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Supplementary File

Role of Common Antihypertensives in the Growth of Abdominal Aortic Aneurysm at the Presurgical Stage

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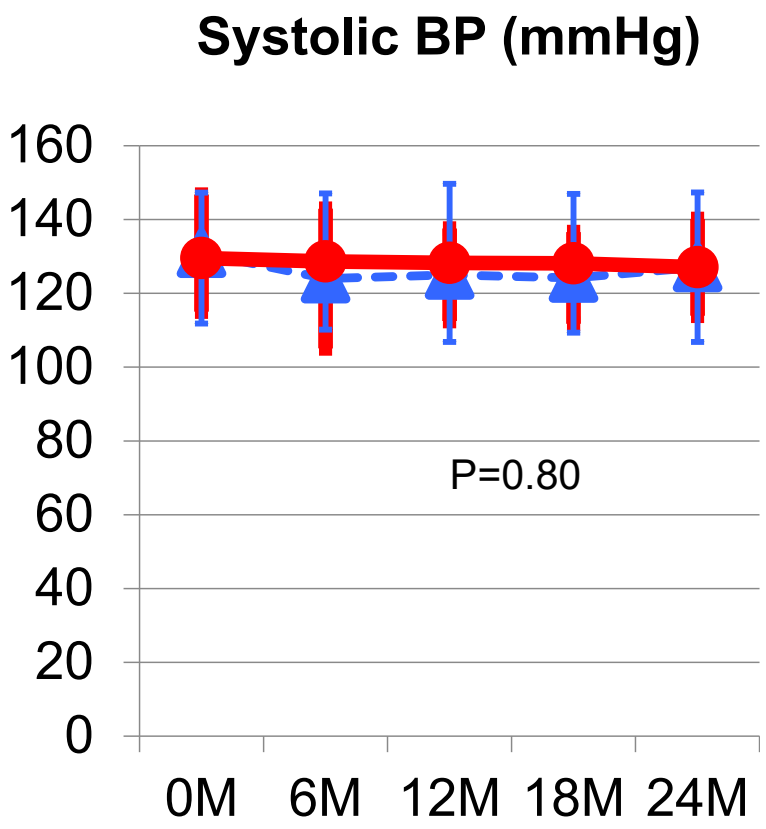
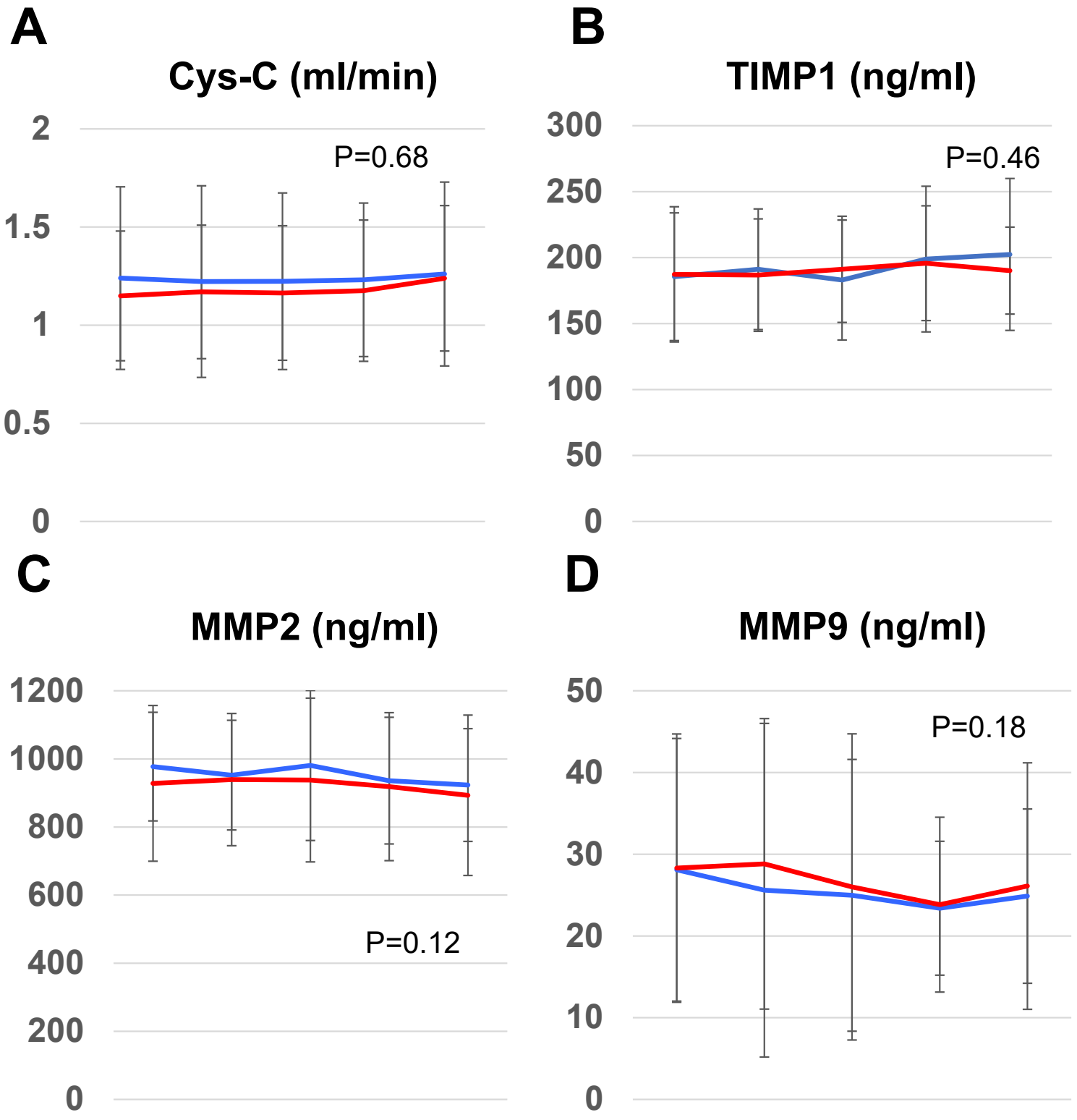


