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Secondary prevention in the acute and early chronic phase after ischemic stroke and transient ischemic attacks with antiplatelet drugs – is antiplatelet monotherapy still reasonable?

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Introduction

Intravenous thrombolysis with recombinant tissue plasminogen activator is the only proven medical treatment for acute ischemic stroke in a time period up to 4.5 hours after onset of stroke symptoms. However, only a minority of patients is eligible for intravenous thrombolysis due to delayed presentation or contraindications to thrombolysis. In the remaining patients, early prevention of recurrent stroke is one of the primary therapeutic targets. Numerous prospective studies have shown that the risk of a subsequent or recurrent ischemic stroke is highest in the first 48 to 72 hours after the initial cerebrovascular ischemic event (1).

We discuss current evidence from randomised trials concerning secondary stroke prevention with antiplatelets in the acute and early chronic phase after TIA and stroke.

Secondary stroke prevention with aspirin in the acute and early chronic post-ischemic phase

Early treatment with aspirin in patients with acute ischemic stroke was investigated in two large clinical trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST). IST was a randomised, unblinded trial that recruited a total of 19435 patients with acute ischemic stroke to receive aspirin (300 mg/daily), one of two doses of subcutaneously administered heparin (5000 U/BID or 12500 U/BID), or both, in a factorial design within 48 hours of stroke symptom onset. Among aspirin-allocated patients there were non-significantly fewer deaths within 14 days (9.0% vs. 9.4%), corresponding to 4 fewer deaths per 1000 patients. At 6 months, 62.2% of patients treated with aspirin were dead or dependent compared with 63.5% of untreated patients. Patients treated with aspirin had significantly fewer recurrent is-

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2 chemic strokes within 14 days (2.8% vs. 3.9%) with no significant excess of hemor-
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4 rhagic stroke (0.9% vs. 0.8%). In contrast to IST, CAST was a randomised placebo-
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6 controlled trial. 21,106 patients were treated with aspirin 160 mg/daily or placebo for
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8 4 weeks, starting within 48 hours after symptom onset. There was a significant reduc-
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10 tion in mortality during the 4 week treatment period in aspirin-allocated patients (3.3%
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12 vs. 3.9%). Furthermore, there were significantly fewer recurrent ischemic strokes in
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14 patients treated with aspirin (1.6% vs. 2.1). Treatment with aspirin was associated
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16 with a non-significant increase in hemorrhagic strokes (1.1% vs. 0.9%).

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18 In a prespecified combined analysis of IST and CAST, aspirin treatment started in the
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20 acute post-ischemic stroke phase resulted in a reduction of 10 deaths or recurrent
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22 strokes and causes 2 hemorrhagic strokes per 1000 treated patients (2).
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25 26 **Abciximab in early secondary prevention**

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29 The intravenous use of the platelet glycoprotein IIb/IIIa inhibitor abciximab has been
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31 considered to be safe when administered within 24 hours after ischemic stroke onset
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33 after two phase II trials had been carried out. However, the phase III trial AbESTT-II
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35 had to be terminated prematurely after enrolment of 808 patients due to a signifi-
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37 cantly increased bleeding rate in the active treatment group (3). During the first 5
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39 days of enrolment, 5.5% of patients who had received intravenously administered
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41 abciximab within 5 hours of onset of stroke had symptomatic or fatal intracranial
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43 hemorrhage versus 0.5% of placebo-treated patients.
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46 47 **The combination of aspirin and extended-release dipyridamole in early secon-** 48 49 **dary stroke prevention**

