Outcome in patients treated with intra-arterial thrombectomy: the optiMAL Blood-Pressure Control (OPTIMAL-BP) Trial

Statistical Analysis Plan

Version :1.0 (final)

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24 # Abbreviation

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Abbreviation	Full title
ACA	Anterior cerebral artery
ASPECTS	Alberta Stroke Program Early CT Score
BA	Basilar artery
BP	Blood pressure
CI	Confidence interval
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
DSMB	Data Safety Management Board
ECASS III	European Cooperative Acute Stroke Study III
eCRF	Electronic case report form
EQ-5D-3L	EuroQoL 5-Dimension Self-Report Questionnaire
HI	Hemorrhage infarction
IAT	Intra-arterial thrombectomy
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
IQR	Interquartile range
MCA	Middle cerebral artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mTICI	Modified Treatment In Cerebral Infarction
NIHSS	National Institute of Health Stroke Scale
OPTIMAL-BP	Outcome in patients treated with intra-arterial thrombectomy: the optiMAL Blood-Pressure Control

OR	Odds ratio
PCA	Posterior cerebral artery
PH	Parenchymal hematoma
PP	Per-protocol
PROBE	Prospective, randomized, open-label trial with blinded end-point assessment
SBP	Systolic blood pressure
TOAST	Trial of Org 10 172 in acute stroke treatment

CONTENTS

1. Administrative information

1.1 Study identifiers

Protocol Version: 2.2 Date: 19 May 2021

Clinical Trials.gov register identifier: NCT04205305

1.2 Revision history

Version	**Date**	**Details**
0.1 (draft)	12 Jan 2023	First draft by Hye Sun Lee, Soyoung Jeon, and Hyo Suk Nam
0.2 (draft)	01 Feb 2023	New version following review by Hye Sun Lee, Soyoung Jeon, Hyo Suk Nam, and Ji Hoe Heo
1.0 (final)	21 Feb 2023	New version following review by Hye Sun Lee, Soyoung Jeon, Hyo Suk Nam, and Ji Hoe Heo

1.3 Contributors to the statistical analysis plan

1.3.1 Roles and responsibilities

Name and ORCID	Affiliation	Role on study	SAP contribution
Prof. Hye Sun Lee (ORCID 0000-0001-6328-6948)	Department of Research Affairs, Biostatistics Collaboration Unit, Yonsei University College	Study statistician	Prepared initial draft and all revisions

	of Medicine, Seoul, Korea		
PhD, Soyoung Jeon (ORCID 0000-0002-9916-1917)	Department of Research Affairs, Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Korea	Study statistician	Prepared initial draft and all revisions
Prof. Ji Hoe Heo (ORCID 0000-0001-9898-3321)	Department of Neurology, Yonsei University College of Medicine	Investigator	Reviewed 0.2 to final version
Prof. Hyo Suk Nam (ORCID 0000-0002-4415-3995)	Department of Neurology, Yonsei University College of Medicine	Principal investigator	Reviewed all versions

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106 **1.3.2 Approvals**

107 The undersigned have reviewed this plan and have deemed it to be the final version and in
108 accordance with the protocol requirements within their respective areas. It is also compliant with the
109 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human
110 Use (ICH) E9 Statistical Principles for Clinical Trials.

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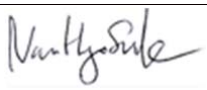
Name	Signature	Date
Prof. Hye Sun Lee		21 Feb 2023

Soyoung Jeon		21 Feb 2023
Prof. Ji Hoe Heo		22 Feb 2023
Prof. Hyo Suk Nam		22 Feb 2023

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2. Introduction

2.1 Study synopsis

We compare the treatment effectiveness and safety between the two groups by dividing them into the intensive control group (less than 140 mmHg of SBP) and the standard control group (SBP 140-180 mmHg) for patients who had successful reopening of occluded large cerebral artery following intra-arterial thrombectomy (IAT).

2.2 Study population

This study being conducted at 19 hospital sites in South Korea, including Severance Hospital, Yonsei University College of Medicine

2.2.1 Inclusion criteria

1. Age ≥20 years
2. Patients who underwent IAT for acute cerebral infarction with large cerebrovascular occlusion (ICA, MCA, M1 or M2, BA, VA, ACA, A1, or PCA, P1)
3. Patients with successful cerebral artery reopening after intraarterial reopening (modified Treatment In Cerebral Infarction score, mTICI 2b or mTICI 3)
4. Patients with elevated BP (SBP ≥140 mmHg) on at least two measurements with a two-minute interval within 2 hours of successful recanalization.

