DESIGN PAPER

# Efficacy and safety of direct oral anticoagulants for intermediate stroke risk in patients with atrial fibrillation (SINGLE-AF): Study design and protocol

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**BACKGROUND** The optimal antithrombotic strategy for patients with atrial fibrillation (AF) with intermediate stroke risk ($CHA_2DS_2$-VASc score of 1 [in males] and 2 [in females]) is uncertain. Although current guidelines provide class IIa recommendations for oral anticoagulant (OAC) treatment in the population, no randomized trials have addressed this therapeutic question.

**OBJECTIVE** This study aimed to conduct a randomized clinical trial evaluating the safety and efficacy of OAC therapy compared with no OAC therapy in patients with AF at intermediate stroke risk.

**METHODS** The Efficacy and Safety of Nonvitamin K Antagonist Oral Anticoagulants for Intermediate Stroke Risk in Patients With Atrial Fibrillation trial is an investigator-initiated, multicenter, open-label, superiority, randomized trial with blinded outcome assessment, enrolling 1800 patients with AF who have 1 nongender stroke risk factor, as indicated by their $CHA_2DS_2$-VASc score scoring 1 (in males) and 2 (in females). Eligible patients will be randomized to receive either OAC therapy with direct OACs (apixaban or rivaroxaban) or no OAC therapy.

**RESULTS** The primary endpoint is a composite of stroke, systemic embolism, major bleeding as defined by the International Society on Thrombosis and Hemostasis criteria, and cardiovascular death, assessed at 2 years after randomization. We hypothesized that OAC therapy would be superior to no OAC therapy for the net composite outcome among patients with AF.

**CONCLUSION** The Efficacy and Safety of Nonvitamin K Antagonist Oral Anticoagulants for Intermediate Stroke Risk in Patients With Atrial Fibrillation trial will evaluate the efficacy and safety of OAC therapy vs no OAC in patients with AF with a single nongender stroke risk factor, aiming to provide evidence to guide anticoagulation strategies in those with intermediate stroke risk.

**KEYWORDS** Atrial fibrillation; Anticoagulation; Major bleeding; Study protocol; Stroke prevention

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## Introduction

Atrial fibrillation (AF) is the most common type of sustained heart rhythm disorder, creating significant economic and public health challenges.[1–5] AF significantly elevates stroke risk, by as much as 5 times. This risk varies among patients and is assessed using the $CHA_2DS_2$-VASc score. This scoring system allocates 1 point each for age 65–74 years, female sex, heart failure, hypertension, vascular

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## KEY FINDINGS

- Efficacy and Safety of Nonvitamin K Antagonist Oral Anticoagulants for Intermediate Stroke Risk in Patients With Atrial Fibrillation (SINGLE-AF) is an investigator-initiated, multicenter, open-label, superiority, randomized trial with blinded outcome assessment.
- The optimal antithrombotic strategy for patients with atrial fibrillation who have an intermediate stroke risk—defined as a $CHA_2DS_2$-VASc score of 1 in men or 2 in women—remains uncertain.
- SINGLE-AF will assess the safety and efficacy of oral anticoagulation therapy compared with no anticoagulation in patients with atrial fibrillation who are at intermediate risk of stroke.
- The primary endpoint is a composite outcome comprising stroke, systemic embolism, major bleeding, and cardiovascular death, evaluated at 2 years after randomization.

disease, and diabetes, whereas age 75 years or older and a history of stroke, transient ischemic attack (TIA), or embolism are each worth 2 points.[6] When the calculated risk, reflected by the $CHA_2DS_2$-VASc score, exceeds a certain threshold, the preventive benefits of an oral anticoagulant (OAC) often outweigh the bleeding risks associated with these drugs.[7] Guidelines currently recommend OAC therapy for men with the $CHA_2DS_2$-VASc score of 2 or more and for women with a score of 3 or more.[1,2] For intermediate-risk individuals, defined as males scoring 1 and females scoring 2, guidelines provide a class IIa recommendation of OAC treatment, suggesting that OAC should be considered based on potential clinical benefits, risks, and patient preferences.

