Dual anti-platelet therapy for secondary prevention in intracranial atherosclerotic disease: a network meta-analysis

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Abstract

Background: Intracranial arterial stenosis (ICAS) is a non-marginal cause of stroke/transient ischemic attacks (TIAs) and is associated with high stroke recurrence rate. Some studies have investigated the best secondary prevention ranging from antithrombotic therapy to endovascular treatment (ET). However, no direct comparison between all the possible treatments is currently available especially between single and dual anti-platelet therapies (SAPT and DAPT).

Aim: To establish whether DAPT is more effective than SAPT in preventing the recurrence of ICAS-related stroke, by means of a network meta-analysis (NMA).

Design: Systematic review and NMA in accordance to PRISMA guidelines.

Data sources and methods: We performed a systematic review of trials investigating secondary prevention (SAPT or DAPT, anticoagulant treatment or ET) in patients with symptomatic ICAS available in MEDLINE, Scopus and Web of Science from January 1989 to May 2021. We defined our primary efficacy outcome as the recurrence of ischemic stroke/TIA. We analysed the extracted data with Bayesian NMA approach.

Results: We identified 815 studies and included 5 trials in the NMA. Sequence generation was adequate in all the selected studies while the allocation concealment method was described in one study. All the included studies reported the pre-specified primary outcomes, and outcome assessment was blinded in all the studies. We used the fixed-effect approach as the heterogeneity was not significant ($p > 0.1$) according to the Cochran's Q statistic. DAPT was superior to SAPT and DAPT + ET in preventing stroke/TIA recurrence [respectively, odds ratio (OR), 0.59; confidence interval (CI), 0.39–0.9; and OR, 0.49, CI, 0.26–0.88], while no difference was found between DAPT and oral anticoagulant therapy (OAC). DAPT was safer than OAC (OR, 0.48; CI, 0.26–0.89) and DAPT + ET (OR, 0.50; CI, 0.35–0.71), while no difference was found between DAPT and SAPT.

Conclusion: DAPT is more effective than SAPT for secondary stroke prevention in patients with symptomatic ICAS, without increasing the risk of haemorrhage.

Registration: Prospero/CRD42019140033.

Keywords: anti-platelet therapy, arterial stenosis, cerebrovascular disease, DAPT, dual anti-platelet therapy, intracranial atherosclerosis disease, intracranial stenosis, ICAS, intracranial arterial stenosis, meta-analysis, stroke

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Introduction

Stroke is a leading cause of death and disability worldwide. Intracranial arterial stenosis (ICAS) is one of the most common causes of stroke.[1,2] ICAS is responsible for approximately 5–10% of strokes in White people, 15–29% of transient ischemic attacks (TIAs) or strokes in Black people, and up to 30–50% of strokes in Asian people.[1] Strokes caused by ICAS are associated with a high risk of recurrence compared with other stroke subtypes.[1,3,4]

Notably, most recurrent strokes occur in the same territory of the first symptomatic event and are often disabling.[3,5,6] Concerning the mechanisms underlying ischemic events, hypoperfusion, artery-to-artery embolism and obstruction of small penetrating arteries can all occur in patients with ICAS and can be hypothesized on the basis of the neuroimaging characteristics.[1,7]

Considering the high rate of recurrence, many therapeutic options for secondary prevention have been investigated, ranging from medical therapy, such as single anti-platelet therapy (SAPT), dual anti-platelet therapy (DAPT) and oral anticoagulation (OAC) therapy with warfarin, to endovascular treatments (ETs).[8–12] Trials investigating the efficacy of ETs have been stopped before enrolment was complete because of safety concerns.

Regarding medical therapy, to the best of our knowledge, there are no randomized controlled clinical trials (RCTs) directly comparing the efficacy of DAPT and SAPT in reducing stroke recurrence in patients with symptomatic ICAS.

We aimed to establish whether DAPT is more effective than SAPT in preventing the recurrence of ICAS-related stroke, by means of a network meta-analysis (NMA) of RCTs.

Materials and methods

Search strategy and selection criteria
NMA is a statistical method to summarize information from studies addressing the same question but testing different interventions. Particularly, it allows performing indirect comparisons between treatments (i.e. comparisons not previously addressed directly) and improves the precision for comparisons with few data.[13]

This meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-NMA) guidelines.[14]

We considered RCTs that included at least two comparison groups with the following treatments: SAPT, DAPT, OAC with warfarin, and ET. We included adult patients (>18 years old) with ischemic stroke or TIA of presumed ICAS origin within 30 days from symptom onset. The diagnosis

of ICAS-related arterial stenosis must have been evaluated by digital subtraction angiography, CT angiography, MR angiography or ultrasound. We defined the primary outcome as early recurrence of ischemic stroke or TIA at 90 days and the secondary efficacy outcome as a composite of ischemic stroke or TIA, myocardial infarction, any haemorrhage, and death from any cause. We defined the safety outcome as the occurrence of any major haemorrhage, which includes intracranial and systemic haemorrhage requiring hospitalization.

