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## **Secondary prevention in minor ischemic stroke with antiplatelet treatment. Systematic review and meta-analysis of comparative studies with aspirin under non-inferiority criteria.**

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**Key words:** secondary prevention; ischemic stroke; antiplatelet treatment; meta-analysis; non-inferiority.

**Abstract.** Minor ischemic stroke is the most frequent presentation of cerebral vascular disease and treatment with antiplatelet drugs can be used for the prevention of its recurrence. This systematic review and meta-analysis was aimed to assess non-inferiority criteria about the effect in the comparison of different antiplatelet schemes using aspirin as active control. Twelve randomized studies with a total of 52204 patients were chosen. All met the inclusion criteria with minor recurrent ischemic stroke as end point and any extracranial bleeding as safety event. The results showed a significant risk reduction of 22% [RR (95% CI) = 0.78 (0.72-0.84),  $p < 0.0001$ , NNT: 67] in the recurrence of ischemic events with any antiplatelet drug (combined or not with aspirin) versus aspirin alone and there were no differences in the bleeding risk [RR (95% CI) = 1.02 (0.74-1.41),  $p = 0.899$ , NNH: 500]. Dual antiplatelet therapy (DAPT) and cilostazol were more effective compared with aspirin alone (22% and 32% risk reduction respectively) but only cilostazol showed a higher reduction (52%) of bleeding events. In conclusion, although in some instances equivalence was demonstrated, a clinical superiority in the risk reduction for recurrent ischemic stroke of any antiplatelet treatment versus aspirin alone was observed. With the sole exception of the cilostazol trials there was an increase of the bleeding risk when the antiplatelet drugs treatments were compared with aspirin alone.

## **Prevención secundaria en el ictus isquémico menor con el tratamiento antiplaquetario. Revisión sistemática y metanálisis de estudios comparativos con aspirina bajo criterios de no inferioridad.**

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**Palabras clave:** prevención secundaria; accidente cerebrovascular isquémico; tratamiento antiplaquetario; metanálisis; no inferioridad.

**Resumen.** El accidente cerebrovascular (ictus) isquémico menor es la presentación más frecuente de enfermedad vascular cerebral y se puede utilizar el tratamiento con fármacos antiplaquetarios para la prevención de su recurrencia. Esta revisión sistemática y metanálisis tuvo como objetivo evaluar los criterios de no inferioridad sobre el efecto en la comparación de diferentes esquemas antiplaquetarios que usan aspirina como control activo. Se eligieron doce estudios aleatorios con un total de 52.204 pacientes. Todos cumplieron los criterios de inclusión para ictus isquémico recurrente menor como desenlace primario y hemorragia extracraneal como evento de seguridad. Los resultados mostraron una reducción significativa del riesgo del 22% [RR (IC 95%) = 0,78 (0,72-0,84),  $p < 0,0001$ , NNT: 67] en la recurrencia de eventos isquémicos con cualquier fármaco antiplaquetario (combinado o no con aspirina) versus aspirina sola y no hubo diferencias en el riesgo de hemorragia [RR (IC 95%) = 1.02 (0.74-1.41),  $p = 0.899$ , NNH: 500]. La terapia antiplaquetaria dual (DAPT) y el cilostazol fueron más efectivos en comparación con la aspirina sola (22% y 32% de reducción de riesgo respectivamente) pero solo el cilostazol mostró una mayor reducción (52%) de los eventos hemorrágicos. En conclusión, aunque en algunos casos se demostró la equivalencia, se observó una superioridad clínica en la reducción del riesgo de accidente cerebrovascular isquémico recurrente de cualquier tratamiento antiplaquetario versus aspirina sola. Con la única excepción de los ensayos con cilostazol, hubo un aumento del riesgo de hemorragia cuando los tratamientos con fármacos antiplaquetarios se compararon con la aspirina sola.

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### **INTRODUCTION**

Acute cerebrovascular disease (ACD) is defined as a focal neurological deficit of generally arterial origin, lasting more than 24 hours and can be classified as ischemic stroke (85%) or intracranial hemorrhage (15%) (1,2). ACD can be stratified by the risk factors and preventive measures. Non-fatal ischemia in the acute ischemic stroke

is diagnosed by the sudden onset of a new or growing neurological deficit that persists for more than 24 hours; an event resulting in an increase in disability of at least one degree on the modified Rankin scale (measurement scale degree of disability or dependence on the daily activities of people with Stroke and neurological disability) (3). Another of the recognized tools for predicting a clinical stroke is the Framingham's stroke risk

profile, which combines modifiable and non-modifiable risks (4). The stratification can be done with different scales such as the National Institute of Health Stroke Scale (NIHSS) (5), the ABCD2 (age, blood pressure, clinical, duration and diabetes type 2 scale) (6), and its recently modified as ABCD3-I including diffusion-weighted imaging (7) to classify the severity or the risk of a cerebrovascular event and its treatment), which highlights the importance of adequate anamnesis and physical examination of patients followed by neuroimaging (MRI) diagnosis.

Brain lacunar infarcts are usually known as a part of the small-vessel disease (SVD) as one of the main manifestation of ischemic stroke. Lacunar infarcts have <1.5 cm diameter that result from occlusion of a single penetrating artery usually located in the basal ganglia, corona radiata, internal capsule, thalamus and the brainstem. Clinically lacunar infarcts are recognized in five types of presentations: pure motor hemiparesis, pure sensory stroke, sensory-motor stroke, dysarthria-clumsy hand syndrome and ataxic hemiparesis (8). The clinically defined transient ischemic attacks (TIA), may not be transient at the tissue level, and be considered as a part of the ischemic stroke spectrum. A TIA is not a pathological entity by itself; it is a milder form in the spectrum of ischemia and is therefore a form of presentation of cerebrovascular disease (8).

