

Cost-Effectiveness of Proton Pump Inhibitor Co-Therapy in Patients Taking Aspirin for Secondary Prevention of Ischemic Stroke

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Abstract

Background Low-dose aspirin (ASA) is effective for secondary prevention of ischemic stroke but can increase the risks of hemorrhagic stroke, upper gastrointestinal bleeding (UGIB), and dyspepsia. Prophylactic administration of proton pump inhibitors (PPIs) reduces the risks of these digestive symptoms. We investigated the cost effectiveness of adding a PPI to ASA therapy for ischemic stroke patients in Japan.

Methods A Markov state-transition model was developed to compare the cost effectiveness of ASA monotherapy with ASA plus PPI co-therapy in patients with histories of upper gastrointestinal ulcers and ischemic stroke. The model takes into account ASA adherence rate and adverse effects due to ASA, including hemorrhagic stroke and UGIB. The analysis was performed from the perspective of healthcare payers in 2013.

Results In the base case, total life-years by PPI co-therapy and monotherapy were 16.005 and 15.932, respectively. The difference in duration of no therapy (no ASA or

PPI) between the therapies was 558.5 days, which would prevent 30.3 recurrences of ischemic stroke per 1000 person-years. The incremental cost-effectiveness ratio of PPI co-therapy relative to monotherapy was ¥1,191,665 (US\$11,458) per life-year gained. In a one-way sensitivity analysis, PPI co-therapy was consistently cost effective at a willingness to pay of ¥5,000,000 (US\$48,077) per life-year gained. In a probabilistic sensitivity analysis, the probability that PPI co-therapy was cost effective was 89.74 % at the willingness to pay.

Conclusions Co-therapy with ASA plus PPI appears to be cost-effective compared with ASA monotherapy. The addition of PPI also appeared to prolong the duration of ASA therapy, thereby reducing the risk of ischemic stroke.

Key Points for Decision Makers

The incidence and care costs of ischemic stroke are increasing, so effective secondary preventative therapy is critical for reducing the impact in public health.

Low-dose aspirin (ASA) is widely used to reduce the risk of ischemic stroke in patients with a history of stroke. However, aspirin is associated with increased risk of upper gastrointestinal bleeding (UGIB).

The analysis suggests that co-therapy with proton pump inhibitors (PPI), which prevents UGIB, was cost effective compared with ASA monotherapy in the Japanese healthcare environment. Also, PPI co-therapy prolonged the duration of ASA therapy, thereby reducing the recurrence of ischemic stroke.

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1 Introduction

The incidence of first-ever ischemic stroke continues to increase globally [1], so effective secondary preventative therapy is critical for reducing long-term morbidity and mortality. In Japan, an estimated 938,000 individuals have a history of ischemic stroke [2], and ischemic stroke care cost the national healthcare system about one trillion yen (roughly 10 billion US dollars) in 2010 [3]. Ischemic stroke has a significant public impact, so prevention of recurrence and aggravation are important.

Low-dose aspirin (ASA) therapy reduces the risk of ischemic stroke in patients with a history of stroke [4, 5], and both American and Japanese guidelines for the prevention of stroke recommend ASA for secondary prevention [6, 7]. However, ASA is associated with increased risk of hemorrhagic stroke [8], upper gastrointestinal bleeding (UGIB), and dyspepsia [9–11]. Prophylactic administration of proton pump inhibitors (PPIs) to patients on ASA monotherapy reduces the risk of digestive symptoms that can lead to discontinuation of ASA [12–19].

Addition of a PPI to ASA for secondary prevention of acute coronary syndrome (ACS) and myocardial infarction (MI) was reported to be cost effective [20, 21], but the cost effectiveness of ASA plus PPI co-therapy for ischemic stroke has not been assessed. To investigate the cost effectiveness of PPI in addition to long-term antiplatelet therapy with ASA in ischemic stroke patients, we compared the efficacy and cost of ASA monotherapy with ASA plus PPI co-therapy using a Markov state-transition model that accounts for ASA adherence rate in clinical practice and adverse effects due to ASA, including hemorrhagic stroke and UGIB.

2 Methods

2.1 Model Structure

We developed a Markov state-transition model using TreeAge Pro 2012 decision modeling software (TreeAge Software Inc, Williamstown, MA, USA) and based in part on the model of Saini et al. [21]. The model included patients in Japan with histories of upper gastrointestinal ulcers and ischemic stroke using ASA for secondary prevention. The starting age was set at 55 years.