We adopted Medical Subject Heading (MeSH) terms keywords in the MEDLINE search, Scopus and ISI Web of Science from January 1989 to May 2021. Moreover, we used the same search terms in the Cochrane Central Register of Controlled Trials (CENTRAL). We searched trial registries for ongoing or unpublished trials relevant to our meta-analysis (clinicaltrials.gov and WHO ICTRP). In order not to miss relevant trials and to reduce the likelihood of language bias, we applied no language restrictions for any of the searches.

The detailed search strategies can be found in the previously published NMA Protocol (Prospero, no. CRD42019140033).

Three authors independently reviewed titles and abstracts of the references retrieved from the above-mentioned search strategy and selected all potentially relevant studies. They obtained the full text of potentially relevant publications and the same authors independently reviewed them against the inclusion criteria of the meta-analysis. Different judgements on eligibility were resolved by consensus. We described and documented systematically all choices regarding including or excluding papers.

Data analysis
Two authors independently assessed the risk of bias in the included studies using Cochrane's 'Risk of bias' assessment tool, composed of seven domains.[15] Disagreement was resolved by iteration, discussion and consensus with a third author. The Bayesian NMA was performed using the Markov Chain Monte Carlo engine WinBUGS software (MRC Biostatistics Unit, Cambridge, UK version 1.6.1) and NetMetaXL (Microsoft-Excel-based NMA Tool).[16] For all analyses, we set the number of burn-in iterations for assessing

convergence of parameter estimates at 10 000 and the model runs at 10 000.

Evaluation of the homogeneity of similar studies is a key aspect of any systematic review. Standard methods to assess the heterogeneity between studies in pairwise meta-analysis calculations include the Cochran's Q statistics. If the p value of the Q statistic was less than 0.05, it suggested that there was significant heterogeneity.[17] If significant heterogeneity existed, a random effects model was applied; otherwise, a fixed-effects model was adopted.

Network diagrams and forest plots were performed in order to summarize the results. Network diagram is the graphical representation of a NMA and is composed of edges and nodes. The nodes represent interventions, and the size of the nodes indicates the number of participants. The edges indicate direct comparisons between different interventions and the thickness of the edges represents the number of trials comparing two interventions.[18] The odds ratios (ORs) or risk ratios (RRs) and their 95% confidence intervals (CIs) were reported according to the data availability. The statistical significance level was set to $p < 0.05$.

Results

We identified 815 papers through MEDLINE, Scopus, Web of Science, CENTRAL, clinicaltrials.gov and WHO ICTRP, and selected 10 potentially relevant studies. After review, only three RCTs met the inclusion criteria for this meta-analysis.[9,10,12] As only two comparisons between treatments were performed in these three trials, specifically DAPT *versus* DAPT plus ET and OAC *versus* SAPT, we did not reach the minimum number of comparisons (three) necessary to perform a NMA able to provide information about the efficacy of SAPT *versus* DAPT. In order to solve this issue, we chose to select from the 10 potentially relevant studies two subgroup analyses of patients with ICAS from RCTs that compared SAPT and DAPT in bigger populations [8,19] (Figure 1). Liu *et al.*[8] is a subgroup analysis of patients with and without ICAS from the CHANCE trial, and we only considered the ICAS sample. Toyoda *et al.*[19] is an RCT conducted in patients with high-risk ischemic stroke attributable to both extracranial and intracranial stenosis. However, we included in our NMA only data from the subgroup of patients with ICAS, which

were available in the Supplementary Material of the trial. The Toyoda subgroup was used only to evaluate early recurrence of ischemic stroke/TIA because there were no available data regarding the composite and safety outcomes in the ICAS subgroup. We excluded four studies[20–23] because the outcome measure was not clinical,[20] the recruited sample included both intracranial and extracranial arterial stenosis,[21,23] or because patients were not recruited in the acute phase.[22]

To evaluate the primary efficacy outcome, which was the early recurrence of ischemic stroke/TIA, we included five studies, three of which were RCTs[9,10,12] while the other two were subgroup analyses.[8,19] Included studies' characteristics are summed up in Table 1.

According to our previously published NMA protocol (Prospero, no. CRD42019140033), our goal was to evaluate the early recurrence of stroke or TIA. However, the duration of the follow-up greatly differed among the included studies for all the considered outcomes, namely, the recurrence of stroke/TIA, the secondary efficacy outcome and the safety. Therefore, we chose to assess each efficacy and safety outcome taking into account the follow-up time reported by each trial.

