

A Randomized Trial on Hemodynamic Optimization of Cerebral Perfusion after Successful Endovascular Therapy in Patients with Acute Ischemic Stroke (HOPE)

Pol Camps-Renom^a Marina Guasch-Jiménez^a Alejandro Martínez-Domeño^a
Luis Prats-Sánchez^a Anna Ramos-Pachón^a Juan Álvarez-Cienfuegos^b
Yolanda Silva^b Gerardo Fortea-Cabo^c Luis Morales-Caba^c
Ana Rodríguez-Campello^d Eva Giralte-Steinhauer^d Alan Flores^e
Xavier Ustrell^e Nicolás López-Hernández^f Diego José Corona-García^f
Mari Mar Freijo-Guerrero^g Alain Luna^g Herbert Tejada-Meza^{h,i}
Javier Marta-Moreno^{i,j} Francisco Moniche^k Blanca Pardo-Galiana^k
Mar Castellanos^l Laura Albert-Lacal^m Ainara Sanz-Monllor^m
Ana Aguilera-Simón^a Rebeca Marín^a Garbiñe Ezcurra-Díaz^a
Álvaro Lambea-Gil^a Joan Martí-Fàbregas^a

^aStroke Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau (IIB-Sant Pau), Barcelona, Spain; ^bStroke Unit, Department of Neurology, Hospital Dr. Josep Trueta, Girona, Spain; ^cStroke Unit, Hospital Universitario La Fe, Valencia, Spain; ^dStroke Unit, Department of Neurology, Hospital del Mar, Neurovascular Research Group, Hospital del Mar Research Institute, Barcelona, Spain; ^eStroke Unit, Department of Neurology, Hospital Universitari de Tarragona Joan XXIII, Institut d'Investigació Sanitària Pere Virgili, Tarragona, Spain; ^fStroke Unit, Department of Neurology, Hospital General Universitario de Alicante, Alicante, Spain; ^gBiobizkaia Health Research Institute, Grupo Neurovascular, Servicio Neurología, Hospital Universitario Cruces, Barakaldo, Spain; ^hStroke Unit, Department of Neurology, and Interventional Neuroradiology Unit, Department of Radiology, Hospital Universitario Miguel Servet, Zaragoza, Spain; ⁱGrupo de Investigación en Neurociencias, Instituto de Investigación Sanitaria (IIS) Aragón, Zaragoza, Spain; ^jStroke Unit, Department of Neurology, Hospital Universitario Miguel Servet, Zaragoza, Spain; ^kStroke Unit, Department of Neurology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; ^lDepartment of Neurology, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; ^mStroke Unit, Department of Neurology, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

Keywords

Ischemic stroke · Endovascular treatment · Blood pressure · Protocol

Abstract

Introduction: In patients with acute ischemic stroke (AIS) secondary to intracranial large vessel occlusion, optimal blood pressure (BP) management following endovascular

treatment (EVT) has not yet been established. The randomized trial on Hemodynamic Optimization of Cerebral Perfusion after Successful Endovascular Therapy in Patients with Acute Ischemic Stroke (HOPE) (clinicaltrials.gov id: NCT04892511) aims to demonstrate whether hemodynamic optimization using different systolic BP targets following EVT according to the degree of final recanalization, is more effective than currently recommended BP management in improving functional outcomes of patients with AIS.

Methods: HOPE is an investigator-initiated multicenter clinical trial with randomized allocation, open-label treatment, and blinded endpoint evaluation (PROBE). Patients with an anterior circulation AIS within 24 h of symptom onset, treated with EVT, and showing successful recanalization (mTICI $\geq$ 2b) at the end of the procedure, are equally allocated (1:1) to hemodynamic optimization according to the study protocol versus BP management according to current guidelines ($\leq$ 180/105 mm Hg). The protocol includes two different targets of systolic BP depending on the recanalization status (mTICI = 2b: 140–160 mm Hg; mTICI = 2c/3: 100–140 mm Hg). The protocol is applied within the first 72 h and includes BP lowering as well as vasopressor therapies when needed. The primary outcome is the proportion of favorable outcome (modified Rankin Scale [mRS] 0–2) at 90 days. Secondary outcomes include the shift on the mRS score, neurological deterioration, symptomatic intracerebral hemorrhage, and mortality. **Conclusion:** The HOPE trial will provide new information on the safety and efficacy of different BP targets following EVT according to the degree of final recanalization in patients with AIS.