Supplementary Figure 1

Chronological changes in systolic blood pressure. There was no difference in the blood pressure control, indicating the impact of CAN (red) or AML(blue) on primary or secondary outcomes are independent of blood-pressure as a confounding factor. Values are mean±SD. P value <0.05 was considered significant.



Supplementary Figure 2

Circulating markers related to the matrix remodeling, both CAN (red line) and AML(blue line) had no significant effect during 2 years follow-up. The ANCOVA analysis was used for the assessment of the secondary outcomes. Values are mean ± SD All statistical tests were 2-sided, and a P value <0.05 was considered significant.

Parameter	Category	CAN (N=67)	AML (N=64)	P-value*	P-value#
Age					
	Min - Max	44 - 88	50 - 86		
	<75	31 (46%)	34 (53%)	0.486	0.433
	75-	36 (54%)	30 (47%)		
Sex				1	0.860
	Male	57 (85%)	56 (86%)		
	Female	10 (15%)	9 (14%)		
Smoke				0.562	0.529
	No	19 (28%)	18 (28%)		
	Yes	20 (30%)	25 (38%)		
	Past	28 (42%)	22 (34%)		
Statin				0.862	0.730
	No	32 (48%)	33 (51%)		
	Yes	35 (52%)	32 (49%)		
CKD				0.732	0.726
	No	34 (51%)	31 (48%)		
	Yes	33 (49%)	34 (52%)		

Suppelementary Table. Overview of Confounding Factors of Study Participants

Values are numbers (N), percentages (%) or ranges of age (year-old). *P-value: T-test, #P-value: Chi-square test. CAN= candesartan treated ; AML = amlodipine treated; CKD = chronic kidney disease

