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Dipyridamole + ASA for secondary prevention after a stroke or TIA¹

Executive Summary

¹ Translation of the executive summary of the final report “Dipyridamol + ASS zur Sekundärprävention nach Schlaganfall oder TIA” (Version 1.0; Status: 14.02.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive summary

With its letter of 20 July 2009, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of dipyridamole + acetylsalicylic acid (ASA) for secondary prevention after a stroke or transient ischaemic attack (TIA).

Research question

The aim of this research was to assess the benefit of treatment with the combination of the two agents dipyridamole plus ASA as secondary prevention after an ischaemic stroke or TIA. This combination therapy was compared to other drug interventions or placebo on the basis of patient-relevant outcomes.

Methods

The assessment was conducted on the basis of randomized controlled trials (RCTs) on the research question outlined above. For this purpose, a systematic search for literature was conducted in the following databases: MEDLINE, EMBASE, BIOSIS, and the Cochrane Central Register of Controlled Trials (Clinical Trials). The search for relevant secondary publications was performed in MEDLINE and EMBASE parallel to the search for relevant primary literature, and also by a search in the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The period up to 2 September 2010 was covered. In addition, study registries and publicly accessible regulatory documents were screened and the manufacturer of the drug approved in Germany (Aggrenox®), Boehringer Ingelheim Pharma GmbH & Co. KG, was asked to provide relevant published and unpublished studies.

The literature screening was undertaken by 2 reviewers independently of each other. After an assessment of the risk of bias, the results of the individual studies were organized according to treatment comparisons and treatment duration for each outcome analysed.

Results

A total of 6 studies were identified as being relevant to the research question of the present benefit assessment. These studies comprised 1 placebo-controlled and 2 active-controlled short-term studies (duration: 7 to 30 days; active control: in each case ASA; size: 40 to 548 patients). The other 3 studies included were long-term studies (duration: 1 to 4.5 yrs.; size: 1,295 to 20,332 patients) and comprised 2 two-arm active-controlled studies (controls: ASA and clopidogrel), as well as a three-arm active-controlled and placebo-controlled study (controls: ASA and placebo).

Information on outcomes

The results for the active controls in the long-term comparisons (ASA / clopidogrel) were pooled.² In order to avoid repetition in the presentation of results, to begin with we note that, for all outcomes investigated, the data on long-term therapy provided no evidence that the observed effect of the control ASA (assessed alone) was to be appraised differently than the effect observed within the framework of data pooling (ASA / clopidogrel).

Overall mortality

In one short-term study no deaths were observed in the placebo comparison and thus no difference between treatment groups was found ($p > 0.999$). In a long-term study, the placebo comparison also showed no statistically significant difference between treatment options (RRR [SE]: 8.5 [8.8]; $p = 0.324$). In the short-term studies, the comparison of dipyridamole + ASA with ASA showed no statistically significant difference between treatment options (RD [95% CI] in the meta-analysis: 0.00 [-0.01; 0.01]). The same applied to dipyridamole + ASA versus ASA / clopidogrel in the long-term studies (RR / HR [95 % CI] in the meta-analysis: 0.98 [0.87; 1.09]).

In summary, for the outcome “overall mortality” in short- and long-term therapy the data provided no proof of a benefit of dipyridamole + ASA. The comparison of dipyridamole + ASA with ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of an additional benefit of dipyridamole + ASA.

Vascular mortality

No vascular deaths were noted in the placebo comparison in the short-term study and thus no difference between treatment groups was shown ($p > 0.999$). In the placebo comparison in the long-term study, no statistically significant difference was shown between treatment options (RRR [SE]: 5.27 [11.73]; $p = 0.541$). The active comparison in the short-term studies investigating dipyridamole + ASA versus ASA showed no statistically significant difference (RD [95% CI] in the meta-analysis: 0.00 [-0.01; 0.01]). The comparison of dipyridamole + ASA with ASA / clopidogrel within the framework of the 3 long-term studies produced a heterogeneous result ($p < 0.2$). A sensitivity analysis excluding the PRoFESS study also produced a heterogeneous result ($p < 0.2$). In connection with the assessment of the individual effects in the 3 studies, this led to the overall conclusion that no difference between treatment options could be assumed for the outcome “vascular mortality”.

