Efficacy and Safety of Dual Antiplatelet Therapy Using Cilostazol with Aspirin or Clopidogrel to Reduce the Rate of Recurrent Ischemic Stroke in Asia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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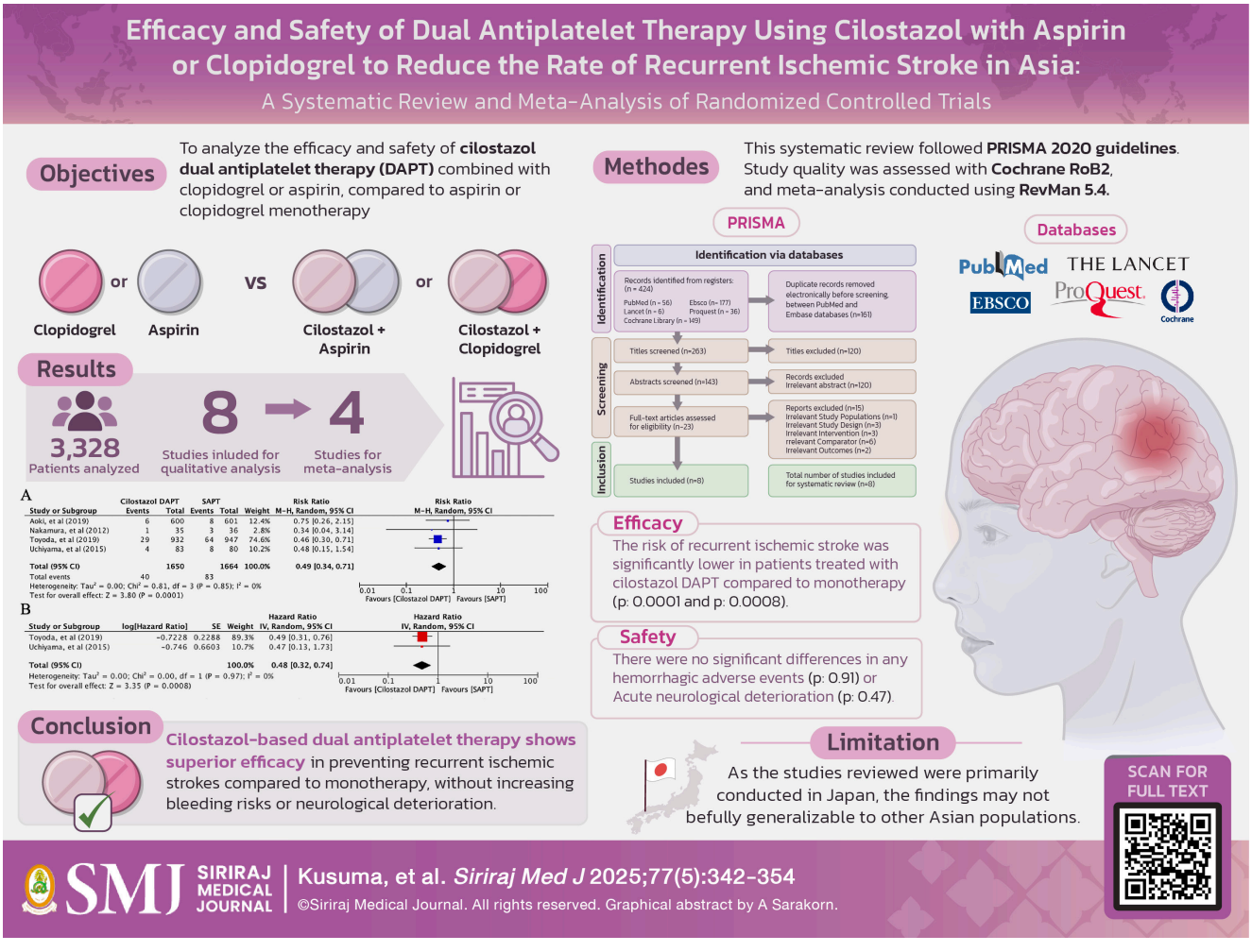

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ABSTRACT

Objective: The stroke mortality rate in Asia is higher than in other regions worldwide. As an antiplatelet medication and phosphodiesterase-3 inhibitor, cilostazol lacks approval for use in ischemic stroke. We intended to analyze the efficacy and safety of cilostazol dual antiplatelet therapy (DAPT) with clopidogrel or aspirin compared to aspirin or clopidogrel monotherapy.

Materials and Methods: This review was carried out under the PRISMA 2020 guidelines, using sources from PubMed, Cochrane Library, EBSCOhost, Proquest, and the Lancet database. The Cochrane Risk of Bias 2 (RoB2) tool for randomized controlled trials was used to grade the quality of studies and Review Manager (RevMan) 5.4 for the meta-analysis.

Results: Eight studies were included in this analysis, with four undergoing quantitative evaluation through meta-analysis, involving 3,328 patients. The risk of recurrent ischemic stroke for patients treated with cilostazol DAPT was significantly lower compared to those receiving monotherapy (risk ratio, RR: 0.49; 95% CI: 0.32–0.71; p: 0.0001) and (hazard ratio, HR: 0.48; 95% CI: 0.32–0.74; p: 0.0008). There were no significant differences in any hemorrhagic adverse events between the treatment groups (RR: 0.98; 95% CI: 0.71-1.36; p: 0.91). Acute neurological deterioration showed no significant differences (RR: 0.55; 95% CI: 0.11-2.77; p: 0.47).

Conclusion: Cilostazol DAPT is more effective than clopidogrel or aspirin alone in preventing recurrent ischemic strokes without significantly increasing hemorrhagic risks or acute neurological decline. However, the study's exclusive focus on a Japanese population limits the generalizability of the findings, highlighting the need for more diverse clinical trials across Asia.

