Supplemental Online Content

Kaesmacher J, Cavalcante F, Kappelhof M, et al; IRIS Collaborators. Time to treatment with intravenous thrombolysis before thrombectomy and functional outcomes in acute ischemic stroke: a meta-analysis. *JAMA*. Published online February 7, 2024. doi:10.1001/jama.2024.0589

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods
eMethods 1 – Systematic Search Strategy

NCBI/NLM PubMed/MEDLINE:
("Infarction, Anterior Cerebral Artery"[Mesh] OR anterior cerebral artery infarction[tiab] OR anterior cerebral artery stroke[tiab] OR ACA infarction*[tiab] OR "Stroke"[Mesh] OR stroke [tiab] OR stroke OR cerebrovascular accident [tiab] OR cerebrovascular accident)

AND ("Tissue Plasminogen Activator"[Mesh]OR alteplase [tiab] OR Actilyse [tiab] OR rTPA [tiab] OR "Thrombolytic Therapy"[Mesh] OR "intravenous thrombolysis"[tiab] OR "intravenous alteplase"[tiab] OR "intravenous treatment"[tiab] OR "medical treatment"[tiab] OR IVT [tiab])

AND ("Thrombectomy"[Mesh] OR "mechanical thrombectomy" [tiab] OR "endovascular treatment"[tiab] OR "intraarterial treatment"[tiab] OR "intraarterial thrombectomy"[tiab] OR "stent retriever"[tiab] OR “endovascular thrombectomy”[tiab])

AND (synergies[tiab] OR synergy[tiab] OR eligible[tiab] OR ineligible[tiab] OR noneligible[tiab] OR bridging[tiab] OR direct[tiab] OR without[tiab] OR concurrent[tiab] OR followed[tiab] OR prior[tiab] OR combined[tiab])

Further information:

Time restriction: Inception – March 9 2023.
Language restriction: None
Independent raters: FC, MK (both raters assessed independently: eligibility for this meta-analysis during abstract and full-text screening as well as risk of bias assessment, see eFigure 2).
Additional rater for discrepancies: KMT (this rater solved discrepancies regarding eligibility of studies and risk of bias assessment).
Automation tools used: No
Database last accessed March 9 2023
Tool used for risk of bias assessment: ROB2 (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials)[1]

No additional records were identified through forward and backward citation tracking. No unpublished trials were identified using the search strategy above. One ongoing trial was identified using https://clinicaltrials.gov/: DIRECT-TNK (Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke; NCT05199194)

Inclusion criteria:

- Human study
- Randomized controlled clinical trial
- Patients planned to undergo endovascular thrombectomy in both treatment arms
- Randomized intervention: pre-interventional intravenous thrombolysis with tPA or TNK
- Publication in a peer-reviewed journal as full article

eMethods 2 – Details and Rational regarding the estimated time metrics

Our approach was based on a similar methodology from previous time-interaction studies in stroke.[2,3] Specifically, for patients recruited in the open phase of the IST-3 trial and allocated to "control" it was not possible to specify a time interval from onset to "treatment" because there was no placebo being administered. In the SAP of IST-3 (see point 5.4.4, "Additional analyses: imputing an 'onset to treatment time' for the open control group") it was specified that the delay from randomization to delivery of the bolus among patients allocated to control will be set to the mean delay observed in patients randomized to alteplase (18 min).[2] The authors used the time-interval between onset and randomization for patients randomized to control and added the IST-3 trial's mean of the interval between randomization and IVT administration in patients allocated to intravenous alteplase.[2] Regarding this simple "imputation", the authors specifically state: […] "For patients included in the open phase of the study, we analysed the determinants of the overall time to treatment in those allocated to rt-PA, and the contribution made by variation in the time from randomisation to the delivery of the bolus. As might be expected, variation in the delay from randomisation to delivery of the bolus (RTDB) was a small proportion of the overall delay from stroke onset to treatment. A multivariate model to predict RTDB accounted for only 10% of the variance in RTDB. We decided that, although imputing an RTDB for each individual patient derived from this model was possible, the marginal gain in accuracy was outweighed by the complexity and a certain lack of transparency. We therefore decided to impute RTDB delay by applying the mean delay of 18 minutes in all cases allocated control, so enabling a time from onset to treatment to be calculated for both treatment groups. We have chosen this simple form of single imputation, as the gain from more complex multiple imputation methods is likely to be small." […] [2]

The same approach was then reiterated for the primary analysis by Emberson et al. including IST-3 data and pooling data of all trials comparing intravenous alteplase versus control.[3,4] Additionally, a similar but slightly different imputation procedure was used in the treatment time analysis by Saver et al. comparing thrombectomy vs. medical management.[5] In this study symptom-onset-to-expected arterial puncture time was calculated as […] Symptom onset–to–expected arterial puncture time was derived by adding to the symptom onset–to-randomization value for each patient in both the endovascular and medical therapy groups the study mean for the time from randomization to arterial puncture of the trial in which they participated). […][5]

To be consistent with the methodology put forward by other authors in the past, we specified the following steps in our pre-registered statistical analysis plan (eMethods 3):

(1) For the primary analysis we will use the method suggested by Saver et al.[5]: We will impute treatment times in both arms using individual symptom-onset-to-randomization times and add the mean time between randomization and IVT administration of the trial the participant was included in and the mean time was derived from participants allocated to and treated with IVT.
(2) For a sensitivity analysis, we will use the method suggested by Sandercock et al. and Emberson et al.[2,3]: We will impute onset-to-expected-IVT times only in patients allocated to thrombectomy alone using the same approach as in (1) and use the "as-observed" onset-to-IVT times for patients allocated to and receiving IVT plus thrombectomy.

Both approaches have been prespecified in the SAP (eMethods 3).

eMethods 3 – Statistical Analysis Plan

Changes Log
(Version change 1.0 >1.1)

(1)
Under "Primary hypothesis and analysis" subheading "primary analysis" it is described that analysis will be carried out with the same adjustment as per IRIS main analysis[6]. However, the wrong adjustment variables are named thereafter. In the IRIS main analysis adjustments variables were:
Citation page 5 of IRIS main SAP[6]:
[…] *"All analyses will be adjusted for the following prognostic variables:*
• *Age*
• *ASPECTS*
• *Atrial fibrillation*
• *Occlusion location on baseline CTA/MRA*
• *Baseline NIHSS*
• *Pre-stroke mRS score*
• *Time from onset to randomization"* […]
We corrected the statistical analysis plan accordingly. Time from onset to randomization was not included, because onset-to-expected-IVT times (including time from onset to randomization times) are already implemented in the model as covariates of interest.
Changes made (page 5 of SAP 1.0): […] ~~Analyses will be adjusted for age (continuous, linear variable), sex (binary variable), pre-stroke mRS (3-step ordinal variable) and baseline National Institutes of Health Stroke Scale (linear variable) as per IRIS main analysis[6].~~ Analyses will be adjusted for age, Alberta Stroke Program Early CT Score, atrial fibrillation, occlusion location on basleline CTA/MRA, baseline NIHSS and pre-stroke mRS score as per IRIS main analysis[6]. […]

(2)
Because a few TNK patients are included, the title was changes to "Effect of treatment delay on efficacy and safety of intravenous thrombolysis before thrombectomy: A meta-analysis of individual participant data" (page 1)

Statistical analysis plan
Version: 1.1 (15.05.2023)

Effect of treatment delay on efficacy and safety of intravenous ~~alteplase~~ thrombolysis before thrombectomy: A meta-analysis of individual participant data

Abbreviations

IRIS: Improving Reperfusion strategies in Ischemic Stroke
IVT: Intravenous thrombolysis
EVT: Endovascular treatment
OR/cOR/acOR: Odds Ratio, common Odds Ratio, adjusted common Odds Ratio
mRS: Modified Rankin Scale

Data set and data preparation

- Data set: Whole IRIS population excluding patients presenting with basilar artery strokes.
- Data preparation:
    - Imputation as per IRIS main analysis[6]: We will use multiple imputation by chained equations to impute five sets of complete data and analysis will be based on pooled results of these five sets in accordance to Rubins law.
    - Calculation of onset-to-expected-IVT metrics:
        - Calculation of time metrics for the primary analysis will be made before imputation of the primary data set. Onset to randomization times are available for all patients.
        - For all patients, onset-to-expected IVT will be derived by adding the respective trial's mean for the time from randomization to administration of intravenous thrombolysis (of patients allocated to IVT + EVT within the respective trial) to the symptom-onset-to randomization time observed for each patient.
        - Rationale: Guidelines regarding intravenous thrombolysis use onset-to-treatment times derived from randomized controlled trials, which evaluated heterogeneity of the treatment effect of intravenous thrombolysis across time. The time, these analyses and guidelines are referring to, is onset to administration of intravenous thrombolysis (or placebo). To make the current analysis as applicable to these guidelines as possible, we have chosen symptom-onset-to-expected-IVT time as the main effect modification to be evaluated. Moreover, there are differences in times from randomization to administration of intravenous thrombolysis across the included trials. Therefore, onset-to-expected-IVT times will more likely represent the true time point at which intravenous thrombolysis was administered or expected to be administered than using only onset-to-randomization times.

Expected treatment effect modification

- Hypothesized nature of association with regards to the change in log odds of the main effect (allocation arm): linear
- For exploratory purposes, we will plot the log Odds of IVT+EVT vs EVT alone for ordinal mRS among quintiles, septiles and deciles of onset-to-expected IVT times. Visual inspection of these changing log Odds across symptom-onset-to-expected IVT times will be done to evaluate if there is evidence that the association deviates from a linear association. Formal testing will be performed using nested models with additional logarithmic, quadratic and cubic-spline transformations. Models improvement of these transformations will be tested against a linear assumption in a simple model using the interaction term and the random-effects term and applying a log-likelihood ratio test. The optimal number of knots for restricted cubic spline transformation will be selected within the model and based on the best fit. The location of knots will be based on quantiles.
- Note: We will formally test the linearity assumption for the primary outcome analysis only, not for secondary outcomes and analyses.

Evaluating the proportional odds assumption for the primary analysis

We will test the proportional odds assumption by testing for evidence of non-proportional odds or scale effects of the treatment group allocation, symptom-onset to expected IVT and covariates in the model. This will be done with likelihood ratio tests of models with and without scaling or nominal effects for each variable. If there is evidence of a breach of the proportional odds assumption, we will run a model relaxing this assumption and allow for nominal (partial proportional odds) and scaling effects (non-proportional odds). We will then evaluate if the magnitude or 95% confidence interval and respective cut-offs of the effect of the interaction term changes considerably when using the updated model.

Power calculation

The estimation of power is based on the following assumptions and observations:

- Assumption: The slope of the interaction term will be the same as observed in trials evaluating IVT vs placebo[4]. The interaction term is expressed relative to the treatment effect. While the treatment effect of trials evaluating IVT vs. placebo and IVT+EVT vs EVT alone is different, the relative change over time may be similar and explained by altering efficacy and safety of IVT over time.
- The OR for mRS 0-1 in the study by Emberson et al.[4] is expressed by OR(x) = exp(0.275 – 0.146 * (x – 4.02)/1.228 (personal communication Prof. Emberson, email 04/18/2023, with x being one standard deviation of time from symptom-onset to administration of IVT or placebo).
- With a binary outcome, a binary treatment group, a continuous time variable and correlations as observed in our data (-0.01 for group*outcome, -0.06 for time* outcome and -0.06 for group*time), a sample size of 2300 would allow to detect an odds ratio of interaction of 0.86 (per standard deviation of time) with a power of 0.47 at an alpha of 0.05. An odds ratio of interaction of 0.81 could be detected with a power of 80%. Calculations were done using simulations implemented in R package «InteractionPoweR» ("Baranger DAA, Finsaas MC, Goldstein BL, Vize CE, Lynam DR, Olino TM (2022). "Tutorial: Power analyses for interaction effects in cross-sectional regressions." PsyArxiv. doi: 10.31234/osf.io/5ptd7"). With an ordinal outcome, the power should be slightly higher, so this is a conservative estimate.

Primary hypothesis and analysis

Primary Research Hypothesis: There is treatment effect heterogeneity of IVT + EVT compared to EVT alone with strata of onset-to-expected-IVT intervals. The effect is in the direction that patients with shorter onset-to-expected-IVT intervals will have a more positive (favorable) treatment effect of IVT+EVT as compared to EVT alone than patients in whom onset-to-expected-IVT intervals are longer. If treatment effect heterogeneity is shown, we will calculate the onset-to-expected-IVT cut-off up to which IVT + EVT is superior to EVT alone (i.e. the cut-off after which IVT+EVT can no longer be considered superior to EVT alone).

Note: The primary SAP in the current version was finalized and published after the primary analysis of IRIS was available. The direction of the interaction term, however, had been defined before and was specifically formulated in the first version of the SAP submitted on 05/24/2022. At this date, no results of the primary analysis of IRIS were available.

Primary analysis: We will use mixed effects ordinal regression (also referred to as cumulative link mixed model) with ordinal 90 day mRS as the primary outcome. Treatment allocation, onset-to-expected-IVT times and their interaction will be used as covariates and the trial and trial-by-treatment as random intercept. Onset to expected-IVT times will be included in the model as a continuous variable assuming a linear dependence between time and the calculated log of the common odds (see section "Expected treatment effect modification"). ~~Analyses will be adjusted for age (continuous, linear variable), sex (binary variable), pre-stroke mRS (3-step ordinal variable) and baseline National Institutes of Health Stroke Scale (linear variable) as per IRIS main analysis[6].~~ Analyses will be adjusted for age, Alberta Stroke Program Early CT Score, atrial fibrillation, occlusion location on basleline CTA/MRA, baseline NIHSS and pre-stroke mRS score as per IRIS main analysis[6]. The common Odds Ratio will be presented in a way that values over 1 represent favorable shifts on the mRS in patients allocated to IVT + EVT.

Calculation and graphical display of an onset-to-expected-IVT cutoff:

Graphical display and treatment delay cutoff: If treatment heterogeneity is shown (p of the interaction between onset-to-IVT time and treatment in the model <.05), we will display the change in the common Odds Ratio over time calculated from the model. The cut-off will be calculated using the Johnson-Neyman regions of significance for an interaction. It is the cut-off at which the effect of allocation to treatment arm changes from significant to non-significant (considering increasing onset-to-expected IVT times). If the overall analysis provides at least *moderate* credibility according to the ICEMAN criteria (see below), we will interpret this cut-off as time point up to which IVT + EVT is superior to EVT and may be favored over EVT alone in clinical practice. After this cut-off, superiority of IVT+EVT cannot be claimed, which, however, does not imply that formal non-inferiority of EVT alone in the time window beyond the cut-off is demonstrated. For interpretation purposes, we will also calculate the cut-off where the lower-bound of the 95% confidence interval of the common Odds Ratio of IVT + EVT vs EVT alone crosses the previously established minimal clinically important difference: an absolute risk difference of 1.3% in the rates of modified Rankin scale 0-2 (corresponding to a common Odds Ratio of 1.05). In other words, we will report the cut-off up to which IVT + EVT is superior to EVT by a margin, which is equal to or greater than the minimal clinically important difference.

In addition:

- We evaluate collinearity of adjustment variables by showing Spearmans's rho as a measure of correlation among the included variables.
- We will use different simulated populations from the model in order to calculate the NNT reflecting that one more patient is at least one score higher on the mRS at different time intervals. For this, the ordinal model will be used and the remaining numeric covariates in the model will be set to their mean value, while for factors variables in the model, an average value, which represents the proportions of each category of the factor, is used (marginal effects of the mean method and not conditional effects method). Other methods to derive at the NNT will be referring to previous considerations[7–9].
- For interpretation purposes, we will illustrate the marginal effect at the mean of IVT + EVT vs. EVT alone by plotting the probabilities of being mRS 0-2 of each allocation group and the probability of being at least one score higher on the mRS if treated with IVT + EVT over different symptom-onset-to-expected-IVT times (30-300 minutes). For this, the ordinal model will be used and the remaining numeric covariates in the model will be set to their mean value, while for factors variables in the model, an average value, which represents the proportions of each category of the factor, is used (marginal effects of the mean method and not conditional effects method).
- In order to visually compare the treatment effect modification of time to treatment in IVT + EVT vs EVT to the treatment effect modification of time to treatment in IVT vs placebo, we will plot the change in OR over time together with the change in OR over time extracted from the model provided

by Emberson et al[4]. This is for demonstration purposes only, and not a formal comparison as the models behind both graphs will be inherently different.