Two strategies, ASA monotherapy and ASA plus PPI co-therapy, were compared by a model-based simulation of a 1-year cycle with a half-cycle correction, and a time horizon of 30 years (Fig. 1). The ASA monotherapy started without PPI and therapy could remain the same or transfer to one of three other states: non-adherence (no therapy),

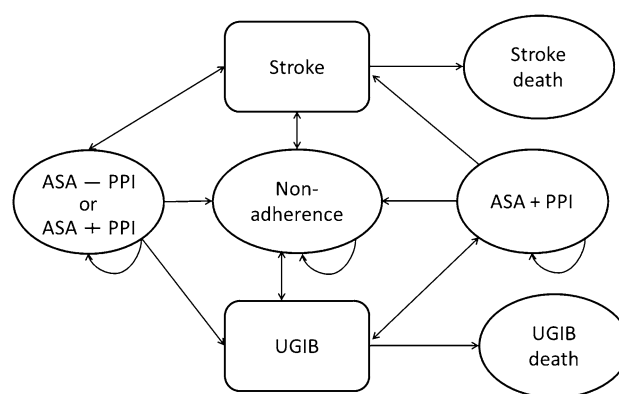


Fig. 1 Structure of Markov model. ASA aspirin, ASA – PPI ASA monotherapy, ASA + PPI ASA plus PPI co-therapy, PPI proton pump inhibitor, UGIB upper gastrointestinal bleeding. The model starts in ASA monotherapy state or ASA plus PPI co-therapy state (ASA – PPI or ASA + PPI)

stroke, or UGIB. Non-adherence returned to ASA monotherapy via stroke or UGIB. Death due to stroke or UGIB was also incorporated in the model (Fig. 1). High dose of a PPI (lansoprazole 30 mg) was used in case of UGIB for 8 weeks after the occurrences. The ASA plus PPI co-therapy started with PPI and the flow of state transition was the same as that for ASA monotherapy. Low dose of a PPI (lansoprazole 15 mg) was used in all states but non-adherence and UGIB.

2.2 Model Parameters in the Base Case

Annual transition probabilities for ischemic stroke, hemorrhagic stroke, UGIB, adherence, and mortality for each health state were set in the Markov model. Costs of drugs, hospitalization for UGIB and stroke, and stroke rehabilitation were taken into account (Table 1). We estimated each probability and cost except drug costs in Japan by literature review via PubMed and the I-Chu-Shi web, which provides Japanese research publications. The analysis was performed from the perspective of healthcare payers.

2.2.1 Ischemic and Hemorrhagic Stroke

Having reviewed relevant clinical trials of patients with a history of ischemic stroke and taking ASA for secondary prevention of ischemic stroke [5, 22–24], we applied the transition probabilities for ASA treatment of stroke patients (27.5 per 1000 patient-years for ischemic stroke, 9.7 per 1000 patient-years for hemorrhagic stroke) from the CSPS2 (Cilostazol for Prevention of Secondary Stroke) trial and the transition probabilities for treatment without ASA (57.8 per 1000 patient-years for ischemic stroke, 7.2 per 1000 patient-years for hemorrhagic stroke) from the CSPS (Cilostazol Stroke Prevention Study) [22, 23]. Transition

