Clevidipine for the Antihypertensive Treatment of Acute Intracerebral Hemorrhage (CLUTCH) - EUROPE

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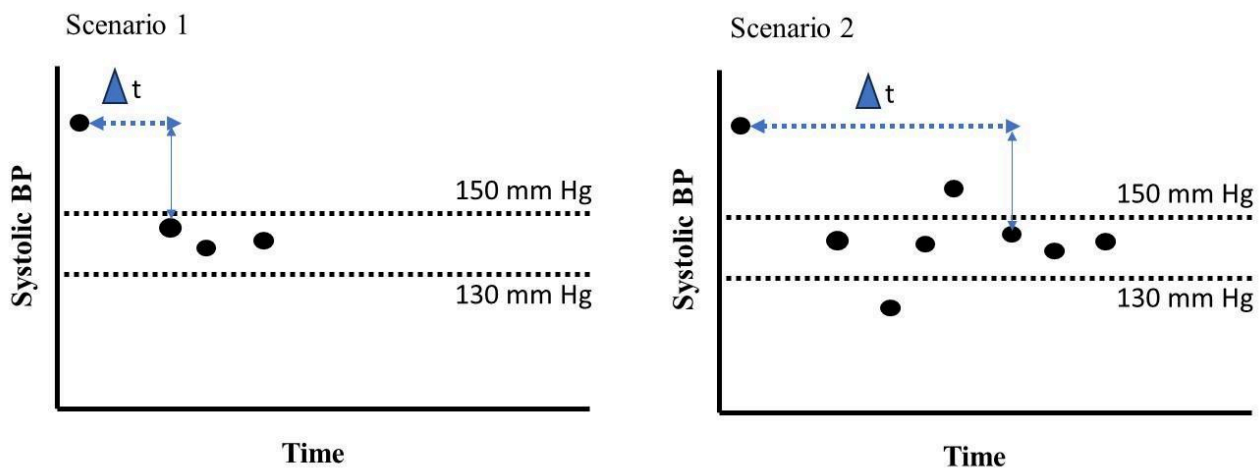
HYPOTHESIS

Primary hypothesis: We hypothesize that among hypertensive patients with intracerebral hemorrhage (ICH), the likelihood of reaching a clinically determined systolic blood pressure (SBP) target with stability within 60 minutes of initiation of treatment will be ≥ 15 % greater for patients treated with intravenous (IV) clevidipine compared with those treated with an alternate IV antihypertensive regimen given per institutional standard.

Primary endpoint: SBP target with stability is defined as achieving a SBP of less than 150 mm Hg, but greater than 130 mm Hg, plus two subsequent consecutive recordings, taken at least 15 minutes apart, remaining within that 130-150 mm Hg range. Achieving therapeutic target within 60 minutes of initiating treatment is recommended by American Heart Association/ American Stroke Association (AHA/ASA) guidelines[1] to reduce the risk of hematoma enlargement (Class of recommendation 2A, benefit exceeds risk, level of evidence B-R, moderate quality evidence from one of more randomized clinical trial or meta-analysis of randomized controlled trials). The time to reach SBP target with stability will be defined by time interval between the SBP at time of initiating IV clevidipine or alternate IV antihypertensive regimen and first of the three consecutive recordings with SBP of less than 150 mm Hg and greater than 130 mm Hg (see Figure 1). The primary endpoint will be determined centrally using the SBP data exported into the enrolling institution's electronic data collection (EDC) system, with filtering to ensure sampling of SBP data at 15 minutes intervals. The programming within the EDC system will calculate the time to reach SBP target with stability, and will therefore avoid ascertainment bias.

Figure 1. Definition of the time to reach SBP target with stability



OBJECTIVES

Primary Objective: To compare the rate of hypertensive subjects with ICH who reach SBP target with stability within 60 minutes of enrollment, among patients treated with IV clevidipine with those treated with alternate IV antihypertensive regimen. SBP target with stability is defined as achieving a SBP of less than 150 mm Hg and greater than 130 mm Hg with two subsequent consecutive recordings at least 15 minutes apart that show SBP of less than 150 mm Hg and greater than 130 mm Hg.

Secondary Objectives

1. To compare the median time to reach target SBP (130 mm -150 mm Hg) after initiation of treatment among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen among subjects with ICH.

2. To compare the proportion of subjects with ICH who reach SBP target among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen within 30 minutes of enrollment.[2]
3. To compare the time-in-target range (TTR), which is the proportion of time with SBP within a defined range after initiation of treatment among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen among subjects with ICH.[3]
4. To compare the rate of hematoma enlargement at 24 hours among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen among subjects with ICH. Hematoma enlargement is defined by a 33% greater increase in hematoma volume at 24 hours compared with baseline hematoma volume.
5. To compare the Standard Deviation (SD) of the mean value of SBP within first 8 hours after initiation of treatment among patients treated with IV clevidipine with those treated with alternate IV antihypertensive regimen among subjects with ICH. The SD is a measure of SBP variability previously used in previous studies.[4,5]
6. To compare the rate of new ischemic lesions among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen among subjects with ICH. New ischemic lesions will be defined by the presence of hyperintensities on diffusion weighted imaging (DWI) if hyperintense signal is relative to surrounding tissue and distinct from ICH with correlation on apparent diffusion coefficient map. New ischemic lesions will be identified by brain magnetic resonance imaging (MRI) acquired between 24 hours and 7 days.
7. To compare the rate of functional independence among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen among subjects with ICH. Functional independence will be defined by the modified Rankin scale (mRS) score of 0-2:
   0 = No symptoms at all; 1 = No significant disability despite symptoms; able to carry out all usual duties and activities, and 2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance. The outcome will be ascertained by a designated investigator certified in mRS scale assessment and not involved in-hospital management of subjects.
8. To compare the rate of neurological deterioration within 24 hours among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen among subjects with ICH. Neurologic deterioration will be defined as a decrease from baseline of 2 or more points in Glasgow Coma Scale score or an increase of 4 or more points in the National Institutes of Health Stroke Scale score that was not associated with sedation or hypnotic agent use and was sustained for at least 8 hours [6].
9. To compare the rate of acute kidney injury (AKI) within 72 hours among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen among subjects with ICH. AKI will be identified based on chemistry panel was performed at baseline and daily serum creatinine measurements up to Day 7 or discharge (whichever comes first). AKI will be defined based on the guidelines provided by the Kidney Disease: Improving Global Outcomes (KDIGO) definition: Increase in serum creatinine by 0.3 mg/dL or more within 48 hours OR. Increase in serum creatinine to 1.5 times baseline or more within the last 7 days OR. Urine output less than 0.5 mL/kg/h for 6 hours [7]
10. To compare the rate of serious adverse events (SAE) related to IV antihypertensive medication within 24 hours of initiating treatment among patients treated with IV clevidipine with those treated with alternate IV antihypertensive regimen among subjects with ICH. SAEs include events that result in death, are life threatening (an event in which the patient was at risk of death at the time of the event), require or prolong inpatient hospitalization, or result in persistent or significant disability or incapacity.[8] Relatedness is a term intended to indicate that a determination has been made by the treating clinician that the event had a reasonable possibility of being related to

exposure to the intervention. This assessment of causality may be based on factors such as biological plausibility, prior experience with the product, and temporal relationship between product exposure and onset of the event, and de-challenge (discontinuation of the product to determine if the SAE resolves) and rechallenge (reintroduction of the product to determine if the SAE recurs).

