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

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Trial PROTOCOL

(Version 1.0 – 09 Jan 2020)

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163 # Abstract

Title	Outcome in Patients Treated with Intraarterial thrombectomy - optiMAL BP control (OPTIMAL-BP) trial
Principle research center	Severance Hospital, Yonsei University College of Medicine
Objective	To investigate whether intensive blood pressure (BP) management during the first 24 hours after successful recanalization leads to better clinical outcomes compared to conventional BP management in patients treated with IAT.
Efficacy outcome measure	**1. Primary outcome** 1) primary efficacy outcome - Functional independence at 3 months, defined as a modified Rankin Scale (mRS) score of 0 to 2 - Differences in mRS ordinal shift analysis 2) primary safety outcomes A. symptomatic ICH within 36 hours B. Stroke-related death within 90 days **2. Secondary outcome** 1) Difference in NIHSS scores at 24 hours after IAT 2) Excellent Day 1 Recovery [Major Neurological Improvement]: NIHSS score of 0-1 or improvement > 8 3) Recanalization status on CT Angiography (CTA) or MR Angiography

	(MRA) at 24 hours 4) Favorable outcome at 1 month (mRS score 0-2) 5) Health-related quality of life, as assessed by the EuroQoL group EQ-5D-3 L, 6) Frequency of occurrence of malignant brain edema
Research design	Multicenter, randomized, open-label, blinded end point evaluation trial
Population	patients with acute ischemic stroke who were treated with IAT due to large vessel occlusion and who achieved successful recanalization (a modified Treatment In Cerebral Infarction score of ≥2b) and elevated systolic BP ≥140 mmHg within 2 hours of successful recanalization
Sample size	668
Inclusion criteria	1. Age ≥20 years 2. Patients who underwent IAT for acute cerebral infarction with large cerebrovascular occlusion 3. Patients with successful cerebral artery reopening after intraarterial reopening (mTICI 2b or mTICI 3) 4. Patients with a mean blood pressure of 140 mmHg or greater on 2 measurements taken between 30 minutes and 1 hour after successful arterial recanalization.
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 impaired pre-disease neurological function (modified Rankin Scale, mRS >2) 5. Serious medical or surgical illness 6. Patients who did not agree to participate in this study
Stop/ out criteria	1. Patients withdrawing consent 2. Patients whose BP is maintained at more than 220 mmHg despite active BP control after IAT 3. If the principal investigator or the investigator determines that the test should be discontinued
Research cycle	BP control within 24 hours, follow-up imaging study at 36 hours, assessment at 1 and 3 months
Interventions	Participants received intensive BP management (targeting systolic BP <140 mmHg) or conventional management (targeting systolic BP between 140-180 mmHg) for 24 h after enrollment
Statistical analysis	In the primary analyses, the efficacy was evaluated among all patients who underwent randomly assigned treatment for 24 hours, had outcome measures up to 3 months, and gave consent. The per-protocol analysis included patients who underwent the assigned treatment and had no major protocol deviations. Binary logistic regression analyses were performed for the primary outcome and the treatment effects were presented as odds ratios (ORs) with 95% confidence intervals (CIs). In addition, risk ratios and risk differences with 95% CIs were calculated. The independent predictors were determined using a multivariable

	logistic regression analysis adjusting age, sex, onset to registration time, and the NIHSS score just before IAT. For the secondary outcome, the common OR representing a shift in mRS scores was calculated using an ordinal logistic regression analysis. Linear regression analyses were performed for the NIHSS score at 24 hours and the EQ-5D-3L score. Subgroup analysis of the primary outcome was performed on prespecified subgroups. The homogeneity of treatment effect across subgroups was evaluated using a logistic regression model.
Sites number	19 stroke centers in South Korea
Research duration	3 months

Abbreviation

Abbreviation	Full title
ABPM	Ambulatory BP monitoring
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

CV	Coefficient of variation
DCT	Data clarification form
DMC	Data Management Center
DSMB	Data Safety Management Board
eCRF	Electronic case report form
EQ-5D-3L	EuroQoL 5-Dimension Self-Report Questionnaire
FLAIR	Fluid-attenuated inverse recovery
GCP	Good Clinical Practice
HI	Hemorrhage infarction
HRQoL	Health-related quality of life
IAT	Intra-arterial thrombectomy
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
ICMJE	International Committee of Medical Journal Editors
iCReaT	Internet based Clinical Research and Trial management system
IRB	Institutional Review Board
MCA	Middle cerebral artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mTICI	Modified Treatment In Cerebral Infarction
NIBP	Non-invasive automatic BP
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
SITS-MOST	Safe Implementation of Thrombolysis in Stroke Monitoring Study
SBP	Systolic blood pressure
SD	Standard deviation
SV	Successive variation
TOAST	Trial of Org 10 172 in acute stroke treatment
VA	Vertebral artery
VIM	Variation independent of the mean

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Overview

Studies have demonstrated that intravenous thrombolysis is effective in improving symptoms of acute cerebral infarction patients, but the treatment is not always successful. Even when administered within an appropriate time frame, only 22.6% of blood clots are dissolved and only about 30% of patients experience improvement. Recently, intra-arterial procedures such as intra-arterial thrombectomy (IAT) have been found to be effective. This procedure uses a stent retriever or catheter to physically remove blood clots from the body. IAT has a high success rate of nearly 80% in terms of vascular re-opening, however, only around 50% of patients show clinical improvement. Therefore, there is a need for new treatment strategies and techniques to reduce the number of patients who do not benefit from the procedure.

BP (BP) is a significant factor in the outcomes of stroke patients who have received recanalization treatment. Patients who have undergone successful recanalization treatment are more likely to experience a spontaneous decline in BP over 12 to 24 hours following IAT than those with persistent occlusion. BP has a direct impact on cerebral perfusion pressure, with low BP potentially decreasing cerebral perfusion pressure and causing harm to ischemic brain areas. Conversely, sustained high BP may increase the risk of intracerebral hemorrhage (ICH) and lead to worse functional outcomes.

The American Heart Association guidelines recommend lowering BP to below 180/105 mmHg in patients who have undergone successful recanalization, with a class of recommendation of IIb and level of evidence B-NR. The European guidelines suggest maintaining BP below 180/105 mmHg during and 24 hours after IAT. In contrast, previous retrospective studies and meta-analyses have indicated a potential association between BP in

the 24 hours following IAT and clinical outcomes, and have suggested that lowering BP may be beneficial. However, the optimal target for BP control in stroke patients who have undergone successful recanalization following IAT remains uncertain.

Research Purpose

The objective of this trial is to establish whether intensive BP-lowering (<140 mmHg) results in a superior clinical outcome compared to conventional BP-lowering (140 - 180 mmHg) following successful recanalization through IAT.

Research agencies and estimated duration of the study

1. Research Institute: 19 hospitals in South Korea including Yonsei University College of Medicine.

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1	Primary investigator	Hyo Suk Nam	Severance Hospital, Yonsei University College of Medicine	hsnam@yuhs.ac
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2. Estimated research period : 5 years from the date of initial approval of the IRB (60 months)

Criteria for inclusion and exclusion of study subjects

1. Inclusion criteria

1. Age ≥20 years

2. Patients who underwent IAT for acute cerebral infarction with large cerebrovascular occlusion

3. Patients with successful cerebral artery reopening after intraarterial reopening (modified Treatment In Cerebral Infarction score, mTICI 2b or mTICI 3)

4. Patients with a mean blood pressure of 140 mmHg or greater on 2 measurements taken between 30 minutes and 1 hour after successful arterial recanalization.

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 impaired pre-disease neurological function (modified Rankin Scale, mRS >2)

5. Serious medical or surgical illness

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

3. Stop / out criteria

1. Patients withdrawing consent

2. Patients whose BP is maintained at more than 220 mmHg despite active BP control after IAT

3. If the principal investigator or the investigator determines that the test should be discontinued

Estimated number of research subjects

1. Number of clinical trial subjects calculated

644 patients (322 in each group, significance level $\alpha=0.05$, statistical power $1-\beta=0.80$, dropout rate 5%)

2. Hypothesis

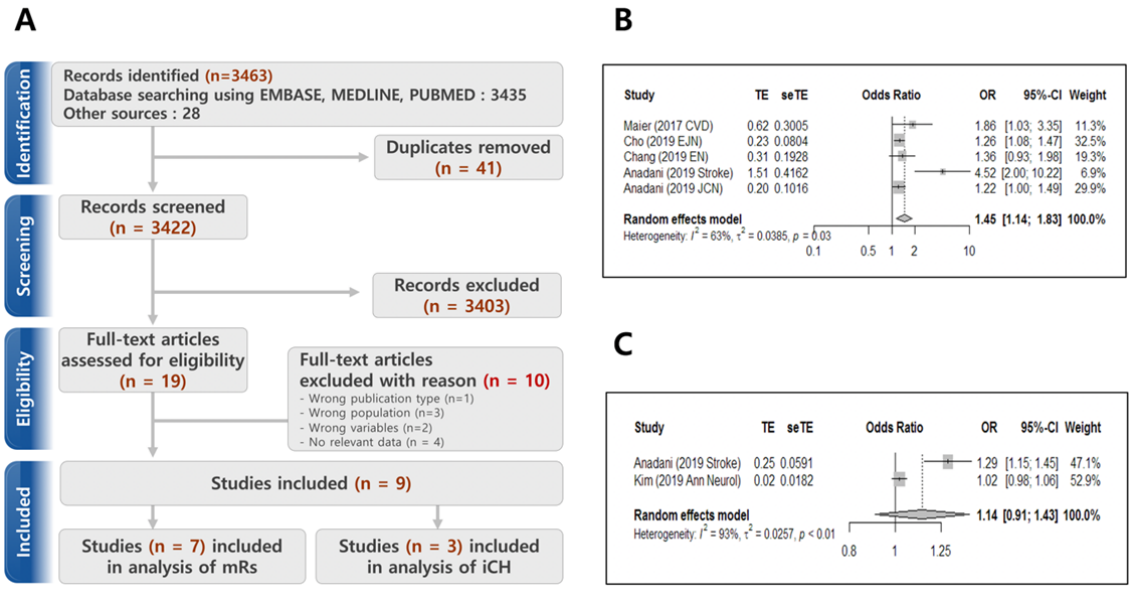
H_0: OR = 1 (the odds ratio for groups A and B is the same)

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

245 restricted to human studies with full English text. The reference lists of retrieved reports were
246 also hand searched for potentially relevant studies not identified in our electronic database
247 search.
248 Studies included in this analysis met the following criteria: (1) IAT for ischemic stroke, (2)
249 inclusion of patients with acute ischemic stroke with large-vessel occlusion, (3) analysis
250 comparing the outcomes according to BP within 24 h after successful recanalization with IAT,
251 and (4) outcome measurements, including mRS score, at 90 days or sICH. We also obtained
252 the baseline characteristics from each study: sample size, intervention type, intervention time,
253 baseline NIHSS score, baseline BP, functional outcome or 90-day mortality, and
254 symptomatic ICH. Two reviewers (YDK and JKC) independently extracted data, and
255 disagreements were resolved by consensus. For continuous outcomes (90-day ordinal mRS
256 score) and dichotomous outcomes (symptomatic ICH), we used the odds ratio (OR) with 95%
257 CI and *P*-values to assess the likelihood of outcomes.
258
259 Of a total of 3,436 articles identified, 9 met the inclusion criteria (Figure A). Among the
260 seven articles regarding the outcome, two were excluded: one because we could not calculate
261 the effect size, and the other because no regression coefficient was reported. Finally, five
262 papers that used continuous SBP were chosen. The OR was calculated using the generic
263 inverse variance estimation method. A 10-mmHg increase in the mean systolic BP ≤ 24 hours
264 after successful recanalization with IAT was correlated with worse 90-day mRS (OR 1.45, 95%
265 CI 1.14–1.83, p = 0.002) (Figure B). Symptomatic ICH was not associated with a mean
266 systolic BP increase of 10 mmHg after successful recanalization with IAT (OR 1.14, 95% CI
267 0.91–1.43, p = 0.267) (Figure C).
268



A study by Goyal et al. used a design similar to ours with an aggressive systolic BP-lowering target of <140 mmHg.[1] They compared an aggressive systolic BP-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 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)			

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.