Table 1 Parameters, ranges, and distributions of the model

Parameter	Base case	Range	Distribution	References
Ischemic stroke				
–ASA	0.0578/year	0.0428–0.0728	β	[22]
+ASA	0.0275/year	0.0218–0.0332	β	[23]
Hemorrhagic stroke				
–ASA	0.0072/year	0.0019–0.0125	β	[22]
+ASA	0.0097/year	0.0063–0.0131	β	[23]
UGIB				
+ASA – PPI	0.0533/year	0.0312–0.0754	β	[15, 16]
+ASA + PPI	0.0127/year	0–0.0268	β	[15, 16]
OR with ASA	5.5	2.5–11.9	Log normal	[27]
Adherence				
+ASA	0.1264/year	0.0648–0.2150	β	[28]
Efficacy of PPI for abdominal discomfort	0.8417	0–1	Triangular	[15, 16]
Mortality				
OR after a first-ever stroke	1.98	1.78–2.20	Log normal	[30]
Ischemic stroke in hospital	0.050/year	0.038–0.068	β	[25]
Ischemic stroke after discharge	0.088/year	0.076–0.100	β	[31]
Hemorrhagic stroke in hospital	0.100/year	0.062–0.150	β	[25]
RR for hemorrhagic stroke after discharge	2.84	2.17–3.72	Log normal	[30]
UGIB in hospital	0.0121/year	0.0046–0.0247	β	[32]
Cost ^a				
ASA	5.6 (0.054)/day	2.8–8.4 (0.027–0.081)	γ	[35]
Branded PPI (lansoprazole 15 mg)	95.2 (0.915)/day	47.6–142.8 (0.458–1.373)	γ	[35]
Branded PPI (lansoprazole 30 mg)	166 (1.60)/day	83–249 (0.80–2.39)	γ	[35]
Generic PPI (lansoprazole 15 mg)	58 (0.56)/day	29–87 (0.28–0.84)	γ	[35]
Generic PPI (lansoprazole 30 mg)	106.5 (1.024)/day	53.3–159.8 (0.512–1.536)	γ	[35]
Ischemic stroke in hospital	1,281,106 (12,318.33)	640,553–1,921,659 (6,159.16–18,477.49)	γ	[25]
Hemorrhagic stroke in hospital	1,517,450 (14,590.87)	758,725–2,276,175 (7,295.43–21,886.30)	γ	[25]
UGIB in hospital	277,470 (2667.98)	138,735–416,205 (1,333.99–4,001.97)	γ	[36, 37]
Rehabilitation of stroke	3,018,400 (29,023.08)	1,509,200–4,527,600 (14,511.54–43,534.62)	γ	[36, 38]

ASA aspirin, ASA – PPI ASA monotherapy, ASA + PPI ASA plus PPI co-therapy, OR odds ratio, PPI proton pump inhibitor; RR relative risk, UGIB upper gastrointestinal bleeding

^a Japanese Yen (United States Dollars)

probabilities were taken from these two studies because (1) there are no clinical trials directly comparing a placebo arm with an ASA arm; (2) a placebo arm was included only in the CSPS; (3) subjects targeted in the CSPS were similar to those in CSPS2, which also included an ASA arm; and (4) many sites in Japan participated in these trials (183 in CSPS and 278 in CSPS2). We assumed that annual transition probabilities related to ischemic and hemorrhagic stroke were not affected by the addition of PPI, and ratios of patients who required rehabilitation after discharge were

set at 44 % for ischemic stroke and 57 % for hemorrhagic stroke [25].

2.2.2 Upper Gastrointestinal Bleeding

The annual transition probabilities for UGIB under ASA plus PPI co-therapy (12.7 per 1000 patient-years) were obtained from a clinical trial with a lansoprazole arm and a gefarnate arm [15, 16]. The probabilities for UGIB under ASA monotherapy (53.3 per 1000 patient-years) were

derived from the gefarnate arm. Although a clinical trial of esomeprazole treatment also reported the effects of PPIs, it was not used because it included gefarnate in both PPI and gefarnate arms [26], so the efficacy of PPI would be overestimated. The UGIB probabilities under no therapy were derived from the probabilities for ASA monotherapy divided by the odds ratio (OR, 5.5) of UGIB caused by the use of ASA in a case-control study [27].

2.2.3 Adherence

Prolonged and uninterrupted ASA use is important to attain the full benefits of this therapy. The discontinuation rate during long-term ASA therapy is known [19], so we also included ASA adherence rate in the model. Adherence rate for ASA was derived from a study of antiplatelet therapy in patients with ischemic cerebrovascular disease in which a platelet aggregation test was performed [28]. These results were used to estimate the adherence rate for ASA monotherapy only because a PPI was not indicated for secondary prevention of upper gastrointestinal ulcer due to ASA when the study was reported, which assumed 12.64 % of patients using ASA monotherapy discontinued the therapy. The adherence rate for ASA plus PPI co-therapy was derived from the withdrawal rate of ASA and the PPI effect (PPI-E) on abdominal discomfort, which assumed that abdominal discomfort was caused by upper gastrointestinal ulcer and UGIB and suppressed by PPI pretreatment. The incidence of those on ASA plus PPI co-therapy was 3.8 % in the lansoprazole arm and that for ASA monotherapy was 24.0 % in the gefarnate arm [15, 16]. From these results, the suppression rate for abdominal discomfort, PPI-E, was estimated as 84 % $[(1 - 3.8/24.0) \times 100]$. Then, the 84 % was applied to only the patients who discontinued ASA therapy due to abdominal discomfort.

