Meta-Regression to Identify Patients Deriving the Greatest Benefit from Dual Antiplatelet Therapy after Stroke or Transient Ischemic Attack Without Thrombolytic or Thrombectomy Treatment

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The patient's profile drawing the greatest benefit from dual antiplatelet therapy (DAPT) after a noncardioembolic, ischemic cerebrovascular event is not well characterized. Aim of this metaregression analysis was to compare DAPT versus single antiplatelet therapy (SAPT) in patients with stroke or transient ischemic attack (TIA). We searched randomized trials evaluating clinical outcome with aspirin plus a P_2Y_{12} inhibitor versus SAPT in patients with noncardioembolic stroke or TIA. Primary end point was the incidence of recurrent stroke; safety outcome measure was major bleeding. Eleven trials were included in the analysis, enrolling 24,175 patients treated with DAPT (aspirin plus clopidogrel, n = 12,074) or SAPT (n = 12,101) after a stroke or TIA event. In the DAPT group the rates of recurrent stroke were lower (7.1% vs 8.8% with SAPT; odds ratios [OR] 0.74, 95% confidence interval 0.62 to 0.88; p = 0.0007) and the incidence of major bleeding was twofold higher (OR 2.01, 1.35 to 3.01; p = 0.0006). Metaregression indicated a positive correlation between prevention of recurrent stroke by DAPT and baseline stroke severity (p = 0.019), baseline risk profile (p = 0.0001), or prevalence of carotid atherosclerosis (p = 0.040). DAPT was more effective when initiated ≤7 days (OR 0.67, 0.58 to 0.77; p < 0.00001) and used for ≤3 months (OR 0.66, 0.58 to 0.76; p < 0.00001) after the event. In conclusion, in patients with stroke or TIA, the highest benefit of DAPT was observed in patients with higher baseline risk profile, greater stroke severity, or concomitant carotid disease, and when DAPT was initiated early and given for ≤3 months. **(Am J Cardiol 2019;124:627−635)**

Single antiplatelet therapy (SAPT), essentially with aspirin, represents the standard antithrombotic treatment after a noncardioembolic, ischemic cerebrovascular event[1]; however, the risk of recurrent events despite SAPT is substantial (up to 10% to 15% at 90 days).[1] Hence, the rationale that a stronger platelet function suppression by a multipathway platelet inhibition may improve outcome. Differently from patients suffering an acute coronary syndrome,[2] the role of DAPT with aspirin plus a P_2Y_{12} antagonist after an ischemic cerebrovascular event is more controversial. Meta-analyses of randomized studies have indicated that, compared to SAPT, the combination of aspirin and clopidogrel in patients with stroke or transient ischemic attack (TIA) overall decreases the rates of recurrent stroke[3,4]; however, the patient's profile associated with the highest protection from recurrent stroke by DAPT, and therefore what patient may draw the greater net clinical benefit from this "more aggressive" antiplatelet strategy is unclear. To provide more robust evidence on the topic we performed a metaregression analysis of randomized trials comparing DAPT (aspirin plus a P_2Y_{12} inhibitor) versus SAPT in patients with noncardioembolic stroke or TIA.

Methods

In this study-level analysis we considered controlled randomized trials evaluating clinical outcome with DAPT (aspirin plus a P_2Y_{12} inhibitor) versus SAPT in patients with a noncardioembolic, ischemic, cerebrovascular event (stroke or TIA). Trials were included regardless of the type of SAPT, the timing of study drug initiation and the follow-up duration. No restriction was used with regard to the type of stroke, except for excluding patients with atrial fibrillation-related stroke. A standardized review protocol was used to define the eligibility criteria for the search and screening of references using the PICO(TSS) framework, which outlines the population, interventions, comparator, outcomes, timing, study setting, and designs of interest.

We searched Medline (through PUBMED), the Cochrane Central Register of Controlled Trials (through Wiley), and Clinicaltrials.gov from inception to January 31, 2019. Search keywords were "stroke," "transient ischemic attack," "single antiplatelet therapy," and "dual antiplatelet therapy," combined with the words "randomized," "recurrent stroke," and

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"major bleeding." Studies presented or published in languages different than English were also considered.

Trials identified as potentially relevant on the basis of title or abstract were selected for full review. Two investigators independently assessed these trials for eligibility (AS, AB). Disagreement was resolved by consensus. This analysis was planned in accordance with current guidelines for systematic reviews and meta-analyses with regression, in particular the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols.[5] Data were extracted onto standard spreadsheets, based on a standardized data configuration protocol.[6] When data about an outcome of interest were not available, the study was not used for such end point. The Cochrane Collaboration tool was used to assess the risk of bias in randomized controlled trials (**Table 1 of the Appendix**).[7] The quality of the included studies was also evaluated according to the Jadad score.[8]

We considered the following end points in the two groups (DAPT vs SAPT):

- Primary end point: rates of recurrent stroke during follow up. The definitions of recurrent stroke were consistent across various studies and are reported in Table 1.
- Safety end point: incidence of major bleeding during follow up, according to the definition used in each study (as indicated in Table 1).