Keywords: Aspirin; cilostazol; clopidogrel; dual antiplatelet; ischemic stroke (Siriraj Med J 2025; 77: 342-354)

INTRODUCTION

Stroke continues to be the second leading cause of death in Asia despite the global establishment of guidelines. It is also the third most prevalent cause of years lost due to disability on a global scale.[1] Stroke affects not just the patient; it also imposes considerable strain on their family and caregivers.[2] Epidemiological studies have shown that Asia had a higher stroke mortality rate compared to other regions, such as Western Europe, America, and Australia, with East Asia holding the highest prevalence worldwide (including Japan, China, and Taiwan).[3] Ischemic stroke, especially those involving large vessel occlusion, continues to be a significant contributor to long-term disability.[4] Understanding of stroke remains lacking, particularly among individuals in high-risk groups.[5] Furthermore, the stroke recurrence incidence is 26% over a period of five years.[6] Previous studies showed that recurrent stroke patients had a higher mortality rate compared to first-time patients.[7] Motor and functional recovery are critical for improving patient outcomes following a stroke. Motor recovery typically occurs within the first 3-6 months post-stroke. During this period, pharmacological interventions are crucial in optimizing the effectiveness of rehabilitation therapies, enhancing both motor function and overall functional recovery.[8]

Studies have shown that the aspirin and clopidogrel regimen effectively decreased the possibility of recurrent cerebrovascular accidents and was recommended in clinical practices. Clopidogrel inhibits platelet aggregation by targeting the P2Y12 receptor pathway, which shares a mechanism with aspirin in platelet aggregation. Despite its use in clinical settings, patients prescribed both aspirin and clopidogrel as dual antiplatelet therapy significantly increased the chance of experiencing massive bleeding within 90 days compared to those prescribed only aspirin.[9] Studies also showed an increased likelihood of both significant and moderate bleeding in those administered both clopidogrel and aspirin. Therefore, there is still a need for an alternative dual antiplatelet therapy.[9,10]

Cilostazol is a phosphodiesterase III (PDE3) inhibitor. It is metabolized by the hepatic cytochrome P450 system, specifically through the CYP3A4 and CYP2C19 enzymes. It does not depend on the cyclooxygenase or platelet P2Y12 receptor pathways for its action.[10] Cilostazol's active metabolites have a reversible effect on phosphodiesterase 3 (PDE3), which inhibits cyclic adenosine monophosphate (cAMP) from breaking down. This mechanism leads to a decrease in platelet reactivity and aggregation. Additionally, cilostazol has a decreased incidence of hemorrhagic events.[10] Some studies have demonstrated that cilostazol significantly reduces the incidence of stroke while also decreasing the risk of cerebral hemorrhage and other forms of bleeding. Moreover, its usage does not increase the number of vascular deaths or mortality events.[10,11]

Few studies have investigated the efficacy and safety measures of cilostazol combined therapy, specifically in the Asian population, which has a high prevalence of stroke. Therefore, this systematic review and meta-analysis sought to evaluate the use of cilostazol in combination with either clopidogrel or aspirin for preventing recurrent ischemic stroke within the Asian population in terms of safety and efficacy. It is anticipated that the results will help to enhance the guidelines for the prevention of recurrent ischemic stroke in Asia. This would lead to a decline in the death rate and disability associated with ischemic stroke.

MATERIALS AND METHODS

Search strategy

This systematic review of randomized controlled trials (RCTs) followed the 2020 guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] Furthermore, PubMed, Cochrane library, EBSCOhost, Proquest, and Lancet databases were searched up to the year 2024, using the following keywords or terms: "cilostazol", "pletaal", "citaz", "naletal", "stazol", "aggravan", "antiplat", "aspirin", "acetylsalicylic acid", "clopidogrel", "plavix", "ischemic stroke", "non hemorrhagic stroke", "cerebral infarction", "brain infarction", "cerebral ischemia", "brain ischemia", "ischemic cerebrovascular accident", and "cerebrovascular ischemia". There were no restrictions on language. The complete search strategy is shown in Supplementary File 1.

Inclusion and exclusion criteria

The inclusion criteria were (a) RCTs that assessed the efficacy and safety of dual antiplatelet therapy (DAPT), combining cilostazol with either aspirin or clopidogrel as the experimental group, compared to single antiplatelet therapy (SAPT) using either aspirin or clopidogrel as the control group for preventing stroke recurrence, (b) studies conducted on the Asian population, and (c) efficacy and safety as the outcome. All non-experimental and non-randomized investigations (including cohort, cross-sectional, or case-control studies), reviews, animal studies, preclinical studies, conference abstracts, book chapters, and commentaries were excluded from this review. Articles without full text and those on irrelevant topics were also excluded. RCTs comparing cilostazol with anticoagulants or a placebo were likewise excluded.

Outcome measures

The efficacy outcome was the risk of recurrent ischemic stroke. Additionally, safety outcomes focused on analyzing any hemorrhagic adverse events and any acute neurological deterioration occurring within 14 days of treatment, as indicated by an increase in the NIHSS score.

Data retrieval and assessment of bias

Data were gathered from the selected studies, which included details such as the author and year of publication, sample size, study design, settings, mean or median age of the study subjects, follow-ups, and outcomes expressed as event counts and hazard ratios (HR) along with their respective 95% confidence intervals (95% CIs). The included studies were evaluated for bias using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs. This tool assessed bias across five domains: the randomization process, variations from intended interventions, bias in outcome measurement, missing outcome data, and selection bias in the reported findings. It also guided reviewers through each domain to facilitate the assessment. In addition, quality assessment was conducted by all five authors, and discrepancies were resolved through consultation with the sixth reviewer until an agreement was reached. We did not conduct an evaluation of publication bias because the meta-analysis comprises fewer than 10 studies.[13]

Statistical analysis

The meta-analysis was performed using Review Manager (RevMan) version 5.4. The efficacy and safety outcomes were evaluated and displayed as dichotomous data to show the risk ratios (RR) and their corresponding 95% CIs. Additionally, the recurrence rate of ischemic stroke was reported using pooled HRs and 95% CIs gathered from each applicable study. A p-value will be included for each item to demonstrate the significance of the results. If there were any sub-analyses or extension studies derived from the same RCTs, the efficacy and safety data for the meta-analysis were gathered exclusively from the core RCT to prevent data duplication.

