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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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4 **Statin and dual antiplatelet therapy for the prevention of early neurological**
5 **deterioration and recurrent stroke in branch atheromatous disease (SATBRAD) -**
6 **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.

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4 *Trial registration number:* ClinicalTrials.gov Identifier: NCT04824911
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8 Keywords: Statin, antiplatelet therapy, early neurological deterioration, recurrent stroke, branch
9 atheromatous disease
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15 **Strengths and limitations of this study**

16

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

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4 short-term functional outcomes without increasing related adverse events¹⁵; it also effectively
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6 stabilized symptomatic intracranial atherosclerotic plaques as documented by high-resolution MRI.¹⁶
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8 DAPT and high-intensity statins are the mainstay treatments for intracranial atherosclerosis
9
10 (ICAS).¹⁷ As BAD and ICAS share the same pathology as atherosclerosis, we postulate that early
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12 intensive medical treatment with DAPT and high-intensity statins may prevent early neurological
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14 deterioration and recurrent stroke. This study aims to evaluate whether intensive medical therapy with
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16 aspirin, clopidogrel and high-intensity statins, can prevent END and recurrent stroke in acute small
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18 subcortical infarction caused by BAD.
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24 **2. Methods**

25 **2.1 Study Design**

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28 In this prospective, non-randomized, historically controlled study, we will compare early
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30 intensive treatment for BAD initiated within 24h of stroke onset, using dual antiplatelet therapy
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32 (aspirin plus clopidogrel) and high-intensity statin treatment, with a historical control group of
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34 BAD patients treated with single antiplatelet therapy, without high-intensity statin treatment.^{18 19}
35
36 The study will be conducted in Chang Gung Memorial Hospital at Chiayi, Taiwan from March
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38 2021 to Feb 2023.
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42 **2.2 Study population**

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44 Patients are eligible to participate if they meet the following inclusion criteria: (1) have a
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46 clinical diagnosis of ischemic stroke with an NIHSS score of 1-8 (2) have an ischemic lesion on
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48 diffuse-weighted imaging located in the striatocapsular territory or brain stem areas, with an axial
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50 diameter ≤ 20 mm (3) have BAD, defined by a visible lesion in three or more axial MRI cuts in
51
52 the lenticulostriate territory or infarcts that extend from the basal surface of the pons (4) could
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54 receive intensive medical treatment within 24h of stroke onset. Patients with $>50\%$ stenosis of
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56 the relevant arteries on magnetic resonance angiography (MRA), including intra- or extra-cranial
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58 internal carotid artery, middle cerebral artery or basilar artery, will be excluded. We will also
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4 exclude patients at high risk of cardioembolic stroke, such as those with atrial fibrillation or heart
5 failure. Full details of the inclusion and exclusion criteria are listed in Table 1.
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8 A historical control group will be drawn from our prospective observation studies, which
9 have been executed between January 2011 and December 2020, and aimed to evaluate and predict
10 END or atrial fibrillation.^{18 19} Patients will be selected if they fulfill the following inclusion
11 criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment.
12 Patients in the historical control group will have received statin treatment once their total
13 cholesterol was ≥ 160 mg/dl or their LDL-C was ≥ 100 mg/dl. High-intensity statin treatment
14 includes atorvastatin 40–80mg or rosuvastatin 20–40mg daily.²⁰ All clinical information and
15 outcomes have been prospectively recorded.
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26 **2.3 Trial intervention**

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28 Dual antiplatelet and high-intensity statin treatment will be administered within 24h of stroke
29 onset (Figure 1). Dual antiplatelet treatment includes aspirin (300mg loading and 100mg/day) and
30 clopidogrel (300mg loading and 75mg/day) and high-intensity statins includes atorvastatin 40-
31 80mg/day or rosuvastatin 20mg/day. Patients will take aspirin and clopidogrel for 21 days and
32 then just take aspirin or clopidogrel alone. High-intensity statins will be maintained for 90 days
33 but a decreased dose is allowed if any side effects occur, including elevated liver functions,
34 elevated creatine-phospho-kinase (CPK) and myalgia or at the judgment of the treating physician.
35 We will follow up with alanine aminotransferase (ALT) and CPK 14 days after treatment and
36 will follow up with ALT, CPK and LDL-C 90 days after treatment. Patients with atherosclerotic
37 plaques in the first MRI will keep high-intensity statin treatment for 6 months.
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51 Neurological deficits will be evaluated by a stroke study nurse using the NIHSS, at the 1st,
52 2nd, 3rd, 7th and 90th day. As END in lacunar infarction is mainly associated with motor deficits,
53 END is defined as an NIHSS score increase ≥ 2 within 7 days of stroke onset.²¹ Clinical outcomes
54 at admission and at 90 days will be evaluated using the modified Rankin Scale (mRS). A good
55 outcome is defined as an mRS score ≤ 1 . Mortality at 3 months and any hemorrhagic complications
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4 will also be recorded. All examinations will be performed after obtaining written informed
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6 consent from the patients or the appropriate family members.
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8 Patients with visible atheromatous plaques in the parental artery in the initial MRI will
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10 receive a follow-up MRI 6 months later to see the interval changes in atheromatous plaques.
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12 13 **2.4 Study Outcomes**

