Short- versus Long-term Dual Anti-platelet Therapy (DAPT) in Secondary Prevention for Ischaemic Stroke – A Network Metanalysis

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Abstract

Aim

This review aimed to compare the efficacy and safety of short-term (=< 3 months) and long-term (>=1 year) dual-antiplatelet therapy (DAPT) in secondary prevention for ischaemic stroke.

Methods and results

We searched MEDLINE, EMBASE (Ovid), PubMed, Cochrane Library, ClinicalTrials.gov and Google Advanced Search for randomised controlled trials. The population consisted of patients with recent ischaemic stroke or transient ischaemic attack. The intervention was DAPT with a combination of aspirin, clopidogrel and dipyridamole compared to either aspirin or clopidogrel in monotherapy. The primary outcome was the rate of all recurrent stroke (ischaemic and haemorrhagic). Secondary outcomes were ischaemic stroke, all bleeding, severe bleeding, all-cause death, cardiovascular death and myocardial infarction. Data were pooled by network metanalysis and pairwise metanalyses.

Sixteen studies with 55,261 participants were included. Compared to aspirin, DAPT with aspirin clopidogrel decreased the risk of recurrent stroke (short-term OR 0.67, 95%CI 0.58-0.77; long-term OR 0.84, 95%CI 0.70-1.01) at the expense of increased risk of bleeding (short-term OR 1.76, 95%CI 1.26-2.46; long-term OR 2.25, 95%CI 1.97-2.57). DAPT with aspirin clopidogrel and clopidogrel in monotherapy had similar long-term risk of recurrent stroke (OR 0.98, 95%CI 0.83-1.14), but DAPT was associated with increased risk of bleeding (OR 2.77, 95%CI 2.21-3.46). Network metanalysis showed that short-term aspirin clopidogrel DAPT had the best risk-benefit profile, followed by long-term aspirin clopidogrel DAPT and clopidogrel alone. Aspirin dipyridamole DAPT was less effective.

Conclusion

Short-term DAPT had better risk-benefit profile than long-term DAPT.

Key words

Stroke; Cerebral infarction; Aspirin; Clopidogrel; Dypiridamole; Dual-antiplatelet therapy

Introduction

Dual anti-platelet therapy (DAPT) with aspirin, clopidogrel or dipyridamole in combination is established in the management of ischaemic stroke. There is however uncertainty on the optimal duration of DAPT for the secondary prevention of stroke.

Guidance from the AHA/ASA (1) supports the use of DAPT for 21 days or for a period of up to 90 days from symptoms onset. The class of recommendation (IIa) and level of evidence (B) are both moderate. The UK NICE guidance (2) is even more vague as it states that people who have had an ischaemic stroke or transient ischaemic attack (TIA) should be treated with clopidogrel or dipyridamol in monotherapy or in combination with aspirin (DAPT) with an “option to continue treatment until they and their clinicians consider it appropriate to stop”.

No trials have compared short vs. long-term DAPT in this context. The rationale of this review was to highlight indirect evidence on the comparative efficacy of short-term vs long-term DAPT by performing a network metanalysis.

The research question and objective were framed as follows (PICOS acronym) (3): in patients with ischaemic stroke or TIA (P = population), short-term DAPT (<3 months), long-term DAPT (>= 1 year) (I = intervention) and monotherapy (either aspirin or clopidogrel) (C = comparison) were evaluated. Prevention of recurrent stroke was the primary efficacy measure (O = outcome). Prevention of ischaemic stroke, all bleeding, severe bleeding, all-cause death, cardiovascular death and myocardial infarction were secondary outcomes. Evidence was derived from randomized controlled trials (RCTs) (S = study design).

Methods

Participants

We identified RCTs with results in English comparing antiplatelet monotherapy vs. DAPT (aspirin, clopidogrel, dipyridamole) in adult (>17 years) patients with a previous ischaemic stroke or transient ischaemic attack (TIA), for the secondary prevention of stroke. Studies of patients receiving intra-arterial treatment, with acute myocardial infarction, coronary artery stenting or coronary artery bypass grafting, with atrial fibrillation, prosthetic heart valves or congenital conditions were excluded.

Interventions

Aspirin clopidogrel and aspirin dipyridamole vs either aspirin or clopidogrel monotherapy were included. Triple antiplatelet treatment, as well as trials evaluating placebo are losing importance in contemporary practice and were excluded.

Outcome measures

The observation and follow-up period had to be >= 7 days, i.e. beyond the immediate management of stroke. Trials were categorized into short-term (treatment and follow-up up to 3 months) and long-term (equal to or longer than 1 year), based on contemporary consensus as in practice guidelines (1). The rate of recurrent stroke was evaluated as primary outcome, including ischaemic, haemorrhagic and fatal and nonfatal stroke. Ischaemic stroke, all-cause death, cardiovascular death and myocardial infarction were secondary efficacy outcomes. All bleeding and severe bleeding were safety outcomes (definitions in **Table S1**). Only RCTs reporting at least one of these clinical outcomes were considered. RCTs reporting only aggregate or surrogate outcomes were excluded.

Electronic searches

MEDLINE, EMBASE (Ovid), PubMed, Cochrane Library, ClinicalTrials.gov were searched for RCTs up to 15 August 2018, with restriction to Human studies in English language. Search strategy/terms are shown in **Table S2**. Google Advanced Search was used for relevant grey literature. References from articles, reviews and study protocols were manually checked.

Selection

Studies were independently searched and selected by two Authors (FP and PA). Cases of disagreement were discussed in consensus involving the other two Authors (MM and SD). References were rejected if it could be determined from the title/abstract that they were not suitable. Full text was obtained in all other cases.

Data extraction

- General: title, authors, report/publication year, duplicate publication
- Participants: total number and number in comparison groups, age, similarity at baseline, losses to follow-up
- Intervention and Comparison: drug name, treatment onset since qualifying stroke, duration of treatment/follow-up, dose
- Outcome: recurrent stroke and secondary outcomes (**Table S1**)

- Study design and characteristics: duration, allocation concealment, blinding, intention-to-treat (ITT) analysis, loss to follow-up

Risk of bias within studies

Within-study risk of bias (4) was assessed according to criteria defined in the Risk of Bias tool (RoB2.0) (5) using free software (RevMan 5.2). Commercial studies were not automatically deemed at high risk. Studies were not rejected on subjective quality criteria other than study design different from RCTs or lack of ITT analysis.

Bias across studies

Bias(es) that may affect the cumulative evidence (publication, selective reporting, industry funding) were evaluated using contour enhanced and comparison-adjusted funnel plots (if >10 studies). The comparison-adjusted funnel plot accounted for the fact that in network metanalysis each set of studies estimated a different summary effect.

Qualitative analysis

Data were extracted as dichotomous variables expressed as event rates in each arm. No studies were cluster randomized trials. The non-pertinent arm in multi-arm RCTs (e.g. placebo arm) was excluded. GRADE criteria were applied to rank the quality of each outcome (6).

Statistical analysis

Network metanalysis was undertaken if participants, treatments and clinical questions were deemed similar enough for meaningful data pooling. The network model was fit using commercial software (STATA/SE 15.0). Relative effect sizes were calculated as odds ratios (ORs) with 95% confidence intervals (CIs). We used a fixed effect model applying only inverse variance (I-V) weighting and a random-effects model weighting using the DerSimonian and Laird (D+L) model to account for heterogeneity. The surface under the cumulative ranking curve (SUCRA) probabilities were used to rank treatments.

The network results were assessed for inconsistency and compared with pairwise metanalyses (applying both fixed effect and random effects models to evaluate heterogeneity). The percentage of variability attributable to heterogeneity was expressed by the I^2 statistic.

Sensitivity analysis was pre-specified to explore if results were sensitive to restriction to low risk of bias studies. A post-hoc analysis evaluated if results were sensitive to the time of treatment onset from the qualifying stroke.

Results

Identification, eligibility and characteristics of the included studies

The initial search (**Table S2**) identified 13,442 outputs. The study selection process **(Figure 1)** followed the PRISMA statement (7). After excluding 5 full-text studies (8-12), 16 RCTs (13-28) with 55,261 patients with previous ischaemic stroke/TIA as qualifying event were included. The number of study participants ranged from 98 to 20,332. The treatment onset period ranged from <12h to 60 months (**Table 1**).

Risk of bias within studies

Six/18 trials were judged at overall low risk of bias, 5/18 at unclear risk, 5/18 at high risk of bias (**Table S3**).

Bias across studies

In the contour enhanced funnel plot **(Figure S1-A)** studies were missing in the middle and lower right area of non-significance, making publication bias or selective outcome bias plausible. The comparison-adjusted funnel plot **(Figure S1-B)** was asymmetric suggesting potential bias from small-study effects in the network.

Qualitative review and pairwise metanalyses

Seven/16 studies were short-term comparisons of DAPT vs monotherapy, 9/16 studies were long-term comparisons. There were no mid-term comparisons providing treatment effects between 3 months and 1 year. According to GRADE criteria (6), the quality of evidence was low for bleeding and moderate for all other outcomes.

Recurrent stroke (**Figure 2**)

Fourteen/16 trials reported on recurrent stroke. Two/16 (ESPRIT, CLAIR) used a combined outcome hence could not be included (**Table 1**). Short DAPT with aspirin clopidogrel was associated with decreased stroke recurrence compared to aspirin (OR 0.67, 95%CI 0.58-0.77; participants = 11,273; studies = 6). CIs were overlapping suggesting consistency (I^2=0%). Long DAPT with aspirin clopidogrel was not more effective than clopidogrel (OR 0.98, 95%CI 0.83-1.14; participants = 7599; MATCH) and findings were only borderline significant for long DAPT with aspirin clopidogrel when compared to aspirin alone (OR 0.84, 95%CI 0.70-1.01; participants = 7,340; studies = 2). No better efficacy was seen for long aspirin dipyridamole compared to aspirin (OR 0.96, 95%CI 0.69-1.33; participants = 5,880; studies = 4) despite high heterogeneity (I^2=64%), nor compared to clopidogrel (OR 1.02, 95%CI 0.93-1.12; participants = 20,332; PROFeSS). The stated pooled ORs were derived from a random-effects model given the likely genuine differences in treatment effects.

Ischaemic stroke (**Figure S2-A**)

Nine/16 trials reported on ischaemic stroke. Short aspirin clopidogrel significantly decreased ischaemic stroke compared to aspirin (OR 0.68, 95%CI 0.58-0.79; participants = 10,510; studies = 4; I^2=0%). Long aspirin clopidogrel was more effective than aspirin (OR 0.79, 95%CI 0.65-0.96; participants = 7,340; studies = 2; I^2=0%), but not more than clopidogrel (OR 0.92, 95%CI 0.79-1.08; participants = 7599; MATCH).

All bleeding (**Figure S2-B)**

Fourteen/16 trials reported on all bleeding. Aspirin clopidogrel DAPT caused increased bleeding: the increase was 2.77-fold for long-term aspirin clopidogrel vs clopidogrel (OR 2.77, 95%CI 2.21-3.46; participants = 7599; MATCH), 2.25-fold for long-term aspirin clopidogrel vs aspirin (OR 2.25, 95%CI 1.97-2.57; participants = 7,340; studies = 2), 1.76-fold for short-term aspirin clopidogrel vs aspirin (OR 1.76, 95%CI 1.26-2.46; participants = 11,178; studies = 6). The trials of aspirin dipyridamole did not report increased bleeding.

Severe bleeding **(Figure S2-C)**

Thirteen/16 trials reported on severe bleeding. Short aspirin clopidogrel was associated with a two-fold increase in severe bleeding compared to aspirin (OR 2.13, 95%CI 1.14-3.98; participants = 10,608; studies = 3). The same was observed for long-term aspirin clopidogrel vs clopidogrel (OR 1.99, 95%CI 1.40-2.81; participants = 7599; MATCH). The other trials did not report increased severe bleeding.

All-cause death, cardiovascular death, myocardial infarction **(Figure S2-D E F)**

Thirteen/16 trials reported on all-cause death, 7 on cardiovascular death, 12 on myocardial infarction. No differences were shown for these outcomes.

Network metanalysis

There was one closed quadrilateral loop (aspirin - long-term aspirin clopidogrel - long-term aspirin dipyridamole - clopidogrel) (**Figure 3**).

The comparison long-term aspirin dipyridamole vs aspirin had the largest contribution in the network (27.9%) (**Figure S3**). The difference between direct and indirect comparisons appeared small (ratio of odds ratio, ROR = 1.001, 95%CI 1.0-1.06) without inconsistency (**Figure S4**).

The indirect comparison aspirin clopidogrel vs aspirin reduced recurrent stroke in the short-term (OR difference -0.03, 95%CI -0.04, -0.01) (**Figure 4**). The direction of effect was the same as in the direct comparisons, the entity was attenuated. For aspirin dipyridamole there was no benefit, also in keeping with direct comparisons. The indirect comparison between short-term and long-term DAPT, i.e. the main research question of this review, did not show evidence in favour of either treatment as the estimates' CIs crossed the line of no effect, suggesting that hypothetical future studies might favour either short or long-term DAPT.

According to the SUCRA hierarchy (**Table 2, Figure 5**), short-term aspirin clopidogrel displayed the best risk-benefit profile with the best rank for reducing stroke (probability of 85.7%) and the 4th rank for avoiding all bleeding (37.9%). Long-term aspirin clopidogrel was 2nd for efficacy (40.4%) and worst for safety (98.0%). Clopidogrel was 3rd for efficacy (30.7%) but was ranked first to avoid severe bleeding (92.9%).

Sensitivity analyses

Studies at high or unclear risk of bias reported larger effect estimates and wider CIs **(Figure S5-A)**. Patients started on DAPT within 48h of the qualifying stroke had lower recurrence of stroke (OR 0.72, 95%CI 0.60-0.86) compared to patients started at a later time (OR 0.92, 95%CI 0.80-1.06) **(Figure S5-B)**. Random-effects univariate metaregression confirmed the association between recurrent stroke and treatment onset, which became borderline significant after adjusting for risk of bias in individual trials (**Table S4**).

Discussion

Main findings

This network metanalysis aimed to provide evidence-based hierarchies of the efficacy and safety of long-term and short-term DAPT with two drugs among aspirin, clopidogrel and dipyridamole for the secondary prevention of stroke in patients with previous stroke or TIA, using monotherapy with aspirin or clopidogrel as comparison. Although this study did not permit to strongly establish the superiority of a treatment over the other, short-term DAPT with aspirin clopidogrel had better risk-benefit profile (best for efficacy, 4th for safety) compared to long-term aspirin clopidogrel (2nd for efficacy, worst for safety). Long-term monotherapy with clopidogrel alone appeared less effective than DAPT but safer (3rd for efficacy, best for safety against severe bleeding).

Broader landscape

A strength of network metanalysis is the ability to combine direct and indirect evidence about the treatments under evaluation. Previous studies selectively looked at either the short-term or long-term efficacy of anti-platelet treatments. Concerning short-term efficacy, a metanalysis by Wong et al. (29) including 14 RCTs and 9012 patients reported that DAPT was more effective than monotherapy in reducing stroke recurrence in patients with a qualifying stroke in the previous 72hrs, in keeping with this study. A pairwise metanalysis by Hao et al. (30) included 3 RCTs and 10447 patients, who were given either DAPT with aspirin clopidogrel or aspirin within 24hrs from the qualifying stroke and were followed-up for 3 months. This study too found that DAPT was more effective than monotherapy in preventing recurrent stroke especially within 21 days of randomisation.

Concerning long-term efficacy, a metanalysis by Lee et al. (31) of 7 RCTs and 39,574 patients reported that DAPT lasting more than 1 year was not associated with reduced risk of recurrent stroke but with higher risk of bleeding compared with clopidogrel in monotherapy.

A network metanalysis by Xie et al. (32) compared several long-term antiplatelet treatments, in the form of DAPT and monotherapy. In that study, long-term DAPT with aspirin clopidogrel was ranked the best type of DAPT and outperformed long-term aspirin dipyridamole, in keeping with this study. In contrast to this study, Xie et al. (32) did not evaluate short-term DAPT and included long-term treatment with a larger number of monotherapy drugs. Particularly trials of cilostazol were included, a drug licensed in China and East Asia but not in the US and Europe. The efficacy and safety of cilostazol were tested in East Asian patients, a group at increased risk of stroke, but not in Western populations. The excellent efficacy of cilostazol found by Xie et al. (32) was not generalizable to other populations and countries therefore was not included in this review.

A pairwise metanalysis by Zhang et al. (33) included 8 RCTs and 20,728 patients. DAPT with aspirin clopidogrel was stratified according to short- or long-term duration. Long-term DAPT was not more effective than short-DAPT in the prevention of stroke. The pairwise metanalyses and treatment ranking performed in the present study updated, extended and confirmed the findings by Zhang et al. (33).

