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**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

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22 **the optiMAL Blood-Pressure Control (OPTIMAL-BP) Trial**

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OPTIMAL-BP

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

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Trial PROTOCOL

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(Version 1.0 – 09 Jan 2020)

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|--|---|
| 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 | <p>1. Primary outcome</p> <p>1) primary efficacy outcome</p> <ul style="list-style-type: none"> - Functional independence at 3 months, defined as a modified Rankin Scale (mRS) score of 0 to 2 - Differences in mRS ordinal shift analysis <p>2) primary safety outcomes</p> <ul style="list-style-type: none"> A. symptomatic ICH within 36 hours B. Stroke-related death within 90 days <p>2. Secondary outcome</p> <p>1) Difference in NIHSS scores at 24 hours after IAT</p> <p>2) Excellent Day 1 Recovery [Major Neurological Improvement]: NIHSS score of 0-1 or improvement > 8</p> <p>3) Recanalization status on CT Angiography (CTA) or MR Angiography</p> |

| | |
|---------------------------|---|
| | <p>(MRA) at 24 hours</p> <p>4) Favorable outcome at 1 month (mRS score 0-2)</p> <p>5) Health-related quality of life, as assessed by the EuroQoL group EQ-5D-3 L,</p> <p>6) Frequency of occurrence of malignant brain edema</p> |
| 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 $\geq 2b$) and elevated systolic BP ≥ 140 mmHg within 2 hours of successful recanalization |
| Sample size | 668 |
| Inclusion criteria | <ol style="list-style-type: none"> 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 | <ol style="list-style-type: none"> 1. Age < 20 years 2. Patients whose BP is less than 140 mmHg after successful recanalization through IAT |

| | |
|-----------------------------|--|
| | <p>3. Patients with contraindications for use of antihypertensive medication</p> <p>4. Patients with impaired pre-disease neurological function (modified Rankin Scale, mRS >2)</p> <p>5. Serious medical or surgical illness</p> <p>6. Patients who did not agree to participate in this study</p> |
| Stop/ out criteria | <p>1. Patients withdrawing consent</p> <p>2. Patients whose BP is maintained at more than 220 mmHg despite active BP control after IAT</p> <p>3. If the principal investigator or the investigator determines that the test should be discontinued</p> |
| Research cycle | <p>BP control within 24 hours, follow-up imaging study at 36 hours, assessment at 1 and 3 months</p> |
| Interventions | <p>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</p> |
| Statistical analysis | <p>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</p> |

| | |
|--------------------------|---|
| | <p>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.</p> <p>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.</p> |
| Sites number | 19 stroke centers in South Korea |
| Research duration | 3 months |

164

165 **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 |

167 **Overview**

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

177

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

185

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

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

194

195 **Research Purpose**

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

199

200 **Research agencies and estimated duration of the study**

201 1. Research Institute: 19 hospitals in South Korea including Yonsei University College of
 202 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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| 19 | Investigator | Jae Guk Kim | Daejeon Eulji Medical Center | mdbluewin@naver.com |

203

204 2. Estimated research period : 5 years from the date of initial approval of the IRB (60 months)

205

206 **Criteria for inclusion and exclusion of study subjects**

207 **1. Inclusion criteria**

208 1. Age ≥ 20 years

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

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

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

215

216 **2. Exclusion criteria**

217 1. Age < 20 years

218 2. Patients whose BP is less than 140 mmHg after successful recanalization through IAT

219 3. Patients with contraindications for use of antihypertensive medication

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

221 5. Serious medical or surgical illness

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

223

224 **3. Stop / out criteria**

225 1. Patients withdrawing consent

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

227 IAT

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

229 discontinued

230

231 **Estimated number of research subjects**

232 **1. Number of clinical trial subjects calculated**

233 644 patients (322 in each group, significance level $\alpha=0.05$, statistical power $1-\beta=0.80$,

234 dropout rate 5%)

235

236 **2. Hypothesis**

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

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

239

240 **3. Sample size calculation**

241 We conducted a systematic review to determine the sample-size calculation. We searched

242 Medline and Embase for relevant clinical studies published between January 1993 and

243 October 2019. The following search terms were used: “BP,” “hypertension,” “thrombectomy,”

244 or “endovascular.” We manually searched references of identified studies. Searches were

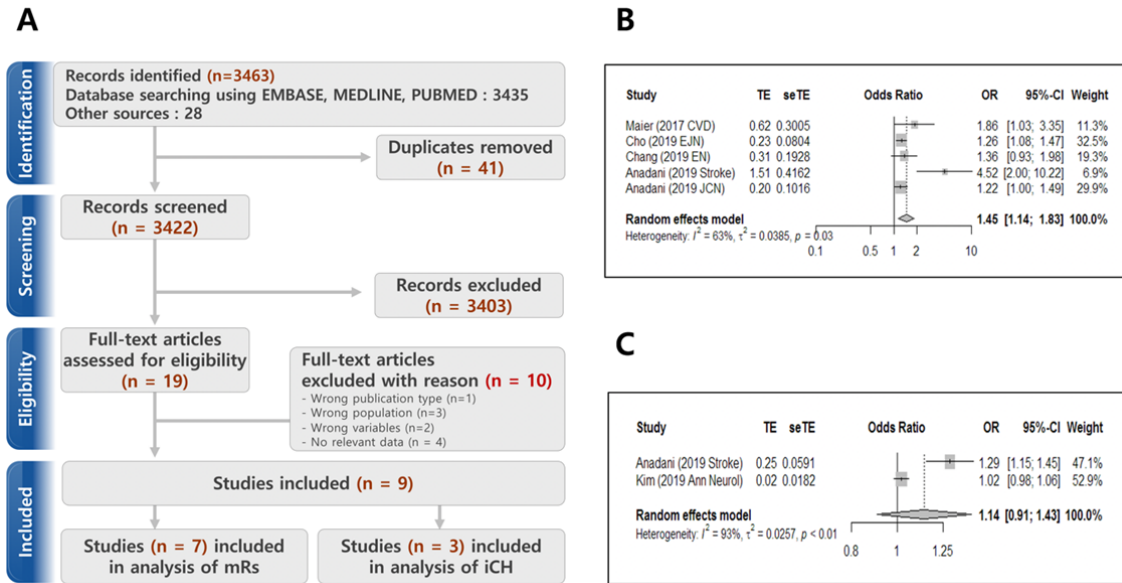
245 restricted to human studies with full English text. The reference lists of retrieved reports were
246 also hand searched for potentially relevant studies not identified in our electronic database
247 search.

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 \leq 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



269

270

271 A study by Goyal et al. used a design similar to ours with an aggressive systolic BP-lowering

272 target of <140 mmHg.¹ They compared an aggressive systolic BP-lowering target of <140 /

273 90 mmHg with a moderate or permissive BP target of <185 / 105 mmHg.

274

| | 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) | | |

275

276 **Outcome according to target BPs in Goyal's article¹**

| | 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%) |

277

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

280

281 $OR \text{ for poor outcome} = \frac{63/67}{3/7} = 2.19$

282 $CI = \left(e^{\ln(OR) - 1.96 \sqrt{\frac{1}{63} + \frac{1}{67} + \frac{1}{3} + \frac{1}{7}}}, e^{\ln(OR) + 1.96 \sqrt{\frac{1}{63} + \frac{1}{67} + \frac{1}{3} + \frac{1}{7}}} \right)$

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

284

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

285

286 where OR1 is from Goyal et al.'s study⁶ and OR2 is from our systematic review. Finally, we

287 used OR = 1.6 after rounding off one decimal place.

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

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

289 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

290 patients). The significance level (two-tailed test) was $\alpha = 0.05$ with a power of $1 - \beta = 0.80$,

291 and the required number of patients per group was 287. The required final sample size was

292 644 (322 per each arm) for a 5% dropout rate.

293

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

295 Analysis will be performed by using the alpha spending function with O'Brien-Fleming's

296 boundary method. The trial will be hold when a null hypothesis is rejected ($Z \geq 2.996$,

297 $\alpha = 0.00274$). Interim analysis will also be conducted in the event that any ethical concerns

298 arise. The DSMB will advise the steering committee if the trial has significant outcome

299 differences between the two arms, lack of efficacy, or safety concerns. The steering

300 committee will make trial continuation decisions.

301

302 **Study Design**

303 1) The study design is a prospective, randomized, open-label trial with blinded end-point

304 assessment (PROBE). In a PROBE trial, the study is prospective, meaning that patients are

305 enrolled before the start of the study, and it is randomized, meaning that patients are

306 randomly assigned to different treatment groups. The study is open-label, meaning that both

307 the patient and the investigator know which treatment the patient is receiving, but it is blinded

308 at the endpoint, meaning that the outcome of the study is assessed in a blinded manner.

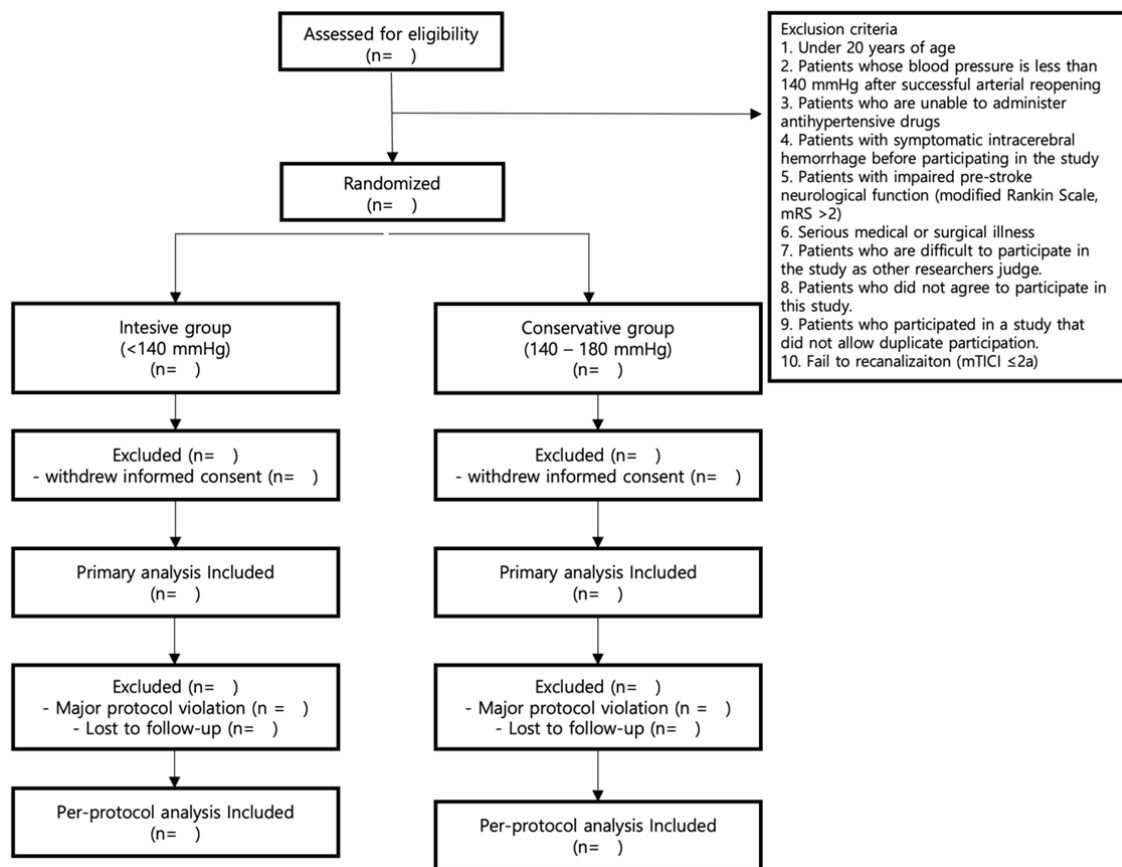
309 2) The study will use a 1:1 ratio of the intensive group (target systolic BP <140 mmHg) and
310 the conventional group (target systolic BP 140 - 180 mmHg) for patients who have achieved
311 successful recanalization after IAT.

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

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

320

321



322

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

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

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

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

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

336

337 **Study methods**

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

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

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

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

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

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

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

358 discretion.

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

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

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

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

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

380

381 **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 |

382

383

1) For the final visit, the main study and the 1st, 2nd, and 4th substudies will be

384

conducted for 3 months, and the 3rd sub-study will be conducted for 1 year.