Consequently, for this outcome the data provided no proof of a benefit of short- or long-term therapy with dipyridamole + ASA. The results for the comparison of dipyridamole + ASA

² The term “ASA / clopidogrel” refers to the pooled results for these 2 drugs.

with ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of an additional benefit of dipyridamole + ASA.

Fatal stroke

Compared to placebo, no fatal strokes occurred in the short-term study and therefore no difference between treatment groups was shown ($p > 0.999$). The placebo comparison in the long-term study showed no statistically significant difference between treatment options (RRR [SE]: 10.65 [19.73]; $p = 0.492$). The comparison of dipyridamole + ASA versus ASA in the short-term study also showed no statistically significant difference for the outcome “fatal stroke” (RD [95% CI] in the meta-analysis: 0.00 [-0.01; 0.01]). The same applied to the comparison of dipyridamole + ASA versus ASA / clopidogrel in the long-term studies (RD [95% CI] in the meta-analysis: -0.00 [-0.00; 0.00]).

In summary, for the outcome “fatal stroke” the data provided no proof of a benefit of short- or long-term therapy with dipyridamole + ASA. The comparison of dipyridamole + ASA with ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of an additional benefit of dipyridamole + ASA.

Vascular deaths (excluding fatal stroke)

As no vascular deaths occurred in the placebo-controlled short-term study, no difference between treatment groups was shown for the outcome “vascular deaths (excluding fatal stroke)” ($p > 0.999$). Likewise, no statistically significant difference was shown in the placebo comparison in the long-term study ($p = 0.872$). No statistically significant difference between treatment options was noted in the comparison of dipyridamole + ASA with ASA in the short-term studies (RD [95% CI] in the meta-analysis: 0.00 [-0.01; 0.01]). A heterogeneous result ($p < 0.2$) was shown in the comparison of dipyridamole + ASA with ASA / clopidogrel (3 long-term studies). Likewise, a sensitivity analysis excluding the PROfESS study yielded a heterogeneous result ($p < 0.2$). In connection with the assessment of the individual effects in the 3 studies, this led overall to the conclusion that, for this outcome, no difference between treatment options could be assumed.

For the outcome “vascular deaths (excluding fatal strokes)” no proof of benefit was therefore shown for short- and long-term treatment with dipyridamole + ASA. The results for the comparison of dipyridamole + ASA with ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of an additional benefit of dipyridamole + ASA.

Cerebrovascular mortality

The 4 outcomes in this category are non-fatal stroke, TIA, the composite outcome “stroke/death” and outcomes representing impairment caused by complications of the ischaemic event.

Non-fatal stroke

Data on the comparison with placebo in short-term therapy were lacking. The placebo comparison in the long-term study showed a statistically significant difference in favour of dipyridamole + ASA (RRR [SE]: 39.90 [6.11]; $p < 0.001$). Only data on one study were available for active-controlled short-term therapy; these data did not show a statistically significant difference between therapy options (dipyridamole + ASA versus ASA in short-term therapy: $p = 0.124$). The comparison of dipyridamole + ASA with ASA / clopidogrel in the long-term studies provided a heterogeneous meta-analysis ($p < 0.2$). In the assessment of individual study findings, opposing results were shown in the 2 ASA-controlled studies (RR / HR [95% CI] in the individual studies: 0.74 [0.60; 0.91] and 1.52 [1.01; 2.29]), whereas no statistically significant difference was shown in the PROfESS study, which included the control clopidogrel (RR / HR [95% CI] in the individual study: 1.04 [0.95; 1.14]). Overall, this information basis led to the conclusion that no evidence exists of an advantage or disadvantage of long-term therapy with dipyridamole + ASA versus ASA / clopidogrel.

In summary, the data provided an indication of a benefit of long-term therapy with dipyridamole + ASA for the outcome “non-fatal stroke”. The comparison between dipyridamole + ASA and ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of an additional benefit of dipyridamole + ASA.

