Supplementary Online Content

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

eMethods 1. RESCUE BRAIN Investigators and Contributors

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eMethods 2. MRI Protocol

The MRI protocol included: (1) a DWI sequence with 24 axial slices of 5-mm thickness, a matrix of 96×64 pixels, echo time (TE) = 98.9 ms, repetition time (TR) = 2825 ms, b = 0 standard acquisition and b = 1000 s/mm^2; (2) a fluid-attenuated inversion recovery (FLAIR) sequence with axial slices of 5-mm thickness (interslices of 1.5 mm), matrix of 256×256, TR = 8800 ms, TE = 140 ms, inversion time (TI) = 2200 ms; (3) a T2* sequence with 6-mm thickness axial slices, TE = 15 ms, TR = 500 ms, 20° angle; and (4) analysis of the circle of Willis using three-dimensional time-of-flight magnetic resonance angiography with 1.4-mm thickness slices, matrix 256 × 192, TR = 2825 ms, and TE = 92.6 ms.

eMethods 3. Statistical Analysis Plan

Statistical Analysis Plan for Final Analysis of RESCUE BRAIN study:

The REmote iSchemic Conditioning in acUtE BRAin INfarction study.

Trial registration: NCT02189928

Protocol version: The SAP has been written based on information contained in the study protocol version 6, dated 24 April 2017.

Roles and Responsibilities of SAP contributors

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Table of Contents

List of Abbreviations

BMI	Body mass index
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
DWI	Diffusion weighted imaging
ECASS 3	European Cooperative Acute Stroke Study 3
IA	Intra-arterial
ICA	Internal carotid artery
ITT	Intent-to-treat
IV	Intravenous
mTICI	Modified treatment in cerebral infarction
MRI	Magnetic resonance imaging
mRs	Modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
PP	Per-protocol
PROBE	Prospective randomized open blinded end-point
TIA	Transient ischemic stroke
rIPerC	remote ischemic per-conditioning
rt-PA	Recombinant tissue plasminogen activator

(1) INTRODUCTION

a. Background and rationale

Currently, recommended treatments for patients with acute ischemic stroke include intravenous (IV) fibrinolysis (recombinant tissue plasminogen activator (rt-PA)), aspirin, and mechanical thrombectomy.(1,2) A potential new treatment—remote ischemic per-conditioning (rIPerC)—involves the application of pressure around a limb (sufficient to stop blood flow) during acute stroke in order to induce transient local ischemia,thus leading to ischemic tolerance in the brain. (3,4)

b. Research hypothesis

The null hypothesis is that there is no difference in infarct growth at 24-hours between intervention (rIPerC) and control groups. The alternative hypothesis is that there is a difference between the two groups.

c. Study Objectives

The primary objective of the RESCUE BRAIN trial is to determine the effectiveness (superiority) of remote ischemic per-conditioning compared to absence of ischemic per-conditioning (control) in addition to usual care for decreasing the infarct growth at 24-hours after inclusion.

Secondary objectives are:

1) To determine the effectiveness of the rIPerC compared to absence of ischemic per-conditioning (control) to improve:
    - clinical efficacy outcomes
    - recanalization rate after IV rtPA
2) To compare the safety of the rIPerC compared to absence ischemic per-conditioning (control).
3) To assess the tolerance and side effects of rIPerC

(2) TRIAL METHODS

a. Trial design

The RESCUE BRAIN trial, is a multicenter, randomized, parallel group, controlled, open-label, with blinded endpoint evaluation (PROBE design). It as an academic trial designed to answer the question: is rIPerC efficative for decreasing the infarct growth. Patients are recruited from 10 stroke centers in France. Adults patients admitted with an acute ischemic stroke (MRI-proven), within 6 hours of the onset of symptoms are randomized to be received either by rIPerC or no ischemic per-conditioning (control) with an allocation ratio of 1:1.

