Journal of the American Heart Association

ORIGINAL RESEARCH

Cost-Effectiveness of Cilostazol Added to Aspirin or Clopidogrel for Secondary Prevention After Noncardioembolic Stroke

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BACKGROUND: The objective of the study was to assess the cost-effectiveness of cilostazol (a selective phosphodiesterase 3 inhibitor) added to aspirin or clopidogrel for secondary stroke prevention in patients with noncardioembolic stroke.

METHODS AND RESULTS: A Markov model decision tree was used to examine lifetime costs and quality-adjusted life years (QALYs) of patients with noncardioembolic stroke treated with either aspirin or clopidogrel or with additional cilostazol 100 mg twice daily. Cohorts were followed until all patients died from competing risks or ischemic or hemorrhagic stroke. Probabilistic sensitivity analysis using Monte Carlo simulation was used to model 10 000 cohorts of 10 000 patients. The addition of cilostazol to aspirin or clopidogrel is strongly cost saving. In all 10 000 simulations, the cilostazol strategy resulted in lower health care costs compared with aspirin or clopidogrel alone (mean $13 488 cost savings per patient; SD, $8087) and resulted in higher QALYs (mean, 0.585 more QALYs per patient lifetime; SD, 0.290). This result remained robust across a variety of sensitivity analyses, varying cost inputs, and treatment effects. At a willingness-to-pay threshold of $50 000/QALY, average net monetary benefit from the addition of cilostazol was $42 743 per patient over their lifetime.

CONCLUSIONS: Based on the best available data, the addition of cilostazol to aspirin or clopidogrel for secondary prevention following noncardioembolic stroke results in significantly reduced health care costs and a gain in lifetime QALYs.

Key Words: cilostazol ■ cost-effectiveness ■ ischemic stroke ■ secondary prevention

The mainstay of long-term medical management for patients with noncardioembolic stroke is antiplatelet therapy along with vascular risk factor reduction.[1] In North America, aspirin and clopidogrel are the most commonly prescribed antiplatelets for long-term secondary stroke prevention. Cilostazol, a selective phosphodiesterase 3 inhibitor, is used in combination with aspirin or clopidogrel in some Asian countries for stroke prevention but is rarely used for this purpose outside of Asia.[2] A recent meta-analysis found that cilostazol added to aspirin or clopidogrel for long-term secondary prevention was associated with lower recurrent ischemic stroke without increased risk of hemorrhagic stroke.[3] Cilostazol is believed to act through pleiotropic effects including decreased cyclic AMP activation, which reduces platelet aggregation.[4–6]

While multiple trials have studied the clinical effectiveness of cilostazol, research into the cost-effectiveness of cilostazol has been limited. Given its low cost, cilostazol has the potential to be a cost-effective treatment for secondary stroke prevention. A Japanese study from 2006 showed that cilostazol was cost-effective when used instead of aspirin for secondary stroke prevention at an incremental cost-effectiveness ratio of ¥1.8 million per quality-adjusted life year (QALY), which equals approximately $16 000 per QALY.[7] In this study, we evaluated the cost-effectiveness of cilostazol added to aspirin or clopidogrel for secondary stroke

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Presented in part at the International Stroke Conference, February 9–11, 2022 in New Orleans, Louisiana, and published in abstract form (Stroke. 2022;53:ATP81.doi: 10.1161/str.53.suppl_1.TP81).

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024992

For Sources of Funding and Disclosures, see page 7.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Modeling based on the best available literature shows the addition of cilostazol to aspirin or clopidogrel following noncardioembolic stroke can result in significantly reduced health care costs and a gain in quality-adjusted life years in the United States.

What Are the Clinical Implications?

- Confirmation with high-quality data from randomized trials that include a high proportion of non-Asian patients is needed.
- Clinicians should consider the use of cilostazol for secondary stroke prevention when caring for patients with a history of noncardioembolic stroke, especially for patients of Asian descent.

Nonstandard Abbreviations and Acronyms

CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events
CATHARSIS	Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis
CSPS.com	Cilostazol Stroke Prevention Study for Antiplatelet Combination
mRS	modified Rankin Scale
PATCH	Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy
POINT	Platelet-Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke Trial
QALYs	quality-adjusted life years
TOSS	Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis

prevention in patients with noncardioembolic stroke from a US payer/Medicare perspective.