Several observational studies have reported a net benefit of vitamin K antagonist (VKA) treatment compared with no anticoagulation or antiplatelet therapy in intermediate-risk patients, although other studies suggest no significant benefit.[8–10] Randomized trials and observational studies have shown that direct OACs (DOACs) offer a better safety and efficacy profile than VKAs in general AF populations, which suggests that DOACs may also present a favorable net benefit for patients with lower risks, especially given their lower association with intracranial hemorrhage than VKAs.[11,12] It is appropriate to designate a lower stroke risk threshold if a DOAC is used. The Randomized Evaluation of Long-Term Anticoagulation Therapy trial for dabigatran and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial for apixaban included lower risk patients with $CHADS_2$ score of 0 or 1, which corresponds to an estimated annual stroke risk of approximately 1%, and indicated that DOACs were preferable to VKAs among the patients with lower risk, both in terms of safety and efficacy.[13,14] However, these studies were not designed to assess the net benefit of DOACs in intermediate-risk individuals compared with no treatment. In Korea, DOAC therapy is not reimbursed for men with a $CHA_2DS_2$-VASc score of 1, which limits the real-world applicability of current recommendations in this patient group.

To date, no randomized trials compare OAC treatment with no treatment in patients with intermediate stroke risk—a question frequently encountered in clinical practice. The Efficacy and Safety of Nonvitamin K Antagonist Oral Anticoagulants for Intermediate Stroke Risk in Patients With Atrial Fibrillation (SINGLE-AF) trial (NCT04437654) is a randomized controlled study focused on determining the best stroke prevention approach for patients at intermediate stroke risk with 1 nongender risk factor, as indicated by their $CHA_2DS_2$-VASc score of 1 (in males) and 2 (in females). The study hypothesizes that OAC therapy with DOACs will lower the risk of net adverse composite outcomes, including stroke, systemic embolism, major bleeding, and cardiovascular death, compared with no OAC therapy.

# Methods

## Study design

The SINGLE-AF trial represents a multicenter, open-label, prospective, randomized superiority trial designed to enroll participants with AF at risk of intermediate stroke risk. The study's overall flowchart is depicted in Figure 1. The study protocol received approval from the institutional review board of each participating center, and patient enrollment commenced in July 2020. The study will be performed in compliance with the ethical standards outlined in the Declaration of Helsinki and the guidelines for Good Clinical Practice.

## Study participants and enrollment criteria

All patients with nonvalvular AF will be screened for eligibility. To be eligible for enrollment, patients must meet the following criteria: (1) age between 19 and 80 years and (2) a $CHA_2DS_2$-VASc score of 1 for men or 2 for women. Key exclusion criteria include (1) significant renal or liver disease, (2) requirement for anticoagulation for reasons other than AF (such as moderate-to-severe mitral valve stenosis, the presence of a mechanical heart valve, or a history of deep vein thrombosis), and (3) significant structural heart disease. Hypertension and atherosclerotic cardiovascular disease (including coronary artery disease) were not considered exclusionary structural heart disease because they constitute single components of the $CHA_2DS_2$-VASc score. Given that the trial was designed to assess anticoagulation strategies in patients with a single non–sex-related stroke risk factor, these conditions were included in the eligible population. Detailed information on the inclusion and exclusion criteria is presented in Table 1. A written