Assumptions and limitations

This study had limitations calling for caution in interpretation. Some may be related to clinical assumptions, definitions and consequent heterogeneity. Some limitations may be due to biases.

We made two important assumptions. Firstly, this review included short-term effects of short-term treatments derived from short follow-up studies and compared them with long-term effects of long-term treatments derived from long follow-up studies. Long follow-up studies in patients receiving short-term treatment were unavailable.

While this review aimed to overcome such a constraint due to the unavailability of directly observed data, findings should be interpreted with caution.

Secondly, this review focused on comparing short-term vs long-term DAPT. Monotherapy was assumed inferior to DAPT, in keeping with contemporary clinical practice (1). Previous metanalyses (29, 34) suggested that it was the number of drugs (in terms of two drugs vs one - not which one) to determine efficacy. This study did not compare monotherapies between themselves or long vs short monotherapy. Studies were coded based on short or long DAPT duration, drug combination (among aspirin, clopidogrel, dipyridamole) and monotherapy drug used as comparison (either aspirin or clopidogrel). The duration of the latter (which depended on trial's follow-up period) was not coded. This allowed the formation of one closed loop in the network.

We also acknowledge some potential bias(es). Studies at high or unclear risk of bias reported higher effect estimates. Publication bias appeared plausible, although it did not occur more often in commercial studies. Spuriously inflated effects in small studies, heterogeneity according to study size (e.g., intervention more intense, patients sicker in small studies), artefacts or chance may also have caused bias (35).

The time of treatment onset was a likely explanation for heterogeneity. While some studies had instated DAPT within 48h of the qualifying stroke, leading to better efficacy in stroke prevention, some had lenient inclusion criteria and allowed treatment to be instated in participants up to 60 months after the qualifying stroke.

Despite relatively narrow age range (63-70 years), differences in trial populations could not be excluded. The studies' publication dates spanned from 1983 to 2018. Some studies had geographic origin which may have conferred increased risk (e.g., JASAP was a Japan-only study). It was plausible that definitions for clinical events and states for patients, determining eligibility and outcomes, varied over time or were applied more or less stringently. It is exemplary that much less heterogeneity was found for outcomes such as "myocardial infarction" compared to "bleeding" for instance, as the definition of "bleeding" could have been less standardized in the different studies. The dose of certain medications (notably aspirin) varied, also reflecting changes over four decades. Changes in treatment of important comorbidities may have played a role as effect modifier, for instance more intense uptake of statins and anti-hypertensive drugs with effect on cardiovascular events.

In this network metanalysis there was one quadrilateral loop and two edges consisted of single studies. The high contribution to the network by aspirin dipyridamole vs aspirin trials may be suboptimal. The inclusion of clopidogrel vs aspirin trials would introduce closed triangular loops which may lend balance and strength to the network, potentially making it more informative. Comparing monotherapies however was not of primary interest in this work.

Policy implication and future perspective

This study is not a call for clinicians and policy making bodies to change clinical practice and practice guidelines. Short-term DAPT remains the recommended first choice for the secondary prevention of stroke. Although evidence was of mixed quality, long-term DAPT with aspirin clopidogrel was ranked worse. Whether the same findings would be generalizable to other populations or groups, e.g. very high-risk patients, patients at increased risk of bleeding, elderly patients over 80 years, diabetic patients, etc. was not answered by this review. The call for clinicians to make decisions based on an individual patient's needs, prioritizing stroke prevention or avoidance of bleeding probably remains appropriate in light of these findings.

A prospective RCT comparing long vs short-term DAPT may be onerous and clinically not justified in light of these findings. Likely, ongoing antiplatelet treatment studies harvesting pharmacogenomics data (CYP450,

genes involved in platelet reactivity etc.) will offer insights to improve the prioritization of treatment regimen in each patient (“personalised medicine”) based on their individual risk profile.

Conclusion

This study showed that DAPT in secondary prevention for stroke offered the best protection over monotherapy in the first 3 months, at the expense of increased risk of bleeding. This strategy appeared superior compared to the continuation of DAPT beyond the first 3 months, when monotherapy with clopidogrel had acceptable efficacy but better protection from severe bleeding.

Acknowledgements

FP has received scholarship support from the European Society of Cardiology (ESC) towards the joint ESC-LSE Executive Master in Health Economics, Outcomes and Management in Cardiovascular Science.
This work forms part of the translational portfolio of the NIHR Cardiovascular Research Centre at Barts, which is supported and funded by the NIHR.
Other Authors: no disclosures.

Conflicts of interest: none declared

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Figure legends

Figure 1. Study selection process

Figure 2. Pairwise metanalyses for recurrent stroke (primary efficacy outcome) by treatment comparisons addressed in the included studies

Fixed effect metanalysis with inverse variance (I-V) weighting and random-effects metanalysis applying the DerSimonian and Laird (D+L) model were reported. The percentage of variability across studies attributable to heterogeneity was expressed by the I^2 statistic. Given the low power of the method, data were considered heterogenous if p was less than 0.10. An I^2 statistic of 0% to 25% might not be important, 25 to 50% may represent moderate heterogeneity, 50% and above indicates considerable heterogeneity.

Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; OR odds ratio
Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)

Figure 3. Network plot of treatment comparisons for recurrent stroke (primary efficacy outcome)

The quantity and quality of evidence are shown through weighting and colouring.
The size of the nodes and the thickness of the edges correspond to the number of studies addressing each direct comparison (total for this outcome n = 14):
AC short vs A = 6 studies
AC long vs A = 2 studies
AC long vs C = 1 study
AD long vs A = 4 studies
AD long vs C = 1 study

The colour of the edges represents the mean overall risk of bias in the corresponding comparison (green = low risk of bias; yellow = some concerns/unclear risk of bias).

Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole

Two studies (ESPRIT, CLAIR) reported on several outcomes of interest but not on recurrent stroke.
The network for all outcomes (total n = 16) included the following:
AC short vs A = 7 studies
AC long vs A = 2 studies
AC long vs C = 1 study
AD long vs A = 5 studies
AD long vs C = 1 study

Figure 4. Estimated differences in treatment effect (OR difference) for recurrent stroke (primary efficacy outcome) from network metanalysis (interval plot)

Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole

Figure 5. Cumulative probability and probability of SUCRA ranking curves for all outcomes. Also refer to Table 2.

Supplemental figure legends

Figure S1-A B. Bias across studies

A funnel plot is a scatterplot of the study effect size versus a measure of its precision. In order to extend the use funnel plots in network meta-analysis, we accounted for estimate effects that were derived from different sets of comparisons. All observed sets of comparisons were reported (36).
The contour enhanced funnel plot **(A)** showed studies were missing in the middle and lower right area of non-significance, making publication bias or selective outcome bias plausible. Asymmetry of the comparison-adjusted funnel plot **(B)** also suggests potential bias from small-study effects in the network.

Figure S2-A. Pairwise metanalyses for ischaemic stroke by treatment comparisons addressed in the included studies

Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)
Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)

Figure S2-B. Pairwise metanalyses for all bleeding by treatment comparisons addressed in the included studies

Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)
Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)

Figure S2-C. Pairwise metanalyses for severe bleeding by treatment comparisons addressed in the included studies

Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)

Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)

Figure S2-D. Pairwise metanalyses for all-cause death by treatment comparisons addressed in the included studies

Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)
Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)

Figure S2-E. Pairwise metanalyses for cardiovascular death by treatment comparisons addressed in the included studies

Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)
Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)

Figure S2-F. Pairwise metanalyses for myocardial infarction by treatment comparisons addressed in the included studies

Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)
Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)

Figure S3. Contribution plot for recurrent stroke (primary efficacy outcome) in the network

The size of the squares is proportional to the percent contribution of the direct comparison defining the column, to the network estimate of the row

Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole

Figure S4. Difference between direct and indirect effect estimates for recurrent stroke in the quadrilateral loop in the network (aspirin – long-term aspirin clopidogrel – long term aspirin dipyridamole – clopidogrel) (inconsistency plot). The included treatment comparisons did not provide closed triangular loops.

Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; ROR ratio of odds ratios

Figure S5-A. Sensitivity analysis for recurrent stroke (primary efficacy outcome). Pairwise metanalysis by risk of bias at the study level

Abbreviations: OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)
Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)

Figure S5-B. Sensitivity analysis for recurrent stroke (primary efficacy outcome). Pairwise metanalysis by time of treatment onset since qualifying stroke event

Abbreviations: OR odds ratio; I-V inverse variance weighting (fixed effect model); D+L DerSimonian and Laird weighting (random-effects model)
Note: intervention = DAPT (AC or AD); control = monotherapy (A or C)

Tables

Table 1. Characteristics of the included studies

Serial	Study ID	Population	Comparison	N per arm	Mean age	Follow-up	Onset	Dose	RCT features	Funding
1	AICLA 1983 (1)	TIA/ischaemic stroke	A vs AD	198/202	63/63	36 months	12 months	A (3x300mg) vs [A (3x300mg) + D (3x75mg)]	Double blind, multiarm, loss to F/U 11%, ITT	Boehringer-Ingelheim
2	ACCSG 1985 (2)	TIA	A vs AD	442/448	63	25 months*	3 months	A (4x325mg) vs A (4x325mg) + D (4x75mg)	Double blind, loss to F/U 4%, ITT	Boehringer-Ingelheim
3	ESPS2 1996 (3)	TIA/ischaemic stroke	A vs AD	1649/1650	67/67	24 months	3 months	A (2x25mg) vs [A (2x25mg) + D (2x200mg)]	Double blind, multiarm, loss to F/U 0.64%, ITT	Boehringer-Ingelheim
4	MATCH 2004 (4)	TIA/ischaemic stroke	AC vs C	3979/3802	66/66	18 months	3 months	[A (75mg) + C (75mg)] vs C (75mg)	Double blind, loss to F/U 4%, ITT	Sanofi, Bristol Myers-Squibb
5	CARESS 2005 (5)	TIA/stroke and >=50% carotid stenosis (Doppler)	AC vs A	51/56	66/63	0.25 month	3 months	[A (75mg) + C (75mg)] vs A (75mg)	Double blind, loss to F/U 0% for extracted endpoint, ITT	Sanofi, Bristol Myers-Squibb
6	ESPRIT 2006 (6)	TIA/ischaemic stroke	AD vs A	1363/1376	63/63	42 months	6 months	A [(30 to 325mg) + D (2x200mg)] vs A (30 to 325mg)	Not blinded, open label, multiarm, loss to F/U <1%, ITT/post-hoc	non-commercial
7	FASTER 2007 (7)	TIA/ischaemic stroke	AC vs A	98/95	69/70	3 months	24 hours	A [(81mg) + C (75mg)] vs A (81mg)	Double blind, multiarm, loss to F/U <1%, ITT	non-commercial/Astra
8	PROFeSS 2008 (8)	Ischaemic stroke	AD vs C	10181/10151	66/66	30 months	6 months	A [2x25mg) + D (2x200mg)] vs C (75mg)	Double blind, loss to F/U 0.6%, ITT	Boehringer-Ingelheim
9	CLAIR 2010 (9)	TIA/stroke and >=50% carotid stenosis(Doppler)	AC vs A	47/53	59/56	0.25 month	7 days	[A (75 to 160mg) + C (75mg)] vs A (75 to 160mg)	Single blind, open label, blinded endpoint, loss to F/U 10%, modif ITT	non-commercial
10	CHARISMA 2011 (10)	TIA/ischaemic stroke	AC vs A	2157/2163	65/65	25 months [a]	60 months	[A (75 to 162mg) + C (75mg)] vs A (75 to 162mg)	Double blind, loss to F/U not stated, ITT	Sanofi
11	JASAP 2011 (11)	Ischaemic stroke	AD vs A	655/639	66/66	15 months	6 months to 1 week	A [2x25mg) + D (2x200mg)] vs A (81mg)	Double blind, loss to F/U <1%, ITT	Boehringer-Ingelheim
12	SPS3 2012 (12)	Ischaemic stroke	AC vs A	1517/1503	63/63	41 months [a]	6 months	[A (325mg) + C (75mg)] vs A (325mg)	Double blind, loss to F/U 13%, ITT	non-commercial
13	CHANCE 2013 (13)	TIA/ischaemic stroke	AC vs A	2584/2586	63/62	3 months	24 hours	A [(75 to 300mg) [b] + C (75mg)] vs A (75 to 300mg)	Double blind, loss to F/U 6% and 7%, ITT	non-commercial
14	Yi X, 2014 (14)	Ischaemic stroke	AC vs A	284/286	70/70	1 month	48 hours	A [(200mg) [c] + C (75mg)] vs A (200 to 100mg)	Blinding not specified, loss to F/U <1%, ITT	non-commercial
15	COMPRESS 2016 (15)	Ischaemic stroke (CT or MRI)	AC vs A	174/178	68/67	1 month	48 hours	[A (100mg) + C (75mg)] vs A (100mg)	Double blind, loss to F/U about 7%, ITT	Sanofi,Bristol Myers-Squibb
16	POINT 2018 (16)	TIA/ischaemic stroke	AC vs A	2432/2449	65/65	3 months	12 hours	A [(50 to 325mg) + C (75mg)] vs A (50 to 325mg)	Double blind, loss to F/U about 7%, ITT	non-commercial

[a] median follow-up
[b] A in combination treatment suspended after day 21 and replaced with placebo
[c] A in combination treatment suspended after day 30
Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole
NOTE: Daily aspirin doses varied from 50 to 1300mg. The daily dose of clopidogrel was 75mg. Daily dipyridamole doses varied from 225 to 400mg

Table 1 (continued). Characteristics of the included studies

Serial	Study ID	Recurrent stroke	Ischaemic stroke	All-cause death	CV death	MI	All bleeding	Severe bleeding	Moderate/mild bleeding
1	AICLA 1983 (1)	A 17/198; AD 18/202	nr	A 10/198; AD 11/202	nr	A 4/198; AD 3/202	A 7/198; AD 6/202	A 2/198; AD 1/202	A 5/198; AD 7/202
2	ACCSG 1985 (2)	A 60/442; AD 53/448	nr	A 38/442; AD 46/448	nr	A 23/442; AD 25/448	A 32/442; AD 30/448	A 6/442; AD 2/448	A 26/442; AD 28/448
3	ESPS2 1996 (3)	A 206/1649; AD 157/1650	nr	A 182/1649; AD 185/1650	nr	A 39/1649; AD 35/1650	A 135/1649; AD 144/1650	A 20/1649; AD 27/1650	A 115/1649; AD 117/1650
4	MATCH 2004 (4)	AC 339/3797; C 347/3802	AC 309/3797; C 333/3802	AC 201/3797; C 201/3802	AC 124/3797; C 121/3802	AC 73/3797; C 68/3802	AC 289/3797; C 110/3802	AC 96/3797; C 49/3802	AC 193/3797; C 61/3802
5	CARESS 2005 (5)	AC 5/51; A 12/56	AC 0/51; A 4/56	nr	nr	AC 1/51; A 0/56	AC 2/51; A 1/56	AC 0/51; A 0/56	AC 2/51; A 1/56
6	ESPRIT 2006 (6)	nr	AD 96/1363; A 116/1376	AD 93/1363; A 107/1376	AD 44/1363; A 60/1376	nr	nr	AD 35/1363; A 53/1376	nr
7	FASTER 2007 (7)	AC 5/98; A 9/95	nr	nr	nr	nr	nr	nr	nr
8	PROFeSS 2008 (8)	AD 916/10181; C 898/10151	nr	AD 739/10181; C 756/10151	AD 435/10181; C 459/10151	AD 178/10181; C 197/10151	AD 535/10181; C 494/10151	AD 419/10181; C 365/10151	nr
9	CLAIR 2010 (9)	nr	nr	AC 0/46; A 0/52	nr	nr	AC 2/46; A 0/52	AC 0/46; A 0/52	AC 2/46; A 0/52
10	CHARISMA 2011 (10)	AC 105/2157; A 131/2163	AC 91/2157; A 114/2163	nr	AC 56/2157; A 72/2163	AC 43/2157; A 32/2163	AC 807/2157; A 444/2163	AC 41/2157; A 37/2163	AC 51/2157; A 24/2163
11	JASAP 2011 (11)	AD 57/652; A 39/639	AD 45/652; A 32/639	AD 4/652; A 10/639	nr	nr	AD 192/652; A 187/639	AD 26/652; A 24/639	AD 166/652; A 163/639
12	SPS3 2012 (12)	AC 125/1517; A 138/1503	AC 100/1517; A 124/1503	AC 113/1517; A 77/1503	nr	AC 31/1517; A 38/1503	AC 105/1517; A 56/1503	nr	nr
13	CHANCE 2013 (13) [d]	AC 212/2584; A 303/2586	AC 204/2584; A 295/2586	AC 10/2584; A 10/2586	AC 6/2584; A 5/2586	AC 3/2584; A 2/2586	AC 60/2584; A 41/2586	AC 4/2584; A 4/2586	AC 33/2584; A 23/2586
14	Yi X, 2014 (14) [e]	AC 5/284; A 18/286	nr	AC 2/284; A 2/286	nr	AC 3/284; A 3/286	AC 16/284; A 15/286	nr	nr
15	COMPRESS 2016 (15)	AC 3/174; A 5/178	AC 2/174; A 5/178	AC 3/174; A 0/178	AC 1/174; A 0/178	AC 0/174; A 1/178	AC 29/174; A 19/178	AC 7/174; A 2/178	AC 22/174; A 17/178
16	POINT 2018 (16)	AC 116/2432; A 156/2449	AC 112/2432; A 155/2449	AC 18/2432; A 12/2449	AC 6/2432; A 4/2449	AC 10/2432; A 7/2449	AC 61/2432; A 22/2449	AC 21/2432; A 9/2449	AC 40/2432; A 13/2449

Intention-to-treat (ITT) samples used for all outcomes
Abbreviations: A aspirin; C clopidogrel; D dipyridamole; AC aspirin clopidogrel; AD aspirin dipyridamole; nr not reported
[d] CHANCE 2103 and CHANCE 2015 were protocol pre-specified analyses at 3 months and 12 months follow-up, although treatment did not continue beyond 3 months (CHANCE 2015 not included)
[e] Yi 2014 and Wang 2015 were analyses at 1 month and 6 months follow-up, although treatment did not continue beyond 1 month (Wang 2015 not included)

Table 2. Estimated SUCRA probabilities of treatments on primary (efficacy) and secondary (efficacy and safety) outcomes

SUCRA was expressed as a percentage probability that a treatment was ranked first for its efficacy on the outcome, where 100% implies a treatment is certain to be the best, and 0% implies a treatment is certain to be the worst.