We also performed sensitivity analyses for recurrent stroke according to the type of index event (stroke vs TIA), the type of SAPT, and the type of stroke (lacunar vs nonlacunar). A sensitivity analysis for recurrent ischemic stroke was also done.

Statistical analyses were done using the Review Manager 5.2 software (available from The Cochrane Collaboration) and the Comprehensive Meta-Analysis software (Biostat, Englewood, NJ). For dichotomous variables, pooled statistics were calculated as weighted odds ratios (ORs) with 95% confidence intervals (CIs) using the random-effects DerSimonian and Laird model.[9] We tested heterogeneity of the included studies with Q statistics and the extent of inconsistency between results with I^2 statistics (significant heterogeneity was considered present for p values <0.10 and/or an I^2 >50%). Presence of publication bias was estimated by funnel plot graph. We used a random effects method of analysis, since it did not assume that a true effect is common to all studies. Sensitivity analyses also included a leave-one-out analysis to assess whether the pooled results were influenced by a single trial. The associations between the results on the primary end point in each trial (effect size) and stroke severity, incidence of recurrent stroke in the control arm (SAPT arm), prevalence of diabetes and of concomitant carotid disease, symptom onset-to-enrollment time, and follow-up duration were assessed by metaregression.[10] Statistical significance was set at p <0.05 (two-tailed).

Results

Eleven randomized trials were overall included in this analysis,[11-21] enrolling a total of 24,175 patients randomly allocated to receive DAPT (n = 12,074) or SAPT (n = 12,101) after an ischemic cerebrovascular event. The progress through the different steps of the search leading to the final number of 11 studies through the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram[5] is illustrated in **Figure 1 of the Appendix**. Main descriptors of the trials are indicated in **Table 1.** All studies evaluated the combination of aspirin plus clopidogrel as DAPT;[11-21] ten investigations[11-17,19-21] used aspirin as SAPT and only one clopidogrel.[18] The mean age in the included population was 64.6±3.4 years. The mean value of the National Institute of Health Stroke Scale (NIHSS) was 3.6±3.9. Follow-up duration ranged from 7 days to 3.4 years (mean 8.3±12.4 months).

The incidence of the primary end point including recurrent stroke was 7.1% in patients on DAPT versus 8.8% in those on SAPT (OR 0.74, 95% CI 0.62 to 0.88; p = 0.0007) (**Figure 1**), with a significant heterogeneity in the studies (I^2 51%; p = 0.03) and without evidence of publication bias. Sensitivity analysis for recurrent stroke in which CARESS and CLAIR studies[12,15] (characterized by a very short follow-up duration, e.g. 7 days) were excluded, yielded consistent results (OR 0.74, 0.63 to 0.89, p = 0.0008). The prevention of recurrent stroke by DAPT was maintained when patients with stroke or TIA as index event were considered separately (stroke only: OR 0.70, 0.58 to 0.86; p = 0.0004; TIA only: OR 0.72, 0.54 to 0.94; p = 0.02; p for interaction 0.95). DAPT use was associated with significant reduction of recurrent stroke also when only those ten studies using aspirin as SAPT were considered (OR 0.71, 0.61 to 0.82; p <0.00001), or when the SPS3 trial, that enrolled specifically patients with lacunar stroke, was excluded from the analysis (OR 0.70, 0.57 to 0.86, p = 0.0008). Sensitivity analysis for recurrent ischemic stroke provided results in favor of DAPT consistent with the analysis on the primary end point including any recurrent stroke (OR 0.71, 95% CI 0.60 to 0.84; p <0.0001).

The rates of major bleeding were 1.8% in patients on DAPT versus 0.9% in those on SAPT (OR 2.01, 1.35 to 3.01; p = 0.0006) (**Figure 1**), without significant heterogeneity in the studies (I^2 41%; p = 0.12) and without publication bias. Sensitivity analysis for major bleeding in which CARESS and CLAIR studies[12,15] were excluded provided similar results (OR 2.01, 1.33 to 3.01, p = 0.0008). The occurrence of intracranial hemorrhages was 0.30% in the DAPT versus 0.21% in the SAPT arm (OR 1.44, 0.87 to 2.40; p = 0.20).

Metaregression indicated a significant correlation between prevention of recurrent stroke by DAPT versus SAPT use and stroke severity at baseline (with higher severity associated with increased benefit: r^2 = 100%; I^2 = 0%; coefficient −0.0799, 95% confidence interval −0.1463 to −0.0134; p = 0.019) (**Figure 2**). Accordingly, the meta-analysis based on different baseline stroke severities showed that the relative reduction of recurrent stroke with DAPT was more pronounced in those studies including patients with greater stroke severity (NIHSS >3: OR 0.36, 0.20 to 0.63; p = 0.0004) and less pronounced in those with lower stroke severity (NIHSS ≤3: OR 0.69, 0.60 to 0.80; p = 0.00001) (p for interaction 0.02) (**Figure 2**), without significant heterogeneity in the studies or publication bias.

Table 1
Main descriptors of the included studies.

