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Statin and dual antiplatelet therapy for the prevention of early neurological deterioration and recurrent stroke in branch atheromatous disease (SATBRAD) - protocol for a prospective historically controlled study

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Abstract

Introduction:

Branch atheromatous disease (BAD) contributes to small-vessel occlusion in cases of occlusion or stenosis of large caliber penetrating arteries, and it is associated with a higher possibility of early neurological deterioration (END) and recurrent stroke in acute ischemic stroke. As the pathology of BAD is due to atherosclerosis, we postulate that early intensive medical treatment with dual antiplatelet therapy (DAPT) and high-intensity statins, may prevent END and recurrent stroke in acute small subcortical infarction caused by BAD.

Methods and analysis:

In this prospective, single-group cohort study, we will compare early DAPT and high-intensity statin treatment with a historical control group of BAD patients who were treated with single antiplatelet therapy without high-intensity statin treatment. Patients will be eligible for enrollment if they are admitted for acute ischemic stroke within 24h, have a National Institutes of Health Stroke Scale (NIHSS) score of 1-8 and are diagnosed with BAD by MRI. Patients will take aspirin, clopidogrel and high-intensity statins (atorvastatin or rosuvastatin) within 24h of stroke onset, followed by aspirin or clopidogrel alone from day 22. The primary endpoint is the percentage of patients who develop END within 7 days of stroke onset (defined as an increase in the NIHSS score ≥2 points) and recurrent stroke within 30 days. The total sample sizes will be 138 for the intervention group and 277 for the control group. A historical control group will be drawn from previous prospective observation studies.

Ethics and dissemination:

The protocol of this study has been approved by the Institutional Review Board of Chang Gung Memorial Hospital (202001386A3). All participants will have to sign and date an informed consent form. The findings arising from this study will be disseminated in peer-reviewed journals and academic conferences.

Trial registration number: ClinicalTrials.gov Identifier: NCT04824911

Keywords: Statin, antiplatelet therapy, early neurological deterioration, recurrent stroke, branch atheromatous disease

Strengths and limitations of this study

1. This will be the first trial to evaluate the effectiveness of dual antiplatelet therapy and high-intensity statins for the prevention of early neurological deterioration and recurrent stroke in patients with acute ischemic stroke from branch atheromatous disease.
2. The findings will provide valuable information to increase understanding of the effectiveness of early intensive medical treatment for branch atheromatous disease after acute stage.
3. A randomized controlled study with a parallel control arm receiving single antiplatelet treatment for milder stroke is against the latest guidelines so it's inevitable to conduct this trial with a historical control group.
4. The use of a historical control group has the inherent drawbacks of nonrandomization and nonblinding so we cannot exclude the possibility of selection, performance, detection and attrition bias.

1. Introduction

Small-vessel occlusion is the most common stroke subtype in Asians; it is caused by the occlusion of deep perforating arteries, mainly by the underlying pathologies of lipohyalinosis or cerebral amyloid angiopathy.[1 2] Branch atheromatous disease (BAD) has also been reported to contribute to small-vessel occlusion in cases of occlusion or stenosis that occur at the origin of large caliber penetrating arteries, due to microatheromas or junctional atherosclerotic plaques.[3] BAD is associated with an increased possibility of early neurological deterioration (END) and recurrent stroke, especially progressive motor deficits, compared with infarction due to hypertensive arteriopathy.[4-6] It has been proposed that BAD should be classified as large artery atherosclerosis rather than small vessel occlusion.[7]

Following acute ischemic stroke, single antiplatelet agents, such as aspirin or clopidogrel, are the mainstay treatment for recurrent stroke prevention. However, the modest effects of single antiplatelet therapy led to the study of combination antiplatelet therapy for the prevention of recurrent stroke. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) and the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trials showed that dual antiplatelet therapy (DAPT) might be beneficial for reducing the probability of ischemic events in patients with high-risk transient ischemic attack (TIA) or minor stroke.[8 9] However, these studies included all non-embolic ischemic stroke types. Some studies also showed that DAPT reduced the possibility of END.[10 11] A retrospective observation study showed that DAPT was beneficial for the primary outcomes of stroke recurrence, myocardial infarction, and all-cause death in patients with large atherosclerotic stroke.[12]

For patients with acute ischemic stroke, the guidelines suggest starting or continuing statin treatment as soon as oral medications can be used safely.[13] Current guidelines also recommend high- or moderate-intensity statin therapy, independent of the baseline low-density lipoprotein cholesterol (LDL-C), to reduce the risk of stroke and cardiovascular events for patients with TIA or ischemic stroke of atherosclerotic origin.[14] High-dose statin treatment in the acute phase of ischemic stroke and TIA significantly reduced National Institutes of Health Stroke Scale (NIHSS) scores and improved

short-term functional outcomes without increasing related adverse events[15]; it also effectively stabilized symptomatic intracranial atherosclerotic plaques as documented by high-resolution MRI.[16]

DAPT and high-intensity statins are the mainstay treatments for intracranial atherosclerosis (ICAS).[17] As BAD and ICAS share the same pathology as atherosclerosis, we postulate that early intensive medical treatment with DAPT and high-intensity statins may prevent early neurological deterioration and recurrent stroke. This study aims to evaluate whether intensive medical therapy with aspirin, clopidogrel and high-intensity statins, can prevent END and recurrent stroke in acute small subcortical infarction caused by BAD.