2.2.2 Exclusion criteria

1. Age <20 years
2. Patients whose BP is less than 140 mmHg after successful recanalization through IAT
3. Patients with contraindications for use of antihypertensive medication

4. Patients with symptomatic ICH before participating in the study after the successful arterial reopening

5. Patients with impaired pre-disease neurological function (modified Rankin Scale, mRS >2)

6. Serious medical or surgical illness

7. Patients who are deemed hard to recruit for the study by the investigators.

8. Patients who did not agree to participate in this study

9. Patients who participated in a study that did not allow duplicate participation

2.3 Study interventions

2.3.1 Randomization

The study was conducted as a prospective, randomized, open-label trial with a blinded end-point assessment (PROBE). After successful arterial reopening, the ratio of the intensive group (<140 mm Hg) and conventional group (140-180 mm Hg) proceeds to 1:1. A four-block design randomization was implemented with a block size of 4. The strata were divided based on participating hospitals and NIHSS score <15, or ≥15, and treatment group (the intensive group or the conventional group).

Investigator generated the random allocation using a computerized random sequence generation that was centrally administrated via a password-protected, web-based program at https://obp.smartstroke.net. Once a selection is made, the randomization record is tagged with the patient study allocated identifier, date and time of randomization. A tagged record cannot be selected more than once. Investigator enrolled participants and assigned according to randomized allocation.

2.3.2 Study treatment

Intensive group : the SBP target was <140 mm Hg, obtaining consent form, measuring BP at 1-hour intervals after obtaining consent, and collecting BP and pulse data up to 24 hours.

Control group : the SBP target was 140-180 mm Hg, obtaining consent form, measuring BP at 1-hour intervals after obtaining consent, and collecting BP and pulse data up to 24 hours.

2.4 Outcomes

2.4.1 Primary outcome

1) primary efficacy outcome

- Functional independence at 3 months, defined as a modified Rankin Scale (mRS) score of 0 to 2

2) primary safety outcomes

A. symptomatic ICH within 36 hours

- ✓ Bleeding or hemorrhagic transformation on MRI or CT performed within 24 ± 12 hours or as symptoms worsen
- ✓ Definition of symptomatic hemorrhage according to the European Cooperative Acute Stroke Study III (ECASS III) meets the following three criteria:
  - Any cerebral hemorrhage
  - NIHSS score worse than 4 points or death
  - When neurological deterioration is associated with cerebral hemorrhage

B. Stroke-related death within 90 days

2.4.2 Secondary outcomes

1) Differences in mRS ordinal shift analysis

2) Difference in NIHSS scores at 24 hours after IAT

3) Excellent Day 1 Recovery [Major Neurological Improvement]: NIHSS score of 0-1 or improvement >8

4) Recanalization status on CT Angiography (CTA) or MR Angiography (MRA) at 24 hours

5) Frequency of occurrence of malignant brain edema

6) Health-related quality of life, as assessed by the EuroQoL group EQ-5D-3L

2.5 Sample size

2.5.1 Number of clinical trial subjects calculated

668 patients (334 in each group, significance level α=0.05, statistical power 1-β=0.80, dropout rate 5%)

2.5.2 Hypothesis

H_0: P_A-P_B = 0 (the ratio of poor outcomes in groups A and B is the same)

H_1: PA-$P_B \neq 0$ (the ratio of poor outcomes between groups A and B is not the same)