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15 The primary outcome will be the percentage of patients with early neurological deterioration
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17 within 7 days and recurrent ischemic stroke within 30 days. Secondary outcomes will include: (1)
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19 the percentage of patients with favorable functional recovery, defined as an mRS ≤ 1 at the 90th
20
21 day, (2) the percentage of patients with new clinical vascular events within 90 days, including
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23 ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction and vascular death, (3) changes
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25 in atherosclerotic plaques, which will be measured by high-resolution MRI at the start of the study
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27 and after 6 months, (4) the number of moderate to severe bleeding events as defined by the
28
29 GUSTO classification,²² and (5) the total mortality rate.
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32 33 **2.5 Sample Size**

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35 In single subcortical infarction, END was reported to occur frequently in BAD with an incidence
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37 of 27% in our previous cohort and 33.8- 40% in other studies.^{10 23} The END rate may decrease to
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39 9.7% in patients with BAD who underwent combination antiplatelet therapy with cilostazol.¹⁰
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41 The total sample sizes will be 138 for the intervention group and 277 for the control group. The
42
43 estimated END rate is 27% for the control group and 15% for the intervention group, with 80%
44
45 power and a two-sided alpha of 0.05. The intent-to-treat (ITT) principle will be applied to the
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47 primary outcome analysis, and the sample size was therefore inflated to safeguard against 5%
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49 lost-to-follow-up in the actual treatment groups, which could dilute the effect size.
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52 53 **2.6 Statistical analysis**

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55 Statistical analyses will be performed using the Statistical Package for the Social Sciences
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57 (SPSS) statistical software (version 25, Chicago, IL, USA). The Kolmogorov-Smirnov test will
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59 be used to examine the normality of continuous variables. The Mann-Whitney U test and
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4 Student's t-test will be used to test for differences between the two groups, as appropriate.
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6 Categorical data will be analyzed using the Chi-squared test. A logistic regression model will be
7
8 used to adjust for baseline confounding factors and to test independent variables for the measured
9
10 outcomes. Variables showing a p value of <0.1 for univariate analysis will be entered into the
11
12 multivariate logistic analysis using the forward selection method. All tests will be two-tailed, and
13
14 a p value <0.05 is considered to indicate a statistically significant difference.
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17 **2.7 Data management**

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19 All the completed documents and the informed consent forms will be stored in a secured
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21 facility, under lock and key. The database for clinical data will be created using Access software
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23 and the access will be limited to principal investigators. A study steering committee will be
24
25 established to ensure that the study conducted to the required standards. The clinical research
26
27 assistant will verify all consent forms, compliance with study protocol and procedures, and data
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29 quality. The research team will make half-yearly reports to the study steering committee. All the
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31 records and documents will be kept for 7 years after the completion of the study.
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35 **2.8 Adverse events**

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37 Any adverse events that occur during the conduct of the study will be reported to the Domain
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39 Specific Research Board (DSRB) according to the local institutional policy. Interim analyses will
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41 be conducted by the study steering committee to monitor the accumulating data and to decide
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43 continuing or stopping the trial.
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46 **2.9 Patient and public involvement:**

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48 Patients and members from stroke associations participated in the preparation and formulation of
49
50 this proposal. Patients with acute ischemic stroke from BAD will be involved in the trial. The
51
52 associations will be involved in plans to disseminate the study results to their members and wider
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54 patient communities.
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57 **2.10 Ethics and dissemination:**

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59 The protocol of this study has been approved by the Institutional Review Board of Chang Gung
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4 Memorial Hospital (202001386A3). The study is registered on ClinicalTrials.gov
5 (NCT04824911). All participants will have to sign and date an informed consent form. The
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7 findings arising from this study will be disseminated in peer-reviewed journals and academic
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9 conferences. The datasets during the current study are available from the corresponding author
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11 on reasonable request.
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14 15 **3. Discussion**