In this NMA, we used the fixed-effect approach as the heterogeneity was not significant ($p > 0.1$) according to the Cochran's Q statistic.

The primary efficacy outcome (ischemic stroke/TIA recurrence) was evaluated at a mean follow-up time of 8.2 months. Specifically, it was assessed at a mean follow-up time of 1.8 years in the WASID trial, at 30 days in the SAMMPRIS trial, at 30 days in the VISSIT trial, at 90 days in the CHANCE subgroup analysis and at a mean follow-up time of 1.4 years in the Toyoda *et al.* trial. The NMA that we performed confirmed that the use of DAPT alone is more effective than DAPT plus ET (OR, 0.49 with 95% CI, 0.26–0.88). In addition, it showed that the use of DAPT compared with SAPT as secondary prevention is more effective in lowering the risk of recurrence of ischemic stroke/TIA (OR, 0.59, 0.39–0.90). There was no statistically significant difference regarding our primary efficacy outcome in the comparison between the use of OAC and DAPT + ET (OR, 0.65, 0.27–1.53), DAPT and OAC (OR, 0.74, 0.41–1.35), OAC and SAPT (OR, 0.80, 0.52–1.21), SAPT and DAPT + ET
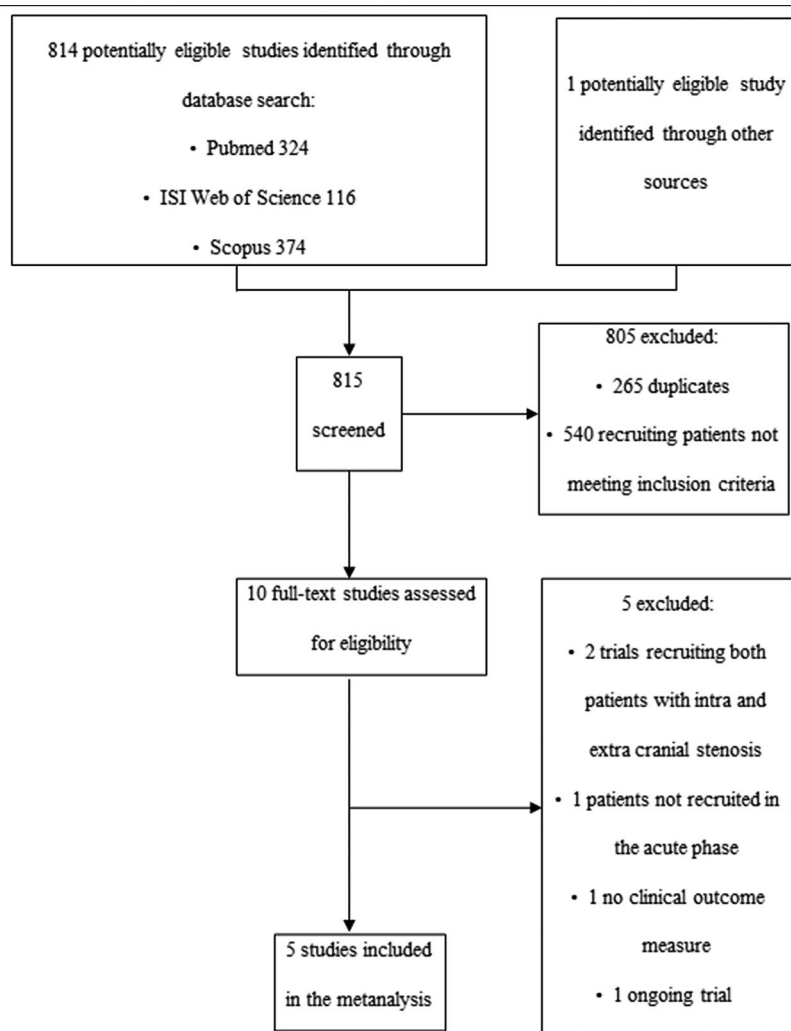
Figure 1. Study selection flowchart.

(OR, 0.82, 0.38–1.70). Figure 2 shows network diagram and forest plot for the primary outcome.

The secondary composite outcome (composite of ischemic stroke or TIA, myocardial infarction, any haemorrhage, death from any cause) was evaluated at a mean follow-up time of 1.5 years. Specifically, it was assessed at a mean follow-up time of 1.8 years in the WASID trial, at 32.4 months in the SAMMPRIS trial, at 1 year in the VISSIT trial and at 90 days in the CHANCE subgroup analysis.