Transient ischaemic attack

No data were available on the placebo-controlled short-term study. A statistically significant difference between treatment options in favour of dipyridamole + ASA was shown in the placebo comparison in the long-term study (RRR: 35.9; $p < 0.001$). The available data on active-controlled short-term therapy (one study) showed no statistically significant difference between treatment options (dipyridamole + ASA versus ASA: $p = 0.282$). The meta-analysis of long-term studies comparing dipyridamole + ASA with ASA / clopidogrel showed heterogeneous results ($p < 0.2$). The assessment of individual study results showed 3 non-statistically significant estimates (RR / HR [95% CI] in the individual studies: 0.83 [0.69; 1.01], 1.02 [0.21; 5.07], and 1.08 [0.92; 1.26]). A sensitivity analysis excluding the PROfESS study was performed to examine heterogeneity, which yielded a homogeneous result and no statistically significant difference (RR / HR [95% CI] in the meta-analysis: 0.84 [0.69; 1.01]). Overall, this information basis led to the conclusion that a statistically significant difference between treatment options could not be assumed for the outcome “TIA”.

Consequently, for this outcome the data provided an indication of a benefit of long-term therapy with dipyridamole + ASA. The comparison with ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of an additional benefit of dipyridamole + ASA.

Composite outcome “stroke / death”

Only results from a placebo- and active-controlled long-term study were available for this outcome. For the placebo comparison, a statistically significant difference in favour of dipyridamole + ASA was shown (RRR [SE]: 24.4 [5.3]; $p < 0.001$). No statistically significant difference was observed in the active comparison of dipyridamole + ASA with ASA (RRR [SE]: 12.9 [6.0]; $p = 0.056$). With regard to the individual components of the composite outcome, on the basis of the study report, both in the placebo comparison and in the active comparison a statistically significant difference was shown in favour of dipyridamole + ASA for the component “stroke” but not for “death”, nor was a notable numerical difference between treatment groups shown for the outcome “death”. Therefore, for the further interpretation of results only individual results of the outcomes included in the composite outcome are drawn upon.

Impairment caused by complications of the ischaemic event

The data available on the operationalization of this outcome referred to 3 scales (MMSE, mRS and NIHSS³).

Data from an active-controlled long-term study were available for the MMSE. They showed no statistically significant difference in the comparison of dipyridamole + ASA with clopidogrel ($p > 0.999$). In this context, the risk of bias on an outcome level was assessed as high, since the proportion of patients who had not been considered in the analysis at all (“unconsidered proportion”) was classified as being inappropriately high. A conclusion with sufficient certainty of results with regard to the outcome concerned was therefore not possible, and the data provided no proof of an additional benefit of dipyridamole + ASA for the MMSE.

Data from 2 studies were available for the mRS. In the short-term study no statistically significant difference between treatment options was shown (dipyridamole + ASA versus ASA: $p = 0.403$). The same applied to the long-term study (dipyridamole + ASA versus clopidogrel: $p = 0.602$). For the outcome mRS, the data therefore provided no proof of an additional benefit in short- and long-term therapy with dipyridamole + ASA.

Data on the NIHSS were reported in one active-controlled short-term study. No statistically significant difference was shown in the comparison of dipyridamole + ASA with ASA ($p = 0.429$). In this context, the risk of bias on an outcome level was assessed as high, since the assessment of the outcome was not blinded. A conclusion with sufficient certainty of results with regard to the outcome concerned was therefore not possible, and the data provided no proof of an additional benefit of dipyridamole + ASA for the NIHSS.

³ Mini Mental State Examination, modified Rankin Scale, National Institute of Health Stroke Scale

Non-fatal myocardial infarction

No data on non-fatal myocardial infarction were reported in the placebo-controlled short-term study. The placebo comparison in the long-term study did not show a statistically significant difference between treatment options (RRR [SE]: 38.23 [18.34]; $p = 0.095$). Only data on one study were available for active-controlled short-term therapy, which did not show a statistically significant difference between treatment options (dipyridamole + ASA versus ASA: $p = 0.352$). Likewise, no statistically significant difference was shown in the comparison of dipyridamole + ASA with ASA / clopidogrel in the long-term studies (OR [95% CI] in the meta-analysis: 0.90 [0.76; 1.08]).

In summary, the data did not provide proof of a benefit of long-term therapy with dipyridamole + ASA for the outcome “non-fatal myocardial infarction”. The comparison of dipyridamole + ASA with ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of an additional benefit of dipyridamole + ASA.