Interpretation: The credibility of the investigated effect modification will be rated according to the ICEMAN guidelines[10], using the ICEMAN questionnaire for randomized controlled trials and meta-analyses of randomized controlled trials. Recommendation on the clinical applicability of the results will be made as per final adjudication as very low, low, moderate or high credibility of the effect modification analysis:

- Very low credibility: Use overall effect for each subgroup.
- Low credibility: Use overall effect for each subgroup but note remaining uncertainty.
- Moderate credibility: Use separate effects for each subgroup but note remaining uncertainty.
- High credibility: Use separate effects for each subgroup.

Secondary analyses

Note: For sensitivity analyses and secondary analyses there is no formal P-value adjustment for multiple testing. All these analyses are explorative.

Secondary analysis regarding the primary hypothesis:

- We will rerun the primary analysis (test for interaction) without imputation and excluding patients with onset-to-expected-IVT times > 4.5.h.
- We will rerun the primary analysis in a per-protocol population. Per-protocol population defined as patients assigned to the EVT alone arm who did not receive IVT prior to EVT, and patients assigned to the IVT plus EVT arm who did receive IVT prior to EVT. Patients who received "rescue alteplase" after EVT according to protocol in MR CLEAN-NO IV are included in their randomization (EVT alone) arm (n=24). Patients who did not undergo EVT (e.g., due to early recanalization) are included. Patients in the IVT plus EVT arm for whom alteplase infusion was started after groin puncture (n=47) are excluded. There are 24 crossovers from the IVT plus EVT to the EVT alone arm, and 40 from the EVT alone to the IVT plus EVT arm; they are excluded. Patients with missing data for IVT administration are excluded. For patients with missing needle or arterial access times, the respective trial mean was used to determine eligibility for the per-protocol analysis.
- In a last step, we will run the primary analysis using the observed onset-to-IVT metrics of the participants allocated to IVT+EVT and using calculated values only for patients allocated to EVT alone and IVT+EVT patients with missing randomization-to-IVT times.

Alternative/secondary outcomes regarding the primary hypothesis:
These will be run as explorative analyses including the evaluation of potential causal explanations (e.g. different efficacy of IVT regarding reperfusion with regards to different strata of onset-to-expected-IVT intervals). For dichotomized outcomes, we will use a mixed-method logistic regression technique using the same adjustment variables and random-effects model as for the primary analysis. If the model does not converge for outcomes, which have a low prevalence (e.g. symptomatic intracranial hemorrhage or early reperfusion), the model will be simplified to just include the interaction term (onset-to-expected-IVT time*allocation arm) and the random effects term. The following secondary outcomes are predefined:

- Functional independence (modified Rankin Score 0-2)
- Early Reperfusion, defined as the absence of a treatable target vessel occlusion
- Thrombolysis In Cerebral Infarction score of 2b-3 at the end of the endovascular procedure
- Symptomatic intracranial hemorrhage as per trial criteria
- Any intracranial hemorrhage on follow-up imaging

Graphical display
If the p-value for the interaction term is <0.05 we will plot the adjusted Odds Ratio over time or the marginal effects of the mean using an x-axis scale from 30 to 300 minutes.
Explorative analyses regarding randomization-to-EVT-start time
Using the above-mentioned methods, we will evaluate treatment effect heterogeneity of IVT + EVT vs. EVT alone across randomization-to-EVT-start intervals using the same methods as outlined above.
Prespecified outcomes for this explorative analysis:

- Ordinal mRS
- Early reperfusion

- Symptomatic intracranial hemorrhage

All effect size estimates are provided with 95% CIs; P values were 2-sided with values less than .05 considered statistically significant. All analyses other than the primary analysis are explorative, without adjustment for multiple comparisons.

For References see last page

eMethods 4 – Further statistical methods

4.1 Simulation process used to calculate the number needed to treat so that one more patient is at least one score lower on the mRS

The predicted corresponding number needed to treat (NNT) so that one patient is at least one point lower on the modified Rankin scale (mRS, less disabled) were derived from the model using predicted marginal probabilities at the mean: For a bootstrapped population, the model of the primary analysis reached convergence and the probability of each mRS category was calculated from the model for each treatment arm at different time points (30-300 min for each 5 minute interval) using marginal probability at the mean. From these probabilities, large hypothetical populations (n=100) were built using draws from a multinomial distribution (draws=10000). A generalized odds ratio (genOR) was calculated within these simulated population. The bootstrapped process was repeated 200 times per imputed data set. The average log(genOR) was calculated using the Wilcoxon–Mann–Whitney genOR defined as GenOR=(Prob(YT < YC) + 0.5Prob(YT = YC))/(Prob(YT > YC) + 0.5Prob(YT = YC))[8], with pairs of observation where the first observation is taken from the treatment group (YT, IVT plus thrombectomy) and the second observation is taken from the control group (YC, thrombectomy alone). Generally speaking it reflects the Odds of having a better outcome when receiving YT (IVT plus thrombectomy), instead of YC (thrombectomy alone). Using the bootstrapped data, a standard error of the log(genOR) was estimated. We used Wilcoxon–Mann–Whitney GenOR rather than Agresti's GenOR because splitting ties leads to more realistic estimates than ignoring ties (for details see Churilov et al.[8]). The process was repeated for each imputed dataset and the log(GenOR) were combined across the 5 imputed datasets using Rubin's Rules. From the combined values, the predicted number needed to treat so that one more patient is at least one point lower (=less disability) on the mRS was calculated using the formula: NNT = 1 + 2/(gOR-1).[8] All NNT results are reported as the next closest integer higher than the calculated value (i.e. 4 for e.g. 3.3 and -1 for e.g. -1.5). Finally, the predicted number needed to treat and associated 95% confidence intervals were plotted against onset-to-expected-IVT times. Predicted absolute risk differences for a better outcome defined as at least one score lower on the mRS were calculated and plotted using the same approach. The results derived from this analysis may not generate the exact same values derived from the primary model itself; hence the 95% confidence interval may cross different thresholds at different onset-to-expected-IVT times. This is because the calculation above uses simulation and bootstrapping procedures, marginal instead of conditional probabilities and generalized Odds Ratios instead of common Odds Ratios; all of which can influence the respective results.

4.2 Methods to derive absolute risk differences in the predicted rates of mRS 0-2 and estimated number needed to treat for one additional patient reaching mRS score of 0-2 based on the primary analysis (ordinal regression model)

Similarly to explained in eMethods 4.1 (see above), all measurements of predicted risk reported as number needed to treat or absolute risk difference were derived from the estimates for the full ordinal regression model resulting from our primary analysis, pooled from the imputed datasets in accordance to Rubin`s rules. To obtain predicted risk differences for the rates of patients reaching mRS 0-2 and the corresponding numbers needed to treat for one additional patient reaching mRS 0-2 at specific time points we estimated marginal probabilities at the means for both treatment arms at specific time points (30-300 min for each 5 minute interval). This produced predicted probabilities for each of the 7-levels at each time point for both treatment arms. At each time point, the absolute risk difference of reaching mRS of 0-2 between the treatment arms was estimated as the difference between the sum of the probabilities of being mRS 0, mRS 1, and mRS 2 in the IVT plus thrombectomy arm and the sum of the probabilities of being mRS 0, mRS 1, and mRS 2 in the thrombectomy alone arm. For each time point, to produce 95% confidence intervals for the predicted probabilities we produced a variance-covariance matrix of the predicted marginal effects at the means (probabilities) of being mRS 0, mRS 1, and mRS 2, in both treatment arms. The standard errors at the margins were then computed mathematically according to the Delta Method. This produced an estimated standard error for the difference between the sums of the probabilities of being in mRS score 0, 1, and 2 in each arm for each time point. The results are reported in terms of absolute risk difference and corresponding 95% confidence interval. Corresponding numbers needed to treat (and 95% confidence intervals) were computed as: NNT = 1/ARD. With NNT results reported as the next closest integer higher than the calculated value (i.e. 4 for e.g. 3.3 and -1 for e.g. -1.5).

4.3 Sensitivity analyses:

The following sensitivity analyses for the primary hypothesis were prespecified (see SAP, eMethods 3).

(1) Excluding participants with onset-to-expected-thrombolysis times >4.5h and using a non-imputed dataset.

(2) Using a population of participants assigned to thrombectomy alone who did not receive intravenous thrombolysis before thrombectomy, and patients assigned to the intravenous thrombolysis plus thrombectomy arm who did receive intravenous thrombolysis prior to thrombectomy. Patients who received intravenous thrombolysis as a rescue after thrombectomy are considered in the thrombectomy alone arm (n=24). Patients who did not undergo thrombectomy (e.g., due to partial or complete recanalization) are included in this analysis. Patients assigned to intravenous thrombolysis plus thrombectomy arm for whom thrombolysis infusion was started after arterial access (n=47) are excluded. In total there were 24 crossovers from the intravenous thrombolysis plus thrombectomy to the thrombectomy alone arm, and 40 from the thrombectomy alone to the intravenous thrombolysis plus thrombectomy arm; they are excluded. For patients with missing needle or arterial access times, the respective trial mean was used for determining eligibility for this per-protocol analysis.
(3) Using observed symptom-onset to thrombolysis times in a non-imputed dataset for participants allocated to and receiving intravenous thrombolysis. Secondary outcomes were evaluated using a mixed-method binary logistic regression technique including the same adjustment variables and random-effects model as the primary analysis.

The following sensitivity analysis was added post-hoc:
(4) Using symptom onset to randomization times in the imputed dataset instead of onset-to-expected-IVT times. This is a post-hoc sensitivity analyses (in contrast to (1)-(3), which were prespecified in the SAP).

4.4 Choosing and estimating the cut-off times

The following cut-offs times were considered:
Prespecified according to the SAP (eMethods 3)

- The time-point at which the lower boundary of the 95% CI of the acOR (reflecting IVT plus thrombectomy vs thrombectomy alone with better outcomes) crosses 1. This is the time-point until which the association of IVT plus thrombectomy vs thrombectomy alone can be considered statistically significant. This was prespecified in the SAP.
- The time-point at which the lower boundary of the 95% CI of the acOR (reflecting IVT plus thrombectomy vs thrombectomy alone with better outcomes) crosses 1.05. This is the time-point until which the association of IVT plus thrombectomy is at least larger than an absolute difference in mRS 0-2 of 1.3% (=minimal clinically important difference)[11].

In addition, two other additional potentially relevant treatment times were calculated (these are post-hoc analyses):

(1) The time-point at which one can be 97.5% certain that an association of IVT + thrombectomy and better functional outcomes is smaller than a 5% absolute difference in mRS 0-2. The absolute difference of 5% was found to be the answer most physicians have chosen at which they feel comfortable skipping IVT before MT based upon a reasonable comparability framework (mode of the answers in the survey)[12]. It is also the non-inferiority margin used in the IRIS main paper[13] and the maximum non-inferiority margin advocated by some of the committee members of the ESO/ESMINT module working group formulating the expedited recommendations on indication for intravenous thrombolysis before thrombectomy.[14] This cut-off is reflected by the time-point at which the upper boundary of the 95% confidence interval of the common Odds Ratio crosses 1.222. This is a post-hoc analysis not specified in the published statistical analysis plan (SAP). This cut-off was calculated using the rate of modified Rankin scale (mRS) 0-2 in the IVT + thrombectomy arm: 50.73%. The associated adjusted common Odds Ratio reflecting a 5% difference was calculated as: (0.5073/1-0.5073) / [(0.5073-0.05)/(1-(0.5073+0.05)] = 1.222.

(2) The time-point at which one can be 97.5% certain that an association of IVT + thrombectomy and better functional outcomes larger than a 3% absolute difference in mRS 0-2 is unlikely to be present. The absolute difference of 3% was found to be the answer more than 50% of physicians would feel comfortable skipping IVT before MT based upon a reasonable comparability framework (median of the answers of the survey).[12] This cut-off is reflected by the time-point at which the upper boundary of the 95% confidence interval of the common Odds Ratio crosses 1.128. This is a post-hoc analysis not specified in the SAP. This cut-off was calculated using the rate of mRS 0-2 in patients allocated to IVT plus thrombectomy: 50.73%. The associated adjusted common Odds Ratio reflecting a 3% difference was calculated as: (0.5073/1-0.5073) / [(0.5073-0.03)/(1-(0.5073+0.03)] = 1.128. Based on the model, the association of IVT plus thrombectomy with better functional outcomes is thus likely smaller than a 3% absolute difference in mRS 0-2 after the time point at which the upper bound of the 95% confidence interval crosses 1.128.

Calculation:

The cut-off points were determined by to the conditional effect of the treatment ($\hat{\beta}treatment_{time_z}$) at each time point (Z).

The conditional effect estimate was calculated as:

$$\hat{\beta}treatment_{time_z} = \hat{\beta}_{treatment} + \hat{\beta}_{treatment:time} * z$$

Where,

$\hat{\beta}_{treatment}$: estimate for treatment effect.

$\hat{\beta}_{treatment:time}$: estimate for the interaction term (treatment*time).

Z : Time (effect modifier)

And the Variance and Standard Error (SE) for the $\hat{\beta}treatment, time{:}\, z$ was computed as:

$$SE_{treatment:time_z} = \sqrt{Var_{\hat{\beta}_{treatment}} + z^2 * Var_{\hat{\beta}_{treatment:time}} + 2 * z * Cov_{\hat{\beta}_{treatment:time},\, \hat{\beta}_{treatment}}}$$

The $\hat{\beta}treatment_{time_z}$ and $SE_{treatment:time_z}$ were computed for each time point (z) between 15min and 270 min.

The cut-off time-point refers to the time point just before the acOR or the 95% CI crossed the respective cut-offs of Odds Ratios (see above).

4.5 Visual comparison to the time-dependency of the effect of IVT vs placebo (Emberson et al.[4])

The intention to visually compare our model to the model provided by Emberson et al.[4] was prespecified in the SAP (eMethods 3). The model was plotted being provided the following information by Prof. Emberson: Personal communication April 18th, 2023: […] Ln OR = 0.275 – 0.146 x (t in hours – 4.02)/1.228 […]

4.6 Used R-packages

For running the primary and secondary analyses the following R-packages were used: mice[15], lme4[16], ordinal[17], genOdds[18], emmeans[19].

eResults

eResults 1 - Credibility assessment

Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN)
in a meta-analysis of randomized controlled trials

Version 1.1

Consider the following important instructions informed by common misapplications of ICEMAN in studies using the instrument

Complete a separate credibility assessment per each effect modifier (e.g., age, comorbidity, drug dose, etc.), outcome (e.g., mortality, stroke, duration of hospital stay), time-point (e.g., 3 months, 6 months), and effect measure (e.g. relative risk, risk difference).

Do not apply ICEMAN if the interaction p-value is 0.1 or larger, i.e., provides very little statistical support for the existence of an effect modification (ICEMAN is designed to address the possible claim of an effect modification rather than the claim of no effect modification).

Response options on the left indicate definitely or probably reduced credibility, response options on the right probably or definitely increased credibility

Completely unclear should be interpreted as probably reduced credibility.

To ensure transparency, provide a supporting comment under each question that provides a rationale for the rating.

To ensure transparency, provide a copy of the completed ICEMAN instrument in the supplement of your article.

CREDIBILITY ASSESSMENT

Essential preliminary considerations to define the possible effect modification of interest

State a single candidate effect modifier (e.g., age or comorbidity): Time from symptom-onset to expected administration of intravenous thrombolysis

Was the effect modifier measured before or at randomization? [X] yes, continue [ ] no, stop here and refer to manual for further instructions

State a single outcome and time-point (e.g., mortality at 1 year follow-up): modified Rankin scale score at 90 days

State a single effect measure (e.g., relative risk or risk difference): acOR with values >1 indicating shift for a lower score (less disability)

1: Is the analysis of effect modification based on comparison within rather than between trials?

[ ] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[X] Completely within
Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.	*Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information*	*Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information*	*All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g., meta-analysis of interactions*

Comment:

2: For within-trial comparisons, is the effect modification similar from trial to trial? [ ] Not applicable: no or one within-RCT comparison

[ ] Definitely not similar	[ ] Probably not similar or unclear	[ ] Mostly similar	[X] Definitely similar
Effect modification reported for two or more trials and clearly different directions	*Effect modification not reported for individual trials or too imprecise to tell*	*Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude*	*Effect modification reported for two or more trials, similar in direction, only some differences in magnitude*

Comment:

3: For between-trial comparisons, is the number of trials large? [X] Not applicable: no between RCT comparison

[ ] Very small	[ ] Rather small or unclear	[ ] Rather large	[ ] Large
1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression	*3-4 in smallest subgroup; 6-10 in continuous meta-regression*	*5-9 in smallest subgroup; 11 to 15 in continuous meta-regression*	*10 or more in smallest subgroup; more than 15 in continuous meta-regression*

Comment:

4: Was the direction of effect modification correctly hypothesized a priori?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[X] Definitely yes
Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	*Vague hypothesis or hypothesized direction unclear*	*No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification*	*Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale*

Comment:

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[ ] Chance a very likely explanation	[X] Chance a likely explanation or unclear	[ ] Chance may not explain	[ ] Chance an unlikely explanation
Interaction or meta-regression p-value >0.05	*Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable*	*Interaction or meta-regression p-value ≤0.01 and >0.005*	*Interaction or meta-regression p-value ≤0.005*

Comment:

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no	[ ] Probably no or unclear	[X] Probably yes	[ ] Definitely yes
Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis	*No mention of number or 4-10 effect modifiers tested and number not considered in analysis*	*No protocol available but unequivocal statement of 3 or fewer effect modifiers tested*	*Protocol available and 3 or fewer effect modifiers tested or number considered in analysis*

Comment: The timing subanalysis was prespecified before the subgroup analysis reported in the main paper of the IRIS collaboration was performed.

7: Did the authors use a random effects model?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[X] Definitely yes
Fixed (or common) effect or fixed effects model explicitly stated	*Probably fixed effect(s) model*	*Probably random (or mixed) effects*	*Random (or mixed) effects explicitly stated*

Comment:

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [ ] not applicable: not continuous

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[X] Definitely yes

Analysis based on exploratory cut point(s), e.g., picking cut point associated with highest interaction p-value	*Analysis based on cut point(s) of unclear origin*	*Analysis based on pre-specified cut point(s), e.g., suggested by prior RCT*	*Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship*

Comment:

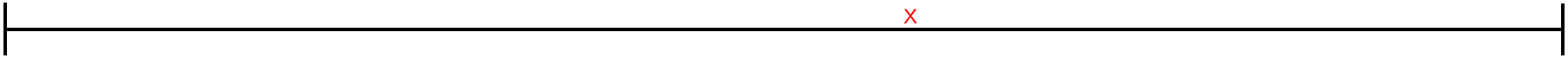
9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) [ ] not applicable

[ ] Yes, probably decrease [X] Yes, probably increase

Comment: Sensitivity analysis with different per-protocol populations, as well as sensitivity analysis excluding trials.

10: How would you rate the overall credibility of the proposed effect modification?
The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:
All responses definitely or probably decrease credibility or unclear → very low
Two or more responses definitely decrease credibility → maximum usually low even if all other responses satisfy credibility criteria
One response definitely decreases credibility → maximum usually moderate even if all other responses satisfy credibility criteria
Two responses probably decrease credibility → maximum usually moderate even if all other responses satisfy credibility criteria
No response options definitely or probably decrease credibility → high very likely

Place a mark on the continuous line (or type “x” in editable version)



Very low credibility	Low credibility	Moderate credibility	High credibility
Minimal to no support for effect modification; Use overall effect for each subgroup	Some but insufficient support for effect modification; Use overall effect for each subgroup but note remaining uncertainty	Likely effect modification; Use separate effects for each subgroup but note remaining uncertainty	Very likely effect modification; Use separate effects for each subgroup

eTables

eTable 1 – Characteristics of the trials included

Characteristics	DIRECT-MT	SKIP	DEVT	MR CLEAN-NO IV	SWIFT DIRECT	DIRECT SAFE
Main inclusion criteria	Age ≥18 years, Baseline mRS of 0-1, ICA/M1/M2: CTA, NIHSS ≥2, ASPECTS: no limit, Onset-IVT≤4.5h	Age ≥18/<86 years, Baseline mRS 0-2, ICA/M1: CTA/MRA, NIHSS≥6, ASPECTS DWI≥5/CT≥6, Onset-puncture <4h	Age ≥18 years, Baseline mRS 0-1, ICA/M1: CTA/MRA, NIHSS: no limit, ASPECTS: no limit, Onset-randomization ≤4 hours 15 min	Age ≥18 years, Baseline mRS 0-1, ICA/M1/proximal M2: CTA/MRA, NIHSS: ≥2, ASPECTS: no limit, Onset-IVT ≤4.5 hours	Age ≥18 years, Baseline mRS 0-1, ICA/M1: CTA/MRA, NIHSS ≥5/<30, ASPECTS: DWI/CT ≥4, Onset-randomization ≤4 hours 15 min	Age ≥18 years, ICA/M1/BA: CTA/MRA, ASPECTS: "small to moderate early ischemic changes", Onset-door ≤4.5 hours
Treatment	EVT (n=327) IVT+EVT (n=329)	EVT (n=101) IVT+EVT (n=103)	EVT (n=116) IVT+EVT (n=118)	EVT (n=273) IVT+EVT (n=266)	EVT (n=201) IVT+EVT (n=207)	EVT (n=146) IVT+EVT (n=147)
Device	Stent retrievers	Any approved device	Stent retrievers	Stent-retrievers recommended as first line	Stent retrievers with proximal protection device	Stent-retrievers as first line
tPA	Alteplase 0.9 mg/kg	Alteplase 0.6 mg/kg	Alteplase 0.9 mg/kg	Alteplase 0.9 mg/kg	Alteplase 0.9 mg/kg	Alteplase 0.9 mg/kg or Tenecteplase
Country	China	Japan	China	Europe	North America and Europe	Australia, New Zealand, China, Vietnam
Design	Non-inferiority	Non-inferiority	Non-inferiority	Superiority (non-inferiority as secondary analysis)	Non-inferiority	Non-inferiority
Median onset to randomization time (min, interquartile range)	171 (125 – 209)	122 (88–170)	169 (137–210)	93 (71—145)	129 (100–170)	138 (109–193)
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; ASPECTS, Alberta Stroke Program Early CT Score; OR, odds ratio; 95% CI, 95% confidence interval; acOR, adjusted common OR; TICI, Thrombolysis in Cerebral Infarction.						

Adapted from Majoie et al.[13], with permission by the authors

eTable 2 – Availability of Time Metrics and Outcomes

	Availability	Percent availability
Onset to randomization	2313/2313	100
Randomization to administration of intravenous thrombolysis	1035/1160 participants allocated to intravenous thrombolysis plus thrombectomy	89.2
Modified Rankin scale at 90 days	2310/2313	99.9
Early recanalization	2233/2313	96.5
eTICI2b–3 at the end of the intervention	2194/2313	94.9
Symptomatic intracranial hemorrhage	2308/2313	99.7
Any intracranial hemorrhage	2257/2313	97.6
All combined	14650/15038	97.4

Abbreviation: eTICI, expanded Thrombolysis in Cerebral Infarction

eTable 3 – Sensitivity analyses of the primary analysis

	Imputation	Onset-to-expected-IVT	Interaction ratio of acOR (95% CI) per hour	Benefit associated with IVT + thrombectomy at 1h, OR (95% CI)	Benefit associated with IVT + thrombectomy at 2h, OR (95% CI)	Interval of a significant association (min)	Point estimate crosses null association at
Primary analysis	used	As described in methods	0.84 (0.72–0.97)	1.49 (1.13–1.96)	1.25 (1.04–1.49)	<2h 20min	3h 14min
Primary analysis (without imputation)	not used	As described in methods	0.85 (0.74–0.99)	1.44 (1.09–1.91)	1.23 (1.03–1.47)	<2h 14min	3h 16min
Sensitivity analyses							
- excluding participants treated >4.5 hours (without imputation)	not used	As described in methods	0.81 (0.69–0.95)	1.53 (1.14–2.06)	1.25 (1.04–1.50)	<2h 15min	3h 4min
- as-observed treatment times	not used	IVT+ thrombectomy: as observed Thrombectomy alone: as described in methods	0.84 (0.72–0.97)	1.46 (1.11–1.93)	1.23 (1.03–1.47)	<2h 13min	3h 9min
- per-protocol analysis[a]	used	As described in methods	0.83 (0.71–0.97)	1.58 (1.17–2.13)	1.31 (1.08–1.59)	<2h 30min	3h 12min
- With onset-to-randomization times (post-hoc)	used	Not used (instead onset-to-randomization times were used)	0.84 (0.73-0.97)	1.44 (1.12-1.87)	1.21 (1.02-1.43)	<2h 11min	3h 4min

Abbreviations: acOR, adjusted common Odds Ratio; 95% CI, 95% confidence interval
Interaction term ratios of acOR <1 represents a decrease in the benefit associated with IVT + thrombectomy versus thrombectomy alone over time (with later treatment).
Interaction term ratios of acOR are presented per hour increase in onset-to-expected-IVT times or onset-to-ranodmization time (last row).
[a]For a clear definition of how per-protocol population were defined, see eMethods 4 (section 4.3)

eTable 4 – Assessment of non-linear relationships

	***P*-value of a likelihood ratio test vs. linear model**	**AIC**	**BIC**
Linear	NA	8083	8197
Restricted Cubic Splines	0.84	8094	8254
Logarithmic transformation	0.50	8082	8196
Quadratic transformation	NA	8083	8197
Square root transformation	0.46	8081	8197

Abbreviations: NA, not available; AIC, Akaike information criterion; BIC, Bayesian information criterion; values are determined from a complete case set without using imputed datasets. P-values of the likelihood ratio test were calculated comparing a nested model additionally including a variable modelling the association of onset-to-expected-IVT*treatment group differently (i.e. using restricted cubic splines with 6 degrees of freedom) and comparing that to the primary model (which assumes a linear).

eTable 5 – Formal testing for evidence of nominal and scaling effects

Variable	*P*-value of a likelihood ratio test comparing the standard model to a model allowing nominal effects	*P*-value of a likelihood ratio test comparing the standard model to a model allowing scaling effects
Treatment arm	0.76	0.74
Onset-to-expected-IVT	0.75	0.42
Treatment arm*onset-to-expected-IVT	0.12	0.72
Age	<0.01	0.15
NIHSS	0.05	0.20
History of atrial fibrillation	<0.01	0.89
Pre-stroke mRS	0.39	0.64
ASPECTS	0.02	<0.01
Occlusion location	0.67	0.49

NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; ASPECTS, Alberta Stroke Program Early CT Score; note that models were run without imputation and without a random-effects term, because nominal and scaling effects are not yet implemented for mixed effects ordinal regression (also referred to as cumulative link mixed model); values are determined from a complete case set without using imputed datasets.

eTable 6 – Leave-One-Study-Out analysis regarding the interaction of onset-to-expected-IVT times and the association of IVT plus thrombectomy vs thrombectomy with early recanalization

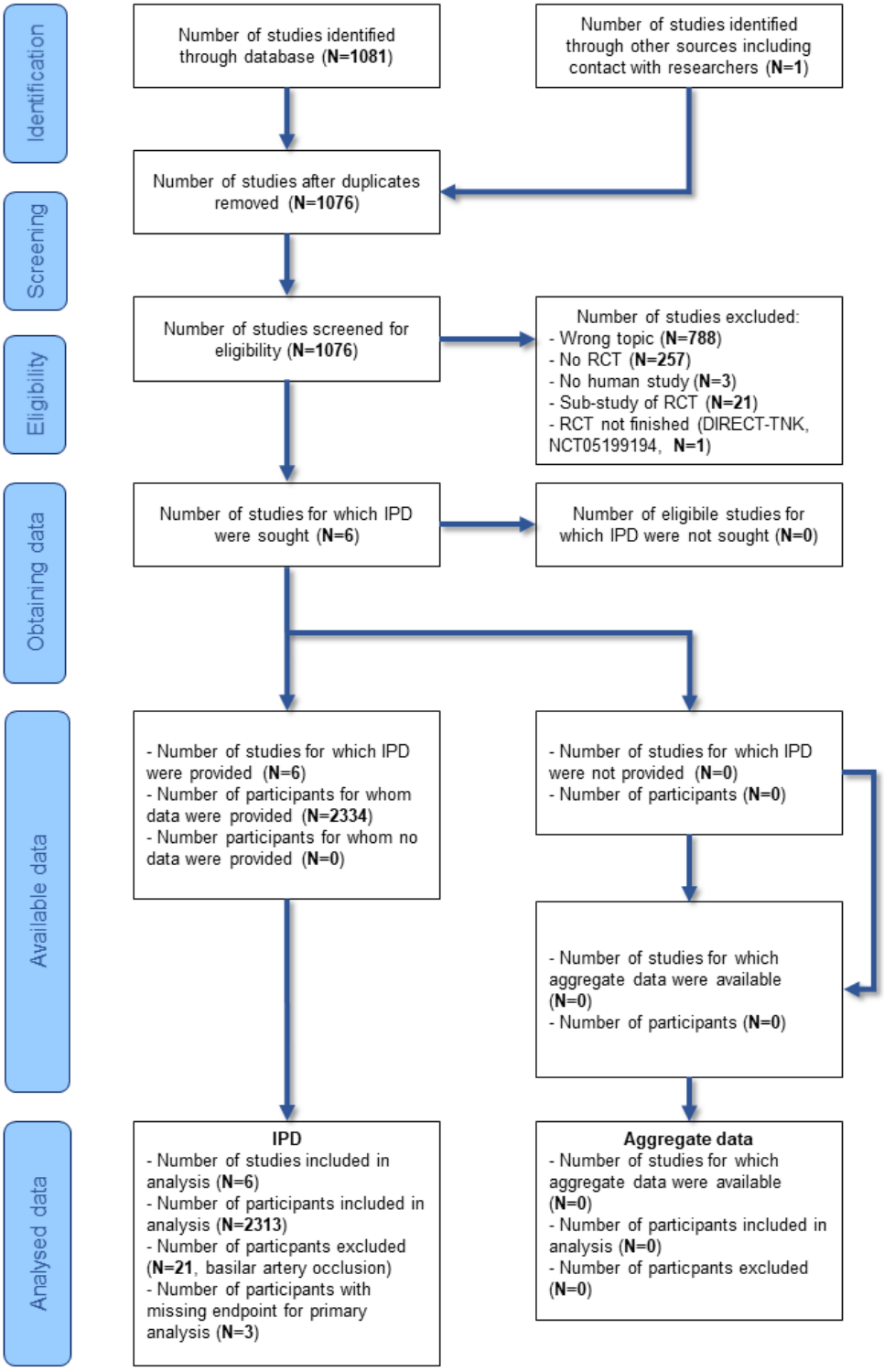
Trial left out	Interaction term aOR per hour delay (95% CI)	p-value interaction
SWIFT DIRECT	1.27 (0.74 - 2.17)	0.4
DEVT	1.34 (0.76 - 2.37)	0.33
DIRECT-MT	0.86 (0.49 - 1.53)	0.61
DIRECTSAFE	1.29 (0.75 - 2.21)	0.37
MRCLEAN-NO IV	2.6 (1.19 - 5.68)	0.021
SKIP	1.3 (0.76 - 2.24)	0.35
The interaction term was calculated as all secondary analyses in each analysis set one of the included trials of this individual patient data meta-analysis was left out. There was evidence for considerable instability of the point estimate and level of significance mainly driven by a large association observed in the DIRECT-MT trial.		

eTable 7 – Interaction of time from randomization to thrombectomy start and associations of intravenous thrombolysis plus thrombectomy with outcomes

	Measure of association	Ratio of OR (95% CI) per hour delay	P for interaction	Direction of the change in associations with increasing time between randomization and arterial puncture
Odinal mRS	acOR	1.01 (0.69–1.48)	0.96	No statistically significant interaction
Early recanalization	aOR	1.04 (0.37–2.95)	0.94	No statistically significant interaction
Symptomatic intracranial hemorrhage	aOR	0.92 (0.37–2.31)	0.86	No statistically significant interaction
Abbreviations: 95% CI, 95% confidence interval; aOR; adjusted Odds Ratio; acOR, adjusted common Odds Ratio; OR; Odds Ratio; TICI, Thrombolysis in Cerebral Infarction; times refer to onset-to-expected-IVT times (see methods).				