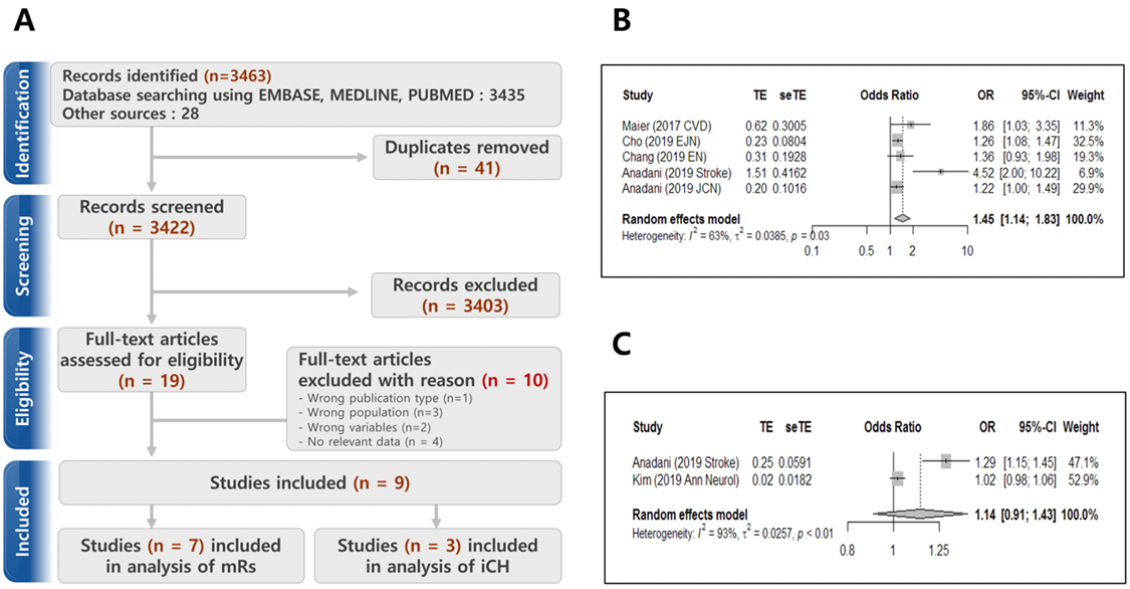
2.5.3 Sample size calculation

We conducted a systematic review to determine the sample-size calculation. We searched Medline and Embase for relevant clinical studies published between January 1993 and October 2019. The following search terms were used: “BP,” “hypertension,” “thrombectomy,” or “endovascular.” We manually searched references of identified studies. Searches were restricted to human studies with full English text. The reference lists of retrieved reports were also hand searched for potentially relevant studies not identified in our electronic database search.

Studies included in this analysis met the following criteria: (1) IAT for ischemic stroke, (2) inclusion of patients with acute ischemic stroke with large-vessel occlusion, (3) analysis comparing the outcomes according to BP within 24 hours after successful recanalization with IAT, and (4) outcome measurements, including mRS score, at 90 days or symptomatic ICH. We also obtained the baseline characteristics from each study: sample size, intervention type, intervention time, baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline BP, functional outcome or 90-day mortality, and symptomatic ICH. Two reviewers (YDK and JKC) independently extracted data, and

disagreements were resolved by consensus. For continuous outcomes (90-day ordinal mRS score) and dichotomous outcomes (symptomatic ICH), we used the odds ratio (OR) with 95% confidence interval (CI) and *P*-values to assess the likelihood of outcomes.

Of a total of 3,436 articles identified, 9 met the inclusion criteria (Figure A). Among the seven articles regarding the outcome, two were excluded: one because we could not calculate the effect size, and the other because no regression coefficient was reported. Finally, five papers that used continuous systolic BP (SBP) were chosen. The OR was calculated using the generic inverse variance estimation method. A 10-mmHg increase in the mean SBP ≤ 24 hours after successful recanalization with IAT was correlated with worse 90-day mRS (OR 1.45, 95% CI 1.14–1.83, p = 0.002) (Figure B). Symptomatic ICH was not associated with a mean SBP increase of 10 mmHg after successful recanalization with IAT (OR 1.14, 95% CI 0.91–1.43, p = 0.267) (Figure C).



235 A study by Goyal et al. used a design similar to ours with an aggressive SBP-lowering target of <140
236 mmHg.[1] They compared an aggressive SBP-lowering target of <140 / 90 mmHg with a moderate or
237 permissive BP target of <185 / 105 mmHg.
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	Studies	Ordinal or logistic regression	OR (95% CI)	Adjusted OR (95% CI) per 10 mmHg for poor outcome	Number of patients	Measurements
1	Maier (2017)[2]	OR (1 mmHg) for good outcome	0.94 (0.88–0.99)	1.86 (1.11–3.59)	168	Continuous SBP
2	Cho (2019)[3]	OR (10 mmHg) for ordinal mRS	1.26 (1.08–1.48)	1.26 (1.08–1.48)	313	Continuous SBP
3	Chang (2019)[4]	OR (10 mmHg) for ordinal mRS	1.36 (0.93–1.98)	1.36 (0.93–1.98)	90	Continuous SBP
4	Anadani (2019)[5]	OR (1 mmHg) for good outcome	0.86 (0.79–0.93)	4.52 (2.07–10.56)	1149	Continuous SBP
5	Anadani (2019)[6]	OR (1 mmHg) for good outcome	0.98 (0.96–0.999)	1.22 (1.01–1.50)	276	Continuous SBP
	Subtotal	OR (10 mmHg) for ordinal mRS		**1.45 (1.14–1.83)**	1996	
6	Goyal (2017)[1]	OR for poor outcome (ref: intensive group)	**2.19 (0.54–8.86)**		140	Target SBP
		OR for good outcome (ref: intensive group)	0.46 (0.11–1.84)			

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240 **Outcome according to target BPs in Goyal's article[1]**

	Good outcome (mRS 0–2)	Poor outcome (mRS 3–6)	Total
Intensive group (Target BP < 140/90 mmHg)	7 (70%)	3 (30%)	10 (100%)
Moderate or permissive group (Target BP < 185/105 mmHg)	67 (52%)	63 (48%)	130 (100%)

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According to the study by Goyal et al., the calculated OR of poor outcome in the moderate or permissive group was 2.19 (95% CI 0.54–8.86) compared with that of the intensive group.