2. Methods

2.1 Study Design

In this prospective, non-randomized, historically controlled study, we will compare early intensive treatment for BAD initiated within 24h of stroke onset, using dual antiplatelet therapy (aspirin plus clopidogrel) and high-intensity statin treatment, with a historical control group of BAD patients treated with single antiplatelet therapy, without high-intensity statin treatment.[18 19] The study will be conducted in Chang Gung Memorial Hospital at Chiayi, Taiwan from March 2021 to Feb 2023.

2.2 Study population

Patients are eligible to participate if they meet the following inclusion criteria: (1) have a clinical diagnosis of ischemic stroke with an NIHSS score of 1-8 (2) have an ischemic lesion on diffuse-weighted imaging located in the striatocapsular territory or brain stem areas, with an axial diameter ≤20mm (3) have BAD, defined by a visible lesion in three or more axial MRI cuts in the lenticulostriate territory or infarcts that extend from the basal surface of the pons (4) could receive intensive medical treatment within 24h of stroke onset. Patients with >50% stenosis of the relevant arteries on magnetic resonance angiography (MRA), including intra- or extra-cranial internal carotid artery, middle cerebral artery or basilar artery, will be excluded. We will also

exclude patients at high risk of cardioembolic stroke, such as those with atrial fibrillation or heart failure. Full details of the inclusion and exclusion criteria are listed in Table 1.

A historical control group will be drawn from our prospective observation studies, which have been executed between January 2011 and December 2020, and aimed to evaluate and predict END or atrial fibrillation.[18 19] Patients will be selected if they fulfill the following inclusion criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment. Patients in the historical control group will have received statin treatment once their total cholesterol was ≥160mg/dl or their LDL-C was ≥100mg/dl. High-intensity statin treatment includes atorvastatin 40–80mg or rosuvastatin 20–40mg daily.[20] All clinical information and outcomes have been prospectively recorded.

2.3 Trial intervention

Dual antiplatelet and high-intensity statin treatment will be administered within 24h of stroke onset (Figure 1). Dual antiplatelet treatment includes aspirin (300mg loading and 100mg/day) and clopidogrel (300mg loading and 75mg/day) and high-intensity statins includes atorvastatin 40-80mg/day or rosuvastatin 20mg/day. Patients will take aspirin and clopidogrel for 21 days and then just take aspirin or clopidogrel alone. High-intensity statins will be maintained for 90 days but a decreased dose is allowed if any side effects occur, including elevated liver functions, elevated creatine-phospho-kinase (CPK) and myalgia or at the judgment of the treating physician. We will follow up with alanine aminotransferase (ALT) and CPK 14 days after treatment and will follow up with ALT, CPK and LDL-C 90 days after treatment. Patients with atherosclerotic plaques in the first MRI will keep high-intensity statin treatment for 6 months.

Neurological deficits will be evaluated by a stroke study nurse using the NIHSS, at the 1st, 2nd, 3rd, 7th and 90th day. As END in lacunar infarction is mainly associated with motor deficits, END is defined as an NIHSS score increase ≥2 within 7 days of stroke onset.[21] Clinical outcomes at admission and at 90 days will be evaluated using the modified Rankin Scale (mRS). A good outcome is defined as an mRS score ≤1. Mortality at 3 months and any hemorrhagic complications

will also be recorded. All examinations will be performed after obtaining written informed consent from the patients or the appropriate family members.

Patients with visible atheromatous plaques in the parental artery in the initial MRI will receive a follow-up MRI 6 months later to see the interval changes in atheromatous plaques.

2.4 Study Outcomes

The primary outcome will be the percentage of patients with early neurological deterioration within 7 days and recurrent ischemic stroke within 30 days. Secondary outcomes will include: (1) the percentage of patients with favorable functional recovery, defined as an mRS ≤1 at the 90th day, (2) the percentage of patients with new clinical vascular events within 90 days, including ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction and vascular death, (3) changes in atherosclerotic plaques, which will be measured by high-resolution MRI at the start of the study and after 6 months, (4) the number of moderate to severe bleeding events as defined by the GUSTO classification,[22] and (5) the total mortality rate.