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17 This will be the first trial to evaluate the effectiveness of DAPT and high-intensity statins for the
18 prevention of early neurological deterioration and recurrent stroke in patients with acute ischemic
19 stroke from BAD. With improvements in imaging, BAD is believed to be caused by atherosclerotic
20 plaques which obstruct the orifices of penetrators^{3 24} and it has been proposed that BAD should be
21 classified as large artery atherosclerosis rather than small vessel occlusion.⁷ DAPT and high-intensity
22 statins are the mainstay treatments for ICAS.¹⁷ Since ICAS and BAD share the same pathology of
23 atherosclerosis, the treatment of DAPT and high-intensity statins may also be effective for BAD. The
24 results of this trial will answer the question of whether optimal treatment for BAD is different from
25 other small subcortical infarction due to other pathologies.
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37 In this trial, we define BAD as a visible lesion in three or more axial MRI cuts in the
38 lenticulostriate territory or infarcts that extend from the basal surface of the pons.³ Although high-
39 resolution vessel-wall MRIs provide a direct way of detecting atherosclerotic plaques involving
40 perforators' parent arteries, the definition in this trial is a more practical way of stroke diagnosis. In
41 addition, microatheroma in the proximal penetrating artery are not visible in vessel-wall imaging and
42 need other advanced sequences to be detected, which may prohibit its widespread use.
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51 Our primary outcome is the percentage of patients with END within 7 days and recurrent ischemic
52 stroke within 30 days, which often lead to greater mortality and functional disability. It is therefore
53 worth evaluating any treatment which could lower END and recurrent stroke. In the secondary
54 outcomes, we will evaluate the changes in atherosclerotic plaques on parental arteries as measured by
55 an initial high-resolution MRI and another 6 months later. To the best of our knowledge, it will be the
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4 first trial to demonstrate plaque changes in BAD after medical treatment.
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6 There are several methodological limitations of this trial. The use of a historical control group has
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8 the inherent drawbacks of nonrandomization and nonblinding so we cannot exclude the possibility of
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10 selection, performance, detection and attrition bias. However, using a single antiplatelet agent for
11
12 milder stroke with an NIHSS score ≤ 3 is against the guidelines and there would be ethical issues if we
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14 conducted a randomized controlled study with a parallel control arm receiving single antiplatelet
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16 treatment. Therefore, our study still provides valuable information to increase understanding of the
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18 effectiveness of DAPT and statins in acute small subcortical infarction from BAD.
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24 **Author contributions**

25
26 YCH and JTY conceptualized and designed the initial protocol. JDL, LCL, HHW and YHT amended
27
28 the initial protocol. YCH drafted the manuscript and received the fund. All authors read and approved
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30 of the protocol prior to submission.
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36
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42 **Competing interests**

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44 None declared.
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49 **Provenance and peer review**

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51 Not commissioned; externally peer reviewed.
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4 **Figure 1.** A schematic diagram of the treatment schedule and study design.
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6 In the intervention group, patients will take aspirin (300mg loading and 100mg/day), clopidogrel
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8 (300mg loading and 75mg/day) and high-intensity statins (atorvastatin 40-80mg/day or rosuvastatin
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10 20mg/day) within 24h of stroke onset, followed by aspirin or clopidogrel alone from day 22. High-
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12 intensity statins includes atorvastatin 40-80mg/day or rosuvastatin 20mg/day. In the historical control
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14 group, patients will be selected from previous prospective studies if they fulfill the following inclusion
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16 criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment.
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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 ≤ 20 mm.
- 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 $<100 \times 10^9/L$) or leukopenia ($<2 \times 10^9/L$)
 - 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.
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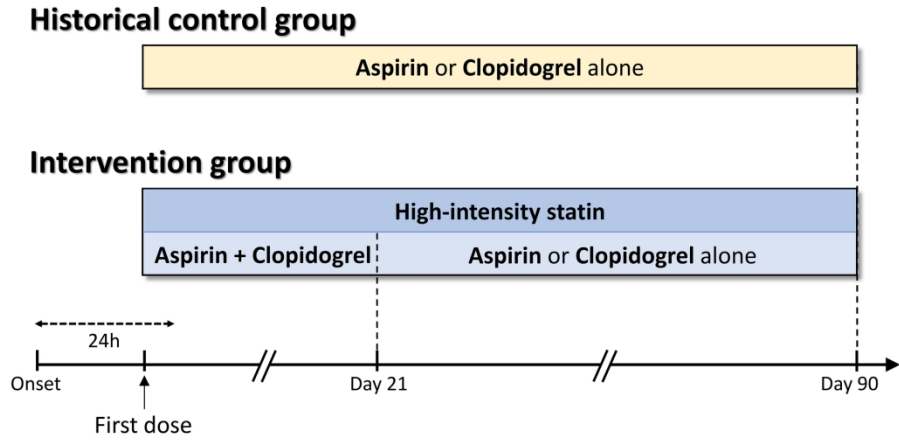


Figure 1/ A schematic diagram of the treatment schedule and study design

199x109mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	3
2			name of intended registry	
3				
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5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	3
7				
8	data set		Registration Data Set	
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12	Protocol version	#3	Date and version identifier	14
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	10
16			support	
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20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	10
21				
22	responsibilities:			
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24	contributorship			
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28	Roles and	#5b	Name and contact information for the trial sponsor	1
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30	responsibilities:			
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32	sponsor contact			
33				
34	information			
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36				
37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	10
39			design; collection, management, analysis, and	
40	responsibilities:		interpretation of data; writing of the report; and the	
41			decision to submit the report for publication, including	
42	sponsor and funder		whether they will have ultimate authority over any of	
43			these activities	
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52	Roles and	#5d	Composition, roles, and responsibilities of the	8
53			coordinating centre, steering committee, endpoint	
54	responsibilities:		adjudication committee, data management team, and	
55				
56	committees			
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1 other individuals or groups overseeing the trial, if
 2
 3 applicable (see Item 21a for data monitoring committee)
 4
 5