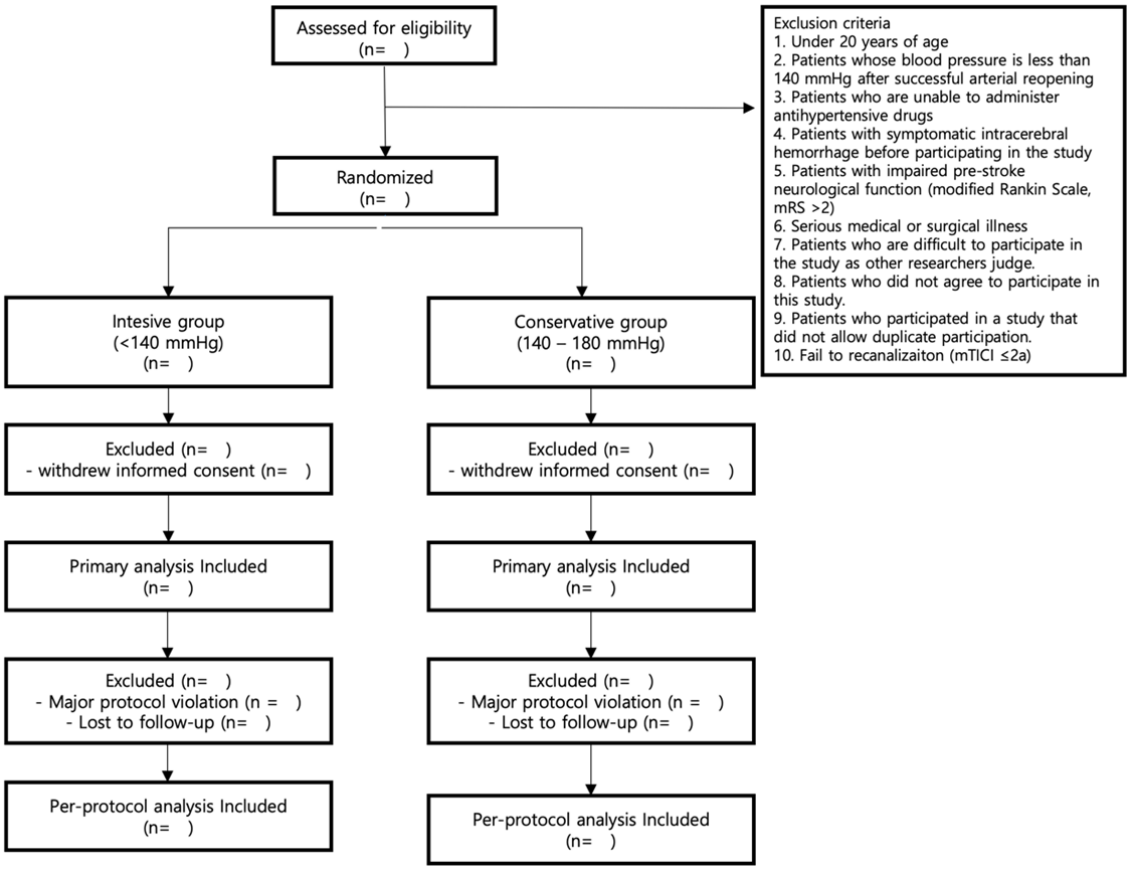
Study Design

1) The study design is a prospective, randomized, open-label trial with blinded end-point assessment (PROBE). In a PROBE trial, the study is prospective, meaning that patients are enrolled before the start of the study, and it is randomized, meaning that patients are randomly assigned to different treatment groups. The study is open-label, meaning that both the patient and the investigator know which treatment the patient is receiving, but it is blinded at the endpoint, meaning that the outcome of the study is assessed in a blinded manner.

2) The study will use a 1:1 ratio of the intensive group (target systolic BP <140 mmHg) and the conventional group (target systolic BP 140 - 180 mmHg) for patients who have achieved successful recanalization after IAT.

3) To prevent imbalance between the groups, randomization was stratified by the enrollment hospital and the degree of neurological impairment as determined by the NIHSS score at admission (<14 points or ≥14 points).

4) The study is a multi-center, prospective study that will include patients admitted to the neurology department of participating hospitals with acute cerebral infarction between January 2020 and December 2023, based on the date of stroke onset. Eligible patients will have undergone IAT in accordance with stroke treatment guidelines and have successfully reopened the arteries. The study will be conducted for five years in the participating hospitals.



5) The study will collect the following data from the eligible participants: medical history, test results, BP parameters (systolic BP, diastolic BP, BP variability, etc.), imaging tests, neurological scores, functional recovery, and quality of life indicators. All data collected will be in accordance with the study inclusion and exclusion criteria.

6) Neurological scores, functional recovery scores, and quality of life indicators will be assessed by independent investigators who are blinded to the participant's treatment group. This helps to ensure unbiased and accurate assessments of these outcomes.

7) All data collected will be entered into an electronic case report form (e-CRF) system and the images of the participants will be anonymized and transmitted to the host institution. This helps to ensure the security and confidentiality of the participant's data and images.

8) The host institution will perform a blinded quantification of the imaging tests. This means

that the investigators at the host institution will not know which group the participant belongs to when analyzing the imaging test results which help to minimize bias.

Study methods

1) The study aims to recruit patients with acute cerebral infarction who have undergone IAT for large cerebral artery occlusion. The selection and exclusion criteria and the treatment of IAT will be based on practice guidelines and institution-specific criteria.

2) The study will include patients who have successfully undergone arterial recanalization (as determined by mTICI 2b or mTICI 3 score) and have a mean BP greater than 140 mmHg, as measured twice within 2 hours of recanalization.

3) The study will use an automated BP device (Omron® HEM 7130) that has been certified as equivalent by the American Medical Device Association and the European Society of Hypertension, and has clinical study evidence A.

4) Patients who meet the inclusion/exclusion criteria and provide informed consent will have their BP and pulse measured at 1-hour intervals for up to 24 hours after providing consent. The BP and pulse data will be collected and recorded.

5) The BP and pulse data will be measured twice and averaged.

6) To achieve and maintain the target systolic BP, local treatment protocols using available intravenous BP-lowering drugs will be permitted. The preferred BP-lowering drug is nicardipine, though other drugs such as labetalol and hydralazine are allowed at the physician's discretion.

7) If BP decreased below 140 mmHg in the conventional group, it will not be actively increased with vasopressor therapies. Treatment will be discontinued, and intravenous fluids and inotropes will be used when hypotension needed to be treated at the physician's

discretion.

8) BP Measurement wil be done every 15 minutes for the first 2 hours, then every 30 minutes for the next 6 hours, then every 1 hour for the next 16 hours after taking blood pressure medication.

9) Radiological follow-up using computed tomography or magnetic resonance imaging will be undergone at 36 hours and at any time when neurological symptoms worsen.

10) BP will be measured using an Omron® HEM 7130 automatic BP machine at 1 or 3 months. To ensure accurate results, participants should refrain from consuming caffeine, alcohol, and smoking for 30 minutes prior to measurement. They should also sit and rest for at least 3-5 minutes before taking the measurement on the upper arm of the non-paralyzed limb. Measurements should be taken with the arm at heart level, slightly bent on a desk without any force, and the person should be sitting with their back against the backrest and feet on the floor without crossing their legs, in accordance with the 2018 Primary Medical Evidence-Based Hypertension Clinical Practice Guidelines.

11) As a substudy, 24-hour ambulatory BP monitoring (ABPM) will be conducted at 1 and 3 months using certified sphygmomanometers from the list provided at www.dableducational.org. BP will be measured at 30-minute intervals and at least 14 valid measurements during the day and 7 valid measurements at night are required to be considered as valid data.

12) A mRS score will be calculated to assess neurological recovery at 3 months. Assessments will be conducted by independent investigators who are unaware of the treatment or control group status.

Research Plan

Research plan	Screening	24hr	F/U visit	End visit	Drop out
	0	24 ± 6 h	1 month ± 14 d	3 month ± 14 d	
Inclusion/exclusion check	X				
History	X				
agreement	X				
BP/pulse	X	X	X	X	X
NIHSS score	X	X			
Modified Rankin scale (mRS)	X (Before stroke)		X	X	X
EQ 5D-3L				X	
BP control treatment		X	X		
Adverse reactions		X			
Brain imaging	X	X[2)]			
Standard Stroke Treatment	X	X	X	X	X
Cardio-cerebrovascular events			X	X	X

1) For the final visit, the main study and the 1st, 2nd, and 4th substudies will be conducted for 3 months, and the 3rd sub-study will be conducted for 1 year.

2) Brain imaging (MRI or CT) performed within 36 hours after IAT.

Screening (0 days)

Selection/exclusion eligibility checked

Vital signs (BP, pulse rate)

History

Obtaining consent

NIHSS Score

Pre-cerebral infarction mRS

Obtaining consent

Brain imaging (MRI, CT, MRA, CTA, digital subtraction angiography)

Randomization

24 hours (24 ± 6 hours)

Vital signs (BP, pulse rate)

NIHSS

BP control treatment

Adverse Reaction Check

Standard Stroke Treatment

36 hours

Brain imaging images taken within 36 hours (MRI or CT)

F/u visit (1 month ± 14 days)

Vital signs (BP, pulse rate)

BP control treatment

Standard Stroke Treatment

Cardio-cerebrovascular events

last visit (3 months ± 14 days)

Vital signs (BP, pulse rate)

mRS

EQ-5D-3L (EuroQoL 5-Dimension Self-Report Questionnaire)

Standard Stroke Treatment

Cardio-cerebrovascular events

End visit (1 year ± 14 days)

Vital signs (BP, pulse rate)

mRS

EQ-5D-3L

Standard Stroke Treatment

Cardio-cerebrovascular events

How to obtain a consent form to participate in a study

1) We will adhere to the guidelines outlined in the Helsinki Declaration and ICH-GCP and will only conduct research after receiving approval from the institutional review board (IRB).
2) Informed consent will be obtained from participants who meet the established inclusion and exclusion criteria for the study.
3) Informed consent will be obtained from research participants who have the capacity to understand the study's purpose, content, and methods. The investigator will provide a full explanation of the study and answer any questions the participant may have. Participation in the study will be completely voluntary and a signed consent form will only be obtained from participants who willingly agree to participate in the study.
4) In cases where the potential research subject is unable to read or comprehend the study information, such as if they are illiterate or blind, the principal investigator is responsible fore ensuring that an neutral third party is present to read the study information to the subject and answer any questions they may have. Once the subject fully understands the study and voluntarily agrees to participate, both the subject and the impartial observer will sign a written consent form to indicate that the subject has provided informed consent. This ensures

that the subject's participation in the study is based on their own free will and understanding of the study's purpose, content, and method.

