Efficacy of antiplatelet therapy in secondary prevention following lacunar stroke: pooled analysis of randomized trials

Cover title: Antiplatelet Therapy in Lacunar Stroke

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Summary

Background and Purpose: Lacunar stroke accounts for approximately 25% of ischemic stroke but optimal antiplatelet regimen to prevent stroke recurrence remains unclear. We aimed to evaluate the efficacy of antiplatelet agents in secondary stroke prevention following a lacunar stroke.

Methods: We searched MEDLINE, EMBASE and the Cochrane library for RCTs that reported risk of recurrent stroke or death with antiplatelet therapy in patients with lacunar stroke. We used random effects meta-analysis and evaluated heterogeneity with I^2.

Results: We included 17 trials with 42,234 participants (mean age 64.4 years, 65% male) and follow up ranging from 4 weeks to 3.5 years. Compared to placebo, any single antiplatelet agent was associated with a significant reduction in recurrence of any stroke (RR 0.77, 0.62-0.97, 2 studies) and ischemic stroke (RR 0.48,0.30-0.78, 2 studies), but not for the composite outcome of any stroke, myocardial infarction or death (RR 0.89,0.75-1.05, 2 studies). When other antiplatelet agents (ticlodipine, cilostazol, and dipyridamole) were compared to aspirin, there was no consistent reduction in stroke recurrence (RR 0.91, 0.75-1.10, 3 studies). Dual antiplatelet therapy did not confer clear benefit over monotherapy (any stroke RR 0.83, 0.68-1.00, 3 studies; ischemic stroke RR 0.80, 0.62-1.02, 3 studies; composite outcome RR 0.90, 0.80-1.02, 3 studies).

Conclusions: Our results suggest that any of the single antiplatelet agents compared to placebo in the included trials is adequate for secondary stroke prevention after lacunar stroke. Dual antiplatelet therapy should not be used for long-term stroke prevention in this stroke subtype.

Keywords

- Lacunar stroke
- Antiplatelet agent
- Aspirin
- Stroke
- Mortality

Introduction

Lacunar stroke or small vessel ischemic stroke represents about 25% of all ischemic strokes [1]. Whilst the functional prognosis of single episode of lacunar stroke is generally good, recurrence is not uncommon [2,3]. The underlying etiology is believed to be cerebral small vessel disease (CSVD) in the form of arteriolosclerosis of deep penetrating arteries. This mechanism is thought to be the most frequent cause of vascular cognitive impairment [4]. Therefore, preventing progression of CSVD is extremely important. Current therapeutic options are however limited and the comparative efficacy of available antiplatelet agents remains uncertain.

Until recently, all of the evidence supporting the use of antiplatelet agents as secondary prevention following lacunar stroke came from subgroup analysis from randomized controlled trials (RCTs) designed to assess the efficacy of these agents in all ischemic stroke subtypes. However, these subgroups generally have small sample sizes. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial was the first to address the question at hand in a RCT with a large (n=3020) well-defined population of magnetic resonance imaging (MRI) confirmed lacunar stroke, comparing aspirin monotherapy to dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. This trial was however terminated early due to lack of efficacy and increased mortality amongst participants randomized to dual antiplatelet therapy [3]. In view of the paucity of data, differing vascular pathology underlying lacunar stroke, and the recent SPS3 trial results, the utility of antiplatelet monotherapy has been questioned in this population [5].

The primary aim of this study is to evaluate the evidence for antiplatelet therapy as secondary stroke prevention in patients with lacunar stroke. We performed a systematic review and pooled meta-analysis of RCTs.

Methods

Eligibility criteria

We included RCTs that evaluated the use of antiplatelet therapy as secondary prevention following acute stroke. Among these trials, only those which reported outcomes separate for lacunar stroke were included. For certain trials additional data were obtained via personal correspondence from the authors.

Outcomes

Primary outcome of interest was any stroke recurrence (ischemic or hemorrhagic). Secondary outcomes of interest were: a) recurrent ischemic stroke and b) composite of any stroke, myocardial infarction and death. We accepted composite outcomes as specified by trial investigators so long as strokes and deaths were captured in the composite end point.

Search strategy

MEDLINE and EMBASE searches with no date limitations or language restrictions were conducted in December 2013 using the broad search terms as shown in Supplementary Data I. Furthermore, we reviewed the bibliography of included trials, Cochrane Reviews and the most recent review by the antithrombotic trialist collaboration for additional studies.

Study selection and data extraction

Two reviewers (CSK and AS) considered all titles and abstracts retrieved from the search for potential eligibility. Where there was disagreement, study inclusion or exclusion was agreed upon by consensus with the other authors. Two reviewers (CSK

and HCC) independently extracted information on study design, participant characteristics, types of interventions, outcomes, results and risk of bias onto a spreadsheet. The two extractions were compared and differences were resolved by consensus. Where there was uncertainty journal authors were contacted for clarification.

Assessment of risk of bias

Two reviewers (CSK and HCC) independently assessed the individual studies' risks of bias in accordance with the recommendations of the Cochrane Collaboration which included baseline differences, blinding, lost to follow up, exposure and outcome ascertainment and conflicts of interest. We planned to assess publication bias using funnel plots if there were >10 studies included in the meta-analysis and there was no significant statistical heterogeneity [6].

Statistical analysis

Fixed effects meta-analysis of dichotomous events was performed using RevMan 5.3 (Nordic Cochrane Centre, København, Denmark) in order to estimate pooled risk ratios (RRs). Statistical heterogeneity was assessed using I^2 statistic, with values of 30-60% representing a moderate level of heterogeneity [7]. We performed secondary analysis considering only ischemic stroke as the outcome. Annual event rates per 100 patient years of follow-up were estimated by adjusting the studies event rate according to the trial's mean follow-up duration.

Results

We included a total of 17 randomized trials that included 42,234 participants with lacunar stroke treated with antiplatelet therapy (mono or dual) or placebo [3,8-23]. We did not include 4 trials (IST [11], PERFORM [21], S-ACCESS [17] and TRA 2P-TIMI50 [22]) in our pooled analysis. IST's composite outcome of death and dependency did not match our criteria and TRA 2P–TIMI50 did not provide number of events. Novel less established agents were excluded from the analysis in an attempt to reduce the level heterogeneity between the different agents' mechanisms of action, but their results are reported separately (Saprogelate (S-ACCESS) [17] and Terutroban (PERFORM) [21] trials). The process of study selection is shown in Supplementary Figure I. Table 1 shows the summary characteristics of the study populations of included studies. Of these 14 were double-blind randomized trials. The mean age was 64 years and 65% of participants were male across 16 studies; one study (IST) reported 61% of participants >70 years of age and one study (CSPS2) [18] did not report the number of male and female participants. All the studies included participants with suspected ischemic stroke or transient ischemic attack and neuroimaging was performed to confirm diagnosis in all but one study (CATS) [9], which relied on neurological evaluation for diagnosis. Only six of the studies formally defined lacunar stroke using criteria such as the TOAST Criteria, modified Fisher criteria or other pre-defined criteria and only one used MRI to verify the diagnosis of lacunar stroke [3].

