Study Protocol

Rationale and design of a prospective, multicenter, cross-sectional study of appropriateness evaluation of the prescription of non-vitamin K antagonist oral anticoagulants for Chinese atrial fibrillation patients (Chi-NOACs-AF trial)

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Background: Non-vitamin K antagonist oral anticoagulants (NOACs) are alternative to vitamin K antagonists (VKAs) for stroke prevention in patients with atrial fibrillation (AF). Along with their widespread clinical use in China, the off-label use of NOACs is commonly seen in real-world practice, which could result in adverse drug events and poor clinical outcomes. However, guideline adherence and label adherence for NOAC prescriptions have not been well evaluated in a real-world setting in China.

Methods: Between January 2021 and June 2021, a total of 1,750 outpatients or inpatients with AF will be consecutively enrolled at 26 canters in China. Data on patient demographics, clinical characteristics, treatment strategies, and prescribing information related to anticoagulation therapy for patients with AF will be collected. Clinical pharmacists will evaluate the rationality of the anticoagulation regimens and NOAC prescriptions based on the guideline recommendations and drug labels that are approved by the National Medical Products Administration. The primary outcomes will be the prevalence of irrational anticoagulation strategies and the inappropriate NOAC prescriptions, as well as potential risk factors associated with inappropriate prescriptions in patients with AF.

Discussion: This study will be the first national, multicenter, prospective study performed by pharmacists to explore real-world data on the appropriateness of NOAC prescription in Chinese patients with AF.

Trial registration: The Chi-NOACs-AF trial (Trial number: ChiCTR2000035908).

Keywords: Atrial fibrillation (AF); direct oral anticoagulants; prescription; off-label; pharmacist; rivaroxaban; dabigatran; edoxaban; risk factors

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Introduction

Atrial fibrillation (AF) is associated with a 5-fold increase in stroke and thromboembolism risk. Despite guidelines advocating the use of oral anticoagulants (OACs) as the only appropriate stroke prevention therapy, the underuse of OACs in patients with AF is common globally, especially in Asia. In China, 60% of patients were prescribed aspirin for stroke prevention; meanwhile, compared to that in American and European populations, a lower (approximately 32%) proportion of patients with AF received OACs for stroke prevention (1). It is worth noting that the guidelines do not mention the proportion of patients using non-vitamin K antagonist oral anticoagulants (NOACs).

Based on randomized clinical trial (RCTs) results, current guidelines have adopted NOACs as the preferred treatment for the prevention of stroke in patients with AF (2-5). Meanwhile, the current evidence from RCTs and real-world studies suggest a variability across NOACs regarding bleeding risk, with a concern for rivaroxaban, but not for dabigatran and apixaban (6,7). In China, besides warfarin, NOACs, including dabigatran, rivaroxaban, and edoxaban, have been approved by the National Medical Products Administration (NMPA) for stroke prevention in patients with AF. Nevertheless, the appropriateness of NOAC prescriptions in real-world practice remains challenging for several reasons. First, the NMPA approved each NOAC with a standard dose and dosage adjustment based on specific factors (e.g., renal function, age) or concomitant medications relevant to patients with AF; however, clinical parameters such as renal function are often unknown, despite these being essential to determine the right NOAC and dose to prescribe. Second, a number of factors need to be considered before deciding whether a patient is a good candidate for receiving NOACs, such as contraindications, renal and hepatic function, and drug-drug interactions. Therefore, appropriate prescriptions of NOACs require a comprehensive understanding of drug labels as well as knowledge of the current guidelines. Third, in the current Chinese medical insurance coverage, prescription of dabigatran and rivaroxaban for stroke prevention in patients with AF is covered only for patients with a high risk of bleeding or labile international normalized ratio (INR) values, which is a barrier to their utilization.

The main problem with the use of warfarin lies in its narrow therapeutic range; in addition, the availability of NOACs may offer more alternatives for stroke prevention in AF. However, inappropriate prescriptions of NOACs have been associated with increased adverse events and poor clinical outcomes in previous studies (8-13). The most common problem of inappropriate prescription is underdosing (14-16), which has been shown to be associated with an increased stroke risk (14-17).

Since the AF guideline recommendations have changed in recent years, new studies are needed to assess the current practices and appropriateness of NOAC prescriptions in China. Therefore, our goal is to describe the current state of OAC use in Chinese patients with AF, to evaluate the appropriateness of NOAC prescriptions, and to identify factors associated with inappropriate prescriptions.