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Introduction

Endovascular treatment (EVT) is a highly effective therapy for patients with acute ischemic stroke (AIS) secondary to intracranial large vessel occlusion (LVO) [1]. However, functional independence (modified Rankin scale [mRS] score 0–2) is observed only in 46% of the patients [1]. Therefore, there is a need for additional therapies that may improve outcomes of patients treated with EVT.

Peri- and postprocedural clinical management might be key points in the treatment sequence that may improve the outcomes. Optimizing hemodynamic status, especially through blood pressure (BP) management, during and after EVT, may lead to improved cerebral perfusion in the critical hours of brain ischemia. On one hand, BP is crucial to maintain collateral circulation in the setting of

an LVO, but on the other hand, it may lead to reperfusion injury following EVT when successful recanalization is achieved. Additionally, any drop of BP during EVT or immediately after can be associated with hypoperfusion and, therefore, with infarct growth. Thus, randomized data are needed to guide optimal BP targets in each stage.

BP decreases after successful recanalization [2]. In patients with unsuccessful recanalization, BP decreases as well but at a later time point. For both, recanalized and non-recanalized patients, sustained elevations in BP over the first 24–48 h are a risk factor for intracranial hemorrhage (ICH) and worse functional outcome [3, 4]. Currently, clinical guidelines recommend maintaining BP lower than 180/105 mm Hg after EVT [5]. However, a lower BP target may be beneficial in patients with complete recanalization [6], decreasing the risk of reperfusion injury [7]. Conversely, maintaining systolic BP over 140 mm Hg may be desirable in patients with incomplete recanalization to preserve brain perfusion pressure by optimizing collateral circulation [8].

Observational data studying different BP targets point to a potential benefit of BP lowering after EVT. In a single-center study [6], the authors reported that a 10-mm Hg increment in maximum systolic BP during the first 24 h after EVT was independently associated with a lower likelihood of 3-month functional independence. Similarly, a multicenter retrospective study compared different systolic BP targets after EVT with successful recanalization (modified Treatment In Cerebral Ischemia [mTICI] score 2b–3) and found that maintaining systolic BP $<$ 140 mm Hg was associated with a higher likelihood of favorable outcome and lower odds of symptomatic ICH (sICH) compared to systolic BP $<$ 180 mm Hg [9]. In a large cohort of patients treated with EVT, the mean systolic BP in patients with ICH was lower following successful recanalization indicating a difference in thresholds for reperfusion injury depending on the degree of recanalization [7]. In summary, BP management after EVT may influence clinical outcomes and recanalization status may change the desired targets to optimize cerebral perfusion.

To date, four clinical trials comparing different BP targets in successfully recanalized patients have been published. The Safety and Efficacy of Intensive Blood Pressure Lowering after Successful Endovascular Therapy in Acute Ischemic Stroke (BP-TARGET) trial, found no significant differences in ICH rates after EVT between intensive systolic BP target of 100–129 mm Hg as compared with a standard care target of 130–185 mm Hg [10]. More concerning, the Second Randomized Controlled Enhanced Control of Hypertension and

Thrombectomy Stroke Study (ENCHANTED2/MT) was stopped early due to safety concerns after observing that the likelihood of poor functional outcome was greater in the more intensive (<120 mm Hg) than the less intensive treatment group (140–180 mm Hg) [11]. Likewise, the recently published Intensive versus Conventional Blood Pressure Lowering after Endovascular Thrombectomy in Acute Ischemic Stroke (OPTIMAL-BP) trial also points to a potential harmful effect of intensive BP lowering (<140 mm Hg) compared to the 140–180 mm Hg target in patients with a final mTICI 2b or greater [12]. Finally, in the Blood Pressure Management after Endovascular Therapy for Acute Ischemic Stroke (BEST-II) trial, which was a futility-design, randomized clinical trial, systolic BP targets of less than either 140 or 160 mm Hg versus the guideline-recommended target of 180 mm Hg or less did not meet prespecified criteria for futility or harm [13].