These recent years have been marked by changes regarding the therapeutic behavior adopted to treat the disease. Currently, many patients with acute ischemic stroke are benefited from treatments such as intravenous thrombolysis and endovascular thrombectomy (5). The main measures indicated in the treatment guidelines for ACD include: a) thrombolytic measures within three hours of the ischemic event (thrombolysis or thrombectomy), and b) antiplatelet, antithrombotic or anticoagulant treatment to avoid stroke recurrence (2,5). The secondary prevention of ischemic stroke uses

antiplatelet agent treatment for non-cardioembolic cerebral ischemic events and oral anticoagulation for cardioembolic ischemic events (e.g. Atrial Fibrillation) (9). According to the 2018 guidelines for the treatment of ACD, aspirin (for its irreversible inhibition effect of cyclooxygenase-1) has been the treatment of choice for ischemic stroke from the second half of the twentieth century to the present day (5,10-12). The use of receptor inhibitors for adenosine diphosphate (ADP) type P2Y<sub>12</sub> has boomed in the two decades of the 21st century (thienopyridines such as ticlopidine, clopidogrel, prasugrel and non-thienopyridines such as ticagrelor, cangrelor and elinogrel) (13), some of them indicated as dual therapy with aspirin versus aspirin alone. Moreover, platelet phosphodiesterase inhibitors (dipyridamol and cilostazol) have been used as antiplatelet agents in the treatment of ischemic stroke by the prevention of cyclic AMP inactivation and irreversible inhibition of platelet function (14,15). The use of other antiplatelet agents with a different mechanism of action has been published such as the so-called platelet receptor antagonists for Glycoprotein IIb-IIIa: tirofiban (16), eptifibatide (17-19) and abxycimab (20,21). However, the studies were performed in small population samples and the results did not support its ordinary use in clinical practice, so the 2018 guidelines on the treatment of acute ischemic accident do not recommend its administration (5).

This systematic review proposes to conduct an analysis of comparative studies between aspirin as active control and studies with antiplatelet agents, using dual therapy (including aspirin) or monotherapy versus aspirin, with a no inferiority approach for effectiveness of clinical trials in reducing events (recurrence) in patients with ischemic stroke. The triple therapy versus aspirin alone will not be included in this systematic review because of its adverse effects (increased risk of bleeding) and actually, this type of treatment should not be indicated in the treatment of ischemic stroke (22).

## METHODOLOGY

### Search strategies

The present review focus exclusively on antiplatelet treatment for non-cardioembolic minor ischemic stroke (summarized in Table I). A twenty year-span (2000-2019) search of bibliography was conducted through PUBMED by MEDLINE, Google Scholar and Cochrane collaboration (Cochrane Systematic Reviews), under the following terminology MESH (Medical Subject Headings): stroke, ischemic stroke, transient ischemic attack (TIA), ischemic

recurrent stroke, minor stroke, non-cardioembolic stroke, ischemic lacunar stroke, aspirin, clopidogrel, prasugrel, ticagrelor, cilostazol, dipyridamole and dual antiplatelet therapy using AND as the connector for the term “Non-inferiority studies”. In relation to exclusion criteria, only randomized clinical trials with more than 300 patients were included in this systematic review and there was no substantial difference (more than 5%) among the number of subjects in the active intervention and control groups. Other reasons for excluding articles are exposed in Fig. 1. Previous systematic reviews

TABLE I

MAIN CHARACTERISTICS OF ANTIPLATELET DRUGS IN THE TREATMENT OF ISCHEMIC STROKE.

Antiplatelet drug	Drug type and Mechanism of action	Type of administration	Half life	Duración of the effect	Adverse effects
Aspirin	acetyl salicilic acid, inhibitor of cyclooxygenase-1	Oral	12 h	10 days	G.I. hemorrhage
Ticlopidine*	Tienopiridine, P2Y12 receptor inhibitor	Oral	12-22 h	15 d	Thrombocytopenia/TTP, G.I.symptoms, aplastic bone marrow
Clopidogrel	Tienopiridine P2Y12 receptor inhibitor	Oral	8 h	5-10 d	Neutropenia, thrombocytopenia, allergic reactions
Prasugrel	Tienopiridine, P2Y12 receptor inhibitor	Oral	12 h	5-9 d	G.I. hemorrhage
Ticagrelor	Cyclopentilriazol primidine, P2Y12 receptor inhibitor	Oral	8-12 h	5 d	Dyspnea, arrhythmia
Cangrelor	ATP Analogue, P2Y12 receptor inhibitor	I.V.	2-5 min	1 h	Dyspnea hypersensitivity reactions
Elinogrel	direct antagonist of P2Y12receptor	Oral / I.V.	12-14 h oral, 50 min I.V.	8-24 h oral, 2 h I.V.	Dyspnea, hepatotoxicity
Dipyridamol	platelet phosphodiesterase Inhibitor	Oral	12 h	5 d	headache, dizziness, diarrhea
Cilostazol	platelet phosphodiesterase 3 Inhibitor	Oral	11-13 h	5 d	headache, tachycardia, diarrhea
Vorapaxar	platelet thrombin receptor Inhibitor (PAR-1)	Oral	2h	7-12 d	headache, dizziness, G.I. symptoms, arthralgia, erythema

Taken and modified from Campuzano Maya G (25). \*currently not indicated.

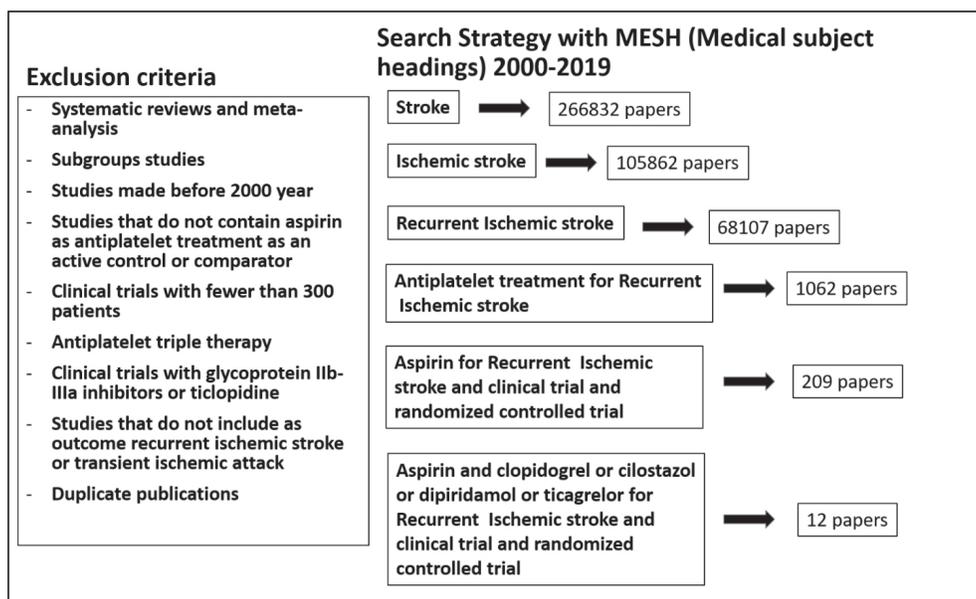


Fig. 1. Search strategy with MESH terminology and exclusion criteria.