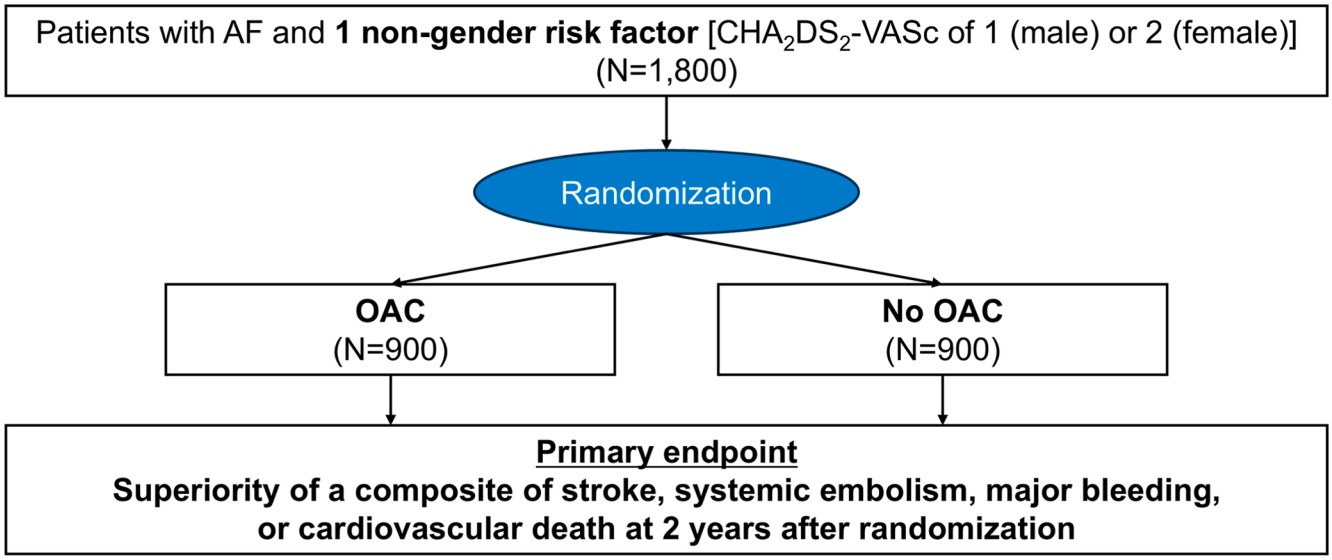


**Figure 1** Flowchart of the SINGLE-AF trial. AF = atrial fibrillation; OAC = oral anticoagulant; SINGLE-AF = Efficacy and Safety of Nonvitamin K Antagonist Oral Anticoagulants for Intermediate Stroke Risk in Patients With Atrial Fibrillation.

**Table 1** Inclusion and exclusion criteria

Inclusion criteria
1. Patient with atrial fibrillation aged between 19 and 80 y*
2. $CHA_2DS_2$-VASc score of 1 (male) or 2 (female)

Exclusion criteria
1. Significant liver (aspartate transaminase and/or alanine transaminase >3 times the upper limit of normal or liver cirrhosis classified as Child–Pugh class B or C) or renal disease (serum creatinine ≥3.5 mg/dL or creatinine clearance <30 mL/min)
2. Requiring anticoagulation owing to surgery with a mechanical prosthetic valve, moderate-to-severe mitral stenosis, or deep vein thrombosis
3. Significant structural heart disease
   A. Moderate mitral regurgitation
   B. Severe valvular regurgitation or stenosis
   C. Dilated cardiomyopathy
   D. Hypertrophic cardiomyopathy
   E. Cardiac amyloidosis
4. Active malignancy
5. Pregnancy or breastfeeding
6. Life expectancy of <1 y
7. Refuse or unable to understand the written informed consent

*Atrial fibrillation will be confirmed by an electrocardiogram (12-lead, multiple, or single leads). All subtypes of atrial fibrillation (paroxysmal, persistent, and permanent) are eligible for enrollment. Paroxysmal atrial fibrillation is defined as atrial fibrillation that terminates spontaneously or with intervention within 7 days of onset; persistent atrial fibrillation as continuous atrial fibrillation lasting more than 7 days or requiring pharmacologic or electrical cardioversion; and permanent atrial fibrillation as atrial fibrillation that is accepted by the patient and physician with no further attempts to restore sinus rhythm.

informed consent will be obtained from each subject before enrollment.

## Randomization and study procedures

Eligible patients will be randomized to receive OAC therapy or no OAC therapy in a 1:1 ratio. Randomization will be conducted using a Web-response permuted-block method with block sizes of 4 or 6, stratified according to the trial center. Patients assigned to the OAC group received either apixaban 5 mg twice daily or rivaroxaban 20 mg once daily. Apixaban was reduced to 2.5 mg twice daily in patients meeting at least 2 of the following criteria: (1) age ≥80 years, (2) body weight of ≤60 kg, and (3) serum creatinine of >1.5 mg/dL.[14] Rivaroxaban was reduced to 15 mg once daily in patients with a creatinine clearance of 15–50 mL/min, calculated using the Cockcroft–Gault formula.[15] In cases of intolerance to apixaban or rivaroxaban, an alternative DOAC could be prescribed at the investigator's discretion. Subjects assigned to the no OAC therapy group will not receive any oral antithrombotic therapy. However, antiplatelet therapy may be administered if clinically indicated (eg, for percutaneous coronary intervention or acute coronary syndrome) in both groups. Detailed information on antithrombotic therapy, including DOAC type, dosing frequency, adherence, and concomitant antiplatelet use, will be systematically recorded and analyzed, and the findings will be presented in the study results. All underlying comorbidities, their specific treatments, and AF-related symptom control will be managed in accordance with current guideline-based recommendations.[1,2] Subjects will be followed for a maximal duration of 24 months. All participants will be followed for a maximum of 24 months.