385

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

386

387 **Screening (0 days)**

388 Selection/exclusion eligibility checked

389 Vital signs (BP, pulse rate)

390 History

391 Obtaining consent

392 NIHSS Score

393 Pre-cerebral infarction mRS

394 Obtaining consent

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

396 Randomization
397
398 **24 hours (24 ± 6 hours)**
399 Vital signs (BP, pulse rate)
400 NIHSS
401 BP control treatment
402 Adverse Reaction Check
403 Standard Stroke Treatment
404
405 **36 hours**
406 Brain imaging images taken within 36 hours (MRI or CT)
407
408 **F/u visit (1 month ± 14 days)**
409 Vital signs (BP, pulse rate)
410 BP control treatment
411 Standard Stroke Treatment
412 Cardio-cerebrovascular events
413
414 **last visit (3 months ± 14 days)**
415 Vital signs (BP, pulse rate)
416 mRS
417 EQ-5D-3L (EuroQoL 5-Dimension Self-Report Questionnaire)
418 Standard Stroke Treatment
419 Cardio-cerebrovascular events

420

421 **End visit (1 year ± 14 days)**

422 Vital signs (BP, pulse rate)

423 mRS

424 EQ-5D-3L

425 Standard Stroke Treatment

426 Cardio-cerebrovascular events

427

428 **How to obtain a consent form to participate in a study**

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

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

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

438 4) In cases where the potential research subject is unable to read or comprehend the study
439 information, such as if they are illiterate or blind, the principal investigator is responsible for
440 ensuring that a neutral third party is present to read the study information to the subject and
441 answer any questions they may have. Once the subject fully understands the study and
442 voluntarily agrees to participate, both the subject and the impartial observer will sign a
443 written consent form to indicate that the subject has provided informed consent. This ensures

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

446 5) In cases where the research subject is unable to fully understand the research due to
447 conditions such as cerebral infarction or other impairments, and is unable to provide a
448 handwritten signature, the investigator will obtain written consent from the legal
449 representative after thoroughly explaining the purpose, content, and methods of the study.

450 However, if the individual is able to provide voluntary consent during the follow-up period,
451 the investigator will make an effort to obtain the individual's consent.

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

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

463 8) Clinical investigators have an ethical and legal obligation to ensure the confidentiality of
464 all information obtained during the study period. This means that all information collected
465 from the study subjects, such as personal identifying information, medical history, and study
466 results, must be kept private and protected from unauthorized access or disclosure.

467 Appropriate measures should be taken to safeguard the data, such as using secure storage

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

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

483

484 **Hypothesis**

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

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

496

497 **Outcome Evaluation Variables**

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

500 **1. Primary outcome**

501 1) primary efficacy outcome

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

504 - Differences in mRS ordinal shift analysis

505

506 2) primary safety outcomes

507 A. symptomatic ICH within 36 hours

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

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

516 B. Stroke-related death within 90 days

517

518 **2. Secondary outcome**

519 1) Difference in NIHSS scores at 24 hours after IAT

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

521 improvement > 8

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

523 4) Frequency of occurrence of malignant brain edema

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

525

526 **3. Observations**

527 1. BP readings (systolic BP and diastolic BP)

528 1) BP during the visit

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

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

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

532 recanalization

533

534 **4. Clinical scale**

535 1) NIHSS scale score measured 24 hours after IAT

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

537 hospital.

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

539 recanalization

540

541 **5. Imaging Findings**

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

543 - Classification of a cerebral hemorrhage

544

| | |
|-----------------------------------|--|
| 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 |

545

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

548 3) Collateral grade by Tan scale score using CTA

549 **0**: absent collateral supply to the occluded MCA territory

550 **1**: collateral supply filling $\leq 50\%$ but $>0\%$ of the occluded MCA territory

551 **2**: collateral supply filling $>50\%$ but $<100\%$ of the occluded MCA territory

552 **3**: 100% collateral supply of the occluded MCA territory

553

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

556

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

558

559 **Clinical Manifestations**

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

561 - Time of onset of symptoms

562 - Time from symptoms to treatment

563 - Severity of stroke using the NIHSS score

564 - Previous history of stroke

565 - Factors such as weight, obesity, hypertension, diabetes, hyperlipidemia, smoking, atrial

566 fibrillation, coronary artery obstructive disease, congestive heart failure, peripheral artery

567 obstructive disease, and active cancer that may increase the risk of cerebral infarction

568 - Any other medical conditions the patient may have

569 - Assessment of patient's neurological functional independence before the onset of stroke

570 using mRS

571 - Identification of the underlying cause of cerebral infarction using Trial of Org 10172 in

572 Acute Stroke Treatment (TOAST)

573 - EQ-5D-3L; Health-related quality of life (HRQoL) was assessed using the EQ-5D-3L. The

574 EQ-5D-3L descriptive system evaluates the state of general health across five dimensions:

575 mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using three

576 levels to indicate the extent of problems: no problems, some/moderate problems, and severe

577 problems. The EQ-5D-3L utility score is a single score calculated using population-based

578 preference weights for each dimension, and expressed as a fraction of perfect health, with a
579 score of 1 representing perfect health, 0 representing death, and negative scores (with a
580 minimum score of -0.109) indicating health states considered worse than death. In this
581 analysis, preference weights derived from the South Korean population were used to
582 calculate the utility scores.⁷ When patients were unable to complete the questionnaire
583 themselves, proxy responders such as caregivers were asked to rate the patient's HRQoL.
584

585 **Data Collection Method**

- 586 1) All clinical data will be collected electronically in an anonymized state using the web-
587 based eCRF (iCReaT) of the Korean National Institutes of Health and the Centers for Disease
588 Control. This system ensures the confidentiality and security of patient information while
589 allowing for efficient data collection and management.
- 590 2) Data for each participating institution will be collected and managed in an integrated
591 manner through this system, ensuring the quality and consistency of data across all sites.
- 592 3) Data management for this study will be handled by the Data Management Center (DMC),
593 a clinical trial center of the Severance Hospital, Yonsei University. This center operates
594 independently and is responsible for all aspects of data management. Before registering in the
595 iCReaT system, the DMC creates databases using standardization guidelines and includes
596 auto-query functions. Investigators will be provided with input guidelines to ensure data
597 reliability and completeness. Data audit will be conducted every month and data cleaning will
598 be conducted biannually to ensure data accuracy. All clinical data will be collected
599 electronically in an anonymized state through the iCReaT system.
- 600 4) This trial will be led by the state and registered with the Korean National Institutes of
601 Health's Centers for Disease Control and Prevention's iCReaT web-based clinical research

602 management system.

603 5) Verify data quality through Quality Control in the DMC, then proceed with database

604 locking. After locking, no data changes or additions will be allowed.

605

606 **Training of investigators**

607 Each of the OPTIMAL-BP investigators received training for the protocol, GCP procedures,

608 as well as the usage of the NIHSS and mRS score. The GCP training was conducted by

609 individual hospitals.

610

611 **Research Recording and Storage**

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

613 2) Clinical information (including image data) will be publicly accessible through research

614 resource through the National database (iCReaT) managed by the Korean Centers for Disease

615 Control. Clinical data will be managed as a national resource under regulations for health and

616 medical tech R&D projects, with no set expiration for stored data use.

617 3) Data sharing follows (International Committee of Medical Journal Editors) ICMJE's "Data

618 sharing statements for clinical trials." Raw clinical data will be shared after database lock and

619 can be shared anonymously for international research collaboration.

620 4) Data sharing requires obtaining consent which include information about it in the research

621 subject's explanatory text and consent form.

622 5) The investigator must retain records and documents related to the research implementation

623 (e.g. test protocol, consent form, etc.) and clinical trial data, as per Article 15 of the Bioethics

624 Law Enforcement Regulations, for 3 years after termination of the trial. After the retention

625 period, documents must be destroyed as per Article 16 of the Personal Information Protection

626 Act Enforcement Decree.

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

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

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

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

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

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

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

649

650 **Data analysis statistical method**

651 **1. Intention-to-treat (ITT) population (primary analysis)**

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

656

657 **2. Per-protocol (PP) analysis**

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

665

666 **3 Analysis of the primary outcome**

667 The primary analysis (ITT population) (see section 3.2.1) and analysis using PP population
668 (3.2.2) will be conducted.

669 **3.1 Binary analysis of mRS**

670 A binary analysis of the mRS at 3 months will be conducted by categorizing the mRS scores
671 as either 'poor' (scores 3-6) or 'favorable' (scores 0-2) outcomes. The effect of the intervention
672 will be presented as the OR of a poor outcome, with a 95% CI and risk difference, with 95%
673 CI. Additionally, adjusted analyses will be performed by adding the following covariates: age

674 (continuous), sex (male vs female), NIHSS score just before IAT (continuous), and onset to
675 randomization time (continuous). The adjusted treatment effect will be reported as the
676 adjusted OR and 95% CI. Subgroup analysis will be conducted for this outcome. The number
677 needed to treatment (or harm) and 95% CI will be reported for this outcome.

678

679 **3.2 Symptomatic intracranial hemorrhage (sICH)**

680 The definition for sICH is based on that in the Safe Implementation of Thrombolysis in
681 Stroke Monitoring Study (SITS-MOST). These will be reported as the number and proportion
682 of subjects experiencing an event. The effect of the intervention will be estimated using the
683 same approach as in the binary analysis of mRS (see Section 3.1). We will apply the covariate
684 adjustments described in Section 3.1; however, no subgroup or imputed analysis will be
685 performed on this outcome.

686

687 **3.3 Death related to the index stroke within 3 months.**

688 A binary analysis of death related to the index stroke within 3 months will be performed. The
689 impact of the intervention will be calculated using the same method as in the binary analysis
690 of mRS (as outlined in Section 3.1). The covariate adjustments described in Section 3.1 will
691 be applied, but no subgroup or imputed analysis will be conducted for this outcome.

692

693 **3.4 Subgroup analyses**

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

- 696 • Age (<65 vs 65 or more)
- 697 • Sex (female vs male)

- 698 • Hypertension (yes vs no)
- 699 • Diabetes (yes vs no)
- 700 • Hyperlipidemia (yes vs no)
- 701 • Smoking (yes vs no)
- 702 • Atrial fibrillation (yes vs no)
- 703 • Congestive heart failure (yes vs no)
- 704 • CAOD (yes vs no)
- 705 • Previous stroke (yes vs no)
- 706 • Active cancer (yes vs no)
- 707 • Pre-stroke mRS
- 708 • Onset time to puncture (<6 vs ≥6 hours)
- 709 • Presumed etiological subtype according to TOAST classification
- 710 • NIHSS score just before IAT (<15 vs >15)
- 711 • TICI score immediately after EVT (2b or 2c vs 3)
- 712 • Occlusion site (ICA, MCA, VBA, PCA, or ACA)
- 713 • Site (Anterior, posterior, or multiple)
- 714 • ASPECTS (0-5, 6-8, 9-10)
- 715 • Collateral grade (good, poor)
- 716 • IV thrombolysis administered (yes vs no)

717

718 The analysis for each subgroup will be performed by adding the subgroup variable and its
 719 interaction with the intervention as fixed effects to the main logistic regression model. The
 720 summary statistics within each subgroup will consist of raw counts and percentages for each
 721 treatment arm, as well as the OR of treatment effect along with a 95% CI. The findings will

722 be displayed in a forest plot, including the p-value for heterogeneity resulting from the
723 interaction between the subgroup variable and the intervention.

724

725 **3.5 Treatment of missing data**

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

727

728 **4 Analysis of the secondary outcome**

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

731

732 **4.1 Shift analysis of mRS**

733 The mRS score reduction will be analyzed using shift analysis. An ordinal logistic regression
734 will be applied to evaluate the distribution of mRS over a 3-month period. The primary
735 impact of the intervention will be calculated as the OR of a lower mRS between the
736 intervention group and the control group, determined from an ordinal logistic model. To
737 verify the proportional odds assumption, a score test will be employed. The graphical
738 representation of shifts across categories will be made through bar plots and binary analysis.
739 To address cases where the proportional odds assumption for covariates is not met, we will
740 use a partial proportional odds logistic regression as a secondary analysis. The covariate
741 adjustments described in Section 3.1 will be applied, but no subgroup analysis or imputed
742 analysis will be conducted for this outcome.

743

744 **4.2 NIHSS score at 24 hours**

745 The NIHSS score at 24 hours will be analyzed as a continuous variable. Univariable and

746 multivariable linear regression analysis will be performed based on treatment groups. No
747 subgroup analysis or imputed analysis will be conducted for this outcome.

748

749 **4.3 Excellent recovery of NIHSS score at 24 hours**

750 The outcome of excellent recovery of NIHSS score at 24 hours (NIHSS 0-1 or improvement
751 of more than 8) will be analyzed using the same approach as the mRS score described in
752 Section 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no
753 subgroup analysis or imputed analysis will be conducted for this outcome.