6 Introduction

7			
8			
9	Background and	#6a	Description of research question and justification for
10			
11	rationale		undertaking the trial, including summary of relevant
12			studies (published and unpublished) examining benefits
13			
14			and harms for each intervention
15			
16			
17			
18			
19	Background and	#6b	Explanation for choice of comparators
20			
21	rationale: choice of		
22			
23	comparators		
24			
25			
26	Objectives	#7	Specific objectives or hypotheses
27			
28			
29	Trial design	#8	Description of trial design including type of trial (eg,
30			parallel group, crossover, factorial, single group),
31			allocation ratio, and framework (eg, superiority,
32			equivalence, non-inferiority, exploratory)
33			
34			
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39	Methods:		
40			
41	Participants,		
42			
43	interventions, and		
44			
45	outcomes		
46			
47			
48			
49	Study setting	#9	Description of study settings (eg, community clinic,
50			academic hospital) and list of countries where data will be
51			collected. Reference to where list of study sites can be
52			obtained
53			
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	14
2				
3			applicable, eligibility criteria for study centres and	
4			individuals who will perform the interventions (eg,	
5			surgeons, psychotherapists)	
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6
12				
13	description		replication, including how and when they will be	
14			administered	
15				
16				
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18				
19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	6
20				
21	modifications		interventions for a given trial participant (eg, drug dose	
22			change in response to harms, participant request, or	
23			improving / worsening disease)	
24				
25				
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28				
29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	6
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32			tablet return; laboratory tests)	
33				
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35				
36	Interventions:	#11d	Relevant concomitant care and interventions that are	6
37				
38	concomitant care		permitted or prohibited during the trial	
39				
40				
41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	7
43				
44			specific measurement variable (eg, systolic blood	
45			pressure), analysis metric (eg, change from baseline, final	
46			value, time to event), method of aggregation (eg, median,	
47			proportion), and time point for each outcome. Explanation	
48			of the clinical relevance of chosen efficacy and harm	
49			outcomes is strongly recommended	
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	13
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
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8				
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10				
11	Sample size	#14	Estimated number of participants needed to achieve	7
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
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21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	7
22			reach target sample size	
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26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
31				
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36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	5
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	5
54	concealment		central telephone; sequentially numbered, opaque,	
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56				
57				
58	mechanism			
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sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#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): [#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

1	Data collection plan:	#18b	Plans to promote participant retention and complete	6
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
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11	Data management	#19	Plans for data entry, coding, security, and storage,	8
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	7
19			outcomes. Reference to where other details of the	
20			statistical analysis plan can be found, if not in the protocol	
21				
22				
23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	7
24	analyses		adjusted analyses)	
25				
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27				
28	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	7
29	population and		adherence (eg, as randomised analysis), and any	
30	missing data		statistical methods to handle missing data (eg, multiple	
31			imputation)	
32				
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36	Methods: Monitoring			
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38				
39	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	8
40	formal committee		summary of its role and reporting structure; statement of	
41			whether it is independent from the sponsor and	
42			competing interests; and reference to where further	
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1 details about its charter can be found, if not in the
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 3 protocol. Alternatively, an explanation of why a DMC is
 4
 5 not needed
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8	Data monitoring:	#21b	Description of any interim analyses and stopping	8
9				
10	interim analysis		guidelines, including who will have access to these	
11				
12			interim results and make the final decision to terminate	
13				
14			the trial	
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18	Harms	#22	Plans for collecting, assessing, reporting, and managing	8
19				
20			solicited and spontaneously reported adverse events and	
21				
22			other unintended effects of trial interventions or trial	
23				
24			conduct	
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28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	8
29				
30			any, and whether the process will be independent from	
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32			investigators and the sponsor	
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35	Ethics and			
36				
37	dissemination			
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41	Research ethics	#24	Plans for seeking research ethics committee / institutional	8
42				
43	approval		review board (REC / IRB) approval	
44				
45				
46	Protocol	#25	Plans for communicating important protocol modifications	8
47				
48	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
49				
50			relevant parties (eg, investigators, REC / IRBs, trial	
51				
52			participants, trial registries, journals, regulators)	
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	8
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
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7				
8				
9	Consent or assent:	#26b	Additional consent provisions for collection and use of	8
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
13				
14				
15				
16	Confidentiality	#27	How personal information about potential and enrolled	8
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	10
27	interests		investigators for the overall trial and each study site	
28				
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31	Data access	#29	Statement of who will have access to the final trial	8
32			dataset, and disclosure of contractual agreements that	
33			limit such access for investigators	
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	8
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
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46				
47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	8
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of 8
 2
 3 authorship professional writers
 4
 5

6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full 8
 7
 8 reproducible protocol, participant-level dataset, and statistical code
 9
 10 research
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 12