5) In cases where the research subject is unable to fully understand the research due to conditions such as cerebral infarction or other impairments, and is unable to provide a handwritten signature, the investigator will obtain written consent from the legal representative after thoroughly explaining the purpose, content, and methods of the study. However, if the individual is able to provide voluntary consent during the follow-up period, the investigator will make an effort to obtain the individual's consent.

6) Before any research involving human subjects can proceed, the IRB must first review and approve the explanatory text and consent form for the subject. After the subject or their legal representative signs the form, the principal investigator must retain one original copy and provide one copy to the subject or legal representative. It's important to allow sufficient time for the individual to read and fully understand the information before signing and receiving a copy of the statement and consent form.

7) It is important to remind that the study participant has the right to withdraw their consent to participate in the trial at any time during the study period. This means that the participant has the freedom to stop taking part in the study and discontinue any further involvement without any negative consequences or penalty. It is crucial to inform the participant of this right and how to exercise it, and to document any withdrawals of consent in the study records.

8) Clinical investigators have an ethical and legal obligation to ensure the confidentiality of all information obtained during the study period. This means that all information collected from the study subjects, such as personal identifying information, medical history, and study results, must be kept private and protected from unauthorized access or disclosure. Appropriate measures should be taken to safeguard the data, such as using secure storage

systems, password-protecting files, and limiting access to authorized personnel only. Additionally, the investigators should ensure that any data shared with external parties, such as sponsors or regulatory authorities, is de-identified or otherwise protected to maintain the confidentiality of the study subjects. It is important for the investigators to inform the participants about their policies and procedures to protect the confidentiality of their information.

9) Observation items and data collection methods refer to the specific aspects of the study that are being observed and the methods used to collect the data. For example, observation items may include vital signs, symptoms, or laboratory test results, while data collection methods may include interviews, surveys, physical exams, or medical imaging. It is important for the observation items and data collection methods to be clearly defined and specified in the study protocol, as they will serve as the basis for data analysis and interpretation. The selection of observation items and data collection methods should be appropriate for the research question and be able to accurately and reliably measure the variables of interest. They should also be feasible and ethical for the study population.

Hypothesis

In the treatment of acute cerebral infarction through IAT, it is hypothesized that the intensive group (a group of patients receiving intensive treatment) will have a better prognosis than the conventional group (a group of patients receiving conventional treatment) after successful arterial recanalization. This prediction is based on the idea that the intensive group will receive a more aggressive and comprehensive treatment plan, which may lead to better outcomes such as increased chances of recovery, reduced disability, and decreased mortality rates. The prediction will be tested through a randomized controlled trial where the patients

will be divided into two groups, the intensive group and the conventional group, and the outcomes will be measured and compared between the groups. The study will be conducted to confirm the hypothesis and to find out the best treatment approach for patients with acute cerebral infarction..

Outcome Evaluation Variables

The outcome endpoints were evaluated twice, one at the end of the interim analysis and one at the end of the study.

1. Primary outcome

1) primary efficacy outcome

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

2) primary safety outcomes

A. symptomatic ICH within 36 hours

- ✓ Bleeding or hemorrhagic transformation on MRI or CT performed within hours or as symptoms worsen

  Definition of symptomatic hemorrhage according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) meets the following criteria: Local or remote parenchymal hemorrhage type 2 on the 36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death.

B. Stroke-related death within 90 days

2. Secondary outcome

1) Difference in NIHSS scores at 24 hours after IAT

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

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

4) Frequency of occurrence of malignant brain edema

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

3. Observations

1.BP readings (systolic BP and diastolic BP)

1) BP during the visit

2) BP measured between 30 minutes and 1 hour after arterial recanalization

3) Hourly BP measured at 1-hour intervals for 24 hours after arterial recanalization

4) Active BP for 24 hours measured at 1-hour intervals at 1 and 3 months after arterial recanalization

4. Clinical scale

1) NIHSS scale score measured 24 hours after IAT

2) The mRS score measured at 1 month, 3 months, and 1 year after discharge from the hospital.

3) Quality of Life Indicators (EQ-5D-3L) measured 3 months and 1 year after arterial recanalization

5. Imaging Findings

1) Cerebral hemorrhage or hemorrhagic transformation occurs on MRI or CT after IAT

- Classification of a cerebral hemorrhage

Hemorrhage infarction type1 (HI1)	Small hyperdense petechiae
Hemorrhage infarction type2 (HI2)	More confluent hyperdensity throughout the infarct zone: without mass effect
Parenchymal hematoma type1 (PH1)	Homogeneous hyperdensity occupying <30% of the infarct zone: some mass effect
Parenchymal hematoma type2 (PH2)	Homogeneous hyperdensity occupying >30% of the infarct zone: significant mass effect. Or, any homogenous hyperdensity located beyond the borders of the infarct zone

2) Size of cerebral infarction measured by diffusion-weighted image, fluid-attenuated inverse recovery (FLAIR) image, or brain CT (when the diffusion-weighted image is not available).

3) Collateral grade by Tan scale score using CTA

0: absent collateral supply to the occluded MCA territory

1: collateral supply filling ≤50% but >0% of the occluded MCA territory

2: collateral supply filling >50% but <100% of the occluded MCA territory

3: 100% collateral supply of the occluded MCA territory

A good collateral status is defined by a Tan scale score of 2 to 3, while poor collateral status corresponds to a Tan scale score of 0 to 1.

4) Recanalization status at 24 hours is defined using CTA or MRA for 24 hours

Clinical Manifestations

The following data will be collected on the patient's clinical manifestations:

- Time of onset of symptoms
- Time from symptoms to treatment
- Severity of stroke using the NIHSS score
- Previous history of stroke
- Factors such as weight, obesity, hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, coronary artery obstructive disease, congestive heart failure, peripheral artery obstructive disease, and active cancer that may increase the risk of cerebral infarction
- Any other medical conditions the patient may have
- Assessment of patient's neurological functional independence before the onset of stroke using mRS
- Identification of the underlying cause of cerebral infarction using Trial of Org 10172 in Acute Stroke Treatment (TOAST)
- EQ-5D-3L; Health-related quality of life (HRQoL) was assessed using the EQ-5D-3L. The EQ-5D-3L descriptive system evaluates the state of general health across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using three levels to indicate the extent of problems: no problems, some/moderate problems, and severe problems. The EQ-5D-3L utility score is a single score calculated using population-based

preference weights for each dimension, and expressed as a fraction of perfect health, with a score of 1 representing perfect health, 0 representing death, and negative scores (with a minimum score of -0.109) indicating health states considered worse than death. In this analysis, preference weights derived from the South Korean population were used to calculate the utility scores.[7] When patients were unable to complete the questionnaire themselves, proxy responders such as caregivers were asked to rate the patient's HRQoL.

Data Collection Method

1) All clinical data will be collected electronically in an anonymized state using the web-based eCRF (iCReaT) of the Korean National Institutes of Health and the Centers for Disease Control. This system ensures the confidentiality and security of patient information while allowing for efficient data collection and management.

2) Data for each participating institution will be collected and managed in an integrated manner through this system, ensuring the quality and consistency of data across all sites.

3) Data management for this study will be handled by the Data Management Center (DMC), a clinical trial center of the Severance Hospital, Yonsei University. This center operates independently and is responsible for all aspects of data management. Before registering in the iCReaT system, the DMC creates databases using standardization guidelines and includes auto-query functions. Investigators will be provided with input guidelines to ensure data reliability and completeness. Data audit will be conducted every month and data cleaning will be conducted biannually to ensure data accuracy. All clinical data will be collected electronically in an anonymized state through the iCReaT system.

4) This trial will be led by the state and registered with the Korean National Institutes of Health's Centers for Disease Control and Prevention's iCReaT web-based clinical research

management system.

5) Verify data quality through Quality Control in the DMC, then proceed with database locking. After locking, no data changes or additions will be allowed.

Training of investigators

Each of the OPTIMAL-BP investigators received training for the protocol, GCP procedures, as well as the usage of the NIHSS and mRS score. The GCP training was conducted by individual hospitals.

Research Recording and Storage

1) Principal investigator must have a list of qualified individuals assigned to the study.

2) Clinical information (including image data) will be publicly accessible through research resource through the National database (iCReaT) managed by the Korean Centers for Disease Control. Clinical data will be managed as a national resource under regulations for health and medical tech R&D projects, with no set expiration for stored data use.

3) Data sharing follows (International Committee of Medical Journal Editors) ICMJE's "Data sharing statements for clinical trials." Raw clinical data will be shared after database lock and can be shared anonymously for international research collaboration.

4) Data sharing requires obtaining consent which include information about it in the research subject's explanatory text and consent form.

5) The investigator must retain records and documents related to the research implementation (e.g. test protocol, consent form, etc.) and clinical trial data, as per Article 15 of the Bioethics Law Enforcement Regulations, for 3 years after termination of the trial. After the retention period, documents must be destroyed as per Article 16 of the Personal Information Protection

Act Enforcement Decree.

6) In case of the investigator's departure (e.g. resignation, retirement), the handover to the new person must be agreed upon mutually.

7) If consent is withdrawn, the investigator will stop collecting new trial data but may still use data collected before the withdrawal.

8) Severance Hospital (the responsible research institution), Clinical Trial Review Committee, and Ministry of Food and Drug Safety may review subject's medical records to verify collected information. Information exposed will be treated as confidential.

9) Principal investigator must keep the signed consent form, and make a subject number and name list for easy searching, stored in a password-protected file in a locked lab.

10) Personal information collected is coded in a non-identifiable form, stored on a locked computer and remains anonymous even when results are reported or published. After study completion, it stays anonymous and stored on a locked computer.

11) In accordance with the Personal Information Protection Act (Article 24) and the Bioethics Act (Articles 16 and 37), research records, including unique identification information, must be kept for 3 years from the end of the study or until a request for destruction is made for clinical research in the public interest.

12) Unique identification information (resident registration number) will be collected to integrate with data held by national agencies, the National Health Insurance Agency, the Health Insurance Review and Evaluation Service, the National Statistics Office, and the National Cancer Center for conducting clinical research in the public interest of the Ministry of Health and Welfare. In addition, the subject has the right to receive an explanation and to agree or reject it.

Data analysis statistical method

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.

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 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.

3.1 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.

3.2 Symptomatic intracranial hemorrhage (sICH)

The definition for sICH is based on that in the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST). 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 3.1). We will apply the covariate adjustments described in Section 3.1; however, no subgroup or imputed analysis will be performed on this outcome.

3.3 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 3.1). The covariate adjustments described in Section 3.1 will be applied, but no subgroup or imputed analysis will be conducted for this outcome.

3.4 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.

3.5 Treatment of missing data

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

4 Analysis of the secondary outcome

The primary analysis (ITT population) (see section 1) and analysis using PP population (see section 2) will be conducted.

4.1 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 3.1 will be applied, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.2 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.

4.3 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 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.4 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 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.5 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 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.6 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.

4.7 Malignant brain edema

The occurrence of malignant brain edema will be analyzed using the same method as the mRS score described in Section 3.1 The covariate adjustments outlined in Section 3.1 will be applied, but no subgroup analysis or imputed analysis will be performed for this outcome.

5 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.

Definitions of protocol violations and deviations

Protocol deviations or violations were classified into two groups: major (reportable) violations and minor (non-reportable) violations.