Supplementary Table I shows the quality assessment of the studies included. Sequence generation of randomization was described in 10 studies and allocation concealment was described in 13 studies. 14 trials were double blind trials and some

means to assess treatment exposure or compliance was considered in 8 trials. All but one study had some form of outcome ascertainment and 4 studies had unclear participant lost to follow-up.

The treatments received, crude events rate, outcomes and results are shown in Supplementary Table II. The follow up of the studies ranged from 4 weeks to 3.5 years.

Any single antiplatelet agent vs. placebo

Overall, patients on antiplatelet monotherapy had significantly lower rates of any stroke as compared to placebo (RR 0.77, 0.62-0.97, 2 trials, CATS [9], ESPS-2 [19]). There was a significant reduction in ischemic stroke (RR 0.48, 0.30-0.78, 2 trials, AICLA [8], Matsumoto [14]) but not in the composite outcome (RR 0.89, 0.75-1.05, 2 trials CAST [10], ESPS-2 [19]). Results of these analyses are shown in Figure 1A-C.

Cilostazol, ticlopidine, dipyridamole, terutobran, sarpogrelate vs. aspirin alone

Overall, the meta-analysis shows no significant advantage of other single agents above aspirin alone. These analyses are shown in Figure 2 A-B. Two trials, PERFORM [21] and S-ACCESS [17], evaluating terutroban and sarpogrelate also found no significant benefit above aspirin alone (terutroban HR 0.90,0.62-1.31, sarpogrelate HR 1.31,0.84-2.04).

Dual antiplatelet therapy (DAPT) vs. aspirin alone

The results of DAPT versus aspirin are shown in Figure 3. Overall, DAPT may possibly have a modest advantage over aspirin but this is driven mainly by the aspirin/dipyridamole data from ESPS-2 [19]. The pooled risk ratio for any stroke, ischemic stroke and the composite outcome were RR 0.83, 0.68-1.00, RR 0.80,0.62-1.02 and RR 0.95,0.85-1.07, respectively.

Dipyridamole/aspirin, clopidogrel/aspirin and ticlopidine vs. clopidogrel alone

We observed no significant advantage of DAPT vs. clopidogrel, or ticlopidine vs. clopidogrel. For this analysis aspirin/dipyridamole did not appear to be superior to clopidogrel alone. Results are shown in Figure 4. Finally, DAPT using vorapaxar in addition to aspirin or clopidogrel use showed no significant benefit on vascular endpoints (HR 0.99,0.75-1.31) [22].

Discussion

The current American Heart Association guidelines [24] state that four antiplatelet regimens (aspirin, clopidogrel, ticlopidine or the combination of dipyridamole and aspirin) have been shown to reduce the risk of ischemic stroke after stroke or TIA. The guidelines further suggest that several factors should be considered such as patient comorbidities, side effects and costs when choosing an agent at an individual level. Suitably, our findings suggest that antiplatelet monotherapy (i.e. aspirin, dipyridamole, clopidogrel, cilostazol, ticlopidine) should be recommended as secondary prevention of stroke among patients with lacunar stroke. Aspirin appears to be as good as any other antiplatelet agents, and is likely the appropriate first line in most because it is less expensive, and generally well tolerated, which may increase long-term adherence to therapy [24]. Cilostazol showed a non-significant trend in reducing strokes when compared with aspirin, however further larger studies are needed to validate these findings and ensure generalizability to non-East Asian populations.

Unfortunately, in view of the limited number of studies which evaluate the role of DAPT we are unable to separate out individual agents and maintain a meaningful pooled analysis. Accordingly, we identified substantial heterogeneity in the effects of DAPT, which vary depending on the choice of the combination and the comparator drugs. Only one trial shows DAPT to be favorable (ESPS-2), but the superiority of dipyridamole and aspirin was not replicated when clopidogrel was used as the control rather than aspirin. Moreover, long-term DAPT with clopidogrel/aspirin led to significantly higher rates of major bleeding in MATCH, and all-cause mortality in SPS3. Therefore, current evidence does not justify the use of long-term DAPT in patient with lacunar stroke.

Our results are in line with those of the SPS3 trial regarding the lack of benefit from clopidogrel and aspirin therapy in lacunar stroke patients. We however did not notice any significant increase in our composite outcome of any stroke, myocardial infarction and death. Limited by the available published data, we were unable to consider mortality rates in isolation, however long-term dual antiplatelet therapy (mean 3.4 years) led to increased all-cause mortality (HR 1.52, 1.14-2.04, p=0.004) in comparison to monotherapy with aspirin within SPS3 [3].

Our study has limitations. There were a limited number of trials and there was insufficient data to investigate particular outcomes such as hemorrhagic stroke or all-cause mortality in isolation. Additionally, lacunar stroke was defined in a heterogeneous manner among the trials with only one study using a strict clinical criteria and MRI verification of the infarct [3], and we were unable to consider the effect specific DAPT regimens in isolation. A final limitation is that our analysis is unable to account for possible differences in treatment-effects between the acute/semi-acute phase following stroke and the chronic phase.

In conclusion, our results suggest that at present antiplatelet monotherapy of the agents included in the trials should be indicated for secondary stroke prevention after a lacunar stroke. Furthermore, current data are insufficient to justify using one antiplatelet agent over another in this particular population.

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Contributors

CSK and AS was involved in design, screening, study selection, data extraction, data analysis and preparation of manuscript. HC was involved in screening and data extraction. PKM was involved in the design, screening and preparation of the manuscript. YKL was involved in the design, study selection, data extractions, data analysis and preparation of manuscript. OB was involved in design and preparation of manuscript.