11. To compare the number of hypotensive episodes (defined as SBP <90 mm Hg) and symptomatic hypotension episodes (defined as SBP <90 mm Hg requiring IV vasopressors or evidence of organ hypoperfusion which includes change in level of consciousness, new or worsening of focal neurological deficits, myocardial ischemia, and oliguria) within 24 hours of initiating treatment among patients treated with IV clevidipine and those treated with alternate IV antihypertensive regimen.[6]

BACKGROUND

Acute hypertensive response

Acute hypertensive response, which is the elevation of blood pressure (BP) above normal and premorbid values that occurs within the first 24 hours of stroke onset,[9] can be seen in 75% of patients with acute ICH.[10] Treatment of acute hypertensive response remains a priority in patients with ICH due to its association with hematoma expansion (HE), perihematomal edema, and death.[11-16] Recent studies suggest that reduction of BP may be well tolerated because of reduced metabolism (hibernation) and preserved autoregulation in the perihematomal region.[17-19]

Data from randomized clinical trials

The Intensive BP Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) randomly assigned 2794 ICH patients within 6 hours of symptom onset to immediate intensive (target SBP <140 mm Hg within 1 h of treatment) or guideline-directed (target <180 mm Hg) SBP management.[20] Among the 2794 participants for whom the primary outcome could be determined, 719 of 1382 participants (52.0%) receiving intensive treatment, as compared with 785 of 1412 (55.6%) receiving guideline-recommended treatment, had a primary outcome event. The primary outcome (poor outcome, defined as death or major disability [per mRS score] at 90 days after randomization occurred in 52.0% and 55.6% of patients randomized to intensive and standard treatments, respectively (odds ratio [OR] with intensive SBP reduction, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06). The ordinal analysis showed significantly lower mRS scores with intensive treatment (OR for greater disability, 0.87; 95% CI, 0.77 to 1.00; P=0.04). The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2) trial randomized 1000 patients within 4·5 h of the onset of symptoms to immediate, intensive (target SBP 110–139 mm Hg) or guideline-directed (140–179 mm Hg) BP management with IV nicardipine, with the aim of achieving these target ranges within 2 hours after randomization.[6] The primary outcome of death or disability (mRS score of 4 to 6) at 90 days post randomization was observed in 38.7% and 37.7% of the patients randomized to intensive and standard treatments, respectively (adjusted relative risk of 1.04, 95%CI, 0.85 to 1.27). There were several key differences between INTERACT-2 and the ATACH-2 trial that are important for interpretation. In INTERACT-2, only 48% of the 2839 participants underwent randomization with an initial SBP of 180 mm Hg or more, whereas all the participants in the ATACH-2 trial had an initial SBP of 180 mm Hg or more. Primary treatment failure was seen in 66% of the participants within 1 hour after randomization in INTERACT2 and in 12.2% of those in the intensive-treatment group within 2 hours after randomization in the ATACH-2 trial.[6,20]

A pre-planned pooled analysis of INTERACT-2 and the ATACH-2 trial analyzed 3829 patients who were randomized at a median time from the onset of ICH of 3·6 h (2·7-4·4). Overall, the mean magnitude of

early SBP reduction was 29 mm Hg (standard deviation of 22 mm Hg), and the subsequent mean SBP achieved was 147 mm Hg.[21] The SBP achieved (the mean of the SBP measurements at five time points between 1 h and 24 h) was associated with functional status (improvement per 10 mm Hg increase adjusted OR 0·90 [95% CI 0·87-0·94], p<0·0001), good outcome [mRS 0-3] (OR 0.90, 95% 0.85-0.95, p<0·0001), and functional independence [mRS 0-2] (OR 0.91, 95% CI 0.87-0.96, p=0·0009). The SBP achieved was also associated with HE (>6 ml increase from baseline) (OR 1.16, 95% CI 1.06-1.27, p=0.0008). The magnitude of SBP reduction (the difference between SBP at randomization and the lowest attained SBP within 1 h) was associated with good outcomes and functional independence. Absolute reduction of SBP of both 20–40 mm Hg and 40–60 mm Hg within 1 hour were associated with good outcome and functional independence (vs reduction of <20 mm Hg). A meta-analysis of five studies, including 4360 patients with acute ICH[22] reported that the risk of death or dependency at 90 days was non-significantly lower with intensive SBP reduction compared with standard SBP reduction (OR: 0.91; 95% CI: 0.80 to 1.02), p=0.106). Intensive SBP reduction was associated with a trend towards lower risk of HE compared with standard SBP reduction (OR: 0.82; 95% CI: 0.68 to 1.00, p=0.056). Another meta-analysis of 50 trials involving 11 494 patients, including patient-level data from 6221 patients (median time from symptom onset to randomization of 3.8 hours) reported that active/intensive BP-lowering interventions within 7 days had no effect on ordinal analysis of mRS scores compared with placebo/guideline treatment (OR 0.97, 95% CI 0.88 to 1.06; p=0.50). Active/intensive BP-lowering interventions reduced absolute (>6 ml, OR 0.75, 95%CI 0.60 to 0.92; p=0.0077) and relative (≥33%, adjusted OR 0.82, 95%CI 0.68 to 0.99; p=0.034) HE.

Blood pressure fluctuation

Recent studies have highlighted the importance of BP variability in acute phase of ICH. An analysis of FAST-MAG trial (Field Administration of Stroke Therapy-Magnesium)[23] demonstrated that SD, coefficient of variation, and successive variation of BP recorded by paramedics in the field and during the first 24 hours of hospital course in patients with ICH were associated with death or disability at 3 months. Neither mean nor maximum systolic BP was associated with these outcomes in multivariable analysis. Another analysis of the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-ICH study cohort[24] found that SD of SBP in first 24 hours was associated with neurological deterioration, and successive variation in the SD of SBP in first 24 hours was associated with death or disability at 3 months. Another analysis of the ATACH-2 trial[25] showed that SBP variability in the first 24 hours was associated with death or disability at 90 days. An analysis of the INTERACT-2[26] found that the SD of SBP in the first 24 hours had a significant linear association with death or major disability at 90 days. In a pooled analysis of INTERACT 2 and ATACH 2,[27] higher SBP variability (the SD of the same measures between 1 hour and 24 hours) was significantly associated with death within 90 days, while lower SBP variability was associated with improved outcomes.

