)	
Nonfatal stroke													
Rankin 0[b]	3	0.18	0.10	4	0.24	0.12	10	0.60	0.19	7	0.42	0.16	
Rankin 1	33	2.00	0.34	31	1.88	0.33	19	1.15	0.26	36	2.18	0.36	
Rankin 2	51	3.09	0.43	36	2.18	0.36	38	2.30	0.37	25	1.52	0.30	<0.01
Rankin 3	50	3.03	0.42	52	3.15	0.43	37	2.24	0.36	17	1.03	0.25	
Rankin 4	57	3.46	0.45	33	2.00	0.34	40	2.42	0.38	26	1.58	0.31	
Rankin 5	16	0.97	0.24	11	0.67	0.20	18	1.09	0.26	8	0.48	0.17	
Total	210	12.73	0.82	167	10.13	0.74	162	9.79	0.73	119	7.21	0.64	<0.001
Fatal stroke	22	1.33	0.28	20	1.21	0.27	28	1.69	0.32	20	1.21	0.27	NS
Nonfatal MI	29	1.76	0.32	17	1.03	0.25	33	2.00	0.34	18	1.09	0.26	0.01
Fatal MI	16	0.97	0.24	22	1.33	0.28	15	0.91	0.23	17	1.03	0.25	NS

a Bilatéral χ^2 test.

b The Rankin scale is a measure of stroke severity. A score of 1 indicates a slightly disabling stroke and a score of 5 indicates a severe disabling stroke.

MI = myocardial infarction; **NS** = not significant.

Cost Data

Secondary Prevention Costs

Daily drug treatment costs of the study drugs were based on French prices in 2000 values (drug costs were deflated by the 1999–2000 increase in the price of drugs in France to obtain 1997 values) obtained from Vidal[2]: (i) $US0.00 per day for placebo; (ii) $US0.106 per day for aspirin 25mg twice daily, corresponding to the daily treatment cost of Kardégic® (1997 French Francs [FF]/$ exchange rate)[3] in doses ranging from 75mg to 300mg; (iii) $US0.352 for dipyridamole 200mg twice daily; and (iv) $US0.563 for the combined treatment with dipyridamole 200mg plus aspirin 25mg twice daily. We assumed that the number of visits were the same in each treatment arm.

Stroke Recurrence Costs

Cost data per degree of severity of stroke recurrence (as measured by the simplified Rankin scale) were derived from the ECIC study,[10] which provided an 18-month assessment of the ambulatory and hospital (short-, mid- and long-term hospital stay) costs in 1997 values ($US1 = FF5.83). The following costing methodology was used in the study.

- The cost of a short-term hospital stay for the acute and post-acute phases of a cerebral infarction was based on the Programme Médicalisé des Systèmes d'Information, a national source of data that is representative of the French public and private not-for-profit hospital costs.
- The cost of ambulatory medicine, nursing care, physiotherapy and tests was based on the data collected by questionnaires and was valued according to the Social Security reimbursement fees.
- Drug costs were computed via: (i) an extrapolation of the pharmaceutical prescriptions at the time of the hospital discharge to the 3-month

2 A French government official publication compiling all drugs reimbursed by the French Social Security, indicating the price and reimbursement rate.

3 The use of trade names is for product identification purposes only and does not imply endorsement. Kardegic® (lysine acetylsalicylate) is a compound that is indicated in the secondary prevention of cardiovascular and cerebrovascular ischaemic events. This compound is a constant price for dosages ranging from 75mg to 300 mg. Therefore, we assumed an equal price for the 25mg dose form.

period following the acute hospital phase; and (ii) an extrapolation of the drug prescriptions declared by the patient in a questionnaire for the next 15 months.

- The cost of equipment to adapt the home was computed from the declarations of the patients and the reimbursed price of the devices.
- The cost of nursing home care was derived from Social Security data.