2.5 Sample Size

In single subcortical infarction, END was reported to occur frequently in BAD with an incidence of 27% in our previous cohort and 33.8- 40% in other studies.[10 23] The END rate may decrease to 9.7% in patients with BAD who underwent combination antiplatelet therapy with cilostazol.[10] The total sample sizes will be 138 for the intervention group and 277 for the control group. The estimated END rate is 27% for the control group and 15% for the intervention group, with 80% power and a two-sided alpha of 0.05. The intent-to-treat (ITT) principle will be applied to the primary outcome analysis, and the sample size was therefore inflated to safeguard against 5% lost-to-follow-up in the actual treatment groups, which could dilute the effect size.

2.6 **Statistical analysis**

Statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS) statistical software (version 25, Chicago, IL, USA). The Kolmogorov-Smirnov test will be used to examine the normality of continuous variables. The Mann-Whitney U test and

Student's t-test will be used to test for differences between the two groups, as appropriate. Categorical data will be analyzed using the Chi-squared test. A logistic regression model will be used to adjust for baseline confounding factors and to test independent variables for the measured outcomes. Variables showing a p value of <0.1 for univariate analysis will be entered into the multivariate logistic analysis using the forward selection method. All tests will be two-tailed, and a p value <0.05 is considered to indicate a statistically significant difference.

2.7 Data management

All the completed documents and the informed consent forms will be stored in a secured facility, under lock and key. The database for clinical data will be created using Access software and the access will be limited to principal investigators. A study steering committee will be established to ensure that the study conducted to the required standards. The clinical research assistant will verify all consent forms, compliance with study protocol and procedures, and data quality. The research team will make half-yearly reports to the study steering committee. All the records and documents will be kept for 7 years after the completion of the study.

2.8 Adverse events

Any adverse events that occur during the conduct of the study will be reported to the Domain Specific Research Board (DSRB) according to the local institutional policy. Interim analyses will be conducted by the study steering committee to monitor the accumulating data and to decide continuing or stopping the trial.

2.9 Patient and public involvement:

Patients and members from stroke associations participated in the preparation and formulation of this proposal. Patients with acute ischemic stroke from BAD will be involved in the trial. The associations will be involved in plans to disseminate the study results to their members and wider patient communities.

2.10 Ethics and dissemination:

The protocol of this study has been approved by the Institutional Review Board of Chang Gung

Memorial Hospital (202001386A3). The study is registered on ClinicalTrials.gov (NCT04824911). All participants will have to sign and date an informed consent form. The findings arising from this study will be disseminated in peer-reviewed journals and academic conferences. The datasets during the current study are available from the corresponding author on reasonable request.

3. Discussion

This will be the first trial to evaluate the effectiveness of DAPT and high-intensity statins for the prevention of early neurological deterioration and recurrent stroke in patients with acute ischemic stroke from BAD. With improvements in imaging, BAD is believed to be caused by atherosclerotic plaques which obstruct the orifices of penetrators[3 24] and it has been proposed that BAD should be classified as large artery atherosclerosis rather than small vessel occlusion.[7] DAPT and high-intensity statins are the mainstay treatments for ICAS.[17] Since ICAS and BAD share the same pathology of atherosclerosis, the treatment of DAPT and high-intensity statins may also be effective for BAD. The results of this trial will answer the question of whether optimal treatment for BAD is different from other small subcortical infarction due to other pathologies.

In this trial, we define BAD as a visible lesion in three or more axial MRI cuts in the lenticulostriate territory or infarcts that extend from the basal surface of the pons.[3] Although high-resolution vessel-wall MRIs provide a direct way of detecting atherosclerotic plaques involving perforators' parent arteries, the definition in this trial is a more practical way of stroke diagnosis. In addition, microatheroma in the proximal penetrating artery are not visible in vessel-wall imaging and need other advanced sequences to be detected, which may prohibit its widespread use.

Our primary outcome is the percentage of patients with END within 7 days and recurrent ischemic stroke within 30 days, which often lead to greater mortality and functional disability. It is therefore worth evaluating any treatment which could lower END and recurrent stroke. In the secondary outcomes, we will evaluate the changes in atherosclerotic plaques on parental arteries as measured by an initial high-resolution MRI and another 6 months later. To the best of our knowledge, it will be the

first trial to demonstrate plaque changes in BAD after medical treatment.

There are several methodological limitations of this trial. The use of a historical control group has the inherent drawbacks of nonrandomization and nonblinding so we cannot exclude the possibility of selection, performance, detection and attrition bias. However, using a single antiplatelet agent for milder stroke with an NIHSS score ≤3 is against the guidelines and there would be ethical issues if we conducted a randomized controlled study with a parallel control arm receiving single antiplatelet treatment. Therefore, our study still provides valuable information to increase understanding of the effectiveness of DAPT and statins in acute small subcortical infarction from BAD.