Several studies presented their primary outcomes using various evaluation and calculation methods. As a result, meta-analyses were performed using a random effects model. This model assumed that treatment effects might vary across specific populations and treated each study with equal weight. Combined effect measures such as HRs were computed using the inverse variance method and the Mantel-Haenszel method for RRs.

The heterogeneity across different research studies was evaluated through the I^2 statistic. A value under 25% signifies minimal variability, while values ranging from 25% to 50% denote small variability. Moderate variability is indicated by scores between 50% and 75%, and high

variability is suggested when the score exceeds 75%. Furthermore, any p-value lower than 0.05 is considered statistically significant.

RESULTS

Study selection

The preliminary search approach uncovered a total of 424 studies. Titles, abstracts, and full texts were independently screened. Studies that did not correspond with the objectives of this review were excluded. The detailed exploration and selection methodology are shown in Fig 1.

Study characteristics and outcomes

This review encompassed eight studies for qualitative evaluation, of which four[14–17] were quantitatively analyzed through meta-analysis. All studies involved patients with noncardioembolic strokes in Japan. The study durations ranged from three months to 3.5 years. Five of these studies[17–21] were part of the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) Trial, with Toyoda et al. (2019)[17] serving as the core RCT. Hoshino et al. (2021)[18] conducted a subgroup analysis comparing the types of dual antiplatelet agents used (cilostazol combined with either aspirin or clopidogrel) against monotherapy within the CSPS.com trial. Uchiyama et al. (2021)[19] focused on specific populations with ischemic stroke and over 50% intracranial arterial stenosis (ICAS). Toyoda et al. (2022)[20] categorized patients according to when they began treatment in the CSPS.com trial, while Nishiyama et al. (2023)[21] analyzed only those with lacunar stroke from the same trial. Among the five studies from the CSPS.com trial included in this review, only data from the core RCT were utilized for meta-analysis; the others were assessed through systematic review. Three studies specifically examined cilostazol and aspirin as combination therapy, whereas the CSPS.com trial evaluated both cilostazol plus either aspirin or clopidogrel as dual therapy. The meta-analysis incorporated data from four studies[14–17], totaling 3,328 patients. Table 1 presents the features of the studies that are part of this review.

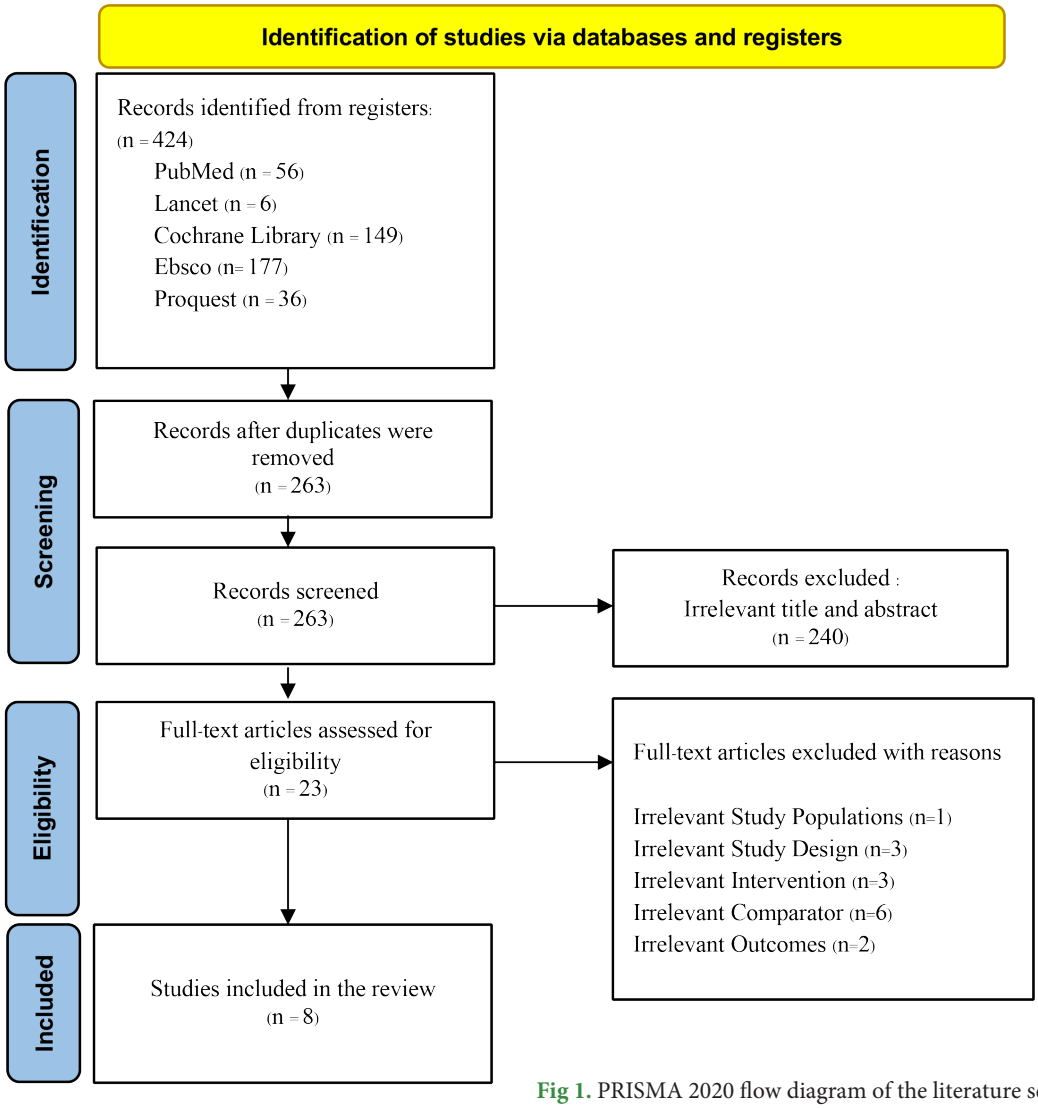

Fig 1. PRISMA 2020 flow diagram of the literature search strategy.