754

755 **4.4 Recanalization status at 24 hours**

756 Recanalization (TICI score $\geq 2b$) at 24 hours will be analyzed using the same approach as the
757 mRS score described in Section 3.1 The covariate adjustments described in Section 3.1 will
758 be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

759

760 **4.5 Favorable outcome at 1 month (mRS score 0-2)**

761 The favorable outcome at 1 month, defined as an mRS score of 0-2, will be analyzed using
762 the same approach as the mRS score described in Section 3.1 The covariate adjustments
763 described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be
764 conducted for this outcome.

765

766 **4.6 Euro-QoL**

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

770

771 **4.7 Malignant brain edema**

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

775

776 **5 Interim analysis plan**

777 The study includes one formal interim analysis after one-half of the patients have completed
778 their 90-day follow-up. In the interim analysis, primary efficacy outcome (favorable outcome
779 at 3 months) analysis will be performed using the alpha spending function with O'Brien–
780 Fleming's boundary method. The trial will be held when a null hypothesis is rejected (Z
781 ≥ 2.996 , $\alpha_1=0.00274$). The interim analysis will also be conducted in the event that any
782 ethical concerns arise. The DSMB will advise the steering committee if the trial has
783 significant outcome differences between the two arms, lack of efficacy, or safety concerns.
784 The steering committee will make trial continuation decisions.

785

786 **Definitions of protocol violations and deviations**

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

789

790 **1. Major (reportable) protocol violations**

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

794 IRB according to relevant national guidelines and timelines.

795

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

800

801 **2. Minor (non-reportable) protocol violations**

802 Minor protocol violations were unapproved changes in the study design or procedures within
803 the investigator's control, not in accordance with the approved protocol but with no major
804 impact on the participant's safety, rights, or study data completeness, accuracy, or reliability.

805 Such violations did not always require reporting to the IRB.

806

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

811

812 **Analysis of potential risks and benefits to patients**

813 **1. Potential hazards:**

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

818 between the standard BP control group (140-180 mmHg) and the active BP control group
819 (<140 mmHg), but if the results of the latter group are favorable, the study may be
820 discontinued and the results shared with participants.

821

822 **2. Potential benefits:**

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

827

828 **3. Risk/ benefit Analysis:**

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

830

831 **Compensation plan and compensation agreement for risks**

832 **caused by research participation**

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

836

837 **Protection measures for vulnerable research subjects**

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

- 841 2) This study examines the criteria for BP control after IAT in stroke patients and all
842 participants will receive the same standard treatment process as other stroke patients,
843 regardless of participation in the study.
- 844 3) Patients participating in this study face minimal potential risks.
- 845 4) Patients or their legal representatives may withdraw from the study at any time, without
846 facing any disadvantages.
- 847 5) In case of harm caused to the subject during the study, we will provide compensation as
848 per the terms of the clinical trial insurance policy and make sure they receive the best
849 possible treatment. However, this compensation will not cover adverse reactions that are not
850 related to the study, symptoms or diseases that are the result of the subject's own mistake or
851 cause, and any deterioration of symptoms that may occur due to the natural progression of the
852 disease.
- 853 6) For vulnerable individuals who are scheduled to participate in the study, written consent
854 will be obtained after a sufficient explanation has been provided to their legal representative
855 and the representative has confirmed their consent. This is to ensure that the individual's
856 rights and well-being are protected during the course of the study.
- 857 7) The collected resident numbers will be securely stored as encrypted files and will only be
858 used for linking with national institution databases. The numbers will be discarded
859 immediately after the completion of the original purpose. Resident numbers will only be
860 collected from individuals who have provided their consent for such collection.

861

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

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

865 be protected at all times.

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

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

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

875

876 **Continuous safety monitoring plan and data safety monitoring**
877 **plan.**

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

882 2) Data and safety monitoring methods and cycles

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

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

888 3) DSMB

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

895 4) Research discontinuation criteria

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

898

899 **Substudies**

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

902

| 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 |

903

904

905 **Research implementation plan**

906

| | 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 | | | | | | | |

907

908

909 **References**

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

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

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

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

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

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

924 7. Park HK, Chun SY, Choi Y, et al. Effects of social activity on health-related quality of life
925 according to age and gender: an observational study. *Health Qual Life Outcomes* 2015; 13:
926 140.

927

928

929 **Outcome in patients treated with intra-arterial thrombectomy:**

930 **the optiMAL Blood-Pressure Control (OPTIMAL-BP) Trial**

931



OPTIMAL-BP

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

932

933

934

Trial PROTOCOL

935

(Version 2.2 – 19 May 2021)

936

937

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| | |
|--|---|
| 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 | <p>1. Primary outcome</p> <p>1) primary efficacy outcome - Functional independence at 3 months, defined as a modified Rankin Scale (mRS) score of 0 to 2</p> <p>2) primary safety outcomes</p> <p> A. symptomatic ICH within 36 hours</p> <p> B. Stroke-related death within 90 days</p> <p>2. Secondary outcome</p> <p>1) Differences in mRS ordinal shift analysis</p> <p>2) Difference in NIHSS scores at 24 hours after IAT</p> <p>3) Excellent Day 1 Recovery [Major Neurological Improvement]: NIHSS score of 0-1 or improvement > 8</p> <p>4) Recanalization status on CT Angiography (CTA) or MR Angiography</p> |

| | |
|---------------------------|--|
| | <p>(MRA) at 24 hours</p> <p>5) Favorable outcome at 1 month (mRS score 0-2)</p> <p>6) Health-related quality of life, as assessed by the EuroQoL group EQ-5D-3 L,</p> <p>7) Frequency of occurrence of malignant brain edema</p> |
| 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 $\geq 2b$) and elevated systolic BP ≥ 140 mmHg within 2 hours of successful recanalization |
| Sample size | 668 |
| Inclusion criteria | <ol style="list-style-type: none"> 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 | <ol style="list-style-type: none"> 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 | <ol style="list-style-type: none"> 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 | <p>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.</p> <p>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.</p> |
| 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 |
| 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 |

1074 **Overview**

1075 Studies have demonstrated that intravenous thrombolysis is effective in improving symptoms
1076 of acute cerebral infarction patients, but the treatment is not always successful. Even when
1077 administered within an appropriate time frame, only 22.6% of blood clots are dissolved and
1078 only about 30% of patients experience improvement. Recently, intra-arterial procedures such
1079 as intra-arterial thrombectomy (IAT) have been found to be effective. This procedure uses a
1080 stent retriever or catheter to physically remove blood clots from the body. IAT has a high
1081 success rate of nearly 80% in terms of vascular re-opening, however, only around 50% of
1082 patients show clinical improvement. Therefore, there is a need for new treatment strategies
1083 and techniques to reduce the number of patients who do not benefit from the procedure.

1084

1085 BP (BP) is a significant factor in the outcomes of stroke patients who have received
1086 recanalization treatment. Patients who have undergone successful recanalization treatment are
1087 more likely to experience a spontaneous decline in BP over 12 to 24 hours following IAT than
1088 those with persistent occlusion. BP has a direct impact on cerebral perfusion pressure, with
1089 low BP potentially decreasing cerebral perfusion pressure and causing harm to ischemic brain
1090 areas. Conversely, sustained high BP may increase the risk of intracerebral hemorrhage (ICH)
1091 and lead to worse functional outcomes.

1092

1093 The American Heart Association guidelines recommend lowering BP to below 180/105
1094 mmHg in patients who have undergone successful recanalization, with a class of
1095 recommendation of IIb and level of evidence B-NR. The European guidelines suggest
1096 maintaining BP below 180/105 mmHg during and 24 hours after IAT. In contrast, previous
1097 retrospective studies and meta-analyses have indicated a potential association between BP in

1098 the 24 hours following IAT and clinical outcomes, and have suggested that lowering BP may
 1099 be beneficial. However, the optimal target for BP control in stroke patients who have
 1100 undergone successful recanalization following IAT remains uncertain.

1101

1102 **Research Purpose**

1103 The objective of this trial is to establish whether intensive BP-lowering (<140 mmHg) results
 1104 in a superior clinical outcome compared to conventional BP-lowering (140 - 180 mmHg)
 1105 following successful recanalization through IAT.

1106

1107 **Research agencies and estimated duration of the study**

1108 1. Research Institute: 19 hospitals in South Korea including Yonsei University College of
 1109 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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| | Investigator | Young Dae Kim | Severance Hospital, Yonsei University College of Medicine | neuro05@yuhs.ac |
| 2 | Investigator | Yo Han Jung | Gangnam Severance Hospital | eyasyohan@gmail.com |
| 3 | Investigator | Dong Hoon Shin, | Gachon University Gil Medical Center | sphincter@naver.com |
| 4 | Investigator | Jang-Hyun Baek | Kangbuk Samsung Hospital | janghyun.baek@gmail.com |
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| 6 | Investigator | Hyungjong Park | Keimyung University School of Medicine | hjpark209042@gmail.com |
| 7 | Investigator | Chi Kyung Kim | Korea University Guro Hospital | ckkim7@gmail.com |
| 8 | Investigator | Jung Hwa Seo | Busan Paik Hospital | sukyoonlee85@gmail.com |
| 9 | Investigator | Jong-Won Chung | Samsung Medical Center | neurocjw@gmail.com |
| 10 | Investigator | Jun Young Chang | Asan Medical Center | kjychang@gmail.com |
| 11 | Investigator | Jun Lee | Yeungnam University School of Medicine | junlee@med.yu.ac.kr |
| 12 | Investigator | Tae-Jin Song | Seoul Hospital, Ewha Woman's University, College of Medicine | knstar@hanmail.net |

| | | | | |
|----|--------------|-----------------|---|------------------------|
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| 16 | Investigator | Bang-Hoon Cho | Korea University Anam Hospital and College of Medicine | fevernakchal@naver.com |
| 17 | Investigator | Joonsang Yoo | Yongin Severance Hospital | quarksea@gmail.com |
| 18 | Investigator | Han-Jin Cho | Pusan National University School of Medicine | chohj75@gmail.com |
| 19 | Investigator | Jae Guk Kim | Daejeon Eulji Medical Center | mdbluewin@naver.com |

1110

1111 2. Estimated research period : 5 years from the date of initial approval of the IRB (60 months)

1112

1113 **Criteria for inclusion and exclusion of study subjects**

1114 **1. Inclusion criteria**

1115 1. Age ≥ 20 years

1116 2. Patients who underwent IAT for acute cerebral infarction with large cerebrovascular
1117 occlusion (ICA, MCA, M1 or M2, BA, VA, ACA, A1, or PCA, P1)

1118 3. Patients with successful cerebral artery reopening after intraarterial reopening (modified
1119 Treatment In Cerebral Infarction score, mTICI 2b or mTICI 3)

1120 4. Patients with elevated BP (systolic BP ≥ 140 mmHg) on at least two measurements with a
1121 two-minute interval within 2 hours of successful recanalization.

1122

1123 **2. Exclusion criteria**

1124 1. Age < 20 years

1125 2. Patients whose BP is less than 140 mmHg after successful recanalization through IAT

1126 3. Patients with contraindications for use of antihypertensive medication

1127 4. Patients with symptomatic ICH before participating in the study after the successful arterial
1128 reopening

- 1129 5. Patients with impaired pre-disease neurological function (modified Rankin Scale, mRS >2)
- 1130 6. Serious medical or surgical illness
- 1131 7. Patients who are deemed hard to recruit for the study by the investigators.
- 1132 8. Patients who did not agree to participate in this study
- 1133 9. Patients who participated in a study that did not allow duplicate participation

1134

1135 **3. Stop / out criteria**

- 1136 1. Patients withdrawing consent
- 1137 2. Patients whose BP is maintained at more than 220 mmHg despite active BP control after
- 1138 IAT
- 1139 3. If the principal investigator or the investigator determines that the test should be
- 1140 discontinued

1141

1142 **Estimated number of research subjects**

1143 **1. Number of clinical trial subjects calculated**

1144 668 patients (334 in each group, significance level $\alpha=0.05$, statistical power $1-\beta=0.80$,

1145 dropout rate 5%)

1146

1147 **2. Hypothesis**

1148 $H_0: P_A - P_B = 0$ (the ratio of poor outcomes in groups A and B is the same)

1149 $H_1: P_A - P_B \neq 0$ (the ratio of poor outcomes between groups A and B is not the same)

1150

1151 **3. Sample size calculation**

1152 We conducted a systematic review to determine the sample-size calculation. We searched
1153 Medline and Embase for relevant clinical studies published between January 1993 and
1154 October 2019. The following search terms were used: “BP,” “hypertension,” “thrombectomy,”
1155 or “endovascular.” We manually searched references of identified studies. Searches were
1156 restricted to human studies with full English text. The reference lists of retrieved reports were
1157 also hand searched for potentially relevant studies not identified in our electronic database
1158 search.