OR for poor outcome = $\frac{63/67}{3/7} = 2.19$

CI = $\left(e^{\ln(OR)-1.96\sqrt{\frac{1}{63}+\frac{1}{67}+\frac{1}{3}+\frac{1}{7}}}, e^{\ln(OR)+1.96\sqrt{\frac{1}{63}+\frac{1}{67}+\frac{1}{3}+\frac{1}{7}}}\right)$

Using these ORs, we calculated the weighted average as follows:

$$OR^{*} = \frac{m_1}{M}OR_1 + \frac{m_2}{M}OR_2 = \frac{140}{539} \times 2.19 + \frac{399}{539} \times 1.45 = 1.64$$

where OR1 is from Goyal et al.'s study[6] and OR2 is from our systematic review. Finally, we used OR = 1.6 after rounding off one decimal place. The OR for intervention group compared to control group is defined as OR=1/1.6=0.625.

The number of patients in each group was calculated as follows:

$$n_A = n_B = \frac{\left(Z_{1-\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta}\sqrt{p_A(1-p_A)+p_B(1-p_B)}\right)^2}{(p_B - p_A)^2}$$

$$where\ \bar{p} = \frac{p_A + p_B}{2}.$$

where $OR = \frac{p_A/(1-p_A)}{p_B/(1-p_B)} = 0.625$, p_B=0.41, p_A=0.30 (ratio of patients with poor outcome).

The significance level (two-tailed test) was $\alpha = 0.05$ with a power of $1-\beta = 0.80$, and the required number of patients per group was 317. The required final sample size was 668 (334 per each arm) for a 5% dropout rate.

Interim analysis will be performed when half of the patients are enrolled in each group. Analysis will

be performed by using the alpha spending function with O'Brien–Fleming's boundary method. The trial will be hold when a null hypothesis is rejected ($Z \geq 2.996$, $\alpha 1 = 0.00274$). Interim analysis will also be conducted in the event that any ethical concerns arise. The DSMB will advise the steering committee if the trial has significant outcome differences between the two arms, lack of efficacy, or safety concerns. The steering committee will make trial continuation decisions.

3. Statistical analysis

3.1 Statistical principles

3.1.1 Primary and Secondary outcomes

This trial will analyze one primary efficacy outcome.

1. Favorable outcome at 3 months, defined mRS score 0-2

Two primary safety outcomes will be analyzed.

1. Symptomatic intracranial hemorrhage (sICH)
2. Death related to the index stroke within 3 months.

Six secondary outcomes will be analyzed including

1. mRS score reduction (shift analysis) at 3 months
2. Excellent recovery of NIHSS score at 24h (NIHSS 0-1 or improvement more than 8)
3. Recanalization status at 24 hours
4. Favorable outcome at 1 month (mRS score 0-2)
5. Quality of life measured by Euro-QoL
6. Malignant brain edema

3.1.2 Software

Analyses will be conducted primarily using SAS (version 9.4, SAS Inc., Cary, NC, USA) and R Statistical Package (Institute for Statistics and Mathematics, Vienna, Austria, ver 4.1.3, www.R-project.org).

3.2 Data sets analyzed

3.2.1 Intention-to-treat (ITT) population (primary analysis)

The ITT population will include all randomized patients, regardless of whether they received the allocated intervention. This will be the population used to evaluate both the efficacy and safety of the treatment. Patients who withdrew informed consent before BP control will be excluded from this population.

3.2.2 Per-protocol (PP) analysis

The PP analysis group will consist of patients from the efficacy analysis who did not commit any significant violations of the protocol. These violations include being below 20 years of age, lacking a final diagnosis of acute ischemic stroke, having SBP less than 140 mmHg, not achieving reperfusion through IAT (as determined by a TICI score of less than 2b), pre-stroke mRS 3 to 5, failing to obtain a blinded assessment of the 3-month outcome, and not having controlled BP for 24 hours as per the assigned intervention (crossover). The PP group will serve as a supplementary analysis to enhance the findings of the ITT population.

3.3 Subject disposition

The flow of patients through the trial will be displayed in a CONSORT (Consolidated Standards of Reporting Trials) diagram. The report will detail the number of patients randomly assigned and met the eligibility criteria for the study, along with the number of patients who were ultimately included. It will also specify the reasons for excluding any non-included patients.

3.4 Patient characteristics and baseline comparisons

The baseline characteristics of patients will be presented by the treatment group. The baseline characteristics of patients will be presented by the treatment group. Discrete variables will be summarized with frequencies and percentages, calculated based on available data. Continuous variables will be summarized with mean and standard deviation, or median and interquartile range (IQR). Baseline data will include all demographic, clinical, and medical information collected at the start of the study, which may be further defined after investigations and after central adjudication of brain and vascular imaging are completed (such as the location and extent of large vessel occlusion, ASPECTS, symptomatic ICH, hemorrhagic transformation, collateral vessel status rating, and infarction volume).

3.5 Protocol deviation

The protocol deviations will be documented and reported as the number of subjects with a deviation. A comprehensive list of all protocol deviations will be given, which will provide insight into the extent and nature of deviations from the study protocol.