Current guidelines

The AHA/ASA guidelines[1] consider lowering SBP to a target range of 130 to 140 mm Hg (from initial SBP between 150-220 mm Hg) to be safe, and may be reasonable in improving functional outcomes in patients presenting with acute ICH of mild to moderate severity. Initiating treatment as soon as possible and careful titration of antihypertensive agents to ensure continuous, smooth, and sustained control of BP were recommended. Acute lowering of SBP to <130 mm Hg in ICH patients is potentially harmful and should be avoided. The safety and efficacy of intensive SBP reduction in patients with SBP >220 mm Hg and in those with large and more severe ICHs (at risk for cerebral perfusion compromise attributable to high intracranial pressure), require more study because these patients were not adequately represented in previous trials. The AHA/ASA guidelines[1] identify the need for more research to better delineate the importance of various BP measures, including the selection and administration method (bolus versus

drip) of antihypertension agent, absolute versus relative reduction in SBP, and prognostic significance of the magnitude of SBP reduction during the first few hours[1]. **The current guidelines emphasize both careful SBP reduction (that is, with avoidance of "overshoot" correction) and avoidance of fluctuation of SBP during treatment.**

DESIGN

The design is a pragmatic randomized (individual patient randomization) clinical trial design. Overall, 15 Hospitals in Europe will be included. To participate, sites will be required to fulfil certain clinical eligibility criteria: (i) have an established acute stroke care program for the management of ICH patients (i.e. in an acute stroke unit or intensive care unit [ICU]), (ii) admit an adequate number of ICH patients (approximately over 50) per annum for the recruitment to be feasible within a reasonable time period. The site must adhere to the protocol, collect data on patients' stay in hospital and the 90- and 180-day clinical outcomes. A contract agreement will be signed before the commencement of recruitment.

INTERVENTION

The treatment goals are consistent with the European Stroke Organisation (ESO)-Karolinska Stroke Update Conference[28]. The ESO-Karolinska Stroke Update Conference[28] which recommends to lower SBP below 140 mm Hg but to keep it above 110 mm Hg and to avoid SBP reduction of >90 mm Hg to prevent AKI (grade B, support from one randomized controlled trial or one statistical review). The ESO guidelines on BP management acknowledges that in patients with acute (<24 hours from symptom onset) ICH, there is continued uncertainty over the benefits and risks (advantages/disadvantages) of intensive SBP lowering on functional outcome.[29] In patients with hyperacute (<6 hours) ICH, the guidelines suggest lowering SBP to below 140 mmHg (and to keep it above 110 mmHg) to reduce hematoma expansion (quality of evidence: moderate strength of recommendation: weak)" The AHA/ASA guidelines[1] state that in ICH of mild to moderate severity presenting with SBP between 150 and 220 mmHg, acute lowering of SBP to a target of 140 mmHg with the goal of maintaining in the range of 130 to 150 mmHg is safe and may be reasonable (class of recommendation 2b, benefit greater than risk, level of evidence B-R, moderate quality evidence from one of more randomized clinical trial or meta-analysis of randomized controlled trials). The guidelines further state medication titration to ensure continuous smooth and sustained control of SBP, avoiding peaks and large variability in SBP, can be beneficial. (Class of recommendation 2A, benefit exceeds risk, level of evidence B-NR, moderate quality evidence from one of more non-randomized studies, observational studies, registry data).

IV CLEVIDIPINE PROTOCOL:

Sites will be trained and instructed to administer IV clevidipine according to Food and Drug Administration and European Medicines Agency label which recommends starting at 1-2 mg/hour, and then doubling the dose initially at short (90 second) intervals. As the BP approaches the goal, the increase in doses should be less than doubling and the time between dose adjustments should be lengthened to every 5-10 minutes. The desired therapeutic response for most patients occurs at doses of 4-6 mg/hour. Most patients have been treated with maximum doses of 16 mg/hour or less. There is limited short-term experience with doses up to 32 mg/hour, and because of lipid load restrictions, no more than 1000 mL or an average of 21 mg/hour of Clevidipine infusion is recommended per 24-hour period. There is little experience beyond 72 hours at any dose.

ALTERNATE IV ANTIHYPERTENSIVE REGIMEN:

The alternate IV antihypertensive regimen would be the standard of care at the trial hospitals; for example, IV urapidil.

SELECTION OF SUBJECTS

Inclusion Criteria

1. Age 18 years or older and less than 90 years.
2. Onset of new neurological deficits within 12 hours at the time of enrollment and IV clevidipine or alternate IV antihypertensive regimen can be initiated within 12 hours of symptom onset.
3. Clinical signs consistent with the diagnosis of stroke, including impairment of language, motor function, cognition, and/or gaze, vision, or neglect.
4. Initial National Institutes of Health Stroke Scale (NIHSS) score of 4 or greater.
5. Total GCS score (aggregate of verbal, eye, and motor response scores) of 5 or greater at enrollment.
6. Computed Tomography (CT) scan of the brain demonstrates intraparenchymal hematoma with manual hematoma volume measurement <60 cc.
7. Admission SBP greater than 150 mmHg but less than 220 mmHg on two repeat measurements at least 5 minutes apart, but no more than 10 minutes apart. The reason for exclusion of ICH patients with initial SBP ≥220 mm Hg is based on a post hoc analysis of ATACH-2, which found that patients with initial SBP ≥220 mm Hg (22.8% of the cohort) reported higher rates of neurological deterioration at 24 hours and renal adverse events until day 7 or discharge in patients treated with intensive SBP reduction compared with standard SBP lowering, without any benefit in reducing hematoma expansion at 24 hours or death or severe disability at 90 days.[30]
8. Patients with anticoagulant-related ICH are eligible as long as anticoagulant reversal is concurrently undertaken consistent with AHA/ASA guidelines or ESO guidelines[31].
9. Patients who will undergo surgical evacuation consistent with AHA/ASA guidelines or local institutional guidelines are eligible unless surgical evacuation is being performed within 6 hours of initiation of IV clevidipine or alternate IV antihypertensive medication regimen. Ultra-early surgery will necessitate use of anesthetic agents which will confound the effect of IV clevidipine or alternate IV antihypertensive medication regimen. Ultra-early surgery/intervention was not used in the minimally invasive catheter evacuation followed by thrombolysis (MISTIE)/ Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR) trials, which required ICH patients to undergo a repeat CT scan after 6 hours to document absence of any hematoma expansion (with ≤5 mL hematoma growth) compared to a previous CT scan prior to any surgical intervention.[32,33]
10. Patients requiring external ventricular drainage consistent with AHA/ASA guidelines or local institutional guidelines are eligible.
11. Efforts to obtain informed consent per EFIC guidelines (U.S.) or adherence to country-specific emergency research informed consent regulations (Canada, Germany, Spain, U.K., Japan).

Exclusion Criteria

1. Time of symptom onset cannot be reliably assessed.
2. Previously known neoplasms, arteriovenous malformation (AVM), or aneurysms.
3. Intracerebral hematoma considered to be related to trauma.
4. ICH located in infratentorial regions such as pons or midbrain (cerebellar ICH is not an exclusion criteria).
5. Subject considered a candidate for immediate surgical intervention by the neurosurgery service.
6. Pregnancy, parturition within previous 30 days, or active lactation.
7. Any history of bleeding diathesis or coagulopathy except anticoagulant related ICH.
8. Platelet count of less than 50,000/mm^3.
9. Known sensitivity to nicardipine or clevidipine.
10. Patient's living will precludes aggressive ICU management.
11. Patients with allergies to soybeans, soy products, eggs, or egg products.
12. Defective lipid metabolism such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia.

13. Patients with severe aortic stenosis.

SCREENING AND ENROLLMENT

Eligibility based on SBP

At least two readings of SBP of 150 mm Hg or more (but less than 220 mm Hg) between symptom onset and the initiation of IV antihypertensive treatment will be required for eligibility. Treatment could be initiated before enrollment to lower the SBP to less than 150 mm Hg, which is consistent with guidelines from the consistent with the AHA/ASA guidelines[1] and the ESO-Karolinska Stroke Update Conference[28] but patients are not eligible if the SBP was already reduced to less than 150 mm Hg before enrollment and therefore not requiring any IV antihypertensive medication. Patients who were already started on IV clevidipine prior to enrollment will not be eligible.