1. Major (reportable) protocol violations

Major protocol violations were unapproved changes in the study design or procedures within the investigator's control, not in line with the approved protocol that may have impacted the participant's safety, well-being, or study data accuracy. Such violations were reported to the

IRB according to relevant national guidelines and timelines.

The DMC considered violations as major if they caused or had the potential to cause significant harm to the participant, affected the participant's clinical or emotional condition, damaged scientific data completeness or soundness, involved willful or knowing misconduct, or showed serious or continuous noncompliance with local, state, or federal regulations.

2. Minor (non-reportable) protocol violations

Minor protocol violations were unapproved changes in the study design or procedures within the investigator's control, not in accordance with the approved protocol but with no major impact on the participant's safety, rights, or study data completeness, accuracy, or reliability. Such violations did not always require reporting to the IRB.

The DMC identified violations as minor if they did not cause harm or a significant risk of substantive harm to the research participant, did not change their clinical or emotional condition or data accuracy, did not involve willful misconduct or serious noncompliance with regulations, or damage data completeness, accuracy, or reliability.

Analysis of potential risks and benefits to patients

1. Potential hazards:

This study aims to examine the outcome of patients after BP control during IAT. As all patients will have BP controlled below the standard of 180 mmHg, the risk to subjects is expected to be low. However, there is a risk of personal information being disclosed, but measures to protect it are in place. There is currently no evidence to support the difference

between the standard BP control group (140-180 mmHg) and the active BP control group (<140 mmHg), but if the results of the latter group are favorable, the study may be discontinued and the results shared with participants.

2. Potential benefits:

The results of this study can contribute to the development of better treatment strategies for cerebral infarction, and ultimately improve the prognosis for future patients. The information collected from this study can also provide valuable insights for the medical community, helping to advance our understanding of cerebral infarction and treatment.

3. Risk/ benefit Analysis:

This study is considered to have low potential risks and high potential benefits.

Compensation plan and compensation agreement for risks caused by research participation

Additionally, the study has taken necessary measures to minimize any potential harm to participants by purchasing Hyundai Marine Fire Insurance's clinical trial compensation insurance, which provides appropriate compensation in case of harm caused by the study.

Protection measures for vulnerable research subjects

1) Obtain written consent from the legal representative of vulnerable research subjects after providing a comprehensive explanation and confirming their agreement to participate in the study (Refer to guidelines on how to obtain consent for participation in a study).

2) This study examines the criteria for BP control after IAT in stroke patients and all participants will receive the same standard treatment process as other stroke patients, regardless of participation in the study.

3) Patients participating in this study face minimal potential risks.

4) Patients or their legal representatives may withdraw from the study at any time, without facing any disadvantages.

5) In case of harm caused to the subject during the study, we will provide compensation as per the terms of the clinical trial insurance policy and make sure they receive the best possible treatment. However, this compensation will not cover adverse reactions that are not related to the study, symptoms or diseases that are the result of the subject's own mistake or cause, and any deterioration of symptoms that may occur due to the natural progression of the disease.

6) For vulnerable individuals who are scheduled to participate in the study, written consent will be obtained after a sufficient explanation has been provided to their legal representative and the representative has confirmed their consent. This is to ensure that the individual's rights and well-being are protected during the course of the study.

7) The collected resident numbers will be securely stored as encrypted files and will only be used for linking with national institution databases. The numbers will be discarded immediately after the completion of the original purpose. Resident numbers will only be collected from individuals who have provided their consent for such collection.

Methods for maintaining the confidentiality of research subjects' identities and research materials

1) The confidentiality of the study participant's information is of utmost importance and will

be protected at all times.

2) The study records will include the subject's initials and assigned number will be collected and stored at the responsible research institution (Severance Hospital) using a de-identification program that replaces the subject's name with their initials and number.

3) The medical records of the subjects may be reviewed by the responsible research institution (Severance Hospital), the Clinical Trial Review Committee, and the Ministry of Food and Drug Safety for verification purposes. Any information obtained during this process will be kept confidential.

4) The signed consent form shall be kept by the lead investigator and a list containing the subject's number and name will be made to allow for easy access to the records.

Continuous safety monitoring plan and data safety monitoring plan.

1) The principal investigator and DMC will continuously monitor the data collected during the study. Personal information and data will be kept confidential by being encoded and stored on a secure computer. The information will remain anonymous even after the study has concluded and will continue to be stored on a locked computer.

2) Data and safety monitoring methods and cycles

(1) Monthly written evaluations of research progress and data management will be carried out by the principal investigator and the responsible party.

(2) The data management procedure will follow established validation specifications. Any errors found are corrected and the data will be checked for completeness, standardized, and consolidated from each institution using a data clarification form (DCF).

3) DSMB

The DSMB, an independent committee, oversees patient safety and tracks recruitment progress. It includes a medical statistician, neurologist, and representative from the Severance Clinical Trial Center. The members' names are confidential but can be provided upon request by the coordinating authority. DSMB reports are kept confidential, except in special cases. The frequency of DSMB meetings is determined prior to the study's start and additional meetings can be called if safety concerns arise.

4) Research discontinuation criteria

In case of non-compliance with significant ethical rules or deviation from the major protocol by the research site or investigator, the trial may be instantly halted.

Substudies

There are four substudies in the OPTIMAL-BP trial. Substudies were embedded within the main trial to recruit as many patients as possible.

N	Substudies
1	Substudy 1. Effects of BP parameters including systolic BP, diastolic BP, and BP variability on the outcome according to treatment group
2	Substudy 2. Personalized BP control using artificial intelligence immediately after IAT in acute cerebral infarction
3	Substudy 3. Analysis of the relationship between post-stable BP control and primary end-point in patients with successful arterial reopening through IAT
4	Substudy 4. Differences according to the degree of collateral circulation on prognosis after reopening through IAT

Research implementation plan

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	Research content	2020.01-2020.03	2020.03 – 2021.02	2021.03 – 2021.12	2022.01 – 2022.10	2022.10 – 2022.11	2022.12 – 2023.06	2023.06– 2023.12
1	IRB Approval							
2	eCRF (iCReaT generation)							
3	Patient enroll							
4	Interim analysis							
5	DMC and iCReaT data completeness monitoring							
6	Reporting results and writing papers							

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References

1. Goyal N, Tsivgoulis G, Pandhi A, et al. Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes. Neurology 2017; 89: 540-547.

2. Maier IL, Tsogkas I, Behme D, et al. High Systolic Blood Pressure after Successful Endovascular Treatment Affects Early Functional Outcome in Acute Ischemic Stroke. Cerebrovasc Dis 2018; 45: 18-25.

3. Cho BH, Kim JT, Lee JS, et al. Associations of various blood pressure parameters with functional outcomes after endovascular thrombectomy in acute ischaemic stroke. Eur J Neurol 2019; 26: 1019-1027.

4. Chang JY and Han MK. Postthrombectomy Systolic Blood Pressure and Clinical Outcome among Patients with Successful Recanalization. Eur Neurol 2019; 81: 216-222.

5. Anadani M, Orabi MY, Alawieh A, et al. Blood Pressure and Outcome After Mechanical Thrombectomy With Successful Revascularization. Stroke 2019; 50: 2448-2454.

6. Anadani M, Orabi Y, Alawieh A, et al. Blood pressure and outcome post mechanical thrombectomy. J Clin Neurosci 2019; 62: 94-99.

7. Park HK, Chun SY, Choi Y, et al. Effects of social activity on health-related quality of life according to age and gender: an observational study. Health Qual Life Outcomes 2015; 13: 140.

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

Trial PROTOCOL

(Version 2.2 – 19 May 2021)

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Table of Contents

1070 # Abstract

Title	Outcome in Patients Treated with Intraarterial thrombectomy - optiMAL BP control (OPTIMAL-BP) trial
Principle research center	Severance Hospital, Yonsei University **College of Medicine**
Objective	To investigate whether intensive **blood pressure (**BP**)** management during the first 24 hours after successful recanalization leads to better clinical outcomes compared to conventional BP management in patients treated with IAT.
Efficacy outcome measure	**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 B. Stroke-related death within 90 days **2. Secondary outcome** 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) Favorable outcome at 1 month (mRS score 0-2) 6) Health-related quality of life, as assessed by the EuroQoL group EQ-5D-3 L, 7) Frequency of occurrence of malignant brain edema
Research design	Multicenter, randomized, open-label, blinded end point evaluation trial
Population	patients with acute ischemic stroke who were treated with IAT due to large vessel occlusion and who achieved successful recanalization (a modified Treatment In Cerebral Infarction score of ≥2b) and elevated systolic BP ≥140 mmHg within 2 hours of successful recanalization
Sample size	668
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 (mTICI 2b or mTICI 3) 4. Patients with elevated BP (systolic BP ≥140 mmHg) on at least two measurements with a two-minute interval within 2 hours of successful recanalization.

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
Stop/ out criteria	1. Patients withdrawing consent 2. Patients whose BP is maintained at more than 220 mmHg despite active BP control after IAT 3. If the principal investigator or the investigator determines that the test should be discontinued
Research cycle	BP control within 24 hours, follow-up imaging study at 24 ± 12 hours, assessment at 1 and 3 months
Interventions	Participants received intensive BP management (targeting systolic BP <140 mmHg) or conventional management (targeting systolic BP between 140-180 mmHg) for 24 h after enrollment

Statistical analysis	In the primary analyses, the efficacy was evaluated among all patients who underwent randomly assigned treatment for 24 hours, had outcome measures up to 3 months, and gave consent. The per-protocol analysis included patients who underwent the assigned treatment and had no major protocol deviations. Binary logistic regression analyses were performed for the primary outcome and the treatment effects were presented as odds ratios (ORs) with 95% confidence intervals (CIs). In addition, risk ratios and risk differences with 95% CIs were calculated. The independent predictors were determined using a multivariable logistic regression analysis adjusting age, sex, onset to registration time, and the NIHSS score just before IAT. For the secondary outcome, the common OR representing a shift in mRS scores was calculated using an ordinal logistic regression analysis. Linear regression analyses were performed for the NIHSS score at 24 hours and the EQ-5D-3L score. Subgroup analysis of the primary outcome was performed on prespecified subgroups. The homogeneity of treatment effect across subgroups was evaluated using a logistic regression model. To show the relationship between mean SBP during 24 h and poor outcomes, we used a 3-knot restricted cubic spline curve.
Sites number	19 stroke centers in South Korea
Research duration	3 months

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1072 # Abbreviation

Abbreviation	Full title
ABPM	Ambulatory BP monitoring
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
CV	Coefficient of variation
DCT	Data clarification form
DMC	Data Management Center
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
FLAIR	Fluid-attenuated inverse recovery
GCP	Good Clinical Practice
HI	Hemorrhage infarction
HRQoL	Health-related quality of life
IAT	Intra-arterial thrombectomy
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage

ICMJE	International Committee of Medical Journal Editors
iCReaT	Internet based Clinical Research and Trial management system
IRB	Institutional Review Board
MCA	Middle cerebral artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mTICI	Modified Treatment In Cerebral Infarction
NIBP	Non-invasive automatic BP
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
SD	Standard deviation
SV	Successive variation
TOAST	Trial of Org 10 172 in acute stroke treatment
VA	Vertebral artery
VIM	Variation independent of the mean

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Overview

Studies have demonstrated that intravenous thrombolysis is effective in improving symptoms of acute cerebral infarction patients, but the treatment is not always successful. Even when administered within an appropriate time frame, only 22.6% of blood clots are dissolved and only about 30% of patients experience improvement. Recently, intra-arterial procedures such as intra-arterial thrombectomy (IAT) have been found to be effective. This procedure uses a stent retriever or catheter to physically remove blood clots from the body. IAT has a high success rate of nearly 80% in terms of vascular re-opening, however, only around 50% of patients show clinical improvement. Therefore, there is a need for new treatment strategies and techniques to reduce the number of patients who do not benefit from the procedure.