Results of the ECIC study (see figure 1) showed that cerebral infarction was associated with an average 18-month direct medical cost amounting to $US11 850 (1997 values, $US1 = FF5.83) in its non disabling forms, to $US13 870 in the case of slightly disabling forms (Rankin = 1), $US20 570 in moderately disabling forms (Rankin = 2 and 3), and to $US39 170 in the case of severely disabling forms (Rankin = 4 and 5). We also noted that rehabilitation costs were strongly sensitive to the level of disability, with the percentage of total direct medical costs ranging from less than 5% in the non disabling and slightly disabling forms to 16.0% in moderately disabling forms, and to 42.0% in severely disabling cerebral infarctions.

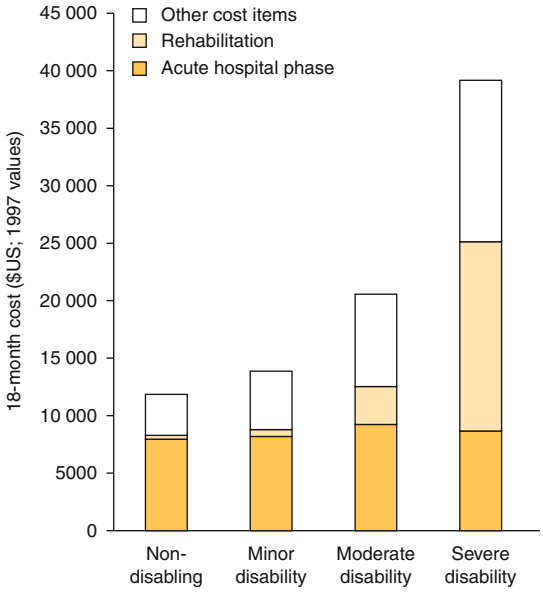

Fig. 1. Components of the 18-month direct medical cost of cerebral infarction according to the severity of the disease in France (1997 $US [$US1 = 5.83 French francs]).[10]

Table IV. Direct medical costs of cerebral infarction. Extrapolation of the Etude du Coût de l'Infarctus Cérébral (Study of the Cost of Cerebral Infarction [ECIC] data[10] to a 24-month period (1997 $US)[a,b]

Disability level	Time	Average cost	SD of cost
No disability	Acute phase	7 962	184
	First year non-acute	2 591	395
	Second year non-acute	2 591	395
	24-month cost	13 144	791
Rankin = 1	Acute phase	8 189	169
	First year non-acute	3 785	423
	Second year non-acute	3 785	423
	24-month cost	15 758	846
Rankin = 2 and 3	Acute phase	9 249	441
	First year non-acute	7 546	1257
	Second year non-acute	7 546	1257
	24-month cost	24 342	2515
Rankin = 4 and 5	Acute phase	8 670	262
	First year non-acute	20 332	1259
	Second year non-acute	20 332	1259
	24-month cost	49 333	2518

a The Rankin scale is a measure of stroke severity. A score of 1 indicates a slightly disabling stroke and a score of 5 indicates a severe disabling stroke.

b SD data for 24-month costs have been rounded.

The 18-month healthcare costs were expressed on a 24-month basis as shown in equation 1:

$$C_{24\ \text{months}} = C_{\text{acute}} + C_{\text{non acute}} \times \frac{24}{18}$$

where costs associated to the acute phase (C_{acute}) are equivalent to the initial hospital stay, and non acute costs ($C_{non\ acute}$) refer to all the other cost items, assuming that the non acute costs are constant over time (see table IV).

Indirect costs were estimated according to the Social Security perspective. Cost from sick leave was computed from the following data: (i) an average time out of the labour force estimated to be 4.5 months in the ECIC sample; (ii) an annual wage per occupied worker equal to $US20 897 in 1996 (INSEE); and (iii) an average rate of social security tax equal to 25% of the annual wage (INSEE).