Hospitalization

Data on hospitalization were only reported in 2 studies. In one short-term study no statistically significant difference was shown in the comparison of dipyridamole + ASA with ASA, as no hospitalizations occurred in either group ($p > 0.999$). Likewise, no statistically significant difference was observed in the long-term study (same comparison: dipyridamole + ASA versus ASA: $p = 0.744$). The data provided no proof of an additional benefit of short- or long-term treatment with dipyridamole + ASA.

Adverse drug effects

For this benefit assessment the outcome “adverse drug effects” was operationalized by means of the evaluation of bleeding and adverse events (AEs). In the assessment of the outcome “bleeding”, major bleeding, minor bleeding and intracranial bleeding were evaluated separately. Separate evaluations were also conducted for the outcome “AEs” (overall AE rates, overall serious AE [SAE] rates, and study discontinuations due to AEs).

Major and minor bleeding

The placebo-controlled short-term study did not report bleeding events. In the placebo comparison of the long-term study, a statistically significant difference between treatment options was shown to the disadvantage of dipyridamole + ASA for major and minor bleeding (in each case $p < 0.001$). Only one active-controlled short-term study reported data on the outcome “minor bleeding” where no statistically significant difference between treatment options was shown (dipyridamole + ASA versus ASA: $p > 0.999$). In the comparison of major bleeding rates under dipyridamole + ASA with those under ASA, no statistically significant difference between treatment options was shown in the short-term studies (RD [95% CI] in the meta-analysis: 0.00 [-0.01; 0.01]). The meta-analysis comparing minor bleeding rates under dipyridamole + ASA with those under ASA / clopidogrel in the long-term studies

showed no statistically significant difference (OR [95% CI] in the meta-analysis: 0.95 [0.82; 1.10]). A sensitivity analysis excluding the PRoFESS study, which was conducted due to the more conservative definition of minor bleeding in this study (only events leading to treatment discontinuation), showed a similar (non-significant) result (OR [95% CI] in the meta-analysis: 1.00 [0.84; 1.20]), nor was the individual result for minor bleeding in the PRoFESS study statistically significant ($p = 0.234$). In the comparison of dipyridamole + ASA with ASA / clopidogrel (3 long-term studies), a statistically significant difference in major bleeding rates was shown in favour of ASA / clopidogrel (OR [95% CI] in the meta-analysis: 1.15 [1.00; 1.31]).

In summary, for the outcomes “major and minor bleeding” the data provide an indication of harm from long-term therapy with dipyridamole + ASA. In short-term therapy, the comparison with ASA provided no proof of greater or lesser harm from dipyridamole + ASA with regard to minor and major bleeding. In long-term therapy, the data provided proof of greater harm from dipyridamole + ASA versus ASA / clopidogrel concerning major bleeding; for minor bleeding no proof of greater or lesser harm was shown.

Intracranial bleeding

No data on intracranial bleeding were available in the placebo-controlled studies (short-term and long-term therapy). In the short-term studies comparing dipyridamole + ASA with ASA, no statistically significant difference between treatment options was shown (RD [95% CI] in the meta-analysis: 0.00 [-0.01; 0.01]). In the long-term studies comparing dipyridamole + ASA with ASA / clopidogrel a statistically significant difference was shown to the disadvantage of dipyridamole + ASA (HR [95% CI] in the meta-analysis: 1.38 [1.09; 1.75]). In short-term therapy, the data provide no proof of greater or lesser harm from dipyridamole + ASA versus ASA. In long-term therapy, a statistically significant difference to the disadvantage of dipyridamole + ASA was shown compared to ASA / clopidogrel. The investigation of effect modifiers for this outcome demonstrated different effects in different age groups (see the section “Subgroup characteristics and other effect modifiers” further below).