Methods

Study design

This study is a national, multicenter, prospective cross-sectional study (Chictr identifier: ChiCTR2000035908). Patients will be consecutively enrolled from 26 sites in seven geographical regions (East China, South China, North China, Central China, Northwest China, Southwest China, and Northeast China) from January 2021 to June 2021, using a competitive inclusion method. Given that AF patients aged ≥75 years is considered a risk factor in stroke risk-stratification tool (CHA_2DS_2-VASc score) and account for over 30% of AF patients in clinical setting (18), this study will included at least 30% of elderly patients to strengthen the representativeness of population. All data for each patient will be collected during a single visit. Patients will be contacted by phone to access detailed information if necessary. This study will be conducted according to the principles of the Declaration of Helsinki (as revised in 2013). Ethics committee of Fuwai Hospital of Chinese Academy of Medical Sciences has approved the study protocol on July 21, 2020 (Approval number: 2020-1356). All participants will sign written informed consent.

Patients and recruitment strategy

Outpatients or inpatients aged ≥18 years with documented AF confirmed by 12 lead-electrocardiography (ECG), pacemaker/ICD electrocardiogram findings, or Holter ECG will be eligible for this study. Patients with transient AF caused by reversible factors (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism) or with a record of deep vein thrombosis, pulmonary embolism, or hip/knee replacement surgery will be excluded. Patient

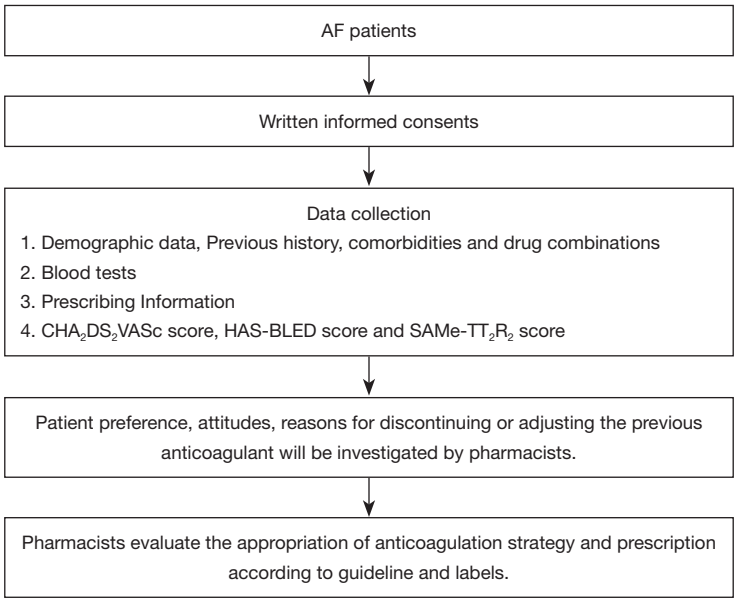

Figure 1 Study flow chart. AF, atrial fibrillation; NOACs, non-vitamin K antagonist oral anticoagulants.

information will be reviewed, and prescriptions will be assessed by a trained pharmacist based on the criteria for appropriateness of antithrombotic therapy and NOAC prescription.

Data collection

Data collection will be performed with an Excel-based case report form by pharmacists at each site after obtaining informed consent from each patient (*Figure 1*). Demographic, clinical, and prescription information will be collected including: age, sex, height, body weight, body mass index (BMI), and lifestyle (smoking and drinking status); latest laboratory data including serum creatinine, haemoglobin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, and INR; comorbidities including congestive heart failure, diabetes mellitus, hypertension, stroke, and vascular disease; medical history including thromboembolism and major bleeding; patients' antithrombotic regimes; and any concurrent medications that interact with OACs, especially antiarrhythmic drugs. In addition, changes in pharmacotherapy, adverse drug reactions, adherence to treatment, and cardiovascular events will also be documented.

Renal function will be estimated by calculating the creatinine clearance (CrCl) using the Cockcroft-Gault method, used in most NOAC trials and guidelines (19,20), since all NOACs have precautions and contraindications based on CrCl.

Assessment of stroke and bleeding risks

CHA2DS2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74, female] and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized Ratio, Elderly, Drugs/alcohol) scores will be used to assess stroke risk and bleeding risks, respectively, in patients with non-valvular AF (*Table 1*). A HAS-BLED score ≥3 indicates a high bleeding risk.