Despite the relevance of these findings, the question of which is the optimal postprocedural BP management following EVT in patients with AIS, is still far from being solved. On one hand, it should be noted that these trials differ in critical points of their design such as the BP goals or the length of the treatment. In addition, important differences existed between study populations in critical features that may influence results, for example, in the proportion of mTICI 2b versus 3 or the proportion of intracranial artery disease. On the other hand, some limitations prevent the generalization of the results from these trials. These include a low median percentage time in the assigned systolic BP target range and considering equally successful recanalization patients with mTICI 2b, 2c, and 3. Pending further randomized data, the AHA guidelines [5] maintain the recommendation of preserving BP $\leq 180/105$ mm Hg for at least 24 h in patients treated with EVT to promote perfusion to ischemic territories while mitigating potential risks of intracranial hemorrhage.

In view of the abovementioned limitations, we believe there is still room for more trials evaluating the safety and efficacy of different BP targets following EVT and that tailored BP management could be the key to enhance the chances of improving clinical outcomes. The lesson learned from the pivotal trials of postprocedural BP management should motivate new clinical research in focusing on the speed in achieving the BP objective, the stability in maintaining the targeted BP range and in considering different BP targets according to the degree of recanalization at the end of the procedure. Last but not least, published trials to date have only studied the effect

of BP lowering, but achieving a predefined BP target with an upper and a lower threshold, may require sometimes using vasopressor therapies.

In the current work, we present the protocol for a randomized trial on Hemodynamic Optimization of Cerebral Perfusion after Successful Endovascular Therapy in Patients with Acute Ischemic Stroke (HOPE), a new ongoing clinical trial testing two different post-procedural BP targets according to the degree of recanalization after EVT. As detailed below, the trial stipulates a BP lowering protocol as well as a vasopressor therapy protocol to achieve the BP target.

Methods

Trial Design

HOPE is an investigator-initiated multicenter clinical trial with randomized allocation, open-label treatment, and blinded endpoint evaluation (PROBE design). Subjects are equally allocated (1:1) to hemodynamic optimization according to the protocol of the trial versus BP management according to current guidelines after EVT. The treatment protocol includes two different targets of systolic BP depending on the recanalization status after the procedure.

Participants

Patients are consecutively screened for eligibility in 15 endovascular-capable stroke centers in Spain considering the following inclusion and exclusion criteria (Table 1).

Inclusion Criteria

1. Anterior circulation AIS secondary to intracranial LVO of the M1, M2, A1 segments, and/or tandem occlusions within 24 h of symptom onset.
2. Successful recanalization at the end of EVT as defined by a mTICI score $\geq 2b$.
3. Prior mRS score <3.
4. Informed consent by the patient or his/her legal representative.

Exclusion Criteria

1. ASPECTS <6.
2. Vertebral, basilar artery, A2, P1-2, or M3-4 segment occlusions.
3. History of ICH
4. Pregnancy
5. Unstable or recent (<3 months) coronary artery disease or congestive heart failure