TABLE 1. Demographic and clinical characteristics of this current study.

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome Efficacy	Outcome Safety	Follow-up	Significance
1	Nakamura et al.[16] 2012, Japan	76 patients	66 (12)	6 months	Non-cardioembolic ischemic stroke	Open-labeled, randomized study. Patients are divided into two groups: 1. SAPT: Aspirin 1x300 mg 2. DAPT: Cilostazol 2x100 mg + Aspirin 1x300 mg	Ischemic stroke recurrence and patients with NIHSS score deterioration after 14 days were greater in the SAPT, while mRS at 6 months was better in the DAPT.	No significant difference in major hemorrhagic events.	MRI and MRA upon admission, NIHSS and mRS score on day 14, and month 6.	**Efficacy outcome:** 1. Stroke recurrence was higher in the SAPT compared to the DAPT (RR: 0.34, 95% CI: 0.04–3.14) 2. The number of patients experiencing neurological deterioration in the NIHSS score after 14 days was greater in the SAPT than DAPT (RR: 0.21, 95% CI: 0.05–0.87, p: 0.013) 3. At month 6, patients in the DAPT had more favorable functional status (mRS 0–1) (RR: 1.48, 95% CI: 1.07–2.06, p: 0.0048). **Safety Outcome:** No significant difference in any hemorrhagic events (1 in SAPT, 0 in DAPT) (RR: 0.33, 95% CI: 0.01–7.93)
2	Uchiyama et al[15]. 2015, Japan	165 patients	68.3 (45–84)	2 years	Non-cardioembolic ischemic stroke patients with >50% intracranial artery stenosis	Open-label, multicenter, randomized controlled trial. Patients were randomized into two groups: 1. DAPT: Cilostazol 200 mg/day + Aspirin 100 mg/day (n = 83) 2. SAPT: Aspirin 100 mg/day (n = 82)	1. Progression of intracranial arterial stenosis was lower in the DAPT group but not statistically significant. 2. The combination therapy tended to reduce vascular events and silent brain infarctions.	No significant difference in major hemorrhagic events.	Clinical and laboratory assessment, MRA, serious adverse events at baseline, 3, 6, 12, and 24 months.	**Efficacy outcome:** 1. Progression of intracranial artery stenosis: DAPT: 9.6%, SAPT: 5.6% (p = 0.53) 2. Emergence of new silent brain infarcts: DAPT 4.8%, SAPT 10.0% (RR: 0.48, 95% CI: 0.04–3.14), mean annual recurrence rate of ischemic stroke (HR: 0.47, 95% CI: 0.13–1.73) **Safety Outcome:** No significant difference in any hemorrhagic events (4 in DAPT, 3 in SAPT) (RR: 1.29, 95% CI: 0.30–5.56)

TABLE 1. Demographic and clinical characteristics of this current study. (Continue)

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome		Follow-up	Significance
							Efficacy	Safety		
3	Aoki et al.[14] 2019, Japan	1208 patients	69 (61-77)	3 months	Non-cardioembolic ischemic stroke	Open label: block randomization scheme, 1. DAPT: 200 mg of cilostazol + 80 to 200 mg of aspirin per day for 14 days, continued by 200 mg of cilostazol per day until three months after onset. 2. SAPT: 80 to 200 mg of aspirin per day for 14 days, followed by 200 mg of cilostazol per day until three months after onset	Patients in both groups showed no notable differences regarding NIHSS deterioration within 14 days, and their mRS status at three months was also comparable. Ischemic stroke recurrence was higher in the SAPT	The incidence of hemorrhagic events and their severity were similar in both groups.	MRI and MRA upon admission and day 7. NIHSS and mRS upon admission, day one, day two, day seven, day 14, 3 months.	**Efficacy outcome:** 1. Recurrent ischemic stroke was higher in the SAPT compared to the DAPT (RR: 0.75, 95% CI: 0.26–2.15). 2. The number of patients experiencing neurological deterioration in the NIHSS score after 14 days was similar between the two groups (RR: 1.09, 95% CI: 0.78–1.53, p: 0.632) 3. The secondary efficacy outcome showed that the prevalence of mRS 0-1 at 3 months was similar between the two groups (RR: 1.07, 95% CI: 0.98–1.16, p: 0.087) **Safety outcome:** No significant difference in any hemorrhagic events (6 in SAPT, 9 in DAPT) (RR: 1.50, 95% CI: 0.54–4.20)
4	Toyoda et al.[17] 2019. Japan (CSPS.com Trial)	1879 patients	71 (64-76)	3.5 years	High-risk non-cardioembolic ischemic stroke	Open label: block randomization scheme, The SAPT (947 patients) received either 81 mg/100 mg aspirin or 50 mg/75 mg clopidogrel once daily. The DAPT (932 patients) received cilostazol (50-100 mg twice daily) along with either aspirin (81 mg or 100 mg) or clopidogrel (50 mg or 75 mg) once daily.	The DAPT group experienced a reduced rate of ischemic stroke recurrence compared to the SAPT group	Safety measures were similar between the DAPT and SAPT groups.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcome:** Ischemic stroke recurrence (RR: 0.46, 95% CI: 0.30–0.71) and mean annual recurrence rate of ischemic stroke (HR 0.49, 95% CI: 0.31–0.76, p = 0.0010) were higher in the SAPT. **Safety outcomes:** No significant difference in any hemorrhagic events (49 in SAPT, 54 in DAPT) (RR: 0.93, 95% CI: 0.65–1.33)

TABLE 1. Demographic and clinical characteristics of this current study. (Continue)