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2 The combination of aspirin plus dipyridamole has been shown to be more effective
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4 than aspirin monotherapy in long-term secondary stroke prevention in the random-
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6 ised trials ESPS-2 and ESPRIT (4, 5). However, enrolment of patients in these trials
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8 occurred up to 6 months after the cerebrovascular ischemic event. The combination
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10 of aspirin (25 mg BID) and extended-release dipyridamole (200 mg BID) was com-
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12 pared with clopidogrel monotherapy (75 mg daily) in more than 20000 patients in the
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14 randomised PRoFESS trial (6). A post-hoc analysis of this trial investigated the 1360
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16 patients who were randomised within 72 hours of ischemic stroke onset (7). There
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18 was no significant difference in death or dependency at 30 days between both anti-
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20 platelet regimen. A non-significant trend towards a reduction of recurrent stroke was
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22 seen with the combination of aspirin and extended-release dipyridamole at 90 days
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24 (1.64% vs. 2.91%; OR 0.56, 95%CI 0.26 to 1.18).
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28 The randomised EARLY trial compared the combination of aspirin (25 mg BID) and
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30 extended-release dipyridamole (200 mg BID) with aspirin monotherapy (100
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32 mg/daily) started within 24 hours of symptom onset in patients with ischemic stroke
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34 (NIHSS score \leq 20) or TIA (8). A total of 543 patients were randomised, 283 receiv-
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36 ing aspirin and extended-release dipyridamole (early initiation group) and 260 receiv-
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38 ing aspirin monotherapy for the initial 7 days (late initiation group). Thereafter, all pa-
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40 tients were treated with the combination antiplatelet therapy. The primary endpoint
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42 was an excellent or good functional outcome at 90 days, defined as a value of 0 or 1
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44 on the modified Rankin scale, which was assessed by a blinded investigator using a
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46 standardised telephone interview. Vascular events and mortality were also assessed
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48 as a composite safety and efficacy endpoint. At day 90, 56% of patients in the early
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50 initiation group and 52% of patients treated with aspirin monotherapy during the first
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52 7 days had a modified Rankin scale value of 0 or 1, a difference that was not statisti-
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1 cally significant. The composite safety and efficacy endpoint occurred in 28 patients
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 3 (10%) in the early combination group and in 38 patients (15%) in the aspirin mono-
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 5 therapy group (hazard ratio 0.73, 95%CI 0.44-1.19) (figure 1). More patients in the
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 7 late initiation group had a recurrent non-fatal stroke, but this difference also did not
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 9 reach statistic significance [26 (10%) vs. 16 (6%); hazard ratio 0.61, 95%CI 0.31-
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 11 1.19].
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13 A total of 955 patients were randomised within the first 72 hours to the combination of
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 15 aspirin and extended-release dipyridamole in EARLY and PRoFESS, while 948 re-
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 17 ceived either aspirin or clopidogrel monotherapy. There were 27 recurrent strokes
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 19 within the first 90 days in patients treated with the combination antiplatelet therapy
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 21 compared with 46 recurrent strokes in patients treated with a single antiplatelet agent
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 23 (absolute risk reduction 2.0%, relative risk reduction 44%, 95%CI: 10% - 64%, p =
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 25 0.015). The Breslow-Day test revealed no indication for heterogeneity between stud-
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 27 ies (p = 0.95).
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32 Dual antiplatelet therapy with Clopidogrel and Aspirin in the acute and early 33 chronic secondary stroke prevention

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 37 The FASTER trial was a randomised controlled pilot study that compared antiplatelet
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 39 therapy with clopidogrel and aspirin with aspirin alone in TIA and stroke patients,
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 41 within 24 hours of symptom onset (9), 392 patients were randomised to an initial
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 43 loading dose of 300 mg Clopidogrel followed by 75 mg daily or placebo. All patients
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 45 received 180 mg aspirin daily. The primary outcome was an ischemic or hemorrhagic
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 47 stroke within 90 days, which did not significantly differ between both treatment arms
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 49 (7.1% on clopidogrel had an ischemic stroke vs. 10.8% on placebo). Intracranial
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 51 hemorrhage occurred in 2 patients in the clopidogrel group.
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2 A combined analysis of patients treated within 24 hours in the FASTER, CHARISMA,
3 CARESS and MATCH trials showed a 34% relative risk reduction in patients on
4 clopidogrel and aspirin (figure 2). In the dual platelet therapy group, 29 out of 214
5 (13.5%) patients suffered a stroke versus 45 out of 213 (14.4%) patients in the aspi-
6 rin monotherapy group (9).

7
8 A meta-analysis of the EARLY and the FASTER trials studied the combined outcome
9 of death, myocardial infarction, ischemic stroke, TIA and intracranial hemorrhage. 57
10 of 481 (11.9%) patients on the combination therapy with aspirin plus dipyridamole or
11 aspirin plus clopidogrel reached the endpoint, as compared to 80 of 454 (17.6%) on
12 aspirin monotherapy (relative risk reduction 42%, $p=0.014$) (8) (figure 3).