Study Investigators

Prior to initiation at each site, neurologists, residents, fellows, ED physicians and nurses, involved in assessment of patients with stroke will be in-serviced CLUTCH-Europe Study Flow. Patient with clinical symptoms and imaging confirmed ICH who arrive in ED will be randomized 1:1 within 12 hours of symptom onset to receive IV clevidine or alternate IV antihypertensive regimen. Only the members of the Stroke Team and the Study Coordinator(s) listed on IRB as "study investigators" who are appropriately certified in all clinical assessments are eligible to randomize and provide study treatment.

Blinding and Unblinding

In the present proposal, the infusion of medication is titrated to target SBP; therefore, the treating physician cannot be blinded to treatment. Blinding of treating physicians also raises safety issues for the subject precluding early detection of relationship between hemodynamic variables and adverse neurological events and delaying corrective measures. Lack of double blinding may exaggerate estimates of treatment benefits; hence, during their planning each participating clinical site must develop strategies to minimize the bias introduced by lack of blinding. Participating centers are required to designate a qualified investigator, certified in mRS assessments, who is blinded to treatment assignment and does not participate in randomizing or treating patients in the trial. This investigator conducts the clinical assessments of treatment efficacy in a blinded manner at 90 and 180 days after randomization. All study personnel are blinded to aggregate data for the entire trial. They have access to the data only for the subjects enrolled at their sites, and not to those at other sites. All study personnel at the CCC and the SDCC are blinded to all data (they do not have access to individual subject's clinical data nor to aggregate clinical data), except those compiled and provided in the open reports.

Screening

All subjects 18 years or older but less than 90 years old who present to the study sites with clinical symptoms of ICH are screened for study eligibility. Data collected and tests performed include demographics and vital signs, medication and medical history, and laboratory measurements required as part of standard care for ED admissions. Additionally, the patient undergoes a CT scan of the bead. If ED personnel suspect an acute stroke, they should immediately call a member of the established stroke team (a pre-requisite for study sites) to the ED to evaluate the patient. A member of the stroke team could be a neurology resident, fellow, or an attending staff neurologist who arrives to the ED in an expeditious manner to evaluate the patient and determine potential study eligibility. Potentially eligible subjects identified by the stroke team are then reviewed by a study investigator or study coordinator to determine

final eligibility before consent and randomization. Prior to randomization, a study investigator performs a neurological assessment using NIHSS and GCS scores.

Hematoma site and volume measurement prior to determining eligibility

The Study Investigator at the clinical site determines the hematoma location on review of the initial CT scan. The hematoma is classified based on location of its major component, defined as ~50% of total hematoma from visual evaluation. The location of deep hematoma is subclassified as: thalamus, putamen, internal or external capsule, or caudate nucleus. Since hematoma volume is required for assessment of eligibility, it is determined at bedside by the stroke neurologist, in-serviced for the study. For the bedside method (length x width x height)/2, the CT slice with the largest area of hemorrhage is identified. Process after screening Patients evaluated during screening are divided into two groups: eligible and non-eligible.

Screen Failure Log

Any patient screened, but not randomized, is tracked on the screen failure log. In addition to age, gender and race, the log captures reason(s) for non-randomization of the patient.

Informed Consent (for eligible subjects)

The trial will used deferred consent procedures wherever approved by local research ethics boards. The patients or their legal representatives will be asked to provide written or electronic informed consent as soon as possible after treatment, within 7 days of randomization, or before discharge, whichever occurs earlier. The process for consent reflects the imperative to treat patients quickly so as not to disadvantage enrolled patients compared with patients not enrolled in the trial.

If a patient is deemed to be eligible for the trial by the study investigator physician this patient will be informed about the study verbally and in writing by the investigator. If the patient – after having been informed and after all open questions being answered – agrees to participate in the study, the patient must personally date and sign the informed consent form. Due to the acute situation, an abbreviated, ethically approved version of the patient information sheet and informed consent form may be used. In addition, the patient receives an ethically approved detailed full patient information and informed consent and can decide at any time whether to continue or end the study without any detrimental effect on their medical care. Many patients may not be able to provide consent due to being incapacitated as a result of the acute hemorrhagic stroke. These patients may only be enrolled in the study by means approved by the German ethics committees based on the legal framework of the German Drug Law.

Randomization

Each subject must be randomized and the study treatment must be initiated within 12 hours of symptom onset. Randomization takes place centrally via the dedicated website. The randomization scheme is the minimization combined with the biased coin method to ensure treatment assignment balance within each clinical site as well as overall for the trial. Eligible subjects are randomized 1: 1 to either the IV clevidipine or alternate IV antihypertensive regimen group. The computer program balances treatment assignment based on current status of treatment group within and across clinical sites. As with many clinical trials, timely recruitment of subjects is one of the critical concerns for the CLUTCH-Europe Trial. Unlike clinical studies of chronic or progressive diseases, we cannot anticipate when, where and how many subjects can be recruited because of the emergency nature of the ICH. Therefore, randomization takes place immediately after the randomization data for the current subject is submitted into the dedicated website. The randomization procedure is implemented as follows: When an eligible

patient at the clinical site is ready to be randomized, a study team member logs onto dedicated website and submits the randomization data for the subject. The computer checks the eligibility to ensure that the subject meets required criteria, assesses the treatment balance within the clinical site, as well as across all the sites, and informs the site of the treatment assigned to that subject. A subject is considered to be in the Trial when the subject is randomized into the trial (given a treatment assignment), and his/her study time begins at this time point.

Adherence and retention

The CLUTCH-Europe trial is recruiting patients with acute medical problems, who at study entry are hospitalized ensuring initial adherence. Retention is enhanced post-discharge by providing education with clear and easy-to-follow written instructions for subjects and their families and reviewing these instructions at the time of discharge and during follow-up visits. These efforts are to be coordinated and overseen under the direction of the PI at each clinical site.

Inability to initiate allocated treatment

A subject may meet eligibility requirements and be randomized, and might be unable to proceed to the study treatment. This could be due to progression of neurological deficits or need for emergent surgery prior to the study intervention, withdrawal of consent, or occurrence of new medical events such as cardiac arrest, respiratory failure, or severe hypotension. Events such as these may render the subject no longer medically fit to receive allocated treatment as determined by the site investigator or treating physician. We expect such events to be uncommon. However, if the subject is randomized, he/she must complete the required study assessments and procedures through Day 180.

Procedure and documentation for premature terminations

A premature termination includes withdrawal of consent or death. The procedure to be followed at the time of premature termination is: (1) to check for the development of adverse events; and (2) to complete the End-of-Study CRF with explanation of why the subject is terminated. In case of death of a subject, additional data on the date and causes of death must be collected. Because primary analysis of trial data is conducted under the intention-to-treat principle, data must be collected for all randomized subjects, except those who specifically withdraw consent to continued participation in the trial. Thus, it is imperative to complete all required research evaluations during hospitalization and post-discharge for all subjects whether or not they received complete treatment with the study drug. All study procedures must be carried out per the protocol whether or not a subject receives treatment according to the protocol or is transferred to another facility.