## Study outcomes

The original primary outcome of this trial was defined as a net composite of stroke, systemic embolism, major bleeding, and all-cause death, assessed 2 years after randomization. In January 2025, a scheduled review by the Data Safety Monitoring Board (DSMB) noted that most of the deaths observed up to that point were noncardiovascular in nature and considered unlikely to be related to treatment. The presence of such

**Table 2** Study outcomes

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|---|
| Primary outcome |
| A composite of stroke, systemic embolism, major bleeding (defined by the ISTH criteria), and cardiovascular death |
| Secondary outcome |
| Stroke |
| Systemic embolism |
| ISTH major bleeding |
| Cardiovascular death |
| ISTH clinically relevant nonmajor bleeding |
| All-cause death |
| Transient ischemic attack |
| Myocardial infarction |
| Pulmonary thromboembolism |
| Hospitalization |

ISTH = International Society on Thrombosis and Hemostasis.

unrelated events was determined to dilute the ability of the trial to assess the treatment effect.[16] After careful deliberation, the DSMB and study leadership, completely blinded to any treatment-specific outcome data, agreed that a cause-specific endpoint would provide a more valid and efficient evaluation of therapy. Accordingly, the primary endpoint was revised to a composite of stroke, systemic embolism, major bleeding, and cardiovascular death, with all-cause mortality retained as a secondary outcome. For clarity, all deaths will also be adjudicated and reported by specific cause. Because restricting the endpoint to cardiovascular death is expected to reduce noise and improve sensitivity to treatment effects, the sample size requirement does not increase, and the original enrollment target and power assumptions remain unchanged.[16] Given that bleeding events generally occur more frequently than ischemic events, such a composite could potentially favor a less intensive antithrombotic approach.[17] Nevertheless, integrating both ischemic and bleeding outcomes provides a balanced assessment of the overall clinical trade-off, which is highly relevant for both patients and clinicians when determining the most appropriate antithrombotic strategy through shared decision making.

Definitions of the clinical outcomes are provided in the Supplemental Material. Stroke is defined as a sudden, focal occlusion deficit resulting from a presumed cerebrovascular cause that persists for more than 24 hours and is not attributable to a readily identifiable cause, such as a tumor or seizure.[18] All suspected stroke events will be confirmed by neuroimaging (computed tomography or magnetic resonance imaging) and independently adjudicated by a blinded clinical endpoint committee. Systemic embolism is defined as abrupt vascular insufficiency accompanied by clinical or radiological evidence of arterial occlusion, occurring in the absence of other likely mechanisms (eg, trauma, atherosclerosis, or instrumentation). Major bleeding events will be defined by the International Society on Thrombosis and Hemostasis criteria.[19] The primary and secondary outcomes are presented in Table 2. Secondary outcomes of the study will include the individual components of the primary outcome. In addition, we will evaluate the incidence of clinically relevant nonmajor bleeding, as defined by the International Society on Thrombosis and Hemostasis criteria[20]; all-cause death; myocardial infarction; pulmonary thromboembolism; TIA; and hospitalization owing to any cause. TIA will be defined as the presence of a new focal neurologic deficit presumed to be vascular in origin, with signs or symptoms lasting less than 24 hours, without evidence of infarction as assessed by brain imaging.[21] The Atrial Fibrillation Effect on Quality-of-Life,[22] frailty assessments (including questionnaires and grip strength measurement), and the Korean-Montreal cognitive assessment will be evaluated at baseline and at the 1- and 2-year follow-up time points. Adjudication of study outcomes will be performed by an independent clinical event adjudication committee, which will remain blinded to treatment allocation and the primary outcome results of the study.