BP (BP) is a significant factor in the outcomes of stroke patients who have received recanalization treatment. Patients who have undergone successful recanalization treatment are more likely to experience a spontaneous decline in BP over 12 to 24 hours following IAT than those with persistent occlusion. BP has a direct impact on cerebral perfusion pressure, with low BP potentially decreasing cerebral perfusion pressure and causing harm to ischemic brain areas. Conversely, sustained high BP may increase the risk of intracerebral hemorrhage (ICH) and lead to worse functional outcomes.

The American Heart Association guidelines recommend lowering BP to below 180/105 mmHg in patients who have undergone successful recanalization, with a class of recommendation of IIb and level of evidence B-NR. The European guidelines suggest maintaining BP below 180/105 mmHg during and 24 hours after IAT. In contrast, previous retrospective studies and meta-analyses have indicated a potential association between BP in

the 24 hours following IAT and clinical outcomes, and have suggested that lowering BP may be beneficial. However, the optimal target for BP control in stroke patients who have undergone successful recanalization following IAT remains uncertain.

Research Purpose

The objective of this trial is to establish whether intensive BP-lowering (<140 mmHg) results in a superior clinical outcome compared to conventional BP-lowering (140 - 180 mmHg) following successful recanalization through IAT.

Research agencies and estimated duration of the study

1. Research Institute: 19 hospitals in South Korea including Yonsei University College of Medicine.

No.	Duty	Investigator	Hospital	e-mail
1	Primary investigator	Hyo Suk Nam	Severance Hospital, Yonsei University College of Medicine	hsnam@yuhs.ac
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2. Estimated research period : 5 years from the date of initial approval of the IRB (60 months)

Criteria for inclusion and exclusion of study subjects

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 (systolic BP ≥140 mmHg) on at least two measurements with a two-minute interval within 2 hours of successful recanalization.

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

3. Stop / out criteria

1. Patients withdrawing consent

2. Patients whose BP is maintained at more than 220 mmHg despite active BP control after IAT

3. If the principal investigator or the investigator determines that the test should be discontinued

Estimated number of research subjects

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. 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 ≠ 0 (the ratio of poor outcomes between groups A and B is not the same)

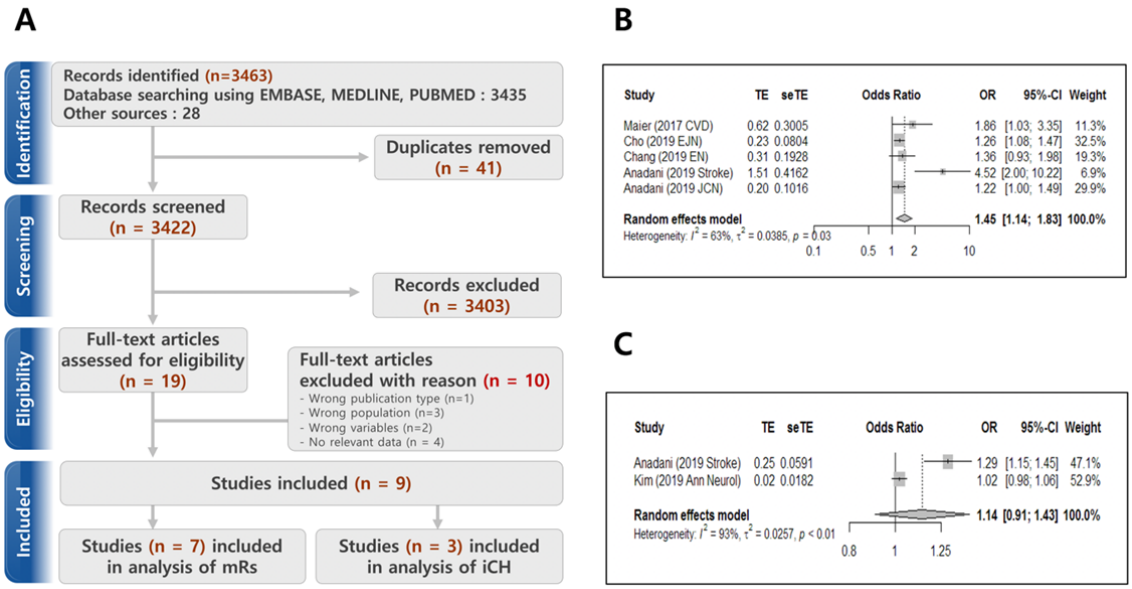
3. Sample size calculation

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 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 systolic BP ≤

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 systolic BP 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 systolic BP-lowering target of <140 mmHg.[1] They compared an aggressive systolic BP-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 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)			

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 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 held 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 Data Safety Management Board (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.

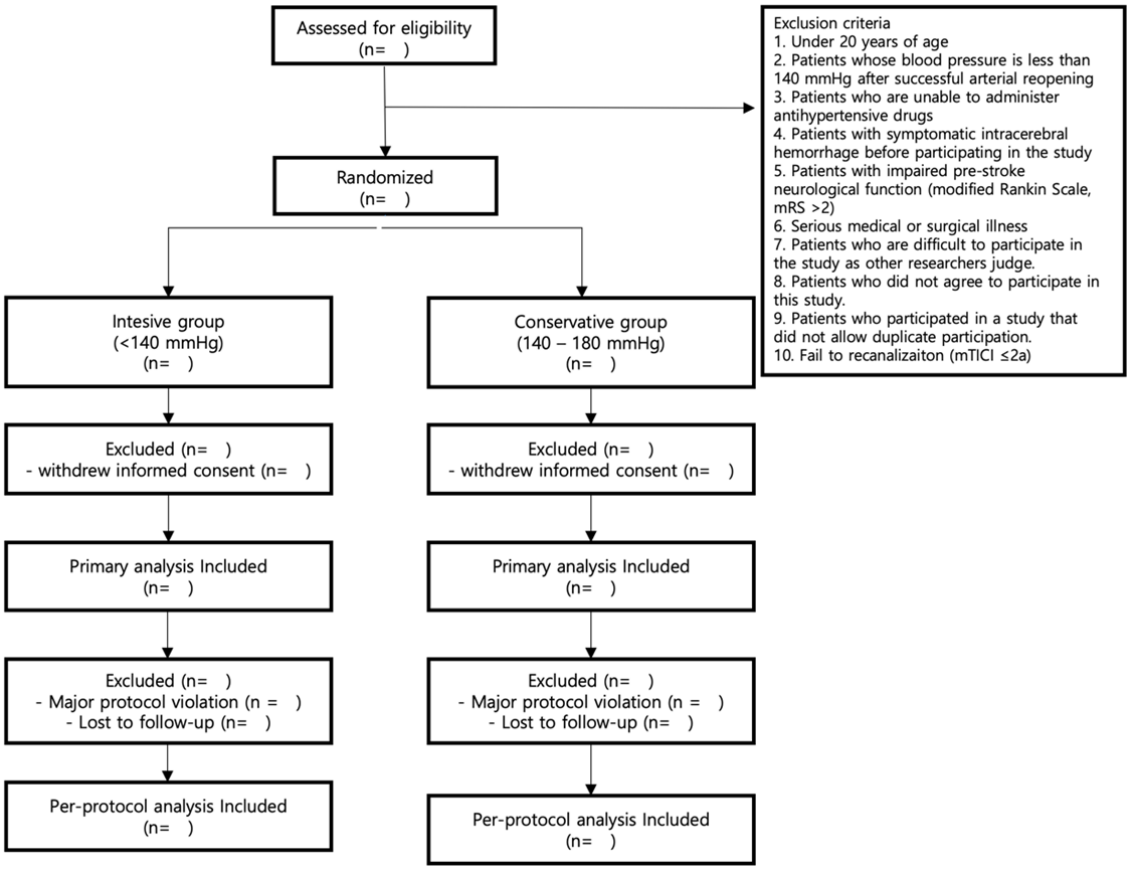
Study Design

1) The study design is a prospective, randomized, open-label trial with blinded end-point assessment (PROBE). In a PROBE trial, the study is prospective, meaning that patients are enrolled before the start of the study, and it is randomized, meaning that patients are randomly assigned to different treatment groups. The study is open-label, meaning that both the patient and the investigator know which treatment the patient is receiving, but it is blinded at the endpoint, meaning that the outcome of the study is assessed in a blinded manner.

2) The study will use a 1:1 ratio of the intensive group (target systolic BP <140 mmHg) and the conventional group (target systolic BP 140 - 180 mmHg) for patients who have achieved successful recanalization after IAT.

3) To prevent imbalance between the groups, randomization was stratified by the enrollment hospital and the degree of neurological impairment as determined by the NIHSS score at admission (<15 points or ≥15 points).

4) The study is a multi-center, prospective study that will include patients admitted to the neurology department of participating hospitals with acute cerebral infarction between January 2020 and December 2023, based on the date of stroke onset. Eligible patients will have undergone IAT in accordance with stroke treatment guidelines and have successfully reopened the arteries. The study will be conducted for five years in the participating hospitals.



5) The study will collect the following data from the eligible participants: medical history, test results, BP parameters (systolic BP, diastolic BP, BP variability, etc.), imaging tests, neurological scores, functional recovery, and quality of life indicators. All data collected will be in accordance with the study inclusion and exclusion criteria.

6) Neurological scores, functional recovery scores, and quality of life indicators will be assessed by independent investigators who are blinded to the participant's treatment group. This helps to ensure unbiased and accurate assessments of these outcomes.

7) All data collected will be entered into an electronic case report form (e-CRF) system and the images of the participants will be anonymized and transmitted to the host institution. This helps to ensure the security and confidentiality of the participant's data and images.

8) The host institution will perform a blinded quantification of the imaging tests. This means

that the investigators at the host institution will not know which group the participant belongs to when analyzing the imaging test results which help to minimize bias.

Study methods

1) The study aims to recruit patients with acute cerebral infarction who have undergone IAT for large cerebral artery occlusion. The selection and exclusion criteria and the treatment of IAT will be based on practice guidelines and institution-specific criteria.

2) The study will include patients who have successfully undergone arterial recanalization (as determined by mTICI 2b or mTICI 3 score) and have a mean BP greater than 140 mmHg, as measured twice within 2 hours of recanalization.

3) The study will use an automated BP device (Omron® HEM 7130) or a non-invasive automatic BP monitor (NIBP monitor) of the same model that has been certified as equivalent by the American Medical Device Association and the European Society of Hypertension, and has clinical study evidence A.

4) Patients who meet the inclusion/exclusion criteria and provide informed consent will have their BP and pulse measured at 1-hour intervals for up to 24 hours after providing consent. The BP and pulse data will be collected and recorded.

5) The initial BP and pulse data will be measured only once, excluding the pulse data.

6) To achieve and maintain the target systolic BP, local treatment protocols using available intravenous BP-lowering drugs will be permitted. The preferred BP-lowering drug is nicardipine, though other drugs such as labetalol and hydralazine are allowed at the physician's discretion.