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome Efficacy	Outcome Safety	Follow-up	Significance
5	Hoshino et al.[18] 2021, Japan (subanalysis of CSPS.com Trial)	1879 patients	71 (64-76)	3.5 years	High-risk and non-cardiembolic ischemic stroke	Open label: block randomization scheme; SAPT using aspirin 81 mg/100 mg (380 patients) or clopidogrel 50 mg/75 mg (567 patients) once daily; and DAPT using cilostazol 2x 50-100 mg combined with aspirin 81 mg/100 mg (383 patients) or clopidogrel 50 mg/75 mg (549 patients) once daily. The subgroup analysis was conducted according to the types of antiplatelet agents used.	1. Ischemic stroke recurrence/annual event rate was significantly lower in the dual regimen with cilostazol and clopidogrel 2. Ischemic stroke recurrence/annual event rate reduction was insignificant between the monotherapy groups	There was no significant difference in severe or life-threatening hemorrhage between the two groups	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcome:** Annual event rate 1. Clopidogrel DAPT vs SAPT : HR 0.447 [95% CI, 0.258, 0.774] 2. Aspirin DAPT vs SAPT : HR 0.569 [95% CI, 0.273, 1.189] **Safety outcome:** Severe or life-threatening hemorrhage 1. Clopidogrel DAPT vs SAPT : HR 0.730 [95% CI, 0.206, 2.588] 2. Aspirin DAPT vs SAPT : HR 0.595 [95% CI, 0.174, 2.034]
6	Uchiyama et al.[19] 2021, Japan (subanalysis of CSPS.com Trial)	547 patients	70 (65-76)	3.5 years	High-risk and non-cardiembolic ischemic stroke and more than 50% ICAS in major intracranial artery	Open-label block randomization scheme: SAPT group (272 patients) using aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily, and DAPT (275 patients) using cilostazol at 2x 50-100 mg combined with aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg	Ischemic stroke recurrence rate was lower in the DAPT.	Severe bleeding occurrence between two groups remained comparable in ICAS patients.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcomes:** 1. Any stroke: DAPT vs SAPT-HR 0.47 [95% CI, 0.24–0.93] 2. Ischemic stroke: DAPT vs SAPT-HR 0.47 [95% CI, 0.23–0.95] 3. Composite vascular events: DAPT vs SAPT-HR 0.48 [95% CI, 0.26–0.90] **Safety outcome:** Major or life-threatening bleeding: DAPT vs SAPT-HR 0.72 [95% CI, 0.12–4.30]

TABLE 1. Demographic and clinical characteristics of this current study. (Continue)

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome		Follow-up	Significance
							Efficacy	Safety		
7	Toyoda et al.[20] 2022. Japan (subanalysis of CSPS.com Trial)	1879 patients	69.8 (9.0)	3.5 years	High-risk and non-cardiembolic ischemic stroke	Open-label block randomization scheme: patients receiving SAPT (aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily) and DAPT (cilostazol 2x 50-100 mg combined with aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily). The subgroup analysis categorized patients into groups based on the timing of starting trial treatment (8–14 days, 15–28 days, and 29–180 days after stroke onset).	Ischemic stroke recurrence decreased in the DAPT during the 15–28 days and 29–180 day intervals, while remaining similar during the 8–14 day period.	Rates of massive hemorrhage were similar across all categorized groups.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcomes:** The recurrence of ischemic stroke: DAPT vs. SAPT in any of the three groups: - 8–14 days: HR 1.02 [0.51–2.04] - 15–28 days: HR 0.34 [95% CI 0.12–0.95]) - 29–180 days: HR 0.27 [0.12–0.63] **Safety outcome:** Major or life-threatening bleeding: DAPT vs. SAPT in any of the three groups: - 8–14 days: HR 0.22 [95% CI 0.03–1.88] - 15–28 days: HR 1.07 [95% CI 0.15–7.60] - 29–180 days: HR 0.76 [95% CI 0.24–2.39]
8	Nishiyama et al.[21] 2023, Japan (subanalysis of CSPS.com Trial)	925 patients	69.5 (9.15)	3.5 years	High-risk and non-cardioembolic lacunar stroke	Open-label block randomization scheme: SAPT group (461 patients) using aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily, and DAPT (464 patients) using cilostazol 2x 50-100 mg combined with aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily.	Ischemic stroke recurrence rate is lower in the DAPT than in the SAPT.	Insignificant events of severe bleeding between the two groups.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcomes:** Ischemic stroke recurrence was significantly lower in DAPT group (HR 0.43 [95% CI, 0.22, 0.84; P = 0.013]) **Safety outcome:** Safety outcome did not differ significantly (HR 0.35 [95% CI, 0.07, 1.75]; P = 0.201)

*N/A = Not Available

Abbreviations: MRI = Magnetic Resonance Imaging; MRA = Magnetic Resonance Angiography; ICAS = Intracranial Artery Stenosis; DAPT = Dual Antiplatelet Therapy; SAPT = Single Antiplatelet Therapy; NIHSS = National Institutes of Health Stroke Scale; mRS = Modified Ranking Score. CSPS.com=Cilostazol Stroke Prevention Study Combination; HR: Hazard Ratio, 95%CI: 95% Confidence Interval, RR: Risk Ratio

Risk of bias assessment

The included studies were evaluated for possible bias using the RCT-specific RoB2 assessment. Fig 2 illustrates the outcomes of the risk assessments conducted across the studies included. Among the eight studies analyzed, seven raised certain concerns, while one exhibited a high risk of bias. The studies were all open-labeled, meaning both participants and study personnel were aware of the treatment, so the results should be interpreted with caution.

Outcome of efficacy analysis

In our efficacy analysis examining the recurrence of ischemic stroke, we evaluated four studies.[14–17] Among these, only the CSPS.com trial employed a cilostazol combination therapy and monotherapy with either clopidogrel or aspirin;[17] the other studies exclusively used aspirin.[14–16] Fig 3A shows that the cilostazol combination treatment significantly reduced the relative risk of recurrent stroke compared to SAPT treatment (RR: 0.49; 95% CI: 0.32–0.71; p: 0.0001), with no significant heterogeneity observed (I^2=0.0%). Additionally, we combined estimates of the incidence of recurrent ischemic stroke into HRs and 95%CIs from two studies. Fig 3B shows that the pooled event rate estimates (HR: 0.48; 95% CI: 0.32–0.74; p: 0.0008; I^2=0%) showed a similar magnitude of the cilostazol combination's positive effect.