Study	N. pts	Countries	Antiplatelet comparison	Index event	Stroke severity to be included (NIHSS)	Age (years)	Time from stroke or TIA	Follow-up duration	Recurrent stroke definition	Major bleeding definition	Jadad score
CARESS	107	Europe	A + C vs A	IS or TIA	<22	64	<90 days	7 days	Any cerebrovascular event	NA	5
CHANCE	5,170	China	A + C vs A	IS or TIA	≤3	63	<24 hours	90 days	Any stroke (ischemic or hemorrhagic)	Fatal or intracranial bleeding; bleeding causing hemodynamic compromise	5
CHARISMA	1,331	Worldwide	A + C vs A	IS or TIA	NA	66	<30 days	25 months	Any stroke (ischemic or hemorrhagic)	Fatal bleeding; bleeding causing hemodynamic compromise	5
CLAIR	100	Asia	A + C vs A	IS or TIA	≤8	57	<7 days	7 days	New acute lesions on diffusion MRI	Serious extracranial bleeding	3
COMPRESS	358	South Korea	A + C vs A	IS	None required	67	<48 hours	30 days	Any stroke (ischemic or hemorrhagic)	Fatal or LT bleeding; bleeding causing disability or requiring ≥3 blood units	5
FASTER	392	North America	A + C vs A	IS or TIA	≤3	69	<24 hours	90 days	Any stroke (ischemic or hemorrhagic)	LT bleeding; bleeding with hemodynamic compromise/Hb drop ≥5 g/L or needing >2 blood units	5
He et al	690	China	A + C vs A	IS or TIA	≤7	62	<72 hours	14 days	IS, with both clinical and imaging findings	Severe intracranial or extracranial bleeding	3
MATCH	7,599	Worldwide	A + C vs C	IS or TIA	None required	66	<90 days	18 months	Any stroke (ischemic or hemorrhagic)	Bleeding with persistent disabling sequelae; bleeding requiring >2 blood units	5
POINT	4,881	Worldwide	A + C vs A	IS or TIA	≤3	65	<12 hours	90 days	Any stroke (ischemic or hemorrhagic)	Bleeding with disability; intracranial bleeding; bleeding requiring ≥2 blood units or hospitalization	5
SPS3	3,020	America and Spain	A + C vs A	Lacunar stroke	NA	63	<180 days	3.4 years	Any IS or intracranial hemorrhage	Fatal bleeding; bleeding requiring blood transfusion or surgery or resulting in permanent functional sequelae	5
Wang et al	574	China	A + C vs A	IS	≤15	69	<48 hours	30 days	IS, with both clinical and imaging findings	Any symptomatic intracranial bleeding or any bleeding requiring blood transfusion	3

A = aspirin; C = clopidogrel; Hb = hemoglobin; IS = ischemic stroke; LT = life-threatening; MRI = magnetic resonance imaging; NA = not available; NIHSS = National Institute of Health Stroke Scale; TIA = transient ischemic attack.