Table V. Total costs and cost-effectiveness ratio for the secondary prevention strategies[a]

Strategy (all twice daily)		Aspirin (acetylsalicylic acid) 25mg	Dipyridamole 200mg	Aspirin 25mg plus dipyridamole 200mg
Cost of the different strategies ($US) [1997 values]				
Drug treatment costs		4 781 307	15 809 160	25 294 655
Sick leave	Minimum 95% CI	1 216 469	1 174 861	823 828
	Mean	1 541 946	1 498 156	1 107 131
	Maximum 95% CI	1 867 657	1 829 427	1 383 671
Direct healthcare cost	Minimum 95% CI	129 749 427	136 141 768	84 068 567
	Mean	170 373 223	179 599 348	118 270 122
	Maximum 95% CI	212 490 635	224 192 143	152 071 267
Total cost	Minimum 95% CI	135 755 549	153 159 746	110 229 470
	Mean	176 696 476	196 906 664	144 671 909
	Maximum 95% CI	219 139 770	241 745 131	178 695 333
Cost per treated patient	Minimum 95% CI	2051	2314	1 665
	Average	2669	2974	2 185
	Maximum 95% CI	3310	3652	2 699
Avoided strokes with combined treatment				
Number of avoided strokes	Minimum 95% CI	60	−97	
	Mean	1831	1646	
	Maximum 95% CI	3624	3418	
Cost-effectiveness ratios ($US) [1997 values]				
Net benefits combined treatment	Minimum 95% CI	20 131 354	−1 267 817	
	Mean	32 024 567	52 231 755	
	Maximum 95% CI	85 466 981	106 776 662	
Cost-effectiveness ratios	Minimum 95% CI	−32 609	4921	
	Mean	23 932	31 555	
	Maximum 95% CI	35 772	74 515	
	Kolmogorov-Smirnov test[a]	p < 0.0001	p < 0.0001	
Statistical significance of the ratios	S' statistics	7325	1243	
	Student's t value	3.3	25.4	
	p-Value	< 0.05	< 0.05	

a Testing the normality of the statistical distribution of the cost-effectiveness ratios.

S' = SD of the mean.

Cost-Effectiveness Ratios

We used cost-effectiveness ratios as defined in the Garber and Phelps[13] framework to assess the economics of dipyridamole 200mg plus aspirin 25mg (ASS) in the secondary prevention of ischaemic stroke compared with a preventive strategy i (aspirin 25mg twice daily or dipyridamole 200mg twice daily). These cost-effectiveness ratios are defined by the following equation (equation 2):

$$\text{Cost effectiveness} = \frac{TC_{ASS} - TC_i + \sum_j (Stroke_{i,j} - Stroke_{ASS,j}) \times CStroke_j}{\sum_j (Stroke_{i,j} - Stroke_{ASS,j})}$$

where TC is the treatment cost, Stroke is the number of incident strokes in each treatment group, CStroke is the cost of a stroke according to the degree of disability, and j is the level of initial disability, as measured by the simplified Rankin scale.

Equation 2 does not take into account the cost of adverse events. Due to the lack of data on the costs of discriminating adverse effects (headaches, diarrhoea and bleeding), we chose not to take them into account in the first steps of the calculations but to evaluate their possible effects on costs in the sensitivity analyses.

Statistical Methods

We performed a Monte Carlo simulation to compute confidence intervals for the cost-effectiveness ratios. This method consists of estimating the statistical distribution of a dependant variable (here, the cost-effectiveness ratio of secondary prevention strategies for ischaemic stroke) according to the statistical distribution of a set of independent variables entering in the estimation of the cost-effectiveness ratio.

The main advantage of this method compared with traditional sensitivity analyses is that we can use statistical tests to determine if the strategy exhibits statistically significant benefits or not. Furthermore, the Monte Carlo simulation gives the limits between which there is a high likelihood the cost-effectiveness ratio might lay (for example, in the usual case, the ratio will range from x to y with a 95% probability of occurrence). This avoids the main problem facing traditional sensitivity analyses, that is the assessment of the robustness of the ratio based on extreme values of parameters, which have a low probability of occurrence (<5%).

We performed the simulations based on a hypothetical cohort of 10 000 cases according to the following parameters: (i) the efficacy parameters of the different preventive strategies according to the severity of the recurrence; (ii) the direct costs of stroke recurrence per degree of severity of episode (Rankin scale); and (iii) the proportion of employed workers at the time of stroke recurrence.