7) If BP decreased below 140 mmHg in the conventional group, it will not be actively increased with vasopressor therapies. Treatment will be discontinued, and intravenous fluids

and inotropes will be used when hypotension needed to be treated at the physician's discretion.

8) If the target BP is achieved, measure it every hour. If the target is not met, take BP measurements every 15 minutes in the first hour after administering medication, every 30 minutes for the next 2 hours, and every hour until 24 hours have passed. If a deviation from the target occurs, necessitating additional medication or adjustments to the current dose, return to measuring BP every 15 minutes.

9) After randomization, the target BP should be reached within 60 minutes.

10) Radiological follow-up using computed tomography or magnetic resonance imaging will be undergone at 24 ± 12 hours and at any time when neurological symptoms worsen.

11) BP will be measured using an Omron® HEM 7130 automatic BP machine at 1 or 3 months. To ensure accurate results, participants should refrain from consuming caffeine, alcohol, and smoking for 30 minutes prior to measurement. They should also sit and rest for at least 3-5 minutes before taking the measurement on the upper arm of the non-paralyzed limb. Measurements should be taken with the arm at heart level, slightly bent on a desk without any force, and the person should be sitting with their back against the backrest and feet on the floor without crossing their legs, in accordance with the 2018 Primary Medical Evidence-Based Hypertension Clinical Practice Guidelines.

12) As a substudy, 24-hour ambulatory BP monitoring (ABPM) will be conducted at 1 and 3 months using certified sphygmomanometers from the list provided at www.dableducational.org. BP will be measured at 30-minute intervals and at least 14 valid measurements during the day and 7 valid measurements at night are required to be considered as valid data.

13) A mRS score will be calculated to assess neurological recovery at 3 months. Assessments

will be conducted by independent investigators who are unaware of the treatment or control group status.

Research Plan

Research plan	Screening	24hr	F/U visit	End visit	Drop out
	0	24 ± 6 h	1 month ± 14 d	3 month ± 14 d	
Inclusion/exclusion check	X				
History	X				
agreement	X				
BP/pulse	X	X	X	X	X
NIHSS score	X	X			
Modified Rankin scale (mRS)	X (Before stroke)		X	X	X
EQ 5D-3L				X	
BP control treatment		X	X		
Adverse reactions		X			
Brain imaging	X	X[2)]			
Standard Stroke Treatment	X	X	X	X	X
Cardio-cerebrovascular events			X	X	X

3) For the final visit, the main study and the 1st, 2nd, and 4th substudies will be conducted for 3 months, and the 3rd sub-study will be conducted for 1 year.

4) Brain imaging (MRI or CT) performed within 24 ± 12 hours after IAT.

Screening (0 days)

Selection/exclusion eligibility checked

Vital signs (BP, pulse rate)

History

Obtaining consent

NIHSS Score

Pre-cerebral infarction mRS

Obtaining consent

Brain imaging (MRI, CT, MRA, CTA, digital subtraction angiography)

Randomization

24 hours (24 ± 6 hours)

Vital signs (BP, pulse rate)

NIHSS

BP control treatment

Adverse Reaction Check

Brain imaging images taken within 24 ± 12 hours (MRI or CT)

Standard Stroke Treatment

F/u visit (1 month ± 14 days)

Vital signs (BP, pulse rate)

BP control treatment

Standard Stroke Treatment

Cardio-cerebrovascular events

last visit (3 months ± 14 days)

Vital signs (BP, pulse rate)

mRS

EQ-5D-3L (EuroQoL 5-Dimension Self-Report Questionnaire)

Standard Stroke Treatment

Cardio-cerebrovascular events

End visit (1 year ± 14 days)

Vital signs (BP, pulse rate)

mRS

EQ-5D-3L

Standard Stroke Treatment

Cardio-cerebrovascular events

How to obtain a consent form to participate in a study

1) We will adhere to the guidelines outlined in the Helsinki Declaration and ICH-GCP and will only conduct research after receiving approval from the institutional review board (IRB).

2) Informed consent will be obtained from participants who meet the established inclusion and exclusion criteria for the study.

3) Informed consent will be obtained from research participants who have the capacity to understand the study's purpose, content, and methods. The investigator will provide a full explanation of the study and answer any questions the participant may have. Participation in the study will be completely voluntary and a signed consent form will only be obtained from participants who willingly agree to participate in the study.

4) In cases where the potential research subject is unable to read or comprehend the study information, such as if they are illiterate or blind, the principal investigator is responsible fore ensuring that an neutral third party is present to read the study information to the subject and answer any questions they may have. Once the subject fully understands the study and

voluntarily agrees to participate, both the subject and the impartial observer will sign a written consent form to indicate that the subject has provided informed consent. This ensures that the subject's participation in the study is based on their own free will and understanding of the study's purpose, content, and method.

5) In cases where the research subject is unable to fully understand the research due to conditions such as cerebral infarction or other impairments, and is unable to provide a handwritten signature, the investigator will obtain written consent from the legal representative after thoroughly explaining the purpose, content, and methods of the study. However, if the individual is able to provide voluntary consent during the follow-up period, the investigator will make an effort to obtain the individual's consent.

6) Before any research involving human subjects can proceed, the IRB must first review and approve the explanatory text and consent form for the subject. After the subject or their legal representative signs the form, the principal investigator must retain one original copy and provide one copy to the subject or legal representative. It's important to allow sufficient time for the individual to read and fully understand the information before signing and receiving a copy of the statement and consent form.

7) It is important to remind that the study participant has the right to withdraw their consent to participate in the trial at any time during the study period. This means that the participant has the freedom to stop taking part in the study and discontinue any further involvement without any negative consequences or penalty. It is crucial to inform the participant of this right and how to exercise it, and to document any withdrawals of consent in the study records.

8) Clinical investigators have an ethical and legal obligation to ensure the confidentiality of all information obtained during the study period. This means that all information collected from the study subjects, such as personal identifying information, medical history, and study

results, must be kept private and protected from unauthorized access or disclosure. Appropriate measures should be taken to safeguard the data, such as using secure storage systems, password-protecting files, and limiting access to authorized personnel only. Additionally, the investigators should ensure that any data shared with external parties, such as sponsors or regulatory authorities, is de-identified or otherwise protected to maintain the confidentiality of the study subjects. It is important for the investigators to inform the participants about their policies and procedures to protect the confidentiality of their information.

9) Observation items and data collection methods refer to the specific aspects of the study that are being observed and the methods used to collect the data. For example, observation items may include vital signs, symptoms, or laboratory test results, while data collection methods may include interviews, surveys, physical exams, or medical imaging. It is important for the observation items and data collection methods to be clearly defined and specified in the study protocol, as they will serve as the basis for data analysis and interpretation. The selection of observation items and data collection methods should be appropriate for the research question and be able to accurately and reliably measure the variables of interest. They should also be feasible and ethical for the study population.

Hypothesis

In the treatment of acute cerebral infarction through IAT, it is hypothesized that the intensive group (a group of patients receiving intensive treatment) will have a better prognosis than the conventional group (a group of patients receiving conventional treatment) after successful arterial recanalization. This prediction is based on the idea that the intensive group will receive a more aggressive and comprehensive treatment plan, which may lead to better

outcomes such as increased chances of recovery, reduced disability, and decreased mortality rates. The prediction will be tested through a randomized controlled trial where the patients will be divided into two groups, the intensive group and the conventional group, and the outcomes will be measured and compared between the groups. The study will be conducted to confirm the hypothesis and to find out the best treatment approach for patients with acute cerebral infarction..

Outcome Evaluation Variables

The outcome endpoints were evaluated twice, one at the end of the interim analysis and one at the end of the study.

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. Secondary outcome

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

3. Observations

1.BP readings (systolic BP and diastolic BP)

1) BP during the visit

2) BP measured between 30 minutes and 1 hour after arterial recanalization

3) Hourly BP measured at 1-hour intervals for 24 hours after arterial recanalization

4) Active BP for 24 hours measured at 1-hour intervals at 1 and 3 months after arterial recanalization

4. Clinical scale

1) NIHSS scale score measured 24 hours after IAT

2) The mRS score measured at 1 month, 3 months, and 1 year after discharge from the hospital.

3) Quality of Life Indicators (EQ-5D-3L) measured 3 months and 1 year after arterial recanalization

5. Imaging Findings

1) Cerebral hemorrhage or hemorrhagic transformation occurs on MRI or CT after IAT

- Classification of a cerebral hemorrhage

Hemorrhage infarction type1 (HI1)	Small hyperdense petechiae
Hemorrhage infarction type2 (HI2)	More confluent hyperdensity throughout the infarct zone: without mass effect
Parenchymal hematoma type1 (PH1)	Homogeneous hyperdensity occupying <30% of the infarct zone: some mass effect
Parenchymal hematoma type2 (PH2)	Homogeneous hyperdensity occupying >30% of the infarct zone: significant mass effect. Or, any homogenous hyperdensity located beyond the borders of the infarct zone

2) Size of cerebral infarction measured by diffusion-weighted image, fluid-attenuated inverse recovery (FLAIR) image, or brain CT (when the diffusion-weighted image is not available).

3) Collateral grade by Tan scale score using CTA

0: absent collateral supply to the occluded MCA territory

1: collateral supply filling ≤50% but >0% of the occluded MCA territory

2: collateral supply filling >50% but <100% of the occluded MCA territory

3: 100% collateral supply of the occluded MCA territory

A good collateral status is defined by a Tan scale score of 2 to 3, while poor collateral status corresponds to a Tan scale score of 0 to 1.

4) Recanalization status at 24 hours is defined using CTA or MRA for 24 hours

Clinical Manifestations

The following data will be collected on the patient's clinical manifestations:

- Time of onset of symptoms
- Time from symptoms to treatment
- Severity of stroke using the NIHSS score
- Previous history of stroke
- Factors such as weight, obesity, hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, coronary artery obstructive disease, congestive heart failure, peripheral artery obstructive disease, and active cancer that may increase the risk of cerebral infarction
- Any other medical conditions the patient may have
- Assessment of patient's neurological functional independence before the onset of stroke using mRS
- Identification of the underlying cause of cerebral infarction using Trial of Org 10172 in Acute Stroke Treatment (TOAST)
- EQ-5D-3L; Health-related quality of life (HRQoL) was assessed using the EQ-5D-3L. The EQ-5D-3L descriptive system evaluates the state of general health across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using three levels to indicate the extent of problems: no problems, some/moderate problems, and severe problems. The EQ-5D-3L utility score is a single score calculated using population-based

preference weights for each dimension, and expressed as a fraction of perfect health, with a score of 1 representing perfect health, 0 representing death, and negative scores (with a minimum score of -0.109) indicating health states considered worse than death. In this analysis, preference weights derived from the South Korean population were used to calculate the utility scores.[7] When patients were unable to complete the questionnaire themselves, proxy responders such as caregivers were asked to rate the patient's HRQoL.

Data Collection Method

1) All clinical data will be collected electronically in an anonymized state using the web-based eCRF (iCReaT) of the Korean National Institutes of Health and the Centers for Disease Control. This system ensures the confidentiality and security of patient information while allowing for efficient data collection and management.

2) Data for each participating institution will be collected and managed in an integrated manner through this system, ensuring the quality and consistency of data across all sites.