Overall rates of adverse events

In the short-term study no statistically significant difference between dipyridamole + ASA and placebo was shown for overall AE rates ($p = 0.221$). The placebo comparison in the long-term study showed a statistically significant difference to the disadvantage of dipyridamole + ASA ($p < 0.001$). In the comparison of overall AE rates under dipyridamole + ASA with those under ASA, a statistically significant difference between treatment options was shown for the short-term studies to the disadvantage of dipyridamole + ASA (OR [95% CI] in the meta-analysis: 2.28 [1.62; 3.22]). The meta-analysis comparing dipyridamole + ASA with ASA (2 long-term studies) produced a heterogeneous result ($p < 0.2$). However, both individual studies showed a statistically significant difference to the disadvantage of

dipyridamole + ASA (OR [95 % CI] in the individual studies: 1.18 [1.03; 1.36] and 1.96 [1.03; 3.70]).

The data provide no proof of harm from short-term therapy with dipyridamole + ASA for the outcome “overall AE rates”. In long-term therapy the data provide an indication of harm from dipyridamole + ASA. The comparison with ASA provided proof of greater harm from short- as well as long-term therapy with dipyridamole + ASA in respect of overall AE rates.

Overall rates of serious adverse events

No statistically significant difference between dipyridamole + ASA and placebo was shown in the short-term study ($p = 0.504$). In the placebo comparison of the long-term study no data on overall SAE rates could be utilized, as only the number of overall SAEs per treatment group was available, and not the number of patients with SAEs. However, the number of overall SAEs was comparable (dipyridamole + ASA vs. placebo: 240 vs. 254). The meta-analysis comparing dipyridamole + ASA with ASA in short-term studies showed no statistically significant difference between treatment options (RD [95 % CI] in the meta-analysis: 0.00 [-0.03; 0.04]).

With regard to the results of the long-term studies including ASA / clopidogrel as a control, the risk of bias on an outcome level was assessed as high for one study included (PRoFESS), as data inconsistency was noted between the populations described in the study report. Analyses were performed with both sets of data. In each case, no statistically significant difference in overall SAE rates was shown versus ASA / clopidogrel in long-term therapy (OR [95 % CI] of the meta-analyses: 0.94 [0.89; 1.00] and 1.01 [0.95; 1.07]). The result does not conflict with the data described above on major and intracranial bleeding (in each case statistically significant differences to the disadvantage of dipyridamole + ASA). It may be assumed that these bleeding events can be allocated to the SAEs; however, for the overall SAE rate the effect is attenuated. Overall, about 4% of patients experienced major bleeding, whereas about 25% experienced an SAE of some sort.

In summary, for the outcome “overall rates of SAEs” the data provide no proof of harm from dipyridamole + ASA. The comparison with ASA (short-term therapy) or ASA / clopidogrel (long-term therapy) provided no proof of greater or lesser harm from dipyridamole + ASA.

Study discontinuations due to adverse events

In the short-term study, no statistically significant difference between dipyridamole + ASA versus placebo was shown for discontinuation rates due to AEs ($p = 0.118$). The placebo comparison in the long-term study showed a statistically significant difference to the disadvantage of dipyridamole + ASA ($p < 0.001$). Both meta-analyses of the active comparisons (short- and long-term studies with dipyridamole + ASA versus ASA, and dipyridamole + ASA versus ASA / clopidogrel) showed a heterogeneous result ($p < 0.2$). In

this context, for the comparison of treatment options in the short-term studies the assessment of individual results was helpful.

No event occurred in the very small AGATE study (RD [95 % CI] in the individual study: 0.00 [-0.09; 0.09]). For the EARLY study a statistically significant difference was shown to the disadvantage of dipyridamole + ASA (RD [95% CI] in the individual study: 0.08 [0.04; 0.11]). Overall this was regarded as providing some evidence of a disadvantage of dipyridamole + ASA. In respect of the long-term studies, 2 of the 3 studies (ESPS-2 and PRoFESS) showed a statistically significant difference to the disadvantage of dipyridamole + ASA. One study (JASAP) did not provide a statistically significant result; however, the point estimate also showed a disadvantage for dipyridamole + ASA (OR [95% CI] in the individual studies: 2.02 [1.62; 2.51], 1.65 [1.52; 1.79], and 1.25 [0.97; 1.61]). Overall the information basis was regarded as evidence of an inferiority of dipyridamole + ASA. For all statistically significant results, a sensitivity analysis excluding discontinuations due to headache did not provide results qualitatively different from the overall analysis. The conclusions on this outcome were therefore determined on the basis of the overall analyses.