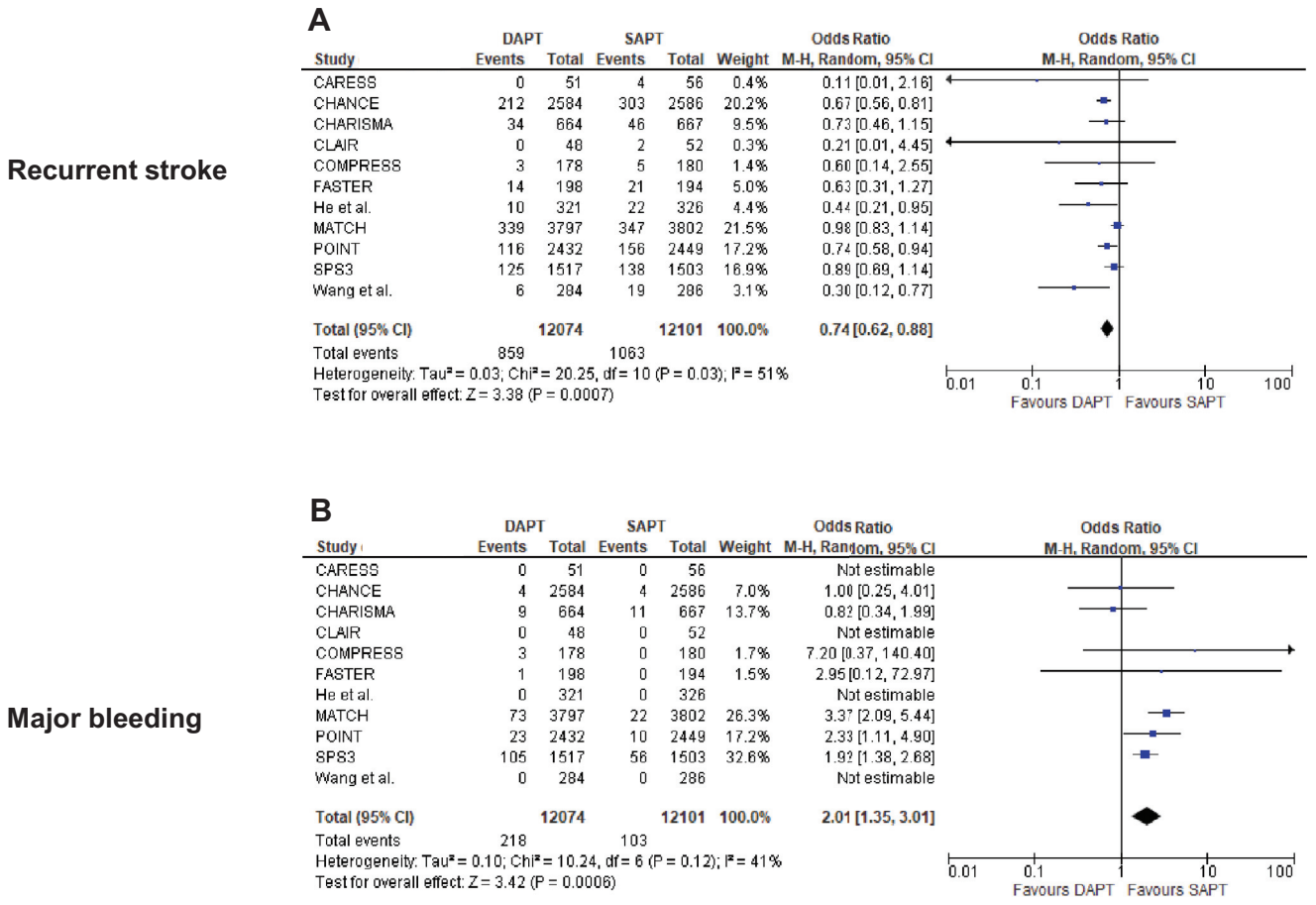

Figure 1. **Meta-analysis for recurrent stroke and major bleeding**.
Panel A. Odds ratios (with 95% confidence interval) for recurrent stroke in patients receiving DAPT versus SAPT. Panel B. Odds ratios (with 95% confidence interval) for major bleeding in patients receiving DAPT versus SAPT.
DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy.

Other variables significantly associated with trial results were incidence of recurrent stroke during follow up in the SAPT arm (with higher incidence associated with increased DAPT benefit: $r^2 = 100\%$; $I^2 = 0\%$; coefficient −0.3202, −0.4819 to −0.1584; p = 0.0001) and prevalence of concomitant carotid disease (with higher prevalence associated with increased DAPT benefit: $r^2 = 0\%$; $I^2 = 49\%$; coefficient −0.0126, −0.0246 to −0.0006; p = 0.040) (**Figure 3**). There was an inverse relation between prevalence of diabetes and trial results, with higher prevalence associated with lower DAPT benefit ($r^2 = 82\%$; $I^2 = 11\%$; coefficient 0.0074, 0.0014 to 0.0134; p = 0.016) (**Figure 3**).

Metaregression showed that the earlier the DAPT initiation after the index event, the higher the relative reduction of recurrent stroke with DAPT use ($r^2 = 65\%$; $I^2 = 23\%$; coefficient 0.0022, 0.0002 to 0.0042; p = 0.033) (**Figure 4**). Metaregression also indicated that the decrease in the rates of recurrent stroke with DAPT was higher in the studies with symptom onset-to-enrollment time ≤7 days (OR 0.67, 0.58 to 0.77; p <0.00001) and lower in those with symptom onset-to-enrollment time >7 days (OR 0.91, 0.78 to 1.07; p = 0.26) (p for interaction 0.0007) (**Figure 4**), without significant heterogeneity in the studies or publication bias.

Metaregression demonstrated a trend toward lower prevention of recurrent stroke by DAPT use with longer follow-up durations ($r^2 = 45\%$; $I^2 = 33\%$; coefficient 0.0003, −0 to 0.0007; p = 0.059) (**Figure 5**). The meta-analysis according to different follow-up durations (**Figure 5**) showed that the reduction of recurrent stroke with DAPT was lower in the studies with follow-up duration >3 months (OR 0.93, 0.82 to 1.06; p = 0.28) and higher in those with ≤3 months duration (OR 0.66, 0.58 to 0.76; p <0.00001) (p for interaction 0.0004), without significant heterogeneity in the studies or publication bias.

Discussion

The net benefit of aspirin plus a P_2Y_{12} inhibitor versus aspirin alone after noncardioembolic stroke or TIA is debated, due to the bleeding risk related to DAPT and the lack of data on the degree of secondary prevention provided by DAPT according to different patients' risk profiles. As a consequence, the combination of aspirin and clopidogrel after an acute stroke is not largely utilized in the real-world (28% prevalence at discharge in a recent multicenter Korean registry).[22] In our meta-analysis we found that, compared to SAPT (essentially aspirin), DAPT use (aspirin