MANAGEMENT DURING SBP TREATMENT

BP measurement and monitoring

Once IV antihypertensive medication is initiated, heart and respiratory rates and transcutaneous oxygen saturation are to be monitored continuously. BP may be monitored regularly according to the below schedule with an automated BP monitor according to institutional protocol. All measurements are to be recorded with subjects in a recumbent position and with elevation of the head of the bed not exceeding 15°. Intra-arterial BP recording is not mandated but can be used by the treating physician based on medical indications. BP measurements are recommended to be taken on the following schedule:

During the first hour after IV clevidipine or alternate IV antihypertensive regimen started:

Every 5 minutes for the first 15 minutes after IV clevidipine or alternate IV antihypertensive regimen is started

Every 15 minutes for the remainder of the first hour, unless the dose is being adjusted (see next bullet point)

Every 5 minutes for 15 minutes during dose adjustments

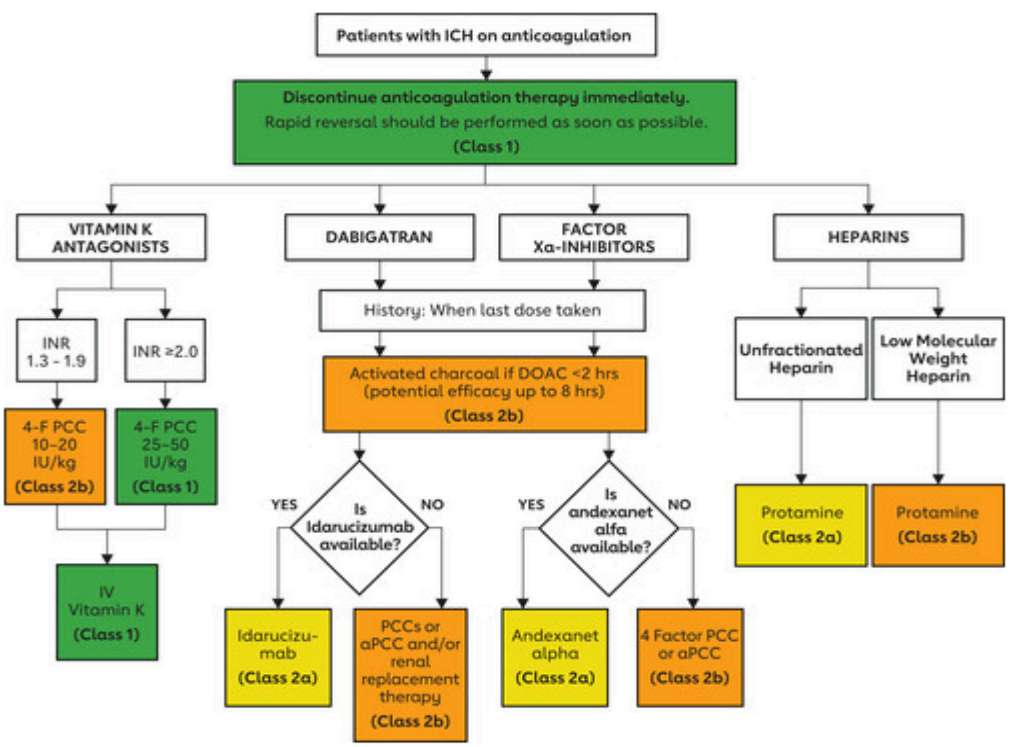
At least every 30 minutes while receiving IV clevidipine or alternate IV antihypertensive regimen

More frequent measurements are recommended if prominent BP changes are observed as determined by the treating physician.

Management of anticoagulant-related ICH

The management of anticoagulant-related ICH should occur concurrent to SBP reduction in appropriate patients. The AHA/ASA guidelines[1] state that treatment should be administered when clinically significant anticoagulant levels are suspected on the basis of type and timing of anticoagulant dosing rather than waiting for results of blood tests (see Figure 3). The guidelines state "four-factor prothrombin complex concentrate (PCC) is superior to plasma for warfarin-associated ICH to rapidly replace vitamin K–dependent coagulation factors and should be given with IV vitamin K to re-establish vitamin K–dependent coagulation factor production. Reversal of the anticoagulant effect of direct thrombin inhibitors and factor Xa inhibitors can be performed rapidly with specific reversal agents (idarucizumab and andexanet alfa, respectively) when available. When specific reversal agents are not available, aPCC or 4-F PCC may promote hemostasis in patients on direct thrombin inhibitors and factor Xa inhibitors. Renal Replacement Therapy (RRT) may reduce dabigatran concentration."

Figure 3. Management of anticoagulant related ICH. Adapted from AHA/ASA guidelines[1]



Surgical evacuation

The AHA/ASA guidelines[1] acknowledge that current evidence does not support specific recommendations for selecting candidates for surgery. As a primary recommendation, minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration, with or without thrombolytic use, is safe and may be useful to reduce mortality. The guidelines suggest that in patients with ICH volume >20 ml or >30 ml with GCS score 5-12, minimally invasive surgery (endoscopic or stereotactic aspiration with or without thrombolytics can be useful to reduce mortality (Class of recommendation 2A, benefit exceeds risk, level of evidence B-R, moderate quality evidence from one of more randomized clinical trial or meta-analysis of randomized controlled trials) but remains uncertain in regards to improving functional outcome (2B, benefit exceeds risk, weak, might be reasonable or considered, level of evidence B-R, moderate quality evidence from one of more randomized clinical trial or meta-analysis of randomized controlled trials) compared with best medical treatment.

Principles of sedation

Sedation is sometimes required to avoid pain and discomfort, even though it can obscure neurological examination and cause hypotension. The protocol does not provide any specific guidance but recommends an assessment-driven protocol that mandates regular pain and sedation assessment using validated tools, provides clear guidance on medication choice and dosing, and makes treating pain a priority over providing sedatives consistent with the clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU (conditional recommendation, moderate quality of evidence).[34] The guidelines suggest using acetaminophen and low-dose ketamine (1–2 μg/kg/hour) as an adjunct to opioid therapy to reduce opioid consumption in adults admitted to the ICU (conditional recommendation, very low quality of evidence). The guidelines also suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence) because of improved short-term outcomes, such as ICU length of stay, duration of mechanical ventilation, and delirium.

Renal evaluation

IV 0.9% sodium chloride (20 mEq/KCl added) is to be administered at l ml/kg/hour unless contraindicated as determined by the treating physician. Urine output volumes are quantitated as part of standard ICU care. The quantitation of input and output on a daily basis is routine practice to ensure euvolemia in ICH patients.

Cardiac monitoring

A 12-lead electrocardiogram (EKG) is recommended at baseline. Continuous 7-lead, 3- channel ST-segment monitoring is to be performed for 24 hours during the infusion of IV clevidipine/alternate IV antihypertensive regimen. Significant ST-segment shift suggestive of myocardial ischemia is defined as horizontal or down sloping ST depression 0.1 mV below baseline or upward ST elevation 0.1 mV above baseline, lasting 1 minute, and separated from other episodes of ST-segment. Additional creatinine kinase and troponin-T samples is to be drawn when clinically indicated or when EKG changes suggest myocardial ischemia.