and meta-analysis were only considered for the discussion part. The Jadad scale for randomized studies was applied for calculation of the quality report of each study (23) and the Cochrane risk of bias tool to assess for individuals' trials (24).

The primary end point for effectiveness was recurrent ischemic stroke and TIA, when a study presented a composite outcome (death, myocardial infarction and stroke), only data corresponding to recurrent ischemic stroke were extracted as an event to be analyzed. The exclusion criteria were: disabling stroke (modified Rankin score 4 out of 6); risk factors for cardioembolic sources such as atrial fibrillation; subcortical infarction with diameter >1.5 cm; recent or remote cortical infarction confirmed by MRI; and a history of intracerebral hemorrhage other than microhemorrhage or cortical ischemic stroke. Among safety or secondary events, major bleeding was chosen according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) definition (25) or PLATO bleeding definition (26). Some studies analyzed only describe hemorrhagic events without discrimination of the type

of bleeding, cases with intracranial hemorrhage were not considered and these were excluded from the study for both effectiveness and safety.

According to search strategies, Table II shows the studies that met the inclusion requirements and were identified and classified as follows: a) Six studies with clopidogrel-aspirin dual therapy (DAPT) versus aspirin as active control: CHARISMA (27), SPS3 (28), CHANCE<sub>2013</sub> (29), Coté (30), COMPRESS (31), POINT (32); b) four studies with cilostazol versus aspirin: CASISP (33), CSPS-2 (34), PICASSO (35), CSPS.com (36); c) one study with ticagrelor versus aspirin: SOCRATES (37) and d) one study of dipyridamole dual therapy (dipyridamole-aspirin versus aspirin): ESPRIT (38).

### Criteria for non-inferiority studies

In “non-inferiority” trials, the main objective is to demonstrate that the efficacy between two treatments is similar, one called new treatment and the other called active control or standard treatment, so there is a need for comparative evidence. The question to ask when trying to conduct non-inferiority studies is: “Is the new treatment at least as effective

**TABLE II**  
COMPARATIVE STUDIES OF PLATELET AGENTS VERSUS ASPIRIN IN SECONDARY PREVENTION OF ISCHEMIC STROKE.

STUDY (YEAR) (REF)	COMPARISON	DESIGN AND DURATION	PATIENTS	PRIMARY OUTCOME	SECURITY OUTCOME
CHARISMA (2006) <sup>27</sup>	CLOPIDOGREL + ASPIRIN VS ASPIRIN + PLACEBO	RDBPC 2-3 YEARS	15603 DAPT: 7802 ASA: 7801	COMPOSITE*/ RECURRENT ISCHEMIC STROKE + TIA	MAJOR EXTRACRANIAL HEMORRHAGE
SPS3 (2012) <sup>28</sup>	CLOPIDOGREL + ASPIRIN VS ASPIRIN + PLACEBO	RDBPC 3-5 YEARS	3020 DAPT: 1517 ASA: 1503	STROKE/RECURRENT ISCHEMIC STROKE + TIA	MAJOR EXTRACRANIAL HEMORRHAGE
CHANCE (2013) <sup>29</sup>	CLOPIDOGREL + ASPIRIN VS ASPIRIN + PLACEBO	RDBPC 90 DAYS	5170 DAPT: 2584 ASA: 2586	STROKE/RECURRENT ISCHEMIC STROKE + TIA	ANY EXTRACRANIAL HEMORRHAGE
Coté (2014) <sup>30</sup>	CLOPIDOGREL + ASPIRIN VS ASPIRIN	RDBPC 3.5 YEARS**	838 DAPT: 427 ASA+P: 411	POST HOC STROKE/ RECURRENT ISCHEMIC STROKE	ANY EXTRACRANIAL HEMORRHAGE
COMPRESS (2016) <sup>31</sup>	CLOPIDOGREL + ASPIRIN VS ASPIRIN + PLACEBO	RDBPC 30 DAYS	334 DAPT: 167 ASA: 167	STROKE/RECURRENT ISCHEMIC STROKE	ANY EXTRACRANIAL HEMORRHAGE
POINT (2018) <sup>32</sup>	CLOPIDOGREL + ASPIRIN VS ASPIRIN + PLACEBO	RDBPC 90 DAYS	4881 DAPT: 2432 ASA: 2449	COMPOSITE*/ RECURRENT ISCHEMIC STROKE	MAJOR EXTRACRANIAL HEMORRHAGE
CASISP (2008) <sup>33</sup>	CILOSTAZOL VS ASPIRIN	RDBPC 12-18 MONTHS	720 CILOSTAZOL: 360 ASA: 359	RECURRENT ISCHEMIC STROKE	ANY EXTRACRANIAL HEMORRHAGE
CSPS-2 (2010) <sup>34</sup>	CILOSTAZOL VS ASPIRIN	RDBCT 1-5 YEARS	2672 CILOSTAZOL: 1337 ASA: 1335	NON CARDIOEMBOLIC STROKE/RECURRENT ISCHEMIC STROKE + TIA	ANY EXTRACRANIAL HEMORRHAGE
PICASSO (2018) <sup>35</sup>	CILOSTAZOL + PLACEBO VS ASPIRIN + PLACEBO	RDBPCT 5 YEARS	1534 CILOSTAZOL: 766 ASA= 768	COMPOSITE/RECURRENT ISCHEMIC STROKE	ALL EXTRACRANIAL HEMORRHAGE
CSPS.com (2019) <sup>36</sup>	CILOSTAZOL + ASPIRIN VS ASPIRIN OR CLOPIDOGREL + ASPIRIN VS ASPIRIN	RCT 3-5 YEARS	1879 DAPT: 932 DIPYRIDAMOL + ASA: 947	RECURRENT ISCHEMIC STROKE + TIA	MAJOR EXTRACRANIAL HEMORRHAGE
SOCRATES (2017) <sup>37</sup>	TICAGRELOR VS ASPIRIN	RDBCT 90 DAYS	13199 TICAGRELOR: 6589 ASA: 6610	COMPOSITE*/ RECURRENT ISCHEMIC STROKE + TIA	MAJOR EXTRACRANIAL HEMORRHAGE
ESPRIT (2006) <sup>38</sup>	DIPYRIDAMOLE + ASPIRIN VS ASPIRIN	RCT 6 MONTHS	2739 D + A: 1363 ASA: 1376	COMPOSITE*/ RECURRENT ISCHEMIC STROKE	MAJOR EXTRACRANIAL HEMORRHAGE