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Figure 1: Risk of outcome with antiplatelet versus placebo

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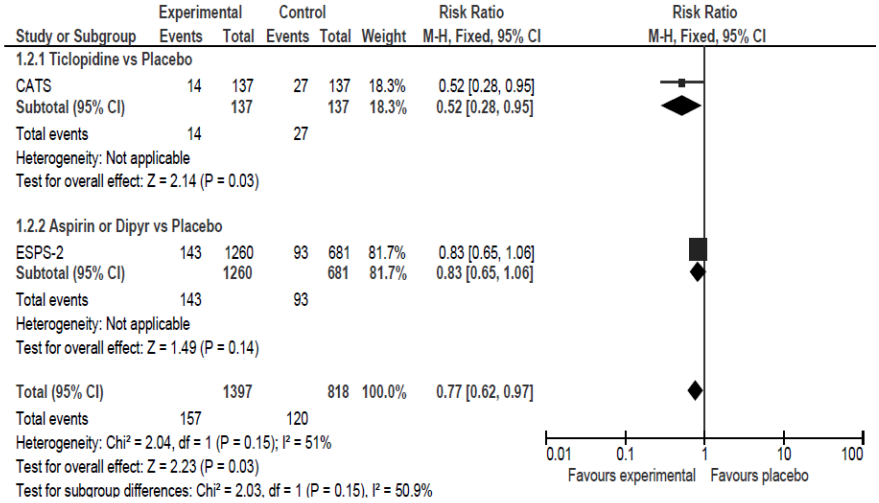
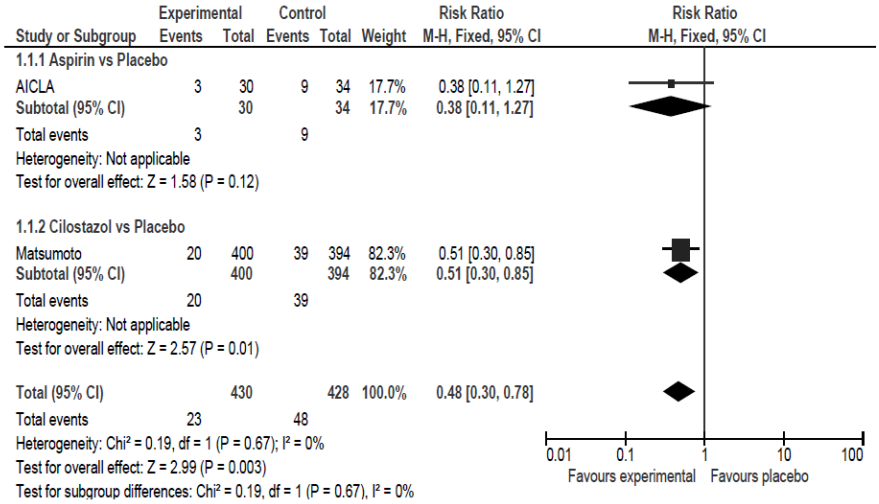
A) Any Stroke



B) Ischemic Stroke



C) Composite Endpoint (any stroke, myocardial infarction and death)

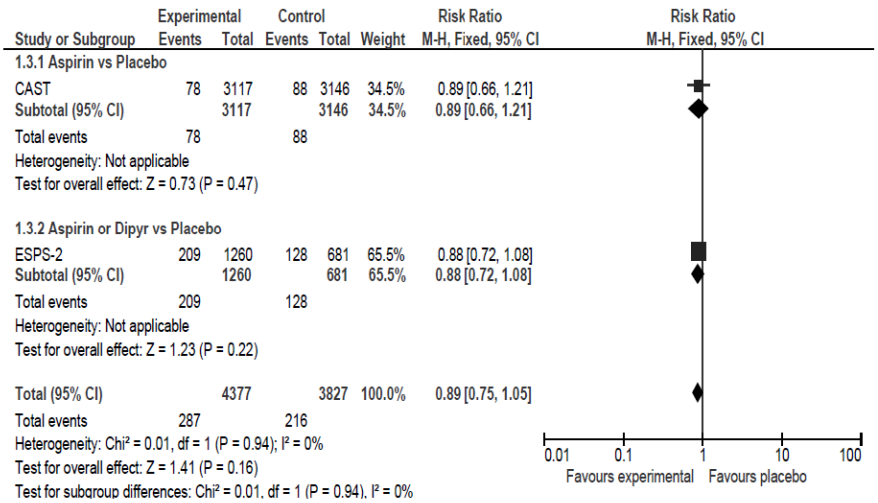


Figure 2: Risk of outcome with antiplatelet monotherapy versus aspirin

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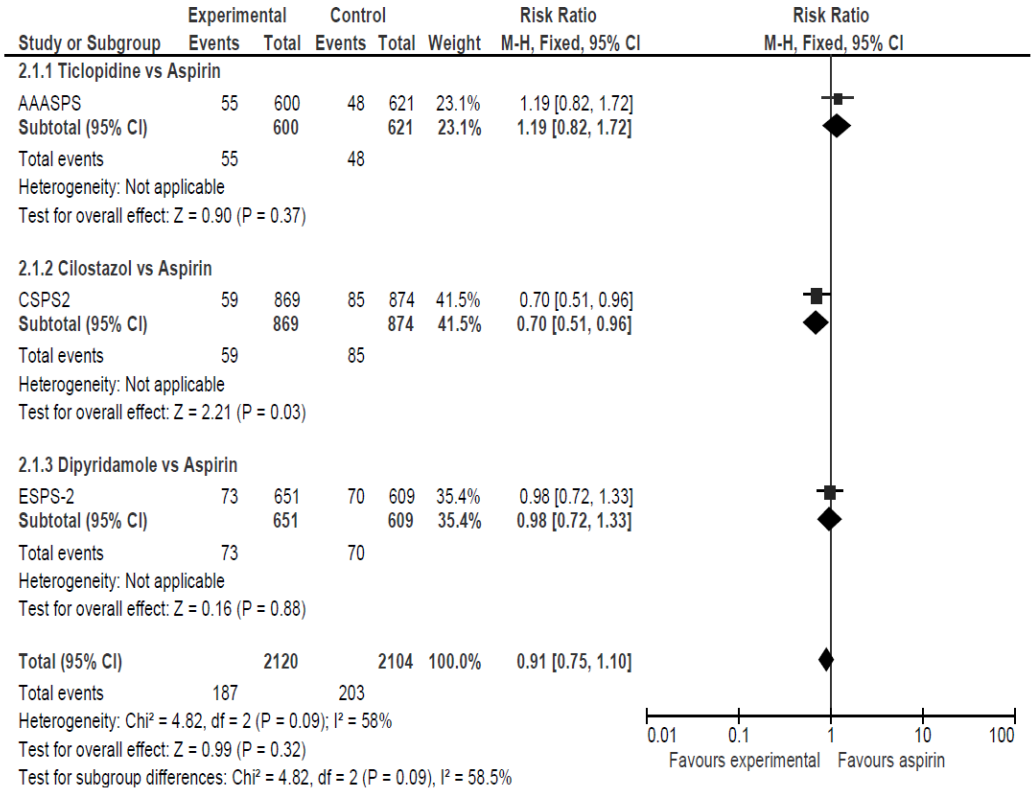
A) Any Stroke



B) Composite Endpoint (any stroke, myocardial infarction and death)