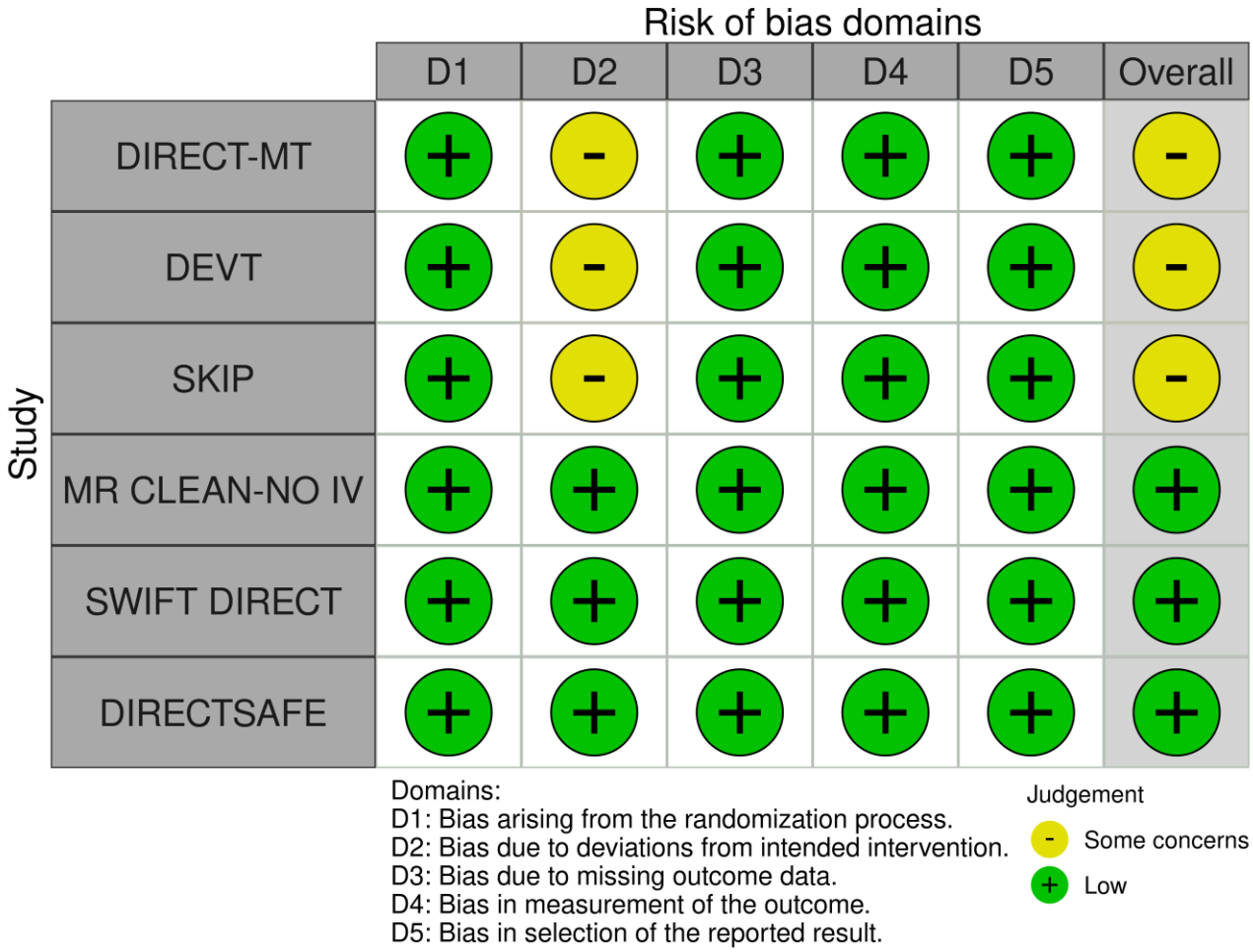
eFigures

eFigure 1 – PRISMA Flow Chart



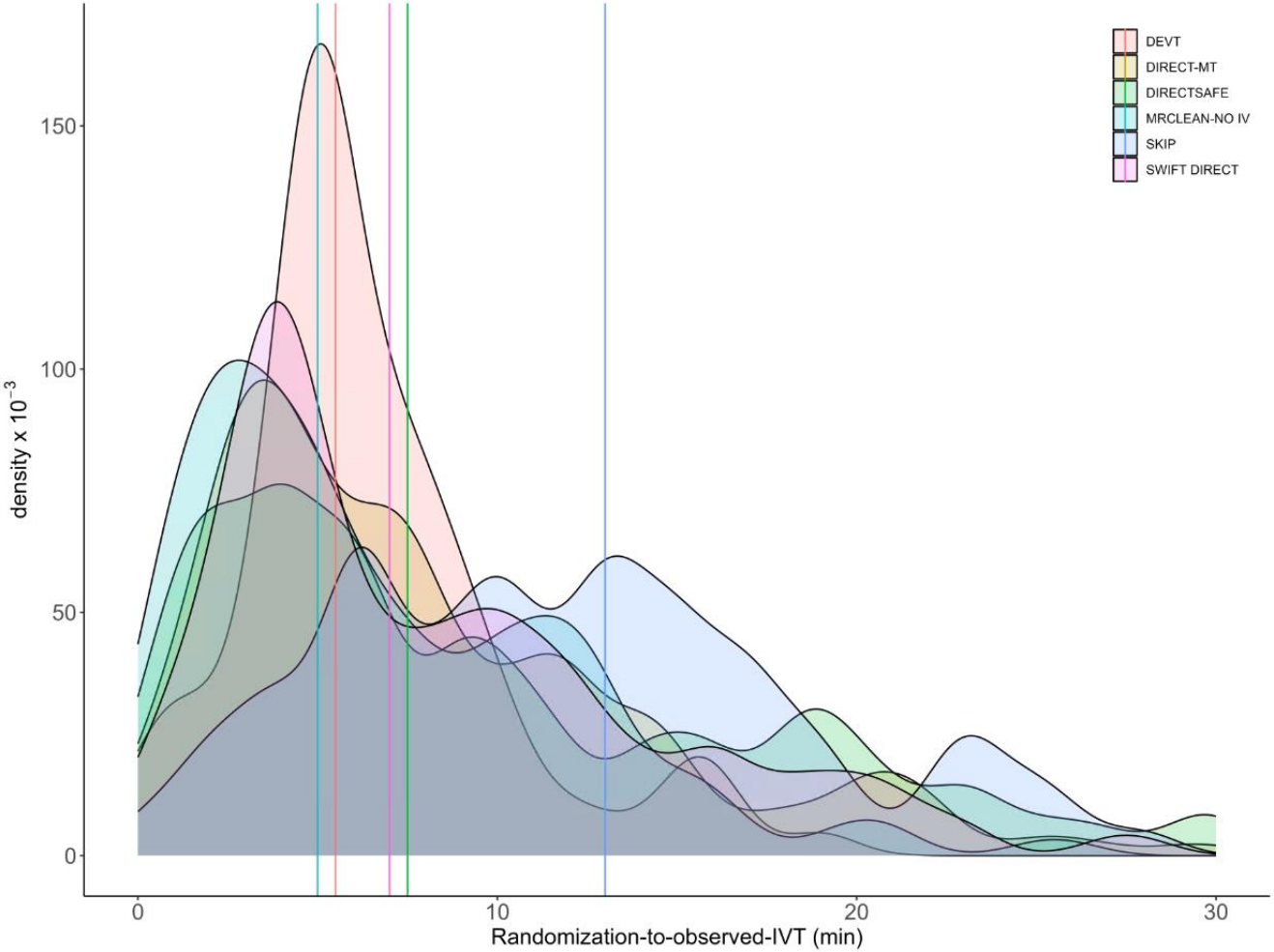
Included trials were randomized controlled clinical trials allocating participants with anterior circulation proximal large-vessel occlusion strokes presenting directly to thrombectomy-capable centers within 4.5 hours from symptom onset to either thrombectomy alone or intravenous thrombolysis (with either alteplase or tenecteplase) plus thrombectomy. RCT, randomized controlled study; IPD, individual participant data; DIRECT-TNK, Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke; NCT05199194.

eFigure 2 – Risk of Bias Across the Included Randomized-Controlled Trials



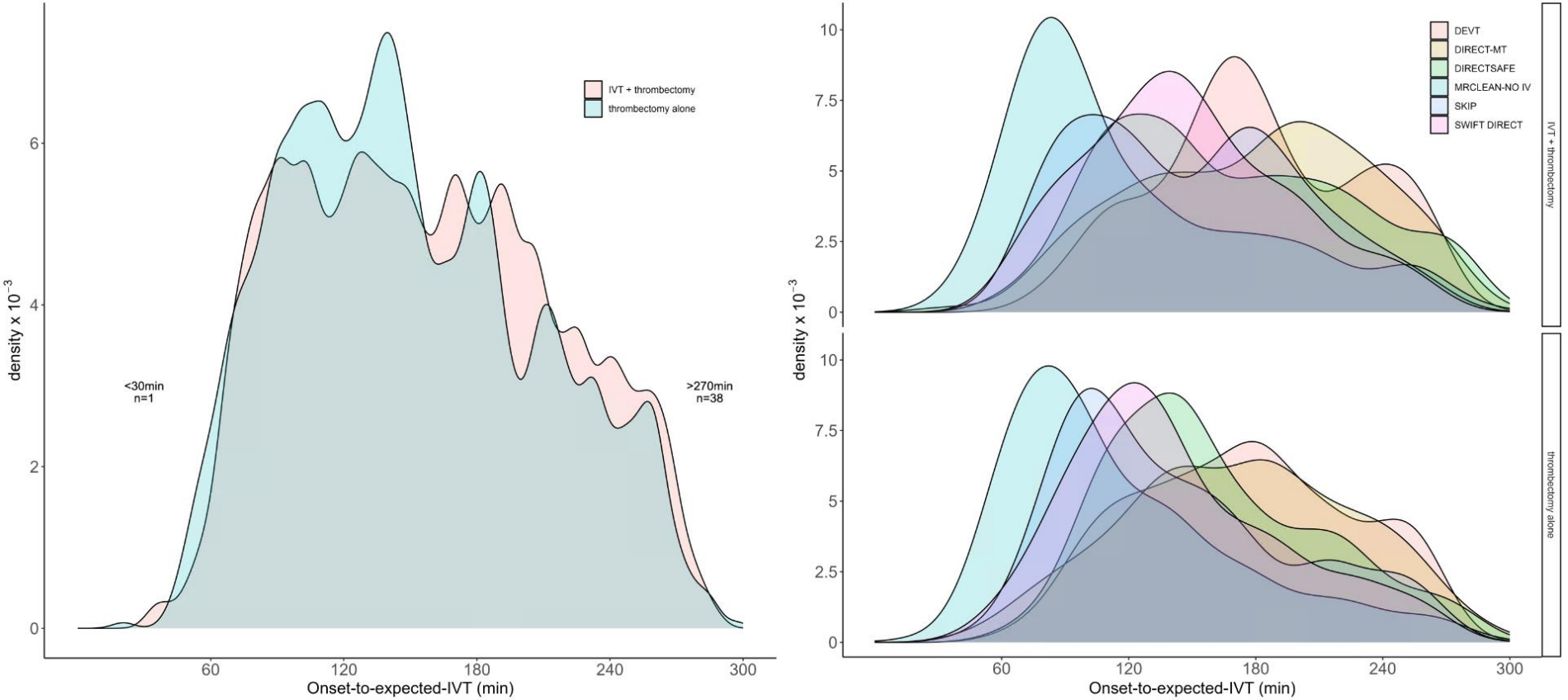
Risk of bias was evaluated by two independent raters (FC, MK) according to the Risk of Bias 2 (Rob2) tool provided by the Cochrane Colaboration and according to instructions provided in https://methods.cochrane.org/sites/methods.cochrane.org/files/uploads/inline-files/RoB%202_Cochrane%20Starter%20Pack_May2022_modified_080323.pdf and https://training.cochrane.org/handbook/current/chapter-08. No automation process was used in the process.

eFigure 3 – Distribution of randomization-to-observed-IVT times



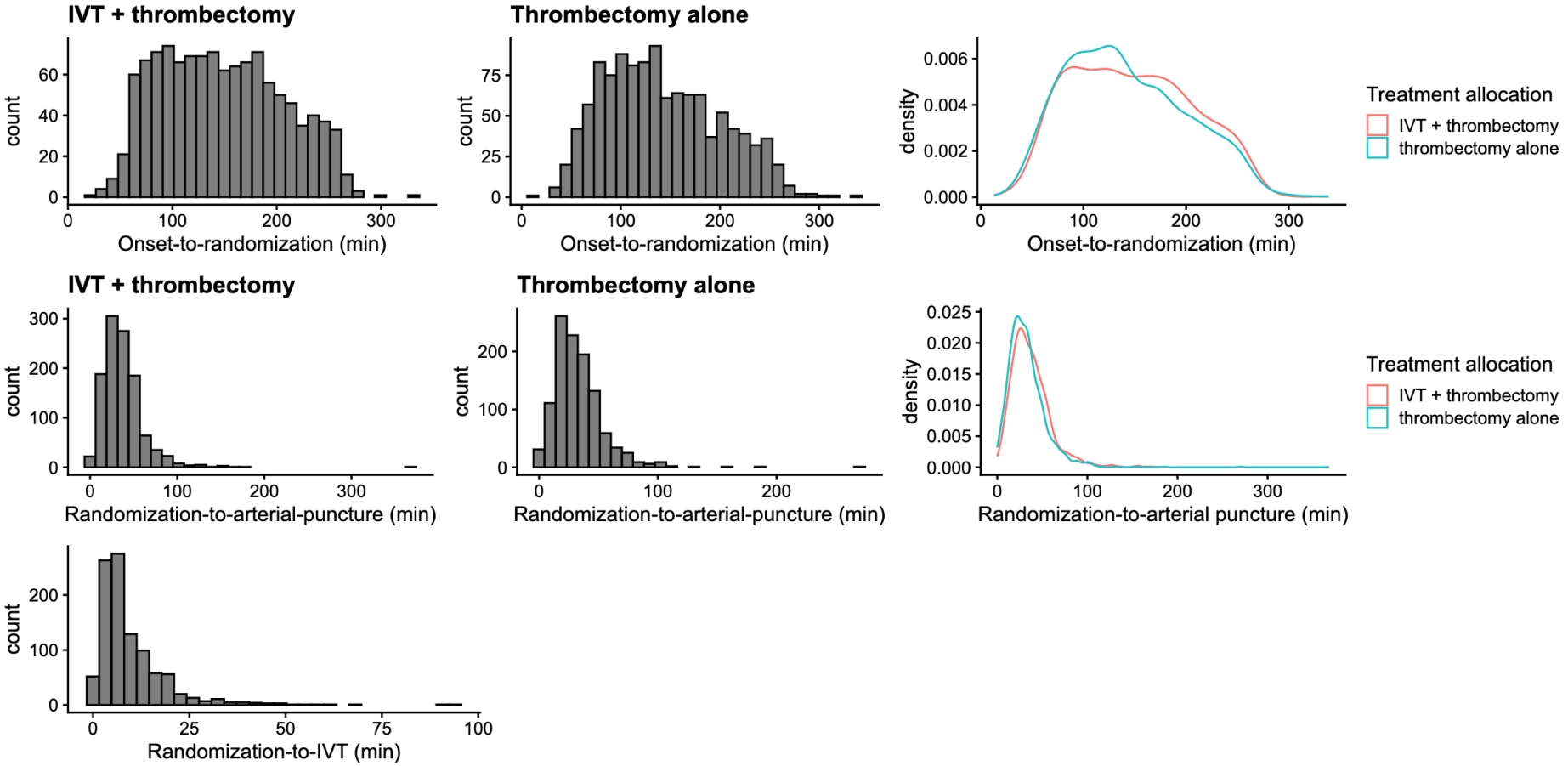
Randomization-to-observed-intravenous thrombolysis (IVT) times are shown per trial for participants allocated to intravenous thrombolysis plus thrombectomy (data available for 1035/1160). Randomization-to-observed-IVT times are defined as the difference between randomization time captured in the electronic randomization database and administration of intravenous thrombolysis (IVT) as collected by the investigators. Vertical lines indicate mean per study. Study means were used to calculate onset-to-expected-IVT intervals. Densities are rescaled for each study and do not represent overall frequencies in the individual participant data meta-analysis. For density plots, the bandwidth (h) of the kernel density estimation was set to 1.