13 Appendices

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 15
 16
 17 Informed consent [#32](#) Model consent form and other related documentation n/a
 18
 19 materials given to participants and authorised surrogates
 20
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22
 23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of n/a
 24
 25 biological specimens for genetic or molecular analysis in
 26
 27 the current trial and for future use in ancillary studies, if
 28
 29 applicable
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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054381.R1
Article Type:	Protocol
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Secondary Subject Heading:	Medical management, Radiology and imaging
Keywords:	STROKE MEDICINE, VASCULAR MEDICINE, Magnetic resonance imaging < RADIOTHERAPY, Neuroradiology < NEUROLOGY, Stroke < NEUROLOGY

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4 1 **Statin and dual antiplatelet therapy for the prevention of early neurological**
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6 2 **deterioration and recurrent stroke in branch atheromatous disease (SATBRAD) :**
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8 3 **protocol for a prospective single-arm study using a historical control for**
9
10 4 **comparison**

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15 6 Yen-Chu Huang¹, MD; Jiann-Der Lee¹, MD; Hsu-Huei Weng², MD, MPH, PhD; Leng-Chieh Lin⁴,
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17 7 MD; Yuan-Hsiung Tsai², MD, PhD; Jen-Tsung Yang^{3*}, MD, PhD.
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59 29 Phone: +886 5 3621000 ext. 2759 Fax: +886 5 3623002
60

1 2 3 4 1 **Abstract**

5 6 2 **Introduction:**

7
8 3 Branch atheromatous disease (BAD) contributes to small-vessel occlusion in cases of occlusion
9
10 4 or stenosis of large caliber penetrating arteries, and it is associated with a higher possibility of early
11
12 5 neurological deterioration (END) and recurrent stroke in acute ischemic stroke. As the pathology of
13
14 6 BAD is due to atherosclerosis, we postulate that early intensive medical treatment with dual antiplatelet
15
16 7 therapy (DAPT) and high-intensity statins, may prevent END and recurrent stroke in acute small
17
18 8 subcortical infarction caused by BAD.
19

20 21 22 9 **Methods and analysis:**

23
24 10 In this prospective, single-center, open-label, non-randomized, single-arm study using a historical
25
26 11 control, we will compare early DAPT and high-intensity statin treatment with a historical control group
27
28 12 of BAD patients who were treated with single antiplatelet therapy without high-intensity statin
29
30 13 treatment. Patients will be eligible for enrollment if they are admitted for acute ischemic stroke within
31
32 14 24h, have a National Institutes of Health Stroke Scale (NIHSS) score of 1-8 and are diagnosed with
33
34 15 BAD by MRI. Patients will take aspirin, clopidogrel and high-intensity statins (atorvastatin or
35
36 16 rosuvastatin) within 24h of stroke onset, followed by aspirin or clopidogrel alone from day 22. The
37
38 17 primary endpoint is the percentage of patients who develop END within 7 days of stroke onset (defined
39
40 18 as an increase in the NIHSS score ≥ 2 points) and recurrent stroke within 30 days. The total sample
41
42 19 sizes will be 138 for the intervention group and 277 for the control group. A historical control group
43
44 20 will be drawn from previous prospective observation studies.
45
46

47 48 49 21 **Ethics and dissemination:**

50
51 22 The protocol of this study has been approved by the Institutional Review Board of Chang Gung
52
53 23 Memorial Hospital (202001386A3). All participants will have to sign and date an informed consent
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55 24 form. The findings arising from this study will be disseminated in peer-reviewed journals and academic
56
57 25 conferences.
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4 1 *Trial registration number:* ClinicalTrials.gov Identifier: NCT04824911

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7
8 3 Keywords: Statin, antiplatelet therapy, early neurological deterioration, recurrent stroke, branch
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10 4 atheromatous disease

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14 15 6 **Strengths and limitations of this study**

- 16
17 7 1. This will be the first trial to evaluate the effectiveness of dual antiplatelet therapy and high-
18
19 8 intensity statins for the prevention of early neurological deterioration and recurrent stroke in
20
21 9 patients with acute ischemic stroke from branch atheromatous disease.
22
23
24 10 2. This trial will recruit patients with National Institutes of Health Stroke Scale scores of 1-8,
25
26 11 which are more severe than current guideline suggestion of scores ≤ 3 for mild stroke with dual
27
28 12 antiplatelet therapy.
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31 13 3. A randomized controlled study with a parallel control arm receiving single antiplatelet treatment
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33 14 for mild stroke is against the latest guidelines so it's inevitable to conduct this trial with a
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35 15 historical control group.
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37 16 4. The use of a historical control group has the inherent drawbacks of nonrandomization and
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39 17 nonblinding so we cannot exclude the possibility of selection, performance, detection and
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41 18 attrition bias.
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44 19 5. Because dual antiplatelet therapy and high-intensity statin treatment are administered
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46 20 simultaneously, it's unable to know each treatment effect.
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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