3.6 BP management

BP measurements collected during the first 24 hours will be summarized using descriptive plots. Calculations will be performed for enrollment, 1-hour, 24-hour, and overall 24-hour mean BP and standard error for each treatment group. The mean between-group difference in SBP and diastolic BP will be calculated using a linear mixed model, this will be provided difference (95% CI) and p-value. Time within the target SBP range will be determined based on individual SBP targets (SBP <140 mmHg, SBP 140-180 mmHg, and SBP <180 mmHg). This will be calculated by dividing the hours spent within the target SBP range by 24 hours. This will be described as mean and standard deviation. SBP considered out of range will be determined if it exceeds at least once any of the following thresholds: >180 mmHg, >200 mmHg, or <100 mmHg. The BP-lowering medications

administered during the first 24 hours will be described as the number and proportion of participants receiving each medication. This will include the number of different intravenous medications used.

3.7 Analysis of the primary outcome

The primary analysis (ITT population) (see section 3.2.1) and analysis using PP population (3.2.2) will be conducted.

3.7.1 Binary analysis of mRS

A binary analysis of the mRS at 3 months will be conducted by categorizing the mRS scores as either 'poor' (scores 3-6) or 'favorable' (scores 0-2) outcomes. The effect of the intervention will be presented as the OR of a poor outcome, with a 95% CI and risk difference, with 95% CI. Additionally, adjusted analyses will be performed by adding the following covariates: age (continuous), sex (male vs female), NIHSS score just before IAT (continuous), and onset to randomization time (continuous). The adjusted treatment effect will be reported as the adjusted OR and 95% CI. Subgroup analysis will be conducted for this outcome. The number needed to treatment (or harm) and 95% CI will be reported for this outcome.

3.7.2 Symptomatic intracranial hemorrhage (sICH)

The definition for sICH is based on that in the European Cooperative Acute Stroke Study III (ECASS III) (see Section 2.4.1). These will be reported as the number and proportion of subjects experiencing an event. The effect of the intervention will be estimated using the same approach as in the binary analysis of mRS (see Section 3.7.1). We will apply the covariate adjustments described in Section 3.7.1; however, no subgroup or imputed analysis will be performed on this outcome.

3.7.3 Death related to the index stroke within 3 months.

A binary analysis of death related to the index stroke within 3 months will be performed. The impact of the intervention will be calculated using the same method as in the binary analysis of mRS (as outlined in Section 3.7.1). The covariate adjustments described in Section 3.7.1 will be applied, but no subgroup or imputed analysis will be conducted for this outcome.

3.7.4 Subgroup analyses

Twenty one pre-specified subgroup analyses will be carried out, irrespective of whether there is a significant treatment effect on the primary outcome. Subgroups are defined as follows:

- Age (<65 vs 65 or more)
- Sex (female vs male)
- Hypertension (yes vs no)
- Diabetes (yes vs no)
- Hyperlipidemia (yes vs no)
- Smoking (yes vs no)
- Atrial fibrillation (yes vs no)
- Congestive heart failure (yes vs no)
- CAOD (yes vs no)
- Previous stroke (yes vs no)
- Active cancer (yes vs no)
- Pre-stroke mRS
- Onset time to puncture (<6 vs ≥6 hours)
- Presumed etiological subtype according to TOAST classification
- NIHSS score just before IAT (<15 vs >15)
- TICI score immediately after EVT (2b or 2c vs 3)
- Occlusion site (ICA, MCA, VBA, PCA, or ACA)

- Site (Anterior, posterior, or multiple)
- ASPECTS (0-5, 6-8, 9-10)
- Collateral grade (good, poor)
- IV thrombolysis administered (yes vs no)

The analysis for each subgroup will be performed by adding the subgroup variable and its interaction with the intervention as fixed effects to the main logistic regression model. The summary statistics within each subgroup will consist of raw counts and percentages for each treatment arm, as well as the OR of treatment effect along with a 95% CI. The findings will be displayed in a forest plot, including the p-value for heterogeneity resulting from the interaction between the subgroup variable and the intervention.

3.7.5 Treatment of missing data

For missing data, no imputation or additional processing will be performed.

3.8 Analysis of the secondary outcome

The primary analysis (ITT population) (see section 3.2.1) and analysis using PP population (3.2.2) will be conducted.

3.8.1 Shift analysis of mRS

The mRS score reduction will be analyzed using shift analysis. An ordinal logistic regression will be applied to evaluate the distribution of mRS over a 3-month period. The primary impact of the intervention will be calculated as the OR of a lower mRS between the intervention group and the control group, determined from an ordinal logistic model. To verify the proportional odds assumption, a score test will be employed. The graphical representation of shifts across categories

will be made through bar plots and binary analysis. To address cases where the proportional odds assumption for covariates is not met, we will use a partial proportional odds logistic regression as a secondary analysis. The covariate adjustments described in Section 3.7.1 will be applied, but no subgroup analysis or imputed analysis will be conducted for this outcome.