Assessment of SAMe-TT_2R_2 score

SAMe-TT_2R_2 scores will be used to predict INR control in warfarin users (19), which has been validated in two Asian population cohorts (21,22). The SAMe-TT_2R_2 scores will be calculated as the sum of points, with one point each for factors including: female sex, age <60 years, medical history of >2 comorbidities (e.g., hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, prior stroke, pulmonary

Table 1 CHA2DS2-VASc score and HAS-BLED score

Items	Definition	Score
CHA2DS2-VASc		
Congestive heart failure/LV dysfunction	Recent decompensated heart failure or the presence of moderate-severe LV systolic impairment on cardiac imaging or hypertrophic cardiomyopathy	1
Hypertension		1
Age ≥75 years		2
Diabetes mellitus	Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1
Stroke/TIA/TE		2
Vascular disease	Angiographically significant CAD, prior MI, PAD or aortic plaque	1
Age 65–74 years		1
Sex category	Female gender	1
Maximum score		9
HAS-BLED		
Hypertension	Systolic blood pressure >160 mmHg	1
Abnormal renal/liver function (1 point for each)	Renal: dialysis, transplantation, or creatinine ≥200 μmol/L; Liver: chronic hepatitis, cirrhosis, or bilirubin >2 ULN with ALT/AST >3 ULN	1 or 2
Stroke	Previous history, particularly lacunar	1
Bleeding	Major bleeding history or predisposition (e.g., anemia or severe thrombocytopenia.)	1
Labile INR (if on warfarin)	Unstable/high INR, or TTR <60%	1
Age	>65 years or extreme frailty	1
Drugs or alcohol excess (1 point each)	Concomitant use of antiplatelet or NSAIDs; and/or excessive alcohol per week	1
Maximum score		8

LVN, left ventricular; BP, blood pressure; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; TIAN, transient ischemic attack; TE, thromboembolism; ULNN, upper limit of normal; ALT/ASTN, alanine aminotransferase/aspartate aminotransferase; NSAIDN, nonsteroidal anti-inflammatory drugs.

disease, hepatic, or renal disease) and treatment medications (interacting drugs, e.g., amiodarone for rhythm control). Two points each will be allotted for tobacco use and non-Caucasian race (23). A SAMe-TT_2R_2 score of 0–2 predicts a good response to VKAs (e.g., high time in therapeutic range (TTR) >65%), while a SAMe-TT_2R_2 score >2 suggests that the patient is less likely to achieve a good TTR on VKAs (17).

Definition of bleeding

According to the International Society of Thrombosis and Haemostasis criteria (24), major bleeding is defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ; this includes intracranial bleeding, intraspinal bleeding, intraocular bleeding, retroperitoneal bleeding, intraarticular or pericardial bleeding, intramuscular bleeding with compartment syndrome, and/or any bleeding causing a 20 g/L (1.24 mmol·L^{-1}) or greater decrease in the haemoglobin level. Blood loss requiring the transfusion of two or more units of whole blood or red blood cells is also considered as major bleeding.

Evaluation criteria for the appropriateness of antithrombotic therapy and NOAC prescription

A prescription of NOACs will be defined as inappropriateness based on indications, choices, or dosages. The appropriateness of antithrombotic therapy and NOAC

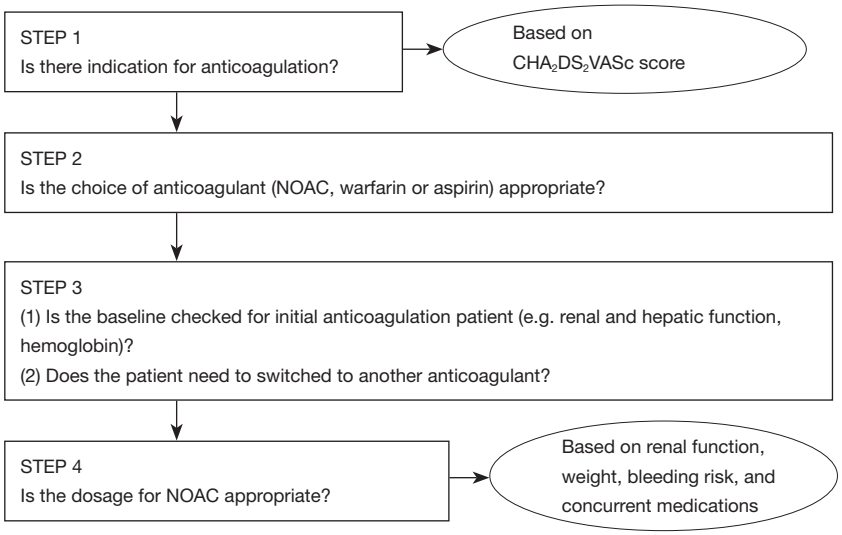

Figure 2 Evaluation flow chart.

prescriptions will be evaluated according to the evaluation flow chart (*Figure 2*) and label recommendations for dabigatran, rivaroxaban, and edoxaban (*Table 2*).