13
14 Whereas the FASTER trial was a pilot study, the projected POINT study will recruit
15 4150 patients treated with a clopidogrel loading dose of 600 mg followed by daily 75
16 mg in combination with 50 – 325 mg aspirin daily in comparison to aspirin monother-
17 apy in patients with TIA and minor stroke initiated within 12 hours of symptom onset
18 (http://clinicaltrials.gov/ct2/show/NCT00991029).

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33 **Bleeding risk in patients treated with a combination of clopidogrel and aspirin** 34 **and potential rebound increase in risk of ischemic stroke recurrence**

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36 According to the MATCH study (10), combination of aspirin plus clopidogrel started in
37 the acute phase should not be given over long term because the combination has no
38 significant benefit but an increased risk of intracranial and systemic bleeding compli-
39 cations. An important question is whether the combination of clopidogrel and aspirin
40 increases the risk of intracranial bleeding during the acute post-ischemic phase as it
41 does during long-term treatment. In order to estimate the early bleeding risk during
42 the acute phase, Geraghty et al. investigated pooled data from the EXPRESS and
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FASTER studies (11). Major or life-threatening bleeding when treated with aspirin plus clopidogrel occurred in 9/241 aspirin-naive patients in 90 days (90-day risk = 4.8%, 95%CI 1.6-8.0) versus in 1/204 prior-aspirin patients ($p = 0.009$). Therefore, the early bleeding risk under aspirin plus clopidogrel seems to be a cause for concern mainly in aspirin-naive patients. These results were based on observational data and an unplanned subgroup analysis from the randomised FASTER trial. It therefore cannot be excluded that there are other differences between the patient groups unrelated to antiplatelet regimens.

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In acute coronary syndrome, early discontinuation of clopidogrel results in a transient rebound increase in risk of recurrence (12). Geraghty et al. investigated whether there is a similar rebound effect in patients with TIA or stroke. In the EXPRESS study, a total of 320 patients were prescribed a 30-day course of aspirin and clopidogrel (both 75 mg daily) acutely after TIA or minor stroke (13). Clopidogrel was stopped after 30 days and aspirin was continued thereafter. There were 5 recurrent ischemic strokes and 7 TIAs during the aspirin and clopidogrel treatment period, but no strokes and 4 TIAs during the 30 days after stopping clopidogrel. A similar temporal trend in stroke risk was seen in the 487 patients prescribed aspirin alone in the acute phase, with 12 and 5 strokes in the equivalent time periods. The upper 95% CI of the observed 0% risk of stroke during the 30 days after stopping clopidogrel was 1.15%. This finding suggests that there is unlikely to be a large rebound effect after discontinuation of a 30-day course of clopidogrel and aspirin in acute TIA and minor ischemic stroke.

A combined antiplatelet treatment as an option for the acute and early secondary stroke prevention

Considering the available evidence, patients with an acute TIA or minor ischemic stroke might benefit from combination of aspirin plus clopidogrel or aspirin plus dipyridamole for at least 30 days. However, one has to keep in mind that most of the available data has been derived from meta-analyses of non-prespecified subgroups from randomised trials. Thus, a possible bias or confounding factors cannot be excluded. There is good evidence from randomised trials for the combination of aspirin and dipyridamole both in the acute, early and long term secondary stroke prevention. As shown before, a combined antiplatelet therapy with aspirin and clopidogrel for a limited time period might result in a lower recurrent stroke rate in the acute and early chronic post-ischemic stroke phase. However, this combination therapy might result in a higher bleeding rate in patients who were not treated with aspirin before. Thus, additional randomised trials are required for this combination and to identify patient subgroups that benefit most. In contrast, the combination of aspirin and clopidogrel has no benefit in long-term secondary stroke prevention but increases the bleeding risk.

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Figure legend

Figure 1: Time to first event that was included in the composite endpoint of non-fatal stroke, TIA, non-fatal myocardial infarction and major bleeding in the EARLY trial.

ASA = acetylsalicylic acid. ER-DP = extended released dipyridamole. HR = hazard ratio.