2.2.4 Mortality

Annual mortality in the health states with no events (no stroke or UGIB) were obtained from the Japanese abridged life table (2012) multiplied by the OR (1.98) of the death rate after ischemic stroke [29, 30]. The annual mortality of ischemic stroke patients was estimated from the death rates during hospitalization (5.0 %) and 1 year after acute hospital discharge (8.8 %) [25, 31]. Although the annual mortality of hemorrhagic stroke patients was estimated by the same procedure as that used for ischemic stroke, death rate after hospital discharge was calculated as ischemic stroke survival rate multiplied by the relative risk (2.84) of hemorrhagic stroke for ischemic stroke [30]. The mortality of UGIB patients during hospitalization (1.21 %) was estimated from the death rate of UGIB in-patients taking

ASA [32]. Mortality from UGIB after hospital discharge was assumed to be the same as that of the health states with no events.

2.2.5 Costs

Only the direct medical costs were evaluated in this study. Costs were calculated in Japanese yen (¥) adjusted to 2013 values using 'Revision of Medical Fee' published by health authorities in Japan and then converted to United States dollars (US\$) based on a currency exchange rate of US\$1 = ¥104 according to the purchasing power parities of 2013 on the OECD [33, 34].

Drug costs were obtained from the 2012 edition of the National Health Index drug list [35]. Base cases were calculated for both branded and generic drugs. Costs for the hospitalizations of ischemic stroke, hemorrhagic stroke and UGIB were estimated as ¥1,281,106 (US\$12,318.33), ¥1,517,450 (US\$14,590.87), and ¥277,470 (US\$2667.98), respectively, using the results of Yoneda et al. [25] and medical fees of the Japanese healthcare system (April 2012 version) [36, 37]. Accurately, rehabilitation costs were estimated as ¥3,018,400 (US\$ 29,023.08) from medical fees [36] and the study by Koga et al. [38].

2.3 Outcome Measures

Clinical outcomes were life-years gained (LYG), duration of no therapy, and lifetime risk which indicated the probability of each event in total life-years. Lifetime risk was calculated from the probability of one health state divided by the total of probabilities of all health states. Economic outcomes were costs and incremental cost-effectiveness ratio (ICER) per LYG. Shiroya et al. reported that mean and median willingness-to-pay (WTP) values were around ¥5,000,000 and that WTP should range from ¥2,000,000 to ¥8,000,000 [39], depending on the severity of health state. In this study, WTP was set to ¥5,000,000 (US\$48,077) per LYG according to the mean. Future costs and life-years were discounted by 2 % per year as recommended by Japanese guidelines [40].

2.4 Sensitivity Analyses

One-way sensitivity analysis was conducted on all parameter assumptions in the model. Parameter values for PPI-E ranged from 0 (no effect) to 1 (full suppression of abdominal discomfort caused by ASA). The costs ranged from 50 to 150 % of the base value. The range of discount rate was between 0 and 4 %. The ranges of other parameters were set based on the 95 % confidential intervals (CIs) of each estimate. Sensitivity analysis was also conducted in the case of changing the starting age to 70 years.

Two-way sensitive analysis was performed using ASA adherence rate and PPI-E.

We also performed a second-order Monte Carlo simulation as a probabilistic sensitivity analysis (PSA). The parameter ranges were the same as those in a one-way sensitivity analysis, and the simulation was run for 10,000 iterations. Transition probabilities were assumed to follow beta distributions. Relative risks and ORs were assumed to follow log-normal distributions. We applied a triangular distribution for PPI-E and gamma distributions for costs.

3 Results

3.1 Base-Case Analysis

In the base-case analysis, total life-years were 16.005 for ASA plus PPI co-therapy and 15.932 for ASA monotherapy (Table 2). That meant 0.073 (26.6 days) was obtained as the LYG due to the increased adherence to ASA. The durations of no therapy in total life-years were 7.396 for ASA monotherapy and 5.866 for ASA plus PPI co-therapy, for a difference of 1.53 years or 558.5 days. The

incidence of ischemic stroke recurrence in patients taking ASA was estimated to be 27.5 per 1000 person-years and that in patients not taking ASA was 57.8 per 1000 person-years [22, 23]. Consequently, PPI co-therapy prevented 30.3 recurrences of ischemic stroke per 1000 person-years. ASA plus PPI co-therapy resulted in fewer UGIB events in a lifetime than ASA monotherapy (1.103 vs 2.538 % lifetime risk). Lifetime risk of hemorrhagic stroke in patients on ASA plus PPI co-therapy was similar to that for ASA monotherapy (0.245 vs 0.238 %). Consequently, the ICER of ASA plus PPI co-therapy relative to ASA monotherapy was ¥1,191,665 (US\$11,458) per LYG (Table 2). In the base-case analysis of generic drug prices, ASA plus PPI co-therapy was dominant compared with ASA monotherapy.