Outcome of safety analysis

The pooled analyses aimed to assess the safety of cilostazol DAPT compared to SAPT. Fig 4A shows that neither significant heterogeneity nor significant differences in hemorrhagic adverse events were found between the two groups (RR: 0.98; 95% CI: 0.71-1.36; p: 0.91; I^2=0.0%). Fig 4B illustrates the significantly high heterogeneity (I2: 80%) and lack of significant differences between the two groups when acute neurological deterioration occurred within 14 days of treatment, as indicated by an increase in the NIHSS score (RR: 0.55, 95%CI: 0.11-2.77, p:0.47).

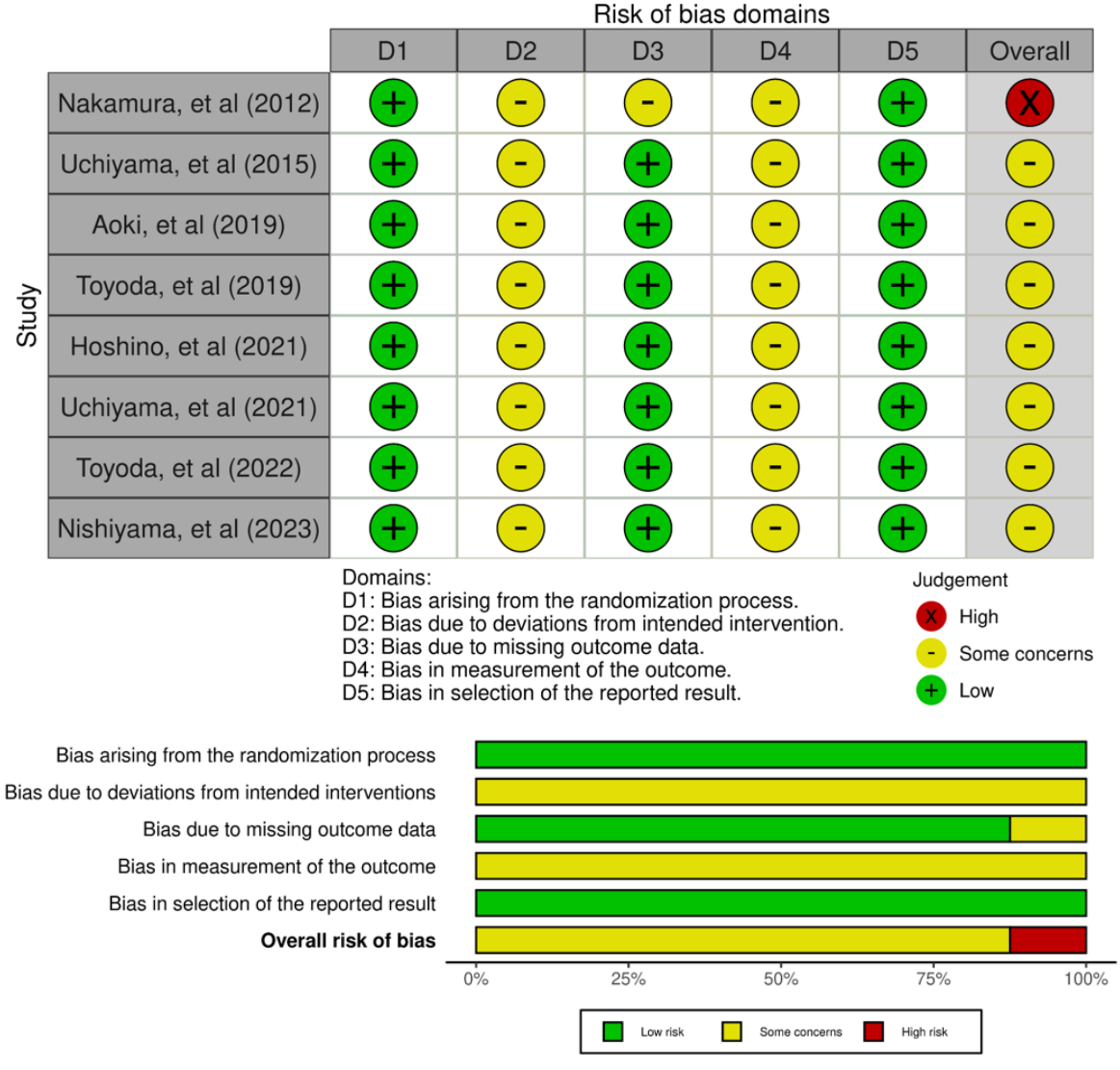

Fig 2. Assessment of bias risk in included studies utilizing the cochrane risk of bias 2 tool.