RDBPC: Randomized double-blind placebo controlled, RDBCT: Randomized double-blind controlled trial, RCT: Randomized controlled trial, TIA: Transient ischemic attack, DAPT: Dual antiplatelet therapy, ASA: Aspirin, P: Placebo, D + ASA. \* A composite outcome means the sum of death, myocardial infarction and stroke. \*\*Mean duration.

as the active control for reducing the risk of events? Of which, two responses can occur: a) H0 (null hypothesis): the new treatment is less effective for event reduction (lower) or is more effective (it is higher) and b) H1 (alternative hypothesis): the new treatment is at least as effective as the active control for event reduction (not lower). Adopting the answer H0 as true is based on a decision rule according to the statistical significance of the p-value. However, the p-value calculated in non-inferiority tests is special; is called “p of non-inferiority” different from the p of superiority; the difference is in the confidence intervals (IC), if in the 95% CI range is not included the unit “1”, we assume that there is significance for superiority (e.g.: 0.78-0.98 or 1.08-2.23), but if the opposite is the 95% CI range the unit “1” is included, namely accepted that there is no statistical significance (e.g. 0.72-1.12), and we would be talking about equivalence or non-inferiority between two treatments as long as the confidence interval does not exceed the non-inferiority limits. The H1 alternative hypothesis will be adopted as true, in circumstances where the experimental treatment is not expected to be more effective than the standard treatment or active control, but the new drug offers additional advantages. Such advantages could be a better safety profile, fewer side effects, easier administration, less need for controls and even a lower total cost (39-42). Not inferiority or equivalence are synonyms: according to the CONSORT declaration (43) for randomized controlled studies, non-inferiority generally applies to the predefined upper limit of a single tale ( $p < 0.025$ ) and equivalence is interpreted when an upper boundary is defined ( $\Delta+$ ) and a lower boundary ( $\Delta-$ ), in this case, the analysis is two tales ( $p < 0.05$ ). However, there is no defined criterion and many authors claim no inferiority or equivalence when the values of the 95% CI fall within the two predefined limits.

#### **How is the non-inferiority limit calculated?**

This systematic review analyses aspirin as standard treatment or active control ver-

sus treatment with other antiplatelet agents in reducing cerebral ischemic thrombotic events (recurrent ischemic stroke and transient ischemic attack), setting limits for non-inferiority or equivalence for antiplatelet agents and aspirin. For the analysis of non-inferiority studies, the upper limit or predefined limit of non-inferiority ( $\Delta+$ ) for aspirin was set at 1.33 according to Shinohara *et al* (34) from a meta-analysis published in 2002 (44), in which was estimated the effect of aspirin versus placebo on the prevention of ischemic stroke events with respect to placebo or lack of treatment. In this way, the upper limit of non-inferiority was set at 1.33 and the lower limit of the non-inferiority limits ( $\Delta-$ ) would be 0.67 ( $1 - 0.33 = 0.67$ ), everything that exceeds those limits is demonstrable for superiority or non-inferiority is not demonstrated.

#### **Statistical analysis. Meta-analysis description**

The guidelines developed according to the recommendations of the PRISMA method (45) were followed. The statements for non-inferiority studies were applied according guidelines of the CONSORT group (43). The selected studies conducted direct comparisons between antiplatelet drugs and aspirin on a primary analysis of effectiveness and safety events. The meta-analysis was developed under the graphical presentation type “Forest plot” with the random effect modality and the relative risk (RR as an effect measure, although estimates may vary slightly from published hazard ratios for individual trials as hazard ratios use failure-time data, vs. event–no event data for RR) with the following components: 1. Study name, 2. Antiplatelet, events/total of patients (%), 3. Aspirin, events/total patients (%), 4. Number Needed to Treat (NNT) for effectiveness and the Number Needed to Harm (NNH) for safety or adverse effect, calculated as the inverse of the absolute risk reduction or increase, 5. Percentage of relative weight of each study and 6. RR (IC95%) and p of each

study. Statistical meta-analysis was carried out with the Comprehensive Meta-Analysis programme (Biostat, Englewood, NJ). As statistical parameters, the consistence for heterogeneity ( $I^2$ ) was determined as low (<25%), moderate (25% to 75%) and high (>75%) by testing the  $\chi^2$  calculation of each meta-analysis (cochrane Q) according to the Higgins formula (46), calculation of Z value and  $p < 0.05$  for statistical significance. The terms clinical and statistical significance refer to reduction or increased risk of events with a significant result or not, for example, there may be the case of clinical significance with reduction or increase of events without statistical significance [Vizcaíno G. 2020, book *Evidence Based Medicine and analysis of clinical research designs, 2<sup>nd</sup> edition*, in press (Spanish)].

**RESULTS**

A systematic review was conducted with meta-analysis on recurrent ischemic stroke and transient ischemic attack of 12 randomized controlled studies with 52204 patients, the main characteristic was to observe whether

there was correspondence with criteria of non-inferiority using aspirin as an active control. For this purpose, they were classified for effectiveness and safety analysis in three groups, the first consisting of the 12 selected studies (antiplatelet drugs vs aspirin alone), the second, those studies that used dual therapy (clopidogrel-aspirin vs aspirin alone) and the third group, the studies describing the effect of cilostazol versus aspirin as active control.