	Treatment				
Outcome & rank	Aspirin	Clopidogrel	Short-term aspirin clopidogrel	Long-term aspirin clopidogrel	Long-term aspirin dipyridamole
Recurrent stroke (primary outcome)					
Best	0.0	6.3	**85.7**	5.8	2.2
2nd	3.2	24.7	9.9	**40.4**	21.8
3rd	12.3	**30.7**	3.2	27.1	26.7
4th	23.3	21.7	1.2	20.4	33.6
Worst	61.3	16.6	0.1	6.4	15.6
Ischaemic stroke					
Best	0.0	9.9	77.4	11.3	1.4
2nd	2.0	17.7	14.5	52.9	12.9
3rd	15.9	32.5	7.6	28.9	15.1
4th	47.2	16.8	0.5	6.1	29.4
Worst	34.9	23.0	0.0	0.9	41.2
All bleeding					
Best	40.9	17.7	11.9	0.0	29.4
2nd	37.7	13.3	19.7	0.0	29.3
3rd	18.6	21.8	29.7	0.1	29.9
4th	2.8	46.1	**37.9**	1.9	11.3
Worst	0.0	1.1	0.8	**98.0**	0.1
Severe bleeding					
Best	0.5	**92.9**	0.6	0.2	5.8
2nd	9.3	5.9	5.2	6.3	73.3
3rd	53.1	1.0	13.5	18.6	13.8
4th	31.9	0.3	38.2	23.7	5.8
Worst	5.2	0.0	42.4	51.1	1.3
All-cause death					
Best	20.5	7.9	9.2	2.8	59.5
2nd	36.7	21.4	22.7	3.2	16.0
3rd	26.4	12.1	34.2	7.0	20.3
4th	13.1	49.3	24.1	10.2	3.3
Worst	3.3	9.3	9.7	76.8	0.8
Cardiovascular death					
Best	0.7	11.8	0.2	18.6	68.7
2nd	1.4	52.1	1.2	23.4	21.8
3rd	4.0	31.3	2.8	53.7	8.3
4th	70.4	2.3	25.1	1.5	0.6
Worst	23.4	2.6	70.6	2.8	0.6
Myocardial infarction					
Best	19.1	8.4	6.8	5.6	60.2
2nd	24.3	35.2	18.6	8.3	13.6
3rd	27.1	13.0	22.0	22.6	15.4
4th	24.7	24.1	26.3	17.0	7.9
Worst	4.9	19.3	26.4	46.6	2.9

Table S3_picture part

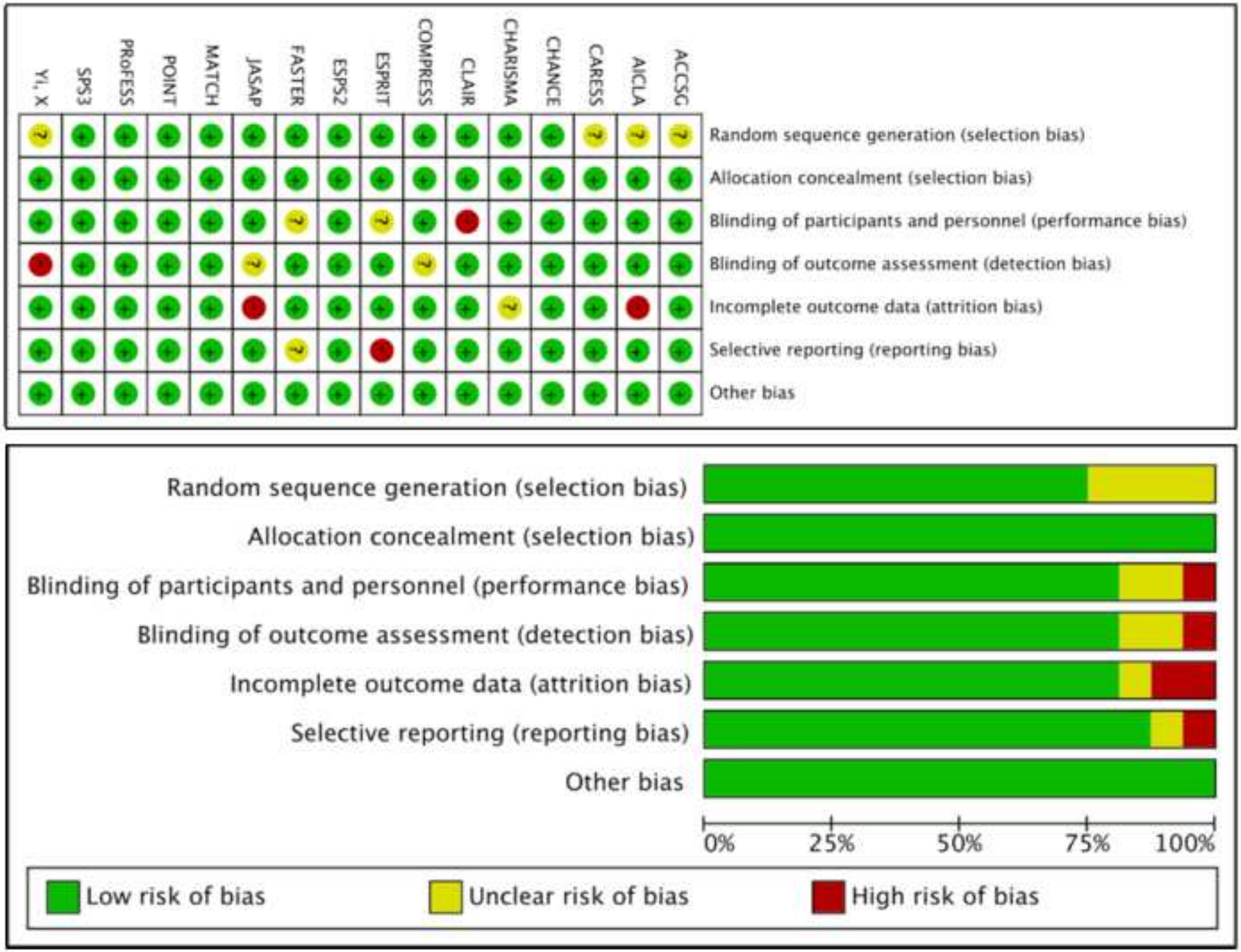


Figure 1

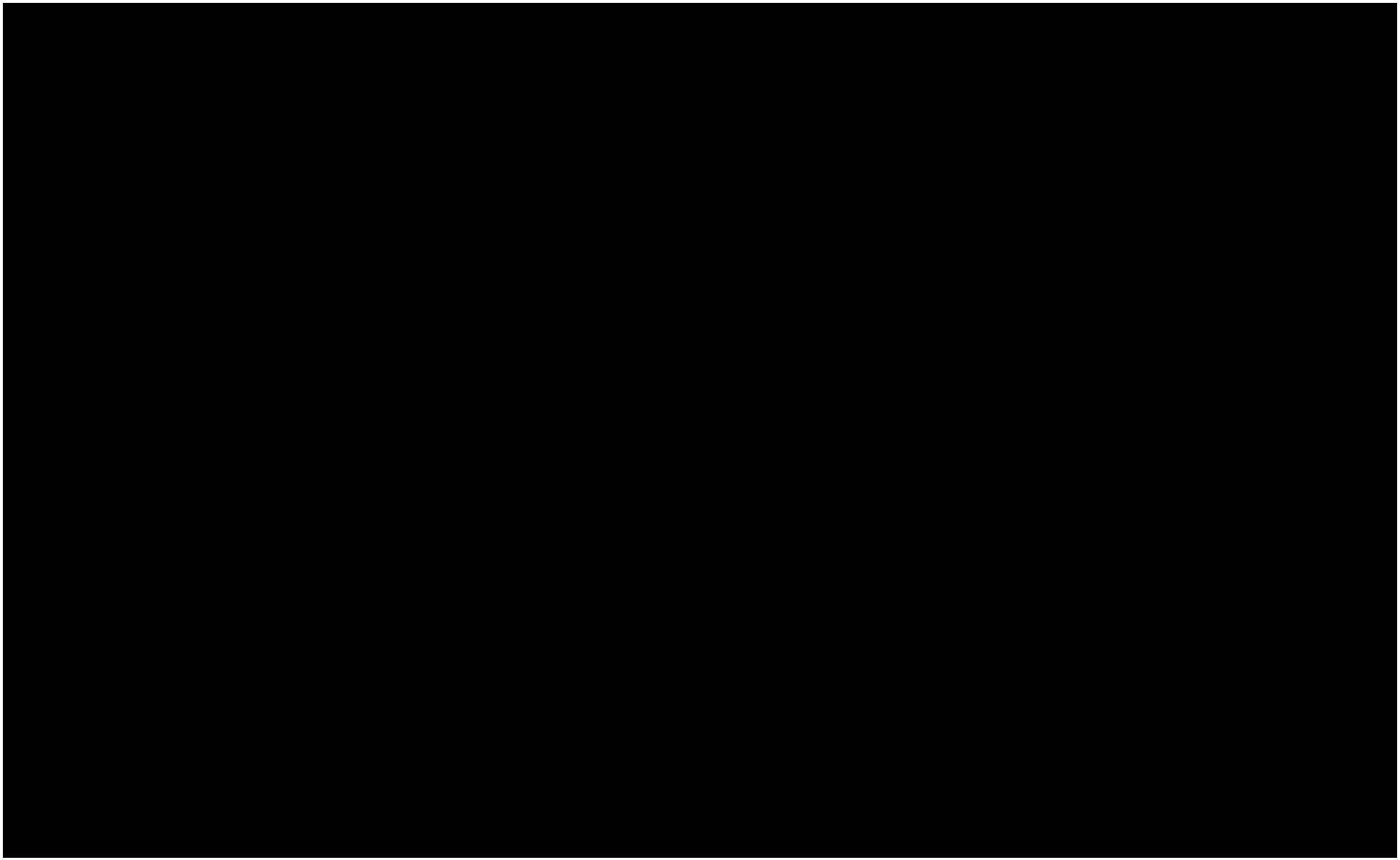


Figure 2

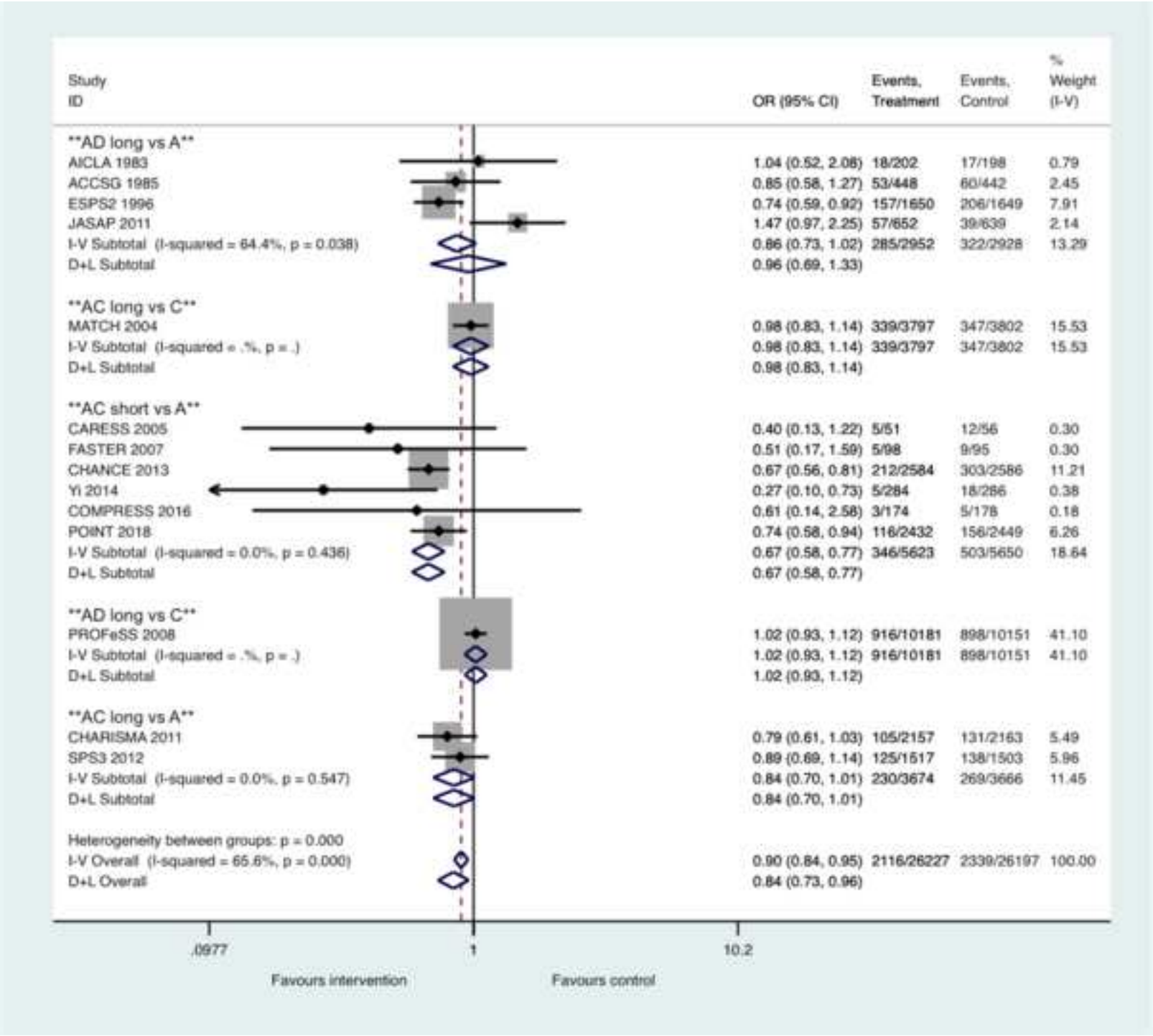

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
AD long vs A
AICLA 1983 1.04 (0.52, 2.08) 18/202 17/198 0.79
ACCSG 1985 0.85 (0.58, 1.27) 53/448 60/442 2.45
ESPS2 1996 0.74 (0.59, 0.92) 157/1650 206/1649 7.91
JASAP 2011 1.47 (0.97, 2.25) 57/652 39/639 2.14
I-V Subtotal (I-squared = 64.4%, p = 0.038) 0.86 (0.73, 1.02) 285/2952 322/2928 13.29
D+L Subtotal 0.96 (0.69, 1.33)
AC long vs C
MATCH 2004 0.98 (0.83, 1.14) 339/3797 347/3802 15.53
I-V Subtotal (I-squared = .%, p = .) 0.98 (0.83, 1.14) 339/3797 347/3802 15.53
D+L Subtotal 0.98 (0.83, 1.14)
AC short vs A
CARESS 2005 0.40 (0.13, 1.22) 5/51 12/56 0.30
FASTER 2007 0.51 (0.17, 1.59) 5/98 9/95 0.30
CHANCE 2013 0.67 (0.56, 0.81) 212/2584 303/2586 11.21
Yi 2014 0.27 (0.10, 0.73) 5/284 18/286 0.38
COMPRESS 2016 0.61 (0.14, 2.58) 3/174 5/178 0.18
POINT 2018 0.74 (0.58, 0.94) 116/2432 156/2449 6.26
I-V Subtotal (I-squared = 0.0%, p = 0.436) 0.67 (0.58, 0.77) 346/5623 503/5650 18.64
D+L Subtotal 0.67 (0.58, 0.77)
AD long vs C
PROFeSS 2008 1.02 (0.93, 1.12) 916/10181 898/10151 41.10
I-V Subtotal (I-squared = .%, p = .) 1.02 (0.93, 1.12) 916/10181 898/10151 41.10
D+L Subtotal 1.02 (0.93, 1.12)
AC long vs A
CHARISMA 2011 0.79 (0.61, 1.03) 105/2157 131/2163 5.49
SPS3 2012 0.89 (0.69, 1.14) 125/1517 138/1503 5.96
I-V Subtotal (I-squared = 0.0%, p = 0.547) 0.84 (0.70, 1.01) 230/3674 269/3666 11.45
D+L Subtotal 0.84 (0.70, 1.01)
Heterogeneity between groups: p = 0.000
I-V Overall (I-squared = 65.6%, p = 0.000) 0.90 (0.84, 0.95) 2116/26227 2339/26197 100.00
D+L Overall 0.84 (0.73, 0.96)
.0977
1
10.2
Favours intervention
Favours control