b. Randomisation

The randomization process is described in full within the clinical trial protocol. To be brief, a web-based randomization procedure using a randomization table provided by an independent statistician (using random permutated blocs of varying sizes, stratified by center and use of IV thrombolysis) was performed.

c. Sample size

Full details of the sample size is described within the clinical trial protocol. A sample size of 100 per group will have 80% power to detect a difference in infarct growth (absolute change in brain infarct volume from baseline to 24 hours) of 15cm^3 with a 0.05 two-sided significance level, by assuming a standard deviation of 36 cm^3 and taking into account an anticipated rate of unusable MRIs of 10%.

d. Framework

Primary and secondary objectives of RESCUE BRAIN trial are testing for superiority.

e. Timing of outcome assessments

The time points at which outcomes are measured in provided in table 1. Full detail of the schedule of the study procedures including expected visit dates and visit windows are described within the clinical trial protocol.

Table 1. The schedule of study procedures related to outcome measures

Outcomes	Baseline (initial MRI)	rIPerC treatment	End of acute stroke treatment	24 hrs Post-Randomization (MRI control)	Day 7 Post Randomization	90 days Post-Randomization
Brain infarct volume	X			X		
NIHSS	X			X	X	X
mTICI	X		X	X		
mRs	X					X
Barthel						X
Intracerebral hemorrhage (ECASS3 classification)				X		
Pain (EVA)		X				
Adverse events		X	X	X	X	X

(3) STATISTICAL PRINCIPLES

a. Confidence intervals and p-values

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

No correction for multiple comparisons will be applied; all secondary objectives will be considered as exploratory. All confidence intervals (CI) presented will be 95%CI and 2-sided.

b. Adherence and Protocol Deviations

Adherence to the intervention is defined as patients who underwent the 4 cycles of inflation/deflation in experimental arm (rIPerC) and none cycle of inflation/deflation in control arm. The number and % of patients with adherence to the intervention will be provided by treatment group, with no formal statistical comparison. The following protocol deviations are pre-defined as major protocol violations with a direct bearing on primary outcome:

1) Patients without adherence to the intervention (as defined above)
2) Patients who did not received the allocated intervention

Protocol deviations are identified and classified as major or minor in blind reviews before the database freezing. The number and % of patients with major and minor protocol deviations will be provided by treatment group, with details of the type of deviation. No formal statistical comparison will be done.

c. Analysis population

Intent-to-treat (ITT): The ITT population will include all randomized patients, regardless of their eligibility and any protocol deviations, according to the treatment group to which they were assigned at randomization. The ITT population will be the primary analysis population for primary and secondary efficacy outcomes.

Per-protocol (PP): The PP population will include all randomized patients excluding:

1) Patients with major protocol deviations
2) Patients without primary outcome measure (DWI measure of brain infarct volume at baseline and 24-hours).

PP analysis will be considered only for primary outcome as a secondary analysis.

Safety population: The safety population will include all randomized patients by comparing patients who underwent at least part of the per-conditioning regimen (at least one cycle of cuff inflation) versus other

patients.

(4) TRIAL POPULATION

a. Screening data

The overall recruitment period will be provided in months.

b. Eligibility

The trial inclusion and exclusion criteria are full detailed in clinical trial protocol. The number of ineligible patients randomized will be reported by treatment group (figure 1).