1159 Studies included in this analysis met the following criteria: (1) IAT for ischemic stroke, (2)
1160 inclusion of patients with acute ischemic stroke with large-vessel occlusion, (3) analysis
1161 comparing the outcomes according to BP within 24 hours after successful recanalization with
1162 IAT, and (4) outcome measurements, including mRS score, at 90 days or symptomatic ICH.

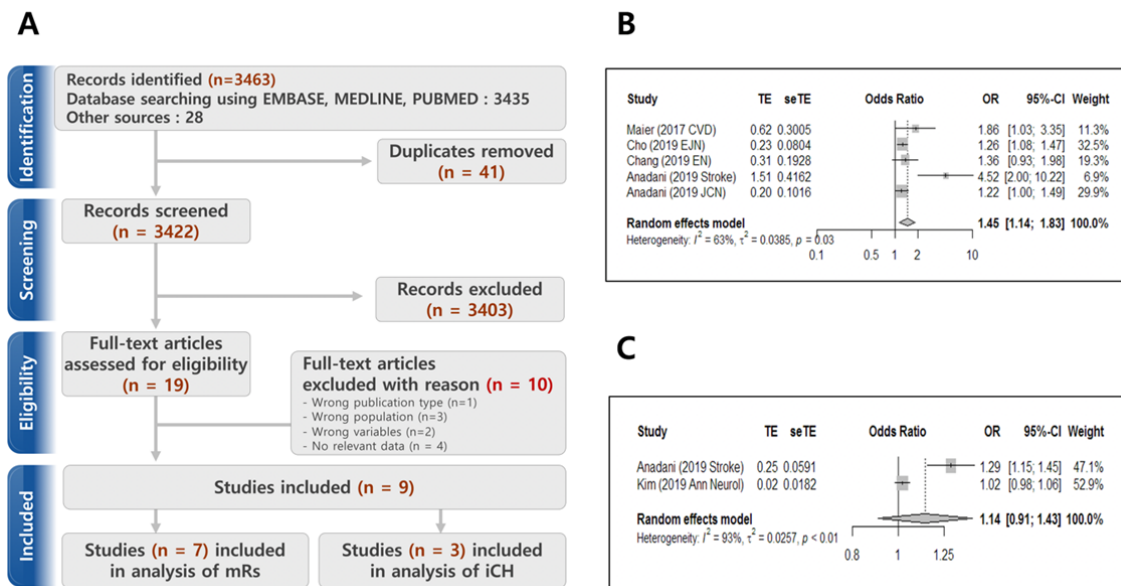
1163 We also obtained the baseline characteristics from each study: sample size, intervention type,
1164 intervention time, baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline
1165 BP, functional outcome or 90-day mortality, and symptomatic ICH. Two reviewers (YDK
1166 and JKC) independently extracted data, and disagreements were resolved by consensus. For
1167 continuous outcomes (90-day ordinal mRS score) and dichotomous outcomes (symptomatic
1168 ICH), we used the odds ratio (OR) with 95% confidence interval (CI) and *P*-values to assess
1169 the likelihood of outcomes.

1170

1171 Of a total of 3,436 articles identified, 9 met the inclusion criteria (Figure A). Among the
1172 seven articles regarding the outcome, two were excluded: one because we could not calculate
1173 the effect size, and the other because no regression coefficient was reported. Finally, five
1174 papers that used continuous systolic BP (SBP) were chosen. The OR was calculated using the
1175 generic inverse variance estimation method. A 10-mmHg increase in the mean systolic BP \leq

1176 24 hours after successful recanalization with IAT was correlated with worse 90-day mRS (OR
 1177 1.45, 95% CI 1.14–1.83, $p = 0.002$) (Figure B). Symptomatic ICH was not associated with a
 1178 mean systolic BP increase of 10 mmHg after successful recanalization with IAT (OR 1.14, 95%
 1179 CI 0.91–1.43, $p = 0.267$) (Figure C).

1180



1181

1182

1183 A study by Goyal et al. used a design similar to ours with an aggressive systolic BP-lowering
 1184 target of <140 mmHg.¹ They compared an aggressive systolic BP-lowering target of <140 /
 1185 90 mmHg with a moderate or permissive BP target of <185 / 105 mmHg.

1186

| | 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) | | | |

1187

1188 **Outcome according to target BPs in Goyal's article¹**

| | 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%) |

1189

1190 According to the study by Goyal et al., the calculated OR of poor outcome in the moderate or
1191 permissive group was 2.19 (95% CI 0.54–8.86) compared with that of the intensive group.

1192

1193
$$\text{OR for poor outcome} = \frac{63/67}{3/7} = 2.19$$

1194
$$\text{CI} = \left(e^{\ln(\text{OR}) - 1.96 \sqrt{\frac{1}{63} + \frac{1}{67} + \frac{1}{3} + \frac{1}{7}}}, e^{\ln(\text{OR}) + 1.96 \sqrt{\frac{1}{63} + \frac{1}{67} + \frac{1}{3} + \frac{1}{7}}} \right)$$

1195 Using these ORs, we calculated the weighted average as follows:

1196

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

1197

1198 where OR1 is from Goyal et al.'s study⁶ and OR2 is from our systematic review. Finally, we
1199 used OR = 1.6 after rounding off one decimal place. The OR for intervention group compared
1200 to control group is defined as OR=1/1.6=0.625.

1201

1202 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 $\bar{p} = \frac{p_A + p_B}{2}$.

1203 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).

1204 The significance level (two-tailed test) was $\alpha = 0.05$ with a power of $1 - \beta = 0.80$, and the
1205 required number of patients per group was 317. The required final sample size was 668 (334
1206 per each arm) for a 5% dropout rate.

1207

1208 Interim analysis will be performed when half of the patients are enrolled in each group.
1209 Analysis will be performed by using the alpha spending function with O'Brien–Fleming's
1210 boundary method. The trial will be held when a null hypothesis is rejected ($Z \geq 2.996$,
1211 $\alpha_1=0.00274$). Interim analysis will also be conducted in the event that any ethical concerns
1212 arise. The Data Safety Management Board (DSMB) will advise the steering committee if the
1213 trial has significant outcome differences between the two arms, lack of efficacy, or safety
1214 concerns. The steering committee will make trial continuation decisions.

1215

1216 **Study Design**

1217 1) The study design is a prospective, randomized, open-label trial with blinded end-point
1218 assessment (PROBE). In a PROBE trial, the study is prospective, meaning that patients are
1219 enrolled before the start of the study, and it is randomized, meaning that patients are
1220 randomly assigned to different treatment groups. The study is open-label, meaning that both
1221 the patient and the investigator know which treatment the patient is receiving, but it is blinded
1222 at the endpoint, meaning that the outcome of the study is assessed in a blinded manner.

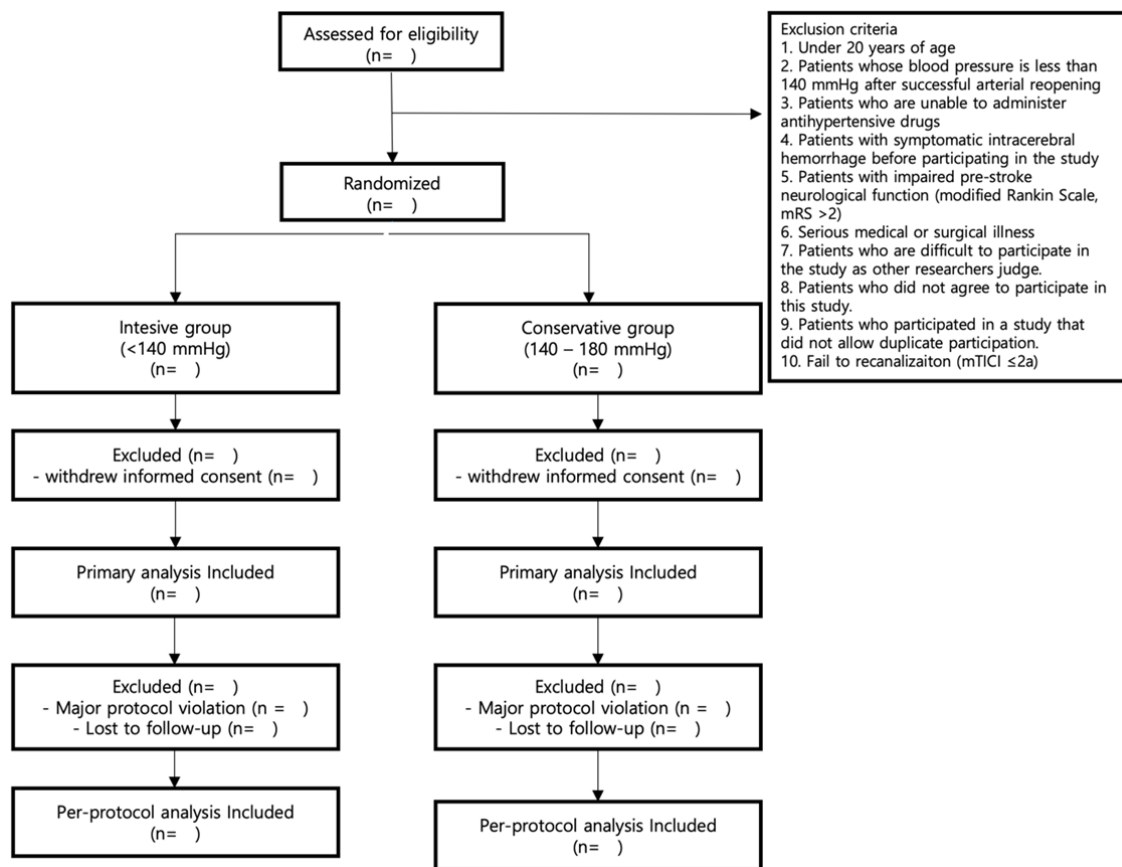
1223 2) The study will use a 1:1 ratio of the intensive group (target systolic BP <140 mmHg) and
1224 the conventional group (target systolic BP 140 - 180 mmHg) for patients who have achieved
1225 successful recanalization after IAT.

1226 3) To prevent imbalance between the groups, randomization was stratified by the enrollment
1227 hospital and the degree of neurological impairment as determined by the NIHSS score at
1228 admission (<15 points or ≥15 points).

1229 4) The study is a multi-center, prospective study that will include patients admitted to the
1230 neurology department of participating hospitals with acute cerebral infarction between
1231 January 2020 and December 2023, based on the date of stroke onset. Eligible patients will
1232 have undergone IAT in accordance with stroke treatment guidelines and have successfully
1233 reopened the arteries. The study will be conducted for five years in the participating hospitals.

1234

1235



1236

1237 5) The study will collect the following data from the eligible participants: medical history,
 1238 test results, BP parameters (systolic BP, diastolic BP, BP variability, etc.), imaging tests,
 1239 neurological scores, functional recovery, and quality of life indicators. All data collected will
 1240 be in accordance with the study inclusion and exclusion criteria.

1241 6) Neurological scores, functional recovery scores, and quality of life indicators will be
 1242 assessed by independent investigators who are blinded to the participant's treatment group.
 1243 This helps to ensure unbiased and accurate assessments of these outcomes.

1244 7) All data collected will be entered into an electronic case report form (e-CRF) system and
 1245 the images of the participants will be anonymized and transmitted to the host institution. This
 1246 helps to ensure the security and confidentiality of the participant's data and images.

1247 8) The host institution will perform a blinded quantification of the imaging tests. This means

1248 that the investigators at the host institution will not know which group the participant belongs
1249 to when analyzing the imaging test results which help to minimize bias.

1250

1251 **Study methods**

1252 1) The study aims to recruit patients with acute cerebral infarction who have undergone IAT
1253 for large cerebral artery occlusion. The selection and exclusion criteria and the treatment of
1254 IAT will be based on practice guidelines and institution-specific criteria.

1255 2) The study will include patients who have successfully undergone arterial recanalization (as
1256 determined by mTICI 2b or mTICI 3 score) and have a mean BP greater than 140 mmHg, as
1257 measured twice within 2 hours of recanalization.

1258 3) The study will use an automated BP device (Omron® HEM 7130) or a non-invasive
1259 automatic BP monitor (NIBP monitor) of the same model that has been certified as equivalent
1260 by the American Medical Device Association and the European Society of Hypertension, and
1261 has clinical study evidence A.

1262 4) Patients who meet the inclusion/exclusion criteria and provide informed consent will have
1263 their BP and pulse measured at 1-hour intervals for up to 24 hours after providing consent.
1264 The BP and pulse data will be collected and recorded.