IN HOSPITAL ASSESSMENTS

Clinical assessments

Frequent neurological and vital sign assessments of patients with ICH are indicated to identify neurological deterioration and prevent secondary complications according to AHA/ASA guidelines[1]. The guidelines further state that in patients with ICH of higher clinical severity, neurological assessments are typically performed hourly for the first 24 hours or until the ICH is stable. Each subject is to be admitted in the ICU or stroke unit for a 24- hour observation period. Subjects are to be examined every 60 minutes by nursing staff, with a comprehensive neurologic examination performed at 2-hour intervals. Neurological deterioration is defined as a decrease of 2 points or more decrease in GCS or an increase of 4 points or more on NIHSS scores from baseline or the last performed GCS or NIHSS score that persists for 8 hours or longer. Each episode of neurological deterioration is to be evaluated and managed under the direct supervision of a stroke neurologist or neurointensivist. After neurological deterioration is detected, IV fentanyl or midazolam infusion should be discontinued (if being used) to ensure that an adequate neurological examination can be performed. A non-contrast CT scan is to be performed; based on the results, and appropriate neurological or neurosurgical intervention should be performed. Neurological status is to be assessed by the NIHSS score by the study investigator at 24 (±3) hours post enrollment. As standard of care, brief history and physical examinations should be performed daily while the subject is in the hospital.

Radiological assessments

The study does not require any neuroimaging to be performed that is not required by clinical criteria or institutional protocol. However, the study recognizes that serial CT scans are recommended by AHA/ASA guidelines[1] in patients with ICH and/or IVH within the first 24 hours after symptom onset and may be useful to evaluate for hematoma expansion. (Class of recommendation 2A, benefit exceeds risk, level of evidence B-NR, moderate quality evidence from one of more non-randomized studies, observational studies, registry data). In patients with ICH and/or IVH and low GCS or neurological deterioration, serial CT scans within the first 24 hours after symptom onset may be useful to evaluate for hematoma expansion, development of hydrocephalus, brain swelling, or herniation. (Class of recommendation 2A, benefit exceeds risk, level of evidence B-NR, moderate quality evidence from one of more non-randomized studies, observational studies, registry data). Therefore, the baseline and non-contrast head CT scan at 24 (±8) hours post-enrollment if site performs as standard of care will be submitted to central neuroimaging core laboratory for identification of hematoma expansion. Hematoma enlargement is defined by a 33% greater increase in hematoma volume at 24 hours compared with baseline hematoma volume.[35] Brain MRI acquired between 24 hours and 7 days if performed as standard of care will be submitted to central neuroimaging core laboratory for identification of new ischemic lesions defined by the presence of hyperintensities on DWI if hyperintense signal is relative to surrounding tissue and distinct from ICH with correlation on apparent diffusion coefficient map.

Laboratory assessments

It is expected that routine clinical laboratory surveillance, including platelet count hemoglobin, hematocrit, and complete chemistry panels, must be performed at baseline, 24 hours, 48 hours, and 72 hours and will be available for ascertainment of AKI.

POST ACUTE HOSPITALIZATION CARE

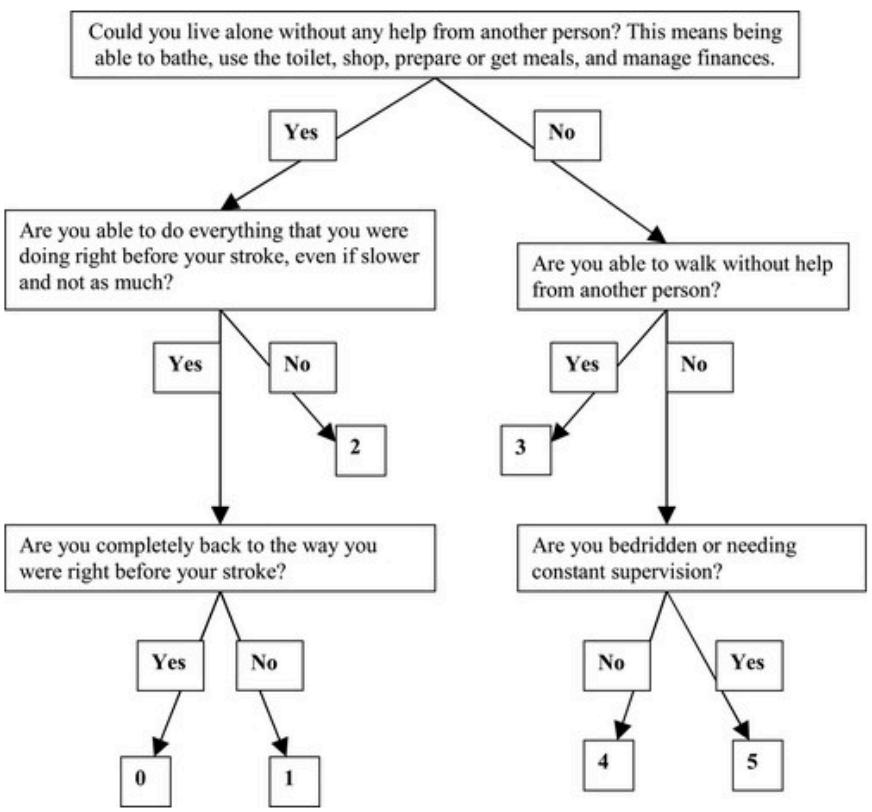
Post-discharge care

The protocol does not provide any specific guidance. Long-term care and rehabilitation after discharge may be based according to principles outlined in previous guidelines particularly the AHA clinical practice guidelines,[36,37] which provide a comprehensive review of evidence-based principles of post-hospitalization care.

Post-discharge follow-up

Post-discharge follow-up for CLUTCH is planned at 90 (±14) days and 180 (±14) days, either through telephone contact and/or in-person clinical evaluation by a qualified investigator (certified in assessment of mRS scores) who did not participate in the recruitment or treatment of the subject during the acute hospitalization and should be designated for the duration of the trial. Each subject will be assigned a score on the mRS (which assesses the degree of disability or dependence in daily activities, with scores ranging from 0 [no symptoms] to 6 [death] using a validated structured interview[38,39] We will recommend the algorithm proposed by Bruno et al.[40] to assign the mRS grade (see Figure 4). The expected time to assign a grade based on the algorithm is approximately 2 minutes. In cases of persistent disagreement between patients and their caregivers, the caregivers' answers will be accepted as more accurate.[41]

Figure 4. Algorithm proposed by Bruno et al.[40] to assign the mRS grade



During the telephone interview, the site staff will also obtain information regarding death and the cause of death and recurrent stroke, as pertinent and available. All subjects are followed to 180 days (±30 days), death, or withdrawal of consent, whichever comes first. Thus, regardless of whether or not a subject has completed the study intervention, all follow-up procedures are to be performed according to the standard schedule. We will use a mobile phone-based questionnaire to assess mRS.[42,43] The application will be designed with friendly interface to be installed on smartphone Mac operation system (OS) or Android

OS. The person performing mRS will be able to use the application and will link to the central data repository.