Table 1. Summary of the inclusion and exclusion criteria of the HOPE trial

Inclusion criteria	Exclusion criteria
• Anterior circulation AIS secondary to intracranial LVO within 24 h of symptom onset • Successful recanalization at the end of EVT as defined by a mTICI score $\geq 2b$ • Prior mRS score < 3 • Informed consent by the patient or his/her legal representative	• ASPECTS < 6 • Vertebral, basilar artery, A2, P1-2, or M3-4 segment occlusions • History of intracranial hemorrhage • Pregnancy • Recent (< 3 months) coronary artery disease or congestive heart failure • Aortic, cervical, or cerebral artery dissection; unruptured aortic/cerebral arterial aneurysm; or known arterio-venous malformation • History of ventricular arrhythmias • Use of monoamine oxidase inhibitors • Risk of hemodynamic infarction

6. Aortic, cervical, or cerebral artery dissection; unruptured aortic/cerebral arterial aneurysm; or known arterio-venous malformation.
7. History of ventricular arrhythmias
8. Use of monoamine oxidase inhibitors
9. Risk of hemodynamic infarction based on the presence of non-revascularized intra/extracranial stenosis

Randomization

A conditional stratified randomization is performed using an online tool (clinapsis.com, Clinical Epidemiology and Healthcare Services) based on two possible recanalization status (mTICI 2b or mTICI 2c/3) and then subjects are equally allocated (1:1) to hemodynamic optimization versus standard care in each recruiting center. The randomization occurs within 1 h after the last angiographic image series and since that time, local investigators have one additional hour to achieve the study BP target (shown in Fig. 1). The recruitment is competitive among centers.

Intervention

Patients allocated to the hemodynamic optimization group are assigned to two different systolic BP targets according to the degree of recanalization after EVT: 100–140 mm Hg for mTICI 2c/3 and 140–160 mm Hg for mTICI 2b. The time interval to reach the desired target is 60 min. Patients allocated to the control arm are treated according to current guidelines ($\leq 180/105$ mm Hg) [5]. To achieve the assigned BP target the study protocol stipulates BP lowering with intravenous labetalol or urapidil, or vasopressor therapy with isotonic saline serum and phenylephrine (shown in Fig. 2, 3). If the patient achieves the assigned BP target without intervention, no treatment is applied. The study protocol is continued

during 72 h after EVT and non-invasive monitorization of BP is performed as follows: 0–24 h, at least every 30 min in the intervention group and at least every 1 h in the control group; 24–72 h, at least every 1 h in the intervention group and at least every 6 h in the control group. If BP target is achieved and stable over repeated BP measurements, during the patient's rest, BP measurements may be spaced at 4-h intervals.

The study protocol is interrupted promptly if a hemorrhagic transformation parenchymal hemorrhage type 2 (PH2) and/or any sICH according to the Heidelberg classification [14] is detected during the first 72 h after EVT, the patient experiences an early stroke recurrence or the patient presents with hemodynamic instability.

Study Outcomes

The primary outcome of the trial is the proportion of favorable outcome at 90 days (mRS 0–2) in an intention-to-treat analysis, in which all patients randomly assigned to one of the arms will be analyzed together, regardless of whether they completed or received the assigned intervention. The secondary outcomes of the trial include (1) the shift in the mRS score at 90 days, also in the intention-to-treat group; (2) neurological deterioration within 72 h (defined as a worsening of the neurological deficit ≥ 4 on the NIHSS); (3) sICH within 72 h; (4) any PH2; and (5) mortality at 90 days.

Data Monitoring Board

All data are entered into an electronic Case Record Form and monitored by external qualified staff. The electronic Case Record Form is managed according to general and specific standards of Good Clinical Practice. All serious adverse events are reviewed by a study monitor. An independent Data Safety and Monitoring