Costs were discounted at 5%.

Results

Cost-Effectiveness Ratios

Table V displays the estimation of the total cost associated with each treatment strategy. According to these results, the average cost per treated patient is approximately $US2669 (95% CI $US2051, $US3310) in the aspirin alone group, $US2974 (95% CI $US2314, $US3652) in the dipyridamole alone group, and $US2185 (95% CI $US1665, $US2699) in the dipyridamole 200mg plus aspirin 25mg group. Most of the total cost was attributable to a direct healthcare costs related to the occurrence of ischaemic strokes, that is, 96.4% of the total cost in the aspirin alone group, 91.2% in the dipyridamole alone group, and 81.8% in the dipyridamole 200mg plus aspirin 25mg group, respectively.

Table V also shows that a preventive treatment with dipyridamole 200mg plus aspirin 25mg is associated with an average decrease in the occurrence of stroke recurrences equal to 1831 cases (95% CI 60, 3624) compared with aspirin alone, and 1646 cases (95% CI −97, 3418) compared with dipyridamole alone. Although the CIs were wide, a t-test comparing the mean with a zero assumption proved to be significant, indicating the mean was significantly different to zero.

According to the estimation of the cost-effectiveness ratios (table V), prevention of stroke recurrence with dipyridamole 200mg plus aspirin 25mg is associated with net benefits per avoided stroke of $US23 932 (95% CI −$US32 609, $US35 772); $p < 0.0001$) compared with aspirin 25mg twice daily alone, and $US31 555 (95% CI $US4921, $US74 515); $p < 0.0001$) compared with dipyridamole alone.

Cost of Adverse Effects

The lack of data on the cost of adverse effects (headaches, diarrhoea, bleeding) led us to compute an *ad hoc* statistical distribution of the average cost of adverse events, by setting the cost-effectiveness ratios to zero. As a consequence, we estimated the average cost of adverse effects (CAE) as equation 3:

Table VI. Results of the simulations on the mean cost ($US, 1997 values) of adverse effects for dipyridamole 200mg plus aspirin (acetylsalicylic acid) 25mg twice daily strategy

Items		Compared with aspirin 25mg twice daily	Compared with dipyridamole 200mg twice daily
Increased no. of adverse effects with the combined treatment	Minimum 95% CI	5024	−1216
	Mean	7234	993
	Maximum 95% CI	9511	3270
Cost of an episode of an adverse effect	Minimum 95% CI	4125	−791 742
	Mean	12 650	174 198
	Maximum 95% CI	23 057	826 491
	Kolmogorov-Smirnov test[a]	p < 0.0001	p < 0.0001
Statistical tests	S' statistics	$49	$79 162
	Cost of managing an adverse effect >$8576	83.9	2.09
	p-Value[a]	<0.05	<0.05

a Tests the normality of the statistical distribution of the mean cost of adverse events.

S' = SD of the mean.

$$TC_{ASS} - TC_i + \sum_j (Stroke_{i,j} - Stroke_{ASS,j}) \times CStroke_j + CSE \times (SE_i - SE_{ASS}) = 0$$

where again TC is the treatment cost of the strategies, Stroke is the number of stroke recurrences, CStroke is the cost of the recurrence, j is the degree of disability, and AE is the total number of adverse effects in each strategy. This led to equation 4:

$$CSE = \frac{TC_{ASS} - TC_i + \sum_j (Stroke_{i,j} - Stroke_{ASS,j}) \times CStroke_j}{SE_{ASS} - SE_i}$$

that is the ratio of the statistical distribution of the net benefits associated with dipyridamole 200mg plus aspirin 25mg compared with a strategy i to the statistical distribution of the differential number of adverse effects in the combined treatment compared with strategy i.

The results of our estimations are displayed in table VI. They show that the average cost of adverse effects has to be greater than $US8600 (approximately FF50 000) to significantly affect the cost effectiveness of dipyridamole 200mg plus aspirin 25mg in our analysis. This is unlikely as most of the adverse effects of dipyridamole 200mg plus aspirin 25mg are only slight to moderate in severity.