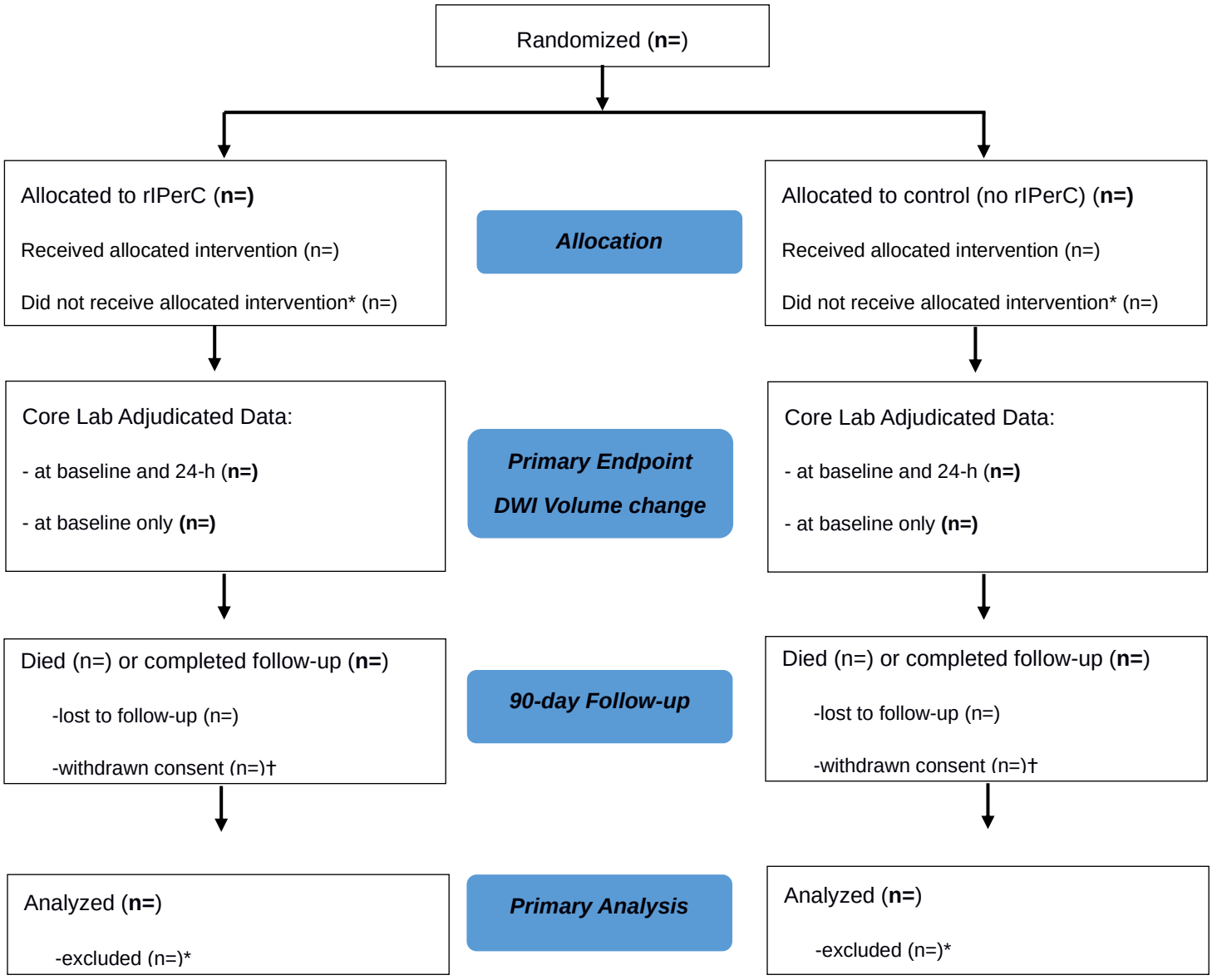
c. Withdrawal/Follow-up-level of withdrawal

The level of withdrawal will be tabulate and classified as:

1) Withdraw consent from follow-up but allow data collected to date to be used
2) Withdraw consent from follow-up and withdraw consent for data collected to date to be used
3) Withdraw due to lost to follow-up
4) Withdraw due to investigator decisions

The timing of withdrawal and reasons for withdrawal will be provided by treatment group according to flow diagram (figure 1).

Figure 1. Flow of participation in the RESCUE BRAIN trial.