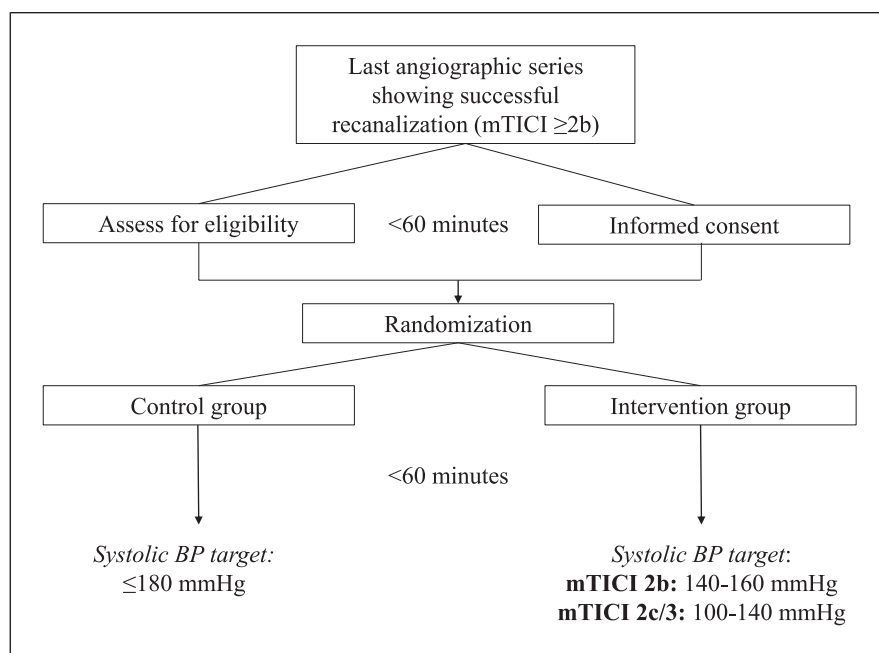


Fig. 1. Flow diagram of the study.