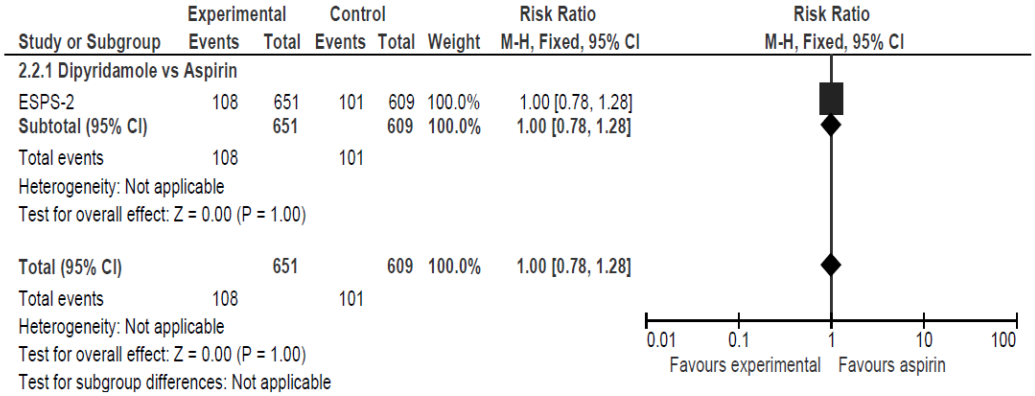
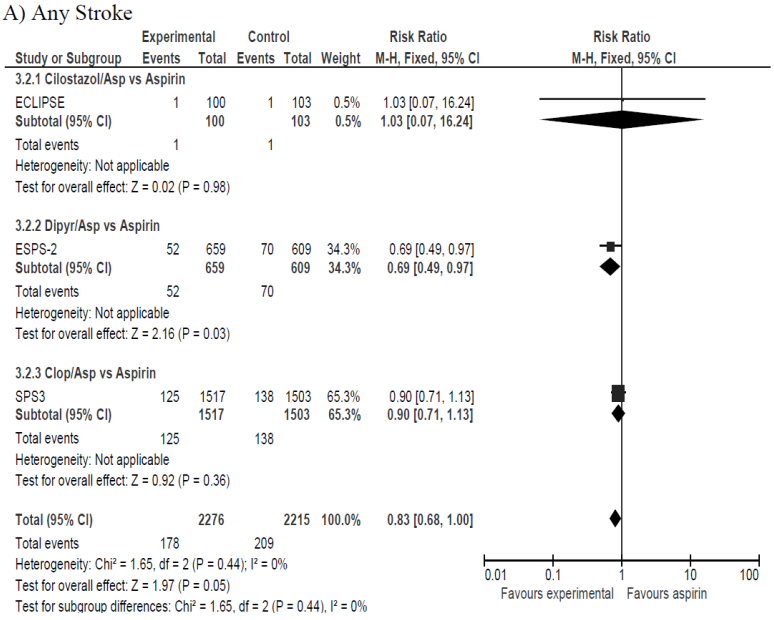


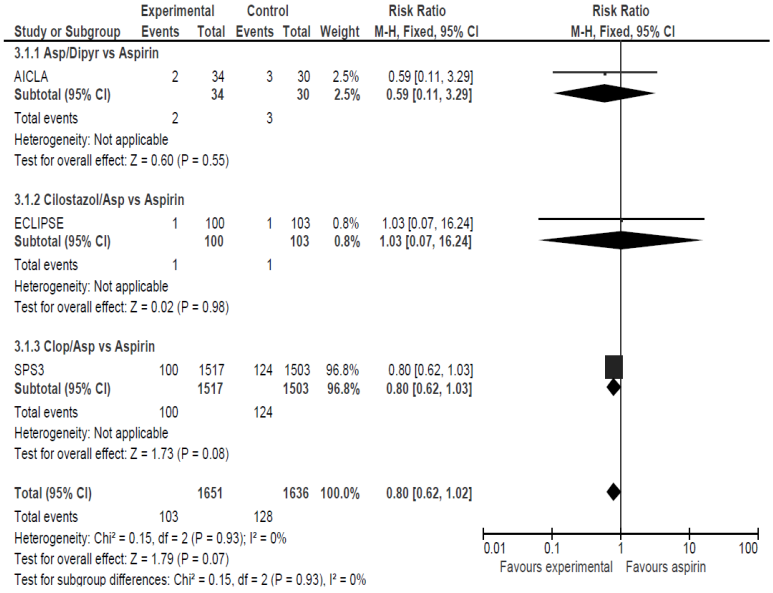
Figure 3: Risk of outcome with dual antiplatelet therapy versus aspirin

Figure 3: Risk of outcome with dual antiplatelet therapy versus aspirin

A) Any Stroke



B) Ischemic Stroke



C) Composite Endpoint (any stroke, myocardial infarction and death)

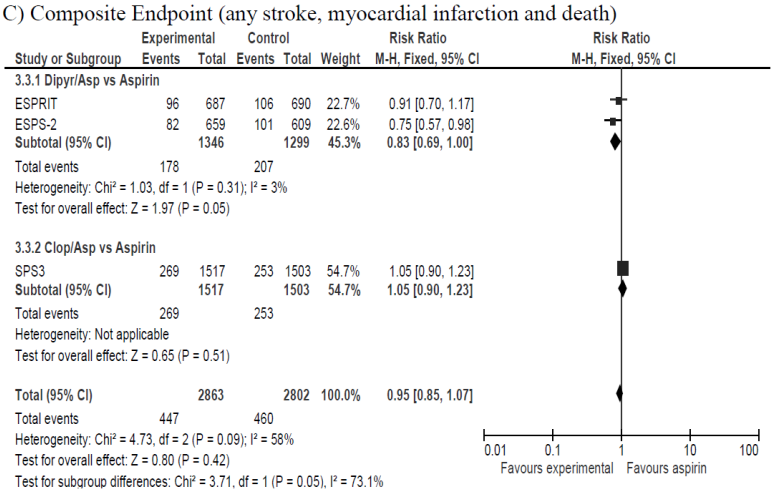
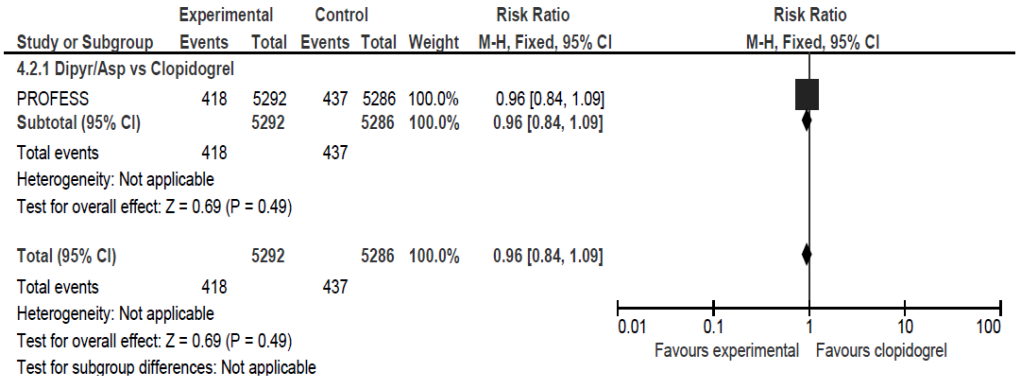