1265 5) The initial BP and pulse data will be measured only once, excluding the pulse data.

1266 6) To achieve and maintain the target systolic BP, local treatment protocols using available
1267 intravenous BP-lowering drugs will be permitted. The preferred BP-lowering drug is
1268 nicardipine, though other drugs such as labetalol and hydralazine are allowed at the
1269 physician's discretion.

1270 7) If BP decreased below 140 mmHg in the conventional group, it will not be actively
1271 increased with vasopressor therapies. Treatment will be discontinued, and intravenous fluids

1272 and inotropes will be used when hypotension needed to be treated at the physician's
1273 discretion.

1274 8) If the target BP is achieved, measure it every hour. If the target is not met, take BP
1275 measurements every 15 minutes in the first hour after administering medication, every 30
1276 minutes for the next 2 hours, and every hour until 24 hours have passed. If a deviation from
1277 the target occurs, necessitating additional medication or adjustments to the current dose,
1278 return to measuring BP every 15 minutes.

1279 9) After randomization, the target BP should be reached within 60 minutes.

1280 10) Radiological follow-up using computed tomography or magnetic resonance imaging will
1281 be undergone at 24 ± 12 hours and at any time when neurological symptoms worsen.

1282 11) BP will be measured using an Omron® HEM 7130 automatic BP machine at 1 or 3
1283 months. To ensure accurate results, participants should refrain from consuming caffeine,
1284 alcohol, and smoking for 30 minutes prior to measurement. They should also sit and rest for
1285 at least 3-5 minutes before taking the measurement on the upper arm of the non-paralyzed
1286 limb. Measurements should be taken with the arm at heart level, slightly bent on a desk
1287 without any force, and the person should be sitting with their back against the backrest and
1288 feet on the floor without crossing their legs, in accordance with the 2018 Primary Medical
1289 Evidence-Based Hypertension Clinical Practice Guidelines.

1290 12) As a substudy, 24-hour ambulatory BP monitoring (ABPM) will be conducted at 1 and 3
1291 months using certified sphygmomanometers from the list provided at
1292 www.dableducational.org. BP will be measured at 30-minute intervals and at least 14 valid
1293 measurements during the day and 7 valid measurements at night are required to be considered
1294 as valid data.

1295 13) A mRS score will be calculated to assess neurological recovery at 3 months. Assessments

1296 will be conducted by independent investigators who are unaware of the treatment or control
 1297 group status.

1298

1299 **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 |

1300

1301 3) For the final visit, the main study and the 1st, 2nd, and 4th substudies will be
 1302 conducted for 3 months, and the 3rd sub-study will be conducted for 1 year.

1303 4) Brain imaging (MRI or CT) performed within 24 ± 12 hours after IAT.

1304

1305 **Screening (0 days)**

1306 Selection/exclusion eligibility checked

1307 Vital signs (BP, pulse rate)

1308 History

1309 Obtaining consent

- 1310 NIHSS Score
- 1311 Pre-cerebral infarction mRS
- 1312 Obtaining consent
- 1313 Brain imaging (MRI, CT, MRA, CTA, digital subtraction angiography)
- 1314 Randomization
- 1315
- 1316 **24 hours (24 ± 6 hours)**
- 1317 Vital signs (BP, pulse rate)
- 1318 NIHSS
- 1319 BP control treatment
- 1320 Adverse Reaction Check
- 1321 Brain imaging images taken within 24 ± 12 hours (MRI or CT)
- 1322 Standard Stroke Treatment
- 1323
- 1324 **F/u visit (1 month ± 14 days)**
- 1325 Vital signs (BP, pulse rate)
- 1326 BP control treatment
- 1327 Standard Stroke Treatment
- 1328 Cardio-cerebrovascular events
- 1329
- 1330 **last visit (3 months ± 14 days)**
- 1331 Vital signs (BP, pulse rate)
- 1332 mRS
- 1333 EQ-5D-3L (EuroQoL 5-Dimension Self-Report Questionnaire)

1334 Standard Stroke Treatment
1335 Cardio-cerebrovascular events
1336
1337 **End visit (1 year ± 14 days)**
1338 Vital signs (BP, pulse rate)
1339 mRS
1340 EQ-5D-3L
1341 Standard Stroke Treatment
1342 Cardio-cerebrovascular events
1343

1344 **How to obtain a consent form to participate in a study**

1345 1) We will adhere to the guidelines outlined in the Helsinki Declaration and ICH-GCP and
1346 will only conduct research after receiving approval from the institutional review board (IRB).
1347 2) Informed consent will be obtained from participants who meet the established inclusion
1348 and exclusion criteria for the study.
1349 3) Informed consent will be obtained from research participants who have the capacity to
1350 understand the study's purpose, content, and methods. The investigator will provide a full
1351 explanation of the study and answer any questions the participant may have. Participation in
1352 the study will be completely voluntary and a signed consent form will only be obtained from
1353 participants who willingly agree to participate in the study.
1354 4) In cases where the potential research subject is unable to read or comprehend the study
1355 information, such as if they are illiterate or blind, the principal investigator is responsible for
1356 ensuring that a neutral third party is present to read the study information to the subject and
1357 answer any questions they may have. Once the subject fully understands the study and

1358 voluntarily agrees to participate, both the subject and the impartial observer will sign a
1359 written consent form to indicate that the subject has provided informed consent. This ensures
1360 that the subject's participation in the study is based on their own free will and understanding
1361 of the study's purpose, content, and method.

1362 5) In cases where the research subject is unable to fully understand the research due to
1363 conditions such as cerebral infarction or other impairments, and is unable to provide a
1364 handwritten signature, the investigator will obtain written consent from the legal
1365 representative after thoroughly explaining the purpose, content, and methods of the study.
1366 However, if the individual is able to provide voluntary consent during the follow-up period,
1367 the investigator will make an effort to obtain the individual's consent.

1368 6) Before any research involving human subjects can proceed, the IRB must first review and
1369 approve the explanatory text and consent form for the subject. After the subject or their legal
1370 representative signs the form, the principal investigator must retain one original copy and
1371 provide one copy to the subject or legal representative. It's important to allow sufficient time
1372 for the individual to read and fully understand the information before signing and receiving a
1373 copy of the statement and consent form.

1374 7) It is important to remind that the study participant has the right to withdraw their consent
1375 to participate in the trial at any time during the study period. This means that the participant
1376 has the freedom to stop taking part in the study and discontinue any further involvement
1377 without any negative consequences or penalty. It is crucial to inform the participant of this
1378 right and how to exercise it, and to document any withdrawals of consent in the study records.

1379 8) Clinical investigators have an ethical and legal obligation to ensure the confidentiality of
1380 all information obtained during the study period. This means that all information collected
1381 from the study subjects, such as personal identifying information, medical history, and study

1382 results, must be kept private and protected from unauthorized access or disclosure.
1383 Appropriate measures should be taken to safeguard the data, such as using secure storage
1384 systems, password-protecting files, and limiting access to authorized personnel only.
1385 Additionally, the investigators should ensure that any data shared with external parties, such
1386 as sponsors or regulatory authorities, is de-identified or otherwise protected to maintain the
1387 confidentiality of the study subjects. It is important for the investigators to inform the
1388 participants about their policies and procedures to protect the confidentiality of their
1389 information.

1390 9) Observation items and data collection methods refer to the specific aspects of the study
1391 that are being observed and the methods used to collect the data. For example, observation
1392 items may include vital signs, symptoms, or laboratory test results, while data collection
1393 methods may include interviews, surveys, physical exams, or medical imaging. It is important
1394 for the observation items and data collection methods to be clearly defined and specified in
1395 the study protocol, as they will serve as the basis for data analysis and interpretation. The
1396 selection of observation items and data collection methods should be appropriate for the
1397 research question and be able to accurately and reliably measure the variables of interest.
1398 They should also be feasible and ethical for the study population.

1399

1400 **Hypothesis**

1401 In the treatment of acute cerebral infarction through IAT, it is hypothesized that the intensive
1402 group (a group of patients receiving intensive treatment) will have a better prognosis than the
1403 conventional group (a group of patients receiving conventional treatment) after successful
1404 arterial recanalization. This prediction is based on the idea that the intensive group will
1405 receive a more aggressive and comprehensive treatment plan, which may lead to better

1406 outcomes such as increased chances of recovery, reduced disability, and decreased mortality
1407 rates. The prediction will be tested through a randomized controlled trial where the patients
1408 will be divided into two groups, the intensive group and the conventional group, and the
1409 outcomes will be measured and compared between the groups. The study will be conducted
1410 to confirm the hypothesis and to find out the best treatment approach for patients with acute
1411 cerebral infarction..

1412

1413 **Outcome Evaluation Variables**

1414 The outcome endpoints were evaluated twice, one at the end of the interim analysis and one
1415 at the end of the study.

1416 **1. Primary outcome**

1417 1) primary efficacy outcome

1418 - Functional independence at 3 months, defined as a modified Rankin Scale (mRS) score of 0
1419 to 2

1420 2) primary safety outcomes

1421 A. symptomatic ICH within 36 hours

1422 ✓ Bleeding or hemorrhagic transformation on MRI or CT performed within 24 ± 12
1423 hours or as symptoms worsen

1424 ✓ Definition of symptomatic hemorrhage according to the European Cooperative Acute
1425 Stroke Study III (ECASS III) meets the following three criteria:

1426 • Any cerebral hemorrhage

1427 • NIHSS score worse than 4 points or death

1428 • When neurological deterioration is associated with cerebral hemorrhage

1429 B. Stroke-related death within 90 days

1430

1431 **2. Secondary outcome**

1432 1) Differences in mRS ordinal shift analysis

1433 2) Difference in NIHSS scores at 24 hours after IAT

1434 3) Excellent Day 1 Recovery [Major Neurological Improvement]: NIHSS score of 0-1 or

1435 improvement > 8

1436 4) Recanalization status on CT Angiography (CTA) or MR Angiography (MRA) at 24 hours

1437 5) Frequency of occurrence of malignant brain edema

1438 6) Health-related quality of life, as assessed by the EuroQoL group EQ-5D-3L

1439

1440 **3. Observations**

1441 1. BP readings (systolic BP and diastolic BP)

1442 1) BP during the visit

1443 2) BP measured between 30 minutes and 1 hour after arterial recanalization

1444 3) Hourly BP measured at 1-hour intervals for 24 hours after arterial recanalization

1445 4) Active BP for 24 hours measured at 1-hour intervals at 1 and 3 months after arterial

1446 recanalization

1447

1448 **4. Clinical scale**

1449 1) NIHSS scale score measured 24 hours after IAT

1450 2) The mRS score measured at 1 month, 3 months, and 1 year after discharge from the

1451 hospital.

1452 3) Quality of Life Indicators (EQ-5D-3L) measured 3 months and 1 year after arterial

1453 recanalization

1454

1455 **5. Imaging Findings**

1456 1) Cerebral hemorrhage or hemorrhagic transformation occurs on MRI or CT after IAT

1457 - Classification of a cerebral hemorrhage

1458

| | |
|-----------------------------------|--|
| 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 |

1459

1460 2) Size of cerebral infarction measured by diffusion-weighted image, fluid-attenuated inverse

1461 recovery (FLAIR) image, or brain CT (when the diffusion-weighted image is not available).

1462 3) Collateral grade by Tan scale score using CTA

1463 **0**: absent collateral supply to the occluded MCA territory

1464 **1**: collateral supply filling $\leq 50\%$ but $>0\%$ of the occluded MCA territory

1465 **2**: collateral supply filling $>50\%$ but $<100\%$ of the occluded MCA territory

1466 **3**: 100% collateral supply of the occluded MCA territory

1467

1468 A good collateral status is defined by a Tan scale score of 2 to 3, while poor collateral status
1469 corresponds to a Tan scale score of 0 to 1.