Discussion

Our results corroborate and reinforce the conclusions of previously published studies on the economic benefit of dipyridamole 200mg plus aspirin 25mg in the secondary prevention of ischaemic stroke. Our study suggests that this preventive strategy may be cost effective in a French context.

Our evaluation was based on new data on the cost of ischaemic stroke and on a statistical framework that allowed us to test the statistical significance of the cost-effectiveness ratios. We used cost data per degree of severity of stroke recurrence which enabled us to measure the impact of dipyridamole plus aspirin in terms of both avoiding stroke recurrences and reducing the severity of stroke recurrence; this has not been assessed in previously published studies. Furthermore, the use of Monte Carlo simulations enabled us to perform parametric statistical tests to assess the statistical significance of the cost-effectiveness ratios. Monte Carlo simulations have the advantage of avoiding sensitivity testing of cost-effectiveness ratios in highly improbable situations (that is situations with a low likelihood to occur),

which is the main problem facing standard univariate sensitivity analysis.

Limitations of our study included the reliance on French epidemiologic data dating from the early 1990s. These were the only precise data on the sex and age of the population sustaining a first stroke, which was needed to consider the consequence of stroke recurrence on work. Another possible bias in the analysis was the necessity to gather different data sources concerning particular populations, namely the Dijon population and the ECIC and ESPS-2 samples, although such gathering is usual to perform an economic analysis. We pooled the epidemiologic data from the Dijon registry and the cost data from the ECIC sample and assumed that the cost of stroke recurrence was not sensitive to age and sex, and that the results of the ESPS-2 sample could be fully extrapolated to the French population Finally, a potential bias comes from the method of estimation of the ambulatory costs of stroke per level of severity in the ECIC study. Indeed, the authors of the study extrapolated a one-time estimation of the post-acute consumption of ambulatory costs to the whole post-acute phase, which may have led to some problems in the estimation of the true time trend of the cost of stroke.

Two antiplatelet-based strategies have proven beneficial in the secondary prevention of ischaemic stroke: dipyridamole 200mg plus aspirin 25mg and aspirin alone.[12] A third strategy, clopidogrel, did not prove to be cost effective in the sole secondary prevention of stroke recurrences,[14] although the clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) trial concluded that a preventive treatment with clopidogrel was associated with a decrease in the risk of deaths, myocardial infarction and stroke, amounting to an 8.7% reduction in relative risk in patients with a history of myocardial infarction, stroke or peripheral arterial obliterative disease, compared with aspirin.[14] Indeed, an analysis of the CAPRIE data by subpopulation and individual criteria shows that clopidogrel is associated with a significant impact limited to patients with a history of peripheral arterial obliterative disease and in preventing myocardial infarction alone.

An economic evaluation of dipyridamole 200mg plus aspirin 25mg compared with aspirin alone in commonly prescribed daily doses (from 75–300 mg/day in the secondary prevention of stroke) is difficult because the ESPS-2 trial used daily doses of aspirin that have not yet been proven to be effective in the secondary prevention of cerebral events. Indeed, evidence exists that aspirin 75mg daily has the same effectiveness as higher dosages in the prevention of cardiovascular events,[15,16] but the equivalence of aspirin 50mg daily with higher daily doses has still to be ascertained. This is a considerable limitation in the work by Sarasin et al.,[4] which compared dipyridamole 200mg plus aspirin 25mg with aspirin 325mg daily. That is why we decided to assess the cost effectiveness of dipyridamole 200mg plus aspirin 25mg compared with aspirin 25mg daily in the context of the ESPS-2 trial.

Conclusion

In the secondary prevention of stroke in France, this study suggests, given its underlying assumptions and data, that aspirin 25mg plus dipyridamole 200mg twice daily is likely to be a cost-effective strategy, when compared with other relevant strategies that were evaluated in the ESPS-2 trial, from a social security perspective.

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Correspondence and offprints: Dr *Jean-Pierre Marissal*, CRESGE-LABORES (URA-CNRS 362), 1, rue Norbert Segard, B.P. 109, F-59016, Lille, France.