METHODS

Model Structure

A Markov model decision tree was used to compare the estimated lifetime costs and QALYs of patients with noncardioembolic stroke treated with monotherapy (aspirin or clopidogrel) to those treated with dual therapy (cilostazol added to aspirin or clopidogrel). The monotherapy strategy contained a mixture of patients treated with aspirin or clopidogrel with the base-case set at 41% aspirin as in the CSPS.com (Cilostazol Stroke Prevention Study for Antiplatelet Combination) study with other proportions examined in a sensitivity analysis.[8] Half-cycle corrections were applied for all analyses. A cycle length of 1 year, a US payer/Medicare perspective, and a discount rate of 3% (as per convention for cost-effectiveness analysis in the United States) applied to both costs and benefits were used. Analyses were conducted using Amua (Amua_0.3.0, Boston, MA). The data that support the findings of this study are available from the corresponding author upon reasonable request. As all data used for modeling were obtained from the literature, no institutional review board approval was sought for this project.

We used a Monte Carlo simulation to model cohorts of 10 000 patients. Cohorts were followed until all patients died either from competing risks or ischemic or hemorrhagic stroke. Four health states were defined for patients in the cohorts: (1) neurologically intact, defined as a score of 0 on the modified Rankin Scale (mRS); (2) mild disability (score of 1–2 on the mRS); (3) moderate to severe disability (score of 3–5 on the mRS); and (4) deceased (mRS score of 6). Further model details are available within our supplement (Figure S1). Worsening of neurological disability was assumed to occur only through recurrent ischemic stroke or intracranial hemorrhage.

Deaths from competing risks were derived using 2017 US life tables and adjusted for age and neurological disability for each cycle, using a relative risk for annual mortality of 1.375 for an mRS score of 1 to 2 and 3.234 for an mRS score of 3 to 5 at each age.[9] Risk of death from nonintracranial hemorrhage (extracranial hemorrhage) was assumed to be captured in competing risks.

Modeled Population

The baseline cohort was modeled with truncated normal distribution to have an average age of 70 years (SD, 9.2), maximum age of 85, and a minimum age of 20 as per the CSPS.com trial. The baseline cohort was distributed in a range of disability states corresponding to the proportions of disability observed 90 days after stroke among patients in the POINT (Platelet-Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke Trial) trial (63% mRS score of 0, 30% mRS score of 1–2, 7% mRS score of 3–5).[10]

Model Estimates

Clinical parameters were derived from published randomized controlled trials of patients with stroke (Table 1). Base rates of recurrent ischemic stroke on aspirin and clopidogrel were derived from the subgroup of patients