3.2 Sensitivity Analysis

One-way sensitivity analysis indicated that the variables PPI cost, PPI-E, annual probability of ischemic stroke with no ASA therapy, and annual probability of UGIB with ASA monotherapy strongly influenced cost-effectiveness estimates (Fig. 2). Analysis using a discount rate of 0–4 % showed that the higher the discount rate, the lower the cost

Table 2 Incremental cost-effectiveness ratios by discount rate

Strategy	Costs ^a	Life-years	ICER ^a
Base case			
2 %; branded cost			
ASA – PPI therapy	2,393,357 (23,013.05)	15.932	–
ASA + PPI therapy	2,480,137 (23,847.47)	16.005	1,191,665 (11,458.32)
2 %; generic cost			
ASA – PPI therapy	2,358,139 (22,674.41)	15.932	–
ASA + PPI therapy	2,333,236 (22,434.96)	16.005	Dominant
Sensitivity analysis			
0 %			
ASA – PPI therapy	3,051,086 (29,337.37)	19.939	–
ASA + PPI therapy	3,148,788 (30,276.81)	20.040	971,306 (9339.48)
1 %			
ASA – PPI therapy	2,692,853 (25,892.82)	17.761	–
ASA + PPI therapy	2,784,652 (26,775.50)	17.846	1,075,912 (10,345.31)
3 %			
ASA – PPI therapy	2,141,291 (20,589.34)	14.387	–
ASA + PPI therapy	2,223,767 (21,382.38)	14.450	1,318,990 (12,682.60)
4 %			
ASA – PPI therapy	1,927,756 (18,536.12)	13.073	–
ASA + PPI therapy	2,006,509 (19,293.36)	13.127	1,458,244 (14,021.58)
Starting age; 70 years			
ASA – PPI therapy	1,449,329 (13,935.86)	9.671	–
ASA + PPI therapy	1,511,838 (14,536.90)	9.690	3,244,591 (31,197.99)

ASA aspirin, ASA – PPI ASA monotherapy, ASA + PPI ASA plus PPI co-therapy, ICER incremental cost-effectiveness ratio, PPI proton pump inhibitor

^a Japanese Yen (United States Dollars)