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4 1 short-term functional outcomes without increasing related adverse events¹⁵; it also effectively
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6 2 stabilized symptomatic intracranial atherosclerotic plaques as documented by high-resolution MRI.¹⁶
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8 3 DAPT and high-intensity statins are the mainstay treatments for intracranial atherosclerosis
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10 4 (ICAS).¹⁷ As BAD and ICAS share the same pathology as atherosclerosis, we postulate that early
11
12 5 intensive medical treatment with DAPT and high-intensity statins may prevent early neurological
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14 6 deterioration and recurrent stroke. This study aims to evaluate whether intensive medical therapy with
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16 7 aspirin, clopidogrel and high-intensity statins, can prevent END and recurrent stroke in acute small
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18 8 subcortical infarction caused by BAD.
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24 10 **2. Methods**

26 11 **2.1 Study Design**

28 12 In this prospective, single-center, open-label, non-randomized, single-arm, historically
29
30 13 controlled study, we will compare early intensive treatment for BAD initiated within 24h of stroke
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32 14 onset, using dual antiplatelet therapy (aspirin plus clopidogrel) and high-intensity statin treatment,
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34 15 with a historical control group of BAD patients treated with single antiplatelet therapy, without
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36 16 high-intensity statin treatment.^{18 19} The study will be conducted in Chang Gung Memorial
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38 17 Hospital at Chiayi, Taiwan from March 2021 to Feb 2023.
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42 18 **2.2 Study population**

44 19 Patients are eligible to participate if they meet the following inclusion criteria: (1) have a
45
46 20 clinical diagnosis of ischemic stroke with an NIHSS score of 1–8 (2) have an ischemic lesion on
47
48 21 diffuse-weighted imaging (DWI) located in the striatocapsular territory or brain stem areas, with
49
50 22 an axial diameter ≤ 20 mm (3) have BAD, defined by a visible ischemic lesion in three or more
51
52 23 axial cuts on DWI in the lenticulostriate territory or infarcts that extend from the basal surface of
53
54 24 the pons (4) could receive intensive medical treatment within 24h of stroke onset. Patients with
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56 25 $>50\%$ stenosis of the relevant arteries on magnetic resonance angiography (MRA), including
57
58 26 intra- or extra-cranial internal carotid artery, middle cerebral artery or basilar artery, will be
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4 1 excluded. We will also exclude patients at high risk of cardioembolic stroke, such as those with
5
6 2 atrial fibrillation or heart failure. Full details of the inclusion and exclusion criteria are listed in
7
8 3 Table 1.
9

10 4 A historical control group will be drawn from our prospective observation studies, which
11
12
13 5 have been executed between January 2011 and December 2020, and aimed to evaluate and predict
14
15 6 END or atrial fibrillation.^{18 19} Patients will be selected if they fulfill the following inclusion
16
17 7 criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment.
18
19 8 Patients in the historical control group will have received statin treatment once their total
20
21 cholesterol was ≥ 160 mg/dl or their LDL-C was ≥ 100 mg/dl. High-intensity statin treatment
22 9 includes atorvastatin 40–80mg or rosuvastatin 20–40mg daily.²⁰ All clinical information and
23
24 10 outcomes have been prospectively recorded.
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26 11

28 12 **2.3 Trial intervention**

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31 13 Dual antiplatelet and high-intensity statin treatment will be administered within 24h of stroke
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33 14 onset (Figure 1). Dual antiplatelet treatment includes aspirin (300mg loading and 100mg/day) and
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35 15 clopidogrel (300mg loading and 75mg/day) and high-intensity statins includes atorvastatin 40-
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37 16 80mg/day or rosuvastatin 20mg/day. Patients will take aspirin and clopidogrel for 21 days and
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39 then just take aspirin or clopidogrel alone. High-intensity statins will be maintained for 90 days
40 17
41 but a decreased dose is allowed if any side effects occur, including elevated liver functions,
42 18
43 elevated creatine-phospho-kinase (CPK) and myalgia or at the judgment of the treating physician.
44 19
45 We will follow up with alanine aminotransferase (ALT) and CPK 14 days after treatment and
46 20
47 will follow up with ALT, CPK and LDL-C 90 days after treatment. Patients with atherosclerotic
48 21
49 plaques in the first MRI will keep high-intensity statin treatment for 6 months.
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51 22

52
53 23 Neurological deficits will be evaluated by a stroke study nurse using the NIHSS, at the 1st,
54
55 24 2nd, 3rd, 7th and 90th day. As END in lacunar infarction is mainly associated with motor deficits,
56
57 END is defined as an NIHSS score increase ≥ 2 within 7 days of stroke onset.²¹ Clinical outcomes
58 25
59 at admission and at 90 days will be evaluated using the modified Rankin Scale (mRS). A good
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4 1 outcome is defined as an mRS score ≤ 1 . Mortality at 3 months and any hemorrhagic complications
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6 2 will also be recorded. All examinations will be performed after obtaining written informed
7
8 3 consent from the patients or the appropriate family members.
9

10 4 Patients with visible atheromatous plaques in the parental artery in the initial MRI will
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12 receive a follow-up MRI 6 months later to see the interval changes in atheromatous plaques.
13 5
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15 6 **2.4 Study Outcomes**