eFigure 4 – Distribution of onset-to-expected-IVT times



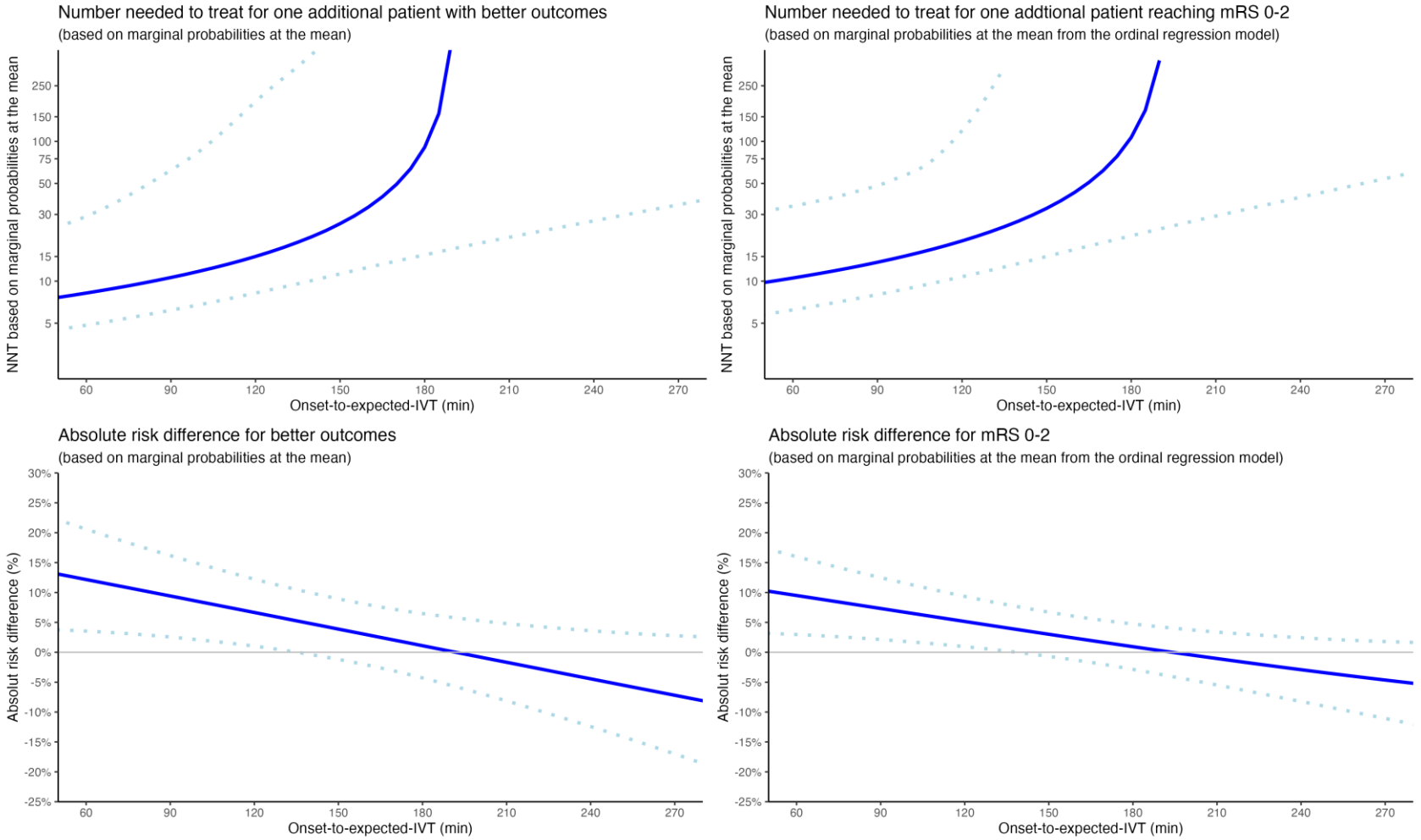
Onset-to-expected-IVT times are shown per treatment allocation and per trial. Densities are rescaled for each study. One participant was expected to be treated with intravenous thrombolysis <30 minutes, while 38 participants were expected to be treated with intravenous thrombolysis later than 4 hours 30 minutes. For density plots, the bandwidth (h) of the kernel density estimation was set to 5 (left panel) and 15 (right panel). Densities in the right panel are rescaled for each study and do not represent overall frequencies in the individual participant data meta-analysis.

eFigure 5 – Histogram of other treatment metrics



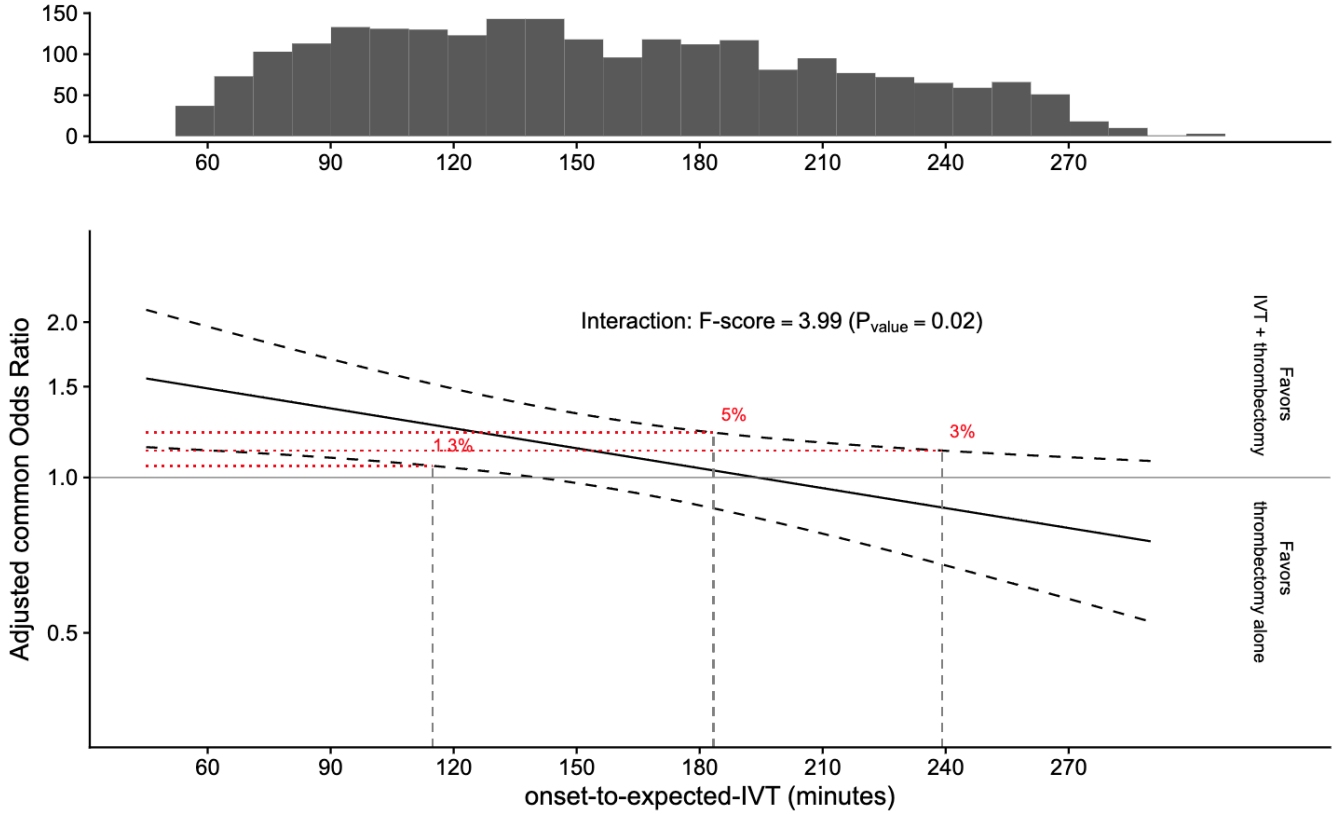
Data on onset to randomization time was available for the complete study population. Data on observed onset-to-needle time was missing for 32 patients in the IVT plus thrombectomy arm. Data on onset to arterial puncture was missing for 25 patients in the IVT plus thrombectomy arm and 24 patients in the thrombectomy alone arm. Three patients were randomized beyond six hours after symptom onset. They were omitted from the histograms and density plots shown above.

eFigure 6– Number needed to treat and absolute risk difference based on predicted probabilities



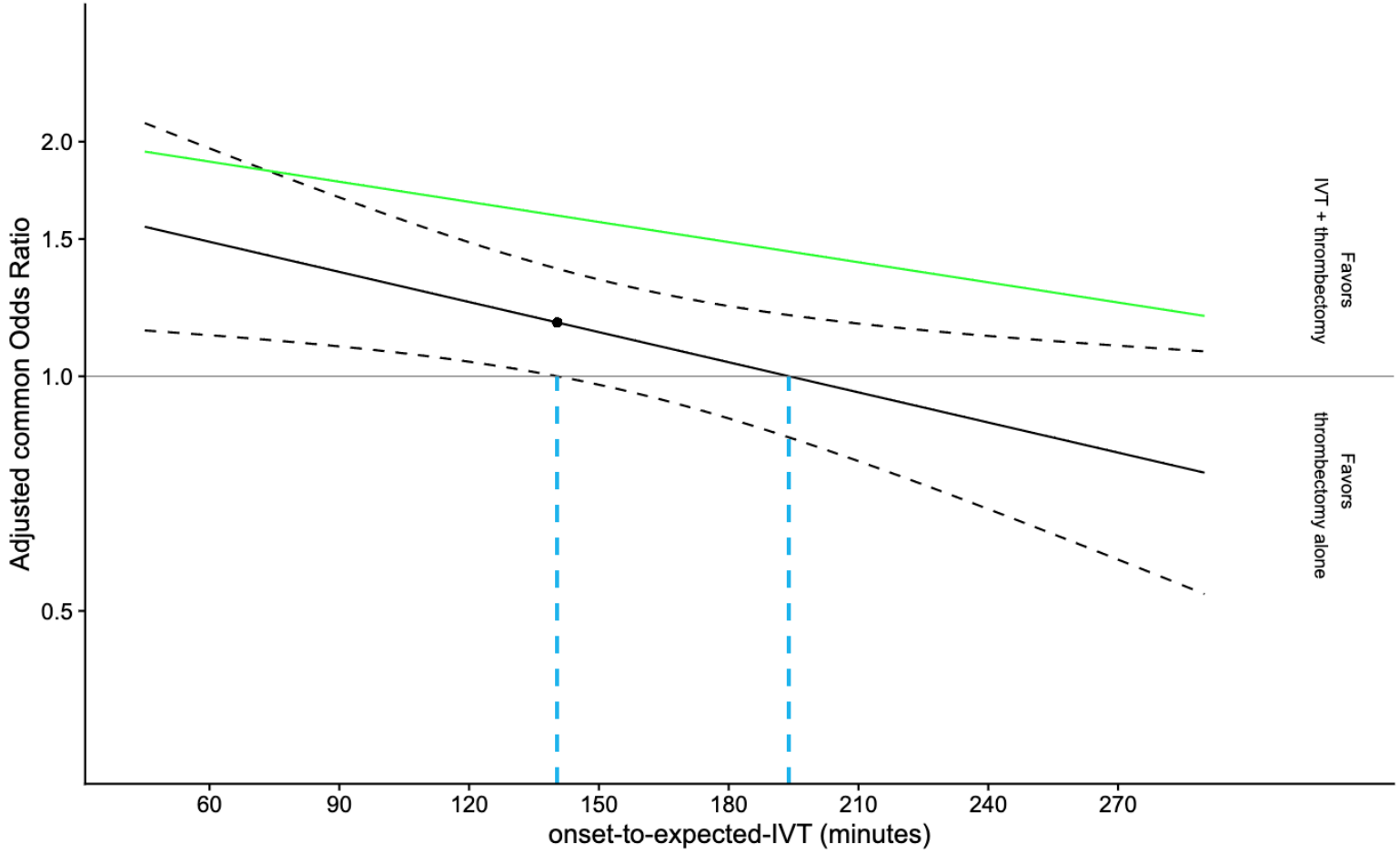
Shown are the predicted number needed to treat and associated 95% CI so that one more patient has a better outcome (at least one point lower on the mRS) with IVT + thrombectomy vs thrombectomy alone (upper right panel), the predicted number needed to treat so that one more patient has an mRS 0-2 when treated with IVT + thrombectomy vs thrombectomy alone (upper left panel). The associated absolute risk differences are shown in the lower panels. For details regarding the calculation see eMethods 4.1 for the panels on the left and eMethods 4.2 for the panels on the right.

eFigure 7 – Influence of onset-to-expected-IVT times on the benefit associated with IVT plus thrombectomy (additional cut-offs)



The solid black line indicates the best model fit of the log odds ratio for a favorable shift on the modified Rankin scale at 90 days associated with intravenous thrombolysis plus thrombectomy vs thrombectomy alone (y-axis, logarithmic scale) and expected treatment delay between symptom-onset to expected administration of intravenous thrombolysis (x-axis, onset-to-expected-IVT in minutes, P for interaction 0.02). The area between the two dashed black lines refers to the 95% confidence interval of the adjusted common Odds Ratio. An adjusted common odds ratio >1 indicates better outcomes (favorable shifts on the modified Rankin scale) associated with intravenous thrombolysis plus thrombectomy. The dashed red lines indicate the cut-offs where there is 97.5% certainty that the association of IVT+thrombectomy and better outcomes is larger than an absolute difference of mRS 0-2 of 1.3%, as well as the cut-offs at which there is 97.5% certainty that the benefit associated with IVT + thrombectomy is likely smaller than an absolute difference of 3% and 5% in the rates of mRS 0-2, respectively. The corresponding onset-to-expected-IVT times of these cut-offs were: 1h 55min (association expected to be larger than a 1.3% benefit), 3h 3min (association expected to be smaller than a 5% benefit), 3h 59min (association expected to be smaller than a 3% benefit). For details regarding these cut-offs see eMethods 4.The upper panel indicates the number of participants observed at each respective bin of onset-to-expected-IVT times.

eFigure 8 – Comparison to trials comparing intravenous thrombolysis versus placebo