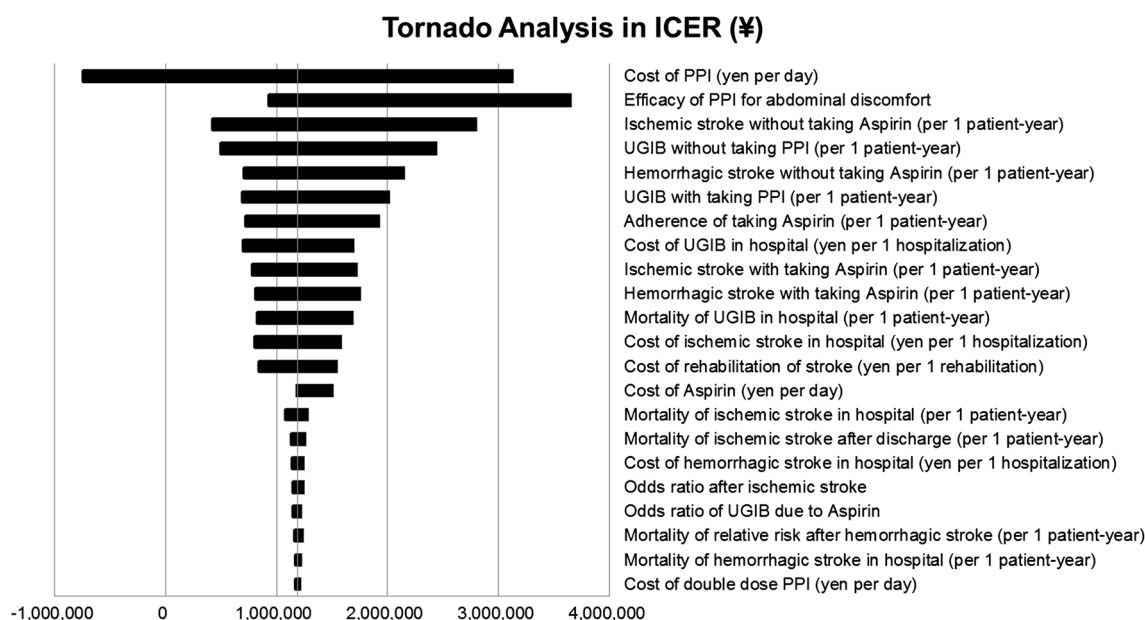


Fig. 2 Tornado diagram of one-way sensitivity analysis. *ICER* incremental cost-effectiveness ratio, *PPI* proton pump inhibitor, *UGIB* upper gastrointestinal bleeding

effectiveness of ASA plus PPI co-therapy (Table 2). However, ASA plus PPI co-therapy was consistently cost effective than ASA monotherapy within the parameter ranges at a WTP of ¥5,000,000 (US\$48,077) per LYG. In the case of 70 years for the starting age, ASA plus PPI co-therapy was similarly cost effective than ASA monotherapy.

The results of a two-way sensitivity analysis of ASA adherence rate and PPI-E indicated ASA plus PPI co-therapy was invariably cost effective than ASA monotherapy at a WTP of ¥5,000,000 (US\$48,077) per LYG. Assuming a WTP of ¥2,000,000 (US\$19,231) per LYG (the lowest WTP estimate of Shirowa et al. [39]), the higher the ASA adherence rate or the stronger the PPI effect for abdominal discomfort, the greater the cost effectiveness of ASA plus PPI co-therapy (Fig. 3).

Results from the PSA (Fig. 4) showed that ASA plus PPI co-therapy was cost effective than ASA monotherapy when WTP was more than ¥1,952,000 (US\$18,769) per LYG. The probability that ASA plus PPI co-therapy was cost effective was 89.74 % when WTP was ¥5,000,000 (US\$48,077) per LYG. The probability that LYG under ASA monotherapy was larger than that under ASA plus PPI co-therapy was only 0.08 %.

4 Discussion

Using a Markov model, we examined whether ASA plus PPI co-therapy was cost effective than ASA monotherapy for secondary prevention of ischemic stroke in patients

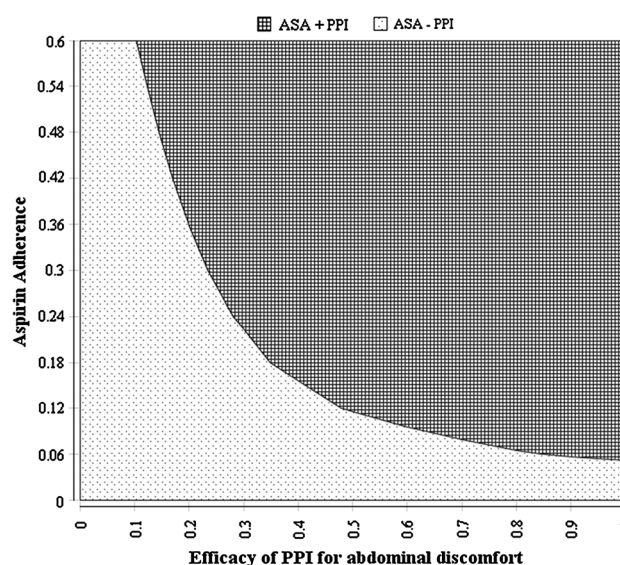
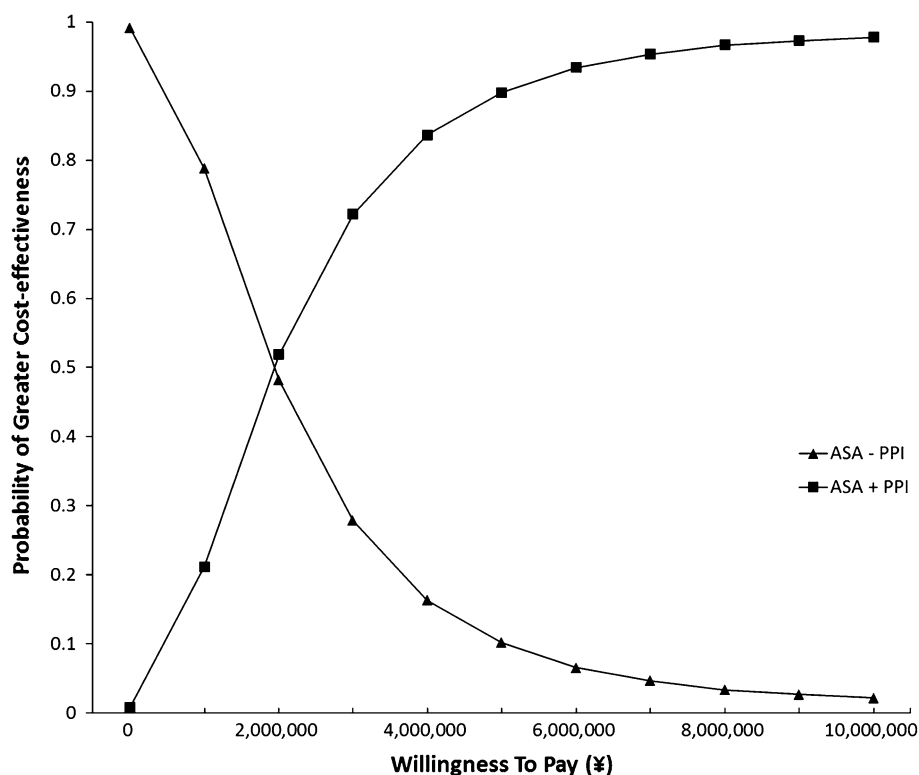