Author contributions

YCH and JTY conceptualized and designed the initial protocol. JDL, LCL, HHW and YHT amended the initial protocol. YCH drafted the manuscript and received the fund. All authors read and approved of the protocol prior to submission.

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Competing interests

None declared.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Figure 1. A schematic diagram of the treatment schedule and study design.

In the intervention group, patients will take aspirin (300mg loading and 100mg/day), clopidogrel (300mg loading and 75mg/day) and high-intensity statins (atorvastatin 40-80mg/day or rosuvastatin 20mg/day) within 24h of stroke onset, followed by aspirin or clopidogrel alone from day 22. High-intensity statins includes atorvastatin 40-80mg/day or rosuvastatin 20mg/day. In the historical control group, patients will be selected from previous prospective studies if they fulfill the following inclusion criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment.

Table 1. Inclusion and exclusion criteria (Issue date: 01 Sep 2020)

Inclusion Criteria

- Clinical diagnosis of ischemic stroke with a National Institute of Health Stroke Scale (NIHSS) score of 1-8
- An ischemic lesion on diffuse-weighted imaging located in the striatocapsular territory or brain stem areas, with an axial diameter ≤20mm.
- Branch atheromatous disease, defined by a visible lesion in three or more axial MRI cuts in the lenticulostriate territory or infarcts that extend from the basal surface of the pons
- Ability to participate within 24h of the time of last known free of new ischemic symptoms.
- Head MRI ruling out hemorrhage or other pathologies, such as vascular malformation, tumor, or abscess, that could explain their symptoms or contraindicate therapy.
- Ability to tolerate high intensity medical therapy, including aspirin at a dose of 50–325mg/day, clopidogrel at 300mg loading and 75mg after day 2 and high-intensity statins (either atorvastatin 40-80mg or rosuvastatin 20mg/day).
- Pre-stroke mRS ≤1

Exclusion Criteria

- Age <18 years.
- At the judgment of the treating physician
- A candidate for thrombolysis, endarterectomy or endovascular intervention.
- Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to the index event.
- Patients with >50% stenosis of the relevant arteries as determined by magnetic resonance angiography (MRA), including the intra- or extra-cranial internal carotid artery, middle cerebral artery or basilar artery.
- Patients with a high risk of cardioembolic stroke, such as those with atrial fibrillation, acute myocardial infarction, severe heart failure or valvular heart disease.
- Those with other determined stroke etiologies, such as vasculitis, shock, antiphospholipid antibody syndrome etc.
- Gastrointestinal bleeding or major surgery within 3 months prior to the index event.
- History of nontraumatic intracranial hemorrhage.
- Clear indication for anticoagulation during the study period (deep venous thrombosis, pulmonary embolism or hypercoagulable state).
- Qualifying ischemic event induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with a life expectancy <3 months.
- Contraindication to clopidogrel, aspirin, atorvastatin or rosuvastatin
  - Known allergy to clopidogrel, aspirin atorvastatin or rosuvastatin
  - Severe renal (serum creatinine >2 mg/dL) or hepatic insufficiency (INR >1.2; ALT >40 U/L or any

resultant complication, such as variceal bleeding, encephalopathy, or jaundice)

- Hemostatic disorder or systemic bleeding in the past 3 months
- Current thrombocytopenia (platelet count <100 x10^9/L) or leukopenia (<2 x10^9/L)
- History of drug-induced hematologic or hepatic abnormalities

- Anticipated requirement for long-term (>7 day) non-study antiplatelet drugs (e.g., dipyridamole, ticagrelor, ticlopidine), or NSAIDs.
- Not willing or able to discontinue prohibited concomitant medications.
- Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
- Other neurological conditions that would complicate assessment of outcomes during follow-up.
- Ongoing treatment in another study of an investigational therapy, or treatment in such a study within the last 7 days.