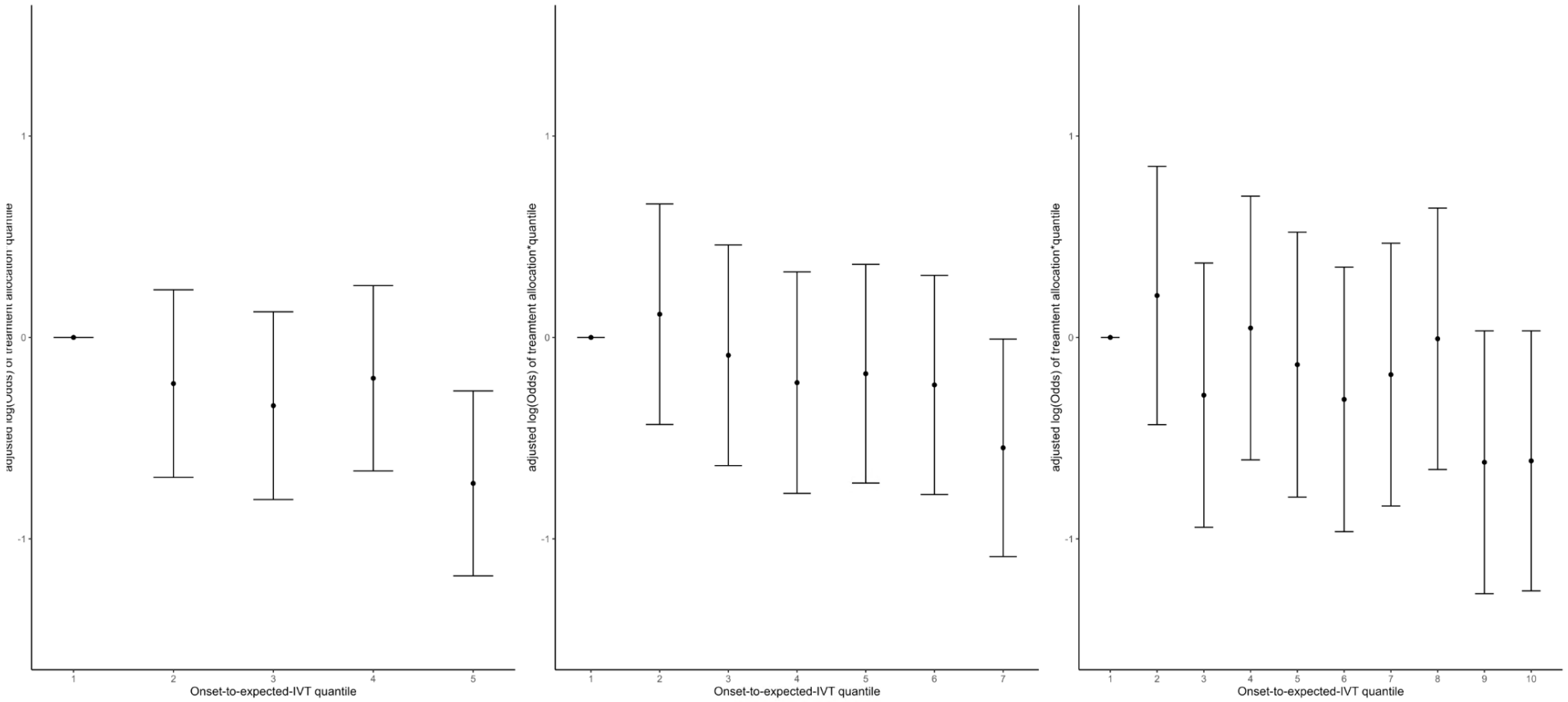
The solid black line indicates the best model fit of the log odds ratio for a favorable shift on the modified Rankin scale at 90 days associated with intravenous thrombolysis plus thrombectomy vs thrombectomy alone (y-axis, logarithmic scale) and expected treatment delay between symptom-onset to expected administration of intravenous thrombolysis (x-axis, onset-to-expected-IVT in minutes, P for interaction 0.02). The area between the two dashed black lines refers to the 95% confidence interval of the adjusted common Odds Ratio. An adjusted common odds ratio >1 indicates better outcomes (favorable shifts on the modified Rankin scale) associated with intravenous thrombolysis plus thrombectomy. The dashed blue lines indicate the time point at which the lower bound of the 95% CI or the point estimate of the adjusted common Odds Ratio crosses 1.0 (2h 20min and 3h 14min, respectively). The green line representes the best fit of the log odds ratio for mRS 0-1 associated with intravenous thrombolysis vs placebo of the model published by Emberson et al.[4]

eFigure 9 – Change in the benefit associated with IVT plus thrombectomy over onset-to-expected –IVT time quantiles

(A) Five quantiles

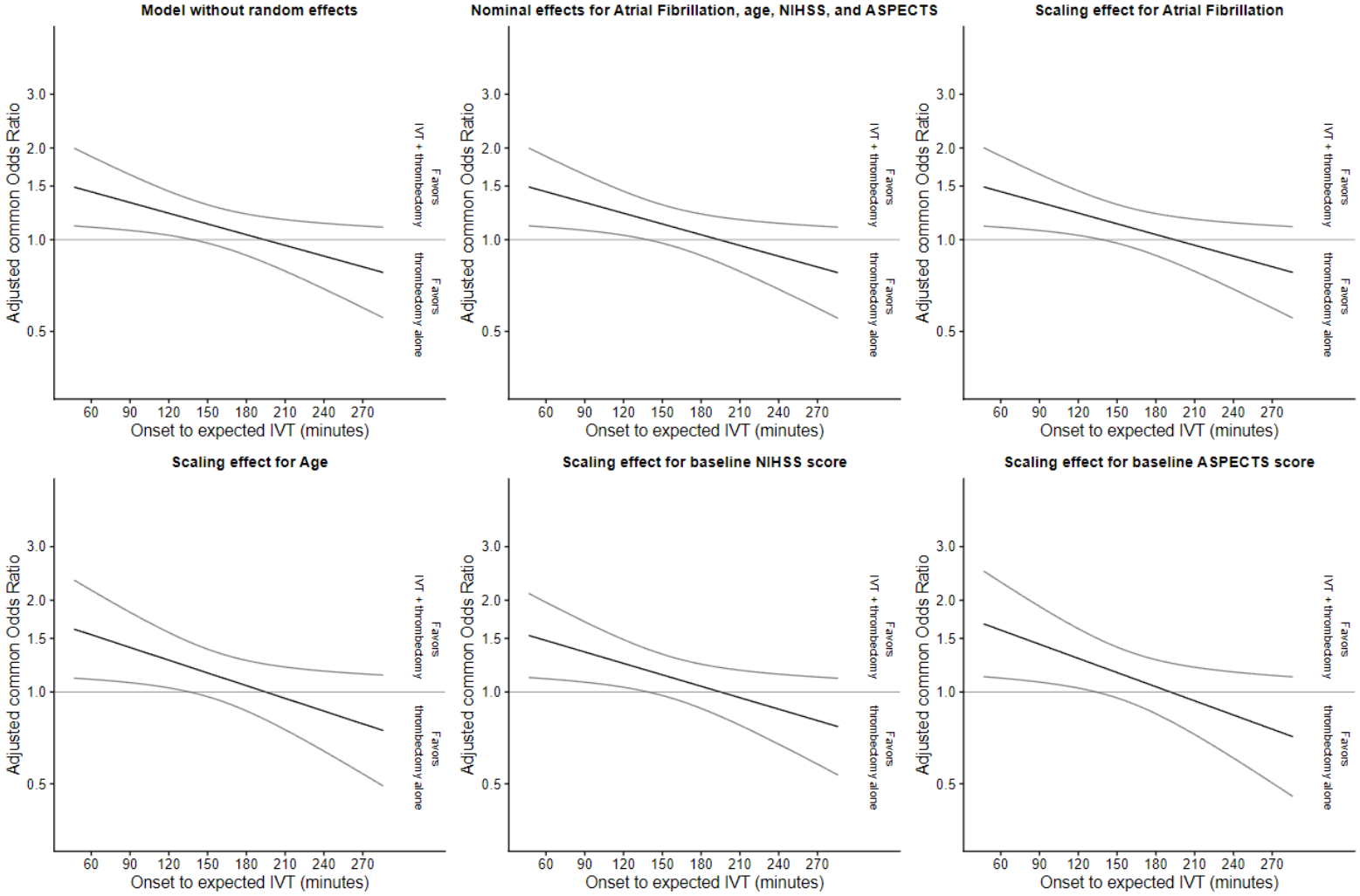
(B) Seven quantiles

(C) Ten quantiles



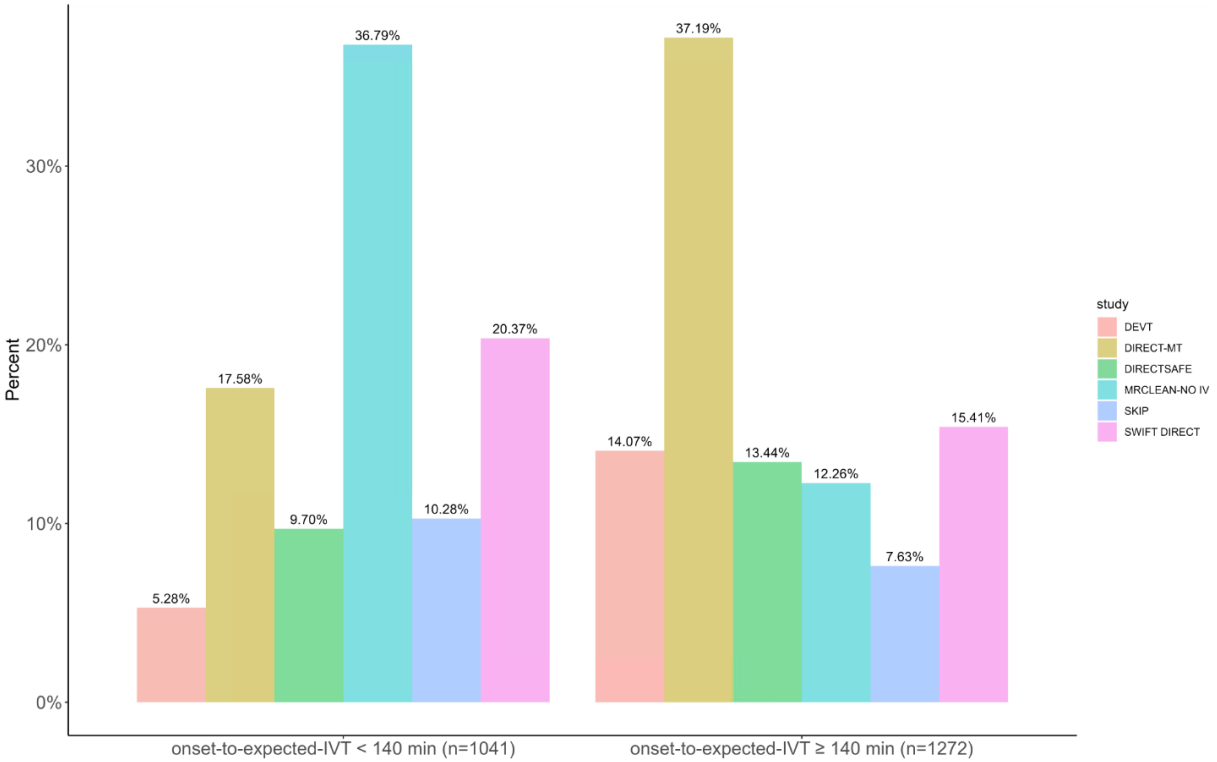
Adjusted log odds of an interaction term with treatment allocation*onset-to-expected-IVT quantile (n=5, 7 and 10) are shown. This term was included in the primary model instead of treatment allocation*onset-to-expected-IVT. Herewith the association can change freely within each quantile stratum. Log odds <0 of the interaction term indicate a decreasing beneficial association in patients treated with intravenous thrombolysis plus thrombectomy over time. The first quantile constitutes the reference category in each graph. In all 3 graphs a linear association between the log odds of the interaction term and increasing quantiles appears an adequate fit.

eFigure 10 – Effect of relaxing the proportional odds assumptions



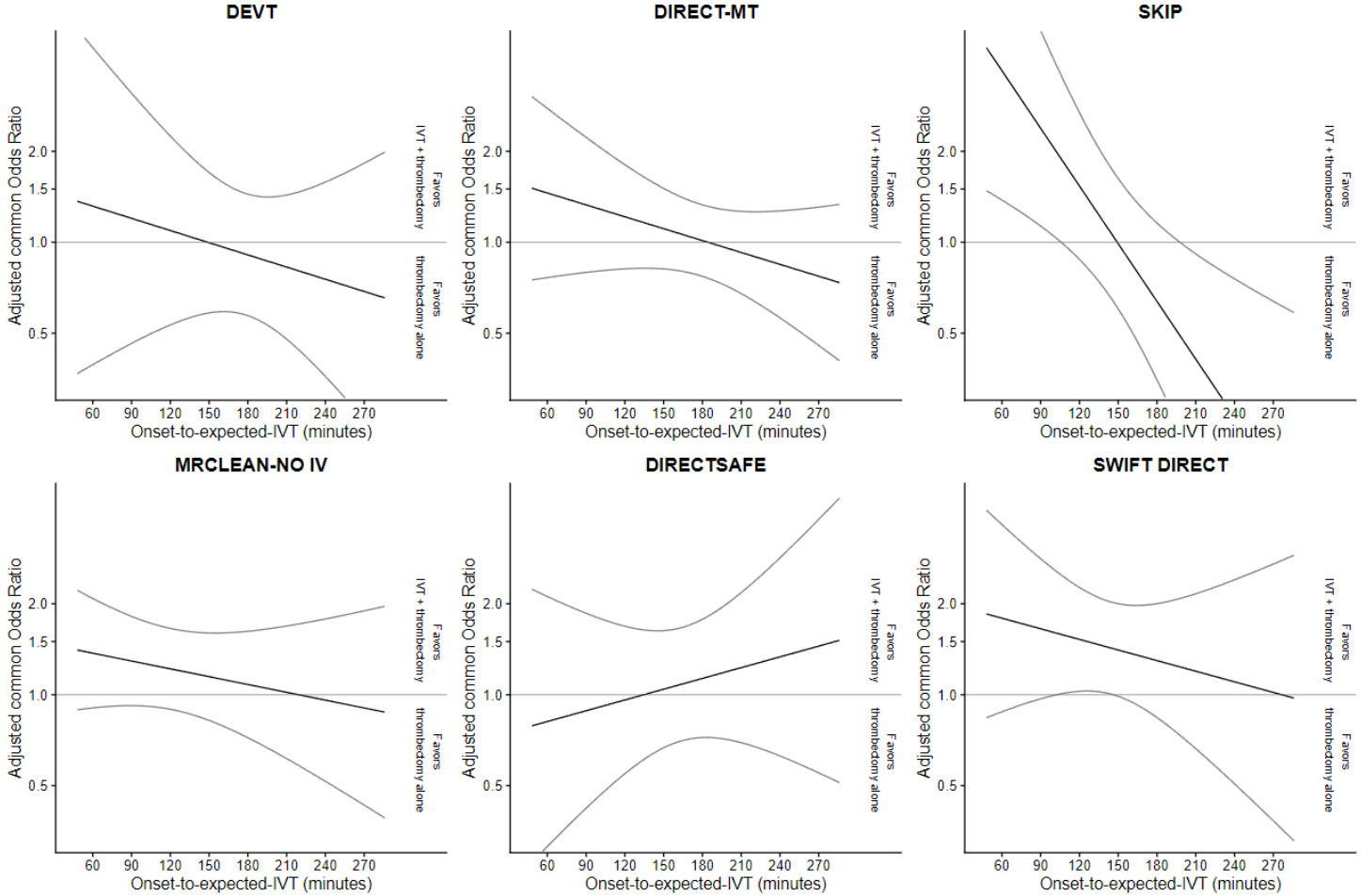
Relaxing the proportional odds assumption using nominal and scaling effects for adjustment variables showed violation of the proportional odds assumption. With implementation of nominal and scaling effects, the 95% confidence intervals are wider, but the overall effect and time point of loss of significance did not vary substantially. Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score.

eFigure 11 – Contribution of participants of each trial before and after 2 hours 20 minutes