**Antiplatelet versus aspirin therapy**

In this meta-analysis on effectiveness and safety was performed based on the combined analysis of 12 studies with different antiplatelet treatments versus aspirin as active control. Fig. 2 shows the effect of the different treatments on the reduction of recurrent ischemic stroke events. With the exception of the COMPRESS study, all studies revealed clinical reduction of ischemic events and 50% of them obtained statistical significance. The combined result showed clinical and significant reduction in the risk of recurrent ischemic stroke of 22% [RR (95% CI)= 0.78 (0.72-0.84),  $p < 0.0001$ ], the absolute risk reduction was 1.5%, the NNT was 67 and studies were consistent for low hetero-

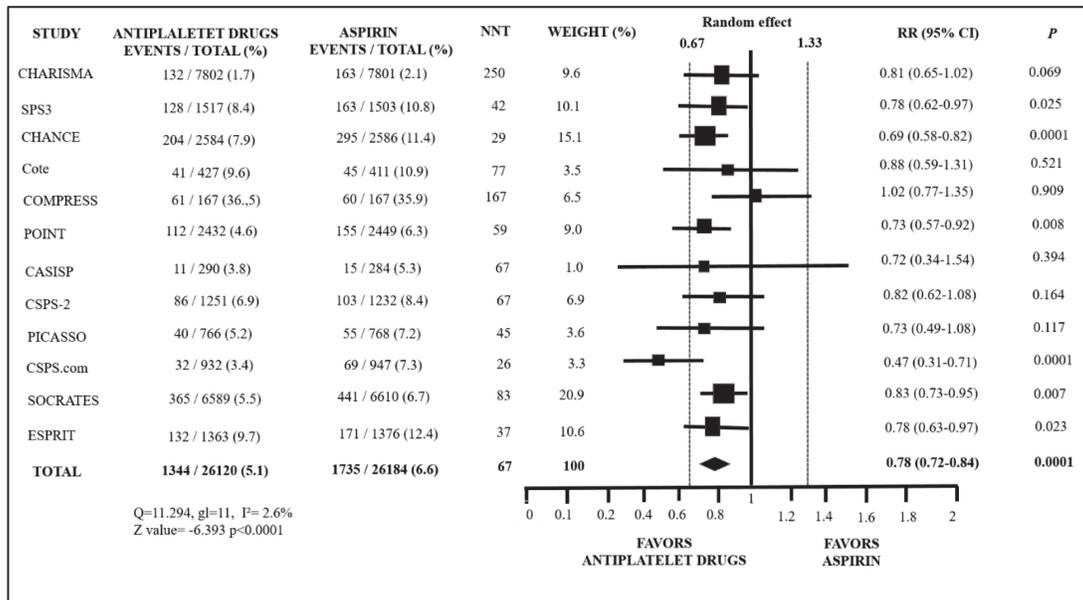


Fig. 2. Meta-analysis of effectiveness in studies with different antiplatelet agents versus aspirin as active control.

geneity ( $I^2 = 2.6\%$ ). Non-inferiority could not be demonstrated, although equivalence might be surrogate it (the composite of the studies lies between the limits of non-inferiority), superiority of antiplatelet over aspirin can be claimed in terms of effectiveness.

The safety meta-analysis (Fig. 3) between antiplatelet studies versus aspirin as an active control showed individually in some studies increased hemorrhagic risk and in others revealed otherwise, manifesting in the result combined as a slight clinical increase but non-significant risk (2%) with antiplatelet drugs [RR (95% CI)=1.02 (0.74-1.41),  $p = 0.899$ ]. The absolute risk increase was 0.2%, the NNH was 500 and the consistency of studies revealed low heterogeneity ( $I^2 = 8.8\%$ ).

**Clopidogrel versus aspirin**

The effect of dual therapy (clopidogrel + aspirin) versus aspirin alone on the reduction of recurrent ischemic stroke events is shown in Fig. 4. It was observed that individually any study did not met criteria for non-inferiority. Studies SPS3, CHANCE<sub>2013</sub> and POINT demonstrated clinical and significant risk reduction. The combined result indicates also a 22%

clinical and significant reduction in ischemic stroke recurrence in favor of dual therapy [RRI (95% CI) = 0.78 (0.70-0.87),  $p < 0.0001$ ] so it was assumed that dual therapy treatment is equivalent when compared to aspirin (does not exceed lower limits), however, in this case, superiority can be claimed. The absolute risk reduction was 1.4%, the NNT was 71 and  $I^2 = 0\%$  (evidence of homogeneity).

Safety analysis (Fig. 5) regarding extra-cranial haemorrhagic manifestations comparing dual therapy (clopidogrel + aspirin) versus aspirin alone reveals that all studies, showed increased hemorrhagic risk for dual therapy. The combined result exhibit a clinical and significant increase in bleeding of 58% with the use of DAPT [RR (95% CI) = 1.58 (1.30-1.93)  $p < 0.0001$ ]. The absolute risk increase was 0.9%, NNH=111 and the consistency of the study showed homogeneity among all studies ( $I^2 = 0\%$ ).

**Cilostazol versus Aspirin**

Analysis on the effectiveness evidence, with the exception of the CSPS.com study, all studies revealed a non-significant risk reduction (Fig. 6), but none of them met