Figure 3

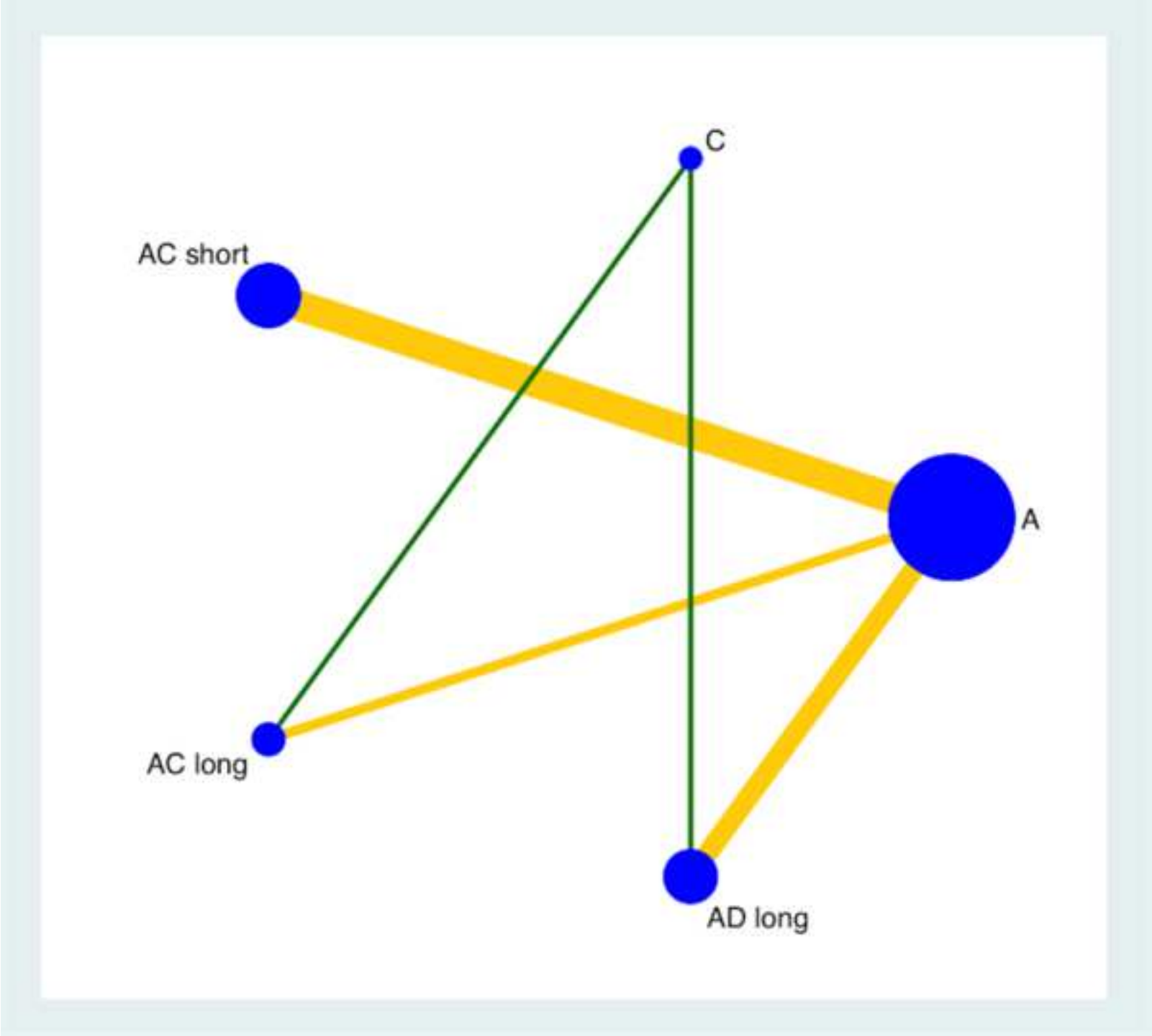


Figure 4

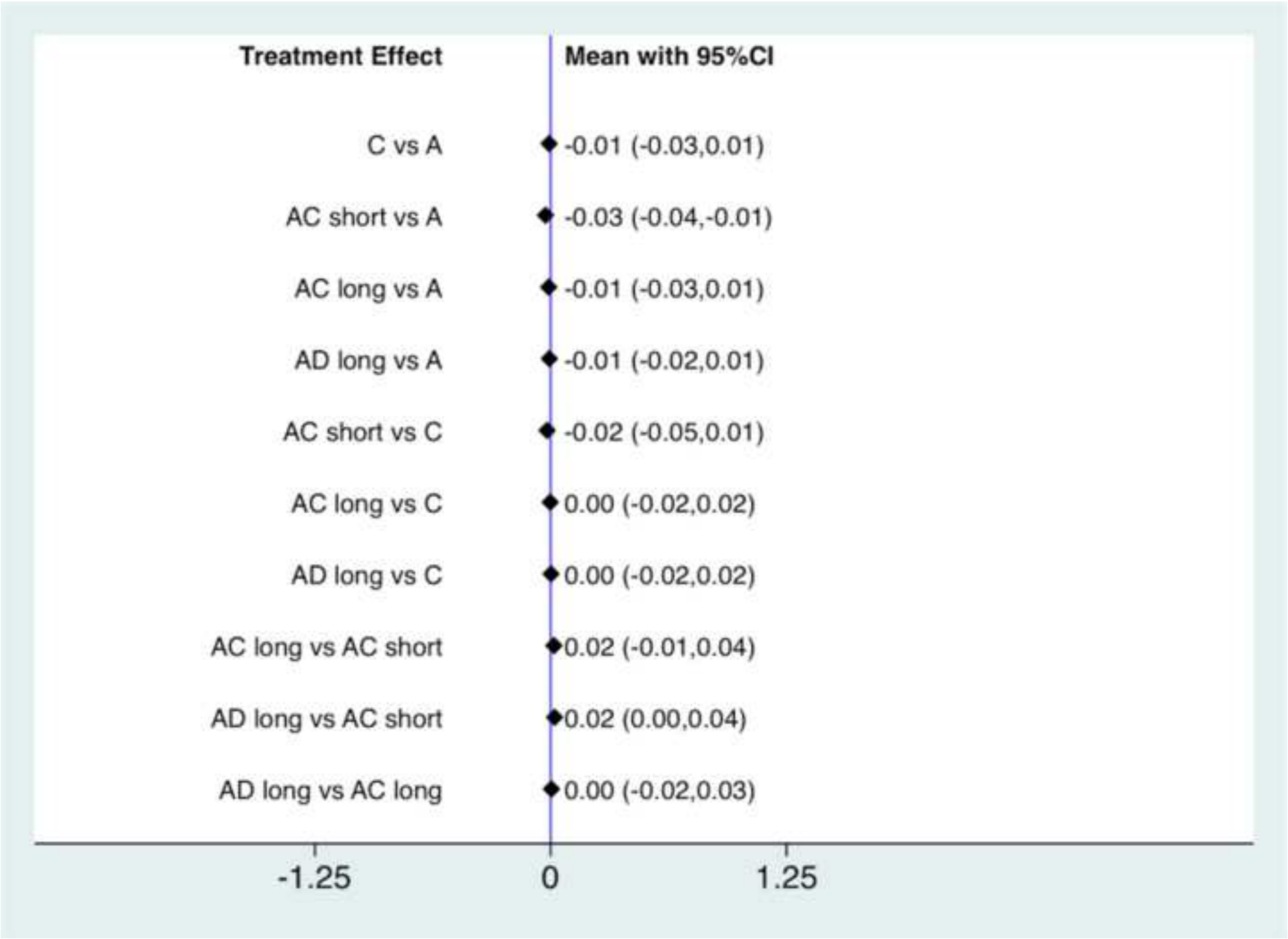

Treatment Effect
Mean with 95%CI
C vs A
-0.01 (-0.03,0.01)
AC short vs A
-0.03 (-0.04,-0.01)
AC long vs A
-0.01 (-0.03,0.01)
AD long vs A
-0.01 (-0.02,0.01)
AC short vs C
-0.02 (-0.05,0.01)
AC long vs C
0.00 (-0.02,0.02)
AD long vs C
0.00 (-0.02,0.02)
AC long vs AC short
0.02 (-0.01,0.04)
AD long vs AC short
0.02 (0.00,0.04)
AD long vs AC long
0.00 (-0.02,0.03)
-1.25
0
1.25

Figure 5

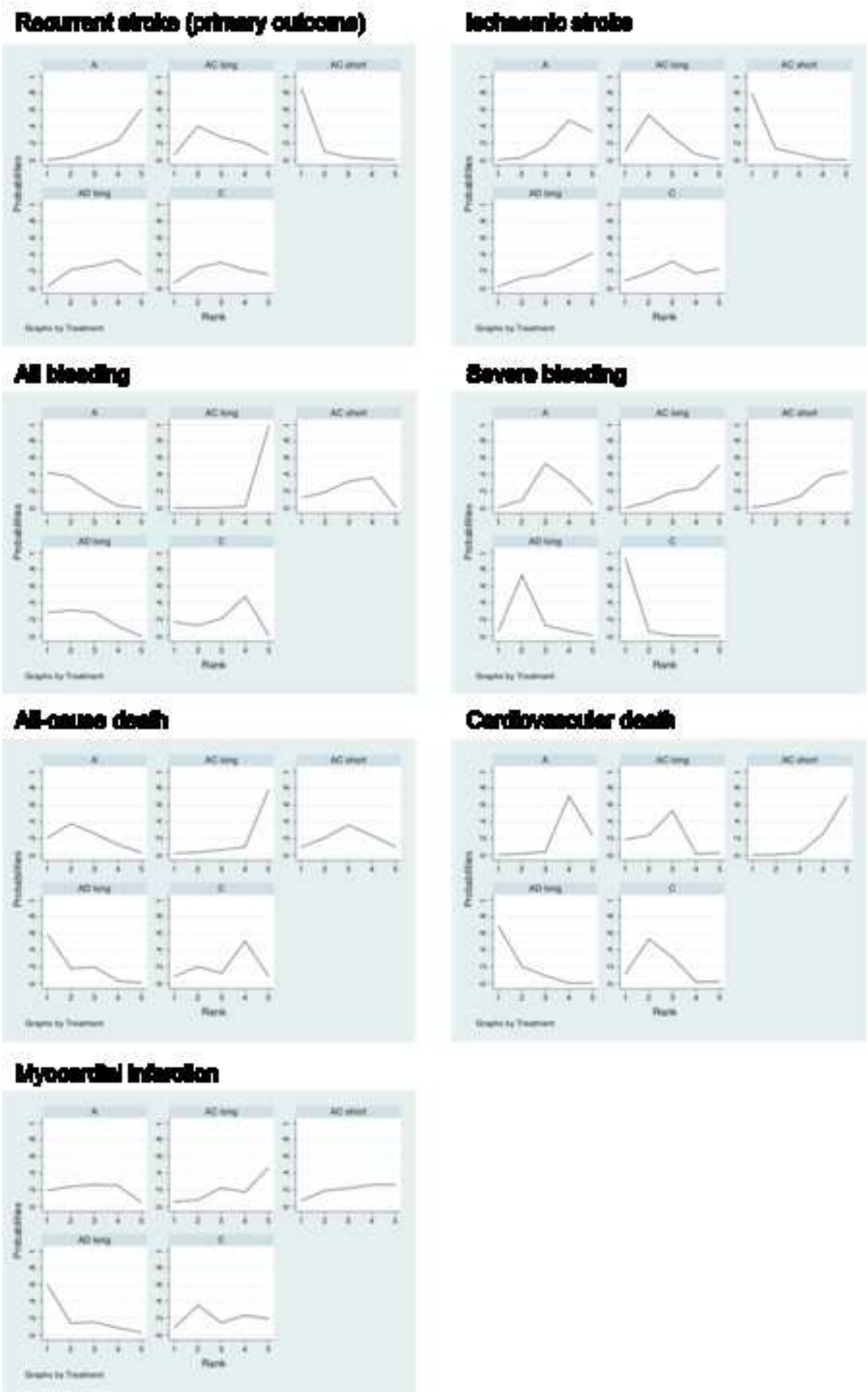

Recurrent stroke (primary outcome)
Ischaemic stroke
All bleeding
Severe bleeding
All-cause death
Cardiovascular death
Myocardial infarction
A
AC long
AC short
AD long
C
Probabilities
Rank
Graphs by Treatment