The use of DAPT was more effective than anticoagulation therapy with OAC (OR, 0.45, 0.23–0.85) and DAPT plus ET (OR, 0.49, 0.34–0.69) in reducing the composite secondary outcome. The use of SAPT compared with OAC is more

effective in lowering the risk of the composite outcome but with a low statistical significance level (OR, 0.70, 0.49–0.99). No statistically significant difference was observed in the comparison between the use of DAPT and SAPT (OR, 0.64, 0.37–1.10).

There was also no statistically significant difference between the use of SAPT and DAPT plus ET (OR, 0.76, 0.39–1.47), and DAPT plus ET and OAC (OR, 0.92, 0.43–1.92). Figure 3 shows network diagram and forest plot for the secondary composite outcome.

The safety outcome (any major haemorrhage) was evaluated at a mean follow-up time of 1.5 years. Specifically, it was assessed at a mean follow-up time of 1.8 years in the WASID trial, at 32.4 months in the SAMMPRIS trial, at 1 year in the VISSIT trial and at 90 days in the CHANCE subgroup analysis.

Our analysis showed that the use of DAPT was safer than anticoagulation therapy with OAC (OR, 0.48, 0.26–0.89) and DAPT plus ET (OR, 0.50, 0.35–0.71).

The use of SAPT was safer than OAC but with a low statistical significance level (OR, 0.70, 0.49–0.99). There was also no statistically significant difference in terms of safety between the use of DAPT and SAPT (OR 0.69, 0.41–1.14).

There was no statistically significant difference regarding the risk of haemorrhage in the comparison between the use of SAPT and DAPT plus ET (OR, 0.72, 0.39–1.36), and DAPT plus ET and OAC (OR, 0.97, 0.47–1.94). Figure 4 shows network diagram and forest plot for the safety outcome. In the Supplementary Materials, we summarize the results obtained for each outcome after having excluded the WASID trial from the analysis to focus exclusively on anti-platelet therapy and found similar results (Supplementary Materials Figures 1, 2 and 3).

We summarize the risk of bias of the included studies in Figure 5.

Sequence generation was adequate in all the reported studies.[8–12,19,24–29] The allocation concealment method was described in CHANCE, but was not reported in WASID, SAMMPRIS, VISSIT and Toyoda. Regarding treatment, two

Table 1. List of included studies and characteristics.

	Population	Study type	Dates	Interventions	Group 1	Group 2	Primary outcome	Primary outcome occurrence in group 1 *versus* group 2
Chimowitz et al.[9] WASID	TIA/stroke (mRS ≤ 3) within 90 days, with 50–99% stenosis of major intracranial artery (with age of at least 40 years)	Double-blind, multicenter clinical trial	February 1999 and July 2003	Aspirin *versus* Warfarin	289 (Warfarin)	280 (Aspirin)	Ischemic stroke, brain haemorrhage or death from vascular causes others than stroke	21.8% *versus* 22.1% *p* = 0.83
Chimowitz et al.[10] SAMMPRIS	Recent TIA/stroke attributed to stenosis of 70–99% of the diameter of a major intracranial artery	Investigator-initiated, randomized, clinical trial	November 2008–April 2011	Aggressive medical management *versus* PTAS + aggressive medical management	224 (ET + DAPT + aggressive medical management)	227 (DAPT for 3 months + aggressive medical management)	Stroke in the territory of the qualifying artery or death during the follow-up period	20.5% *versus* 11.5% *p* = 0.009
Zaidat et al.[12] VISSIT	18–85 years of age; and had symptomatic intracranial stenosis (70%–99%) involving the internal carotid, middle cerebral, intracranial vertebral or basilar arteries with a hard transient ischemic attack (TIA) or stroke attributable to the territory of the target lesion within the past 30 days.	Randomized multicenter clinical trial	January 2009–June 2012	Medical therapy alone *versus* balloon-expandable stent plus medical therapy	58 (ET + DAPT)	53 (DAPT for 3 months)	Stroke or hard TIA in the territory of the qualifying artery within 12 months of randomization	36.2% *versus* 15.1% *p* = 0.02
Toyoda et al.[19] (Intracranial Subgroup analysis)	Clinical diagnosis of noncardioembolic stroke that developed between 8 and 180 days before the start of the protocol treatment aged 20–85 years	Multicentre, open-label, randomized controlled trial	13 December 2013, to 31 March 2017	SAPT *versus* DAPT (with cilostozol)	272 (SAPT)	275 (DAPT with cilostazol for at least 6 months)	Ischemic stroke during the follow-up period	9.2% *versus* 4% *p* < 0.001
Wang et al.[24] CHANCE (ICAS subgroup analysis)	Minor stroke (with ICAS)	Randomized, double-blind, placebo-controlled clinical trial	October 2009 and July 2012	SAPT *versus* DAPT	250 (SAPT)	231 (DAPT for 21 days)	Stroke event (ischemic or haemorrhagic) at 90 days	13.6% *versus* 11.3% *p* < 0.001