3) Data management for this study will be handled by the Data Management Center (DMC), a clinical trial center of the Severance Hospital, Yonsei University. This center operates independently and is responsible for all aspects of data management. Before registering in the iCReaT system, the DMC creates databases using standardization guidelines and includes auto-query functions. Investigators will be provided with input guidelines to ensure data reliability and completeness. Data audit will be conducted every month and data cleaning will be conducted biannually to ensure data accuracy. All clinical data will be collected electronically in an anonymized state through the iCReaT system.

4) This trial will be led by the state and registered with the Korean National Institutes of Health's Centers for Disease Control and Prevention's iCReaT web-based clinical research

management system.

5) Verify data quality through Quality Control in the DMC, then proceed with database locking. After locking, no data changes or additions will be allowed.

Training of investigators

Each of the OPTIMAL-BP investigators received training for the protocol, GCP procedures, as well as the usage of the NIHSS and mRS score. The GCP training was conducted by individual hospitals.

Research Recording and Storage

1) Principal investigator must have a list of qualified individuals assigned to the study.

2) Clinical information (including image data) will be publicly accessible through research resource through the National database (iCReaT) managed by the Korean Centers for Disease Control. Clinical data will be managed as a national resource under regulations for health and medical tech R&D projects, with no set expiration for stored data use.

3) Data sharing follows (International Committee of Medical Journal Editors) ICMJE's "Data sharing statements for clinical trials." Raw clinical data will be shared after database lock and can be shared anonymously for international research collaboration.

4) Data sharing requires obtaining consent which include information about it in the research subject's explanatory text and consent form.

5) The investigator must retain records and documents related to the research implementation (e.g. test protocol, consent form, etc.) and clinical trial data, as per Article 15 of the Bioethics Law Enforcement Regulations, for 3 years after termination of the trial. After the retention period, documents must be destroyed as per Article 16 of the Personal Information Protection

Act Enforcement Decree.

6) In case of the investigator's departure (e.g. resignation, retirement), the handover to the new person must be agreed upon mutually.

7) If consent is withdrawn, the investigator will stop collecting new trial data but may still use data collected before the withdrawal.

8) Severance Hospital (the responsible research institution), Clinical Trial Review Committee, and Ministry of Food and Drug Safety may review subject's medical records to verify collected information. Information exposed will be treated as confidential.

9) Principal investigator must keep the signed consent form, and make a subject number and name list for easy searching, stored in a password-protected file in a locked lab.

10) Personal information collected is coded in a non-identifiable form, stored on a locked computer and remains anonymous even when results are reported or published. After study completion, it stays anonymous and stored on a locked computer.

11) In accordance with the Personal Information Protection Act (Article 24) and the Bioethics Act (Articles 16 and 37), research records, including unique identification information, must be kept for 3 years from the end of the study or until a request for destruction is made for clinical research in the public interest.

12) Unique identification information (resident registration number) will be collected to integrate with data held by national agencies, the National Health Insurance Agency, the Health Insurance Review and Evaluation Service, the National Statistics Office, and the National Cancer Center for conducting clinical research in the public interest of the Ministry of Health and Welfare. In addition, the subject has the right to receive an explanation and to agree or reject it.

Data analysis statistical method

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.

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 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.

3.1 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.

3.2 Symptomatic intracranial hemorrhage (sICH)

The definition for sICH is based on that in the European Cooperative Acute Stroke Study III (ECASS III). 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 3.1). We will apply the covariate adjustments described in Section 3.1; however, no subgroup or imputed analysis will be performed on this outcome.

3.3 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 3.1). The covariate adjustments described in Section 3.1 will be applied, but no subgroup or imputed analysis will be conducted for this outcome.

3.4 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.

3.5 Treatment of missing data

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

4 Analysis of the secondary outcome

The primary analysis (ITT population) (see section 1) and analysis using PP population (see section 2) will be conducted.

4.1 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 3.1 will be applied, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.2 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.

4.3 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 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.4 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 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.5 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 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

4.6 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.

4.7 Malignant brain edema

The occurrence of malignant brain edema will be analyzed using the same method as the mRS score described in Section 3.1 The covariate adjustments outlined in Section 3.1 will be applied, but no subgroup analysis or imputed analysis will be performed for this outcome.

5 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.

Definitions of protocol violations and deviations

Protocol deviations or violations were classified into two groups: major (reportable) violations and minor (non-reportable) violations.

1. Major (reportable) protocol violations

Major protocol violations were unapproved changes in the study design or procedures within the investigator's control, not in line with the approved protocol that may have impacted the participant's safety, well-being, or study data accuracy. Such violations were reported to the IRB according to relevant national guidelines and timelines.

The DMC considered violations as major if they caused or had the potential to cause significant harm to the participant, affected the participant's clinical or emotional condition, damaged scientific data completeness or soundness, involved willful or knowing misconduct, or showed serious or continuous noncompliance with local, state, or federal regulations.

2. Minor (non-reportable) protocol violations

Minor protocol violations were unapproved changes in the study design or procedures within the investigator's control, not in accordance with the approved protocol but with no major impact on the participant's safety, rights, or study data completeness, accuracy, or reliability. Such violations did not always require reporting to the IRB.

The DMC identified violations as minor if they did not cause harm or a significant risk of substantive harm to the research participant, did not change their clinical or emotional condition or data accuracy, did not involve willful misconduct or serious noncompliance with regulations, or damage data completeness, accuracy, or reliability.

Analysis of potential risks and benefits to patients

1. Potential hazards:

This study aims to examine the outcome of patients after BP control during IAT. As all patients will have BP controlled below the standard of 180 mmHg, the risk to subjects is expected to be low. However, there is a risk of personal information being disclosed, but measures to protect it are in place. There is currently no evidence to support the difference between the standard BP control group (140-180 mmHg) and the active BP control group

(<140 mmHg), but if the results of the latter group are favorable, the study may be discontinued and the results shared with participants.

2. Potential benefits:

The results of this study can contribute to the development of better treatment strategies for cerebral infarction, and ultimately improve the prognosis for future patients. The information collected from this study can also provide valuable insights for the medical community, helping to advance our understanding of cerebral infarction and treatment.

3. Risk/ benefit Analysis:

This study is considered to have low potential risks and high potential benefits.

Compensation plan and compensation agreement for risks caused by research participation

Additionally, the study has taken necessary measures to minimize any potential harm to participants by purchasing Hyundai Marine Fire Insurance's clinical trial compensation insurance, which provides appropriate compensation in case of harm caused by the study.

Protection measures for vulnerable research subjects

1) Obtain written consent from the legal representative of vulnerable research subjects after providing a comprehensive explanation and confirming their agreement to participate in the study (Refer to guidelines on how to obtain consent for participation in a study).

2) This study examines the criteria for BP control after IAT in stroke patients and all

participants will receive the same standard treatment process as other stroke patients, regardless of participation in the study.

3) Patients participating in this study face minimal potential risks.

4) Patients or their legal representatives may withdraw from the study at any time, without facing any disadvantages.

5) In case of harm caused to the subject during the study, we will provide compensation as per the terms of the clinical trial insurance policy and make sure they receive the best possible treatment. However, this compensation will not cover adverse reactions that are not related to the study, symptoms or diseases that are the result of the subject's own mistake or cause, and any deterioration of symptoms that may occur due to the natural progression of the disease.

6) For vulnerable individuals who are scheduled to participate in the study, written consent will be obtained after a sufficient explanation has been provided to their legal representative and the representative has confirmed their consent. This is to ensure that the individual's rights and well-being are protected during the course of the study.

7) The collected resident numbers will be securely stored as encrypted files and will only be used for linking with national institution databases. The numbers will be discarded immediately after the completion of the original purpose. Resident numbers will only be collected from individuals who have provided their consent for such collection.

Methods for maintaining the confidentiality of research subjects' identities and research materials

1) The confidentiality of the study participant's information is of utmost importance and will be protected at all times.

2) The study records will include the subject's initials and assigned number will be collected and stored at the responsible research institution (Severance Hospital) using a de-identification program that replaces the subject's name with their initials and number.

3) The medical records of the subjects may be reviewed by the responsible research institution (Severance Hospital), the Clinical Trial Review Committee, and the Ministry of Food and Drug Safety for verification purposes. Any information obtained during this process will be kept confidential.

4) The signed consent form shall be kept by the lead investigator and a list containing the subject's number and name will be made to allow for easy access to the records.

Continuous safety monitoring plan and data safety monitoring plan.

1) The principal investigator and DMC will continuously monitor the data collected during the study. Personal information and data will be kept confidential by being encoded and stored on a secure computer. The information will remain anonymous even after the study has concluded and will continue to be stored on a locked computer.

2) Data and safety monitoring methods and cycles

(1) Monthly written evaluations of research progress and data management will be carried out by the principal investigator and the responsible party.

(2) The data management procedure will follow established validation specifications. Any errors found are corrected and the data will be checked for completeness, standardized, and consolidated from each institution using a data clarification form (DCF).

3) DSMB

The DSMB, an independent committee, oversees patient safety and tracks recruitment

progress. It includes a medical statistician, neurologist, and representative from the Severance Clinical Trial Center. The members' names are confidential but can be provided upon request by the coordinating authority. DSMB reports are kept confidential, except in special cases. The frequency of DSMB meetings is determined prior to the study's start and additional meetings can be called if safety concerns arise.

4) Research discontinuation criteria

In case of non-compliance with significant ethical rules or deviation from the major protocol by the research site or investigator, the trial may be instantly halted.

Substudies

There are four substudies in the OPTIMAL-BP trial. Substudies were embedded within the main trial to recruit as many patients as possible.

N	Substudies
1	Substudy 1. Effects of BP parameters including systolic BP, diastolic BP, and BP variability on the outcome according to treatment group
2	Substudy 2. Personalized BP control using artificial intelligence immediately after IAT in acute cerebral infarction
3	Substudy 3. Analysis of the relationship between post-stable BP control and primary end-point in patients with successful arterial reopening through IAT
4	Substudy 4. Differences according to the degree of collateral circulation on prognosis after reopening through IAT

Research implementation plan

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	Research content	2020.01-2020.03	2020.03 – 2021.02	2021.03 – 2021.12	2022.01 – 2022.10	2022.10 – 2022.11	2022.12 – 2023.06	2023.06– 2023.12
1	IRB Approval							
2	eCRF (iCReaT generation)							
3	Patient enroll							
4	Interim analysis							
5	DMC and iCReaT data completeness monitoring							
6	Reporting results and writing papers							

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References

1. Goyal N, Tsivgoulis G, Pandhi A, et al. Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes. Neurology 2017; 89: 540-547.

2. Maier IL, Tsogkas I, Behme D, et al. High Systolic Blood Pressure after Successful Endovascular Treatment Affects Early Functional Outcome in Acute Ischemic Stroke. Cerebrovasc Dis 2018; 45: 18-25.

3. Cho BH, Kim JT, Lee JS, et al. Associations of various blood pressure parameters with functional outcomes after endovascular thrombectomy in acute ischaemic stroke. Eur J Neurol 2019; 26: 1019-1027.

4. Chang JY and Han MK. Postthrombectomy Systolic Blood Pressure and Clinical Outcome among Patients with Successful Recanalization. Eur Neurol 2019; 81: 216-222.

5. Anadani M, Orabi MY, Alawieh A, et al. Blood Pressure and Outcome After Mechanical Thrombectomy With Successful Revascularization. Stroke 2019; 50: 2448-2454.

6. Anadani M, Orabi Y, Alawieh A, et al. Blood pressure and outcome post mechanical thrombectomy. J Clin Neurosci 2019; 62: 94-99.