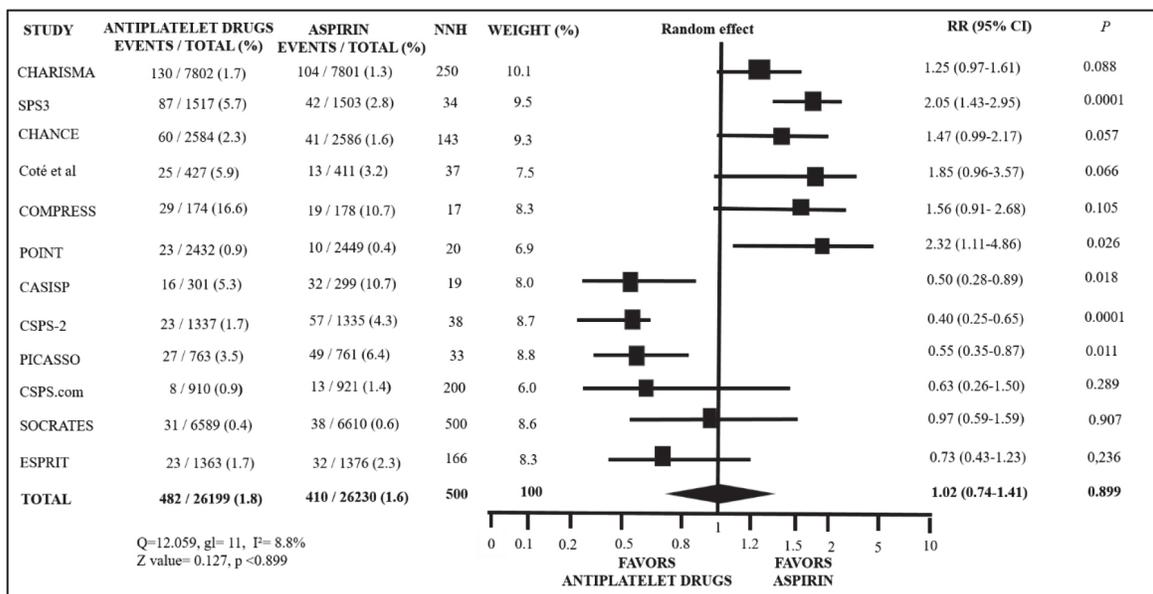


Fig. 3. Security meta-analysis. Effect of antiplatelet treatment versus aspirin as active control.

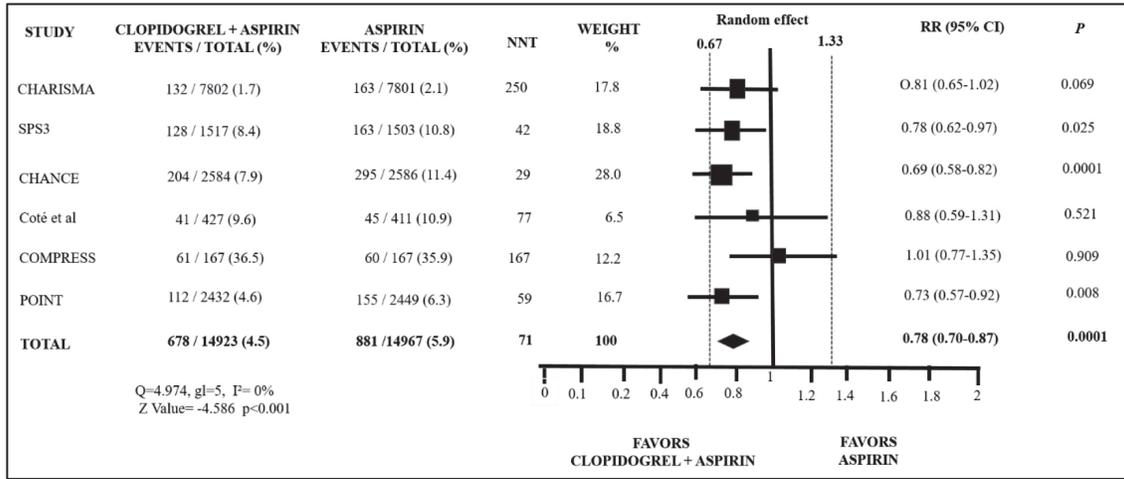


Fig. 4. Meta-analysis of effectiveness with dual therapy (clopidogrel + aspirin) versus aspirin alone.

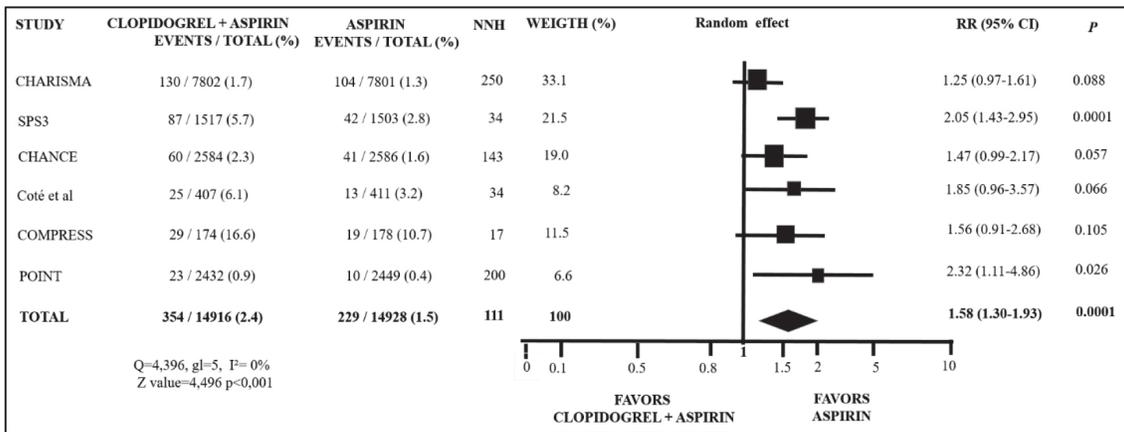


Fig. 5. Security meta-analysis between dual therapy (clopidogrel + aspirin) versus aspirin alone.