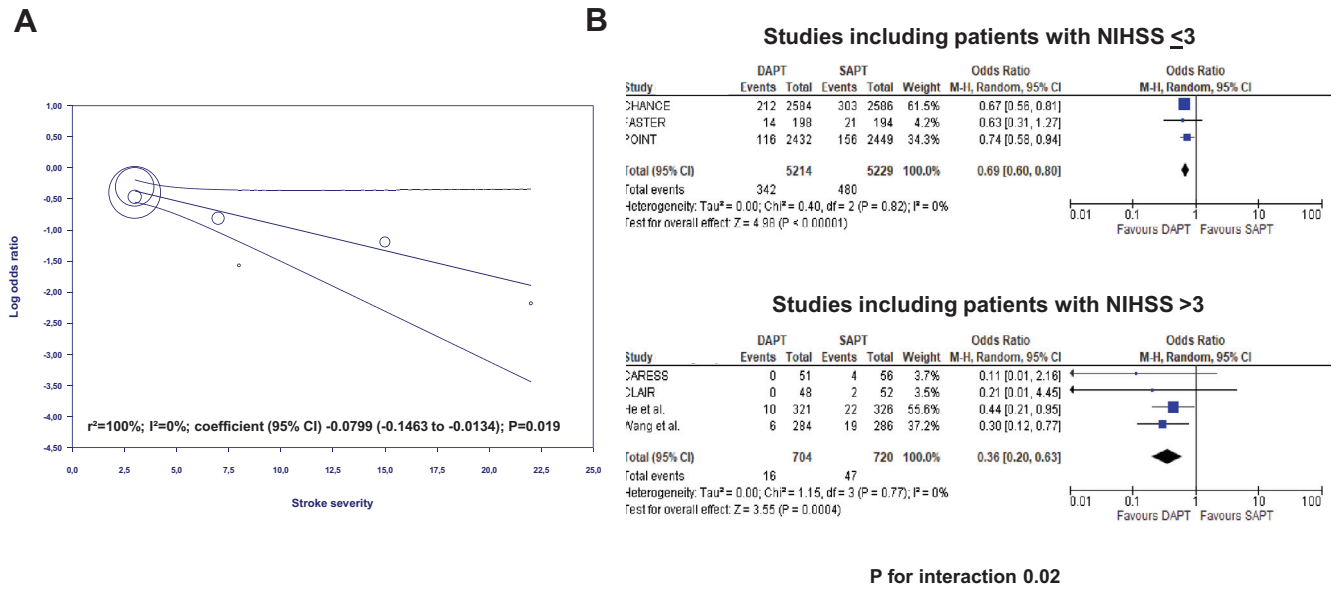

Figure 2. **Analysis according to stroke severity**.
Panel A. Meta-regression graphs describing the effect of baseline stroke severity by NIHSS on the log odds ratio for recurrent stroke with DAPT. The relation was significant, suggesting that stroke severity is positively correlated to DAPT benefit. The panel includes regression line with 95% confidence interval. Each circle represents a study, telescoped by its weight in the analysis. Panel B. Odds ratios (with 95% confidence interval) for recurrent stroke with DAPT versus SAPT according to baseline stroke severity (NIHSS ≤3 or >3).
CI = confidence interval; DAPT = dual antiplatelet therapy; NIHSS = National Institute of Health Stroke Scale; SAPT = single antiplatelet therapy.

plus clopidogrel) was overall associated with a 26% relative reduction and 1.7% absolute reduction of recurrent stroke at a mean follow up of 8 months. There was a significant heterogeneity in the trials and this was the rationale to further proceed with the metaregression analysis. All included studies considered any stroke event in the end point of recurrent stroke; this allowed also a safety evaluation of DAPT regarding a possible increase of hemorrhagic stroke. However, 97% of recurrent strokes were ischemic and our sensitivity analysis on ischemic stroke as outcome measure yielded consistent results. Moreover, in the DAPT arm we demonstrated a twofold relative increase and 0.9% absolute increase of major bleeding versus SAPT, without difference in the incidence of intracranial hemorrhages. This higher bleeding risk in patients on DAPT made the identification of those drawing the highest protection from recurrent stroke even more relevant, to derive the "ideal" patients with stroke or TIA in whom DAPT may achieve the greatest net clinical benefit.

Metaregression indicated a positive correlation between stroke severity at baseline and efficacy of DAPT. In particular, the relative reduction of recurrent stroke by DAPT was significantly higher in those studies including stroke patients with NIHSS >3, although such analysis is based on 16% of the overall population and may be underpowered. However, this result is consistent with our findings indicating that higher the incidence of stroke in the control arm (e.g. the higher was the baseline patients' risk profile), greater the degree of stroke prevention with DAPT use; in fact, stroke severity is considered an independent predictor of poorer outcome.[1] Other recognized predictors of recurrent events are older age, previous history of stroke/TIA, high blood pressure, and concomitant multisite atherosclerotic disease.[1,23,24] Thus, the presence of the abovementioned indicators of a higher risk may characterize a setting of patients potentially candidates to DAPT.

Notably, in our metaregression a more elevated prevalence of carotid atherosclerotic disease was associated with a more pronounced stroke reduction by DAPT use; this supports that DAPT may be more beneficial in patients with atherothrombotic stroke/TIA by preventing further atherothrombotic events. We observed that the higher was the prevalence of diabetes in the studies, the lower was the efficacy of DAPT. A higher baseline platelet reactivity and an impaired response to clopidogrel in patients with diabetes compared to those without may explain our findings.[25,26] However, the presence of confounders in the present analysis resulting in an apparent association at the trial level between diabetes and DAPT efficacy cannot be excluded.