16
17 7 The primary outcome will be the percentage of patients with early neurological deterioration
18
19 within 7 days and recurrent ischemic stroke within 30 days. Secondary outcomes will include: (1)
20 8 the percentage of patients with favorable functional recovery, defined as an mRS ≤ 1 at the 90th
21
22 9 day, (2) the percentage of patients with new clinical vascular events within 90 days, including
23
24 10 ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction and vascular death, (3) changes
25
26 11 in atherosclerotic plaques, which will be measured by high-resolution MRI at the start of the study
27
28 12 and after 6 months, (4) the number of moderate to severe bleeding events as defined by the
29
30 GUSTO classification,²² and (5) the total mortality rate.
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32
33 14

35 15 **2.5 Sample Size**

36
37 16 In single subcortical infarction, END was reported to occur frequently in BAD with an incidence
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39 of 27% in our previous cohort and 33.8- 40% in other studies.^{10 23} The END rate may decrease to
40 17
41 9.7% in patients with BAD who underwent combination antiplatelet therapy with cilostazol.¹⁰
42 18
43 The total sample sizes will be 138 for the intervention group and 277 for the control group. The
44 19
45 estimated END rate is 27% for the control group and 15% for the intervention group, with 80%
46 20
47 power and a two-sided alpha of 0.05. The intent-to-treat (ITT) principle will be applied to the
48
49 21 primary outcome analysis, and the sample size was therefore inflated to safeguard against 5%
50
51 22 lost-to-follow-up in the actual treatment groups, which could dilute the effect size.
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53 23
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55 24 **2.6 Statistical analysis**

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57 25 Statistical analyses will be performed using the Statistical Package for the Social Sciences
58
59 (SPSS) statistical software (version 25, Chicago, IL, USA). The Kolmogorov-Smirnov test will
60 26

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4 1 be used to examine the normality of continuous variables. The Mann-Whitney U test and
5
6 2 Student's t-test will be used to test for differences between the two groups, as appropriate.
7
8 3 Categorical data will be analyzed using the Chi-squared test. A propensity score matching
9
10 4 analysis will be used to measure and balance pre-determined covariates between two groups. A
11
12 5 logistic regression model will be used to test independent variables for the measured outcomes.
13
14 6 Variables showing a p value of <0.1 for univariate analysis will be entered into the multivariate
15
16 7 logistic analysis using the forward selection method. All tests will be two-tailed, and a p value
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18 8 <0.05 is considered to indicate a statistically significant difference.
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21 9 **2.7 Data management**

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23
24 10 All the completed documents and the informed consent forms will be stored in a secured
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26 11 facility, under lock and key. The database for clinical data will be created using Access software
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28 12 and the access will be limited to principal investigators. A study steering committee will be
29
30 13 established to ensure that the study conducted to the required standards. The clinical research
31
32 14 assistant will verify all consent forms, compliance with study protocol and procedures, and data
33
34 15 quality. The research team will make half-yearly reports to the study steering committee. All the
35
36 16 records and documents will be kept for 7 years after the completion of the study.
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40 17 **2.8 Adverse events**

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42 18 Any adverse events that occur during the conduct of the study will be reported to the Domain
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44 19 Specific Research Board (DSRB) according to the local institutional policy. Interim analyses will
45
46 20 be conducted by the study steering committee to monitor the accumulating data and to decide
47
48 21 continuing or stopping the trial.
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51 22 **2.9 Patient and public involvement:**

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53 23 Patients and members from stroke associations participated in the preparation and formulation of
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55 24 this proposal. Patients with acute ischemic stroke from BAD will be involved in the trial. The
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57 25 associations will be involved in plans to disseminate the study results to their members and wider
58
59 26 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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1 **Figure 1.** A schematic diagram of the treatment schedule and study design.

2 In the intervention group, patients will take aspirin (300mg loading and 100mg/day), clopidogrel
3 (300mg loading and 75mg/day) and high-intensity statins (atorvastatin 40-80mg/day or rosuvastatin
4 20mg/day) within 24h of stroke onset, followed by aspirin or clopidogrel alone from day 22. High-
5 intensity statins includes atorvastatin 40-80mg/day or rosuvastatin 20mg/day. In the historical control
6 group, patients will be selected from previous prospective studies if they fulfill the following inclusion
7 criteria: took aspirin or clopidogrel alone and did not receive high-intensity statin treatment.