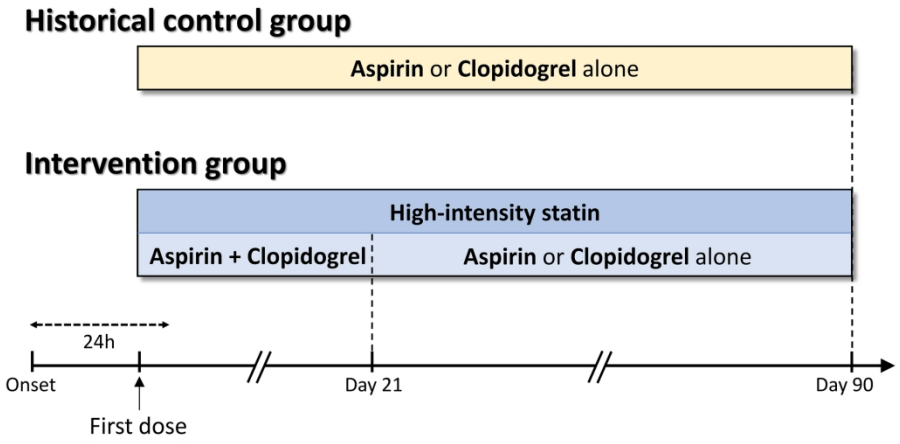

Figure 1/ A schematic diagram of the treatment schedule and study design

199x109mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	10
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	8

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	14
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	5

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	8

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Statin and dual antiplatelet therapy for the prevention of early neurological deterioration and recurrent stroke in branch atheromatous disease (SATBRAD) : protocol for a prospective single-arm study using a historical control for comparison

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Statin and dual antiplatelet therapy for the prevention of early neurological deterioration and recurrent stroke in branch atheromatous disease (SATBRAD) : protocol for a prospective single-arm study using a historical control for comparison

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Abstract

Introduction:

Branch atheromatous disease (BAD) contributes to small-vessel occlusion in cases of occlusion or stenosis of large caliber penetrating arteries, and it is associated with a higher possibility of early neurological deterioration (END) and recurrent stroke in acute ischemic stroke. As the pathology of BAD is due to atherosclerosis, we postulate that early intensive medical treatment with dual antiplatelet therapy (DAPT) and high-intensity statins, may prevent END and recurrent stroke in acute small subcortical infarction caused by BAD.

Methods and analysis:

In this prospective, single-center, open-label, non-randomized, single-arm study using a historical control, we will compare early DAPT and high-intensity statin treatment with a historical control group of BAD patients who were treated with single antiplatelet therapy without high-intensity statin treatment. Patients will be eligible for enrollment if they are admitted for acute ischemic stroke within 24h, have a National Institutes of Health Stroke Scale (NIHSS) score of 1-8 and are diagnosed with BAD by MRI. Patients will take aspirin, clopidogrel and high-intensity statins (atorvastatin or rosuvastatin) within 24h of stroke onset, followed by aspirin or clopidogrel alone from day 22. The primary endpoint is the percentage of patients who develop END within 7 days of stroke onset (defined as an increase in the NIHSS score ≥2 points) and recurrent stroke within 30 days. The total sample sizes will be 138 for the intervention group and 277 for the control group. A historical control group will be drawn from previous prospective observation studies.

Ethics and dissemination:

The protocol of this study has been approved by the Institutional Review Board of Chang Gung Memorial Hospital (202001386A3). All participants will have to sign and date an informed consent form. The findings arising from this study will be disseminated in peer-reviewed journals and academic conferences.

Trial registration number: ClinicalTrials.gov Identifier: NCT04824911

Keywords: Statin, antiplatelet therapy, early neurological deterioration, recurrent stroke, branch atheromatous disease

Strengths and limitations of this study

1. This will be the first trial to evaluate the effectiveness of dual antiplatelet therapy and high-intensity statins for the prevention of early neurological deterioration and recurrent stroke in patients with acute ischemic stroke from branch atheromatous disease.
2. This trial will recruit patients with National Institutes of Health Stroke Scale scores of 1-8, which are more severe than current guideline suggestion of scores ≦3 for mild stroke with dual antiplatelet therapy.
3. A randomized controlled study with a parallel control arm receiving single antiplatelet treatment for mild stroke is against the latest guidelines so it's inevitable to conduct this trial with a historical control group.
4. The use of a historical control group has the inherent drawbacks of nonrandomization and nonblinding so we cannot exclude the possibility of selection, performance, detection and attrition bias.
5. Because dual antiplatelet therapy and high-intensity statin treatment are administered simultaneously, it's unable to know each treatment effect.

1. Introduction

Small-vessel occlusion is the most common stroke subtype in Asians; it is caused by the occlusion of deep perforating arteries, mainly by the underlying pathologies of lipohyalinosis or cerebral amyloid angiopathy.[1 2] Branch atheromatous disease (BAD) has also been reported to contribute to small-vessel occlusion in cases of occlusion or stenosis that occur at the origin of large caliber penetrating arteries, due to microatheromas or junctional atherosclerotic plaques.[3] BAD is associated with an increased possibility of early neurological deterioration (END) and recurrent stroke, especially progressive motor deficits, compared with infarction due to hypertensive arteriopathy.[4-6] It has been proposed that BAD should be classified as large artery atherosclerosis rather than small vessel occlusion.[7]