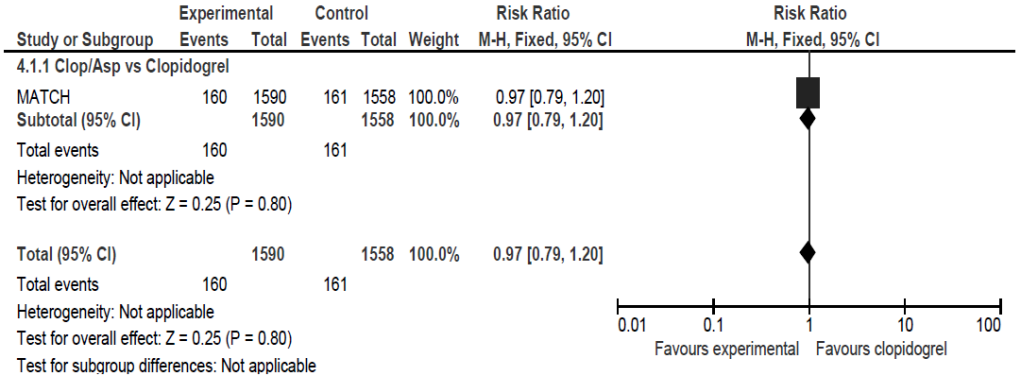
Figure 4: Risk of outcome with other antiplatelet regimens versus clopidogrel

Figure 4: Risk of outcome with other antiplatelet regimens versus clopidogrel

A) Any Stroke



B) Ischemic Stroke



C) Composite Endpoint (any stroke, myocardial infarction and death)

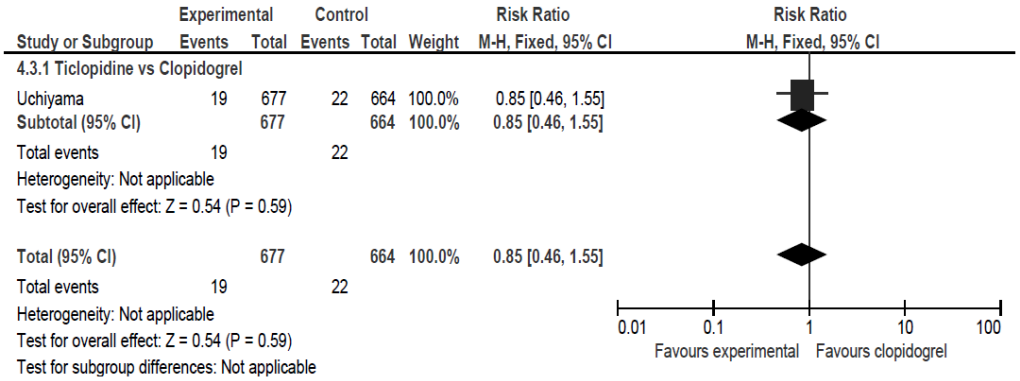


Table 1: Study design and participant characteristics

Study	Midyear of study	Years of study	Design; country	No. of patients with lacunar stroke(%)	Intervention	Mean age	% Male	Participant selection	Stroke ascertainment	Definition of lacunar stroke specified
AICLA [8]	1976	Oct 1975 to Dec 1978	Double blind, multicenter randomized trial; four centers in France.	98(16%)	ASA/ASA+dipyridamole/placebo	63	70%	Participants had at least one cerebral or retinal atherothrombotic ischemic event whether transient or complete.	Neurological assessment with history and CT scan and cerebral angiography was optional.	No
CATS [9]	Prior to 1989	Prior to 1989	Double blind, multicenter randomized controlled trial; 25 centers in Canada.	274(26%)	Ticlopidine/placebo	65	62%	Patients with thromboembolic stroke no less than 1 week or more than 4 months before entry to the study.	Diagnosis was based on a neurological evaluation and assessment of clinical course and required a sudden onset of a new neurological deficit with demonstrable residual effects at time of randomization.	No.
ESPS-2 [19]	1992	Feb 1989 to Mar 1995	Double blind, multicenter randomized controlled trial; 16 centers, 6 countries.	2600(59%)	ASA/dipyridamole/ASA+dipyridamole/placebo	66	61%	Participants with minor ischemic stroke or TIA.	Ischemic vascular accident is defined as neurological deficit due to involvement of	Yes. Small vessel disease had signs and symptoms of 1 of the classical

									the brain or brainstem without symptoms or signs of hemorrhage or tumour.	lacunar syndromes (pure motor stroke, pure sensory stroke, ataxic hemiparesis or dysarthria clumsy hand syndrome).
IST [11]	1993	Jan 1991 to May 1996	Open randomized trial; international 467 hospital from 36 countries.	4616(24%)	ASA/control	61% > 70 years	54%	Participants with acute stroke with onset less than 48 hours previously and no evidence of intracranial hemorrhage.	All patients were CT scanned and eligibility was based on view of responsible physician. Classification of stroke type was based on neurological deficits.	No.
Matsumoto 2005 [14]	1994	Apr 1992 to Mar 1996	Double blind randomized control trial; 183 institutes in Japan.	794(74%)	Cilostazol/placebo	65	66%	Participants aged <80 years with onset of cerebral infarction between 1 and 6 months confirmed on CT or MRI scan and no serious complications were present.	Diagnosis confirmed on CT or MRI imaging.	No.
CAST [10]	1995	Nov 1993 to Mar 1997	Multicenter randomized controlled trial; 413 hospitals in China.	6263(30%)	ASA/placebo	63	64%	Participants were within 48 hours of onset of symptoms of suspected acute ischemic stroke	Patient judged to be within 48 hours of onset of symptoms of suspected acute ischemic stroke	No.

								and had no clear indication for or contraindications to aspirin.	and had CT scan.	
Uchiyama 2009 [23]	1999	July 1996 to Nov 2003	Double blind, multicenter randomized trial; Japan.	1341(73%)	Clopidogrel/ticlopidine	65	71%	Participants had recent ischemic stroke (Must have occurred > 8 days prior to enrolment)	Brain infarcts were documented by computed tomography or magnetic resonance imaging.	No.
MATCH [13]	2001	Dec 2000 to Apr 2002	Double blind, multicenter randomized controlled trial; International 507 centers in 28 countries.	3148(53%)	ASA+clopdiogrel/clopidogrel	66	63%	Participants had ischemic stroke or TIA in the previous 3 months with one or more of five additional risk factors within 3 years.	Diagnosis and stroke type according to TOAST criteria with MRI or CT imaging.	Yes. Small vessel occlusion defined as one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction.
ESPRIT [15]	2001	Jul 1997 to Dec 2005	Multicenter randomized controlled trial; International 79 hospital from 14 countries.	1377(50%)	ASA+dipyridamole/ASA	63	65%	Participants had TIA within 6 months or minor stroke of arterial origin.	Data collected by checklist and classification was on basis of CT or MR scan and clinical features.	Small vessel disease was used as lacunar stroke but not defined.
S-ACCESS [17]	2002	Apr 2001 to Nov	Double blind, multicenter randomized trial; 113	963(64%)	Sarpogrelate/ASA	65	72%	Participants with cerebral infarction based on NINDS	Symptoms, signs and evidence on CT or MR imaging.	No.