DATA ASCERTAINMENT AND COLLECTION SCHEDULE

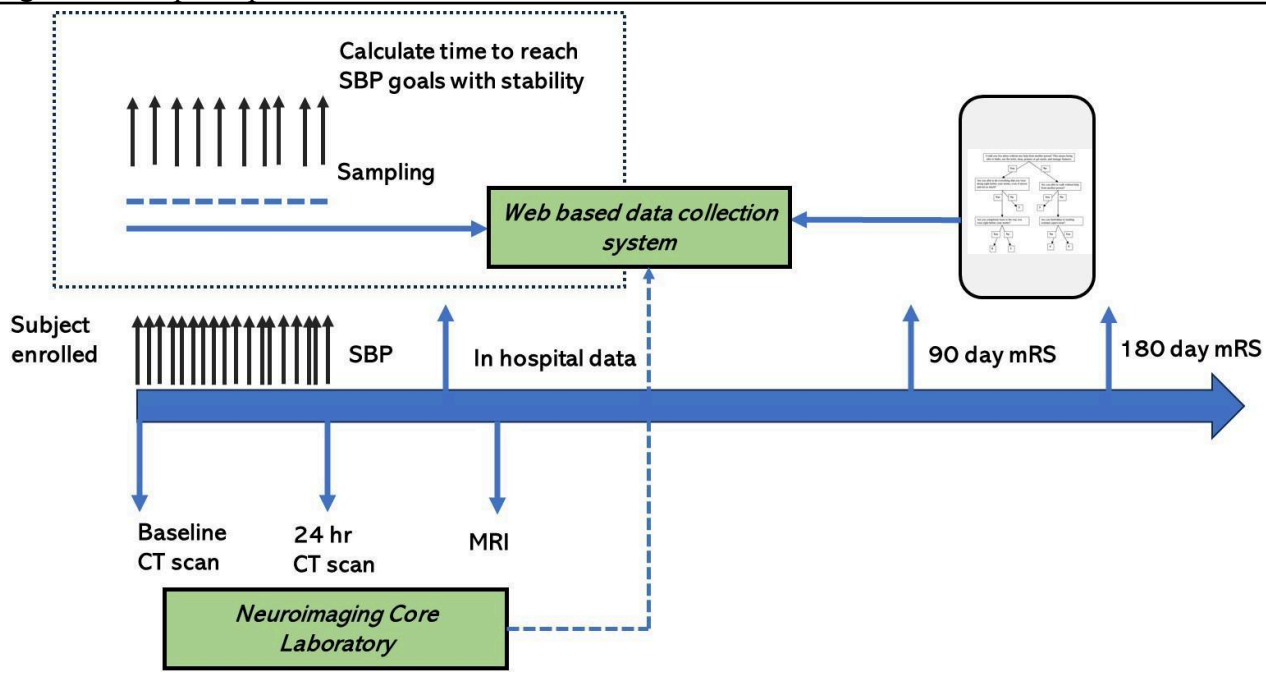
The schedule of data collection is presented in Table 2. The research team will retrospectively extract a de-identified data set from the electronic medical records including SBP data (at a rate of 1 sample per 5 minutes), and infusion rate for first 24 hours post enrollment.

Table 2. Schedule of data ascertainment and collection

	Baseline	24 hours	48 hours	72 hours	Day 7 or discharge (whichever comes first)	Day 90 (phone/ in person visit)	Day 180 (phone/ in person visit)
Screening Eligibility	×						
Enrollment	×						
Demographics/ED examination	×						
Medical history	×						
Cardiology/ 12 lead EKG	×						
Prior medications	×						
Vital signs	×	×	×	×			
GCS score	×	×					
NIHSS score	×	×					
Laboratory tests	×	×	×	×	x		
CT scan head	×	*					
Clevidipine/alternate IV medication administration	×	×	×	×			
Additional IV medication	×	×	×	×			
MRI brain				*			
Hospital discharge summary					×		
Concomitant medications		×	×		×		
Concomitant procedures		×	×		×		
SAEs		×				×	×
Modified Rankin scale						×	×
Follow up						×	×
End of Study							×

Figure 5 highlights the principles of data ascertainment and collection with particular emphasis on reducing manual data entry and the complexity of case report forms. *, to be performed if clinically indicated (not mandated by trial).

Figure 5. The principles of data ascertainment and collection.



STATISTICAL CONSIDERATIONS

Sample size calculation

This is a multi-center randomized clinical trial with the primary aim of testing the superiority of IV clevidipine with alternate IV antihypertensive medication in patients with ICH. The primary endpoint is the proportion of patients who reached three consecutive SBP recordings between 130-150 mm Hg within 60 minutes. Formally, we will test the null hypothesis $H_o: \mu_p - \mu_s \leq \Delta$ (p is not superior to s) against the alternative $H_A: \mu_p - \mu_s > \Delta$ (p is superior to s), where Δ is the minimal clinically important difference (MCID), which we set at 15%. The overall Type I error (α) is set at 0.05 and power at 0.8 (β = .2) providing a sample size of 240 participants.[44] Power and sample size for the design is calculated under the assumption that the observed values in patients treated with alternate IV antihypertensive medication will be 15% (see Table 2). The proportion is estimated based on the results of the ATACH-2 trial.[6] To account for attrition, missing data and failures to treat as randomized, the statistically necessary sample size was inflated by 10%, giving a target enrollment of 264 participants. For certain analyses such as hematoma expansion and new cerebral ischemic lesions, the sample size is based on availability since the trial does not require neuroimaging that is not performed as routine care.

Table 2. Assumptions used for sample size calculations

Alternate IV antihypertensive regimen	IV clevidipine treatment	Alternate IV antihypertensive regimen	IV clevidipine treatment	Total number	Inflated by 10%

15%	30%	120	120	240	264
15%	35%	72	72	144	159
10%	25%	100	100	200	210
10%	30%	62	62	124	139

Interim analysis

The trial will involve two interim analyses conducted after one-half and two thirds of subject accrual, and a final analysis if the study runs to full term. Test statistics/p-values at each analysis will be compared to the following boundaries, allowing for early stopping with a conclusion of non-superiority, or early termination for futility. An O'Brien-Fleming type[45] spending rule will be used to control the overall Type I error. The futility of continuing the study will be based on conditional power.[46] The statistical analysis plan indicates the test statistic and corresponding two-sided p-value thresholds for each interim analysis, such that stopping the trial early for futility and overwhelming efficacy maybe considered (see Table 3).

Table 3. Principles for determining futility and overwhelming efficacy during interim analysis

Alternate IV antihypertensive regimen	IV clevidipine treatment	p-value for overwhelming efficacy	p-value for futility
66	66	<0.0161	≥0.652
99	99	<0.0203	≥0.293
132	132	Complete	Complete

Minimal clinically important difference

In previous randomized controlled trials comparing IV nicardipine vs nitroprusside and IV nicardipine vs labetalol have used a MCID of ≥7.5% to demonstrate superiority in the proportion of patients reaching BP treatment goals within 30 or 60 minutes.[47,48] An increase in proportion of patients who reach therapeutic goal (<150 mm Hg) within 60 minutes is expected to increase the proportion of patients who achieve functional independence at 90 days by 50% (relative increase) based on secondary analysis of ATACH 2. An increase in proportion of patients who achieve therapeutic goal (<150 mm Hg) within 60 minutes by 7.5%, assuming that 46% of the patients achieve functional independence at 90 days (combined value from ATACH 2 and INTERACT 2 that may be expected in "non-clevidipine group"),[27] will lead to an increase in functional independence at 90 days by absolute value of 1.75 in every 100-patient cohort. For simple and safe therapies for acute stroke, MCIDs derived from observations of actual physician behavior and medical guidelines have ranged between 1%–1.5%[49-52] In a survey of 122 academic stroke neurologists, the median MCID was 1.3% in the absolute increase needed in the proportion of patients achieving functional independence at 3 months to consider a novel, safe agent as clinically worthwhile.[50]

Statistical analysis

The pre-specified primary analysis for primary endpoint will be conducted under the intention-to-treat principle, with adjustment for the effects of age, GCS score, and presence or absence of IVH. The analysis of the dichotomized 3-month mRS score (3 to 6 vs. 0 to 2) will be based on the generalized linear model with log-link function with Poisson distribution (rather than binomial distribution, because of convergence issues). Missing data for mRS maybe imputed with the use of the multiple-imputation

method that generates and analyzes 100 samples (with the use of a computer simulation) of the trial data, each with a variable imputed value for the missing data, and results are subsequently compiled.