Study protocol: Effect of Antihypertensive Treatment on Aortic Aneurysm Control in Hypertensive Patients with Aortic Aneurysm Complications

1. Title of the study

AAA (aortic aneurismal remodeling by ARB) Study

2. Background

Abdominal aortic aneurysms with a maximum diameter of over 5 cm require surgery due to the high risk of rupture, but for aneurysms in the preliminary stage of size, blood pressure control with antihypertensive medication is generally considered to be the first choice, and it is believed that maintaining antihypertensive status can prevent aneurysm growth. However, it is not clear which antihypertensive is the most effective. However, the selection criteria for antihypertensive treatment of patients with unruptured aneurysms, including which antihypertensive agent is most effective, have yet to be determined. On the other hand, an animal study in mice reported in 2006 that an angiotensin II receptor blocker (ARB), an antihypertensive agent, suppressed aortic aneurysm growth by a mechanism independent of its antihypertensive effect (Science 2006). A large clinical study in Japan reported that an angiotensin II receptor blocker (ARB) suppressed aneurysm growth by an independent mechanism (Lancet 2007). Furthermore, a cohort study published in 2008 (NEJM2008) shows that ARBs inhibit aortic remodeling in pediatric patients with Marfan syndrome. Still, no clinical studies about abdominal aortic aneurysm remodeling have been reported on ARBs in adults.

3. Aim

The objective of the study is to compare the effect of candesartan (Blopress®) and amlodipine (Norvasc®) on the aortic aneurysmal enlargement and associated factors including various biomarkers (high sensitivity CRP, MDA-LDL, TIMP-1, MMP-2, 9) in the patients with preoperative or inoperable abdominal aneurysms with hypertension for two years.

4. Study groups

Nagoya University Hospital, Nagoya Daiichi Red Cross Hospital, Nagoya Daini Red Cross Hospital, and Saiseikai Kumamoto Hospital

5. Eligibility

A. Inclusion criteria

(1) Patients with aortic aneurysms in the preoperative stage (3.0 cm to <4.5 cm in static digital images in the transverse multi-slice plain CT)

(2) Age: 40 years or older

(3) Blood pressure level:

(a) Systolic blood pressure 120 mmHg or higher (untreated with antihypertensive drugs)

(b) No question (patients on antihypertensive treatment)

(4) Sex: male and postmenopausal female

(5) Patients with the written consent of their own free will

(6) Patients with an aortic aneurysm diameter that is equivalent to a surgical indication

Patients with aortic aneurysms considered surgically indicated but for which surgery was not indicated due to complications or other reasons, or patients who voluntarily refused surgical treatment and for whom written consent for this study was obtained of the patient's own free will. Patients with abdominal aortic aneurysms larger than 4.5 cm in diameter are also eligible for the study.

(7) Participants prescribed antihypertensive medications such as ARBs, ACE inhibitors, mineral corticoid receptor antagonists, and calcium channel blockers (CCBs) were allowed to enroll in the study with consent to change their oral medications according to the assignment.

(8) At each visit, blood pressure values were referred to as office blood pressure values. In case of concern regarding patients with white coat hypertension or masked hypertension, the attending physician referred to his/her home blood pressure during regular records to confirm their eligibility.

(9) The target value of antihypertensive should be set at a systolic blood pressure of 120 mmHg -135 mmHg. Therefore, patients who are untreated with antihypertensive agents and whose systolic blood pressure is less than 120 mmHg at entry should be excluded.

(10) Insufficient antihypertensive cases (systolic blood pressure >135 mmHg)

For the ARB group, antihypertensive agents other than CCB can be added; for the CCB group, antihypertensive agents other than ARB can be added. Study discontinuation could be determined by considering the priority for antihypertensive management by the attending physician.