1470

1471 4) Recanalization status at 24 hours is defined using CTA or MRA for 24 hours

1472

1473 **Clinical Manifestations**

1474 The following data will be collected on the patient's clinical manifestations:

1475 - Time of onset of symptoms

1476 - Time from symptoms to treatment

1477 - Severity of stroke using the NIHSS score

1478 - Previous history of stroke

1479 - Factors such as weight, obesity, hypertension, diabetes, hyperlipidemia, smoking, atrial

1480 fibrillation, coronary artery obstructive disease, congestive heart failure, peripheral artery

1481 obstructive disease, and active cancer that may increase the risk of cerebral infarction

1482 - Any other medical conditions the patient may have

1483 - Assessment of patient's neurological functional independence before the onset of stroke

1484 using mRS

1485 - Identification of the underlying cause of cerebral infarction using Trial of Org 10172 in

1486 Acute Stroke Treatment (TOAST)

1487 - EQ-5D-3L; Health-related quality of life (HRQoL) was assessed using the EQ-5D-3L. The

1488 EQ-5D-3L descriptive system evaluates the state of general health across five dimensions:

1489 mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using three

1490 levels to indicate the extent of problems: no problems, some/moderate problems, and severe

1491 problems. The EQ-5D-3L utility score is a single score calculated using population-based

1492 preference weights for each dimension, and expressed as a fraction of perfect health, with a
1493 score of 1 representing perfect health, 0 representing death, and negative scores (with a
1494 minimum score of -0.109) indicating health states considered worse than death. In this
1495 analysis, preference weights derived from the South Korean population were used to
1496 calculate the utility scores.⁷ When patients were unable to complete the questionnaire
1497 themselves, proxy responders such as caregivers were asked to rate the patient's HRQoL.
1498

1499 **Data Collection Method**

- 1500 1) All clinical data will be collected electronically in an anonymized state using the web-
1501 based eCRF (iCReaT) of the Korean National Institutes of Health and the Centers for Disease
1502 Control. This system ensures the confidentiality and security of patient information while
1503 allowing for efficient data collection and management.
- 1504 2) Data for each participating institution will be collected and managed in an integrated
1505 manner through this system, ensuring the quality and consistency of data across all sites.
- 1506 3) Data management for this study will be handled by the Data Management Center (DMC),
1507 a clinical trial center of the Severance Hospital, Yonsei University. This center operates
1508 independently and is responsible for all aspects of data management. Before registering in the
1509 iCReaT system, the DMC creates databases using standardization guidelines and includes
1510 auto-query functions. Investigators will be provided with input guidelines to ensure data
1511 reliability and completeness. Data audit will be conducted every month and data cleaning will
1512 be conducted biannually to ensure data accuracy. All clinical data will be collected
1513 electronically in an anonymized state through the iCReaT system.
- 1514 4) This trial will be led by the state and registered with the Korean National Institutes of
1515 Health's Centers for Disease Control and Prevention's iCReaT web-based clinical research

1516 management system.

1517 5) Verify data quality through Quality Control in the DMC, then proceed with database

1518 locking. After locking, no data changes or additions will be allowed.

1519

1520 **Training of investigators**

1521 Each of the OPTIMAL-BP investigators received training for the protocol, GCP procedures,

1522 as well as the usage of the NIHSS and mRS score. The GCP training was conducted by

1523 individual hospitals.

1524

1525 **Research Recording and Storage**

1526 1) Principal investigator must have a list of qualified individuals assigned to the study.

1527 2) Clinical information (including image data) will be publicly accessible through research

1528 resource through the National database (iCReaT) managed by the Korean Centers for Disease

1529 Control. Clinical data will be managed as a national resource under regulations for health and

1530 medical tech R&D projects, with no set expiration for stored data use.

1531 3) Data sharing follows (International Committee of Medical Journal Editors) ICMJE's "Data

1532 sharing statements for clinical trials." Raw clinical data will be shared after database lock and

1533 can be shared anonymously for international research collaboration.

1534 4) Data sharing requires obtaining consent which include information about it in the research

1535 subject's explanatory text and consent form.

1536 5) The investigator must retain records and documents related to the research implementation

1537 (e.g. test protocol, consent form, etc.) and clinical trial data, as per Article 15 of the Bioethics

1538 Law Enforcement Regulations, for 3 years after termination of the trial. After the retention

1539 period, documents must be destroyed as per Article 16 of the Personal Information Protection

1540 Act Enforcement Decree.

1541 6) In case of the investigator's departure (e.g. resignation, retirement), the handover to the
1542 new person must be agreed upon mutually.

1543 7) If consent is withdrawn, the investigator will stop collecting new trial data but may still
1544 use data collected before the withdrawal.

1545 8) Severance Hospital (the responsible research institution), Clinical Trial Review Committee,
1546 and Ministry of Food and Drug Safety may review subject's medical records to verify
1547 collected information. Information exposed will be treated as confidential.

1548 9) Principal investigator must keep the signed consent form, and make a subject number and
1549 name list for easy searching, stored in a password-protected file in a locked lab.

1550 10) Personal information collected is coded in a non-identifiable form, stored on a locked
1551 computer and remains anonymous even when results are reported or published. After study
1552 completion, it stays anonymous and stored on a locked computer.

1553 11) In accordance with the Personal Information Protection Act (Article 24) and the Bioethics
1554 Act (Articles 16 and 37), research records, including unique identification information, must
1555 be kept for 3 years from the end of the study or until a request for destruction is made for
1556 clinical research in the public interest.

1557 12) Unique identification information (resident registration number) will be collected to
1558 integrate with data held by national agencies, the National Health Insurance Agency, the
1559 Health Insurance Review and Evaluation Service, the National Statistics Office, and the
1560 National Cancer Center for conducting clinical research in the public interest of the Ministry
1561 of Health and Welfare. In addition, the subject has the right to receive an explanation and to
1562 agree or reject it.

1563

1564 **Data analysis statistical method**

1565 **1. Intention-to-treat (ITT) population (primary analysis)**

1566 The ITT population will include all randomized patients, regardless of whether they received
1567 the allocated intervention. This will be the population used to evaluate both the efficacy and
1568 safety of the treatment. Patients who withdrew informed consent before BP control will be
1569 excluded from this population.

1570

1571 **2. Per-protocol (PP) analysis**

1572 The PP analysis group will consist of patients from the efficacy analysis who did not commit
1573 any significant violations of the protocol. These violations include being below 20 years of
1574 age, lacking a final diagnosis of acute ischemic stroke, having SBP less than 140 mmHg, not
1575 achieving reperfusion through IAT (as determined by a TICI score of less than 2b), pre-stroke
1576 mRS 3 to 5, failing to obtain a blinded assessment of the 3-month outcome, and not having
1577 controlled BP for 24 hours as per the assigned intervention (crossover). The PP group will
1578 serve as a supplementary analysis to enhance the findings of the ITT population.

1579

1580 **3 Analysis of the primary outcome**

1581 The primary analysis (ITT population) (see section 3.2.1) and analysis using PP population
1582 (3.2.2) will be conducted.

1583 **3.1 Binary analysis of mRS**

1584 A binary analysis of the mRS at 3 months will be conducted by categorizing the mRS scores
1585 as either 'poor' (scores 3-6) or 'favorable' (scores 0-2) outcomes. The effect of the intervention
1586 will be presented as the OR of a poor outcome, with a 95% CI and risk difference, with 95%
1587 CI. Additionally, adjusted analyses will be performed by adding the following covariates: age

1588 (continuous), sex (male vs female), NIHSS score just before IAT (continuous), and onset to
1589 randomization time (continuous). The adjusted treatment effect will be reported as the
1590 adjusted OR and 95% CI. Subgroup analysis will be conducted for this outcome. The number
1591 needed to treatment (or harm) and 95% CI will be reported for this outcome.

1592

1593 **3.2 Symptomatic intracranial hemorrhage (sICH)**

1594 The definition for sICH is based on that in the European Cooperative Acute Stroke Study III
1595 (ECASS III). These will be reported as the number and proportion of subjects experiencing
1596 an event. The effect of the intervention will be estimated using the same approach as in the
1597 binary analysis of mRS (see Section 3.1). We will apply the covariate adjustments described
1598 in Section 3.1; however, no subgroup or imputed analysis will be performed on this outcome.

1599

1600 **3.3 Death related to the index stroke within 3 months.**

1601 A binary analysis of death related to the index stroke within 3 months will be performed. The
1602 impact of the intervention will be calculated using the same method as in the binary analysis
1603 of mRS (as outlined in Section 3.1). The covariate adjustments described in Section 3.1 will
1604 be applied, but no subgroup or imputed analysis will be conducted for this outcome.

1605

1606 **3.4 Subgroup analyses**

1607 Twenty one pre-specified subgroup analyses will be carried out, irrespective of whether there
1608 is a significant treatment effect on the primary outcome. Subgroups are defined as follows:

- 1609 • Age (<65 vs 65 or more)
- 1610 • Sex (female vs male)
- 1611 • Hypertension (yes vs no)

- 1612 • Diabetes (yes vs no)
- 1613 • Hyperlipidemia (yes vs no)
- 1614 • Smoking (yes vs no)
- 1615 • Atrial fibrillation (yes vs no)
- 1616 • Congestive heart failure (yes vs no)
- 1617 • CAOD (yes vs no)
- 1618 • Previous stroke (yes vs no)
- 1619 • Active cancer (yes vs no)
- 1620 • Pre-stroke mRS
- 1621 • Onset time to puncture (<6 vs ≥6 hours)
- 1622 • Presumed etiological subtype according to TOAST classification
- 1623 • NIHSS score just before IAT (<15 vs >15)
- 1624 • TICI score immediately after EVT (2b or 2c vs 3)
- 1625 • Occlusion site (ICA, MCA, VBA, PCA, or ACA)
- 1626 • Site (Anterior, posterior, or multiple)
- 1627 • ASPECTS (0-5, 6-8, 9-10)
- 1628 • Collateral grade (good, poor)
- 1629 • IV thrombolysis administered (yes vs no)

1630

1631 The analysis for each subgroup will be performed by adding the subgroup variable and its
 1632 interaction with the intervention as fixed effects to the main logistic regression model. The
 1633 summary statistics within each subgroup will consist of raw counts and percentages for each
 1634 treatment arm, as well as the OR of treatment effect along with a 95% CI. The findings will
 1635 be displayed in a forest plot, including the p-value for heterogeneity resulting from the

1636 interaction between the subgroup variable and the intervention.

1637

1638 **3.5 Treatment of missing data**

1639 For missing data, no imputation or additional processing will be performed.

1640

1641 **4 Analysis of the secondary outcome**

1642 The primary analysis (ITT population) (see section 1) and analysis using PP population (see
1643 section 2) will be conducted.

1644

1645 **4.1 Shift analysis of mRS**

1646 The mRS score reduction will be analyzed using shift analysis. An ordinal logistic regression
1647 will be applied to evaluate the distribution of mRS over a 3-month period. The primary
1648 impact of the intervention will be calculated as the OR of a lower mRS between the
1649 intervention group and the control group, determined from an ordinal logistic model. To
1650 verify the proportional odds assumption, a score test will be employed. The graphical
1651 representation of shifts across categories will be made through bar plots and binary analysis.
1652 To address cases where the proportional odds assumption for covariates is not met, we will
1653 use a partial proportional odds logistic regression as a secondary analysis. The covariate
1654 adjustments described in Section 3.1 will be applied, but no subgroup analysis or imputed
1655 analysis will be conducted for this outcome.

1656

1657 **4.2 NIHSS score at 24 hours**

1658 The NIHSS score at 24 hours will be analyzed as a continuous variable. Univariable and
1659 multivariable linear regression analysis will be performed based on treatment groups. No

1660 subgroup analysis or imputed analysis will be conducted for this outcome.

1661

1662 **4.3 Excellent recovery of NIHSS score at 24 hours**

1663 The outcome of excellent recovery of NIHSS score at 24 hours (NIHSS 0-1 or improvement

1664 of more than 8) will be analyzed using the same approach as the mRS score described in

1665 Section 3.1 The covariate adjustments described in Section 3.1 will be utilized, but no

1666 subgroup analysis or imputed analysis will be conducted for this outcome.

1667

1668 **4.4 Recanalization status at 24 hours**

1669 Recanalization (TICI score $\geq 2b$) at 24 hours will be analyzed using the same approach as the

1670 mRS score described in Section 3.1 The covariate adjustments described in Section 3.1 will

1671 be utilized, but no subgroup analysis or imputed analysis will be conducted for this outcome.

1672

1673 **4.5 Favorable outcome at 1 month (mRS score 0-2)**

1674 The favorable outcome at 1 month, defined as an mRS score of 0-2, will be analyzed using

1675 the same approach as the mRS score described in Section 3.1 The covariate adjustments

1676 described in Section 3.1 will be utilized, but no subgroup analysis or imputed analysis will be

1677 conducted for this outcome.

1678

1679 **4.6 Euro-QoL**

1680 The total Euro-QoL score will be analyzed as a continuous variable. Univariable and

1681 multivariable linear regression analysis will be performed based on treatment groups. No

1682 subgroup analysis or imputed analysis will be conducted for this outcome.

1683

1684 **4.7 Malignant brain edema**

1685 The occurrence of malignant brain edema will be analyzed using the same method as the
1686 mRS score described in Section 3.1. The covariate adjustments outlined in Section 3.1 will be
1687 applied, but no subgroup analysis or imputed analysis will be performed for this outcome.