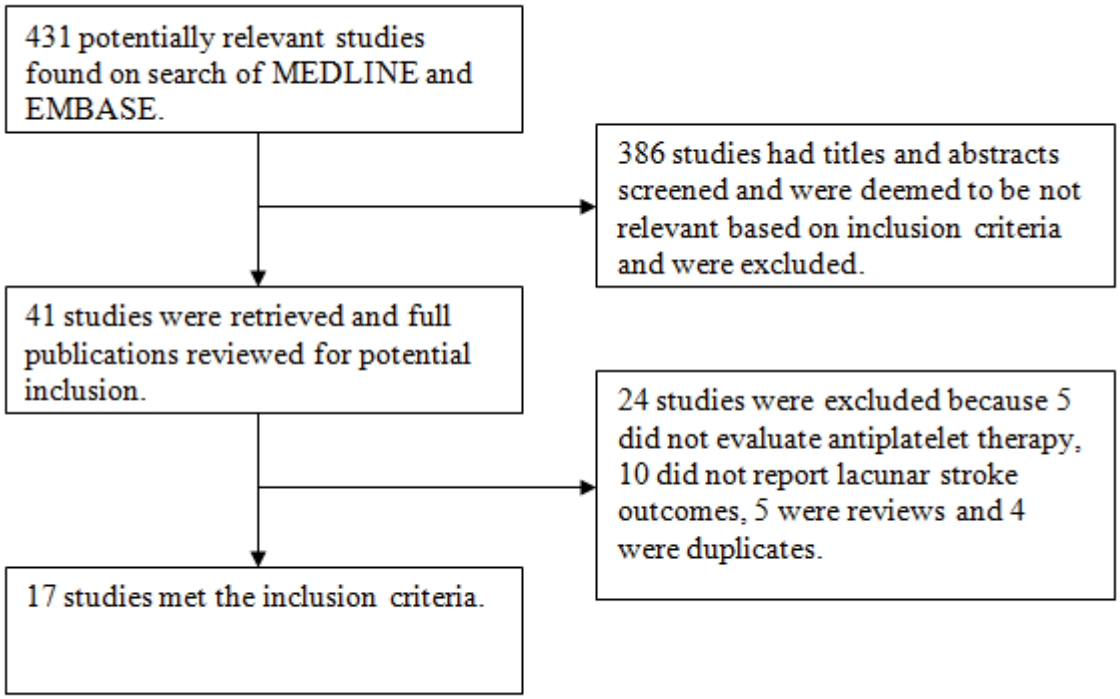
		2003	institutes in Japan.					criteria.		
PROFESS [16]	2005	Sept 2003 to Feb 2008	Double blind, multicenter randomized controlled trial; International, 695 centers in 35 countries.	10578(52%)	ASA+dipyridamole/clopidogrel	66	64%	Participants had recent ischemic stroke (within 90 days of randomization) with symptoms lasting >24 hours or evidence of cerebral infarction on CT or MRI scan, clinical and neurological stability before randomization and age >55 years. Excluded were those with contraindication for antiplatelet agents.	Symptoms of ischemic stroke with evidence of a recent brain infarction on CT or MRI scan.	No.
CSPS2 [18]	2005	Dec 2003 to Oct 2006	Double blind, multicenter randomized trial; 278 sites in Japan.	1743(65%)	cilostazol/ASA	63	NA	Participants with non-cardioembolic cerebral infarction (NINDS-III classification) with evidence on CT or MRI scan and age 20-79 years.	NINDS-III classification with evidence on CT or MRI scan of non-cardioembolic cerebral infarction.	No.
AAASPS [12]	2006	Dec 1992 to Oct 2001	Double blind, multicenter randomized trial; 62	1221(68%)	Ticlodipine/ASA	61	53%	Participants were black race of age 29-85 years of age with	Cranial computed tomographic scan or	No.

			centers in USA.					non-cardioembolic ischemic stroke with onset at least 7 days but not more than 90 days with neurological imaging and measurable neurological deficits consistent with cerebral infarction.	magnetic resonance imaging of the brain consistent with cerebral infarction.	
SPS3 [3]	2007	2003 to 2011	Double blind, multicenter randomized trial; international, 7 countries.	3020(100%)	ASA+clopidogrel/ASA	63	63%	Participants had recent lacunar stroke.	Clinical diagnosis with investigations including an MRI, ECG, ECHO, standard blood tests and imaging of cervical and intracranial arteries.	Yes. Clinical lacunar syndrome that corresponded to an ischemic lesion measuring 2.0 cm or less in diameter on MRI on DWI or <1.5 cm on FLAIR/T1.
PERFORM [21]	2007	Feb 2006 to Apr 2008	Double blind, multicenter randomized controlled trial; International 802 centers in 46 countries.	1733(9%)	Tetroban/ASA	67	63%	Participants were aged 55 years or older, who had had an ischemic stroke or arterial retinal ischemic event more than 48	Ischemic stroke was confirmed by brain imaging.	Yes. Ischemic stroke was categorized into lacunar stroke based on prior defined

								hours and less than 3 months preceding inclusion or a TIA in the previous 8 days.		criteria.
ECLIPSE [20]	2007	Nov 2006 to Oct 2008	Double blind, multicenter randomized trial; 8 hospitals in Korea.	203(100%)	ASA+cilostazol/ASA	65	75%	Participants were eligible for the trial if they experienced their first lacunar infarction within the preceding 7 days and were 45 years of age or older.	All registered patients had a brain CT and/or MRI to exclude hemorrhages and other causes.	Yes. Lacunar infarction was classified according the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification System.
TRA 2P-TIMI 50 [22]	2009	Sept 2007 to Dec 2011	Double blind, multicenter randomized trial; international, 1032 sites, 32 countries.	2262(47%)	Vorapaxar/placebo and concomitant medications	65	67%	Patients had previous ischemic stroke who were hospitalized or evaluated in an acute stroke clinic with a final diagnosis of ischemic stroke within 2 weeks to 12 months before randomization.	Ischemic stroke based on history of hospitalization with final diagnosis of nonhemorrhagic stroke.	Yes. Small artery occlusion defined by lacunar stroke generally <15 mm subcortical size according to TOAST criteria.