7. Park HK, Chun SY, Choi Y, et al. Effects of social activity on health-related quality of life according to age and gender: an observational study. Health Qual Life Outcomes 2015; 13: 140.

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

OPTIMAL-BP

Outcome in Patients Treated with Intraarterial Recanalization Therapy - Optimal Arterial Blood Pressure Control

TRIAL PROGRESS

1. List of OPTIMAL-BP trial group and trial investigators

Steering committee

Ji Hoe Heo (Chair), Sun U Kwon, Oh Young Bang, and Hyo Suk Nam

Executive committee

Hyo Suk Nam (Chair), Yo Han Jung, Jong-Won Chung, Jun Young Chang, Seong Hwan Ahn, Hyungjong Park, Kwon-Duk Seo, Tae-Jin Song, Yang-Ha Hwang, Jun Lee, Jung Hwa Seo, Dong Hoon Shin, Chi Kyung Kim, Jang-Hyun Baek, Yoonkyung Chang, Bang-Hoon Cho, Joonsang Yoo, Han-Jin Cho, Jae Guk Kim

Data Safety Monitoring Board

Chung Mo Nam (Chair), Jong Yun Lee, Hye-Yeon Choi

Statisticians

Hye Sun Lee, Soyoung Jeon

Imaging and Events Adjudication Committee

Byung Moon Kim (Chair), JoonNyung Heo, Hyungwoo Lee, Minyoul Baik, Jang-Hyun Baek

Performance Publishing Committee

Young Dae Kim (Chair), Ji Hoe Heo, Hyo Suk Nam, Hyungjong Park, Tae-Jin Song, Bang-Hoon Cho, Seong Hwan Ahn

OPTIMAL-BP trial Principal Investigators and Coordinators (center, with numbers of patients in parentheses)

Department of Neurology, Yonsei University College of Medicine, Seoul, Korea (26), Department of Neurology, Gachon University Gil Medical Center, Incheon, Korea (6), Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (2), Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea (6), Department of Neurology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, South Korea (1), Department of Neurology, Brain Research Institute, Keimyung University School of Medicine, Daegu, Korea (43), Department of Neurology, Korea University Guro Hospital and College of Medicine, Seoul, Korea (1), National Health Insurance Service Ilsan Hospital, Goyang, Korea (17), Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea (8), Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (0), Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea (17), Department of Neurology, Yeungnam University School of Medicine, Daegu, Korea (0), Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea (2), Department of Neurology, Seoul Hospital, Ewha Woman's University, College of Medicine, Seoul, Korea (37), Department of Neurology, Chosun University School of Medicine, Gwangju, Korea (52), Department of Neurology, Korea University Anam Hospital and College of Medicine, Seoul, Korea (59), Department of Neurology, Pusan National University School of Medicine, Busan, Korea (6), Department of Neurology, Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Korea (22).

2. Timelines and changes of the protocol

date	Name of document/event	Brief summary of change/note
09 January, 2020	OPTIMAL-BP Protocol V1.0	
13 March, 2020	OPTIMAL-BP Protocol V 1.1	■ Adding stratified randomization ■ randomization was stratified by the enrollment hospital and the degree of neurological impairment as determined by the National Institutes of Health Stroke Scale (NIHSS) score at admission (<15 points or ≥15 points).
18 March, 2020	DMC First Meeting	■ Defining the role of the DM (data management) team
09 April, 2020	OPTIMAL-BP Protocol V 1.2	■ Change the consent form
11 May, 2020	OPTIMAL-BP Protocol V 1.3	■ Change the BP measurement interval
28 May, 2020	DM Second Meeting	■ Paper CRF inspection ■ Data cleaning
12 June, 2020	OPTIMAL-BP Protocol V 1.4	■ Change the investigators in the participating hospital ■ Change the consent form
18 June, 2020	First patient enrollment	
23 June, 2020	OPTIMAL-BP 1st Meeting of Investigators	■ Report the current status of the trial ■ Discuss the enrollment issues
26 June, 2020	OPTIMAL-BP Protocol V 1.5	■ Change the investigators in the participating hospital ■ Change the inclusion criteria • Patients should have elevated BP (SBP ≥140 mmHg) on at least two measurements with a two-minute interval within 2 hours of successful recanalization. ■ Adding in the exclusion criteria • Symptomatic intracerebral hemorrhage before participating in the trial ■ Adding trial method • Reaching target BP within 60 minutes
30 June, 2020	DMC Third Meeting	■ Open the eCRF site ■ Check visit interval ■ Check eCRF schedule
01 July, 2020	OPTIMAL-BP Sub-study Investigator Meeting	■ Discuss the substudy with cardiology ■ Remove the one year follow-up requirement of ambulatory BP monitoring it the substudy

03 August, 2020	OPTIMAL-BP Protocol V1.6	■ Modify methods • Check BP, pulse rate once except enroll BP and pulse rate
28 October, 2020	OPTIMAL-BP Protocol V 1.7	■ Change the exclusion criteria • Add deemed hard to recruit for the study by the investigators ■ Update the eCRF
13 January, 2021	OPTIMAL-BP 2nd Meeting of Investigators	■ Report the current status of the trial ■ Discuss the research grants
03 February, 2021	OPTIMAL-BP Protocol V 1.8	■ Modify the sample size from 644 to 668 (see below) ■ Change the consent form
29 April, 2021	OPTIMAL-BP Protocol V 1.9	■ Add a participating centers ■ Change the definition of symptomatic intracerebral hemorrhage (from SITS-MOST to ECASS III) ■ Change the consent form ■ Modify eCRF
12 May, 2021	OPTIMAL-BP 3rd Meeting of Investigators	■ Report the current status of the trial ■ Discuss the ongoing trials ■ Research Q&A
09 August, 2021	OPTIMAL-BP Protocol V 2.0	■ Change the inclusion criteria • Add definition of the large vessel occlusion (ICA, MCA, M1 or M2, ACA, A1, PCA, P1)'
31 August, 2021	OPTIMAL-BP Protocol V 2.1	■ Change the investigators in the participating hospital
28 October, 2021	OPTIMAL-BP 4th Meeting of Investigators	■ Report the current status of the trial ■ Discussion the 24-hour ambulatory BP monitoring in substudy ■ Discuss the log when CT or MRI are uploaded ■ Discuss enhance patient enrollment ■ Research Q&A
26 April, 2022	OPTIMAL-BP Protocol V 2.2	■ Add exclusion criteria • Participated in a study that did not allow duplicate participation
25 May, 2022	OPTIMAL-BP 5th Meeting of Investigators	■ Report the current status of the trial ■ Discuss the research grant ■ Discuss enhance patient enrollment ■ Other agenda
17 November, 2022	DSMB meeting	■ Recommended suspending recruitment due to safety concerns
28 November, 2022	OPTIMAL-BP 6th Meeting of Investigators	■ Report the current status of the trial ■ Report the decision of the DSMB ■ Discuss the study discontinuation ■ Research Q&A

29 November, 2022	Patient recruitment ceased	
08 March, 2023	Last patient follow-up	

Change the sample size at OPTIMAL-BP Protocol V 1.8 (03 February 2021)

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

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)

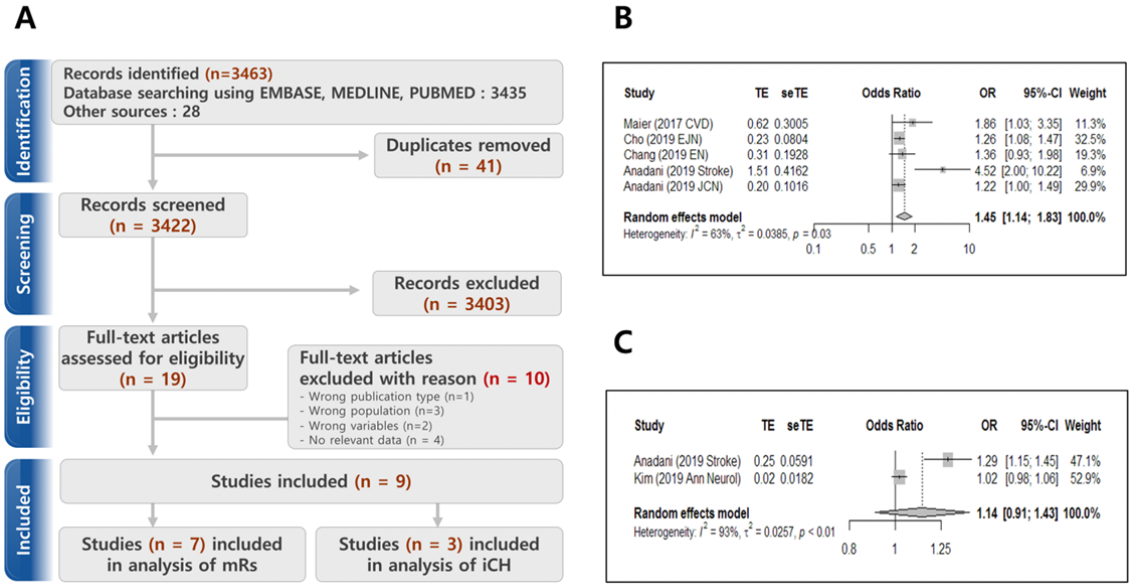
H_1: OR≠1 (the odds ratio for groups A and B is not the same)

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 h 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 systolic BP ≤ 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 systolic BP 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 systolic BP-lowering target of <140 mmHg.[1] They compared an aggressive systolic BP-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 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)			

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.

3. Major protocol violations

	Classification	Description	total
Major	Exclusion criteria	Pre-stroke mRS 3 to 5	12
Major	Follow up at 3 month	Lost to follow up before 3 month 2 transfer to other hospital before 24 hours 1 lost to follow-up after 1 month	3
Major	Crossover	The patient was managed as the intensive (SBP <140 mmHg) group despite being randomized to the conventional (SBP 140-180 mmHg) group.	2

4. Minor protocol violations

	Classification	Description	total
Minor	TICI at 24 hours	Missing	18
Minor	Collateral score	Missing	17
Minor	EQ-5D-3L	EQ-5D-3L was not collected.	11
Minor	Follow up at 1 month	Unable to follow up at 1 month	11
Minor	NIHSS at 1day	Missing data	4
Minor	ASPECTS	ASPECTS was not collected due to no CT before IAT	3

5. Screening Failure (n = 1300)

SBP <140 mmHg after successful recanalization (n = 705)

Did not agree to participate in this study (n = 119)

Deemed hard to recruit for the study by the investigators (n = 119)

Fail to recanalization (mTICI ≤2a) (n = 104)

Participated in a study that did not allow duplicate participation (n = 77)

Impaired pre-stroke neurological function (mRS ≥3) (n = 49)

Symptomatic intracerebral hemorrhage before participating in the trial (n = 48)

Serious medical or surgical illness (n = 46)

Cancer (n = 15)

Cardiac or aorta disease (n = 14)

Severe anemia or hematologic disease (n = 4)

Chronic kidney disease (n = 4)

Pneumonia (n = 4)

Sepsis (n = 2)

Cholecystitis (n = 1)

Hemothorax (n = 1)

Radius fracture (n = 1)

Age <20 years (n = 3)

Others (n = 30)

Covid-19 infection (n = 11)

Investigator error (n = 5)

Foreigner (n = 2)

Immediate transfer to other hospitals (n = 2)

No guardian (n = 2)

Advanced dementia (n = 2)

Unknown (n = 6)