Table 1. Model Inputs

Variable	Estimate	Distribution	References
Annual risk of recurrent ischemic stroke %,*			
Clopidogrel only	5.2	Beta (315, 5739)	CAPRIE trial[11]
Aspirin only	5.7	Beta (338, 5641)	CAPRIE trial[11]
Clopidogrel with cilostazol	2.5	Beta (154, 5900)	CAPRIE trial[11] adjusted with HR from CSPS.com (0.49)[8]
Aspirin with cilostazol	2.8	Beta (166, 5813)	CAPRIE trial[11] adjusted with HR from CSPS.com 0.49)[8]
Annual risk of major bleeding %*	2.4	Beta (45, 1834)	CSPS.com[8]
% major extracranial bleeding	66.7	Beta (30, 15)	CSPS.com[8]
% intracranial bleeding	33.3	Beta (15, 30)	CSPS.com[8]
Outcomes after recurrent ischemic stroke, %			
mRS 0	17.1	Dir (46, 120, 86, 18)	POINT trial[10]
mRS 1–2	44.4	Dir (46, 120, 86, 18)	POINT trial[10]
mRS 3–5	31.8	Dir (46, 120, 86, 18)	POINT trial[10]
Death	6.7	Dir (46, 120, 86, 18)	POINT trial[10]
Outcomes after intracranial hemorrhage, %			
mRS 0	1.9	Dir (4, 24, 110, 73)	PATCH trial[12]
mRS 1–2	11.4	Dir (4, 24, 110, 73)	PATCH trial[12]
mRS 3–5	52.1	Dir (4,24,110,73)	PATCH trial[12]
Death	34.6	Dir (4,24,110,73)	PATCH trial[12]
Health utilities after stroke (USA)			
mRS 0	0.92	N (0.92, 0.12^2) truncated at 1 and −0.5	VISTA study[13]
mRS1–2	0.81	N (0.81, 0.14^2) truncated at 1 and −0.5	VISTA study[13]
mRS3–5	0.40	N (0.40, 0.22^2) truncated at 1 and −0.5	VISTA study[13]
Costs (2020 USD)			
Annual cost of cilostazol	$109.16	N/A	National Acquisition Center (NAC) Contract Catalog Search Tool[15] (CCST)-Median cost
Annual cost of clopidogrel	$27.55	N/A	National Acquisition Center (NAC) Contract Catalog Search Tool[15] (CCST)-Median cost
Annual cost of aspirin	$3.39	N/A	National Acquisition Center (NAC) Contract Catalog Search Tool[15] (CCST)-Median cost
Annual health maintenance cost of mRS 0 following stroke	$10 569	N/A	Cost study[14]
Annual health maintenance cost of mRS 1–2 following stroke	$13 985	N/A	Cost study[14]
Annual health maintenance cost of mRS 3–5 following stroke	$51 514	N/A	Cost study[14]
Event cost of ischemic stroke			
18–34 y	$19 183	N/A	Cost study[21]
35–44 y	$17 275	N/A	Cost study[21]
45–54 y	$15 589	N/A	Cost study[21]
55–64 y	$14 866	N/A	Cost study[21]
65–74 y	$13 620	N/A	Cost study[21]
75–84 y	$13 146	N/A	Cost study[21]
>85 y	$12 456	N/A	Cost study[21]
Event cost of intracranial hemorrhage			
18–34 y	$38 464	N/A	Cost study[21]
35–44 y	$41 962	N/A	Cost study[21]

(*Continued*)

Table 1. Continued

Variable	Estimate	Distribution	References
45–54 y	$36 145	N/A	Cost study[21]
55–64 y	$32 166	N/A	Cost study[21]
65–74 y	$24 601	N/A	Cost study[21]
75–84 y	$16 905	N/A	Cost study[21]
>85 y	$14 813	N/A	Cost study[21]
Event cost of extracranial hemorrhage	$7 306	N/A	Cost study[22]

CAPRIE indicates Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events; CSPS.com, Cilostazol Stroke Prevention Study for Antiplatelet Combination; mRS, modified Rankin Scale; N/A, not applicable; PATCH, Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy; POINT, Platelet-Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke Trial; and VISTA, The Virtual International Stroke Trials Archive.

*Further details on parameter derivation are available within the supplemental materials.

enrolled with strokes in the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial.[11] Details on parameter derivations are provided in the supplement (Table S1). Recurrence rates with the addition of cilostazol were calculated from the base rates using a hazard ratio of 0.49 as observed in the CSPS.com trial. In CSPS.com, rates of major bleeding over the median 1.4-year follow-up were similar for those on cilostazol in addition to aspirin or clopidogrel (31/932; 3.3%) compared with those on monotherapy (31/947; 3.3%) which is in keeping with a recent meta-analysis that showed no increased risk of bleeding with cilostazol.[3] There was a numerically lower number of intracranial hemorrhages among those taking cilostazol in addition to aspirin or clopidogrel (8/932; 0.85%) compared with those on monotherapy (13/947; 1.4%) in the CSPS.com trial. Because there is no physiological explanation for reduced intracranial hemorrhage with the addition of cilostazol and to be conservative, we used the overall rate of intracranial hemorrhage within the CSPS.com trial (21/1879; 1.1%) for mono and dual therapy strategies in our model. Further details on bleeding parameter derivations are available within our supplemental materials (Table S2).