Figure S1_A

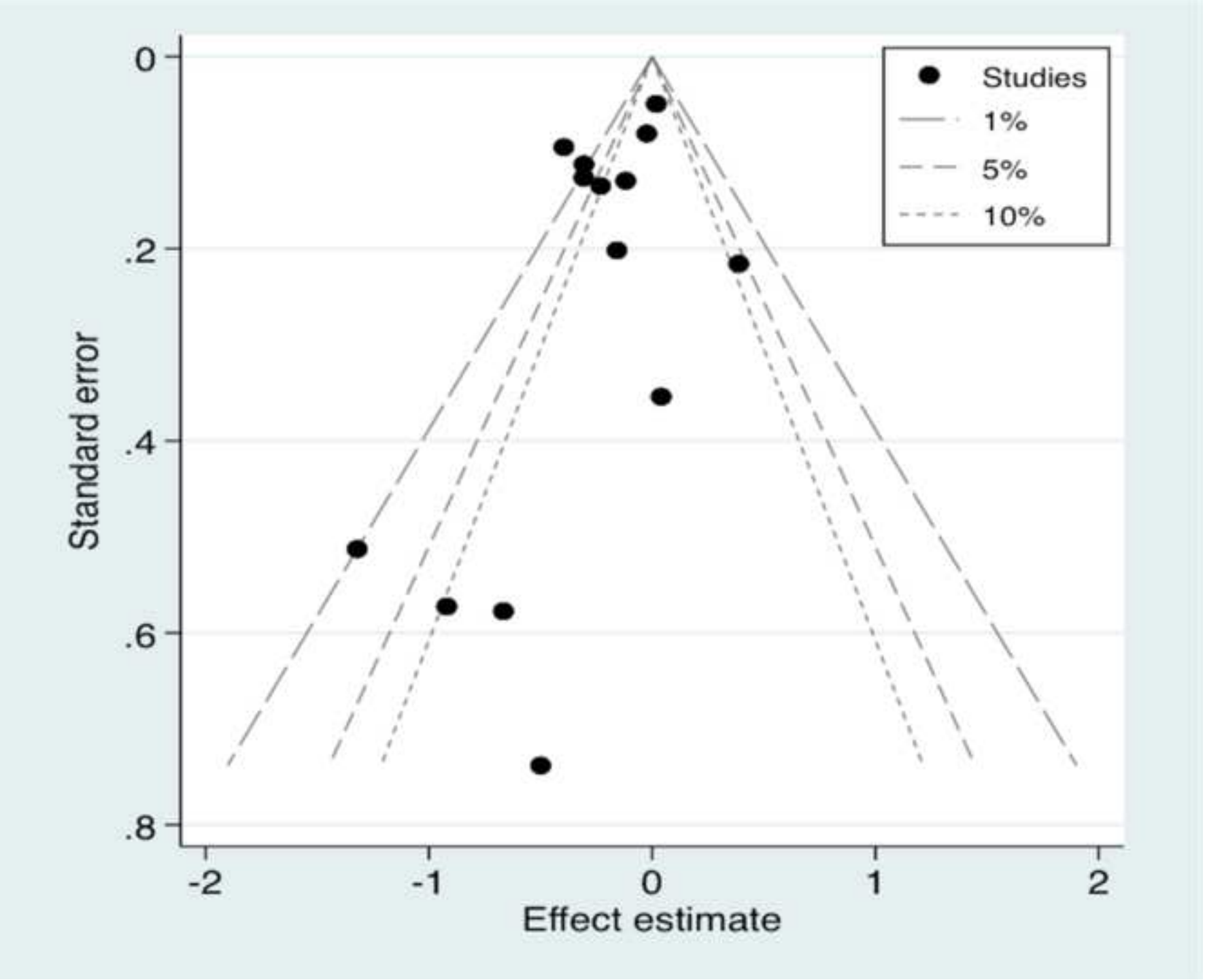


Figure S1_B

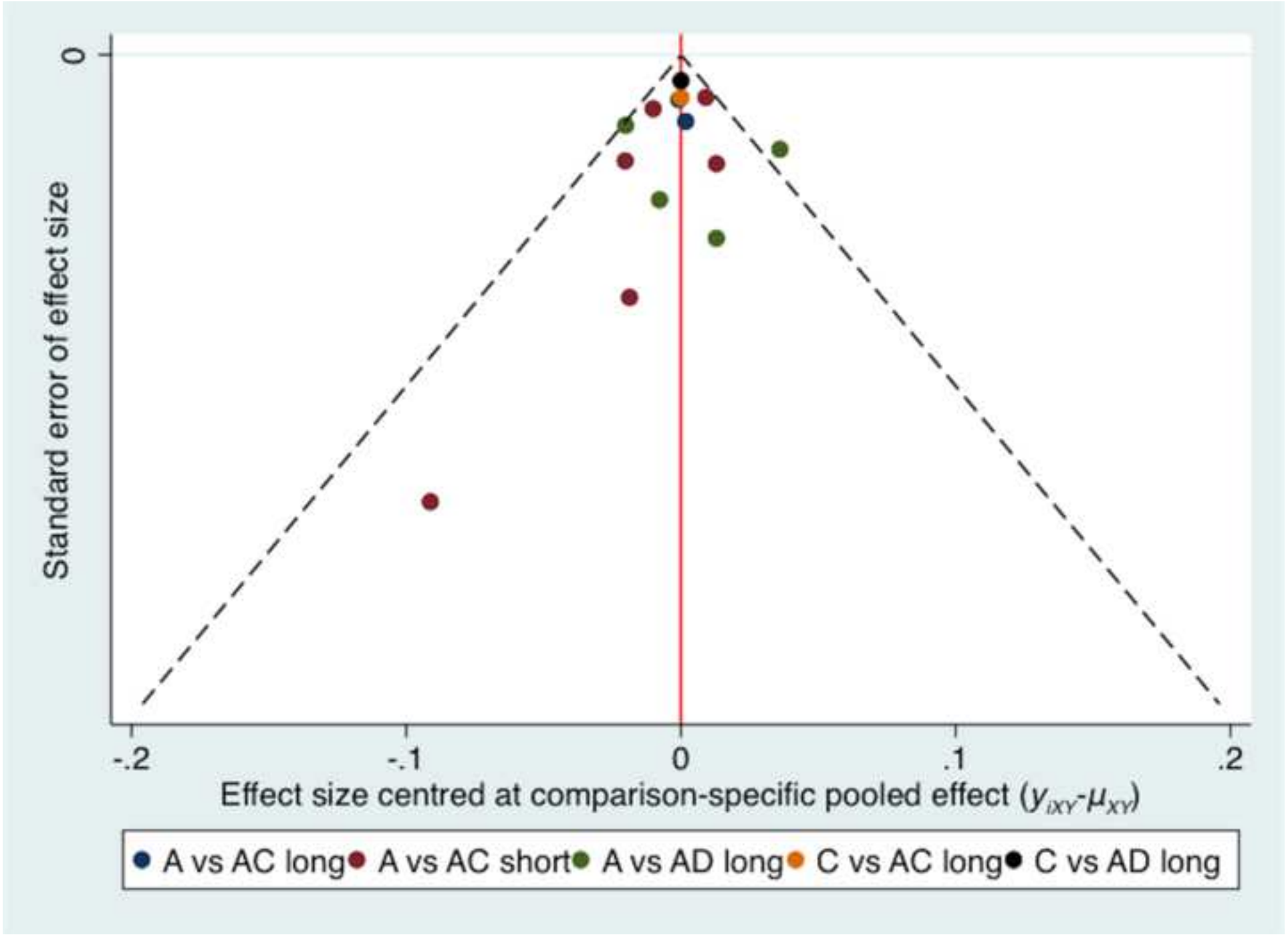

0
Standard error of effect size
-.2
-.1
0
.1
.2
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
A vs AC long
A vs AC short
A vs AD long
C vs AC long
C vs AD long

Figure S2_A

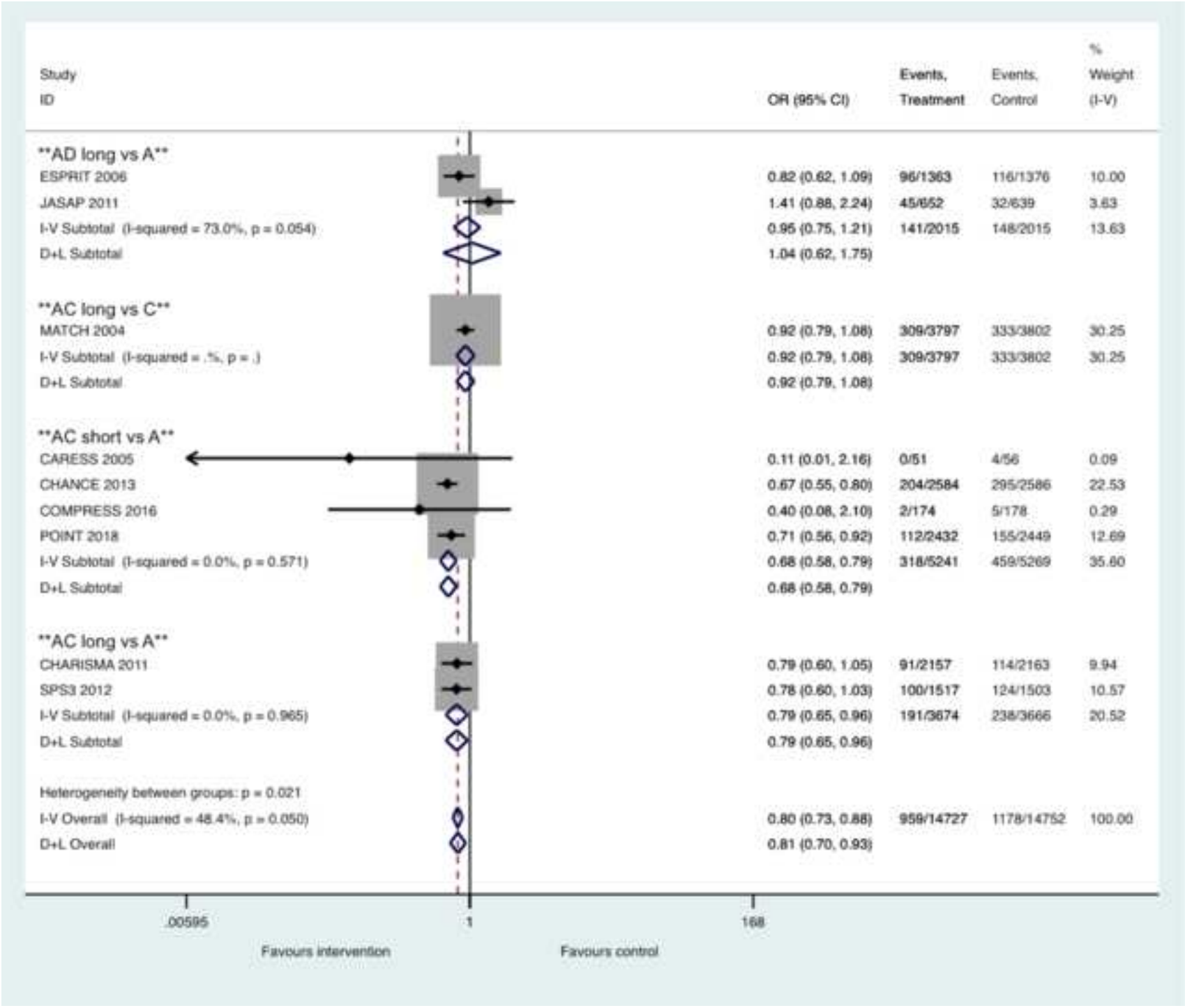

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
AD long vs A
ESPRIT 2006 0.82 (0.62, 1.09) 96/1363 116/1376 10.00
JASAP 2011 1.41 (0.88, 2.24) 45/652 32/639 3.63
I-V Subtotal (I-squared = 73.0%, p = 0.054) 0.95 (0.75, 1.21) 141/2015 148/2015 13.63
D+L Subtotal 1.04 (0.62, 1.75)
AC long vs C
MATCH 2004 0.92 (0.79, 1.08) 309/3797 333/3802 30.25
I-V Subtotal (I-squared = .%, p = .) 0.92 (0.79, 1.08) 309/3797 333/3802 30.25
D+L Subtotal 0.92 (0.79, 1.08)
AC short vs A
CARESS 2005 0.11 (0.01, 2.16) 0/51 4/56 0.09
CHANCE 2013 0.67 (0.55, 0.80) 204/2584 295/2586 22.53
COMPRESS 2016 0.40 (0.08, 2.10) 2/174 5/178 0.29
POINT 2018 0.71 (0.56, 0.92) 112/2432 155/2449 12.69
I-V Subtotal (I-squared = 0.0%, p = 0.571) 0.68 (0.58, 0.79) 318/5241 459/5269 35.60
D+L Subtotal 0.68 (0.58, 0.79)
AC long vs A
CHARISMA 2011 0.79 (0.60, 1.05) 91/2157 114/2163 9.94
SPS3 2012 0.78 (0.60, 1.03) 100/1517 124/1503 10.57
I-V Subtotal (I-squared = 0.0%, p = 0.965) 0.79 (0.65, 0.96) 191/3674 238/3666 20.52
D+L Subtotal 0.79 (0.65, 0.96)
Heterogeneity between groups: p = 0.021
I-V Overall (I-squared = 48.4%, p = 0.050) 0.80 (0.73, 0.88) 959/14727 1178/14752 100.00
D+L Overall 0.81 (0.70, 0.93)
.00595
1
168
Favours intervention
Favours control

Figure S2_B

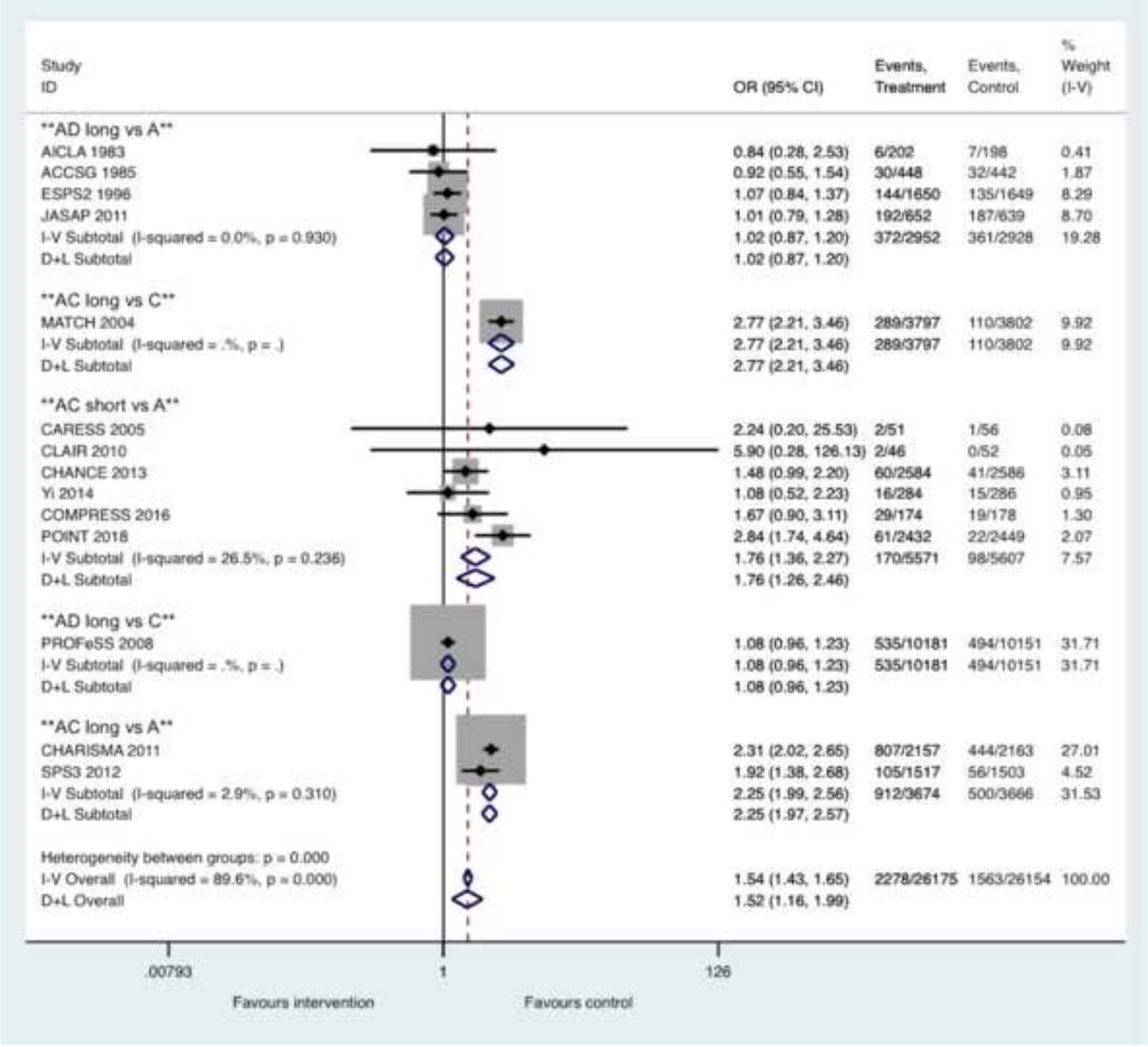

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
AD long vs A
AICLA 1983 0.84 (0.28, 2.53) 6/202 7/198 0.41
ACCSG 1985 0.92 (0.55, 1.54) 30/448 32/442 1.87
ESPS2 1996 1.07 (0.84, 1.37) 144/1650 135/1649 8.29
JASAP 2011 1.01 (0.79, 1.28) 192/652 187/639 8.70
I-V Subtotal (I-squared = 0.0%, p = 0.930) 1.02 (0.87, 1.20) 372/2952 361/2928 19.28
D+L Subtotal 1.02 (0.87, 1.20)
AC long vs C
MATCH 2004 2.77 (2.21, 3.46) 289/3797 110/3802 9.92
I-V Subtotal (I-squared = .%, p = .) 2.77 (2.21, 3.46) 289/3797 110/3802 9.92
D+L Subtotal 2.77 (2.21, 3.46)
AC short vs A
CARESS 2005 2.24 (0.20, 25.53) 2/51 1/56 0.08
CLAIR 2010 5.90 (0.28, 126.13) 2/46 0/52 0.05
CHANCE 2013 1.48 (0.99, 2.20) 60/2584 41/2586 3.11
Yi 2014 1.08 (0.52, 2.23) 16/284 15/286 0.95
COMPRESS 2016 1.67 (0.90, 3.11) 29/174 19/178 1.30
POINT 2018 2.84 (1.74, 4.64) 61/2432 22/2449 2.07
I-V Subtotal (I-squared = 26.5%, p = 0.236) 1.76 (1.36, 2.27) 170/5571 98/5607 7.57
D+L Subtotal 1.76 (1.26, 2.46)
AD long vs C
PROFeSS 2008 1.08 (0.96, 1.23) 535/10181 494/10151 31.71
I-V Subtotal (I-squared = .%, p = .) 1.08 (0.96, 1.23) 535/10181 494/10151 31.71
D+L Subtotal 1.08 (0.96, 1.23)
AC long vs A
CHARISMA 2011 2.31 (2.02, 2.65) 807/2157 444/2163 27.01
SPS3 2012 1.92 (1.38, 2.68) 105/1517 56/1503 4.52
I-V Subtotal (I-squared = 2.9%, p = 0.310) 2.25 (1.99, 2.56) 912/3674 500/3666 31.53
D+L Subtotal 2.25 (1.97, 2.57)
Heterogeneity between groups: p = 0.000
I-V Overall (I-squared = 89.6%, p = 0.000) 1.54 (1.43, 1.65) 2278/26175 1563/26154 100.00
D+L Overall 1.52 (1.16, 1.99)
.00793
1
126
Favours intervention
Favours control