Following acute ischemic stroke, single antiplatelet agents, such as aspirin or clopidogrel, are the mainstay treatment for recurrent stroke prevention. However, the modest effects of single antiplatelet therapy led to the study of combination antiplatelet therapy for the prevention of recurrent stroke. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) and the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trials showed that dual antiplatelet therapy (DAPT) might be beneficial for reducing the probability of ischemic events in patients with high-risk transient ischemic attack (TIA) or minor stroke.[8 9] However, these studies included all non-embolic ischemic stroke types. Some studies also showed that DAPT reduced the possibility of END.[10 11] A retrospective observation study showed that DAPT was beneficial for the primary outcomes of stroke recurrence, myocardial infarction, and all-cause death in patients with large atherosclerotic stroke.[12]

For patients with acute ischemic stroke, the guidelines suggest starting or continuing statin treatment as soon as oral medications can be used safely.[13] Current guidelines also recommend high- or moderate-intensity statin therapy, independent of the baseline low-density lipoprotein cholesterol (LDL-C), to reduce the risk of stroke and cardiovascular events for patients with TIA or ischemic stroke of atherosclerotic origin.[14] High-dose statin treatment in the acute phase of ischemic stroke and TIA significantly reduced National Institutes of Health Stroke Scale (NIHSS) scores and improved

short-term functional outcomes without increasing related adverse events[15]; it also effectively stabilized symptomatic intracranial atherosclerotic plaques as documented by high-resolution MRI.[16]

DAPT and high-intensity statins are the mainstay treatments for intracranial atherosclerosis (ICAS).[17] As BAD and ICAS share the same pathology as atherosclerosis, we postulate that early intensive medical treatment with DAPT and high-intensity statins may prevent early neurological deterioration and recurrent stroke. This study aims to evaluate whether intensive medical therapy with aspirin, clopidogrel and high-intensity statins, can prevent END and recurrent stroke in acute small subcortical infarction caused by BAD.

2. Methods

2.1 Study Design

In this prospective, single-center, open-label, non-randomized, single-arm, historically controlled study, we will compare early intensive treatment for BAD initiated within 24h of stroke onset, using dual antiplatelet therapy (aspirin plus clopidogrel) and high-intensity statin treatment, with a historical control group of BAD patients treated with single antiplatelet therapy, without high-intensity statin treatment.[18 19] The study will be conducted in Chang Gung Memorial Hospital at Chiayi, Taiwan from March 2021 to Feb 2023.

2.2 Study population

Patients are eligible to participate if they meet the following inclusion criteria: (1) have a clinical diagnosis of ischemic stroke with an NIHSS score of 1−8 (2) have an ischemic lesion on diffuse-weighted imaging (DWI) located in the striatocapsular territory or brain stem areas, with an axial diameter ≤20mm (3) have BAD, defined by a visible ischemic lesion in three or more axial cuts on DWI in the lenticulostriate territory or infarcts that extend from the basal surface of the pons (4) could receive intensive medical treatment within 24h of stroke onset. Patients with >50% stenosis of the relevant arteries on magnetic resonance angiography (MRA), including intra- or extra-cranial internal carotid artery, middle cerebral artery or basilar artery, will be

excluded. We will also exclude patients at high risk of cardioembolic stroke, such as those with atrial fibrillation or heart failure. Full details of the inclusion and exclusion criteria are listed in Table 1.

A historical control group will be drawn from our prospective observation studies, which have been executed between January 2011 and December 2020, and aimed to evaluate and predict END or atrial fibrillation.[18 19] Patients will be selected if they fulfill the following inclusion criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment. Patients in the historical control group will have received statin treatment once their total cholesterol was ≥160mg/dl or their LDL-C was ≥100mg/dl. High-intensity statin treatment includes atorvastatin 40–80mg or rosuvastatin 20–40mg daily.[20] All clinical information and outcomes have been prospectively recorded.

2.3 Trial intervention

Dual antiplatelet and high-intensity statin treatment will be administered within 24h of stroke onset (Figure 1). Dual antiplatelet treatment includes aspirin (300mg loading and 100mg/day) and clopidogrel (300mg loading and 75mg/day) and high-intensity statins includes atorvastatin 40-80mg/day or rosuvastatin 20mg/day. Patients will take aspirin and clopidogrel for 21 days and then just take aspirin or clopidogrel alone. High-intensity statins will be maintained for 90 days but a decreased dose is allowed if any side effects occur, including elevated liver functions, elevated creatine-phospho-kinase (CPK) and myalgia or at the judgment of the treating physician. We will follow up with alanine aminotransferase (ALT) and CPK 14 days after treatment and will follow up with ALT, CPK and LDL-C 90 days after treatment. Patients with atherosclerotic plaques in the first MRI will keep high-intensity statin treatment for 6 months.