For neurological outcomes following recurrent stroke, results from the POINT trial were modeled using a Dirichlet distribution.[10] For neurological outcomes after intracranial hemorrhage while on antiplatelet therapy, results from the PATCH (Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy) trial were used.[12] The clinical consequences of recurrent ischemic and hemorrhagic strokes were assumed to be the same for the first and subsequent recurrence. The health utility scores associated with various mRS states was calculated using US-specific preference weights (obtained using the time trade-off method) obtained from the literature and multiplied with life years to obtain QALYs.[13]

Annual costs associated with living with mild and severe neurological disability were extracted from the literature.[14] Median medication costs were obtained through identifying all entries for aspirin 81 mg, clopidogrel 75 mg, and cilostazol 100 mg within the National Acquisition Center Contract Catalogue Search Tool[15] and using 121% of the Federal Supply Schedule drug costs as recommended by the Health Economics Resource Center of the US Division of Veteran Affairs Research and Development.[16] Costs were inflated to 2020 US dollar amounts using medical care inflation from the consumer price index.[17]

RESULTS

Base-Case Calculation

Using a deterministic cohort simulation, the dual therapy strategy (cilostazol added to aspirin or clopidogrel) dominates. Dual therapy is associated with an average lifetime cost of $182 531 for an average of 8.7 QALYs per patient compared with the monotherapy strategy, which is associated with an average cost of $195 379 for an average of 8.1 QALYs per patient.

Sensitivity Analysis

Probabilistic sensitivity analysis was used to simulate 10 000 cohorts of 10 000 patients. In 10 000/10 000 simulations, the dual therapy strategy resulted in lower health care costs compared with aspirin or clopidogrel alone (mean $13 488 lower per patient; SD, $8087). In 10 000/10 000 simulations, the dual therapy strategy resulted in higher QALYs (mean, 0.585 more QALYs per patient lifetime; SD, 0.290) confirming that the dual therapy strategy of adding cilostazol to either aspirin or clopidogrel is dominant (better health outcomes at lower costs; Figure; Figure S2). At a willingness-to-pay threshold of $100 000/QALY, average net monetary benefit resulting from the addition of cilostazol was $71 998 ($13 488 in cost savings + $58 510 reflecting the monetary value of the 0.585 gained QALYs) per patient over their lifetime. At a willingness to pay of $50 000/QALY, the net monetary benefit was $42 743 ($13 488 +$29 255) per patient over their lifetime.