Adopted from The Lancet Neurol, 9,159-166, Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T, Eschenfelder CC, Leonard J, Weissenborn K, Kastrup A, Haberl R; EARLY Investigators. Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial. Copyright (2010), with permission from Elsevier.

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Figure 2: Fixed-effects meta-analysis of 90-day risk of the combined outcome of stroke, TIA, acute coronary syndrome, and all-cause death in stroke and TIA patients enrolled within 24 h of onset in the FASTER, CHARISMA, CARESS and MATCH trial. Note that x-axis is a logarithmic scale.

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Figure 3: Comparison of the composite endpoint non-fatal stroke, TIA, non-fatal myocardial infarction and major bleeding in the first 7 days in the EARLY and FASTER

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2 trial. Data are number of patients with events included in the composite endpoint
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4 (number of patients at risk). There was no heterogeneity between studies, $p=1.00$.

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6 ASA = acetylsalicylic acid. NIHSS = National Institute of Health Stroke Scale.

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10 Grond M, Schumacher H, Machnig T, Eschenfelder CC, Leonard J, Weissenborn K,
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12 Kastrup A, Haberl R; EARLY Investigators. Early treatment with aspirin plus ex-
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16 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint
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Conflict of interest

Prof. Dr. Hans-Christoph Diener received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, D-Pharm, Fresenius, GlaxoSmith-Kline, Janssen Cilag, MSD, MindFrame, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Servier, Solvay, Thrombogenics, Wyeth, Yamaguchi. Financial support for research projects was provided by Astra/Zeneca, GSK, Boehringer Ingelheim, Novartis, Janssen-Cilag, Sanofi-Aventis.

Prof. Dr. H.-C. Diener has no ownership interest and does not own stocks of any pharmaceutical company.

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Dr. Ralph Weber has no conflicts of interest.

Prof. Dr. Christian Weimar received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Asubio, Novartis, Novo-Nordisk, Sanofi-Aventis.

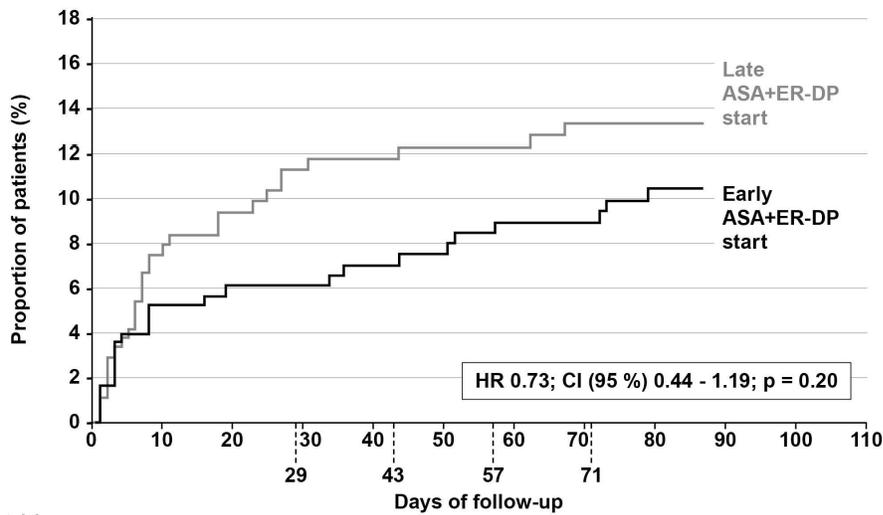
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Number at risk		Days of follow-up						
		0	29	43	57	71		
Late ASA+ER-DP start	260	195	181	176	171	167	159	
Early ASA+ER-DP start	283	213	201	194	190	188	169	

Figure 1: Time to first event that was included in the composite endpoint of non-fatal stroke, TIA, non-fatal myocardial infarction and major bleeding in the EARLY trial. ASA = acetylsalicylic acid. ER-DP = extended released dipyridamole. HR = hazard ratio. Adopted from The Lancet Neurol, 9,159-166, Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T, Eschenfelder CC, Leonard J, Weissenborn K, Kastrup A, Haberl R; EARLY Investigators. Early treatment with aspirin plus extend-ed-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EAR-LY trial): a randomised, open-label, blinded-endpoint trial. Copyright (2010), with permission from Elsevier.