DAPT, dual anti-platelet therapy; ET, endovascular treatment; ICAS, intracranial arterial stenosis, PTAS, percutaneous transluminal angioplasty and stenting; SAPT, single anti-platelet therapy.
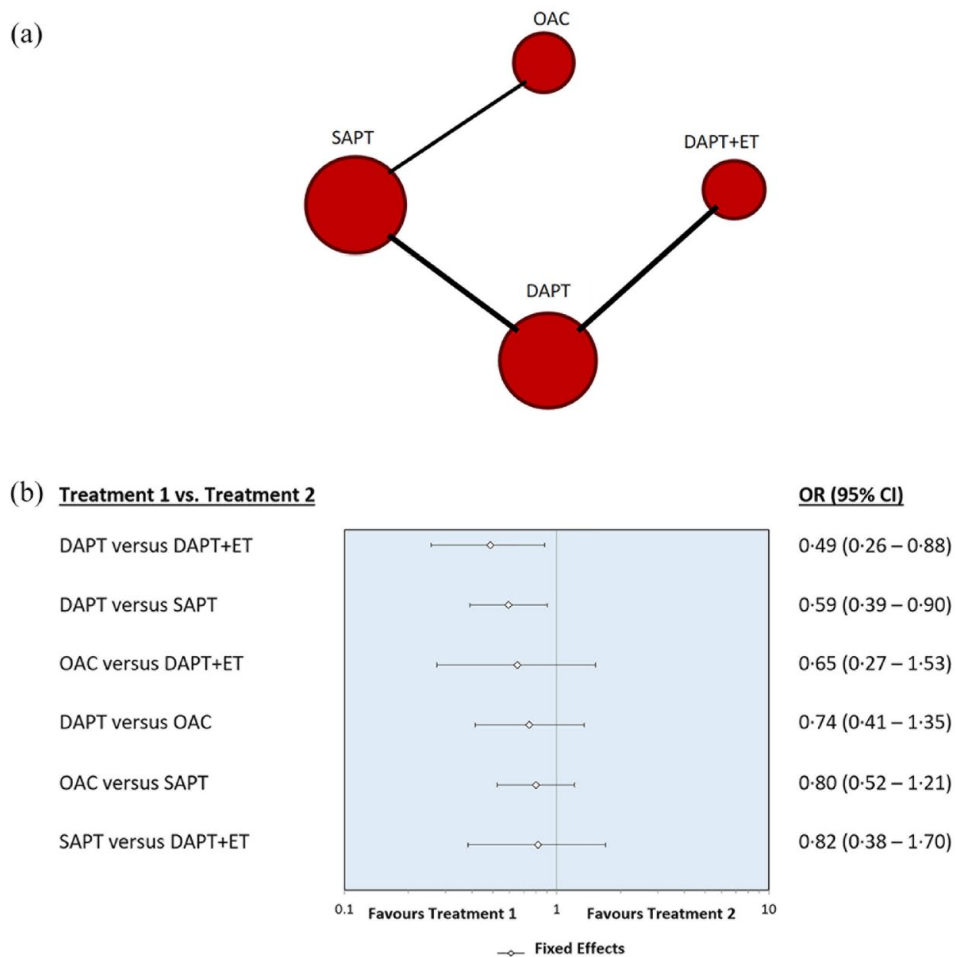
Figure 2. (a) Network diagram and (b) forest plot for the primary efficacy outcome.

of the selected studies were double-blinded (WASID, CHANCE), while the remaining three were not (Toyoda, SAMMPRIS, VISSIT). The choice not to blind participants depended on the use of invasive angiography for SAMMPRIS and VISSIT. Outcome assessment was blinded in all the selected studies. WASID reported that 1.8% and 2.8% of the patients in the SAPT and OAC groups, respectively, were lost to follow-up. SAMMPRIS reported that 5% and 3% of the patients in the DAPT and percutaneous transluminal angioplasty and stenting (PTAS) groups were lost to follow-up. VISSIT had 11.3% and 2% of patients lost to follow-up, respectively, in the DAPT and ET groups. Toyoda *et al.* reported a loss to follow-up rate of 8.8% and 5.3% for the SAPT and the DAPT groups. In the CHANCE trial, 0.7% of patients were lost to follow-up. All the included studies reported the pre-specified primary outcomes. However, we considered the subgroup of patients with ICAS for CHANCE and Toyoda, this being a potential source of bias. A possible bias in four of the included studies comes from incomplete recruitment of patients. WASID and SAMMPRIS prematurely stopped patients' enrolment because of safety concerns. VISSIT was stopped soon after SAMMPRIS publication. Toyoda did not reach the planned sample size because of slow recruitment. Finally, we considered ICAS subgroups of CHANCE and Toyoda trials; therefore, the sample size was not calculated specifically to evaluate treatment effects in the ICAS sample.