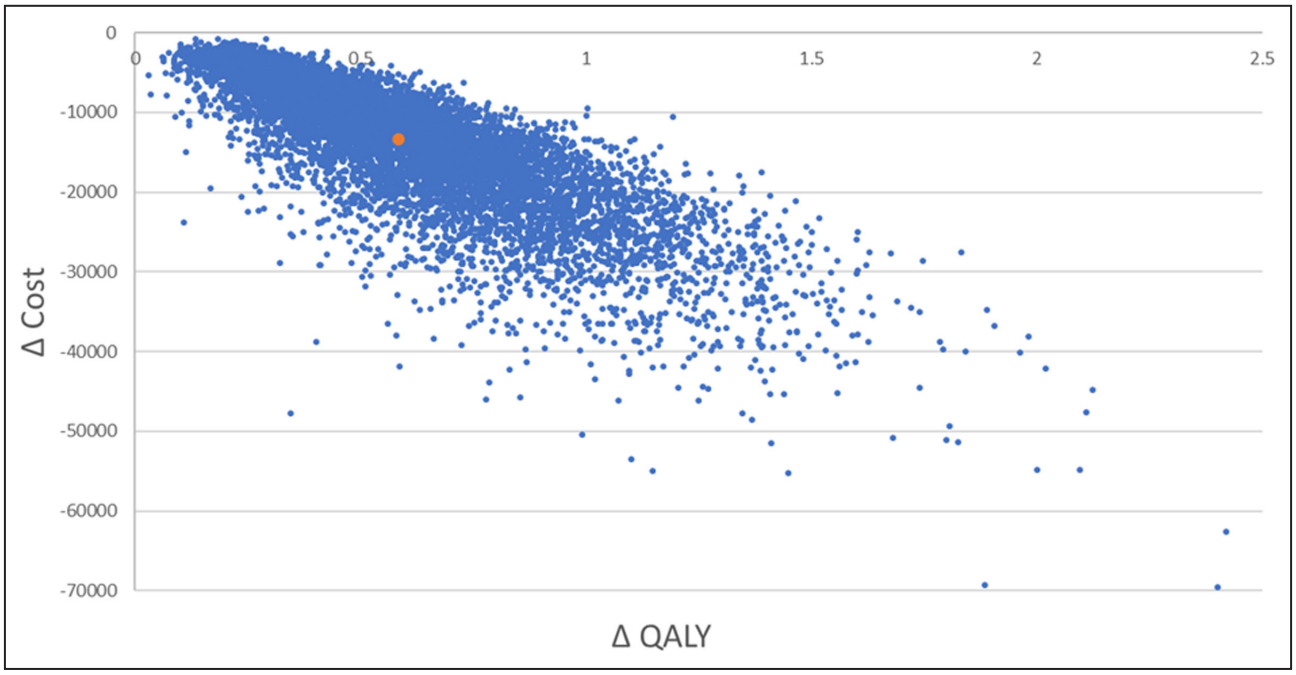

Figure. Probabilistic sensitivity analysis.
The blue dots indicate the average incremental costs and QALYs of the addition of cilostazol to aspirin or clopidogrel for secondary stroke prevention in 10 000 cohorts of 10 000 patients. In all 10 000 simulations, the cilostazol strategy resulted in cost savings and a gain in QALYs compared with aspirin or clopidogrel alone. The orange dot represents the mean cost savings and QALYs gained with the addition of cilostazol across the 10 000 cohorts. QALYs indicates quality-adjusted life years.

The results of 1-way sensitivity analyses, in which the addition of cilostazol to aspirin or clopidogrel is considered cost-effective if associated with an incremental cost-effectiveness ratio <$50 000/QALY, are shown in Table 2. Cilostazol is cost-effective or cost saving over the full range of all sensitivity analyses, with the only exception of extremely conservative estimates for the cilostazol treatment effect (hazard ratio, 0.997–0.999).

DISCUSSION

The objective of our study was to evaluate the cost-effectiveness of cilostazol added to aspirin or clopidogrel for secondary stroke prevention. In both our base-case model and across most sensitivity analyses, the addition of cilostazol to aspirin or clopidogrel was both cost saving and led to a gain in QALYs. In the base model, cilostazol resulted in an average cost savings of $12 848 and a gain of 0.6 QALYs per patient. The pronounced cost saving of cilostazol results from its relatively low annual cost ($109 per patient per year) compared with the cost of hospitalization for recurrent stroke and the long-term health care costs associated with neurological disability from recurrent stroke.

Sensitivity analyses demonstrate that cilostazol would have remained cost-effective even if the assumptions of our input parameters were incorrect. For example, cilostazol remained cost effective in a model where all patients were disabled at baseline (30% of patients with an mRS score of 1–2 and 70% with an mRS score of 3–5). In reality, the proportion of disabled patients is much lower; 40% of participants in the POINT study and 75% of stroke survivors in an international prospective cohort study had an mRS score > 0.[17] This indicates that cilostazol would be cost-effective when used in almost all secondary prevention situations because cost savings of cilostazol are smallest among patients with disability. Our result are also robust against a wide range of effects on hemorrhage. In our base model, we assumed similar bleeding risks with and without cilostazol, consistent with the results of CSPS.com[8] and a recent meta-analysis,[3] which showed no elevated risk of major systemic hemorrhage or hemorrhagic stroke when cilostazol was added to aspirin or clopidogrel. In the sensitivity analysis, the cilostazol strategy remained cost saving even in an extreme scenario when cilostazol was associated with a 2.5-fold increase in risk of major bleeding (combined intracranial and extracranial).

Our study has limitations. First, because of limitations in high-quality micro-costing data of US health care costs available in current literature, costs related to intracranial hemorrhage and ischemic stroke were kept constant regardless of the patient's baseline mRS score. Similarly, patients' annual likelihood of stroke or intracranial hemorrhage within the mono and dual therapy arms were kept constant regardless of baseline mRS score or