3.8.2 NIHSS sore at 24 hours

The NIHSS score at 24 hours will be analyzed as a continuous variable. Univariable and multivariable linear regression analysis will be performed based on treatment groups. No subgroup analysis or imputed analysis will be conducted for this outcome.

3.8.3 Excellent recovery of NIHSS score at 24 hours

The outcome of excellent recovery of NIHSS score at 24 hours (NIHSS 0-1 or improvement of more than 8) will be analyzed using the same approach as the mRS score described in Section 3.7.1 The covariate adjustments described in Section 3.7.1 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

3.8.4 Recanalization status at 24 hours

Recanalization (TICI score ≥2b) at 24 hours will be analyzed using the same approach as the mRS score described in Section 3.7.1 The covariate adjustments described in Section 3.7.2 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

3.8.5 Favorable outcome at 1 month (mRS score 0-2)

The favorable outcome at 1 month, defined as an mRS score of 0-2, will be analyzed using the same approach as the mRS score described in Section 3.7.1 The covariate adjustments described in Section 3.7.2 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this

outcome.

3.8.6 Euro-QoL

The total Euro-QoL score will be analyzed as a continuous variable. Univariable and multivariable linear regression analysis will be performed based on treatment groups. No subgroup analysis or imputed analysis will be conducted for this outcome.

3.8.7 Malignant brain edema

The occurrence of malignant brain edema will be analyzed using the same method as the mRS score described in Section 3.7.1 The covariate adjustments outlined in Section 3.7.2 will be applied, but no subgroup analysis or imputed analysis will be performed for this outcome.

3.9 Interim analysis plan

The study includes one formal interim analysis after one-half of the patients have completed their 90-day follow-up. In the interim analysis, primary efficacy outcome (favorable outcome at 3 months) analysis will be performed using the alpha spending function with O'Brien–Fleming's boundary method. The trial will be held when a null hypothesis is rejected ($Z \geq 2.996$, $\alpha 1 = 0.00274$). The interim analysis will also be conducted in the event that any ethical concerns arise. The DSMB will advise the steering committee if the trial has significant outcome differences between the two arms, lack of efficacy, or safety concerns. The steering committee will make trial continuation decisions.

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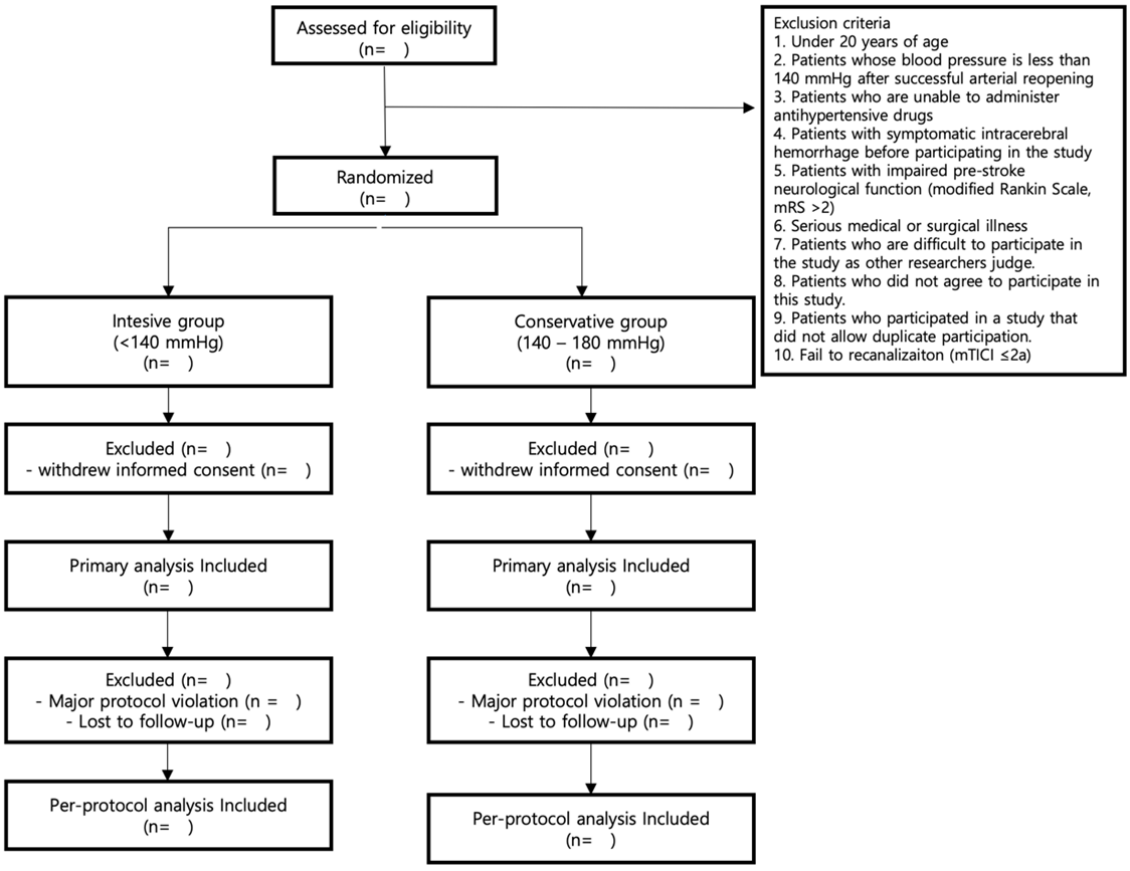
513 outcomes in large vessel occlusion strokes. Neurology 2017;89:540-547.
514