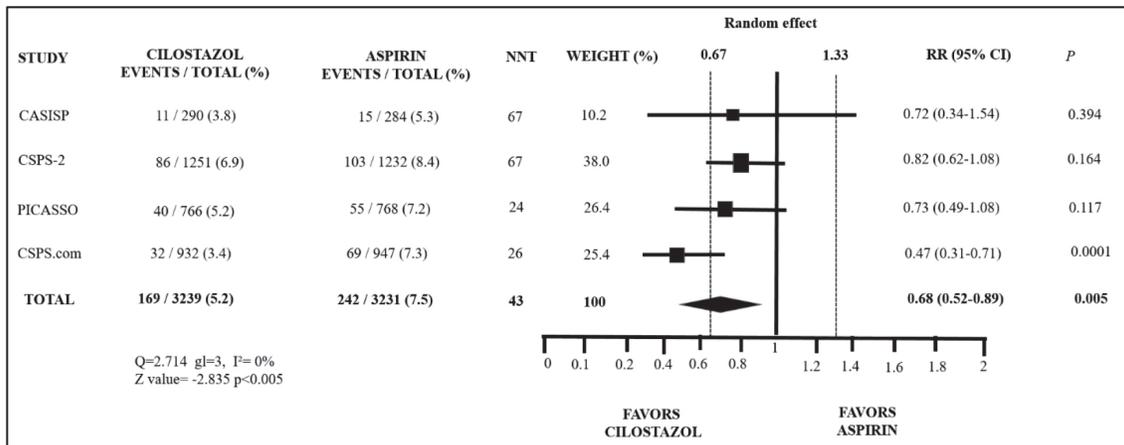


Fig. 6. Meta-analysis of effectiveness among cilostazol versus aspirin.

non-inferiority criteria with aspirin as active control. The combined result shows a clinical and significant reduction in favor of cilostazol in recurrent stroke of 32% [RR (95% CI) = 0.68 (0.52-0.89),  $p < 0.005$ ] so that cilostazol superiority over aspirin can be observed. The absolute risk reduction was 2.3%, the NNT= 43 and there was homogeneity between studies ( $I^2 = 0\%$ ).

The safety analysis of the presence of extracranial bleeding events in recurrent ischemic stroke determined that cilostazol revealed a reduction in bleeding events in all studies compared to aspirin (Fig. 7). The combined result shows a clinical and significant reduction of 52% [RR (95% CI) = 0.48 (0.37-0.63),  $p < 0.005$ ] for the risk of bleeding favoring treatment with cilostazol. The absolute risk reduction was 2.4%, the NNH was 42 and studies were consistent in demonstrating homogeneity ( $I^2 = 0\%$ ).

**DISCUSSION**

The present systematic review, revealed a superiority (22%, absolute risk reduction 1.4%) in the reduction of events of recurrent ischemic stroke with any antiplatelet treatment modality against aspirin alone. Non-inferiority or equivalence was observed between antiplatelet drugs and aspirin alone although superiority can be claimed. The se-

curity analysis demonstrated two groups of results, one with increased bleeding risk and other group on the contrary, showed no differences in the global result. A clinical and significant risk reduction (22%, absolute risk reduction 1.4%) about the recurrence of ischemic ictus was observed in the group of DAPT (clopidogrel-aspirin) against aspirin alone but with a significant 58% higher risk of bleeding (absolute risk increment 0.9%). The group of studies with cilostazol vs aspirin showed a superiority in the risk reduction of recurrent ischemic events with cilostazol and also, in the bleeding events against aspirin (32% and 52% respectively, absolute risk reduction 2.3% and 2.4% respectively). On the other hand, the studies with ticagrelor and dipyridamole-aspirin versus aspirin alone paper exhibited a clinical but not quite significant lower risk reduction in the recurrence of ischemic ictus but no evidence of differences in the bleeding risk was observed.

The pharmacological use of aspirin on the prevention of recurrent ischemic stroke and TIA, was analyzed in other 12 randomized studies finding a reduction of 54% in events with the use of aspirin at 12 weeks in relation to control and 74% reduction in disability or fatal ischemic stroke (47). In systematic reviews related to the use of DAPT (clopidogrel + aspirin) versus aspirin

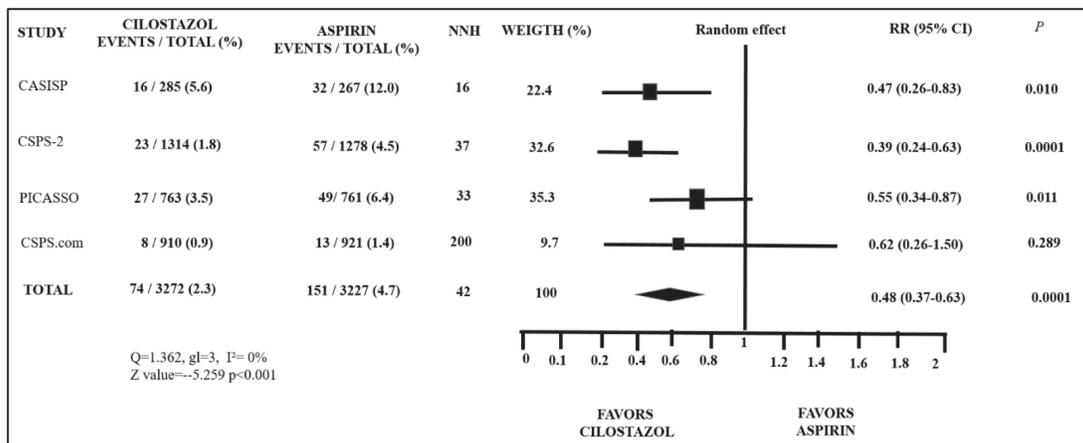


Fig. 7. Security meta-analysis between cilostazol versus aspirin.

alone (48), there was a 27% of significant risk reduction for dual therapy in fatal and non-fatal ischemic stroke (RR 0.73; 95% CI: 0.59-0.91; participants 4006; studies 5; moderate quality evidence). However, the risk of higher bleeding was attributed to the group with dual therapy (RR 1.44, CI 95%: 1.25-1.64; participants 33300; studies 10; evidence of moderate quality). It is also mentioned similar findings published by Palacio *et al.* (49) with the present systematic review, with DAPT vs aspirin alone, they found that DAPT reduced ischemic stroke by 23% (odds ratio = 0.77; 95% CI: 0.70-0.85) and the risk of major bleeding was increased by 40% (odds ratio = 1.40, 95% CI: 1.26-1.55) by dual antiplatelet therapy. Patients who have presented acute minor ischemic stroke or TIA receiving DAPT could have a better prognostic if this modality is discontinued between 10 to 21 days after the initiation of therapy (50).