Neurological deficits will be evaluated by a stroke study nurse using the NIHSS, at the 1st, 2nd, 3rd, 7th and 90th day. As END in lacunar infarction is mainly associated with motor deficits, END is defined as an NIHSS score increase ≥2 within 7 days of stroke onset.[21] Clinical outcomes at admission and at 90 days will be evaluated using the modified Rankin Scale (mRS). A good

outcome is defined as an mRS score ≤1. Mortality at 3 months and any hemorrhagic complications will also be recorded. All examinations will be performed after obtaining written informed consent from the patients or the appropriate family members.

Patients with visible atheromatous plaques in the parental artery in the initial MRI will receive a follow-up MRI 6 months later to see the interval changes in atheromatous plaques.

2.4 Study Outcomes

The primary outcome will be the percentage of patients with early neurological deterioration within 7 days and recurrent ischemic stroke within 30 days. Secondary outcomes will include: (1) the percentage of patients with favorable functional recovery, defined as an mRS ≤1 at the 90th day, (2) the percentage of patients with new clinical vascular events within 90 days, including ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction and vascular death, (3) changes in atherosclerotic plaques, which will be measured by high-resolution MRI at the start of the study and after 6 months, (4) the number of moderate to severe bleeding events as defined by the GUSTO classification,[22] and (5) the total mortality rate.

2.5 Sample Size

In single subcortical infarction, END was reported to occur frequently in BAD with an incidence of 27% in our previous cohort and 33.8- 40% in other studies.[10 23] The END rate may decrease to 9.7% in patients with BAD who underwent combination antiplatelet therapy with cilostazol.[10] The total sample sizes will be 138 for the intervention group and 277 for the control group. The estimated END rate is 27% for the control group and 15% for the intervention group, with 80% power and a two-sided alpha of 0.05. The intent-to-treat (ITT) principle will be applied to the primary outcome analysis, and the sample size was therefore inflated to safeguard against 5% lost-to-follow-up in the actual treatment groups, which could dilute the effect size.

2.6 **Statistical analysis**

Statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS) statistical software (version 25, Chicago, IL, USA). The Kolmogorov-Smirnov test will

be used to examine the normality of continuous variables. The Mann-Whitney U test and Student's t-test will be used to test for differences between the two groups, as appropriate. Categorical data will be analyzed using the Chi-squared test. A propensity score matching analysis will be used to measure and balance pre-determined covariates between two groups. A logistic regression model will be used to test independent variables for the measured outcomes. Variables showing a p value of <0.1 for univariate analysis will be entered into the multivariate logistic analysis using the forward selection method. All tests will be two-tailed, and a p value <0.05 is considered to indicate a statistically significant difference.

2.7 Data management

All the completed documents and the informed consent forms will be stored in a secured facility, under lock and key. The database for clinical data will be created using Access software and the access will be limited to principal investigators. A study steering committee will be established to ensure that the study conducted to the required standards. The clinical research assistant will verify all consent forms, compliance with study protocol and procedures, and data quality. The research team will make half-yearly reports to the study steering committee. All the records and documents will be kept for 7 years after the completion of the study.

2.8 Adverse events

Any adverse events that occur during the conduct of the study will be reported to the Domain Specific Research Board (DSRB) according to the local institutional policy. Interim analyses will be conducted by the study steering committee to monitor the accumulating data and to decide continuing or stopping the trial.

2.9 Patient and public involvement:

Patients and members from stroke associations participated in the preparation and formulation of this proposal. Patients with acute ischemic stroke from BAD will be involved in the trial. The associations will be involved in plans to disseminate the study results to their members and wider patient communities.

2.10 Ethics and dissemination:

The protocol of this study has been approved by the Institutional Review Board of Chang Gung Memorial Hospital (202001386A3). The study is registered on ClinicalTrials.gov (NCT04824911). All participants will have to sign and date an informed consent form. The findings arising from this study will be disseminated in peer-reviewed journals and academic conferences. The datasets during the current study are available from the corresponding author on reasonable request.

Author contributions

YCH and JTY conceptualized and designed the initial protocol. JDL, LCL, HHW and YHT amended the initial protocol. YCH drafted the manuscript and received the fund. All authors read and approved of the protocol prior to submission.

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Competing interests

None declared.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Figure 1. A schematic diagram of the treatment schedule and study design.

In the intervention group, patients will take aspirin (300mg loading and 100mg/day), clopidogrel (300mg loading and 75mg/day) and high-intensity statins (atorvastatin 40-80mg/day or rosuvastatin 20mg/day) within 24h of stroke onset, followed by aspirin or clopidogrel alone from day 22. High-intensity statins includes atorvastatin 40-80mg/day or rosuvastatin 20mg/day. In the historical control group, patients will be selected from previous prospective studies if they fulfill the following inclusion criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment.