5. Figure

Figure 1. CONSORT flowchart



6. Summary of statistical analysis plan change

1. Sample size change

An error was identified in the sample size calculation (see red fonts), leading to an adjustment from 644 to 688 participants after receiving approval from the Institutional Review Board.

Sample size calculation in OPTIMAL-BP Protocol V 1.0

1. Number of clinical trial subjects calculated

644 patients (322 in each group, significance level α=0.05, statistical power 1-β=0.80, dropout rate 5%)

2. Hypothesis

H_0: OR = 1 (the odds ratio for groups A and B is the same)

H_1: OR≠1 (the odds ratio for groups A and B is not the same)

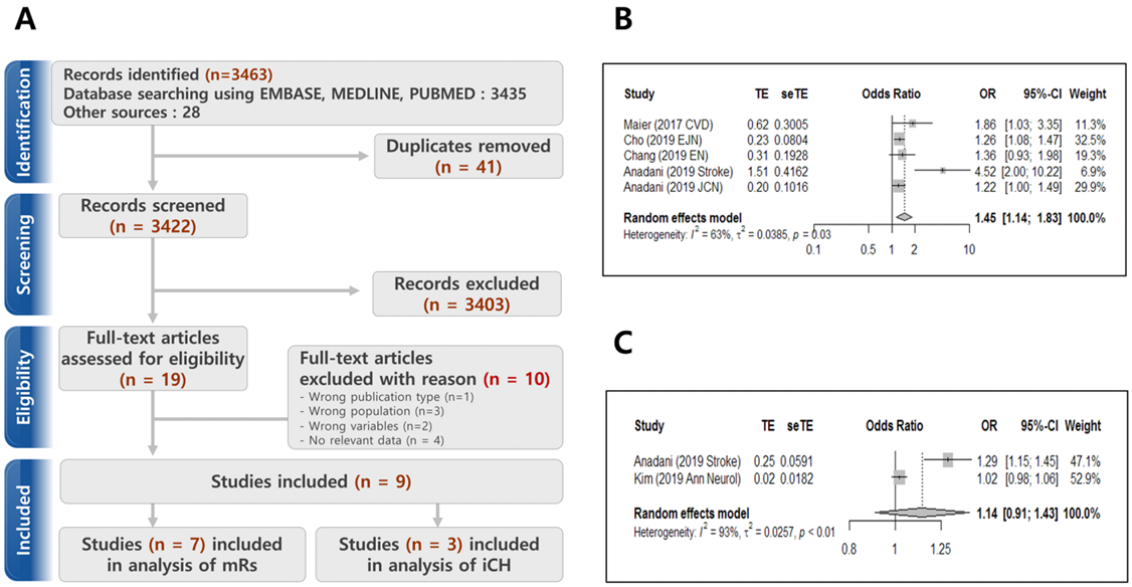
3. Sample size calculation

We conducted a systematic review to determine the sample-size calculation. We searched Medline and Embase for relevant clinical studies published between January 1993 and October 2019. The following search terms were used: “BP,” “hypertension,” “thrombectomy,” or “endovascular.” We manually searched references of identified studies. Searches were restricted to human studies with full English text. The reference lists of retrieved reports were also hand searched for potentially relevant studies not identified in our electronic database search.

Studies included in this analysis met the following criteria: (1) IAT for ischemic stroke, (2) inclusion of patients with acute ischemic stroke with large-vessel occlusion, (3) analysis comparing the outcomes according to BP within 24 hours after successful recanalization with

IAT, and (4) outcome measurements, including mRS score, at 90 days or sICH. We also obtained the baseline characteristics from each study: sample size, intervention type, intervention time, baseline NIHSS score, baseline BP, functional outcome or 90-day mortality, and symptomatic ICH. Two reviewers (YDK and JKC) independently extracted data, and disagreements were resolved by consensus. For continuous outcomes (90-day ordinal mRS score) and dichotomous outcomes (symptomatic ICH), we used the odds ratio (OR) with 95% CI and *P*-values to assess the likelihood of outcomes.