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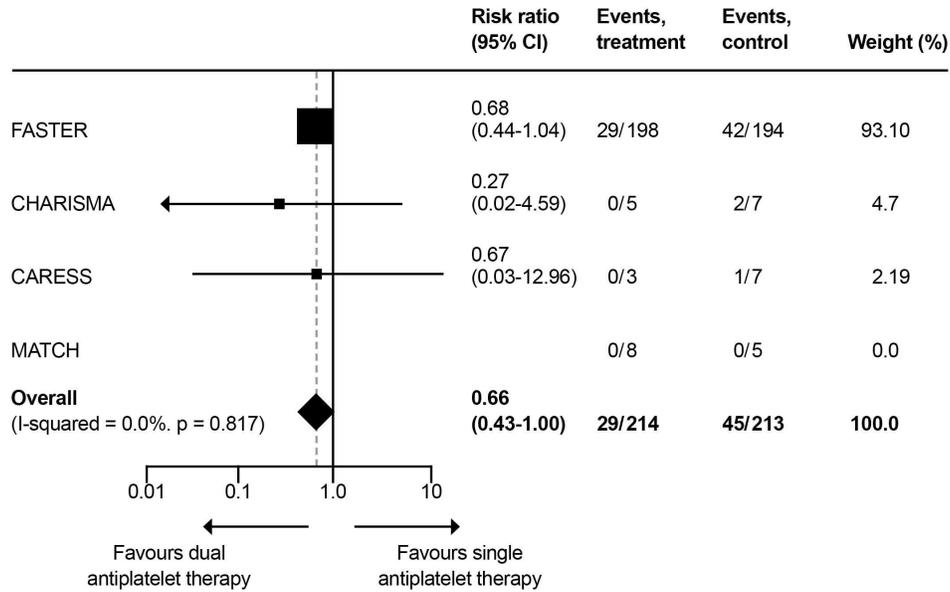


Figure 2: Fixed-effects meta-analysis of 90-day risk of the combined outcome of stroke, TIA, acute coronary syndrome, and all-cause death in stroke and TIA patients enrolled within 24 h of onset in the FASTER, CHARISMA, CARESS and MATCH trial. Note that x-axis is a logarithmic scale.

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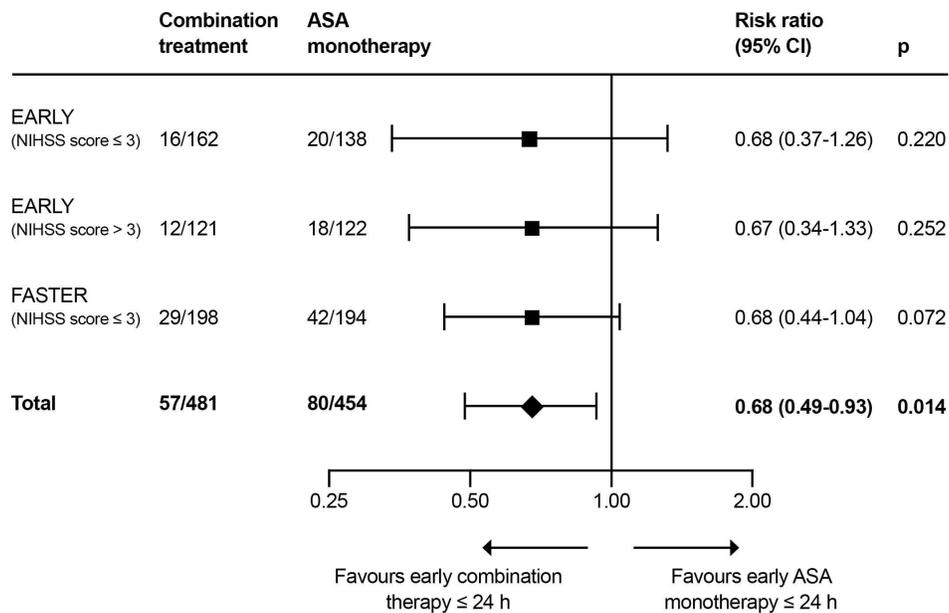


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