Published data on the use of tienopiridines versus aspirin found a significant reduction in ischemic events favorable to the tienopiridines group [622 / 11355 (5.5%) versus 704 / 11423 (6.2%), OR 0.89; 95% CI: 0.79-0.99]; in relation to the extracranial major hemorrhage, the data showed no significant difference between the two groups [(100 / 9753 (1.03% vs 102 / 9752 (1.05%); OR: 0.98, 95% CI: 0.74-1.29)] (51). Moreover, a systematic review of recurrent ischemic stroke with data collected from seven clinical trials (41042 participants) reported that the use of antiplatelets (mainly aspirin) was associated with a significant reduction in recurrent ischemic stroke [(OR 0.77; 95% CI: 0.69-0.87;  $p < 0.00001$ ), NNT 140] (12).

One of the most important questions regarding treatment is when to start antiplatelet treatment. In patients at high risk of recurrent stroke, a recent clinical practice guide about the use of DAPT (clopidogrel + aspirin) versus aspirin monotherapy (6), the patient was classified as high risk (ABCD2 scale >4) after an AIS (acute ischemic stroke) or a minor ischemic stroke without

neurological deficit (NIHSS scale <3) and sets to start with dual therapy as soon as possible after the ischemic event (high evidence quality, strong degree of recommendation) for 10 to 21 days and then continue indefinitely with a single antiplatelet agent (6).

In relation to lacunar ischemic stroke, a systematic review found that any antiplatelet treatment against placebo after an ischemic stroke reduces the frequency of stroke recurrence in general (absolute risk reduction: 3.5%; NNT: 29) and ischemic stroke (absolute risk reduction: 5.9%; NNT: 17) (52).

Treatment with cilostazol (phosphodiesterase inhibitor-3) has been used because it offers in addition to its antiplatelet function, protection of the vascular endothelium and arteriolar vasodilation (53).

Another aspect to consider is the presence of resistance to aspirin or clopidogrel in patients with vascular brain disease, when this occurs, the prognosis of recurrence increases (54). Platelet functionalism identifies "non-responders" through platelet aggregation with arachydonate ( $\geq 20\%$  with 0.5mg/mL) and ADP ( $\geq 70\%$  with 5-mol/L) for aspirin and clopidogrel when aggregation is greater than 40% with 5-mmol/L for ADP. It was found a study of 324 patients with ischemic stroke 43% and 35% of non-responders for aspirin and clopidogrel respectively (55). In these cases, increased doses of aspirin or the addition of another antiplatelet agent may reduce recurrence of ischemic events (56, 57). Lee *et al.* (58) reported a 30% reduction in the risk of ischemic stroke in non-responders to aspirin when clopidogrel or ticagrelor was added. In another study the effectiveness between prasugrel and clopidogrel was compared with a reduction in the risk of stroke after an acute coronary accident, presumably the most powerful and lasting effect of prasugrel favors this reduction (59).

This systematic review has several limitations. The effectiveness analysis in the different studies was determined only for recurrent ischemic stroke and transient ischemic

attack as the primary end point, when the study showed a composite outcome (death, myocardial infarction and stroke) only data for ischemic stroke and transient ischemic attack were extracted. Patients with moderate-to-severe stroke, those with cardioembolic stroke, and those who were candidates for thrombolysis or thrombectomy were not studied in this systematic review. No secondary efficacy events were analyzed. When seemingly duplicate studies were analyzed, the initial study was chosen, for example, the CHANCE study has several publications in different journals and in different years apparently with the same number of cases and equal number of events (29, 60, 61).

To unify the measure of effect in meta-analysis, relative risk (RR) was chosen, even though some studies have reported it as a measure of hazard ratio, odds ratio or percentage difference. On the other hand, the safety analysis mainly studied major bleeding events, although some studies included total data because they only reported bleeding events without discrimination of the grade of severity, knowing that in this case it might be evidence of confusion. No data on hemorrhagic stroke were analyzed, because the main adverse effect of antiplatelet treatment is bleeding and with this specific outcome the data on major extracranial bleeding could not be reliably estimated. On the other hand, in some of the articles analyzed here, there was an important reduction of hemorrhagic ictus with clopidogrel and cilostazol versus aspirin alone (32, 35).

In some studies, there was a multiple scheme of treatment against aspirin, for example the CSPS.com study (36) used clopidogrel-aspirin and cilostazol-aspirin, so for comparison the last modality of treatment was chosen. For the PICASSO study (35), probucol a lipid lowering drug was added to cilostazol or aspirin and despite the safety outcome was hemorrhagic ictus, only data for ischemic stroke was extracted from the composite primary outcome. There were marked differences between the studies re-

lated to the duration of them; therefore, the results of meta-analysis should be carefully analyzed when comparing short-term studies with longer ones.

In conclusion, a long-term treatment with aspirin monotherapy is recommended in some systematic reviews (12,62) for a minor ischemic stroke event or small vessel disease presented as lacunar stroke or TIA; and as one the alternatives, is clopidogrel (as dual therapy) with a reduction of ischemic stroke of 25%, when installed for a short time (<1 month of the primary event occurred) and lower risk of bleeding compared to long-term therapy (63). Other systematic reviews also point out to the increased effect of dual therapy (28% reduction in the risk of ischemic stroke recurrence), but with moderate to severe bleeding events showed an increase of 64% (64). Cilostazol has been proven efficacy and safety against aspirin, so it could be another alternative. Other combinations were also referred in a systematic review that analyzed dual therapy with aspirin plus dipyridamole (65) or aspirin with prasugrel or ticagrelor (66), with outcomes favoring dual therapy versus monotherapy; but the hemorrhagic risk, although not significant, is increased with the combination of antiplatelet drugs. It is recommended before deciding treatment to avoid recurrence, to determine the origin or cause conditioning the stroke, identifying its dependence about other factors (e.g. high blood pressure) and stratification of the patient's risk. This systematic review evidences that, although in some instances non-inferiority could not be demonstrated, a clinical non-significant risk reduction in recurrent ischemic stroke was observed in the majority of any antiplatelet versus aspirin alone; and that the combined result can be expressed as superiority over aspirin alone on the risk reduction in the recurrence of minor ischemic stroke. With the sole exception of cilostazol trials, there was an increase of the bleeding risk when the antiplatelet drugs regimens were compared with aspirin alone.

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