Discussion
Our analysis indicates that the use of DAPT is more effective than SAPT in reducing the risk of recurrence of ischemic stroke at a mean follow-up of 8 months. However, the use of DAPT was not
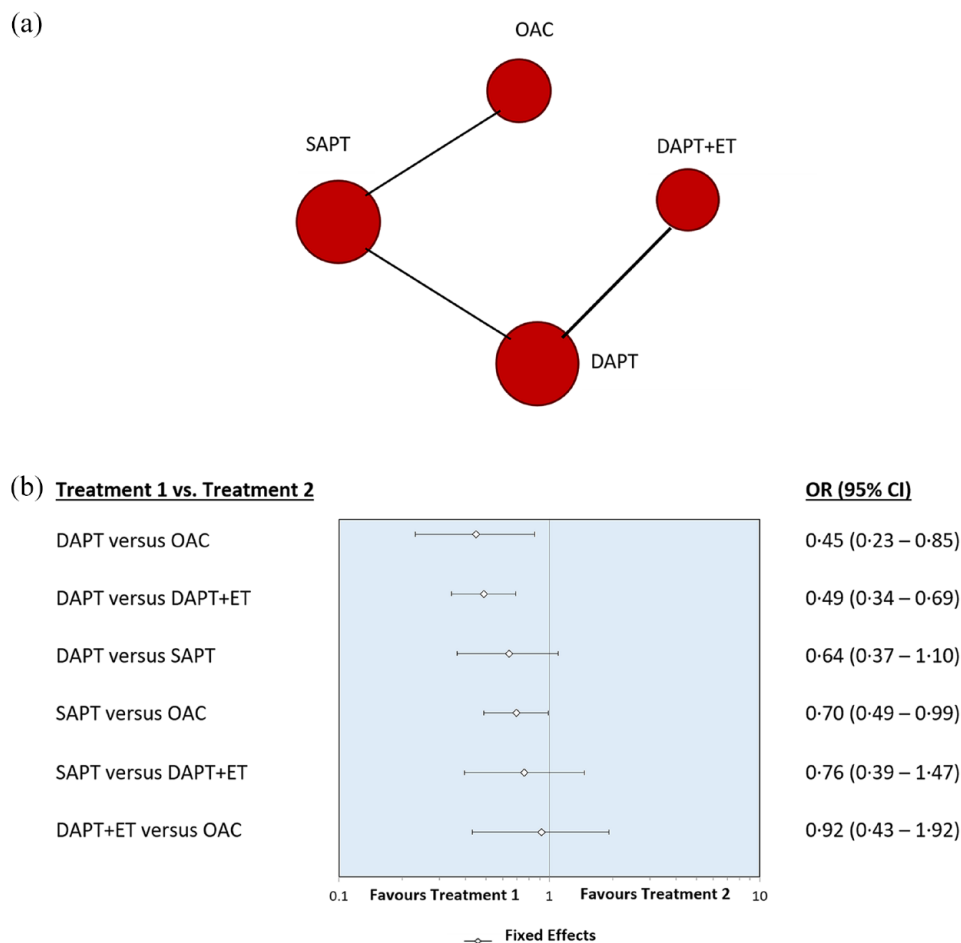
(a)

(b)

Treatment 1 vs. Treatment 2	OR (95% CI)
DAPT versus OAC	0·45 (0·23 − 0·85)
DAPT versus DAPT+ET	0·49 (0·34 − 0·69)
DAPT versus SAPT	0·64 (0·37 − 1·10)
SAPT versus OAC	0·70 (0·49 − 0·99)
SAPT versus DAPT+ET	0·76 (0·39 − 1·47)
DAPT+ET versus OAC	0·92 (0·43 − 1·92)

Figure 3. (a) Network diagram and (b) forest plot for the secondary efficacy outcome.