Table 2. Results of 1-Way Sensitivity Analyses

	Dominant	Cost-effective (<$50 000/ QALY)
Cost of cilostazol (range, $0–3000)	$0–1285	$1285–3000
Event cost of ischemic stroke (range, $1000–1 000 000)	$1000–1 000 000	…
Event cost of intracranial hemorrhage (range, $3000–300 000 000)	$3000–1 214 064	$1 214 065–3 000 000
Annual health maintenance cost of mRS 0 following stroke (range, $0–100 000)	$0–23 750	$23 751–100 000
Annual health maintenance cost of mRS 1–2 following stroke (range, $1000–100 000)	$1000–100 000	…
Annual health maintenance cost of mRS 3–5 following stroke (range, $5000–500 000)	$16 249–500 000	$5000–16 249
HR of cilostazol added to aspirin for recurrent ischemic stroke (range, 0–1)	0–0.955	0.956–0.997
HR of cilostazol added to clopidogrel for recurrent ischemic stroke (range, 0–1)	0–0.953	0.953–0.996
Annual rate of recurrent stroke on monotherapy, % (range, 2.4%–15%)*	2.4–15	…
Risk of major bleeding (intracranial and extracranial) on dual therapy/single therapy, % (range, 0%–250%)	100–250	…
Proportion on aspirin (vs clopidogrel), % (range, 0%–100%)	0–100	…
Mean age at baseline, y (range, 20–85 y)	20–85 y	…
Percentage with no disability (mRS 0) at baseline (range, 0%–70%)†	0–70	…

HR indicates hazard ratio; mRS, modified Rankin Scale; and QALY, quality-adjusted life year.

*Annual stroke recurrence rates on aspirin or clopidogrel monotherapy were varied from 2.4%, as seen in the Secondary Prevention of Small Subcortical Strokes trial[23] of patients with lacunar infarction, up to 15%, seen in the Warfarin-Aspirin Symptomatic Intracranial Disease[24] and Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis[25] trials for those with intracranial atherosclerosis, to reflect 2 common etiologies of noncardioembolic stroke at the extremes of recurrence rates.

†In the sensitivity analysis, the percentage of patients with mRS 1–2 was kept constant at 30%. The remaining 70% was split between the mRS 0 and mRS 3–5 categories. At one extreme of the sensitivity analysis there were 70% of patients with mRS 0, 30% with mRS 1–2, and 0% with mRS 3–5. At the other extreme there were 0% of patients with mRS 0, 30% with mRS 1–2, and 70% with mRS 3–5.

prior history of recurrent stroke. If higher baseline neurological disability and prior history of recurrent stroke significantly increase health care costs and likelihood of recurrent stroke, the current model may underestimate the cost savings associated with cilostazol use.

Second, patients' neurological disability resulting from recurrent ischemic stroke or intracranial hemorrhage are derived from outcomes at 3 months, as this is a common end point used in stroke trials. This may be an underestimate of total recovery because further neurological recovery can be seen beyond 3 months[18] and may result in less long-term disability than modeled here. However, our sensitivity analysis shows that cilostazol remains cost saving even if annual maintenance costs for patients with an mRS score of 3 to 5 are as low as $16 249 per year (a cost that is only slightly more than the estimated cost of patients with an mRS score of 1–2 in our base model) and was costsaving for all modeled maintenance costs for patients with an mRS score of 1 to 2. This suggests that cilostazol would remain cost saving even after adjusting for neurological improvements that might occur after 3 months.

Third, for simplification within our model, neurological worsening was assumed to occur only through recurrent strokes or hemorrhage. A variety of other neurological diseases, especially neurodegenerative conditions such as dementia or Parkinsonism, are associated with worsening neurological function in older patients. However, these neurodegenerative conditions will either occur at equal rates in those treated with dual and monotherapy or may even be benefited by cilostazol because of prevention of silent cerebral ischemia. Omission of neurological dysfunction from these conditions would therefore either have no impact or potentially lead to underestimation of the cost savings associated with cilostazol use.

Fourth, some of our model inputs are derived from older clinical trials, and it is possible that stroke recurrence rates have since reduced because of better control of vascular risk factors. However, cilostazol remained a dominant strategy, even in the extreme scenario when the annual rate of recurrent stroke on monotherapy was set as low as 2.4%.