B. Exclusion criteria

(1) Premenopausal women

(2) Patients with pregnancy

(3) Patients with a history of hypersensitivity to any component of the target drug

(4) Patients with coronary angina pectoris being treated with CCB

(5) Past medical history of malignancy within five years
(6) patients of end-stage renal diseases including hemodialysis
(7) Other patients were judged inappropriate for the subject by the study investigator, study co-principal investigator, or the patient's primary care physician.

C. Medication and blood pressure control

Patients were recruited between June 18th, 2009, and September 30th, 2013 on a consecutive basis, without pre-registration. The study was conducted for two years using the PROBE (Prospective Randomized Open Blinded End-Point) method, with a parallel group comparison of two actual drugs (candesartan and amlodipine).

Dosage, administration, and duration of study drug:

Candesartan (Blopress®) 2-12 mg/day, once daily after breakfast (CAN group)

Amlodipine (Norvasc®) 2.5-10 mg/day, once daily after breakfast (AML group)

Patients were assigned to each group by Stratified Randomization by use of the study website that automatically decided according to the adjustment factors (age, gender, smoking, statin use, CKD (eGFR less than 60 ml/min/1.72m2) at the time of patient registration.

Once agreed with the informed consent, patients were randomized to either the CAN or AML group. The target control range of the systolic blood pressure level was pre-specified between 120-135 mmHg to minimize the effect of blood pressure. Therefore, patients who are untreated with antihypertensive agents and whose systolic blood pressure is less than 120 mmHg at entry should be excluded. During the study, if the blood pressure control may turn insufficient (i.e., systolic blood pressure more than 135 mmHg), the addition of antihypertensive agents other than the study drugs including any renin-angiotensin-aldosterone blockers was permitted according to the attending doctor’s decision.

6. Primary and secondary endpoints

After two years of follow-up, the primary and secondary outcomes were assessed as follows.

(a) Primary endpoint

Change in abdominal aortic aneurysm diameter (% increase) measured by abdominal CT.

(b) Secondary endpoints

Incidences of surgical repair, cardiovascular events, and all cause death. Changes in biomarkers, and physiological indices.

7. Examination procedure

(a) Measurement of aneurysm diameter by plain and multi-slice CT, measured perpendicular to the central vessel line (baseline, 6, 12, 18, and 24 months). Static digital images in the transverse plane of the AAA were obtained at the point of maximal diameter. Each image was anonymized before measurement and transferred to the core laboratory for analysis in a blind manner.
(b) Blood pressure measurement (baseline, 6, 12, 18, and 24 months)
(c) Blood collection (15 ml per visit, 75 ml for the entire study) for measurement of biomarkers* (high sensitivity CRP, MDA-LDL, TIMP-1, MMP-2,9, Cystatin C, TGF-β1) (baseline, 6, 12, 18, and 24 months)
(d) Electrocardiogram (observation of changes in heart rate): (baseline, 6, 12, 18, and 24 months)
(f) Echocardiography (LVEF, LVDs, LVDd, LAD, IVSTd, PWTd, E/A, E/e', Dct): (baseline, 6, 12, 18, and 24 months)
(k) PWV (Pulse Wave Velocity)/ABI (Blood Pressure Ratio between upper arm and ankle) (optional item): (baseline, 6, 12, 18, and 24 months)
(k) Carotid artery ultrasound (optional): (baseline, 6, 12, 18, and 24 months)

8. Expected side effects
Hepatic dysfunction (candesartan: <0.1%, Norvasc: <0.1%), hypotension (candesartan: <0.1%, Norvasc: <0.1%), hypersensitivity to the ingredients of the target drug (candesartan: <0.1%, Norvasc: <0.1%)