Of a total of 3,436 articles identified, 9 met the inclusion criteria (Figure A). Among the seven articles regarding the outcome, two were excluded: one because we could not calculate the effect size, and the other because no regression coefficient was reported. Finally, five papers that used continuous SBP were chosen. The OR was calculated using the generic inverse variance estimation method. A 10-mmHg increase in the mean SBP $\leq$ 24 hours after successful recanalization with IAT was correlated with worse 90-day mRS (OR 1.45, 95% CI 1.14–1.83, p = 0.002) (Figure B). Symptomatic ICH was not associated with a mean SBP increase of 10 mmHg after successful recanalization with IAT (OR 1.14, 95% CI 0.91–1.43, p = 0.267) (Figure C).



A study by Goyal et al. used a design similar to ours with an aggressive SBP-lowering target of <140 mmHg.[1] They compared an aggressive SBP-lowering target of <140 / 90 mmHg with a moderate or permissive BP target of <185 / 105 mmHg.

	Studies	Ordinal or logistic regression	OR (95% CI)	Adjusted OR (95% CI) per 10 mmHg for poor outcome	Number of patients	Measurements
1	Maier (2017)[2]	OR (1 mmHg) for good outcome	0.94 (0.88–0.99)	1.86 (1.11–3.59)	168	Continuous SBP
2	Cho (2019)[3]	OR (10 mmHg) for ordinal mRS	1.26 (1.08–1.48)	1.26 (1.08–1.48)	313	Continuous SBP
3	Chang (2019)[4]	OR (10 mmHg) for ordinal mRS	1.36 (0.93–1.98)	1.36 (0.93–1.98)	90	Continuous SBP
4	Anadani (2019)[5]	OR (1 mmHg) for good outcome	0.86 (0.79–0.93)	4.52 (2.07–10.56)	1149	Continuous SBP
5	Anadani (2019)[6]	OR (1 mmHg) for good outcome	0.98 (0.96–0.999)	1.22 (1.01–1.50)	276	Continuous SBP
	Subtotal	OR (10 mmHg) for ordinal mRS		**1.45 (1.14–1.83)**	1996	
6	Goyal (2017)[1]	OR for poor	**2.19 (0.54–8.86)**		140	Target SBP

		outcome (ref: intensive group)				
		OR for good outcome (ref: intensive group)	0.46 (0.11–1.84)			

Outcome according to target BPs in Goyal's article[1]

	Good outcome (mRS 0–2)	Poor outcome (mRS 3–6)	Total
Intensive group (Target BP < 140/90 mmHg)	7 (70%)	3 (30%)	10 (100%)
Moderate or permissive group (Target BP < 185/105 mmHg)	67 (52%)	63 (48%)	130 (100%)

According to the study by Goyal et al., the calculated OR of poor outcome in the moderate or permissive group was 2.19 (95% CI 0.54–8.86) compared with that of the intensive group.

OR for poor outcome = $\frac{63/67}{3/7} = 2.19$

CI = $\left(e^{\ln(OR)-1.96\sqrt{\frac{1}{63}+\frac{1}{67}+\frac{1}{3}+\frac{1}{7}}}, e^{\ln(OR)+1.96\sqrt{\frac{1}{63}+\frac{1}{67}+\frac{1}{3}+\frac{1}{7}}} \right)$

Using these ORs, we calculated the weighted average as follows:

$$OR^{*} = \frac{m_1}{M} OR_1 + \frac{m_2}{M} OR_2 = \frac{140}{539} \times 2.19 + \frac{399}{539} \times 1.45 = 1.64$$

where OR1 is from Goyal et al.'s study[6] and OR2 is from our systematic review. Finally, we used OR = 1.6 after rounding off one decimal place.

The number of patients in each group was calculated as follows:

$$n_A = n_B = \left(\frac{1}{p_A(1-p_A)} + \frac{1}{p_B(1-p_B)}\right)\left(\frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{\ln(OR^*)}\right)^2.$$

where $OR = \frac{p_A(1-p_A)}{p_B(1-p_B)}$ = 1.6 (weighted averaged OR) and p_B = 0.41 (ratio of poor outcome patients). The significance level (two-tailed test) was $\alpha = 0.05$ with a power of $1-\beta = 0.80$, and the required number of patients per group was 287. The required final sample size was 644 (322 per each arm) for a 5% dropout rate.

Interim analysis will be performed when half of the patients are enrolled in each group. Analysis will be performed by using the alpha spending function with O'Brien–Fleming's boundary method. The trial will be hold when a null hypothesis is rejected ($Z \geq 2.996$, $\alpha 1 = 0.00274$). Interim analysis will also be conducted in the event that any ethical concerns arise. The DSMB will advise the steering committee if the trial has significant outcome differences between the two arms, lack of efficacy, or safety concerns. The steering committee will make trial continuation decisions.