Table 1. Inclusion and exclusion criteria (Issue date: 01 Sep 2020)

Inclusion Criteria

- Clinical diagnosis of ischemic stroke with a National Institute of Health Stroke Scale (NIHSS) score of 1–8
- An ischemic lesion on diffuse-weighted imaging located in the striatocapsular territory or brain stem areas, with an axial diameter ≤20mm.
- Branch atheromatous disease, defined by a visible ischemic lesion in three or more axial cuts on DWI in the lenticulostriate territory or infarcts that extend from the basal surface of the pons
- Ability to participate within 24h of the time of last known free of new ischemic symptoms.
- Head MRI ruling out hemorrhage or other pathologies, such as vascular malformation, tumor, or abscess, that could explain their symptoms or contraindicate therapy.
- Ability to tolerate high intensity medical therapy, including aspirin at a dose of 50–325mg/day, clopidogrel at 300mg loading and 75mg after day 2 and high-intensity statins (either atorvastatin 40-80mg or rosuvastatin 20mg/day).
- Pre-stroke mRS ≤1

Exclusion Criteria

- Age <18 years.
- At the judgment of the treating physician
- A candidate for thrombolysis, endarterectomy or endovascular intervention.
- Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to the index event.
- Patients with >50% stenosis of the relevant arteries as determined by magnetic resonance angiography (MRA), including the intra- or extra-cranial internal carotid artery, middle cerebral artery or basilar artery.
- Patients with a high risk of cardioembolic stroke, such as those with atrial fibrillation, acute myocardial infarction, severe heart failure or valvular heart disease.
- Those with other determined stroke etiologies, such as vasculitis, shock, antiphospholipid antibody syndrome etc.
- Gastrointestinal bleeding or major surgery within 3 months prior to the index event.
- History of nontraumatic intracranial hemorrhage.
- Clear indication for anticoagulation during the study period (deep venous thrombosis, pulmonary embolism or hypercoagulable state).
- Qualifying ischemic event induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with a life expectancy <3 months.
- Contraindication to clopidogrel, aspirin, atorvastatin or rosuvastatin
  - Known allergy to clopidogrel, aspirin atorvastatin or rosuvastatin
  - Severe renal (serum creatinine >2 mg/dL) or hepatic insufficiency (INR >1.2; ALT >40 U/L or any

resultant complication, such as variceal bleeding, encephalopathy, or jaundice)

- Hemostatic disorder or systemic bleeding in the past 3 months
- Current thrombocytopenia (platelet count <100 x10^9/L) or leukopenia (<2 x10^9/L)
- History of drug-induced hematologic or hepatic abnormalities

- Anticipated requirement for long-term (>7 day) non-study antiplatelet drugs (e.g., dipyridamole, ticagrelor, ticlopidine), or NSAIDs.
- Not willing or able to discontinue prohibited concomitant medications.
- Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
- Other neurological conditions that would complicate assessment of outcomes during follow-up.
- Ongoing treatment in another study of an investigational therapy, or treatment in such a study within the last 7 days.

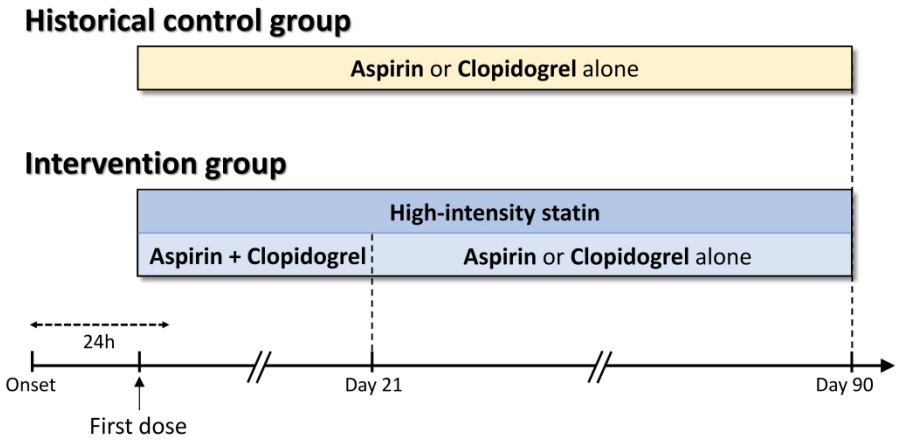

Figure 1/ A schematic diagram of the treatment schedule and study design

199x109mm (600 x 600 DPI)

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	10
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	8

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	14
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	5

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	8

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a