## Sample size estimation

We hypothesized that OAC therapy would be superior to no OAC therapy in terms of net clinical benefit. Based on the reported outcomes of the subgroup analysis of the ARISTOTLE trial and observational data,[8,9,14,23] the 2-year event rate of the primary composite outcome would be 2.0% in the OAC therapy group and 4.5% in the no OAC therapy group. Considering an attrition rate of 12% and aiming for 80% power and a 5% 2-sided alpha error, a total of 1800 patients will be required, with 900 patients allocated to each arm of the trial.

## Data collection and management

A baseline evaluation will be performed to assess the patients' demographics, electrocardiographic data, comorbidities, and quality of life. Baseline cardiac investigations include an electrocardiogram and an echocardiogram to assess left atrial size and/or volume, left ventricular dimensions, ejection fraction, and diastolic function. All collected data will be anonymized before being entered into the online database (https://icreat.nih.go.kr). Data collection will occur both at the baseline and after each follow-up evaluation. Clinical follow-up visits will be conducted at 3, 6, 12, 18, and 24 months at the enrolling study center as in-person visits. Remote assessments will be permitted only when an in-person visit is not feasible. An independent data monitoring committee will continuously review the study's execution.

## Statistical analyses

Continuous variables will be expressed as means ± standard deviations or medians with interquartile ranges, depending on the distribution. Categorical variables will be displayed as frequencies and percentages. For comparisons, the Student *t* test or Mann-Whitney U test will be used for continuous variables, whereas the $\chi^2$ test or Fisher's exact test will be used for categorical variables, as suitable.

The primary analyses will be performed on the intention-to-treat population. For the primary objective, the cumulative event rate during clinical follow-up will be estimated using the Kaplan–Meier method, with a 95% confidence interval calculated for the difference in event rates. The intention-

to-treat population will include all randomized patients, compared according to their assigned group regardless of the treatment actually given. The primary endpoint analysis will also be performed on the per-protocol population, excluding patients with major protocol deviations such as ineligibility, absence of informed consent, or failure to receive the assigned treatment. Patients lost to follow-up and therefore unavailable for assessment of the primary endpoint will be treated as censored in the estimation of Kaplan–Meier event rates. In addition, data will be censored at the time a patient's $CHA_2DS_2$-VASc score increases to $\geq$2 in men or $\geq$3 in women, at which point initiation of OAC therapy will be permitted in accordance with class I guideline recommendations.[1] As a sensitivity analysis, we will use an unmatched-pair win-ratio approach, comparing each patient in 1 group with all patients in the other to enable a hierarchical evaluation of outcomes without requiring matched pairs.[24] The win ratio will be calculated based on survival without an event in each pair. To incorporate pairs in which no clear winner could be assigned, we will also estimate win odds. Confidence intervals for both metrics will be derived by applying a logarithmic transformation to stabilize variance, followed by back-transformation to the original scale. The time-to-event secondary outcomes will be analyzed in the same way as the primary outcome, and both the cumulative event rates and rate differences between groups will be presented to facilitate clinical interpretation. Given the potential for type I error arising from multiple comparisons, analyses of the secondary outcomes will be interpreted as exploratory. Missing variables will not be imputed for planned analyses, except where specified otherwise. Patients with missing values will be excluded from variable-related analyses but included in analyses not related to the missing variable. There are no planned formal interim analyses or guidelines for stopping the study. However, the DSMB will review safety data in a blinded manner. The DSMB will discuss and determine whether early termination is required owing to safety concerns. A 2-sided $P$ value of $<$.05 will be considered statistically significant.