Metaregression also demonstrated that the earlier was DAPT initiation, the greater was its benefit; in particular, the relative reduction of recurrent stroke was higher in those studies with a symptom onset-to-enrollment time ≤7 days. Moreover, we observed that stroke prevention by DAPT use was prevalent in trials with follow-up duration ≤3 months. These findings are consistent with previous data indicating that in patients suffering an ischemic cerebral event the percentage of stroke recurrence is more pronounced in the first weeks, especially after an atherothrombotic event;[23,27] the risk of recurrent stroke tends to decline after 3 months, when the bleeding risk related to DAPT (which is expected to linearly increase over time) may be predominant. Notably, in most European countries the clopidogrel labeling excludes its use in the first 7 days after stroke.

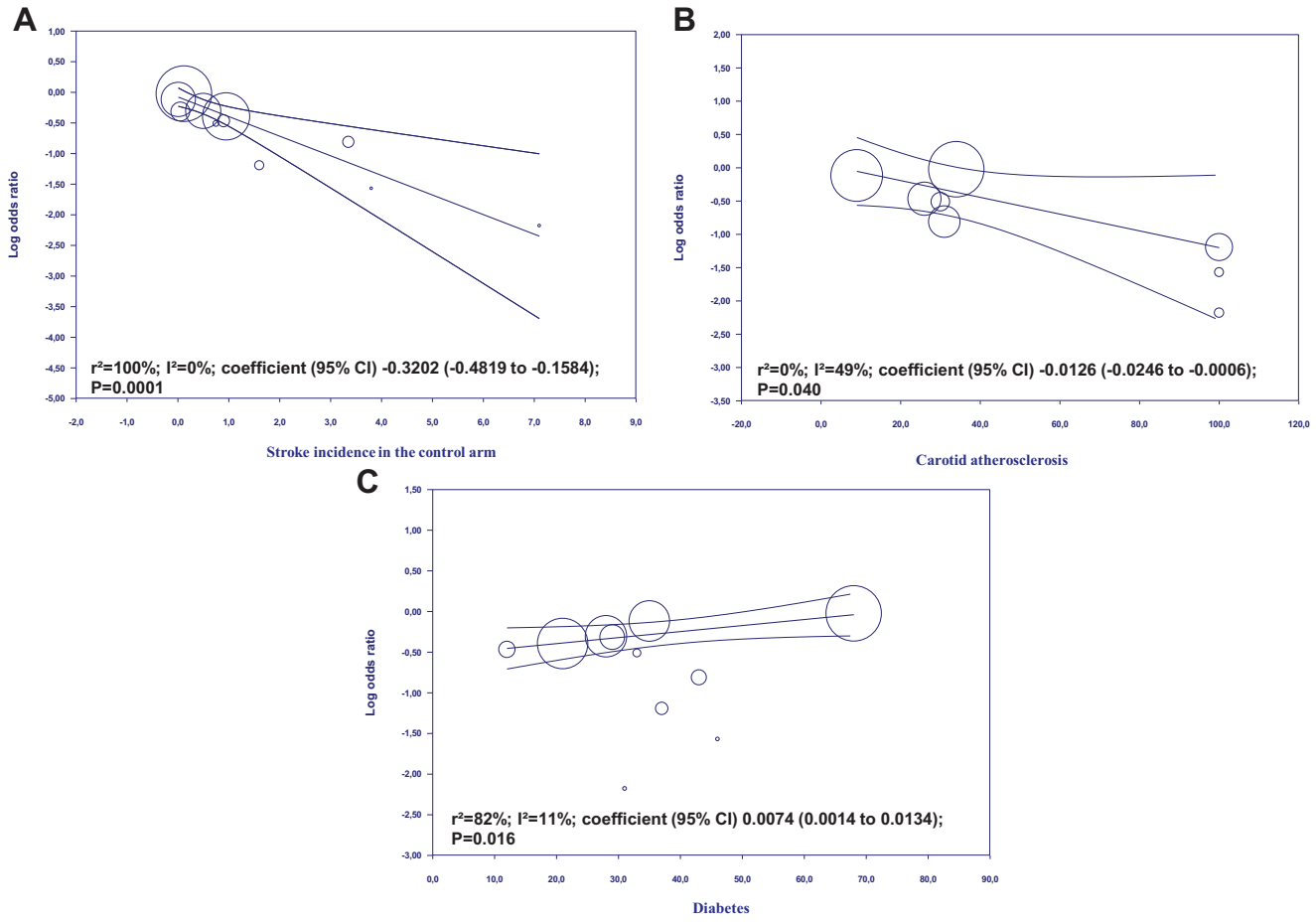

Figure 3. **Meta-regression for concomitant carotid disease, baseline risk profile and diabetes**.
Panel A. Meta-regression graphs describing the effect of the incidence of recurrent stroke during follow up in the control arm (SAPT arm) on the log odds ratio for recurrent stroke with DAPT. The relation was significant, suggesting that the incidence of recurrent stroke in the control arm is positively correlated to DAPT benefit. Panel B. Meta-regression graphs describing the effect of significant carotid atherosclerosis on the log odds ratio for recurrent stroke with DAPT. The relation was significant, suggesting that carotid disease is positively correlated to DAPT benefit. Panel C. Meta-regression graphs describing the effect of diabetes mellitus on the log odds ratio for recurrent stroke with DAPT. The relation was significant, suggesting that diabetes is negatively correlated to DAPT benefit.
Each panel includes regression line with 95% confidence interval. Each circle represents a study, telescoped by its weight in the analysis.
CI = confidence interval.