Figure S2_C

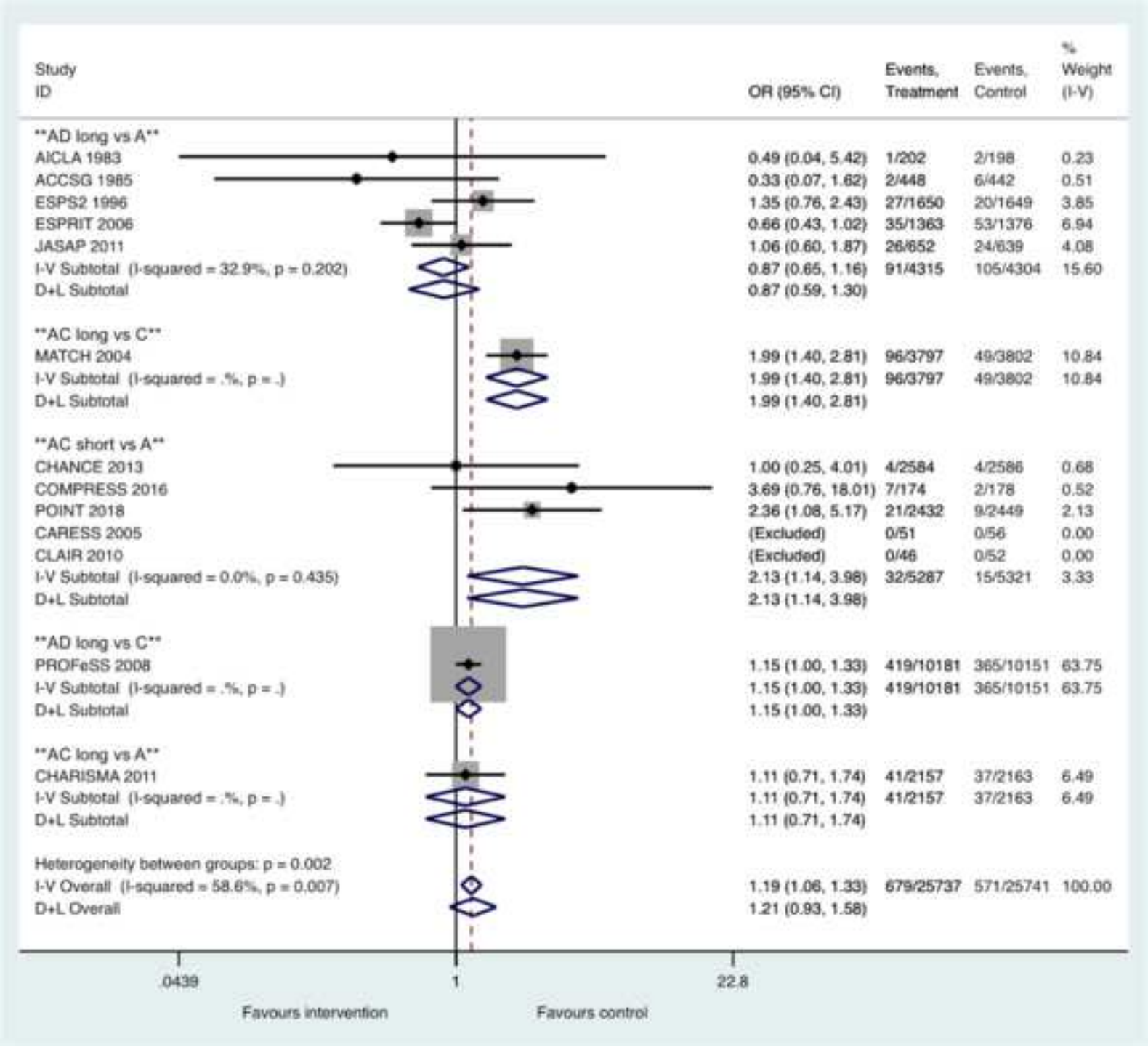

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
AD long vs A
AICLA 1983 0.49 (0.04, 5.42) 1/202 2/198 0.23
ACCSG 1985 0.33 (0.07, 1.62) 2/448 6/442 0.51
ESPS2 1996 1.35 (0.76, 2.43) 27/1650 20/1649 3.85
ESPRIT 2006 0.66 (0.43, 1.02) 35/1363 53/1376 6.94
JASAP 2011 1.06 (0.60, 1.87) 26/652 24/639 4.08
I-V Subtotal (I-squared = 32.9%, p = 0.202) 0.87 (0.65, 1.16) 91/4315 105/4304 15.60
D+L Subtotal 0.87 (0.59, 1.30)
AC long vs C
MATCH 2004 1.99 (1.40, 2.81) 96/3797 49/3802 10.84
I-V Subtotal (I-squared = .%, p = .) 1.99 (1.40, 2.81) 96/3797 49/3802 10.84
D+L Subtotal 1.99 (1.40, 2.81)
AC short vs A
CHANCE 2013 1.00 (0.25, 4.01) 4/2584 4/2586 0.68
COMPRESS 2016 3.69 (0.76, 18.01) 7/174 2/178 0.52
POINT 2018 2.36 (1.08, 5.17) 21/2432 9/2449 2.13
CARESS 2005 (Excluded) 0/51 0/56 0.00
CLAIR 2010 (Excluded) 0/46 0/52 0.00
I-V Subtotal (I-squared = 0.0%, p = 0.435) 2.13 (1.14, 3.98) 32/5287 15/5321 3.33
D+L Subtotal 2.13 (1.14, 3.98)
AD long vs C
PROFeSS 2008 1.15 (1.00, 1.33) 419/10181 365/10151 63.75
I-V Subtotal (I-squared = .%, p = .) 1.15 (1.00, 1.33) 419/10181 365/10151 63.75
D+L Subtotal 1.15 (1.00, 1.33)
AC long vs A
CHARISMA 2011 1.11 (0.71, 1.74) 41/2157 37/2163 6.49
I-V Subtotal (I-squared = .%, p = .) 1.11 (0.71, 1.74) 41/2157 37/2163 6.49
D+L Subtotal 1.11 (0.71, 1.74)
Heterogeneity between groups: p = 0.002
I-V Overall (I-squared = 58.6%, p = 0.007) 1.19 (1.06, 1.33) 679/25737 571/25741 100.00
D+L Overall 1.21 (0.93, 1.58)
.0439
1
22.8
Favours intervention
Favours control

Figure S2_D

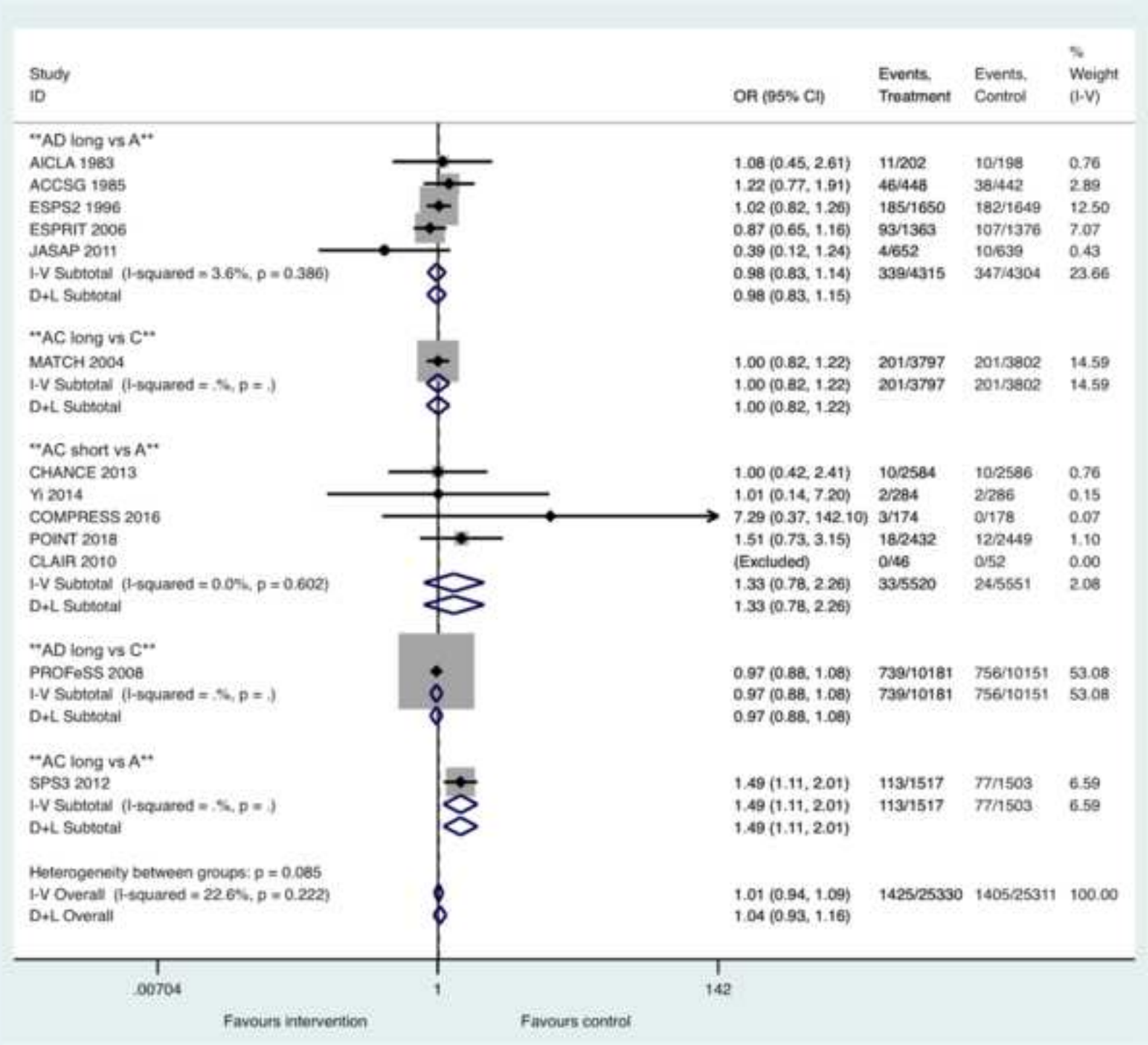

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
AD long vs A
AICLA 1983 1.08 (0.45, 2.61) 11/202 10/198 0.76
ACCSG 1985 1.22 (0.77, 1.91) 46/448 38/442 2.89
ESPS2 1996 1.02 (0.82, 1.26) 185/1650 182/1649 12.50
ESPRIT 2006 0.87 (0.65, 1.16) 93/1363 107/1376 7.07
JASAP 2011 0.39 (0.12, 1.24) 4/652 10/639 0.43
I-V Subtotal (I-squared = 3.6%, p = 0.386) 0.98 (0.83, 1.14) 339/4315 347/4304 23.66
D+L Subtotal 0.98 (0.83, 1.15)
AC long vs C
MATCH 2004 1.00 (0.82, 1.22) 201/3797 201/3802 14.59
I-V Subtotal (I-squared = .%, p = .) 1.00 (0.82, 1.22) 201/3797 201/3802 14.59
D+L Subtotal 1.00 (0.82, 1.22)
AC short vs A
CHANCE 2013 1.00 (0.42, 2.41) 10/2584 10/2586 0.76
Yi 2014 1.01 (0.14, 7.20) 2/284 2/286 0.15
COMPRESS 2016 7.29 (0.37, 142.10) 3/174 0/178 0.07
POINT 2018 1.51 (0.73, 3.15) 18/2432 12/2449 1.10
CLAIR 2010 (Excluded) 0/46 0/52 0.00
I-V Subtotal (I-squared = 0.0%, p = 0.602) 1.33 (0.78, 2.26) 33/5520 24/5551 2.08
D+L Subtotal 1.33 (0.78, 2.26)
AD long vs C
PROFeSS 2008 0.97 (0.88, 1.08) 739/10181 756/10151 53.08
I-V Subtotal (I-squared = .%, p = .) 0.97 (0.88, 1.08) 739/10181 756/10151 53.08
D+L Subtotal 0.97 (0.88, 1.08)
AC long vs A
SPS3 2012 1.49 (1.11, 2.01) 113/1517 77/1503 6.59
I-V Subtotal (I-squared = .%, p = .) 1.49 (1.11, 2.01) 113/1517 77/1503 6.59
D+L Subtotal 1.49 (1.11, 2.01)
Heterogeneity between groups: p = 0.085
I-V Overall (I-squared = 22.6%, p = 0.222) 1.01 (0.94, 1.09) 1425/25330 1405/25311 100.00
D+L Overall 1.04 (0.93, 1.16)
.00704
1
142
Favours intervention
Favours control

Figure S2_E

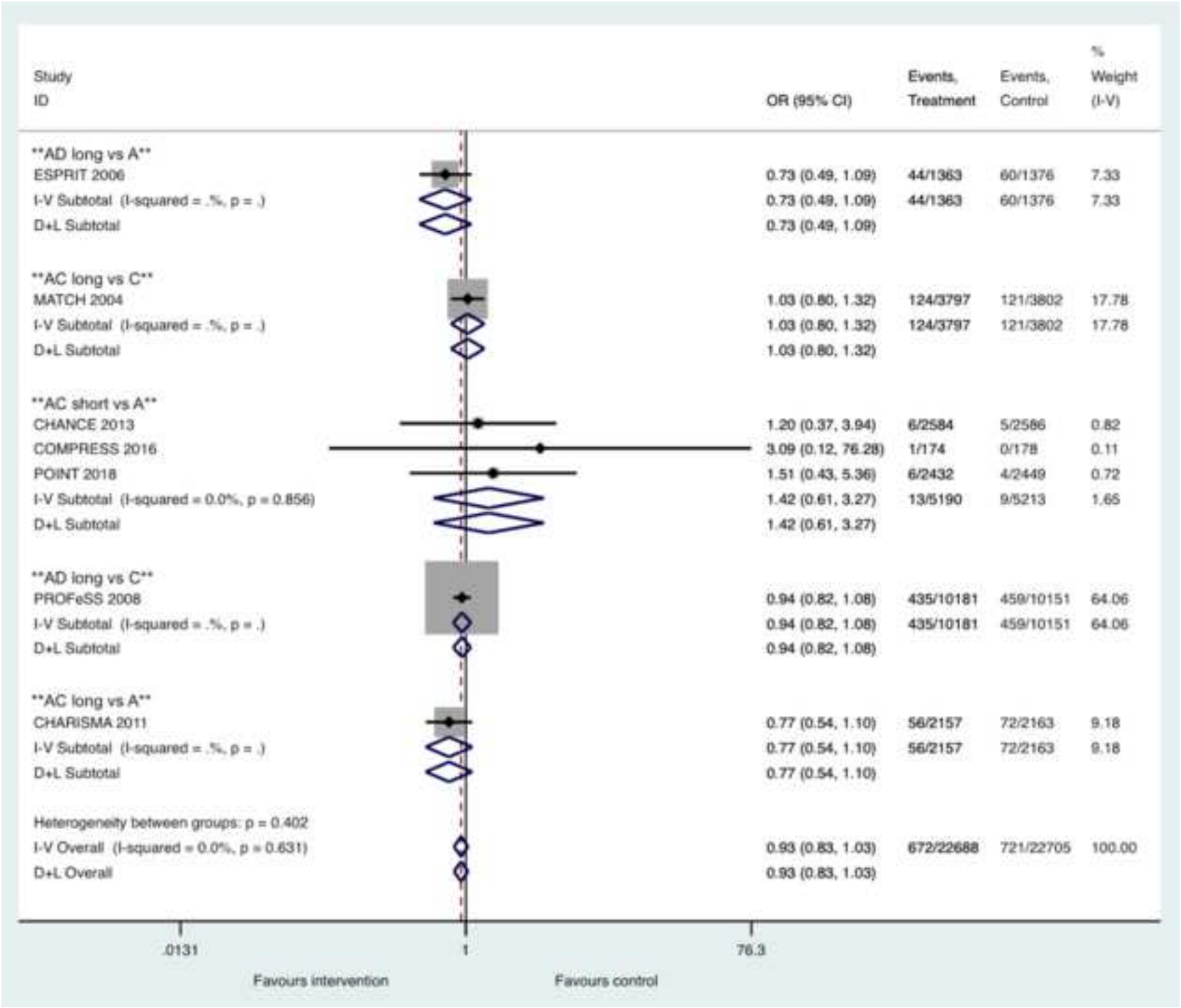

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
AD long vs A
ESPRIT 2006 0.73 (0.49, 1.09) 44/1363 60/1376 7.33
I-V Subtotal (I-squared = .%, p = .) 0.73 (0.49, 1.09) 44/1363 60/1376 7.33
D+L Subtotal 0.73 (0.49, 1.09)
AC long vs C
MATCH 2004 1.03 (0.80, 1.32) 124/3797 121/3802 17.78
I-V Subtotal (I-squared = .%, p = .) 1.03 (0.80, 1.32) 124/3797 121/3802 17.78
D+L Subtotal 1.03 (0.80, 1.32)
AC short vs A
CHANCE 2013 1.20 (0.37, 3.94) 6/2584 5/2586 0.82
COMPRESS 2016 3.09 (0.12, 76.28) 1/174 0/178 0.11
POINT 2018 1.51 (0.43, 5.36) 6/2432 4/2449 0.72
I-V Subtotal (I-squared = 0.0%, p = 0.856) 1.42 (0.61, 3.27) 13/5190 9/5213 1.65
D+L Subtotal 1.42 (0.61, 3.27)
AD long vs C
PROFeSS 2008 0.94 (0.82, 1.08) 435/10181 459/10151 64.06
I-V Subtotal (I-squared = .%, p = .) 0.94 (0.82, 1.08) 435/10181 459/10151 64.06
D+L Subtotal 0.94 (0.82, 1.08)
AC long vs A
CHARISMA 2011 0.77 (0.54, 1.10) 56/2157 72/2163 9.18
I-V Subtotal (I-squared = .%, p = .) 0.77 (0.54, 1.10) 56/2157 72/2163 9.18
D+L Subtotal 0.77 (0.54, 1.10)
Heterogeneity between groups: p = 0.402
I-V Overall (I-squared = 0.0%, p = 0.631) 0.93 (0.83, 1.03) 672/22688 721/22705 100.00
D+L Overall 0.93 (0.83, 1.03)
.0131
1
76.3
Favours intervention
Favours control