1688

1689 **5 Interim analysis plan**

1690 The study includes one formal interim analysis after one-half of the patients have completed
1691 their 90-day follow-up. In the interim analysis, primary efficacy outcome (favorable outcome
1692 at 3 months) analysis will be performed using the alpha spending function with O'Brien–
1693 Fleming's boundary method. The trial will be held when a null hypothesis is rejected (Z
1694 ≥ 2.996 , $\alpha_1=0.00274$). The interim analysis will also be conducted in the event that any
1695 ethical concerns arise. The DSMB will advise the steering committee if the trial has
1696 significant outcome differences between the two arms, lack of efficacy, or safety concerns.
1697 The steering committee will make trial continuation decisions.

1698

1699 **Definitions of protocol violations and deviations**

1700 Protocol deviations or violations were classified into two groups: major (reportable)
1701 violations and minor (non-reportable) violations.

1702

1703 **1. Major (reportable) protocol violations**

1704 Major protocol violations were unapproved changes in the study design or procedures within
1705 the investigator's control, not in line with the approved protocol that may have impacted the
1706 participant's safety, well-being, or study data accuracy. Such violations were reported to the
1707 IRB according to relevant national guidelines and timelines.

1708

1709 The DMC considered violations as major if they caused or had the potential to cause
1710 significant harm to the participant, affected the participant's clinical or emotional condition,
1711 damaged scientific data completeness or soundness, involved willful or knowing misconduct,
1712 or showed serious or continuous noncompliance with local, state, or federal regulations.

1713

1714 **2. Minor (non-reportable) protocol violations**

1715 Minor protocol violations were unapproved changes in the study design or procedures within
1716 the investigator's control, not in accordance with the approved protocol but with no major
1717 impact on the participant's safety, rights, or study data completeness, accuracy, or reliability.
1718 Such violations did not always require reporting to the IRB.

1719

1720 The DMC identified violations as minor if they did not cause harm or a significant risk of
1721 substantive harm to the research participant, did not change their clinical or emotional
1722 condition or data accuracy, did not involve willful misconduct or serious noncompliance with
1723 regulations, or damage data completeness, accuracy, or reliability.

1724

1725 **Analysis of potential risks and benefits to patients**

1726 **1. Potential hazards:**

1727 This study aims to examine the outcome of patients after BP control during IAT. As all
1728 patients will have BP controlled below the standard of 180 mmHg, the risk to subjects is
1729 expected to be low. However, there is a risk of personal information being disclosed, but
1730 measures to protect it are in place. There is currently no evidence to support the difference
1731 between the standard BP control group (140-180 mmHg) and the active BP control group

1732 (<140 mmHg), but if the results of the latter group are favorable, the study may be
1733 discontinued and the results shared with participants.

1734

1735 **2. Potential benefits:**

1736 The results of this study can contribute to the development of better treatment strategies for
1737 cerebral infarction, and ultimately improve the prognosis for future patients. The information
1738 collected from this study can also provide valuable insights for the medical community,
1739 helping to advance our understanding of cerebral infarction and treatment.

1740

1741 **3. Risk/ benefit Analysis:**

1742 This study is considered to have low potential risks and high potential benefits.

1743

1744 **Compensation plan and compensation agreement for risks**
1745 **caused by research participation**

1746 Additionally, the study has taken necessary measures to minimize any potential harm to
1747 participants by purchasing Hyundai Marine Fire Insurance's clinical trial compensation
1748 insurance, which provides appropriate compensation in case of harm caused by the study.

1749

1750 **Protection measures for vulnerable research subjects**

1751 1) Obtain written consent from the legal representative of vulnerable research subjects after
1752 providing a comprehensive explanation and confirming their agreement to participate in the
1753 study (Refer to guidelines on how to obtain consent for participation in a study).

1754 2) This study examines the criteria for BP control after IAT in stroke patients and all

- 1755 participants will receive the same standard treatment process as other stroke patients,
1756 regardless of participation in the study.
- 1757 3) Patients participating in this study face minimal potential risks.
- 1758 4) Patients or their legal representatives may withdraw from the study at any time, without
1759 facing any disadvantages.
- 1760 5) In case of harm caused to the subject during the study, we will provide compensation as
1761 per the terms of the clinical trial insurance policy and make sure they receive the best
1762 possible treatment. However, this compensation will not cover adverse reactions that are not
1763 related to the study, symptoms or diseases that are the result of the subject's own mistake or
1764 cause, and any deterioration of symptoms that may occur due to the natural progression of the
1765 disease.
- 1766 6) For vulnerable individuals who are scheduled to participate in the study, written consent
1767 will be obtained after a sufficient explanation has been provided to their legal representative
1768 and the representative has confirmed their consent. This is to ensure that the individual's
1769 rights and well-being are protected during the course of the study.
- 1770 7) The collected resident numbers will be securely stored as encrypted files and will only be
1771 used for linking with national institution databases. The numbers will be discarded
1772 immediately after the completion of the original purpose. Resident numbers will only be
1773 collected from individuals who have provided their consent for such collection.

1774

1775 **Methods for maintaining the confidentiality of research subjects'**
1776 **identities and research materials**

- 1777 1) The confidentiality of the study participant's information is of utmost importance and will
1778 be protected at all times.

1779 2) The study records will include the subject's initials and assigned number will be collected
1780 and stored at the responsible research institution (Severance Hospital) using a de-
1781 identification program that replaces the subject's name with their initials and number.
1782 3) The medical records of the subjects may be reviewed by the responsible research
1783 institution (Severance Hospital), the Clinical Trial Review Committee, and the Ministry of
1784 Food and Drug Safety for verification purposes. Any information obtained during this process
1785 will be kept confidential.
1786 4) The signed consent form shall be kept by the lead investigator and a list containing the
1787 subject's number and name will be made to allow for easy access to the records.

1788

1789 **Continuous safety monitoring plan and data safety monitoring**
1790 **plan.**

1791 1) The principal investigator and DMC will continuously monitor the data collected during
1792 the study. Personal information and data will be kept confidential by being encoded and
1793 stored on a secure computer. The information will remain anonymous even after the study has
1794 concluded and will continue to be stored on a locked computer.

1795 2) Data and safety monitoring methods and cycles

1796 (1) Monthly written evaluations of research progress and data management will be carried out
1797 by the principal investigator and the responsible party.

1798 (2) The data management procedure will follow established validation specifications. Any
1799 errors found are corrected and the data will be checked for completeness, standardized, and
1800 consolidated from each institution using a data clarification form (DCF).

1801 3) DSMB

1802 The DSMB, an independent committee, oversees patient safety and tracks recruitment

1803 progress. It includes a medical statistician, neurologist, and representative from the Severance
1804 Clinical Trial Center. The members' names are confidential but can be provided upon request
1805 by the coordinating authority. DSMB reports are kept confidential, except in special cases.
1806 The frequency of DSMB meetings is determined prior to the study's start and additional
1807 meetings can be called if safety concerns arise.

1808 4) Research discontinuation criteria

1809 In case of non-compliance with significant ethical rules or deviation from the major protocol
1810 by the research site or investigator, the trial may be instantly halted.

1811

1812 **Substudies**

1813 There are four substudies in the OPTIMAL-BP trial. Substudies were embedded within the
1814 main trial to recruit as many patients as possible.

1815

| 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 |

1816

1817

1818 **Research implementation plan**

1819

| | 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 | | | | | | | |

1820

1821

1822 **References**

1823 1. Goyal N, Tsivgoulis G, Pandhi A, et al. Blood pressure levels post mechanical
1824 thrombectomy and outcomes in large vessel occlusion strokes. *Neurology* 2017; 89: 540-547.

1825 2. Maier IL, Tsogkas I, Behme D, et al. High Systolic Blood Pressure after Successful
1826 Endovascular Treatment Affects Early Functional Outcome in Acute Ischemic Stroke.
1827 *Cerebrovasc Dis* 2018; 45: 18-25.

1828 3. Cho BH, Kim JT, Lee JS, et al. Associations of various blood pressure parameters with
1829 functional outcomes after endovascular thrombectomy in acute ischaemic stroke. *Eur J*
1830 *Neurol* 2019; 26: 1019-1027.

1831 4. Chang JY and Han MK. Postthrombectomy Systolic Blood Pressure and Clinical Outcome
1832 among Patients with Successful Recanalization. *Eur Neurol* 2019; 81: 216-222.

1833 5. Anadani M, Orabi MY, Alawieh A, et al. Blood Pressure and Outcome After Mechanical
1834 Thrombectomy With Successful Revascularization. *Stroke* 2019; 50: 2448-2454.

1835 6. Anadani M, Orabi Y, Alawieh A, et al. Blood pressure and outcome post mechanical
1836 thrombectomy. *J Clin Neurosci* 2019; 62: 94-99.

1837 7. Park HK, Chun SY, Choi Y, et al. Effects of social activity on health-related quality of life
1838 according to age and gender: an observational study. *Health Qual Life Outcomes* 2015; 13:
1839 140.

1840

1841

1842 **Outcome in patients treated with intra-arterial thrombectomy:**
1843 **the optiMAL Blood-Pressure Control (OPTIMAL-BP) Trial**

1844



1845

1846

1847

1848

TRIAL PROGRESS

1849

1850

1851

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1853

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1858 **4. Minor protocol violations 112**

1859

1860 **5. Screening Failure 112**

1861

1862

1863 **1. List of OPTIMAL-BP trial group and trial investigators**

1864 **Steering committee**

1865 Ji Hoe Heo (Chair), Sun U Kwon, Oh Young Bang, and Hyo Suk Nam

1866

1867 **Executive committee**

1868 Hyo Suk Nam (Chair), Yo Han Jung, Jong-Won Chung, Jun Young Chang, Seong Hwan Ahn,

1869 Hyungjong Park, Kwon-Duk Seo, Tae-Jin Song, Yang-Ha Hwang, Jun Lee, Jung Hwa Seo,

1870 Dong Hoon Shin, Chi Kyung Kim, Jang-Hyun Baek, Yoonkyung Chang, Bang-Hoon Cho,

1871 Joonsang Yoo, Han-Jin Cho, Jae Guk Kim

1872

1873 **Data Safety Monitoring Board**

1874 Chung Mo Nam (Chair), Jong Yun Lee, Hye-Yeon Choi

1875

1876 **Statisticians**

1877 Hye Sun Lee, Soyoung Jeon

1878

1879 **Imaging and Events Adjudication Committee**

1880 Byung Moon Kim (Chair), JoonNyung Heo, Hyungwoo Lee, Minyoul Baik, Jang-Hyun Baek

1881

1882 **Performance Publishing Committee**

1883 Young Dae Kim (Chair), Ji Hoe Heo, Hyo Suk Nam, Hyungjong Park, Tae-Jin Song, Bang-

1884 Hoon Cho, Seong Hwan Ahn

1885

1886

1887 **OPTIMAL-BP trial Principal Investigators and Coordinators (center, with numbers of**
1888 **patients in parentheses)**
1889 Department of Neurology, Yonsei University College of Medicine, Seoul, Korea (26),
1890 Department of Neurology, Gachon University Gil Medical Center, Incheon, Korea (6),
1891 Department of Neurology, Gangnam Severance Hospital, Yonsei University College of
1892 Medicine, Seoul, Korea (2), Department of Neurology, Kangbuk Samsung Hospital,
1893 Sungkyunkwan University School of Medicine, Seoul, Korea (6), Department of Neurology,
1894 Kyungpook National University Hospital, School of Medicine, Kyungpook National
1895 University, Daegu, South Korea (1), Department of Neurology, Brain Research Institute,
1896 Keimyung University School of Medicine, Daegu, Korea (43), Department of Neurology,
1897 Korea University Guro Hospital and College of Medicine, Seoul, Korea (1), National Health
1898 Insurance Service Ilsan Hospital, Goyang, Korea (17), Department of Neurology, Busan Paik
1899 Hospital, Inje University College of Medicine, Busan, South Korea (8), Department of
1900 Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul,
1901 Korea (0), Department of Neurology, Asan Medical Center, University of Ulsan College of
1902 Medicine, Seoul, Korea (17), Department of Neurology, Yeungnam University School of
1903 Medicine, Daegu, Korea (0), Department of Neurology, Yongin Severance Hospital, Yonsei
1904 University College of Medicine, Yongin, Korea (2), Department of Neurology, Seoul Hospital,
1905 Ewha Woman's University, College of Medicine, Seoul, Korea (37), Department of
1906 Neurology, Chosun University School of Medicine, Gwangju, Korea (52), Department of
1907 Neurology, Korea University Anam Hospital and College of Medicine, Seoul, Korea (59),
1908 Department of Neurology, Pusan National University School of Medicine, Busan, Korea (6),
1909 Department of Neurology, Mokdong Hospital, Ewha Womans University College of
1910 Medicine, Seoul, Korea (22).