Finally, in our base model, we used the treatment effect of cilostazol for secondary stroke prevention (hazard ratio, 0.49) from the CPSP.com trial, a large Japanese open-label randomized controlled trial. The effect observed in the CSPS.com trial is similar to that reported in a recent meta-analysis[3] of 18 trials of cilostazol for secondary stroke prevention. Most of these trials were conducted in Asian stroke centers, which see

a higher proportion of patients with stroke secondary to intracranial atherosclerosis. Data from previous trials such as the Korean Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis[19] trial suggest that the addition of cilostazol to aspirin may reduce the progression of intracranial atherosclerosis. A Japanese trial, CATHARSIS (Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis),[20] demonstrated a lower combined secondary end point of all vascular events and new silent brain infarcts but no difference in intracranial atherosclerosis progression. It is possible that non-Asian patients with stroke who are less likely to have stroke secondary to intracranial atherosclerosis respond differently to cilostazol. There are also differences in stroke risk factors such as tobacco use and hypertension between Asia and North America, which further limits generalizability of the CSPS.com trial to Western populations of patients with stroke. However, even if cilostazol is less effective in Western populations, our sensitivity analysis shows that cilostazol remains cost saving up to a hazard ratio of 0.95. Nevertheless, to get confirmation of the cost-effectiveness of cilostazol outside of Asia, it is important to obtain evidence of cilostazol's treatment effect from an adequately powered double-blind randomized controlled trial with a racially diverse study population.

CONCLUSIONS

Based on the best available current data, the addition of cilostazol to aspirin or clopidogrel for secondary prevention results in significantly reduced health care costs and a gain in lifetime QALYs for patients with noncardioembolic stroke. Confirmation with high-quality data from randomized trials that include a high proportion of non-Asian patients is needed to increase generalizability.

ARTICLE INFORMATION

Received December 8, 2021; accepted April 5, 2022.

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Sources of Funding

Dr Zhou received salary support from a fellowship grant from StrokeNet (NINDS U24NS107220) and a project grant from the Canadian Institute of Health Research (RN387091 - 420683).

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Estimation of recurrent stroke rates

The annual rates of stroke recurrence for patients on aspirin or clopidogrel were calculated using the subgroup of patients with prior strokes provided in table 7 of the CAPRIE manuscript. We have provided the calculations below in Table S1. Where rates are x/n, we used alpha=x and beta=n-x for beta parameters. Recurrence rates with the addition of cilostazol were calculated from these base rates using a hazard ratio of 0.49 as observed in the CSPS.com trial.

Estimation of hemorrhage rates

The risk of major bleed was derived from CSPS.com (table 2 and 3 within the main manuscript) and then adjusted to the number of events expected annually (median follow up of the CSPS.com trial was 1.4 years, supplementary Table 2). In CSPS.com, rates of major bleeding over the median 1.4 year follow up were similar for those on cilostazol in addition to ASA or clopidogrel (31/932, 3.3%) vs. monotherapy (31/947, 3.3%) which is in keeping with a recent meta-analysis. The same bleeding risk was used in both arms. There were 45 expected events of major bleeding annually, 15 of which would be intra-cranial.

Table S1. Event rates on ASA and Clopidogrel, derived from CAPRIE

Events of Interest	Clopidogrel	Aspirin
Non-fatal stroke (table 7, line 1-2, column 2)	298	322
Fatal Stroke (table 7, line 1-2, column 3)	17	16
All strokes (calculated)	315	338
Total person years at risk (table 7, line 1-2, column 1)	6054	5979
Annual rate (calculated)	0.0520	0.0565

Table S2. Bleeding events in CSPS.com adjusted to expected events per year

Types of bleeding	Number of events in study (1.4-year median follow up)			Expected number of events within 1 year (annual rate)*		
	Cilostazol	Control	Total	Cilostazol	Control	Total
	n=932	n=947	N=1879	n=932	n=947	n=1879
All bleeding (Table 3) †	38	33	71	27.73 (3.0%)	24.00 (2.5%)	52 (2.8%)
Minor Bleeding (Table 2) †	7	2	9	5.00 (0.5%)	1.43 (0.2%)	6 (0.3%)
Intra-cranial bleeding (Table 3) †	8	13	21	5.74 (0.6%)	9.35 (1.0%)	15 (0.8%)
Major Extracranial bleeding (calculated)	23	18	41	16.64 (1.8%)	12.9 (1.4%)	30 (1.6%)
Total major bleeding	31	31	62	22.73 (2.4%)	22.58 (2.4%)	45 (2.4%)

Cilostazol indicates the active treatment arm in CSPS.com in which patients were randomized to treatment with cilostazol plus aspirin or clopidogrel; Control indicates the arm in which patients were randomized to treatment with aspirin or clopidogrel alone.