This study has various limitations. Overall risk of bias in this analysis is very low, but cannot be completely excluded. Included trials had different patients' risk profiles, symptom onset to-enrollment times, and follow-up durations; these factors could be potential confounders, but the heterogeneity in the studies has represented the basis for performing the metaregression analysis. The studies essentially refer to patients not receiving fibrinolysis or thrombectomy for the stroke event; thus, is it unknown the extent to which the observed outcome with DAPT applies to a context of larger use of reperfusion treatments. It is also unknown whether our results also apply to the specific setting of patients with stroke/TIA caused by an intracranial arterial stenosis.[28] Furthermore, an underestimation of the potential for trial level confounding of the metaregression analysis cannot be excluded. As this is a study-level analysis, we had no access to individual patients' data and we were not able to evaluate outcome of DAPT versus SAPT in specific subgroups of patients (e.g. according to specific risk profiles) and to adjust for potential confounders. Furthermore, we included randomized studies, where the prevalence of hypertensive drugs, antidiabetic agents, and statin therapy was similar in patients receiving DAPT and SAPT; however, we cannot exclude that a better control of glucose levels or arterial pressure or lipids may have in part driven the favorable outcome with DAPT. Finally, as patients did not undergo continuous heart rhythm monitoring during the hospitalization for the index event, it is unknown whether imbalances in the prevalence of subclinical atrial fibrillation between SAPT and DAPT groups could have affected our results.

In conclusion, our metaregression may help to identify the patient's profile associated with the greatest clinical benefit from the use of aspirin plus clopidogrel after stroke or TIA, for example patient having a high-risk, atherothrombotic TIA or atherothrombotic stroke with NIHSS >3, in whom DAPT can be initiated ≤7 days from the acute event and stopped at 3 months. This analysis can add