Missing data

Missing data is inevitable in a large-scale trial, but we do not expect this to be a major issue due to the short-term follow-up and mortality, and data collection that is both largely automated and consistent with routine care. We have inflated the sample size to account for the expected patient loss. When data are missing completely at random (MCAR), complete-case analysis does not bias the treatment estimates but may reduce power. When the probability that data are missing is a function of observed data elements, the mechanism is missing at random (MAR). Under the MAR mechanism unbiased estimates are obtained using covariate adjustment, which is already reflected in our data analysis plan. Further, if the missing data exceeds expectation (> 10-15% of enrolled cases), we will estimate group effects and test hypotheses using multiple imputation (MI) under a various pattern-mixture schemes. All MI complete datasets will be analyzed with standard statistical methods and Rubin's combination rule to obtain a point estimate. Both estimates from MI and complete case analyses will be reported. Multiple imputation under MAR mechanisms is available in SAS/STAT® multiple imputation procedure (SAS/STAT software, Version 15.2 of the SAS System for Windows. Copyright © 2020 SAS Institute Inc., SAS Institute Inc., Cary, North Carolina, USA). Missing data become problematic for data missing not at random (NMAR). Sensitivity analyses that replace missing data with observations over the range of plausible values will be used to account for potential NMAR.

Heterogeneity of treatment effects

We will use the Patient-Centered Outcomes Research Institute (PCORI) standards for testing heterogeneity of treatment effects (HTE).[53] We will assess consistency of treatment effect in 10 pre-specified univariate subgroups: age (<55, 56-79, ≥80 yrs), time interval from symptom onset to initiation of treatment (<6 hours and ≥6 hours), initial SBP (<180 mm Hg and ≥180 mm Hg), initial GCS score (<8 and ≥8), initial hematoma volume (<30 cc and ≥30 cc), location of hematoma (basal ganglia or thalamus versus lobar versus infratentorial), interfacility transfer (yes, no), intraventricular extension (yes, no), site recruitment (<median value and ≥median value), and baseline serum glucose (<140 mg/dl, ≥140 mg/dl). The expected number of subjects in CLUTCH in each of these subgroups ranges from 150 to 500 subjects. The subgroups have been pre-specified based on prognostic significance.[54,55]The relative risk (with 95% CI) will be calculated and displayed graphically as forest plots. We will estimate the treatment effects (net benefit) *within each subgroup* in separate analyses (E_1 and E_2, respectively). A test for statistical interaction comparing the two subgroups will be calculated based on the subgroup treatment effects (E_1 and E_2) and their corresponding standard errors. The z value which gives a test of the null hypothesis that in the population the difference between subgroups (d) is zero by comparing the value of z to the standard normal distribution will be used to provide the p-value. The Gail-Simon test will be used for qualitative interaction if IV clevidipine in one subgroup shows harmful effects and another shows benefit.[56]An alternative and perhaps more typical approach is to include treatment arm by subgroup interaction effects in a linear model. However, interaction models do not add to the analysis because these interaction effects will be seriously underpowered.[57,58]

Secondary analyses

There are 11 secondary analyses comparing median time to reach target SBP, the proportion of subjects with ICH who reach SBP target within 30 minutes of enrollment, the time-in-target range in first 24 hours, rates of hematoma expansion; new ischemic lesions on MRI, AKI, and functional independence at/within 90-days, and comparing the SD of the SBP in first 8 hours after enrollment. Mean values will be compared using independent sample two tailed t-test. If the distribution of the data is not normal, Wilcoxon Signed-Rank test for data with unequal variances may be considered. For median values,

comparisons will be made using Kruskal-Wallis test. This overall approach is similar to the above proposed primary outcome analysis. Nominal and ordinal scale outcomes will be analyzed using nominal and ordinal logistic regression with standard error computed by the method of generalized estimating equations.[59] Depending on the observed distribution of the SD outcome, a linear mixed model or count data model such as Poisson regression will be used. Depending on the scale of the specific variable, treatment effect estimates will be presented as unadjusted and adjusted ORs, difference of proportions and means (with 95% Cis). Confidence intervals excluding 1.0 for ORs, and zero for risk and mean differences, provide additional support for the superiority of IV clevidipine. Beyond age, GCS score, hematoma volume, and presence or absence of IVH, additional covariates will be identified from previous studies as those factors having a meaningful impact on these outcomes.[54,55] In addition, variable selection methods such stepwise regression or the least absolute shrinkage and selection operator (LASSO model)[151] may be applied to assess the best set of covariates to include in a particular regression model. These analysis results will be treated as supportive evidence (or lack thereof) of the treatment effect of IV clevidipine, rather than conclusive evidence. Efficacy analyses of the ordinal shift in mRS score will be done for the full range of adjudicated mRS scores (0–6) using the Cochran-Mantel-Haenszel shift test, followed by proportional odds logistic regression subject to the validity of shift analysis model assumptions. We may use multivariate analysis to compare the differences in new ischemic lesions on MRI between clevidipine and non-clevidipine groups to adjust for differences in time periods of MRI acquisition if there are differences identified between the two groups.

Tertiary analyses

We will also confirm the prognostic significance of the primary endpoint, SBP target with stability (defined as achieving a SBP of less than 150 mm Hg and greater than 130 mm Hg with two subsequent consecutive recordings at least 15 minutes apart with SBP of less than 150 mm Hg and greater than 130 mm Hg). We will evaluate the relationship between achieving SBP target with stability within 60 minutes with HE within 24 hours, new cerebral ischemic lesions on MRI within 7 days, AKI, and functional independence at 180 days. A logistic regression model will be used to adjust for age, initial GCS score, hematoma volume and presence or absence of IVH. We will also evaluate the outcome variable of mRS entered as an ordinal variable in the model. We will also evaluate the relationship between time to reach SBP with stability entered as a continuous variable with the outcomes of HE within 24 hours, new cerebral ischemic lesions on MRI within 7 days, AKI, and functional independence at 180 days. A linear regression model will be used that will adjust for age, initial GCS score, hematoma volume and presence or absence of IVH. We will also evaluate the outcome variable of mRS entered as an ordinal variable in the model.

Safety analyses

Safety analyses will include between-group comparisons of SAEs by patient, Standardized Medical Dictionary for Regulatory Activities (MedDRA) code, and organ system.

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