Fig. 3 Two-way sensitivity analysis of ASA adherence rate and effect of PPI on abdominal discomfort due to ASA at a willingness to pay of 2 million yen. The area of *grid pattern* indicates that ASA + PPI therapy was cost effective compared with ASA - PPI therapy. The area of *polka-dot pattern* indicates that ASA - PPI therapy was cost effective compared with ASA + PPI therapy. ASA aspirin, ASA - PPI ASA monotherapy, ASA + PPI ASA plus PPI co-therapy, PPI proton pump inhibitor

with histories of upper gastrointestinal ulcers and ischemic stroke. The model included ASA adherence and adverse effects due to ASA (hemorrhagic stroke and UGIB). The ICER for ASA plus PPI co-therapy was ¥1,191,665 (US\$11,458) per LYG for branded drugs. Co-therapy was

Fig. 4 Cost-effectiveness acceptability curves. ASA aspirin, ASA - PPI ASA monotherapy, ASA + PPI ASA plus PPI co-therapy, PPI proton pump inhibitor



cost effective than monotherapy at a WTP of ¥5,000,000 (US\$48,077) per LYG.

The cost effectiveness of prophylactic PPI treatment in patients taking ASA for secondary prevention has been investigated for both MI and ACS [20, 21], and both studies reported that PPI co-therapy was cost effective than ASA monotherapy. These results were sensitive to PPI cost. Although the cost of PPIs also strongly influenced our results, ASA plus PPI co-therapy would remain cost effective in the sensitivity analysis. Strategies for improving ASA adherence are critical because discontinuation was significantly associated with the occurrence of stroke and other adverse clinical outcomes [19]. The probability of ASA discontinuation was estimated to be 20 % at the end of the first year in MI patients and 25 % in ACS patients with no complications [20, 21]. Differences in adherence rates have been reported between countries [41, 42], so we used a domestic adherence rate for cost-effectiveness analysis, although our estimated probability of discontinuation was lower (13 %) than that of other studies on MI and ACS [28]. Addition of a PPI also reduced the risk of ASA treatment discontinuation among patients with high gastrointestinal risk [43], and the efficacy of the PPI was estimated to be 84 % from results of a clinical trial comparing gefarnate and lansoprazole arms [15]. PPIs are known to be metabolized by *CYP2C19*, which contains genetic polymorphisms that vary in frequency across ethnicities [44]. Thus, the efficacy of PPI co-therapy and

hence the cost effectiveness of co-therapy over ASA monotherapy may also vary among countries or races, limiting generalization of our results.

Hemorrhagic stroke was included as an adverse effect of ASA because it has a significant influence on clinical outcomes in patients on ASA therapy [8]. Moreover, the incidence of hemorrhagic stroke in patients on ASA therapy is 2-fold higher in Japan than the US [45]. However, the improved cost effectiveness of co-therapy remained after one-way sensitivity analysis of the incidence of hemorrhagic stroke.