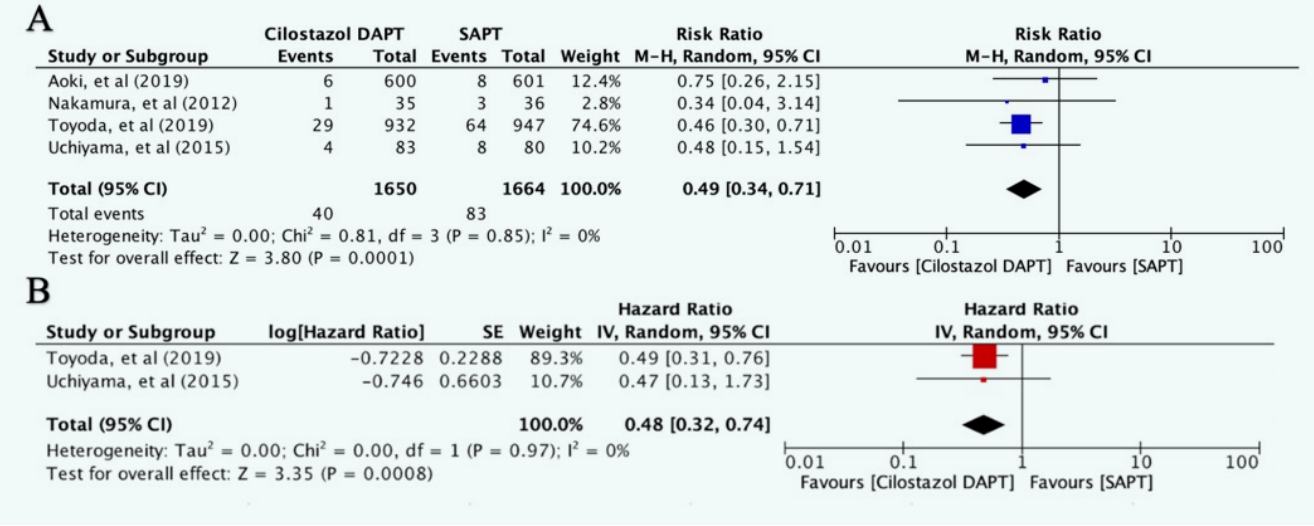

Fig 3. Meta-analysis forest plots: (A) Pooled RR of recurrent ischemic stroke; (B) Pooled HR of recurrent ischemic stroke.

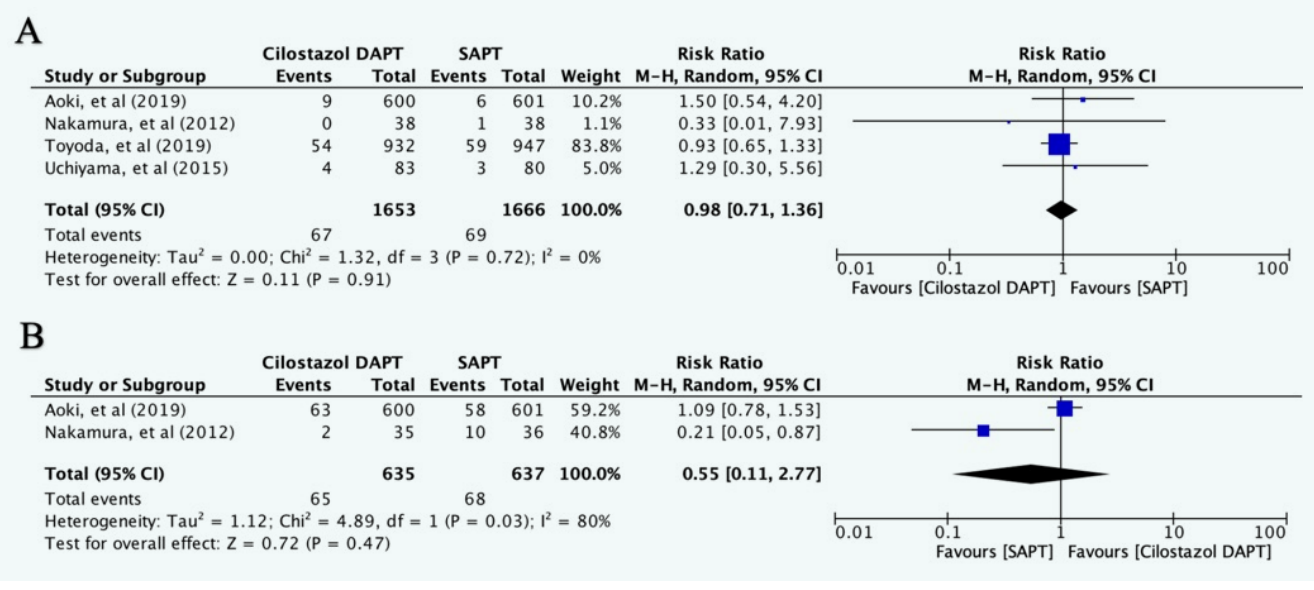

Fig 4. Meta-analysis forest plots: (A) Any hemorrhagic adverse events; (B) Acute neurological deterioration (NIHSS score increase) within 14 days of drug administration.

DISCUSSION

We found that dual antiplatelet therapy with cilostazol significantly reduced the incidence of recurrent ischemic strokes in our meta-analysis comparing the safety and efficacy of cilostazol in combination therapy to monotherapy with aspirin or clopidogrel. Importantly, this approach did not elevate the risk of any hemorrhagic complications or lead to acute neurological deterioration.

For our qualitative analysis, we also included several sub-analysis studies from the clinical investigation of cilostazol for stroke prevention, known as the CSPS combination trial. The CSPS combination trial revealed that DAPT incorporating cilostazol significantly lowers the probability of recurrent ischemic stroke in comparison to SAPT. In this multicenter, randomized controlled study, cilostazol's safety and efficacy in combination with either clopidogrel or aspirin were assessed in patients who had high-risk non-cardioembolic ischemic strokes.[17] Additionally, Hoshino et al.'s CSPS sub-analysis showed that cilostazol plus clopidogrel is a more effective combination than either cilostazol alone or cilostazol plus aspirin in lowering the risk of ischemic stroke recurrence.[18] Nishiyama et al. conducted a subanalysis study on the CSPS combination trial specifically for patients with only lacunar stroke, resulting in a similar result to its core experiment.[21] A subanalysis of the CSPS.com trial by Toyoda et al. showed that DAPT with cilostazol is more effective than monotherapy in preventing recurrent noncardioembolic strokes in patients who start treatment 15 days or more after the onset of a stroke, while not raising

the risk of bleeding.[20] This suggests that a continuous DAPT strategy could be feasible after a stroke, transitioning from aspirin and clopidogrel during the acute and subacute phases to a combination of cilostazol with either aspirin or clopidogrel beginning 15 days post-stroke or later.[20] In a RCT involving 1,201 participants, Aoki et al. reported that starting cilostazol in combination with aspirin within 48 hours of stroke onset did not reduce the frequency of a composite outcome that encompassed worsening neurological function, recurrent symptomatic strokes, and transient ischemic attacks (TIAs) within 14 days. Additionally, when compared to aspirin alone, a non-significant trend ($p = 0.086$) indicated a similar incidence of hemorrhagic stroke and a higher rate of favorable modified Rankin Scale scores (0–1) at three months.[14] Consequently, additional clinical trials are required to assess the efficacy and safety of cilostazol's DAPT in comparison to standard DAPT, particularly focusing on the timing of administration.