superior to SAPT in lowering the risk of the composite of secondary outcomes, at a mean follow-up time of 1.5 years. In addition, we found that DAPT did not increase the risk of haemorrhage at a mean follow-up time of 1.5 years. The significant difference between the time points at which the primary and secondary outcomes have been evaluated could explain the lack of effect of DAPT in reducing the occurrence of the composite secondary outcome. Indeed, ICAS patients are likely to have a systemic atherosclerotic disease which entails an increased risk of cardiovascular morbidity and death.[30] Moreover, in minor stroke, regardless of the occurrence of ICAS, the effect of DAPT in reducing ischemic stroke/TIA is mostly observed within the first 10 days.[31] As a consequence, considering that the secondary outcome has been evaluated at a mean follow-up time of 1.5 years, the occurrence of the composite outcome could be similar between SAPT and DAPT groups, even though the risk of haemorrhage was not increased by DAPT. Our results confirm that DAPT is more effective than DAPT plus ET in lowering both the risk of recurrence of ischemic stroke or TIA and the incidence of the composite of secondary outcomes. Moreover, DAPT proves to be safer than DAPT plus ET. The use of DAPT also appears more effective than OAC in reducing the risk of incidence of secondary outcomes. Finally, OAC is associated to a higher risk of bleeding than both DAPT and SAPT. The reported evidence is actually stronger than what can arise from the available individual trials or subgroups analyses. In fact, the use of a combination of clopidogrel and aspirin for 90 days followed by aspirin alone is currently suggested as secondary prevention for patients with a recent ischemic event (within 30 days) and a 70–99% ICAS.[1] The recommendation comes from the results of SAMMPRIS that showed that the
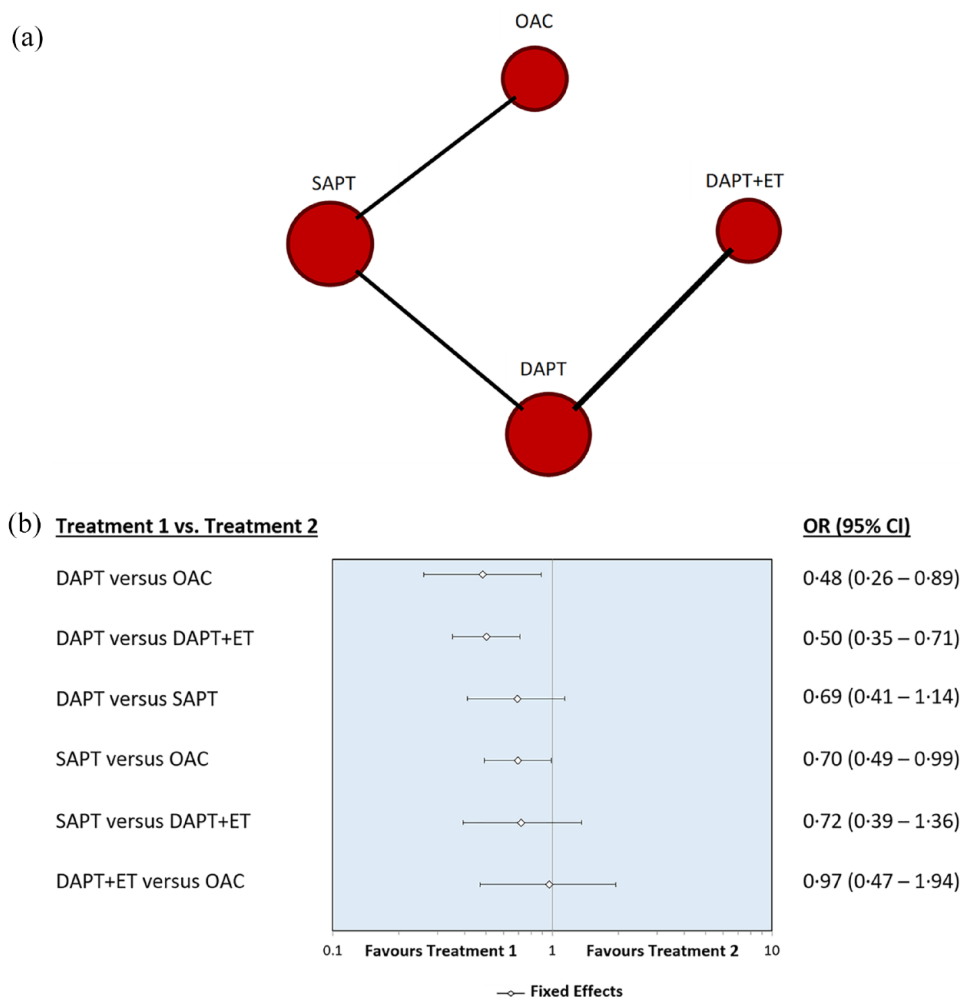
Figure 4. (a) Network diagram and (b) forest plot for the safety outcome.