Addition of PPI to the ASA regimen prolonged the duration of ASA therapy and consequently prevented 30.3 recurrences of ischemic stroke per 1000 person-years compared with ASA monotherapy. A beneficial effect of PPI co-therapy was also proposed for MI and ACS [20, 21]. As national medical care expenditures are rising due to aging (24.1 % of the Japanese population was over 65-years-old in 2013) [3, 46], Japan is emphasizing prevention of cerebrovascular diseases such as ischemic stroke to sustain the social security system [47]. Other countries that face such rapid aging may need to adopt the same approach to provide cost-effective healthcare services.

4.1 Limitations

Several limitations warrant mention. First, some parameters were only estimates. Moreover, the model is

limited by the number of possible state transitions included. However, these estimates were derived from the best available studies and sensitivity analyses were performed for confirmation. Also, other treatments to prevent relapse of ischemic stroke (e.g., clopidogrel) were not considered. Second, adverse effects of long-term PPI therapy were not considered. Long-term PPI therapy has been reported to increase the risk of fracture, community-acquired pneumonia, enteric infection, vitamin deficiency, and adverse cardiovascular events [48–53]. However, these risks were identified in observational studies and remain controversial. Moreover, the estimated magnitudes of these risks were low. Third, the PPI-induced suppression of abdominal discomfort due to ASA may be underestimated because we used data from the gefarnate arm of a study instead of the placebo arm, which would lead to a smaller difference in the incidence of abdominal discomfort compared with ASA monotherapy. Accordingly, PPI co-therapy could be even cost effective than estimated here. Fourth, although adherence rate may change over time, the same rate was used in this study because hospitalizations due to ischemic stroke, hemorrhagic stroke, and UGIB occurred and hospitalized patients would be given instructions on the use of drugs during hospitalizations to restart the withdrawn drugs. Even if the adherence rate decreases or increases gradually, the change would have an insignificant effect on our results because the one-way sensitivity analysis about adherence of taking aspirin showed ASA plus PPI co-therapy was cost effective than ASA monotherapy. Fifth, our analysis used LYG rather than quality-adjusted life-years (QALYs) because data on QALYs for Japanese are limited and extrapolating QALYs of patients with incident stroke would overestimate QALYs of recurrent patients, which is the population of interest in our study. It is also notable that WTP in our analysis, ¥5,000,000 (US\$48,077) per LYG, was originally established based on QALYs for Japanese [39]. The value of WTP based on LYG would be lower than that based on QALYs, implying that co-therapy with ASA plus PPI would be cost effective than ASA monotherapy because the ICER was low (¥1,191,665/US\$11,458 per LYG). Sixth, annual mortality rates for ischemic and hemorrhagic stroke during hospitalization were estimated from ten stroke centers across Japan [25]. Tsugawa et al. [54] reported that hospitals with a lower number of discharged patients had higher mortality than those with high numbers of discharged patients (OR of mortality was 1.46 for ischemic stroke and 2.05 for hemorrhagic stroke). However, sensitivity analysis indicated that ASA plus PPI treatment was still cost effective using higher mortality estimates. Finally, subarachnoid hemorrhage was not included in our model. Although the mortality from subarachnoid

hemorrhage is higher than that of ischemic and hemorrhagic stroke [54, 55], the incidence rate is lower [55, 56]. Considering the results of sensitivity analysis on the mortality and incidence rates of ischemic and hemorrhagic stroke, including subarachnoid hemorrhage would have no impact on our results.

5 Conclusion

In conclusion, this analysis suggests that PPI co-therapy in patients taking ASA for secondary prevention of ischemic stroke, was cost effective compared with ASA monotherapy in the Japanese healthcare environment. Also, PPI co-therapy prolonged the duration of ASA therapy, thereby reducing the recurrence of ischemic stroke. Given the increasing number of patients with a history of ischemic stroke, further study of prophylactic and cost-effective treatments for ischemic stroke are warranted.

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Author contributions NT, KM, and KK contributed to the concept and design. NT contributed to acquisition of data. NT, KM, and ST contributed to analysis and interpretation of data. NT, KM, ST, and KK contributed to the writing of the manuscript and critical revision of the manuscript. All authors approved the final version of the manuscript. KK is the guarantor of the article.

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