9. Sample size setting
The target number of patients: Candesartan group: 100 cases, Amlodipine group: 100 cases.
The prevalence of abdominal aortic aneurysm (AAA) is low, ranging from 0.5% to 3.2% of the population, or approximately 3 cases per 100,000 people per year, which was mentioned in the Japanese guideline (JCS guideline version 2011). The number of AAA patients in the study group, namely Tokai and Kumamoto areas, out of a population of 3-4 million, is likely to be estimated at around 100-120. There were no reports on the effects of angiotensin II receptor inhibitors (including those other than candesartan) on patients with AAA when this study was designed; we set the target number of patients by referring to previously published clinical studies that have examined changes in AAA diameter using other agents. In a study (Aust. N.Z. J. Surg (1998) 68, 21-24), it was reported that beta-receptor blockers reduced abdominal aortic diameter in 112 patients with AAA, of which the rate of change in AAA diameter was 2.5 mm per year (95% CI 0.18-0.32 mm) for AAA of 3cm diameter group and 4.4 mm per year (95% CI 0.3-0.58 mm) for a 4 cm one. We thus assumed that the annual AAA augmentation rate is about 10%. In another prospective clinical study examining the impact of angiotensin II receptor inhibitor (losartan)

treatment intervention in patients with thoracic aortic aneurysms in Marfan syndrome (N Engl J Med 2008;358:2787-95), in a total of 83 patients with a median observation period of 26 months, the z-score, an index of change in aortic aneurysm diameter adjusted for patient-to-surface area and age, was reduced from 0.97±1.55 to -0.5±0.43 per year.

Assuming that candesartan might have a similar effect on AAA progression, with a change in AAA of -4 mm ± 0.05 mm in each group after 24 months of treatment, or assuming that losartan has the same inhibitory effect on AAA progression as it has on thoracic aneurysm enlargement assuming a risk rate of 5%, a power of 80%, and a dropout rate of 10%, the target number of patients to be enrolled to detect a significant difference between the two groups would require at least 100 patients in each group. Despite the estimated patient number based on the AAA prevalence around the study area (Tokai and Kumamoto area) being assumed to be 100-120, we decided the target number as 100 cases for each group, for total 200 cases to achieve more statistical significance.

References

Habashi JP, Judge DP, Holm TM, et al.: Losartan, An AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 2006; 312(5770): 117-21. 2.

Mochizuki S, Dahlof B, Shimizu M, et al.: Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): Lancet 2007; 369(9571): 1431-9. 3.

Brooke, B. S., Habashi, J. P., Judge, D. P. et al.: Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. NEJM 2008; 358(26): 2787-95.

Ishimaru S, Kato M, Kuribayashi S, Matsuo H, Miyata T, Nakajima Y, et al. Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection (JCS 2011) - Digest Version. Circulation Journal 2013; 77: 789-828

Englund R, Hudson P, Hanel K, Stanton A. Expansion rates of small abdominal aortic aneurysms. Aust N Z J Surg. 1998 Jan;68:21-24

eTable 3. Fillable Checklist*: CONSORT-Outcomes (for combined completion of CONSORT 2010 and CONSORT-Outcomes 2022 items)[a]

Section	Item No.	CONSORT 2010 Item	CONSORT-Outcomes 2022 item	Location Reported[b]
Title and abstract				
	1a	Identification as a randomized trial in the title	-	N/A
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	-	Abstract
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	-	Methods & Response to the Reviewers
	2b	Specific objectives or hypotheses	-	Methods & Response to the Reviewers
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	-	Methods & Response to the Reviewers
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-	N/A
Participants	4a	Eligibility criteria for participants	-	Methods & UMIN registry (#2216)
	4b	Settings and locations where the data were collected	-	Methods & UMIN registry (#2216)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered (for specific guidance see TIDieR checklist and guide)	-	Methods & UMIN registry (#2216)
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	-	Methods & UMIN registry (#2216)
	6a.1		Provide a rationale for the selection of the domain for the trial's primary outcome	Methods & Response to the Reviewers
	6a.2		Describe the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, mean,	Methods, UMIN registry (#2216) & Response to the Reviewers