* Reasons will be provided
† Level of consent withdrawal will be provided

d. Baseline patient characteristics

Detail of baseline characteristics are reported in table 2. Baseline characteristics will be described, in overall and according treatment groups. Quantitative variables will be expressed as mean (standard deviation) or median (interquartile range) for non-Gaussian distribution. Categorical variables will be expressed as frequencies and percentages. Normality of distribution will be assessed graphically and using the Shapiro-Wilk test. The number of missing data will be also reported. No formal statistical comparisons will be done; clinical importance of any imbalance will be noted.

Table 2. Baseline patient's characteristics

Characteristics	**Overall** (N=)	**rIPerC** (N=)	**Control** (N=)
Baseline demographics and medical history			
Age, years			
Men			
BMI			
Medical history			
Hypertension			
Diabetes			
Hypercholesterolemia			
Current smoking			
Former smoking			
Coronary artery disease			
Previous stroke or TIA			
Previous atrial fibrillation			
Previous cardiac insufficiency			
Previous antithrombotic therapy			
Antiplatelet			
Anticoagulant			
Current stroke event			
Admission Systolic blood pressure, mmHg			
Admission Diastolic blood pressure, mmHg			
Admission Glucose, mmol/l			
Admission NIHSS score			
Pre-stroke mRS			
0			
1			
2			
3			
>3			
Time from symptom onset to baseline MRI			
Occlusion at MRI			
None			
M1-MCA			
M2-MCA			
Carotid T			
Cervical ICA			

Others
Baseline brain infarct volume, cm^3
IV thrombolysis
Onset to IV thrombolysis time[1], min
Endovascular treatment
Onset to groin puncture time[2], min

[1] data reported for IV thrombolysis treated patients. [2] data reported for endovascular treated patients.

(5) Analysis

Data on primary and secondary efficacy/safety outcomes will be performed by the Julien Labreuche and Professor Alain Duhamel from Biostatistics Department of University of Lille.

a. Ouctome definitions

- Primary efficacy outcome is the absolute change in brain infarct volume from baseline to 24-h assessed by blinded core laboratory DWI reading.

- Secondary efficacy outcomes are:

a) the relative change in brain infarct volume from baseline to 24-h assessed by blinded core laboratory DWI reading.

b) the absolute change in NIHSS from baseline to 24-h.

c) the rate of excellent outcome defined as Barthel score≥95 at 90-day

d) global disability assessed by overall distribution of the mRs at 90 days (shift analysis combining scores of 5 and 6)

e) the rate of excellent functional outcome defined by a mRs ≤1 at 90-day or equal to pre-stroke mRs.

f) the rate of successful recanalization in patients treated by IV thrombolysis defined by a mTICI 2b/3 at 24-hours MRI

- Safety outcomes are:

a) the rate of symptomatic intracerebral hemorrhage on brain imaging at 24h (according to ECASS3 classification)

b) the rate of early neurological deterioration defined as NIHSS increase ≥4 from baseline to 24h

c) the rate of all-cause mortality at 90-day

d) rIPerC related events (deep vein thrombosis, acute limb ischemia, skin lesion)

e) rIPerC tolerance assessed by visual analog scale for pain during per-conditioning ischemic

e) serious adverse events (definitions are detailed in protocol)

b. Analysis methods

- Primary efficacy outcome:

The absolute change in brain infarct volume from baseline to 24h will be calculated and compared between the two treatment group using the constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger (5) including center as random effect and IV thrombolysis as covariable (fixed effect). This model will be used in view of the potential advantages of the cLDA compared to the conventional longitudinal analysis of covariance (ANCOVA) model. (6) In the cLDA, both the baseline and post-baseline values are modeled as dependent variables using a linear mixed model (using an unstructured covariance pattern model), and the true baseline means are constrained to be the same for the 2 treatment groups. Hence, the cLDA provides an adjustment for the observed baseline difference in estimating the treatment effects, using all available baseline and post-baseline values. The between-group mean differences in 24-hour change in brain infarct volume will be estimated by the time-by-arm interaction as treatment effect size. Since we expected a log-distribution of brain infarct volume, we planned to perform analysis on log-transformed brain infarct volume. If normality of model residuals are not satisfied, nonparametric analysis will be used; absolute changes between baseline and 24 hours will be calculated and compared between the 2 treatments groups using non-parametric analysis of covariance adjusted for baseline values. (7, 8). As a secondary analysis, comparison in primary outcome measure will be performed after-pre-specified adjustment for age, sex, admission NIHSS, admission glucose level, endovascular treatment and time from stroke onset to MRI by including pre-specified confounders as covariables in cLDA model.