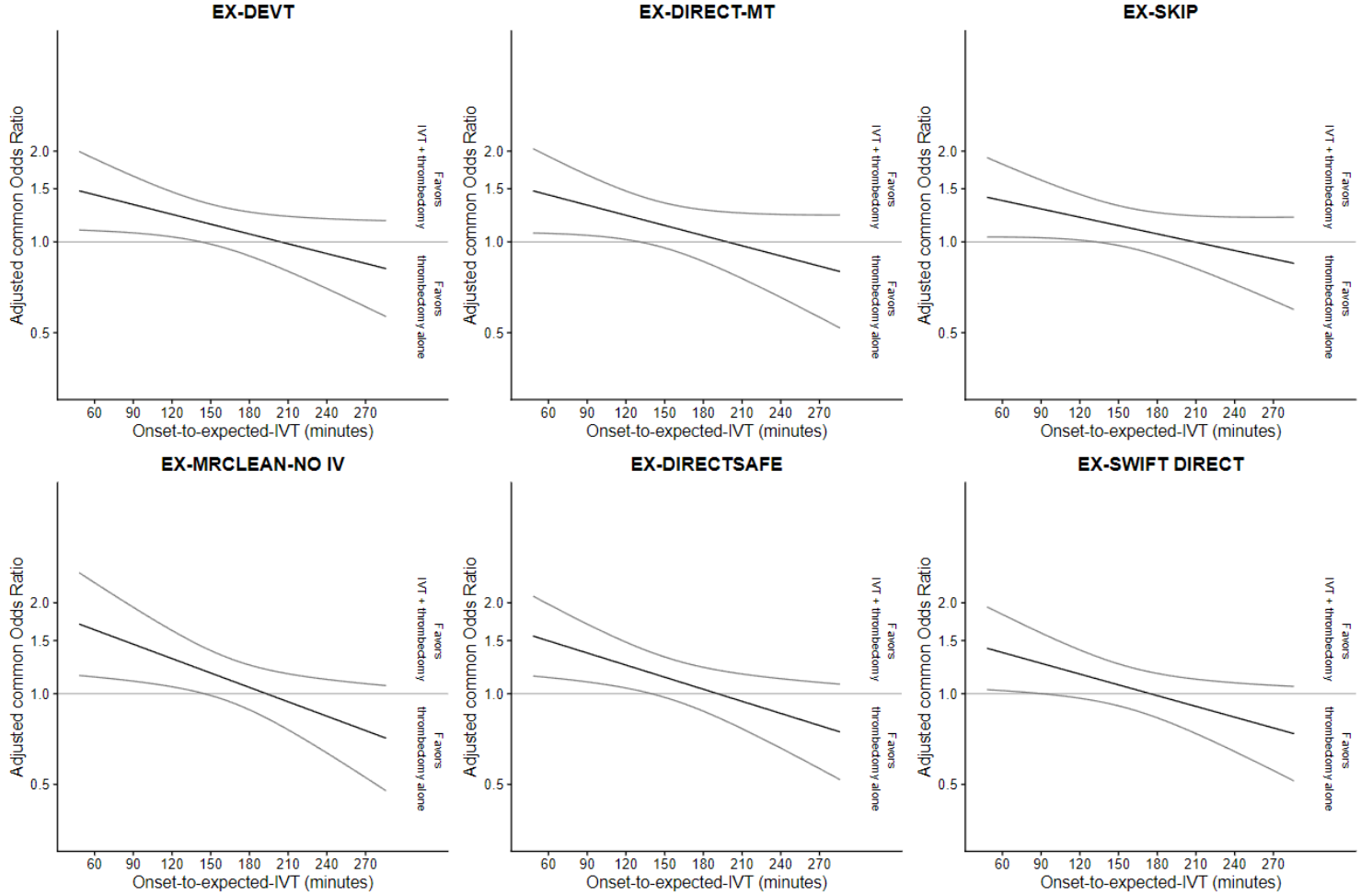
The proportion of participants of each trial for participants with onset-to-expected IVT times shorter than or equal to/greater than 140 minutes is shown. Of the participants with onset-to-expected-IVT times <2h 20min, 37% were included in the MRCLEAN-NO IV trial, while 37% of participants with onset-to-expected-IVT ≥2h 20min were enrolled in DIRECT MT. Across the other trials there were almost equal proportion of participants with onset-to-expected-IVT times < and ≥ 2h 20min. The cut-off of 2h 20min was based on the primary analysis as the time point where the lower bound of the 95% confidence interval of the estimated treatment effect of intravenous thrombolysis plus thrombectomy vs thrombectomy alone first crossed 1.0.

eFigure 12 – Study-level associations



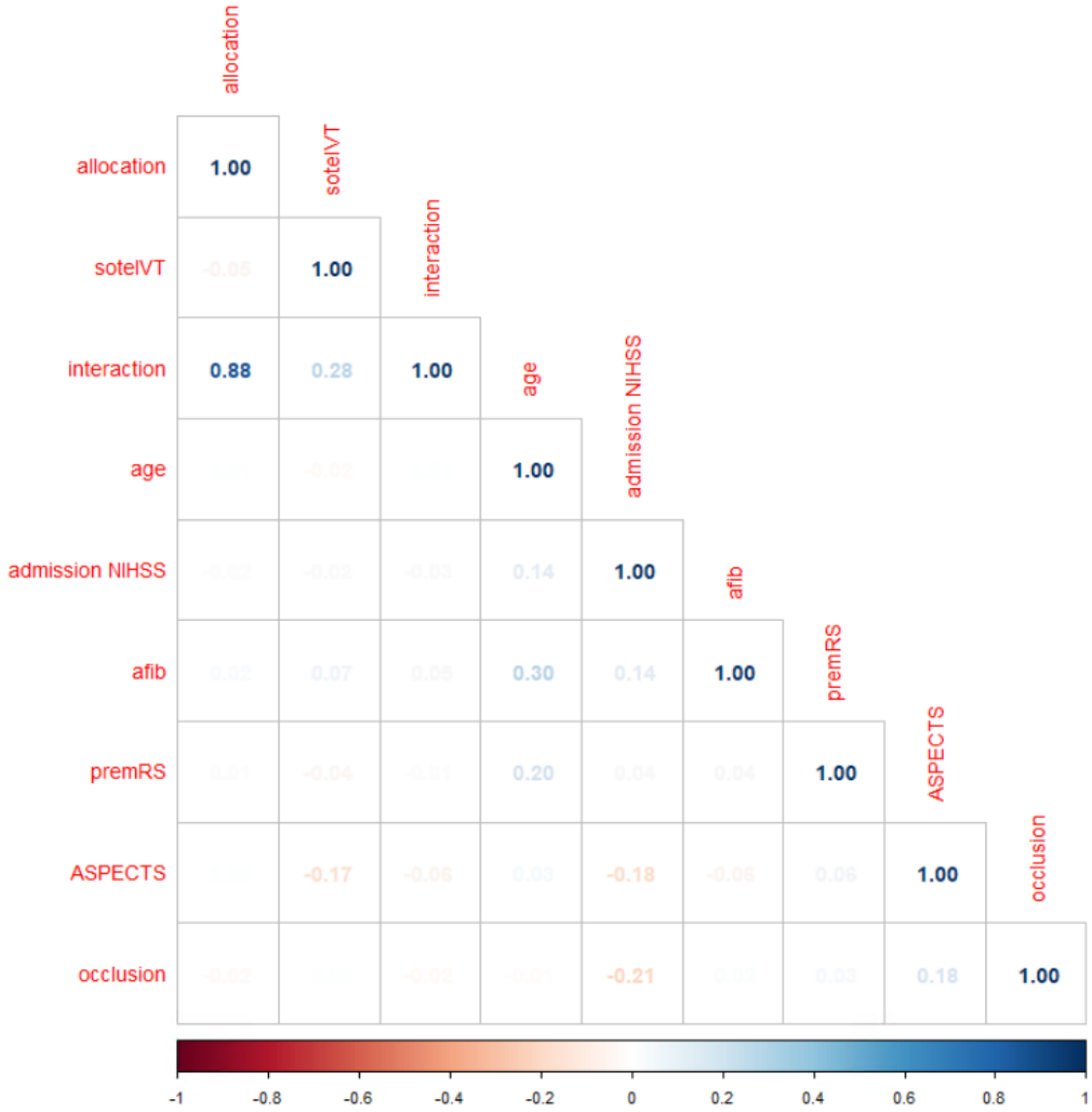
The black lines indicate the best model fit of the log odds ratio for a favorable shift on the 90-day modified Rankin scale in participants treated with intravenous thrombolysis plus thrombectomy versus thrombectomy alone (y-axis) and expected treatment delay to intravenous thrombolysis (x-axis) for each trial. The grey lines indicate associated 95% confidence intervals. An adjusted common odds ratio >1 indicates better outcomes (favorable shifts on the modified Rankin scale) associated with intravenous thrombolysis plus thrombectomy. The decrease of the adjusted common Odds Ratio over time was strong in SKIP, whereas in DIRECT SAFE the association of intravenous thrombolysis plus thrombectomy versus thrombectomy alone with better outcomes was higher in patients treated later. Models were run as per the primary analysis but without a random-effects term.

eFigure 13 – Leave-one-study-out associations



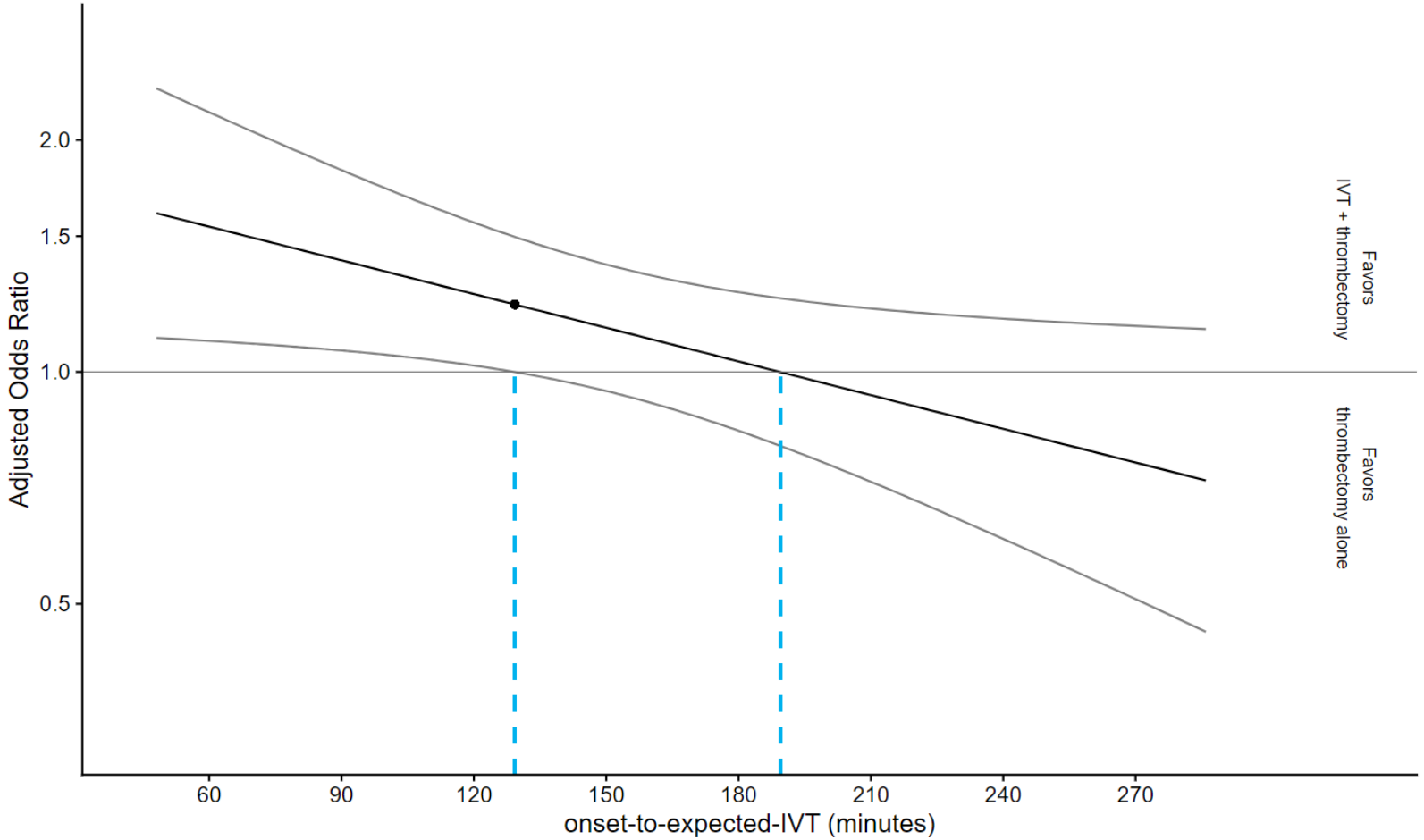
The black lines indicate the best model fit of the log odds ratio for a favorable shift on the 90-day modified Rankin scale in participants treated with intravenous thrombolysis plus thrombectomy versus thrombectomy alone (y-axis) and expected treatment delay to intravenous thrombolysis (x-axis) for a population where one trial was excluded each time. The headings of the plots indicate which trial was left out in the analysis depicted by the respective graph (e.g. EX-DEVT indicating that individual participant data from DEVT was left out from the analysis). The grey lines indicate associated 95% confidence intervals. An adjusted common odds ratio >1 indicates better outcomes (favorable shifts on the modified Rankin scale) associated with intravenous thrombolysis plus thrombectomy.

eFigure 14 – Correlation matrix of covariates in the primary model



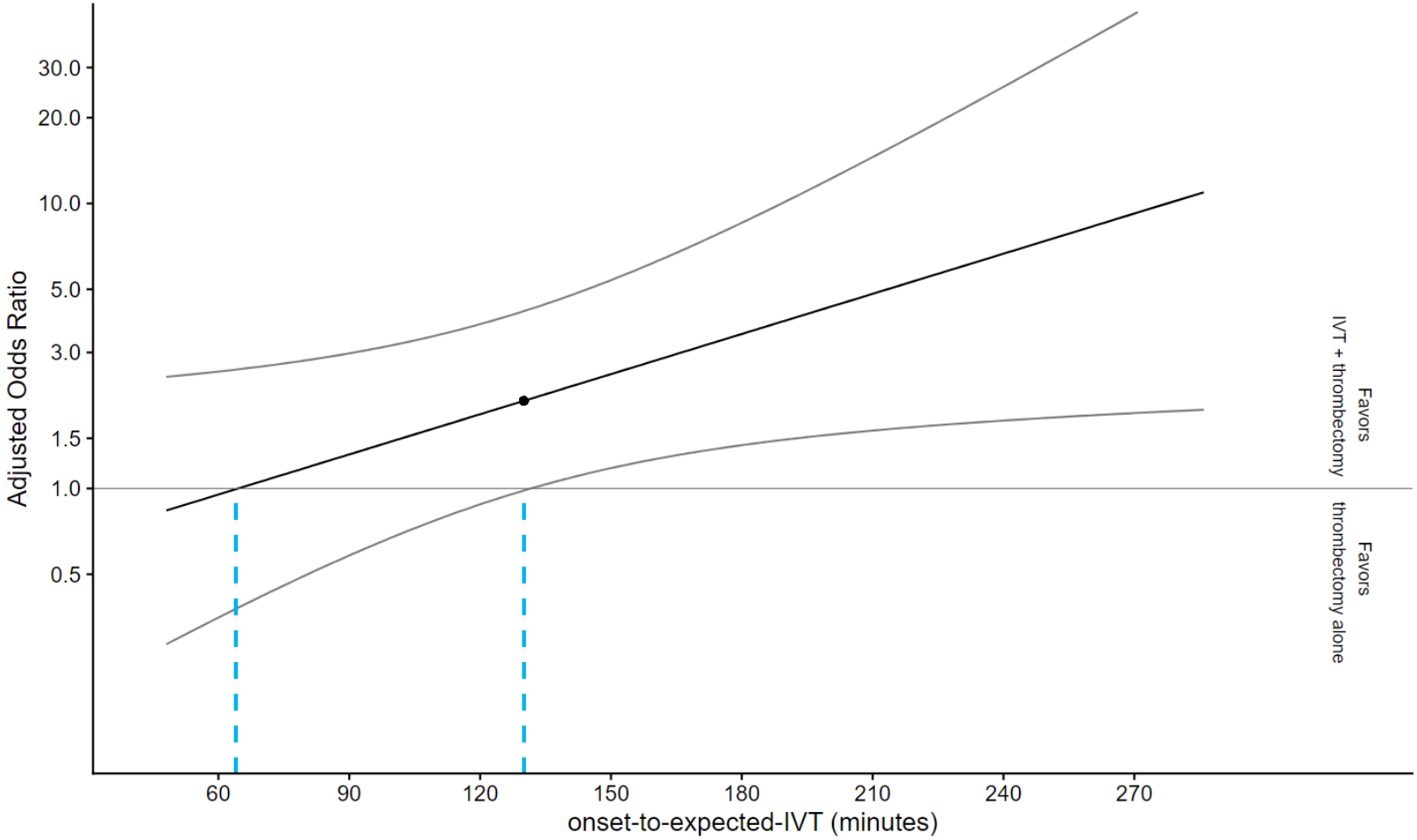
The correlation coefficients (Spearman's rho) of the dependent variables in the model are shown. Shades of red indicate a negative association, while shades of blue indicate a positive association. Shading to white indicates less observed correlation. The variable names are as follows: allocation, intravenous thrombolysis plus thrombectomy versus thrombectomy alone; soteIVT, symptom-onset-to-expected-IVT; interaction, interaction term symptom-onset-to-expected-IVT*group allocation; NIHSS, National Institutes of Stroke Scale Score; afib, atrial fibrillation; premRS, pre-stroke modified Rankin scale; ASPECTS, Alberta Stroke Program Early CT Score; occlusion, type of occlusion on qualifying CT angiography or MR angiography.