Cilostazol is not advised for the prevention of secondary strokes in the guidelines of the European Stroke Organization. In the United States, it has received a less favorable recommendation for use in patients who have had a stroke or transient ischemic attack (TIA) associated with moderate to severe stenosis of intracranial arteries. In contrast, cilostazol is considered the primary antiplatelet agent for preventing secondary strokes in Japan and several other countries in Asia. The Japan Stroke Society's prevention guidelines recommend that cilostazol DAPT using either aspirin or clopidogrel is a valid option for patients with noncardioembolic stroke or TIA, especially those with cervical or intracranial artery stenosis or multiple vascular risk factors.[10] The CSPS and CATHARSIS trials both demonstrated that cilostazol in combination therapy is effective and safe for preventing recurrent strokes in patients with stenosis of intracranial arteries.[15,19]

There are several limitations to this review. The potential for bias due to the absence of blinding in the included RCTs significantly impacts the reliability of both efficacy and safety outcomes in this review. The open-label design introduces potential biases in outcome assessment, particularly for subjective endpoints like neurological improvement and adverse event reporting. This limitation must be considered when interpreting the results, as it may lead to overestimation of benefits or underestimation of risks associated with cilostazol-based dual antiplatelet therapy. For example, in the Nakamura et al. study, primary and secondary endpoints relied heavily on subjective NIHSS and mRS assessments, raising concerns about evaluator bias, especially for subtle improvements or marginally significant outcomes.[16] The Uchiyama et al. study on intracranial arterial stenosis patients could be influenced in the interpretation of imaging studies and assessment of stroke recurrence.[15] The study by Aoki et al., despite having a large sample size, may have been influenced by issues in assessing early neurological deterioration and reporting adverse events.[14] The Toyoda et al. CSPS.com trial, which forms the core of several included studies, may have been influenced by knowledge of treatment allocation in assessing both efficacy and safety outcomes.[17] Sub-analyses from this trial inherit this limitation, potentially affecting assessment of outcomes across different antiplatelet combinations and patient subgroups.[18–21] Seven studies raised concerns during the risk of bias assessment, while one study showed a high risk. This systemic limitation in the current evidence base for cilostazol-based dual antiplatelet therapy in stroke prevention must be considered when interpreting the findings. Future studies should use double-blind designs to reduce biases and provide stronger evidence. It is also important to standardize outcome measures and ensure objective evaluation of clinical and radiological results to improve the reliability of future research.

Another limitation of the review is its focus on East Asian populations, particularly Japanese patients, which may restrict the applicability of the findings to other Asian subpopulations due to the significant diversity across the region. Stroke epidemiology, risk factors, and healthcare systems vary substantially among Asian countries, influencing the applicability of these results. For example, stroke incidence and prevalence vary widely, with Japan and Taiwan reporting some of the highest rates, while Malaysia has notably lower rates. Similarly, the distribution of stroke subtypes differs significantly; hemorrhagic strokes are more prevalent in countries like India and Vietnam compared to East Asian nations, where ischemic strokes are more common.[3] This difference is critical, as cilostazol-based therapies are primarily targeted at ischemic strokes, potentially limiting their effectiveness in regions with a higher burden of hemorrhagic strokes.

Socioeconomic and cultural factors also play a role in affecting stroke risk and treatment responses. For instance, dietary habits, lifestyle patterns, and ongoing economic transitions differ significantly across Asian countries, further complicating the generalization of findings. While East Asian populations share some similarities, the broader Asian region encompasses considerable heterogeneity, making it difficult to apply the review's findings universally.[3] Additionally, the prevalence of stroke risk factors shows significant regional variation. Hypertension is most common in Mongolia and Pakistan,

while diabetes mellitus is more frequently observed in Papua New Guinea and India.[3] These variations in risk factor profiles could influence the outcomes of cilostazol-based treatment, as the interaction between these conditions and therapeutic efficacy may differ across populations. Furthermore, disparities in healthcare systems exacerbate these challenges. Advanced healthcare infrastructure in Japan and South Korea facilitates timely and effective treatment, while resource limitations in Nepal and Bangladesh may delay or restrict access to cilostazol-based therapies, thereby reducing their potential impact.[3]

Importantly, we have not identified any studies specifically investigating the effectiveness and safety of dual antiplatelet therapy with cilostazol in combination with aspirin or clopidogrel in Asian subpopulations other than Japan. The small number of studies included in this review also poses a challenge regarding limited statistical power, preventing us from conducting subgroup analyses to further refine outcomes related to factors such as treatment timing after stroke onset, dosage, gender, or age. Further studies are needed to evaluate cilostazol-based therapy throughout all of Asia, considering regional differences in stroke rates, risk factors, and healthcare systems to provide stronger evidence for improved treatment strategies for recurrent ischemic stroke in diverse Asian populations.

CONCLUSION

In summary, dual antiplatelet therapy that includes cilostazol has demonstrated greater effectiveness than clopidogrel or aspirin alone in preventing recurrent ischemic strokes. Additionally, this combination therapy did not significantly increase the risk of hemorrhagic complications or cause acute neurological deterioration. However, since the studies reviewed were primarily conducted in Japan, the findings may not be directly applicable to other Asian populations. Given the regional variations in stroke rates, risk factors, and healthcare systems, further clinical trials are needed to assess cilostazol-based therapy across diverse Asian populations, which would provide stronger evidence and inform more effective treatment strategies for ischemic stroke in Asia.

Data Availability Statement

The evidence for the findings in this review article comes from the primary sources mentioned. No new data was created or examined for this study.

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Conflict of Interest

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Registration Number of Clinical Trial

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Author Contributions

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Use of Artificial Intelligence

None

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