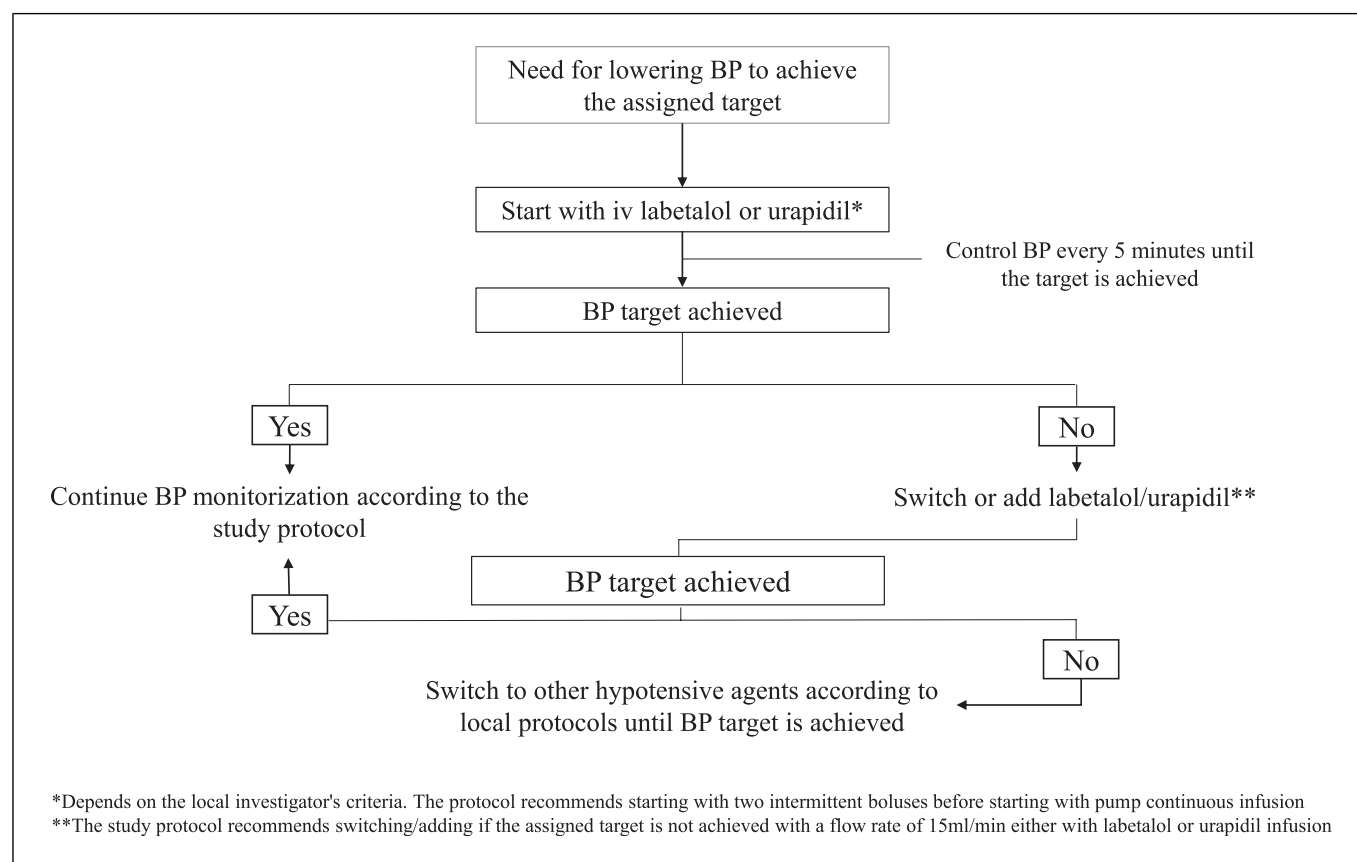


Fig. 2. Study protocol for lowering BP.