eFigure 15 – Change in the association between intravenous thrombolysis plus thrombectomy versus thrombectomy alone and rates of mRS 0-2



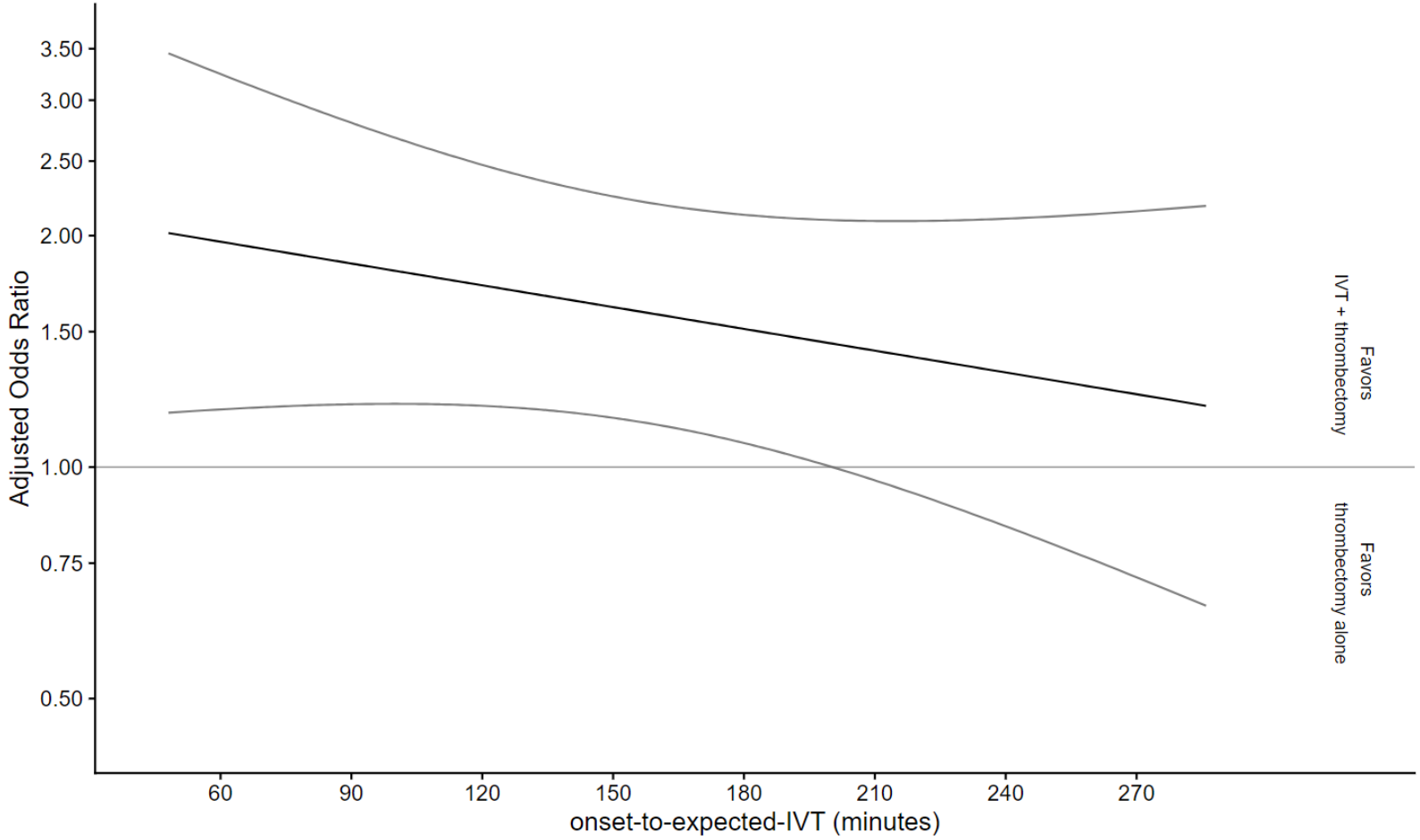
The black line indicates the best model fit of the log odds ratio for modified Rankin scale 0–2 of participants treated with intravenous thrombolysis plus thrombectomy versus thrombectomy alone (y-axis) and expected treatment delay to intravenous thrombolysis (x-axis, *P* for interaction 0.03). The grey lines indicate the associated 95% confidence interval. An adjusted common odds ratio >1 indicates that higher rates of modified Rankin scale 0–2 were associated with intravenous thrombolysis plus thrombectomy. Dashed blue lines indicate the time-points where the lower boundary of the 95% CI of the estimated association or the point estimate of the association crossed 1.0 (2h 9min and 3h 9min, respectively).

eFigure 16 - Change in the association of intravenous thrombolysis plus thrombectomy versus thrombectomy alone and early recanalization on first angiographic images



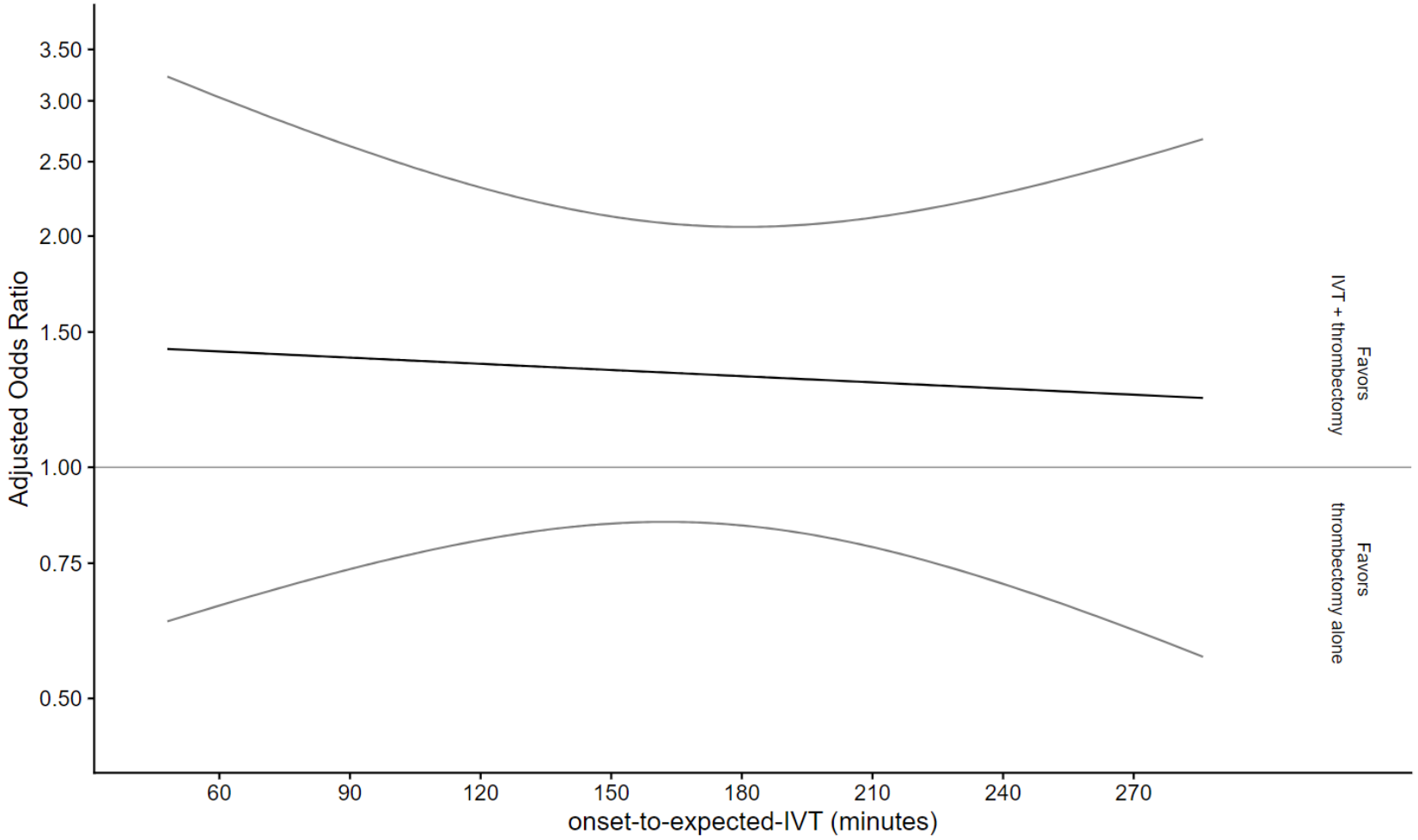
The black line indicates the best model fit of the log odds ratio for early recanalization of participants treated with intravenous thrombolysis plus thrombectomy versus thrombectomy alone (y-axis) and expected treatment delay to intravenous thrombolysis (x-axis, *P* for interaction 0.03). The grey lines indicate the associated 95% confidence interval. An adjusted common odds ratio >1 indicates that higher rates of early recanalization were associated with intravenous thrombolysis plus thrombectomy. Dashed blue lines indicate the time points where the point estimate of the estimated association or the lower boundary of the 95% CI of the estimated association crossed 1.0 (1h 4min and 2h 10min, respectively).

eFigure 17 - Change in the association of intravenous thrombolysis plus thrombectomy versus thrombectomy alone and successful reperfusion (TICI2b-3) at the end of the endovascular intervention



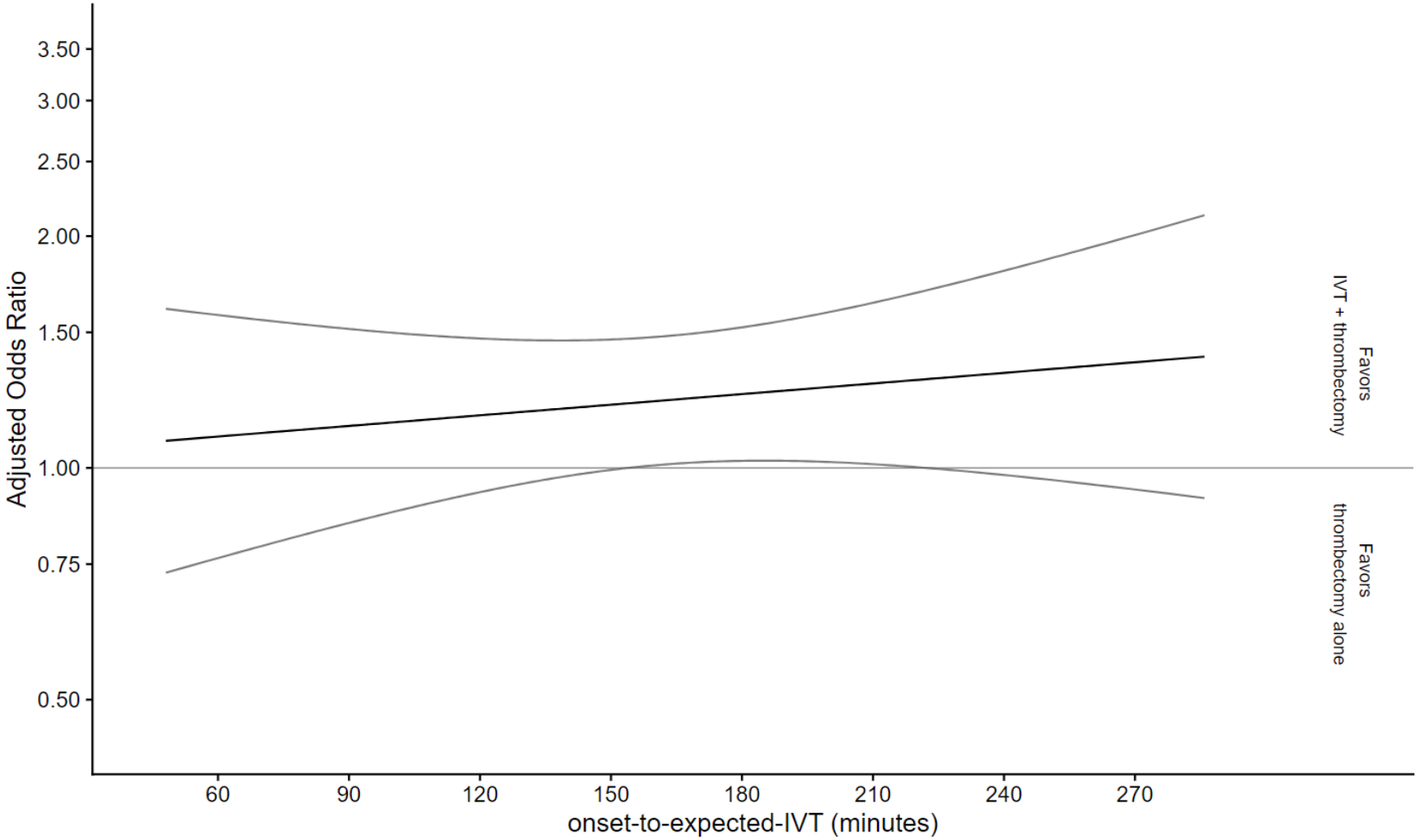
The black line indicates the best model fit of the log odds ratio for successful reperfusion (Thrombolysis in Cerebral Infarction score 2b–3) of participants treated with intravenous thrombolysis plus thrombectomy versus thrombectomy alone (y-axis) and expected treatment delay to intravenous thrombolysis (x-axis). The interaction was not significant (*P* for interaction 0.26). The grey lines indicate the associated 95% confidence interval. An adjusted common odds ratio >1 indicates that higher rates of successful reperfusion were associated with intravenous thrombolysis plus thrombectomy.

eFigure 18 - Change in the risk of symptomatic intracranial hemorrhage after intravenous thrombolysis plus thrombectomy versus thrombectomy alone



The black line indicates the best model fit of the log odds ratio for any intracranial hemorrhage in participants treated with intravenous thrombolysis plus thrombectomy versus thrombectomy alone (y-axis) and expected treatment delay to intravenous thrombolysis (x-axis). The interaction was not significant (*P* for interaction 0.86). The grey lines indicate the associated 95% confidence interval. An adjusted common odds ratio >1 indicates a higher risk associated with intravenous thrombolysis plus thrombectomy.

eFigure 19 - Change in the risk of any intracranial hemorrhage after intravenous thrombolysis plus thrombectomy versus thrombectomy alone



The black line indicate the best model fit of the log odds ratio for any intracranial hemorrhage in participants treated with intravenous thrombolysis plus thrombectomy versus thrombectomy alone (y-axis) and expected treatment delay to intravenous thrombolysis (x-axis). The interaction was not significant (*P* for interaction 0.49). The grey lines indicate the associated 95% confidence interval. An adjusted common odds ratio >1 indicates a higher risk associated with intravenous thrombolysis plus thrombectomy.

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