*Expected number of events within 1 year = n x annual rate, where the annual rate = -Ln(1-Study rate from CSPS.com)/1.4

†Table numbers refer to the tables in the publication of the CSPS.com trial (Toyoda et al. Lancet Neurol. 2019)

Figure S1: State diagram of health states modeled and possible transitions between health states during cycles.

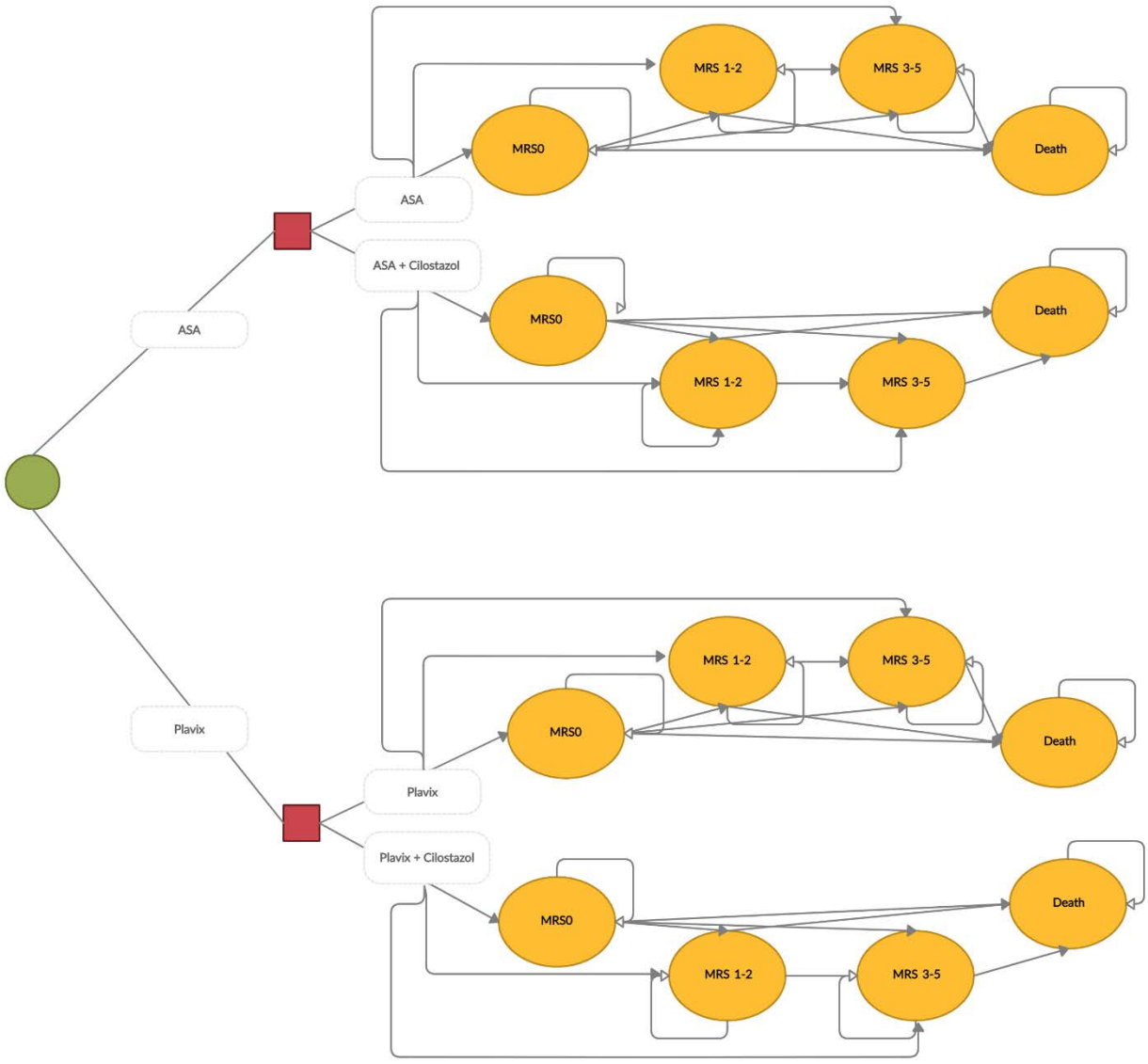

Figure S2: distribution of average lifetime QALYs gained and cost-savings per patients for 10,000 simulations within the probabilistic sensitivity analysis