30-day rate of ischemic stroke and death in the medical treatment group (DAPT and intensive risk factor management) was considerably lower than in both the aspirin and OAC arms of the WASID trial. This was also supported by the CLAIR trial, showing that DAPT was more effective than SAPT in reducing micro-embolic signals detected by transcranial Doppler on day 2 and 7 after randomization in patients with recently (<7 days) symptomatic ICAS.[20] However, the above-mentioned recommendation[1] was more an experts' opinion than an actual comparison of quantitative data. Therefore, the purpose of this analysis was to offer an objective statistical comparison of all the data currently available on this topic. As stated in the protocol, our goal was to perform a NMA with data obtained only from RCTs. However, that could not be achieved. In fact, only three RCTs met the inclusion criteria

for this NMA, and only two comparisons between two groups of treatments were performed, specifically DAPT *versus* DAPT plus ET and OAC *versus* SAPT. These data were not sufficient to perform a NMA able to provide information about the direct and indirect comparisons of the four considered treatments. In fact, at least three different comparisons between these treatments were required. Therefore, we chose to include two other studies wherein a third comparison was performed, specifically SAPT *versus* DAPT.[8,19] Liu *et al.*[8] is a subgroup analysis of patients with and without ICAS from the CHANCE trial, while Toyoda *et al.*[19] is an RCT conducted in patients with high-risk ischemic stroke attributable to both extracranial and intracranial stenosis. However, our NMA only included data from the subgroup of patients with ICAS. We acknowledge that, as a result of the inclusion of these two study

Figure 5. Risk of bias of the included studies.

subgroups, the level of the evidence is lower than a NMA of RCTs because of the inherent risk of bias due to subgroup analyses.

Another issue is the difference between the time points at which the outcomes had been evaluated in the included studies. According to the NMA protocol, we wanted to evaluate the primary and secondary efficacy outcomes and the safety outcome at 90 days, but the length of the follow-up time differed among the included studies, and only the CHANCE subgroup analysis reported the outcomes at 90 days. For this reason, we evaluated the outcomes at a time point that is the average of the follow-up times of all the included studies for every considered outcome. Furthermore, patients were

not administered the same kind and dose of DAPT in all the included trials, and even the duration of DAPT differed significantly among the studies. Specifically, in the DAPT arm of the Toyoda trial, a combination of cilostazol with aspirin or clopidogrel was used, while patients in the other three trials wherein DAPT was used were all administered aspirin in association with clopidogrel, although at a slightly different dose. Consequently, it can be argued that a different composition of the DAPT could have an impact on the results obtained with this NMA. However, a previous trial[32] designed to compare the efficacy of two different combinations of DAPT administered for 7 months, namely aspirin and clopidogrel *versus* aspirin and cilostazol, in patients with

symptomatic ICAS, did not show any significant difference in terms of progression of the arterial stenosis, recurrence of ischemic stroke and occurrence of major haemorrhagic complications between these treatments. Therefore, it is reasonable to assume that our results were not influenced by the use of DAPT with cilostazol in the Toyoda trial.

Considering the available data and especially the different duration of DAPT in the trials we chose to consider, it is not possible to establish with certainty how long DAPT should be administered in ICAS patients. About this issue, we have to consider that the pooled meta-analysis of CHANCE and POINT trials demonstrated that in minor stroke, regardless of the presence of ICAS, DAPT reduces ischemic events mostly within the first 10 days after the index event without increasing the risk of major haemorrhage. On the contrary, from day 11 to day 90, DAPT does not reduce the risk of major ischemic events, while it does not increase the risk of major haemorrhages, but only that of minor haemorrhages.[31] According to these results, for patients with minor stroke, regardless of the presence of ICAS, DAPT is currently recommended for 21 days. However, it is well established that patients with ischemic stroke caused by ICAS have a significantly higher risk of recurrence compared with that of patients with other stroke subtypes[1,3,4] and that a new ischemic event is often disabling.[3,5,6] Our NMA shows that DAPT is more effective than SAPT in symptomatic ICAS and that the risk of haemorrhage is not increased. Therefore, considering the high risk of recurrence of ischemic stroke in ICAS patients[1,3,4] and taking into account the results from the pooled meta-analysis of CHANCE and POINT trials,[31] we think that it could be reasonable to administer DAPT for at least 3 months in patients with symptomatic ICAS.

Conclusion

This NMA suggests that DAPT is more effective than SAPT for secondary stroke prevention in patients with ICAS, without increasing the risk of haemorrhage.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Giuseppe Reale: Conceptualization; Investigation; Validation; Writing – original draft.

Aurelia Zauli: Investigation; Writing – original draft.

Giuseppe La Torre: Investigation; Methodology.

Alice Mannocci: Data curation; Formal analysis; Investigation; Software.

Michael V. Mazya: Investigation; Visualization; Writing – review & editing.

Marialuisa Zedde: Project administration; Writing – review & editing.

Silvia Giovannini: Investigation; Writing – review & editing.

Marco Moci: Investigation; Visualization; Writing – review & editing.

Chiara Iacovelli: Data curation; Formal analysis; Investigation.

Pietro Caliandro: Conceptualization; Investigation; Project administration; Supervision; Validation; Writing – review & editing.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials
Not applicable.

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Supplemental material
Supplemental material for this article is available online.

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