- Secondary efficacy outcomes:

The relative change in brain infarct volume from baseline to 24-h will be calculated and compared between the two treatment groups using a linear mixed model including center as random effect and IV thrombolysis as covariable (fixed effect). The between-group mean differences will be estimated as treatment effect size. If normality of model residuals is not satisfied (even after log-transformation), nonparametric analysis (Mann-Whitney U test) will be used.

The absolute change in NIHSS from baseline to 24-h will be calculated and compared between the two treatment group using a cLDA model including center as random effect and IV thrombolysis as covariable

(fixed effect). If normality of model residuals are not satisfied (even after log-transformation), nonparametric analysis will be used; absolute changes between baseline and 24 hours will be calculated and compared between the 2 treatments groups using non-parametric analysis of covariance adjusted for baseline values. (7, 8).

For each secondary efficacy binary outcomes (excellent outcomes defined by 90-day Barthel and modified ranking scores, successful reperfusion in IV-thrombolysis treated patients), the numbers and percentages will be reported for each treatment group, and compared using a mixed logistic regression model including center as random effect and IV thrombolysis (except for successful reperfusion) as covariable (fixed effect); adjusted ORs will be calculated as the treatment effect size. The secondary efficacy ordinal outcome (distribution of mRS at 90-day, after combining scores of 5 and 6) (9) will be described by the median (IQR) for each treatment group and compared using a mixed ordinal logistic regression model including center as random effect and IV thrombolysis as covariable (fixed effect); adjusted common OR per 1-point improvement will be calculated as the treatment effect size.

- Safety outcomes:

For the rate of symptomatic intracerebral hemorrhage, early neurological deterioration, and serious adverse events (based on subject counts and not on event counts), the numbers and percentages will be reported for each treatment group, and compared using a mixed logistic regression model including center as random effect and IV thrombolysis as covariable (fixed effect); adjusted ORs will be calculated as the treatment effect size. The rate of specific serious adverse events will be evaluated only descriptively for each treatment group.

All-cause mortality rate at 90-day will be estimated using the Kaplan-Meier method. The number of mortality and Kaplan-Meier event rate at 90-day will be reported for each treatment group. All-cause mortality will be between the two treatment groups by using a frailty model (Cox proportional hazard model with center as random effect and IV thrombolysis as covariates).

rIPerC related events and visual analog scale for pain during per-conditioning ischemic will be evaluated only descriptively in patients with received at least part of the per-conditioning regimen.

c. Subgroup analyses

As exploratory analysis, heterogeneity in treatment effect size on primary outcome according to randomization stratification factor (use of IV thrombolysis) will be evaluated. Estimate (mean difference in infarct growth) in each stratum will be calculated using cLDA model (as defined in primary analysis of primary outcome) and formal interaction test will be done.