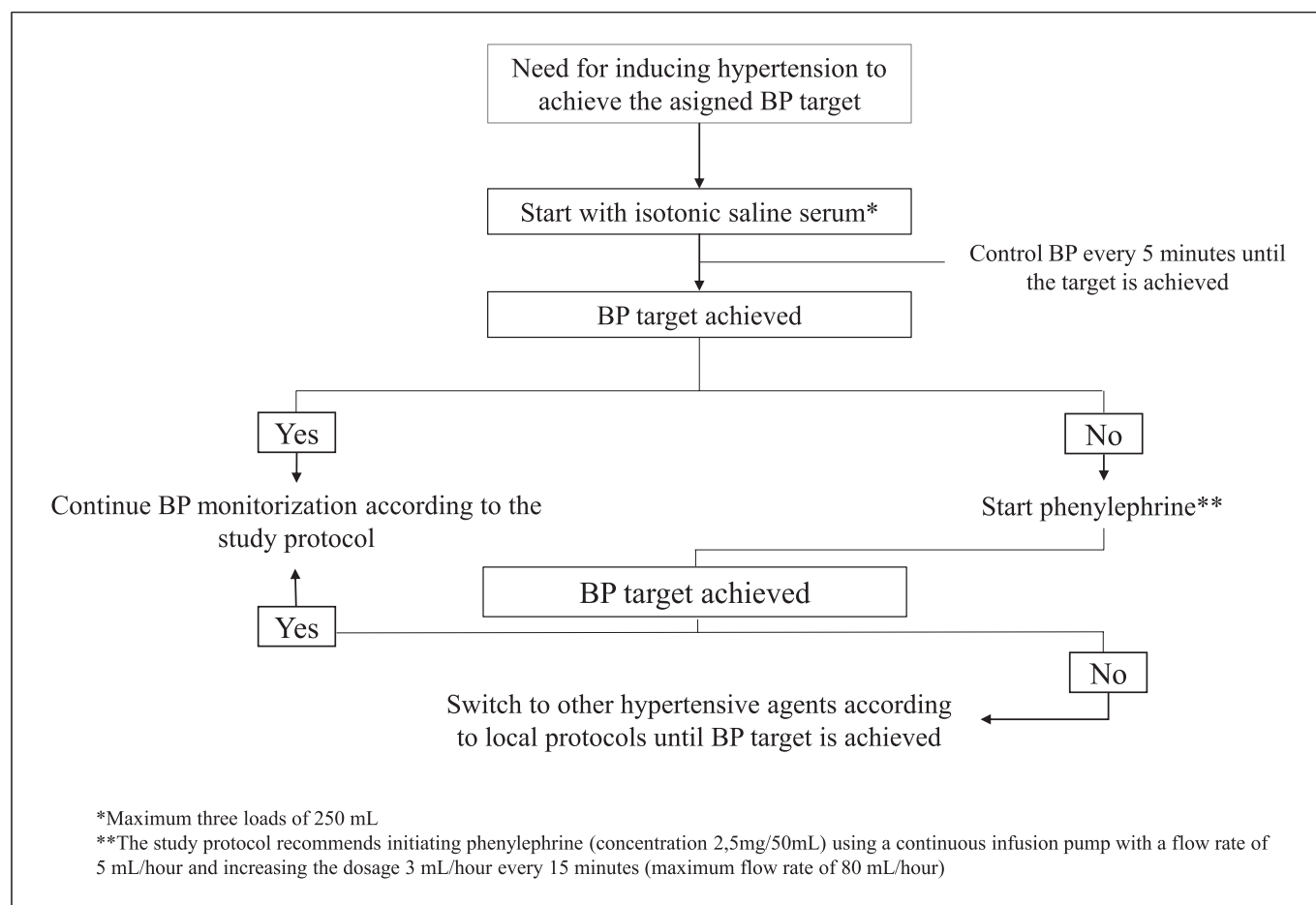


Fig. 3. Study protocol for vasopressor therapy.

Board (DSMB) is in charge of monitoring the safety and the general development of the trial. The DSMB is also in charge of recommending an eventual early termination based on the planned interim analyses (at 250 and 500 enrolled patients). The DSMB has already made an early evaluation with 130 patients enrolled after the publication of the ENCHANTED2/MT trial and have recommended continuing with the inclusion without changes in the protocol.

Sample Size Estimates

We have initially based the sample size estimation on prior observational data from Goyal et al. [6]. In this study, the investigators reported a proportion of patients with favorable outcomes (mRS 0–2) at 3 months of follow-up among patients with successful recanalization of 50% in the group with permissive BP management (<185/105 mm Hg) compared to 70% in the group with a BP target <160/90 mm Hg during the first 24 h ($p = 0.041$).

Considering these prior findings, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, we have calculated that 407 subjects would be necessary for the control group (routine BP management) and 407 in the intervention group (hemodynamic optimization) to find a statistically significant a proportion difference between groups of 10% (half of the difference found by Goyal M et al. [6]). We did this approach to assure that the trial would have enough power to conclude in favor or against the null hypothesis. It has been anticipated a drop-out rate of 5%.

After the recent publication of the meta-analysis of the first four clinical trials of BP management following EVT [15], we recalculated the sample size. We took as a reference the difference reported to be statistically significant between groups in the meta-analysis, which was 10%. The difference was the same as our initial estimation based on observational data, although the proportion of favorable outcomes in the reference group was slightly

higher. According to this new estimation of the sample size, with the hypothesis that our intervention may be capable to improve a 10% proportion of favorable outcome, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 393 subjects are necessary in each arm. For both sample size estimations, we used the normal corrected method using Stata V17 (TX, USA).

Statistical Analyses

Primary and Secondary Effect Analyses

A direct comparison between the two trial arms will be made considering the score on the mRS at 90 days after randomization. This will be an intention-to-treat analysis. The primary effect parameter will be the odds ratio of achieving functional independence (mRS 0–2) with its 95% confidence interval using logistic regression.

The secondary efficacy outcome will be the odds ratio of a shift in the direction of a better outcome on the mRS with its 95% confidence interval. The common odds ratio will be estimated with ordinal logistic regression. To increase the power of the study, the primary and secondary efficacy analyses will all be adjusted for the following major prognostic variables: age, baseline NIHSS, and time from onset to randomization.