Section	Item No.	CONSORT 2010 Item	CONSORT-Outcomes 2022 item	Location Reported[b]
			proportion), and the time point for each outcome	
	6a.3		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	N/A
	6a.4		If the outcome data were continuous, but were analyzed as categorical (method of aggregation), specify the cutoff values used	N/A
	6a.5		If outcome assessments were performed at several time points after randomization, state the time points used for the analysis	N/A
	6a.6		If a composite outcome was used, define all individual components of the composite outcome	N/A
	6a.7		Identify any outcomes that were not prespecified in a trial registry or trial protocol	N/A
	6a.8		Provide a description of the study instruments used to assess the outcome (eg, questionnaires, laboratory tests) along with reliability, validity, and responsiveness in a population similar to the study sample	Methods & UMIN registry (#2216)
	6a.9		Describe who assessed the outcome (eg, nurse, parent) and any qualifications or trial-specific training necessary to administer the study instruments to assess the outcome	Methods
	6a.10		Describe any processes used to promote outcome data quality during data collection (eg, duplicate measurements) and after data collection (eg, range checks of outcome data values), or state where these details can be found	Methods & Response to the Reviewers
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-	N/A
Sample size	7a	How sample size was determined	-	Methods & Response to the Reviewers

Section	Item No.	CONSORT 2010 Item	CONSORT-Outcomes 2022 item	Location Reported[b]
	7a.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	Methods and Results
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-	N/A
Randomization				
Sequence generation	8a	Method used to generate the random allocation sequence	-	Methods & UMIN registry (#2216)
	8b	Type of randomization; details of any restriction (such as blocking and block size)	-	Methods & UMIN registry (#2216)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-	N/A due to PROBE design
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	-	UMIN registry (#2216)
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	-	N/A due to PROBE design
	11b	If relevant, description of the similarity of interventions	-	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	-	Methods & Response to the Reviewers
	12a.1		Describe any methods used to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	N/A
	12a.2		State and justify any criteria for excluding any outcome data from the analysis and reporting, or report that no outcome data were excluded	N/A

Section	Item No.	CONSORT 2010 Item	CONSORT-Outcomes 2022 item	Location Reported[b]
	12a.3		Describe the methods used to assess patterns of missingness (eg, missing not at random), and describe the methods used to handle missing outcome items or entire assessments	Methods & UMIN registry (#2216)
	12a.4		Provide a definition of the outcome analysis population relating to nonadherence of the trial protocol (eg, as a randomized analysis)	N/A
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-	UMIN registry (#2216)
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	-	Methods, Figure1 & UMIN registry (#2216)
	13b	For each group, losses and exclusions after randomization, together with reasons	-	Methods, Figure1 & UMIN registry (#2216)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-	Methods
	14b	Why the trial ended or was stopped	-	Methods & IRB report
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-	Table 1
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% CI)	-	Results
	17a.1		Include the results for all prespecified outcome analyses or state where the results can be found if not in this report	Results and Figures
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted	-	Results and Figures

Section	Item No.	CONSORT 2010 Item	CONSORT-Outcomes 2022 item	Location Reported[b]
		analyses, distinguishing prespecified from exploratory		
	18.1		If there were any analyses that were not prespecified, explain why they were performed	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-	UMIN registry (#2216)
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-	Discussion
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	-	Discussion
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-	Discussion
Other Information				
Registration	23	Registration number and name of trial registry	-	Methods & UMIN registry (#2216)
Protocol	24	Where the full trial protocol can be accessed, if available	-	Methods & UMIN registry (#2216)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	-	Sources of Funding UMIN registry (#2216)

*A fillable version of the CONSORT-Outcomes 2022 checklist can be found at http://www.consort-statement.org

[a]It is strongly recommended that this checklist be read in conjunction with the CONSORT-Outcomes and CONSORT Statement papers for important clarification on the items. The CONSORT Statement checklist is distributed under the terms of the Creative Commons Attribution License.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.