SUPPLEMENTAL MATERIAL

Supplementary Figure I: Flow diagram of study selection



Supplementary Table I: Quality of included trials

Study	Sequence generation	Allocation concealment	Blinding	Treatment; exposure; ascertainment	Outcome; outcome ascertainment	Follow up; lost to follow up
AICLA [1]	Patients were randomized using a established randomization schedule, balanced for every 6 patients.	Unclear.	Double-blind.	330 mg ASA, placebo, 330 mg ASA and 75 mg dipyridamole, three times a day; exposure for duration of study; at each follow up patients were asked about drug habits and urine salicylate measurements were performed.	Ischemic stroke; clinical diagnosis with CT scan.	3 years; 11% withdrew from study not related to health problems, 41% discontinued treatment, and 8% withdrew from study.
CATS [2]	Randomization code used for randomization.	Unclear.	Double-blind.	500 mg ticlopidine, placebo; ascertained by pill counting.	Any stroke; events were classified by steering committee.	2 years; 4 patients loss to follow up.
ESPS-2 [3]	Treatment group allocation was determined by a randomization system based on the minimization technique and taking into account various factors.	Unclear.	Double-blind.	Aspirin 50 mg, modified-release dipyridamole 400 mg, aspirin and dipyridamole combined and placebo; exposure for 2 years; unclear ascertainment.	Any stroke. Unclear ascertainment.	Up to 2 years; unclear loss to follow up.
IST [4]	Computer allocated the study treatments using a minimization algorithm which reduced any imbalance in recorded prognostic features between treatment groups.	Adequate allocation concealment where patients were allocated by telephoning the central randomization service at Clinical Trial Service Unit, Oxford, UK.	Not fully double-blind.	300 mg ASA or control (avoid aspirin); exposure for study duration; medication in hospital so compliance not an issue.	Death or dependence; outpatient collection of data, coordinating centre mail a validated questionnaire, or telephone call interview (coordinated centrally).	6 months (0.5 years); 74 lost at 6 months.
Matsumoto 2005 [5]	Randomization was performed by the dynamic balancing method adjusted for several variables.	Adequate allocation concealment by central Registration and Analysis Center, an independent organization set up at Tokyo University for the present study.	Double-blind.	100 mg cilostazol twice daily vs. placebo; exposure duration of study; unclear ascertainment.	Ischemic stroke; Evaluation Committee classified all events.	2 years (1.8 years in cilostazol, 1.6 years in placebo); unclear lost to follow up.
CAST [6]	Randomization was by prepacked, sequentially numbered trial envelopes.	Adequate allocation concealment with prepacked sealed envelopes produced centrally.	Unclear blind.	160 mg ASA, placebo; exposure duration of study; compliance not an issue because nurse administered medication.	Death or non-fatal stroke; clinical diagnosis with CT scan.	4 weeks (0.08 years); unclear loss to follow up.
Uchiyama 2009 [7]	Unclear.	Unclear.	Double-blind.	75 mg clopidogrel or ticlopidine 200 mg; exposure for 26 weeks or	Combined ischemic stroke, MI and vascular	26 and 52 weeks; 7 excluded from

				52 weeks; unclear ascertainment.	death; follow up with examination in clinic visit or telephone call.	analysis but 562 discontinued treatment.
MATCH [8]	Sequence generation was based on a computer-generated list of treatment numbers.	Adequate allocation concealment which was done centrally, with an interactive voice response system (by phone).	Double-blind.	75 mg clopidogrel daily with 75 mg of aspirin or placebo daily; unclear ascertainment.	Ischemic stroke; follow-up visit and telephone calls.	1.5 years; 13 participants were lost to follow up.
ESPRIT [9]	Treatment allocation was by means of computer generated randomization codes stratified by hospital before the start of the trial.	Adequate allocation concealment with randomization by means of a telephone call, fax, or email to the central trial office.	Non-blinded.	30-325 mg ASA daily with or without 200 mg dipyridamole twice daily, exposure for duration of study; medication compliance asked a follow-up.	Ischemic stroke and all cardiac events (MI, sudden death and death from cardiac causes); 3 member committee audited outcome events and independently classified events.	3.5 years; 106 participants were lost to follow up, 554 discontinued treatment.
S-ACCESS [10]	Patients were randomly assigned according to an allocation table that was generated by using random numbers by a person who was not part of this study.	Adequate allocation concealment with web-based randomization.	Double-blind.	100 mg sarpogrelate three times a day vs. 81 mg ASA once daily; exposure for duration of study; unclear ascertainment.	Ischemic stroke; diagnosis by clinical evaluation with Efficacy End Point Committee.	1.59 years; 11 not included in efficacy analysis.
PROFESS [11]	Unclear.	Adequate allocation concealment by a central telephone randomization system.	Double-blind.	25 mg aspirin and 200 mg extended release dipyridamole twice daily or 75 mg clopidogrel daily; exposure for duration of study; compliance was questioned at follow up visits.	Any stroke; ascertained by central committee using TOAST criteria to classify event.	2.5 years; 0.6% were lost to follow up in each arm.
CSPS2 [12]	The randomization table was generated with SAS and random allocation was done with a dynamic balancing method to minimize differences in the distribution of baseline variables between the two groups.	Adequate allocation concealment with remote randomization by contract research organisation at the registration centre.	Double-blind.	100 mg cilostazol twice daily vs. 81 mg ASA daily; exposure study duration, unclear ascertainment.	Any stroke; independent data monitoring committee.	2.42 years; 85 not included in analysis, 793 discontinued drug and 4 lost to follow up.
AAASPS [13]	Patients were randomized using a algorithm using a length of block varying from 2 to 8 with a ratio of patients receiving ticlopidine to aspirin of 1:1.	Adequate allocation concealment with automated phone registration.	Double-blind	650 mg ASA, 500 mg ticlopidine; exposure duration of study; ascertained by pill counting.	Any stroke; blinded adjudication committee.	1.54 years; 522 participants withdrew from study but all were included in analysis.
SPS3 [14]	Randomization assignments were	Adequate allocation concealment	Double-	325 mg ASA daily with or	Any stroke, ischemic	3.4 years; no loss to

	generated using a permuted-block design (variable block size).	using central web-based system.	blind.	without 75 mg clopidogrel daily; exposure for duration of study; adherence measured by pill count.	stroke, death and MI; ascertained by the blinded Events Adjudication Committee.	follow up.
PERFORM [15]	The allocation sequence was generated by the sponsor through in-house application software. The randomization was balanced, non-adaptive, and stratified by country, with blocks of size four.	Adequate allocation concealment by a central interactive response system (telephone or internet).	Double-blind.	30 mg terutroban daily vs. 100 g aspirin daily; unclear ascertainment.	Ischemic stroke, MI, vascular death. Independent Data Monitoring Committee.	28.3 months; 20 excluded, 58 lost to follow up and 382 withdrew consent.
ECLIPSE [16]	A blocked randomization procedure generated by a statistician was used by the central trial pharmacist randomized patients.	Adequate allocation concealment with randomization by central trial pharmacist who produced identical study kits.	Double-blind.	100 mg cilostazol BD or placebo and ASA 100 mg daily; study duration of 90 days; unclear ascertainment.	Any stroke (ischemic stroke data also provided); follow up with transcranial doppler and examination.	90 days; no lost to follow up.
TRA 2P-TIMI 50 [17]	Unclear.	Adequate allocation concealment by a central computerized telephone system.	Double-blind.	2.5 mg vorapaxar daily vs. placebo added to standard antiplatelet therapy; unclear ascertainment.	Cardiovascular death, MI or stroke; ascertained by a Clinical Events Committee blinded to treatment allocation.	Median 24 months (up to 3 years). 32 lost to follow up and 532 withdrew consent for follow up.