For peer review only

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4 **Table 1.** Inclusion and exclusion criteria (Issue date: 01 Sep 2020)
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7 **Inclusion Criteria**

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- 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 ≤ 20 mm.
 - 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

28 **Exclusion Criteria**

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- 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 $<100 \times 10^9/L$) or leukopenia ($<2 \times 10^9/L$)
 - 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.
-

Historical control group



Intervention group

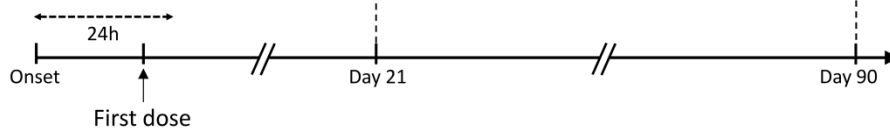
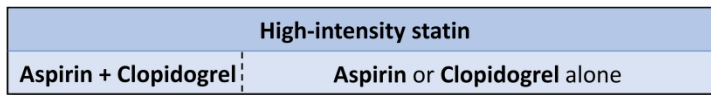


Figure 1/ A schematic diagram of the treatment schedule and study design

199x109mm (600 x 600 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	3
2			name of intended registry	
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6	Trial registration:	#2b	All items from the World Health Organization Trial	3
7	data set		Registration Data Set	
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11	Protocol version	#3	Date and version identifier	14
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15	Funding	#4	Sources and types of financial, material, and other	10
16			support	
17				
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20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	10
21	responsibilities:			
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23	contributorship			
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28	Roles and	#5b	Name and contact information for the trial sponsor	1
29	responsibilities:			
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31	sponsor contact			
32	information			
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38	Roles and	#5c	Role of study sponsor and funders, if any, in study	10
39	responsibilities:		design; collection, management, analysis, and	
40			interpretation of data; writing of the report; and the	
41	sponsor and funder		decision to submit the report for publication, including	
42			whether they will have ultimate authority over any of	
43			these activities	
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52	Roles and	#5d	Composition, roles, and responsibilities of the	8
53	responsibilities:		coordinating centre, steering committee, endpoint	
54			adjudication committee, data management team, and	
55	committees			
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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

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	14
2			applicable, eligibility criteria for study centres and	
3			individuals who will perform the interventions (eg,	
4			surgeons, psychotherapists)	
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6
12			replication, including how and when they will be	
13	description		administered	
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19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	6
20			interventions for a given trial participant (eg, drug dose	
21	modifications		change in response to harms, participant request, or	
22			improving / worsening disease)	
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29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	6
30			and any procedures for monitoring adherence (eg, drug	
31	adherence		tablet return; laboratory tests)	
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36	Interventions:	#11d	Relevant concomitant care and interventions that are	6
37			permitted or prohibited during the trial	
38	concomitant care			
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42	Outcomes	#12	Primary, secondary, and other outcomes, including the	7
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline, final	
45			value, time to event), method of aggregation (eg, median,	
46			proportion), and time point for each outcome. Explanation	
47			of the clinical relevance of chosen efficacy and harm	
48			outcomes is strongly recommended	
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	13
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
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11	Sample size	#14	Estimated number of participants needed to achieve	7
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
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21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	7
22			reach target sample size	
23				
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26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
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36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	5
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	5
54	concealment		central telephone; sequentially numbered, opaque,	
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58	mechanism			
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sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#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): [#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

1	Data collection plan:	#18b	Plans to promote participant retention and complete	6
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
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11	Data management	#19	Plans for data entry, coding, security, and storage,	8
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	7
19			outcomes. Reference to where other details of the	
20			statistical analysis plan can be found, if not in the protocol	
21				
22				
23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	7
24	analyses		adjusted analyses)	
25				
26				
27				
28	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	7
29	population and		adherence (eg, as randomised analysis), and any	
30	missing data		statistical methods to handle missing data (eg, multiple	
31			imputation)	
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37	Methods: Monitoring			
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49	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	8
50	formal committee		summary of its role and reporting structure; statement of	
51			whether it is independent from the sponsor and	
52			competing interests; and reference to where further	
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1 details about its charter can be found, if not in the
 2 protocol. Alternatively, an explanation of why a DMC is
 3 not needed
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8	Data monitoring:	#21b	Description of any interim analyses and stopping	8
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
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18	Harms	#22	Plans for collecting, assessing, reporting, and managing	8
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
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28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	8
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
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35	Ethics and			
36	dissemination			
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41	Research ethics	#24	Plans for seeking research ethics committee / institutional	8
42	approval		review board (REC / IRB) approval	
43				
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46	Protocol	#25	Plans for communicating important protocol modifications	8
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	8
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
4				
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9	Consent or assent:	#26b	Additional consent provisions for collection and use of	8
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
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16	Confidentiality	#27	How personal information about potential and enrolled	8
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	10
27	interests		investigators for the overall trial and each study site	
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32	Data access	#29	Statement of who will have access to the final trial	8
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	8
40	trial care		compensation to those who suffer harm from trial	
41			participation	
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47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	8
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of 8
 2 authorship professional writers
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 4
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6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full 8
 7 reproducible protocol, participant-level dataset, and statistical code
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 11 research
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14 Appendices

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 16
 17 Informed consent [#32](#) Model consent form and other related documentation n/a
 18 materials given to participants and authorised surrogates
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 23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of n/a
 24 biological specimens for genetic or molecular analysis in
 25 the current trial and for future use in ancillary studies, if
 26
 27 applicable
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