Figure S2_F

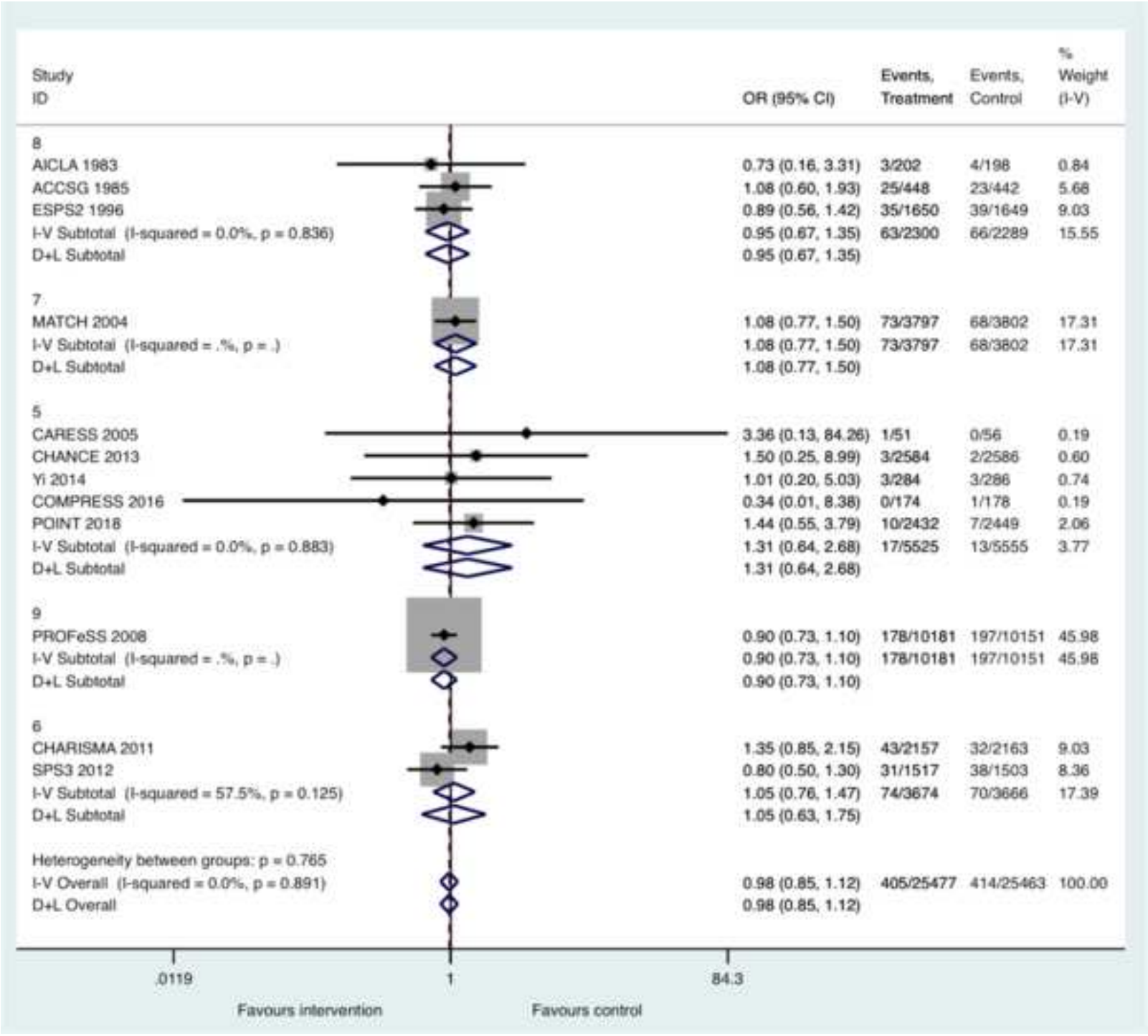
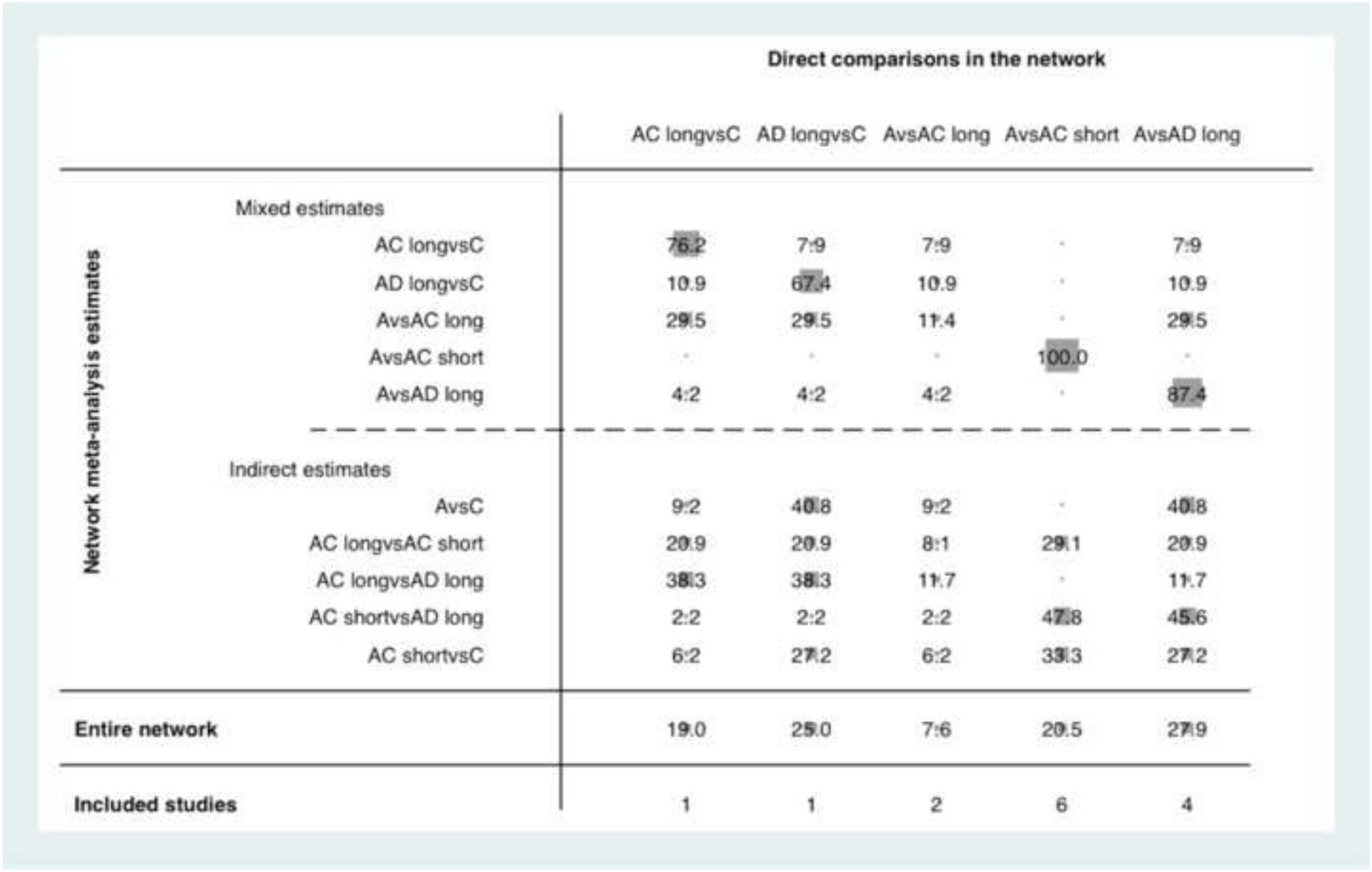

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
8
AICLA 1983 0.73 (0.16, 3.31) 3/202 4/198 0.84
ACCSG 1985 1.08 (0.60, 1.93) 25/448 23/442 5.68
ESPS2 1996 0.89 (0.56, 1.42) 35/1650 39/1649 9.03
I-V Subtotal (I-squared = 0.0%, p = 0.836) 0.95 (0.67, 1.35) 63/2300 66/2289 15.55
D+L Subtotal 0.95 (0.67, 1.35)
7
MATCH 2004 1.08 (0.77, 1.50) 73/3797 68/3802 17.31
I-V Subtotal (I-squared = .%, p = .) 1.08 (0.77, 1.50) 73/3797 68/3802 17.31
D+L Subtotal 1.08 (0.77, 1.50)
5
CARESS 2005 3.36 (0.13, 84.26) 1/51 0/56 0.19
CHANCE 2013 1.50 (0.25, 8.99) 3/2584 2/2586 0.60
Yi 2014 1.01 (0.20, 5.03) 3/284 3/286 0.74
COMPRESS 2016 0.34 (0.01, 8.38) 0/174 1/178 0.19
POINT 2018 1.44 (0.55, 3.79) 10/2432 7/2449 2.06
I-V Subtotal (I-squared = 0.0%, p = 0.883) 1.31 (0.64, 2.68) 17/5525 13/5555 3.77
D+L Subtotal 1.31 (0.64, 2.68)
9
PROFeSS 2008 0.90 (0.73, 1.10) 178/10181 197/10151 45.98
I-V Subtotal (I-squared = .%, p = .) 0.90 (0.73, 1.10) 178/10181 197/10151 45.98
D+L Subtotal 0.90 (0.73, 1.10)
6
CHARISMA 2011 1.35 (0.85, 2.15) 43/2157 32/2163 9.03
SPS3 2012 0.80 (0.50, 1.30) 31/1517 38/1503 8.36
I-V Subtotal (I-squared = 57.5%, p = 0.125) 1.05 (0.76, 1.47) 74/3674 70/3666 17.39
D+L Subtotal 1.05 (0.63, 1.75)
Heterogeneity between groups: p = 0.765
I-V Overall (I-squared = 0.0%, p = 0.891) 0.98 (0.85, 1.12) 405/25477 414/25463 100.00
D+L Overall 0.98 (0.85, 1.12)
.0119
1
84.3
Favours intervention
Favours control

Figure S3



Network meta-analysis estimates	Direct comparisons in the network				
	AC longvsC	AD longvsC	AvsAC long	AvsAC short	AvsAD long
Mixed estimates					
AC longvsC	76.2	7.9	7.9	·	7.9
AD longvsC	10.9	67.4	10.9	·	10.9
AvsAC long	29.5	29.5	11.4	·	29.5
AvsAC short	·	·	·	100.0	·
AvsAD long	4.2	4.2	4.2	·	87.4
Indirect estimates					
AvsC	9.2	40.8	9.2	·	40.8
AC longvsAC short	20.9	20.9	8.1	29.1	20.9
AC longvsAD long	38.3	38.3	11.7	·	11.7
AC shortvsAD long	2.2	2.2	2.2	47.8	45.6
AC shortvsC	6.2	27.2	6.2	33.3	27.2
Entire network	19.0	25.0	7.6	20.5	27.9
Included studies	1	1	2	6	4

Figure S4


Loop
ROR
95%CI
(truncated)
Loop-specific
Heterogeneity(τ^2)
A-AC long-AD long-C
1.001
(1.00,1.06)
0.000
1
3

Figure S5_A

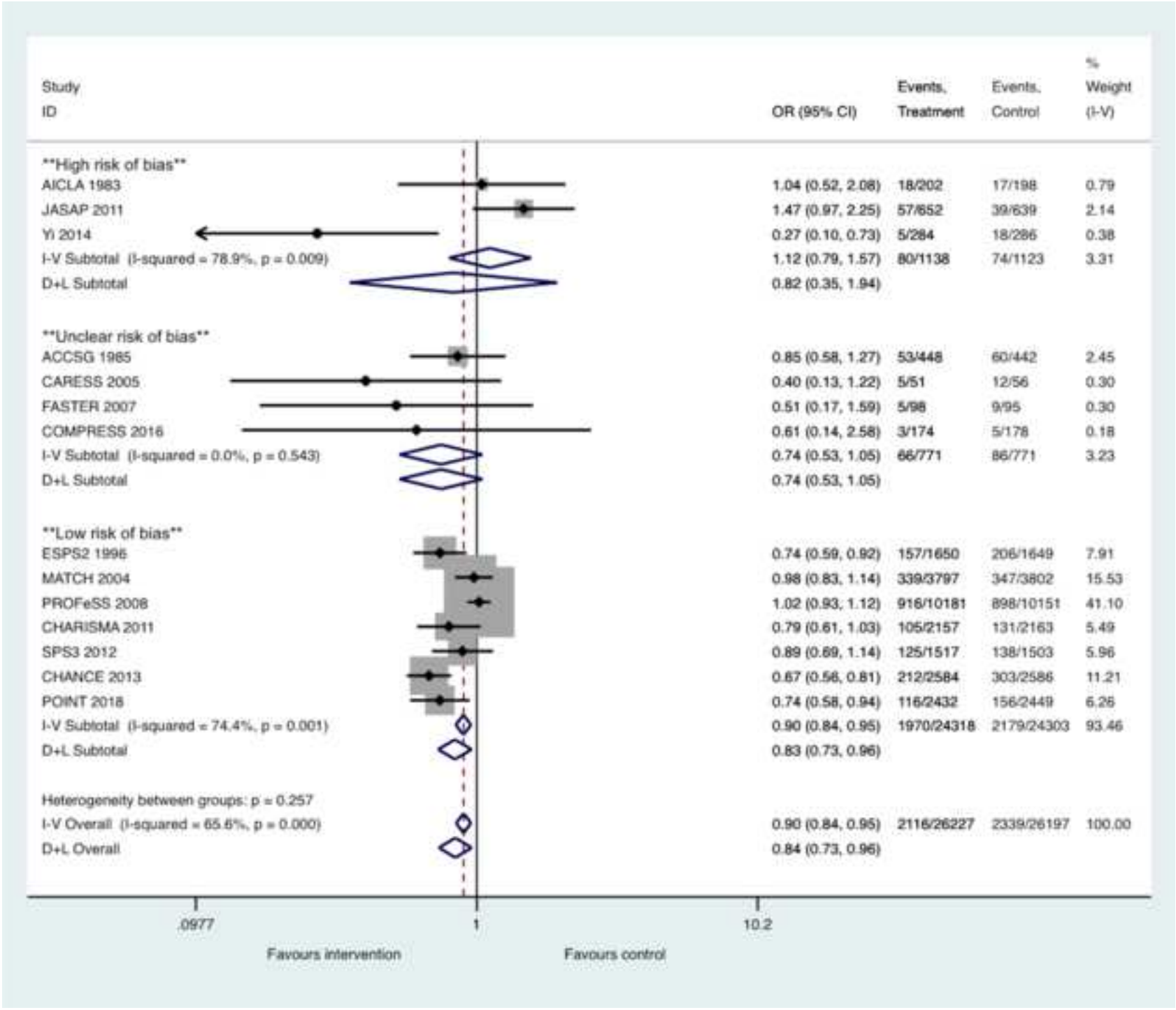
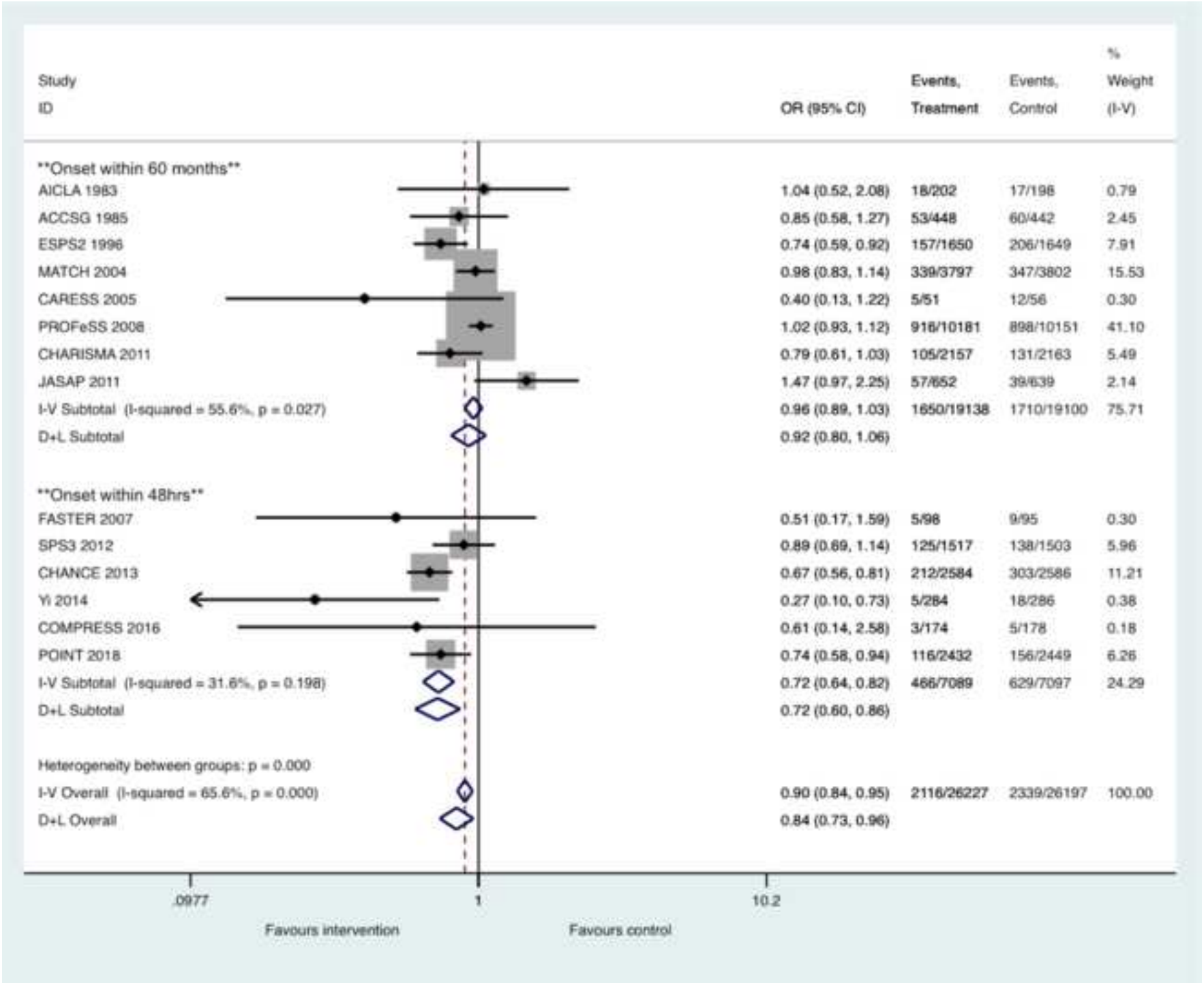

Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
High risk of bias
AICLA 1983 1.04 (0.52, 2.08) 18/202 17/198 0.79
JASAP 2011 1.47 (0.97, 2.25) 57/652 39/639 2.14
Yi 2014 0.27 (0.10, 0.73) 5/284 18/286 0.38
I-V Subtotal (I-squared = 78.9%, p = 0.009) 1.12 (0.79, 1.57) 80/1138 74/1123 3.31
D+L Subtotal 0.82 (0.35, 1.94)
Unclear risk of bias
ACCSG 1965 0.85 (0.58, 1.27) 53/448 60/442 2.45
CARESS 2005 0.40 (0.13, 1.22) 5/51 12/56 0.30
FASTER 2007 0.51 (0.17, 1.59) 5/98 9/95 0.30
COMPRESS 2016 0.61 (0.14, 2.58) 3/174 5/178 0.18
I-V Subtotal (I-squared = 0.0%, p = 0.543) 0.74 (0.53, 1.05) 66/771 86/771 3.23
D+L Subtotal 0.74 (0.53, 1.05)
Low risk of bias
ESPS2 1996 0.74 (0.59, 0.92) 157/1650 206/1649 7.91
MATCH 2004 0.98 (0.83, 1.14) 339/3797 347/3802 15.53
PROFeSS 2008 1.02 (0.93, 1.12) 916/10181 898/10151 41.10
CHARISMA 2011 0.79 (0.61, 1.03) 105/2157 131/2163 5.49
SPS3 2012 0.89 (0.69, 1.14) 125/1517 138/1503 5.96
CHANCE 2013 0.67 (0.56, 0.81) 212/2584 303/2586 11.21
POINT 2018 0.74 (0.58, 0.94) 116/2432 156/2449 6.26
I-V Subtotal (I-squared = 74.4%, p = 0.001) 0.90 (0.84, 0.95) 1970/24318 2179/24303 93.46
D+L Subtotal 0.83 (0.73, 0.96)
Heterogeneity between groups: p = 0.257
I-V Overall (I-squared = 65.6%, p = 0.000) 0.90 (0.84, 0.95) 2116/26227 2339/26197 100.00
D+L Overall 0.84 (0.73, 0.96)
.0977
1
10.2
Favours intervention
Favours control

Figure S5_B


Study
ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (I-V)
Onset within 60 months
AICLA 1983 1.04 (0.52, 2.08) 18/202 17/198 0.79
ACCSG 1985 0.85 (0.58, 1.27) 53/448 60/442 2.45
ESPS2 1996 0.74 (0.59, 0.92) 157/1650 206/1649 7.91
MATCH 2004 0.98 (0.83, 1.14) 339/3797 347/3802 15.53
CARESS 2005 0.40 (0.13, 1.22) 5/51 12/56 0.30
PROFeSS 2008 1.02 (0.93, 1.12) 916/10181 898/10151 41.10
CHARISMA 2011 0.79 (0.61, 1.03) 105/2157 131/2163 5.49
JASAP 2011 1.47 (0.97, 2.25) 57/652 39/639 2.14
I-V Subtotal (I-squared = 55.6%, p = 0.027) 0.96 (0.89, 1.03) 1650/19138 1710/19100 75.71
D+L Subtotal 0.92 (0.80, 1.06)
Onset within 48hrs
FASTER 2007 0.51 (0.17, 1.59) 5/98 9/95 0.30
SPS3 2012 0.89 (0.69, 1.14) 125/1517 138/1503 5.96
CHANCE 2013 0.67 (0.56, 0.81) 212/2584 303/2586 11.21
Yi 2014 0.27 (0.10, 0.73) 5/284 18/286 0.38
COMPRESS 2016 0.61 (0.14, 2.58) 3/174 5/178 0.18
POINT 2018 0.74 (0.58, 0.94) 116/2432 156/2449 6.26
I-V Subtotal (I-squared = 31.6%, p = 0.198) 0.72 (0.64, 0.82) 466/7089 629/7097 24.29
D+L Subtotal 0.72 (0.60, 0.86)
Heterogeneity between groups: p = 0.000
I-V Overall (I-squared = 65.6%, p = 0.000) 0.90 (0.84, 0.95) 2116/26227 2339/26197 100.00
D+L Overall 0.84 (0.73, 0.96)
.0977
1
10.2
Favours intervention
Favours control

Supplemental material

Table S1. Definitions

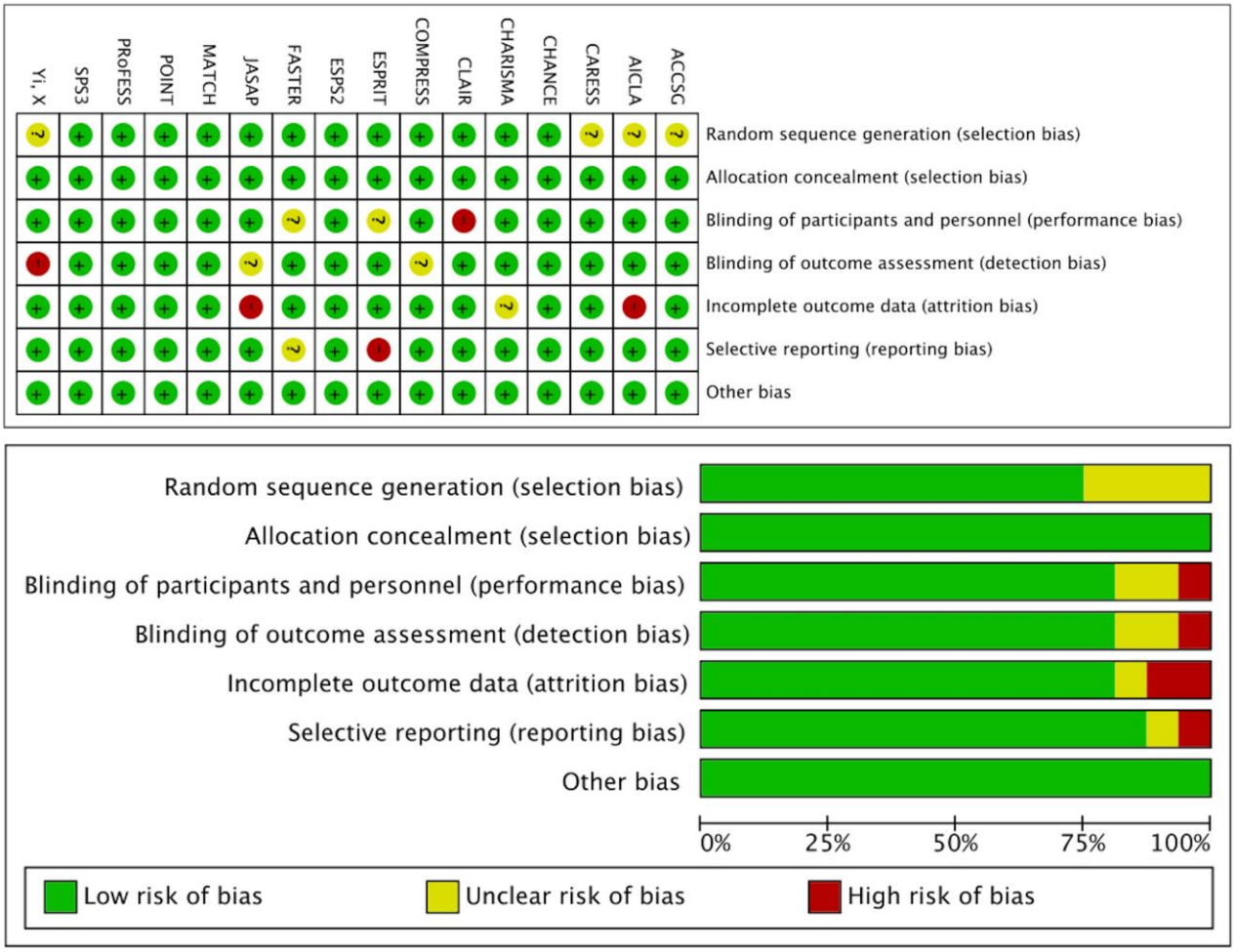
Recurrent stroke (primary efficacy outcome)	New extracranial, intracranial, lacunar, retinal infarction of ischaemic and haemorrhagic origin; presenting with sudden onset of neurological deficit and/or CT/MR imaging evidence of infarction, not attributable to other cause (tumour, seizure, brain infection, metabolic disease or degenerative neurologic disease); fatal and nonfatal; disabling and non-disabling
Ischaemic stroke	As above with exclusion of haemorrhagic cause i.e. acute extravasation of blood into the brain parenchyma or subarachnoid space
All bleeding	Bleeding from all causes, including cranial and extracranial (gastrointestinal, haematuria), regardless of severity also including minor bleeding (e.g. nosebleed); disabling and non-disabling
Severe bleeding	Intracranial or ocular haemorrhage or other haemorrhage causing hemodynamic compromise requiring blood or fluid replacement, or inotropic support or surgery, or hospitalization, or prolongation of an existing hospitalization; disabling and non-disabling
All-cause death	Death during follow-up from any cause
Cardiovascular death	Death due to stroke (ischaemic and haemorrhagic), systemic haemorrhage, myocardial infarction, heart failure, pulmonary emboli, sudden cardiac death, arrhythmia
Myocardial infarction	Clinical/ECG/biomarker diagnostic criteria

Table S2. Search strategy

		Results				
		MEDLINE (Ovid)	EMBASE (Ovid)	PubMed	Cochrane Library database	Clinical Trials.gov
Item	Searches					
1	aspirin	62653	205065	62704	12154	1278
2	exp ASPIRIN	42485	na	na	5635	na
3	clopidogrel	12821	54774	12849	4729	835
4	Plavix	285	3151	na	116	na
5	dipyridamole	10229	25028	10261	1359	85
6	acetyl salicylic acid	763	na	923	181	1278
7	dual antiplatelet	3784	8771	4342	1217	193
8	aspirin-dipyridamole	258	310	2322	121	12
9	Aggrenox	38	334	51572	35	10
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	78174	236177	78601	15963	3691
11	exp STROKE	114897	383165	290361	8879	4206
12	stroke	251218	171225	na	56425	na
13	cerebrovascular accident	4062	170345	293234	8461	na
14	exp Cerebral Infarction	29404	67206	46253	980	567
15	cerebral infarction	28211	19721	na	4310	na
16	transient ischaemic attack	1640	2574	24979	1887	96
17	11 or 12 or 13 or 14 or 15 or 16	278055	473955	312370	59135	4869
18	randomised	90083	132048	90010	123446	11006
19	randomized	746910	954038	815370	794090	148534
20	exp Randomized Controlled Trials as Topic	119424	148543	607016	23124	15301
21	18 or 19 or 20	777969	1006235	846007	835589	174841
22	10 and 17	8206	34116	8855	4039	193
23	21 and 22	2524	6893	2651	2324	168
24	limit 23 to (English language and humans)	2139	6351	2460	2324	168

Note: Search criteria were centred on three main areas/MeSH terms: anti-platelet aggregation, stroke and study design as randomised controlled trial. Logical operators (‘or’, ‘and’) were used to combine search outputs. First we summed all outputs within each of these three areas (‘or’); then we selected outputs at the intersection between the three areas (‘and’).

Table S3. Within-study risk of bias assessment



Note: Each domain was scored as low, high or uncertain/some concerns, where low indicated that the study was less open to bias. A study was judged at low risk of bias if all domains were at low risk. A study was judged at high risk if one or more domains were at high risk. A study was judged at unclear risk/some concerns if one or more raised some concerns.

- Overall bias and funding: Six/16 trials were judged at overall low risk of bias, 3/6 were commercially funded. Five/16 trials were judged at unclear risk of bias, 4/5 had commercial funding. Five/16 trials were judged at high risk of bias, 2/5 were commercial.
- Allocation: All RCTs allegedly used a random sequence generation; 4/16 studies however raised concerns or reported insufficient data.
- Blinding: Two/16 studies were open label; 2/16 did not specify blinding. The other studies were double blinded.
- Incomplete outcome data: Two/16 studies did not specify reasons for withdrawals, losses to follow-up and protocol deviations.

Selective reporting: In 2/16 studies, although the primary outcomes were reported as per protocol, the secondary outcomes appeared selected.

Table S4. Random-effects metaregression between recurrent stroke (primary efficacy outcome) and treatment onset (univariate), and between recurrent stroke and treatment onset as well as risk of bias at study level (multivariate).

OR	Coefficient	95% CI		Standard error	t	p
Univariate						
Onset	0.0576	0.00455	0.111	0.0244	2.37	0.036
Constant	0.604	0.334	0.875	0.124	4.87	0.000
Multivariate						
Onset	0.0537	-0.000873	0.108	0.0248	2.17	0.053
Risk of bias	0.101	-0.0915	0.294	0.0876	1.16	0.272
Constant	0.503	0.166	0.839	0.153	3.29	0.007

OR: odds ratio
Onset: time of treatment onset from qualifying stroke
Risk of bias: assessed in individual studies using RoB2.0 tool