Supplementary Table II: Treatments, outcomes, crude events and follow up of studies included

Study	Midyear of study	Treatment experimental/control	Outcome	Experimental events	Total	Adjusted to time (outcome/yr)	Control events	Total	Adjusted to time (outcome/yr)	Trial follow-up duration (mean)	Reported HRs (95% CI) for outcome
AICLA [1]	1976	ASA/placebo	Ischemic stroke	3	30	3.33%	9	34	8.82%	3 years	-
	1976	ASA+dipyridamole/ASA	Ischemic stroke	2	34	1.96%	3	30	3.33%	3 years	-
CATS [2]	Prior to 1989	Ticlopidine/placebo	Any stroke	14	137	5%	27	137	10%	2 years	
ESPS-2 [3]	1992	ASA/placebo	Any stroke	70	609	6.4%	93	681	7.9%	1.7-1.8 years	0.82 (0.60-1.11)
	1992	Dipyridamole/placebo	Any stroke	73	651	6.3%	93	681	7.9%	1.7 years	0.80 (0.59-1.08)
	1992	ASA+dipyridamole/placebo	Any stroke	52	659	4.4%	93	681	7.9%	1.7-1.8 years	0.56 (0.40-0.78)
	1992	ASA+dipyridamole/ASA	Any stroke	52	659	4.4%	70	609	6.4%	1.8 years	0.68 (0.48-0.97)
	1992	ASA/placebo	Composite vascular events*	101	609	9.4%	128	681	11.0%	1.7-1.8 years	0.86 (0.66-1.11)
	1992	Dipyridamole/placebo	Composite vascular events*	108	651	9.5%	128	681	11.0%	1.7 years	0.86 (0.67-1.12)
	1992	ASA+dipyridamole/placebo	Composite vascular events*	82	659	7.0%	128	681	11.0%	1.7-1.8 years	0.64 (0.48 – 0.84)
	1992	ASA+dipyridamole/ASA	Composite vascular events*	82	659	7.0%	101	609	9.4%	1.8 years	0.74 (0.55-0.99)
IST [4]	1993	ASA/control	Death or dependence	1112	2308	-	1116	2308	-	6 months = 0.5 years	-
Matsumoto 2005 [5]	1994	Cilostazol/placebo	Ischemic stroke	20	400	2.97%	39	394	5.25%	2 years (1.8 years in cilostazol, 1.6 years in placebo)	-
CAST [6]	1995	ASA/placebo	Any (non-fatal) stroke or death	78	3117	-	88	3146	-	4 weeks = 0.08 years	
Uchiyama 2009 [7]	1999	Clopidogrel/ticlopidine	Ischemic stroke, MI, vascular death	19	677	2.8%	22	664	3.3%	Up to 1 year.	
MATCH [8]	2001	ASA+clopdiogrel/clopidogrel	Ischemic stroke	160	1590	7.70%	161	1558	8.10%	18 months = 1.5 years	

ESPRIT [9]	2001	ASA+dipyridamole/ ASA	Ischemic stroke and all cardiac events (MI, sudden death and death from cardiac causes)	96	687	3.99%	106	690	4.39%	3.5 years	
S-ACCESS [10]	2002	Sarpogrelate/ASA	Ischemic stroke	46	484	5.95%	35	479	4.53%	1.59 years	HR 1.31 (0.84-2.04)
PROFESS [11]	2005	ASA+dipyridamole/ clopidogrel	Any stroke	418	5292	3.16%	437	5286	3.31%	2.5 years	
CSPS2 [12]	2005	cilostazol/ASA	Any stroke	59	869	3.06%	85	874	4.07%	2.42 years	HR 0.752 (0.542-1.042)
AAASPS [13]	2006	Ticlodipine/ASA	Any stroke	55	600	6%	48	621	5%	1.54 years	
SPS-3 [14]	2007	ASA+clopidogrel/A SA	Ischemic stroke	100	1517	2.00%	124	1503	2.40%	3.4 years	0.82 (0.63-1.09)
	2007	ASA+clopidogrel/A SA	Any stroke	125	1517	2.50%	138	1503	2.70%	3.4 years	0.92 (0.72-1.16)
	2007	ASA+clopidogrel/A SA	Any stroke, MI, death.	269	1517	-	253	1503	-	3.4 years	-
PERFORM [15]	2007	Tetroban/ASA.	Ischemic stroke, MI and vascular death.	54	856	2.55%	61	877	2.98%%	28.3 months = 2.35 years	0.90 (0.62-1.13)
ECLIPSE [16]	2007	ASA+cilostazol/AS A	Any stroke (all events ischemic)	1	100	-	1	103	-	0.25 years	-
TRA 2P-TIMI 50 [17]	2009	Vorapaxar/placebo and concomitant medications	Any stroke, MI, cardiovascular death.	-	2262 (total)	3.80%	-	2262 (total)	3.77 %	3 years	0.99 (0.75-1.31)

*Composite vascular events defined as nonfatal stroke, nonfatal MI, a nonfatal vascular events (DVT, PE, peripheral artery occlusion, venous retinal vascular event) or vascular death.

Supplementary Data I: Search Strategy

Database: Embase <1974 to 2013 Week 50>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 Aspirin or Clopidogrel or Ticlopidine or Dipyridamole or Prasugrel or Ticagrelor or Cilostazol or Dipyridamole {No Related Terms} (6084)
2 Platelet aggregation inhibitors or Antiplatelet {No Related Terms} (69182)
3 Platelet Aggregation Inhibitors {No Related Terms} (5716)
4 Stroke or cerebrovascular disease or cerebrovascular accident {No Related Terms} (8654)
5 Stroke/ (186298)
6 Brain Ischemia/ (112183)
7 Cerebrovascular Disorders/ (91210)
8 randomised controlled trial or randomized controlled trial or randomised controlled study or randomized controlled study {No Related Terms} (9836)
9 Randomized Controlled Trial/ (755711)
10 1 or 2 or 3 (77570)
11 4 or 5 or 6 or 7 (355197)
12 8 or 9 (755716)
13 10 and 11 and 12 (536)
14 remove duplicates from 13 (431)

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