1911 **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 | <ul style="list-style-type: none"> ■ 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 | <ul style="list-style-type: none"> ■ Defining the role of the DM (data management) team |
| 09 April, 2020 | OPTIMAL-BP Protocol V 1.2 | <ul style="list-style-type: none"> ■ Change the consent form |
| 11 May, 2020 | OPTIMAL-BP Protocol V 1.3 | <ul style="list-style-type: none"> ■ Change the BP measurement interval |
| 28 May, 2020 | DM Second Meeting | <ul style="list-style-type: none"> ■ Paper CRF inspection ■ Data cleaning |
| 12 June, 2020 | OPTIMAL-BP Protocol V 1.4 | <ul style="list-style-type: none"> ■ 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 | <ul style="list-style-type: none"> ■ Report the current status of the trial ■ Discuss the enrollment issues |
| 26 June, 2020 | OPTIMAL-BP Protocol V 1.5 | <ul style="list-style-type: none"> ■ Change the investigators in the participating hospital ■ Change the inclusion criteria <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • Symptomatic intracerebral hemorrhage before participating in the trial ■ Adding trial method <ul style="list-style-type: none"> • Reaching target BP within 60 minutes |
| 30 June, 2020 | DMC Third Meeting | <ul style="list-style-type: none"> ■ Open the eCRF site ■ Check visit interval ■ Check eCRF schedule |
| 01 July, 2020 | OPTIMAL-BP Sub-study Investigator Meeting | <ul style="list-style-type: none"> ■ Discuss the substudy with cardiology ■ Remove the one year follow-up requirement of ambulatory BP monitoring in the substudy |

| | | |
|-------------------|---|--|
| 03 August, 2020 | OPTIMAL-BP Protocol V1.6 | <ul style="list-style-type: none"> ■ Modify methods <ul style="list-style-type: none"> • Check BP, pulse rate once except enroll BP and pulse rate |
| 28 October, 2020 | OPTIMAL-BP Protocol V 1.7 | <ul style="list-style-type: none"> ■ Change the exclusion criteria <ul style="list-style-type: none"> • Add deemed hard to recruit for the study by the investigators ■ Update the eCRF |
| 13 January, 2021 | OPTIMAL-BP 2nd Meeting of Investigators | <ul style="list-style-type: none"> ■ Report the current status of the trial ■ Discuss the research grants |
| 03 February, 2021 | OPTIMAL-BP Protocol V 1.8 | <ul style="list-style-type: none"> ■ Modify the sample size from 644 to 668 (see below) ■ Change the consent form |
| 29 April, 2021 | OPTIMAL-BP Protocol V 1.9 | <ul style="list-style-type: none"> ■ 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 | <ul style="list-style-type: none"> ■ Report the current status of the trial ■ Discuss the ongoing trials ■ Research Q&A |
| 09 August, 2021 | OPTIMAL-BP Protocol V 2.0 | <ul style="list-style-type: none"> ■ Change the inclusion criteria <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> ■ Change the investigators in the participating hospital |
| 28 October, 2021 | OPTIMAL-BP 4th Meeting of Investigators | <ul style="list-style-type: none"> ■ 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 | <ul style="list-style-type: none"> ■ Add exclusion criteria <ul style="list-style-type: none"> • Participated in a study that did not allow duplicate participation |
| 25 May, 2022 | OPTIMAL-BP 5th Meeting of Investigators | <ul style="list-style-type: none"> ■ Report the current status of the trial ■ Discuss the research grant ■ Discuss enhance patient enrollment ■ Other agenda |
| 17 November, 2022 | DSMB meeting | <ul style="list-style-type: none"> ■ Recommended suspending recruitment due to safety concerns |
| 28 November, 2022 | OPTIMAL-BP 6th Meeting of Investigators | <ul style="list-style-type: none"> ■ 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 | |

1912

1913 **Change the sample size at OPTIMAL-BP Protocol V 1.8 (03 February 2021)**

1914 An error was identified in the sample size calculation, leading to an adjustment from 644 to
 1915 688 participants after receiving approval from the Institutional Review Board (IRB).

1916

1917 **Sample size calculation in OPTIMAL-BP Protocol V 1.0**

1918 **1. Number of clinical trial subjects calculated**

1919 644 patients (322 in each group, significance level $\alpha=0.05$, statistical power $1-\beta=0.80$,
 1920 dropout rate 5%)

1921

1922 **2. Hypothesis**

1923 H_0 : OR = 1 (the odds ratio for groups A and B is the same)

1924 H_1 : OR \neq 1 (the odds ratio for groups A and B is not the same)

1925

1926 **3. Sample size calculation**

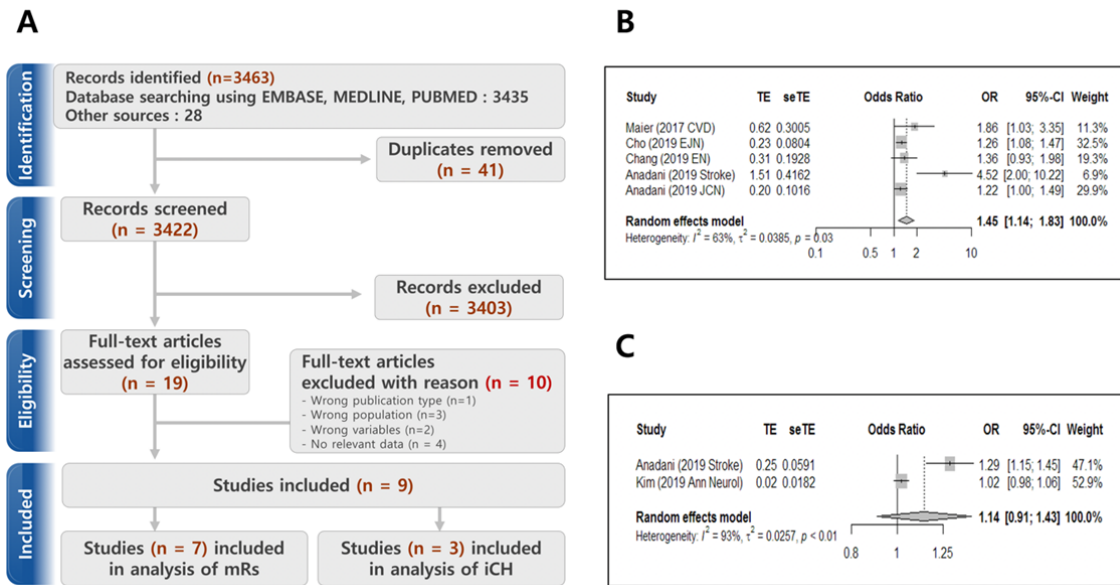
1927 We conducted a systematic review to determine the sample-size calculation. We searched
 1928 Medline and Embase for relevant clinical studies published between January 1993 and
 1929 October 2019. The following search terms were used: “BP,” “hypertension,” “thrombectomy,”
 1930 or “endovascular.” We manually searched references of identified studies. Searches were
 1931 restricted to human studies with full English text. The reference lists of retrieved reports were
 1932 also hand searched for potentially relevant studies not identified in our electronic database
 1933 search.

1934 Studies included in this analysis met the following criteria: (1) IAT for ischemic stroke, (2)
1935 inclusion of patients with acute ischemic stroke with large-vessel occlusion, (3) analysis
1936 comparing the outcomes according to BP within 24 h after successful recanalization with IAT,
1937 and (4) outcome measurements, including mRS score, at 90 days or sICH. We also obtained
1938 the baseline characteristics from each study: sample size, intervention type, intervention time,
1939 baseline NIHSS score, baseline BP, functional outcome or 90-day mortality, and
1940 symptomatic ICH. Two reviewers (YDK and JKC) independently extracted data, and
1941 disagreements were resolved by consensus. For continuous outcomes (90-day ordinal mRS
1942 score) and dichotomous outcomes (symptomatic ICH), we used the odds ratio (OR) with 95%
1943 CI and *P*-values to assess the likelihood of outcomes.

1944

1945 Of a total of 3,436 articles identified, 9 met the inclusion criteria (Figure A). Among the
1946 seven articles regarding the outcome, two were excluded: one because we could not calculate
1947 the effect size, and the other because no regression coefficient was reported. Finally, five
1948 papers that used continuous SBP were chosen. The OR was calculated using the generic
1949 inverse variance estimation method. A 10-mmHg increase in the mean systolic BP \leq 24 hours
1950 after successful recanalization with IAT was correlated with worse 90-day mRS (OR 1.45, 95%
1951 CI 1.14–1.83, $p = 0.002$) (Figure B). Symptomatic ICH was not associated with a mean
1952 systolic BP increase of 10 mmHg after successful recanalization with IAT (OR 1.14, 95% CI
1953 0.91–1.43, $p = 0.267$) (Figure C).

1954



1955

1956

1957 A study by Goyal et al. used a design similar to ours with an aggressive systolic BP-lowering

1958 target of <140 mmHg.¹ They compared an aggressive systolic BP-lowering target of <140 /

1959 90 mmHg with a moderate or permissive BP target of <185 / 105 mmHg.

1960

| | 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) | | |

1961

1962 **Outcome according to target BPs in Goyal's article¹**

| | 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%) |

1963

1964 According to the study by Goyal et al., the calculated OR of poor outcome in the moderate or
1965 permissive group was 2.19 (95% CI 0.54–8.86) compared with that of the intensive group.

1966

1967 $OR \text{ for poor outcome} = \frac{63/67}{3/7} = 2.19$

1968 $CI = \left(e^{\ln(OR) - 1.96 \sqrt{\frac{1}{63} + \frac{1}{67} + \frac{1}{3} + \frac{1}{7}}}, e^{\ln(OR) + 1.96 \sqrt{\frac{1}{63} + \frac{1}{67} + \frac{1}{3} + \frac{1}{7}}} \right)$

1969 Using these ORs, we calculated the weighted average as follows:

1970

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

1971

1972 where OR1 is from Goyal et al.'s study⁶ and OR2 is from our systematic review. Finally, we

1973 used OR = 1.6 after rounding off one decimal place.

1974 The number of patients in each group was calculated as follows:

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

1975 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

1976 patients). The significance level (two-tailed test) was $\alpha = 0.05$ with a power of $1 - \beta = 0.80$,

1977 and the required number of patients per group was 287. The required final sample size was

1978 644 (322 per each arm) for a 5% dropout rate.

1979

1980 Interim analysis will be performed when half of the patients are enrolled in each group.

1981 Analysis will be performed by using the alpha spending function with O'Brien-Fleming's

1982 boundary method. The trial will be hold when a null hypothesis is rejected ($Z \geq 2.996$,

1983 $\alpha = 0.00274$). Interim analysis will also be conducted in the event that any ethical concerns

1984 arise. The DSMB will advise the steering committee if the trial has significant outcome

1985 differences between the two arms, lack of efficacy, or safety concerns. The steering

1986 committee will make trial continuation decisions.

1987

1988 **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 |

1989

1990 **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 |

1991

1992

1993 **5. Screening Failure (n = 1300)**

1994 SBP <140 mmHg after successful recanalization (n = 705)

1995 Did not agree to participate in this study (n = 119)

1996 Deemed hard to recruit for the study by the investigators (n = 119)

1997 Fail to recanalization (mTICI \leq 2a) (n = 104)

1998 Participated in a study that did not allow duplicate participation (n = 77)

1999 Impaired pre-stroke neurological function (mRS \geq 3) (n = 49)

2000 Symptomatic intracerebral hemorrhage before participating in the trial (n = 48)

2001 Serious medical or surgical illness (n = 46)

2002 Cancer (n = 15)

| | |
|------|---|
| 2003 | Cardiac or aorta disease (n = 14) |
| 2004 | Severe anemia or hematologic disease (n = 4) |
| 2005 | Chronic kidney disease (n = 4) |
| 2006 | Pneumonia (n = 4) |
| 2007 | Sepsis (n = 2) |
| 2008 | Cholecystitis (n = 1) |
| 2009 | Hemothorax (n = 1) |
| 2010 | Radius fracture (n = 1) |
| 2011 | Age <20 years (n = 3) |
| 2012 | Others (n = 30) |
| 2013 | Covid-19 infection (n = 11) |
| 2014 | Investigator error (n = 5) |
| 2015 | Foreigner (n = 2) |
| 2016 | Immediate transfer to other hospitals (n = 2) |
| 2017 | No guardian (n = 2) |
| 2018 | Advanced dementia (n = 2) |
| 2019 | Unknown (n = 6) |