A second subgroup analysis will be also done according to occlusion/recanalization subgroups (no initial occlusion, recanalized occlusion, and persistent occlusion). Estimate (mean difference in infarct growth) in each stratum will be calculated using cLDA model (as defined in primary analysis of primary outcome) and formal interaction test will be done.

d. Missing data

Under the ITT principle, all patients who are randomized are included in the primary efficacy analysis. Missing values on primary and secondary efficacy outcomes will be treated by multiple imputation procedure. Missing data will be imputed under missing at random assumption by using regression switching approach (multivariate imputation by chained equations with m=10 imputations) with predictive mean matching method for continuous variables, logistic regression models (binomial, ordinal or multinomial) for categorical variables. The imputation procedure will be perform using main baseline characteristics, and treatment groups. Treatment effect estimates obtained in multiple imputed data sets will be combined using the Rubin's rules. A sensitivity analysis will be performed on the basis of available data (i.e. complete case analysis).

e. Sensitivity analyses

A sensitivity analysis conducted in PP population will be performed for primary outcome only.

f. Additional analyses

No additional analyses are planned.

g. Statistical software

Data will be analyzed using the SAS software (Version 9.4. SAS Institute Inc, Cary, NC, USA). Other packages such as R software may be used if necessary.

(6) References

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eTable. Complete-Case Analysis of Primary and Secondary Efficacy Outcomes

	RIPerC		Control		Effect size	Value (95% CI)	*P* Value
	n	Value	n	Value			
Brain infarct volume, cm^3							
Baseline, median (IQR)	88	9.1 (3.4-38.1)	92	12.1 (3.8-32.0)			
24 hours, median (IQR)	88	12.6 (3.1-49.4)	92	18.6 (4.8-64.9)			
Mean (log_e) change (95% CI)	88	0.29 (0.11-0.48)[a]	92	0.36 (0.18-0.54)[a]	Mean difference (log_e)	–0.07 (–0.31-0.19)[a]	.61[a]
% change in brain infarct volume at 24 hours	86	36.5 (–6.7-96.7)	90	35.2 (–10.0-106.0)	NA	NA	.78
NIHSS score							
Baseline, median (IQR)	93	9 (6-15)	94	10 (7-17)			
24 hours, median (IQR)	93	5 (2-9)	94	7 (2-12)			
Mean (log_e) change (95% CI)	93	–0.59 (–0.75 to –0.43)[a]	94	–0.51 (–0.67 to –0.35)[a]	Mean difference (log_e)	–0.08 (–0.31-0.15)[a]	.48[a]
Successful recanalization in IV-treated patients	63	49 (77.8)	61	51 (83.6)	OR	0.70 (0.28-1.78)	.46
90-day Barthel ≥95	66	49 (74.2)	68	46 (67.7)	OR	1.42 (0.64-3.13)	.38
Excellent outcome[b]	70	41 (58.6)	76	33 (43.4)	OR	1.87 (0.95-3.66)	.067
Favorable outcome[b]	70	53 (75.7)	76	54 (71.1)	OR	1.27 (0.60-2.69)	.52
90-day mRS, median (IQR)	70	1 (1-3)	76	2 (1-3)	Common OR[c]	1.48 (0.82-2.67)	.19