The study will have two formal interim analyses of 250 and 500 subjects for efficacy and futility. Overwhelming efficacy will be estimated using O'Brien–Fleming boundaries on the binary outcome of 90-day mRS 0–2 versus 3–6. The criterion for determination of futility will be based on conditional power, defined as the probability of rejecting the null hypothesis at the final analysis given the data accumulated and under the assumption that the alternative hypothesis under the original design is true. A fall below 20% on the conditional power will be considered a criterion of futility. Then the DSMB will evaluate all study information including recruitment and secondary outcomes to consider stopping the study.

Secondary Safety Analyses

The following safety outcomes will be presented as the odds of presenting the adverse event comparing both arms with its 95% confidence interval. These odds ratios will be estimated using logistic regression analysis and will be adjusted with the same statistical approach as the effect analyses. These include (1) neurological deterioration within 72 h; (2) sICH within the first 72 h; (3) any PH2; and (4) mortality at 90 days.

Trial Status

Patient recruitment started in June 2021 and is expected to finish in the last quarter of 2025.

Discussion

Postprocedural BP management may influence clinical outcomes in patients with AIS treated with EVT. Defining optimal postprocedural BP targets requires randomized data. The first trials reporting data on BP management after EVT and clinical outcomes have failed to demonstrate any clinical benefit of intensive BP lowering. More concerning, ENCHANTED2/MT and OPTIMAL-BP trials found harm in the <120 mm Hg group. We believe that more clinical trials are needed to establish the safety and efficacy of different BP goals and we hypothesize that the optimal BP targets after EVT may vary according to the degree of recanalization achieved at the end of the procedure. Although no interaction was seen in ENCHANTED2/MT and OPTIMAL-BP trials between intensive BP lowering and final mTICI, we believe that HOPE might add valuable information as it is one thing to test for interaction between the intervention and final mTICI and another to randomize in a stratified way according to this variable. In this regard, the HOPE trial presents a unique design and, in addition to stratifying targets according to the final mTICI, allows the use of vasopressors for maintaining the targeted systolic BP. Despite there is uncertainty about the efficacy of the use of vasopressors in patients with acute ischemic stroke, we believe that they may be useful for maintaining a more permissive BP target (140–160 mm Hg) in patients with mTICI 2b. In addition, data from a recent clinical trial showed safety and potential efficacy with phenylephrine-induced hypertension in patients with an acute ischemic stroke not eligible for revascularization therapies [16]. We believe that this approach might be the key to optimizing brain perfusion in the critical hours of brain ischemia in patients with a successful but incomplete recanalization.

In conclusion, the HOPE trial aims to provide new information on the efficacy and safety of two different BP targets following EVT according to the degree of final recanalization in patients with AIS secondary to anterior intracranial LVO. The trial will give valuable information due to its stratified randomization design considering different targets between mTICI 2b and mTICI 2c/3 and allow both lowering and increasing BP according to the desired BP objective.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Hospital de la Santa Creu i Sant Pau, Approval No. [IIBSP-HOP-2021-01], EUDRACT No. [2021-000022-10].

Although, for acute phase randomization, verbal consent is accepted, all of the patients give written informed consent to participate in the study afterward. In case the patient is not able to sign, consent is requested from the next of kin.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.C.R.: conceptualization, funding acquisition, methodology, supervision, and writing-original draft. M.G.J.: investigation and writing – original draft. A.M.D., L.P.S., A.R.P., J.A.C., Y.S.B., G.F.C., L.M.C., A.R.C., E.G.S., A.F., X.U., N.L.H., D.C.G., M.F.G., A.L., H.T.M., J.M.M., F.M., B.P.G., L.A.L., A.S.M., G.E.D., and A.L.G.: investigation and writing – review and editing. M.C.: writing – review and editing. A.A.S. and R.M.: investigation, project administration, and writing-review and editing. J.M.F.: conceptualization, funding acquisition, methodology, supervision, and writing-review and editing.

Data Availability Statement

All data generated and analyzed during this study is included in the main article. Further inquiries will be directed to the corresponding author.

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