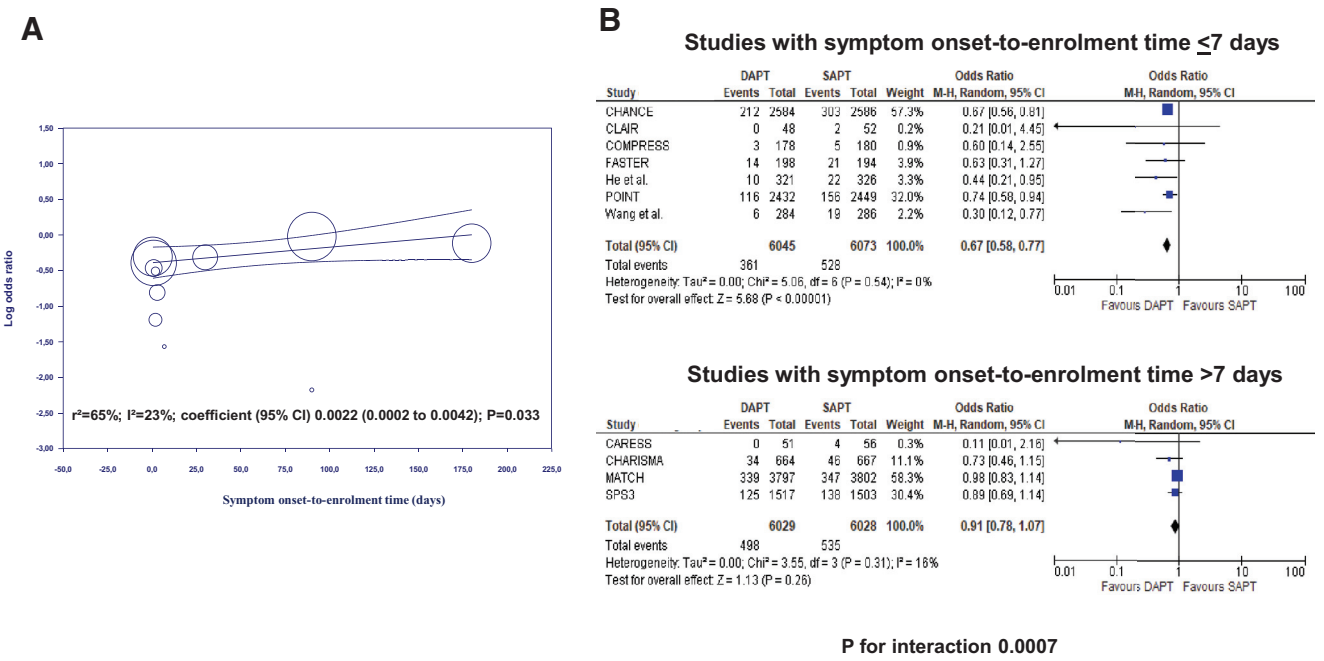

Figure 4. **Analysis according to symptom onset-to-enrollment time**.
Panel A. Meta-regression graphs describing the effect of symptom onset-to-enrollment time on the log odds ratio for recurrent stroke with DAPT. The relation was significant, suggesting that symptom onset-to-enrollment is negatively correlated to DAPT benefit. The panel includes regression line with 95% confidence interval. Each circle represents a study, telescoped by its weight in the analysis. Panel B. Odds ratios (with 95% confidence interval) for recurrent stroke with DAPT versus SAPT according to symptom onset-to-enrollment times (≤7 or >7 days).
CI = confidence interval; DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy.

evidence to current postacute antithrombotic therapy after a noncardioembolic, ischemic cerebral event and more specifically address current guideline recommendations; indeed, American guidelines refer only to the CHANCE trial (level of evidence B) and only indicate (class of recommendation IIa) to initiate DAPT <24 hours from a minor

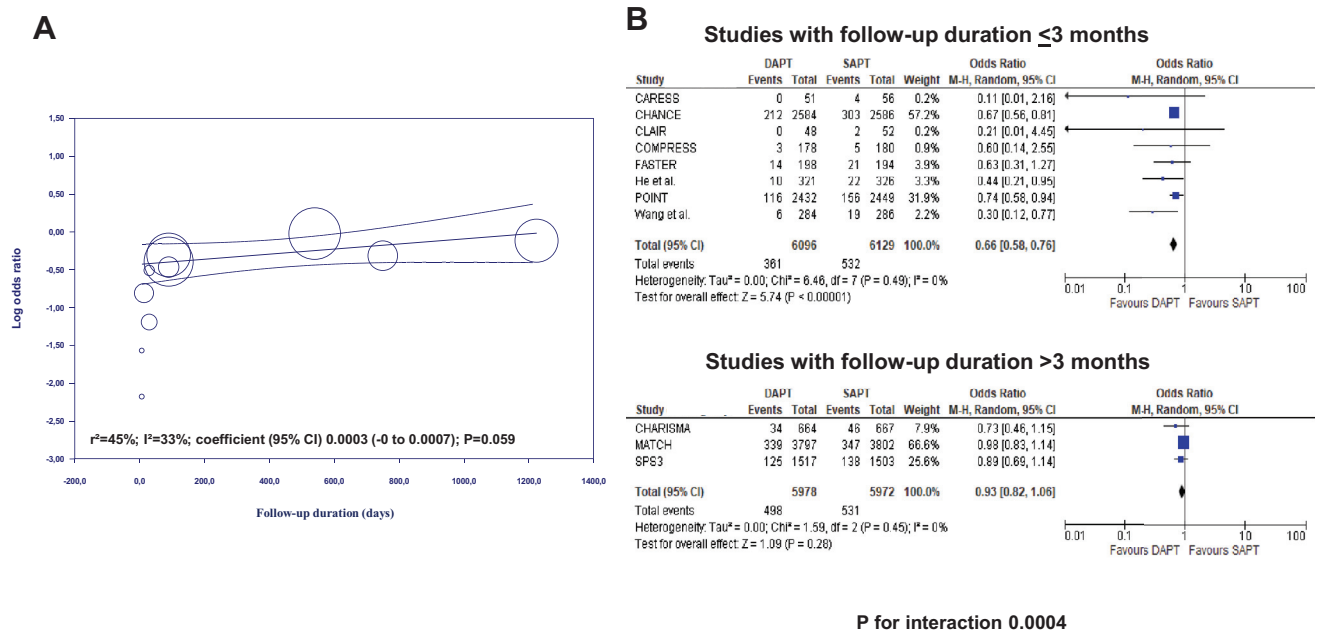

Figure 5. **Analysis according to follow-up durations**.
Panel A. Meta-regression graphs describing the effect of follow-up duration on the log odds ratio for recurrent stroke with DAPT. The relation was significant, suggesting that follow-up duration is negatively correlated to DAPT benefit. The panel includes regression line with 95% confidence interval. Each circle represents a study, telescoped by its weight in the analysis. Panel B. Odds ratios (with 95% confidence interval) for recurrent stroke with DAPT versus SAPT according to follow-up durations in the different studies (≤3 or >3 months).
CI = confidence interval; DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy.

stroke for 21 days up to 3 months.[1] However, our results are hypothesis-generating and need confirmation; the patient's profile identified in the present study might represent the target population of a randomized trial comparing aspirin plus clopidogrel versus aspirin alone after noncardioembolic stroke or TIA, with a combined net clinical end point, including both ischemic and bleeding events, as primary outcome measure.

Disclosures

GP: speaker/consultant/advisory board for Amgen, Sanofi, Bayer, Boehringer-Ingelheim, BMS-Pfizer, Daiichi Sankyo, Astra Zeneca, Sigma-Tau, Malesci, PIAM, and MSD. AS, AB, FP, VP, GS, MP: no disclosure.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.013.

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