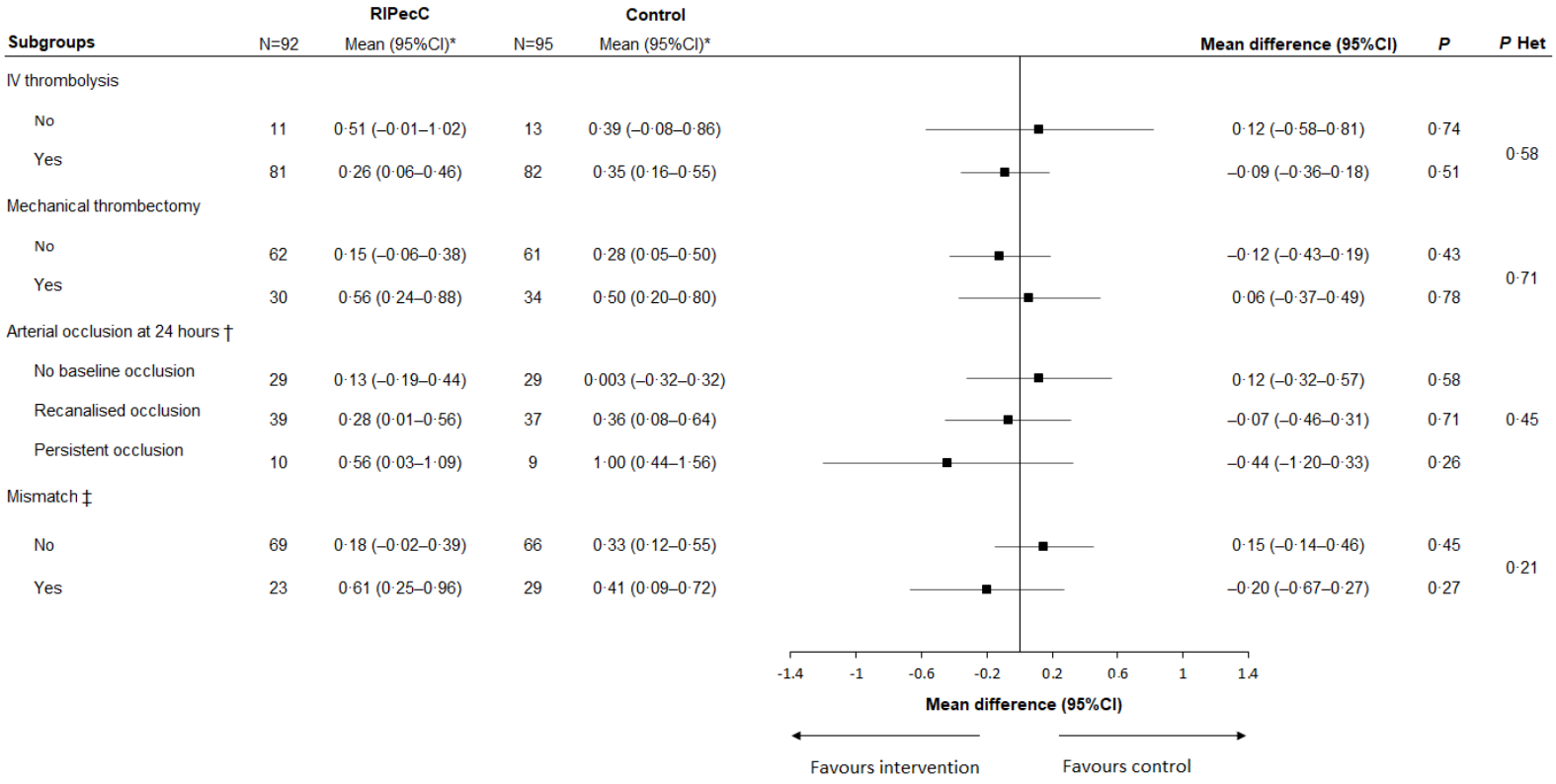
Abbreviations: CI, confidence interval; IQR, interquartile range; IV, intravenous; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; RIPerC, remote ischemic per-conditioning.

[a] Calculated using constrained longitudinal data analysis model adjusted for center (included as random effect) and IV thrombolysis.

[b] Excellent outcome was defined as 90-day mRS 0-1 or equal to pre-stroke mRS. Favorable outcome was defined as 90-day mRS 0-2 or equal to pre-stroke mRS.

[c] Common OR for 1-point improvement in mRS (after 5 and 6 were combined), computed using the ordinal mixed logistic model.

eFigure. Subgroups Analyses for the Primary Outcome: Absolute Change in Brain Infarction Volume From Baseline to 24 Hours



Abbreviations: CI, confidence interval; IV, intravenous; Het, heterogeneity; RIPerC, remote ischemic per-conditioning.
* Calculated among patients with at least one baseline or 24-hour brain infarct volume using constrained longitudinal data analysis model on log transformed (+1) volume, adjusted for center (included as a random effect).
† Arterial occlusion status at 24 hours was missing in 34 patients (n = 14 in RIPerC group).
‡ Unplanned subgroup analysis.