In summary, for the outcome “discontinuation rates due to AEs”, the data provided no proof of harm for short-term therapy with dipyridamole + ASA; for long-term therapy the data provided an indication of harm. For short-term therapy the data provided an indication of greater harm from dipyridamole + ASA versus ASA. The results for long-term therapy showed proof of greater harm from dipyridamole + ASA versus ASA / clopidogrel.

Health-related quality of life

The data available for the operationalization of this outcome referred to the quality-of-life instrument EQ-5D, for which data from a long-term study were available. In the comparison of dipyridamole + ASA with clopidogrel, this study showed a statistically significant difference to the disadvantage of dipyridamole + ASA ($p = 0.007$). In this context, the risk of bias on an outcome level was assessed as high, since the proportion of patients who had not been considered in the analysis at all (“unconsidered proportion”) was classified as being inappropriately high. A conclusion with sufficient certainty of results with regard to the outcome concerned was therefore not possible, and the data provided no proof of an additional benefit of dipyridamole + ASA for health-related quality of life.

Subgroup characteristics and other effect modifiers

The majority of available data on subgroup characteristics did not show different effects in subgroups. In some cases, different effects were suggested or demonstrated. However, with one exception, this did not change the overall conclusion. The exception referred to a result for age subgroups with regard to the outcome “intracranial bleeding” in the long-term PRoFESS study, which included the control clopidogrel (age classification: $< 65, \geq 65$ to $< 75, \geq 75$ years). The results showed a p-value of 0.046 across all 3 age groups. The separate pairwise comparisons of the groups < 65 and ≥ 65 to < 75 years, as well as ≥ 65

to < 75 years and ≥ 75 years yielded p-values of 0.059 and 0.678 (OR [95% CI]: < 65: 2.08 [1.39; 3.12], ≥ 65 to < 75: 1.16 [0.74; 1.82], ≥ 75 : 1.01 [0.63; 1.62]). Therefore it can only be assumed for the under 65-year-olds that the effect in this age group was demonstrably different from the effect in the other age groups.

The PRoFESS study had a major impact on the overall treatment effect for the outcome “intracranial bleeding” and no suggestion of an increased risk of bias existed. Therefore, in summary the conclusion for this outcome was divided for long-term therapy with dipyridamole + ASA versus ASA / clopidogrel. The overall information basis showed a statistically significant difference here to the disadvantage of dipyridamole + ASA and therefore provided proof of greater harm from this combination (HR [95% CI] in the meta-analysis: 1.38 [1.09; 1.75]). Due to the above-mentioned data on the effect modification in age groups it could be concluded that this proof of greater harm from dipyridamole + ASA is limited to the age group < 65 years.

Conclusions

There is an indication of a benefit of combination therapy with dipyridamole + ASA in respect of prevention of non-fatal strokes and TIAs in long-term (at least 12 months) treatment. There is no proof that combination therapy reduces mortality. This indication of a benefit is accompanied by indications of harm due to major and minor bleeding, study discontinuations due to AEs, and overall AEs.

There is no proof that combination therapy with dipyridamole + ASA has an additional benefit versus monotherapy with a thrombocyte aggregation inhibitor (ASA or clopidogrel). In this context there is no evidence that this conclusion differs if ASA or clopidogrel alone are assessed as comparator therapy. The lack of an additional benefit is accompanied by proof of greater harm with combination therapy. This greater harm is particularly due to the more frequent occurrence of major bleeding in long-term therapy. This is the result of a primarily medically founded summarizing assessment of dipyridamole + ASA versus the (pooled) controls ASA and clopidogrel. In both cases, a separate comparison with each control produced statistically non-significant results to the (numerical) disadvantage of combination therapy, which, however, became statistically significant in the pooling of the (non-heterogeneous) data.

In addition, patients under 65 years of age experienced more intracranial bleeding events (versus clopidogrel). The data do not provide proof that other SAEs occur more often with dipyridamole + ASA than with ASA or clopidogrel. In addition, the data provide an indication (in short-term therapy) and proof (in long-term therapy) that study discontinuations due to AEs are more common with combination therapy.

Keywords: aspirin; ASA; dipyridamole; aspirin, dipyridamole drug combination; brain infarction; secondary prevention; isch(a)emic attack, transient; systematic review

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