## Discussion

Emerging evidence, including the "tipping point" analysis based on Markov state transition models, suggests that DOACs offer a net benefit when the annual stroke risk exceeds 0.9%, which aligns with the estimated risk for the $CHA_2DS_2$-VASc score of 1 (in males) or 2 (in females).[7] Observational studies provide indirect support for OAC use in intermediate-risk patients. Data indicate that, for males with $CHA_2DS_2$-VASc scores of 1 or females with scores of 2, the annual stroke risk approaches or exceeds 1%, highlighting a potential net benefit for anticoagulation therapy.[8,9,23,25] In addition, aspirin shows no net benefit over no antithrombotic treatment, whereas OACs consistently demonstrate a positive net benefit.[8,26] A Norwegian nationwide cohort study demonstrated that OAC was associated with a reduced risk of the combined outcome of ischemic stroke, major bleeding, and mortality in patients with AF at intermediate stroke risk, whereas nonanticoagulated patients had a higher risk of stroke than anticoagulated patients with AF, and the risk of intracranial hemorrhage associated with anticoagulation was generally low.[27] DOACs have shown improved safety and efficacy profiles compared with VKAs,[11] yet their utility in truly intermediate-risk patients remains underexplored. Data from pivotal DOAC trials such as the Randomized Evaluation of Long-Term Anticoagulation Therapy and ARISTOTLE trials provide indirect evidence of their effectiveness and safety, but these studies were not designed to assess the net benefit of DOACs in intermediate-risk individuals compared with no treatment.[13,14] Despite these observations, evidence shows significant variability in the contemporary stroke rates of patients with $CHA_2DS_2$-VASc scores of 1 (males) or 2 (females).[28] Observational studies reveal that, in most cohorts, annual stroke rates for these patients fall below the critical tipping point of 0.9%, where the net clinical benefit of DOACs is generally established.[10] This suggests that most of these individuals may not experience sufficient benefit from anticoagulation therapy to outweigh the associated risks. Observational data indicate substantial heterogeneity in stroke risk within this population, influenced by individual nongender risk factors.[29] These findings highlight the limitations of the $CHA_2DS_2$-VASc score in accurately stratifying risk for intermediate-risk patients.[30,31]

The trial's findings will offer critical insights into net adverse clinical outcomes—including stroke, systemic embolism, major bleeding, and cardiovascular mortality—and are expected to inform clinical decision making and guide future recommendations for this patient population. In interpreting our findings, it is important to acknowledge the inherent limitations of using a composite outcome that combines ischemic and bleeding events. Although such composite outcomes are commonly adopted in anticoagulation trials,[32,33] this practice is frequently driven by feasibility considerations, given that powering a study for individual endpoints such as ischemic stroke alone would require substantially larger sample sizes. Therefore, interpretation of composite outcomes must be approached with caution, recognizing that their statistical convenience may come at the expense of clinical clarity. To address these concerns and provide a more intuitive representation of the clinical trade-offs, we additionally performed a win-ratio analysis, which hierarchically prioritizes beneficial outcomes (stroke reduction) over adverse outcomes (major bleeding) without forcing them into a single pooled estimate. This method allows patient-level comparison based on clinical relevance and provides further insight into the balance between efficacy and safety beyond the constraints of a traditional composite endpoint.

This trial will enroll East Asian participants, whose baseline ischemic and bleeding risk profiles differ from those of other populations, which may limit the generalizability of the findings. Echocardiographic parameters—particularly left atrial size, strain, and the presence of left ventricular diastolic dysfunction—have been shown to provide incremental prognostic value for stroke risk, especially among patients with intermediate $CHA_2DS_2$-VASc scores who do not yet

meet guideline-based indications for anticoagulation.[34,35] Likewise, circulating biomarkers reflecting atrial remodeling, inflammation, or myocardial stress have emerged as promising adjuncts to clinical risk assessment.[36] These imaging and biomarker-based predictors are currently under active investigation and may be particularly relevant to populations such as those enrolled in this trial, in whom traditional clinical scores may not fully capture the underlying substrate for thromboembolic events.

## Conclusion

The SINGLE-AF trial will evaluate the efficacy and safety of OAC therapy vs no OAC in patients with AF with a $CHA_2DS_2$-VASc score of 1 in men or 2 in women.

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**Authorship:** All authors attest they meet the current ICMJE criteria for authorship.

**Patient Consent:** All participants will provide informed consent to participate in the study.

**Ethics Statement:** The study protocol received approval from the institutional review board of each participating center, and patient enrollment began in July 2020. The study will be performed in compliance with the ethical standards outlined in the Declaration of Helsinki and the guidelines for Good Clinical Practice.

**Data Availability:** No data are used because this manuscript is a study protocol. Data associated with this trial will be made available from the corresponding author on request, considering privacy-sensitive information.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2025.12.008.

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