First, patients will be categorised into the antithrombotic therapy-appropriate and antithrombotic therapy-inappropriate groups according to the 2018 American College Chest Physicians recommendation for AF (19). Specifically, the recommendations state that (I) aspirin has no role in stroke prevention in patients with non-valvular AF; (II) in patients with a "low risk" CHA2DS2-VASc score (e.g., 0 in males or 1 in females), no antithrombotic therapy is recommended; (III) in patients with a CHA2DS2-VASc score ≥1 (beyond female sex alone), antithrombotic therapy should be considered, and NOACs are preferred over vitamin K antagonists (VKAs); and (IV) NOACs should not be used in patients with moderate-to-severe mitral stenosis or prosthetic heart valves.

In addition to the inappropriate indications and choices mentioned above, the appropriateness of NOAC dosing will be evaluated based on patient-specific factors such as age, renal and hepatic function, weight, bleeding risk, and concurrent medications according to the approved NMPA label. These patients will be categorised into four groups based on their NOAC dose: on-label standard dose, on-label reduced dose, underdosing, and overdosing. An overdosed prescription will be defined as a prescription for a standard dose of a NOAC despite the patient meeting the dose reduction criteria. An underdosed prescription will be defined as a prescription for a reduced dose of a NOAC despite the patient meeting the standard dose criteria.

For inappropriate prescriptions, interventions will be provided by pharmacists through discussion with the individual prescribers, and the acceptance of the intervention proposals will be documented.

Quality control

All pharmacists who have obtained the qualification certificate in anticoagulation therapy issued by the National Health Commission of the People's Republic of China will be considered suitably trained for conducting this study. We established and released an expert consensus on the standard operating procedure and pharmacists practice management handbook (ISBN 978-7-5192-6715-5) for anticoagulation clinics in 2019 (25). A standardised data collection form was designed to collect information. To interpret each data item, online conferences will be conducted to discuss the details prior to data entry. Data reported by each site will be collected and reserved at the central office computer with a local area network every month. If the data manager detects general errors in data input or data itself, they will reach out to the relevant investigators to solve the potential errors.

Outcomes

The primary outcomes are as follows: the prevalence of OAC use in Chinese patients with AF; the prevalence and factors associated with the inappropriate prescription

Table 2 Dosing considerations for non-vitamin K antagonist oral anticoagulants on Chinese package labeling

Drugs	Standard dosing	Weight <60 kg	Renal impairment dosing	Hepatic impairment	Drug-drug interaction	Possible drug-drug interactions*
Dabigatran	150 mg bid		CrCl 30–50 mL/min: 150 mg bid/110 mg bid (high risk of bleeding); CrCl <30 mL/min: avoid	Child-Pugh C: avoid	110 mg bid: verapamil Avoid with: cyclosporin, tacrolimus, ketoconazole, itraconazole, dronedarone, rifampicin, ritonavir, voriconazole, carbamazepine, phenytoin, phenobarbital, St. John's wort	Increase dabigatran plasma level: amiodarone, quinidine, clarithromycin, erythromycin, posaconazole, imatinib, crizotinib, nilotinib, lapatinib, abiraterone, enzalutamide, tamoxifen Reduce dabigatran plasma level: vinblastine, sunitinib, doxorubicin, vandetanib, dexamethasone
Rivaroxaban	20 mg qd	Consider 15 mg qd	CrCl 15–50 mL/min: 15 mg qd; CrCl <15 mL/min: avoid	Child-Pugh B: avoid; Child-Pugh C: avoid	Not recommend: itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, dronedarone, rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort	Increase rivaroxaban plasma level: cyclosporin, tacrolimus, amiodarone, quinidine, clarithromycin, erythromycin, fluconazole, imatinib, crizotinib, nilotinib, lapatinib, abiraterone, enzalutamide, tamoxifen Reduce rivaroxaban plasma level: vinblastine, sunitinib, doxorubicin, vandetanib, dexamethasone
Edoxaban	60 mg qd	30 mg qd	CrCl: 15–50 mL/min: 30 mg qd	Child-Pugh C: avoid	30 mg qd: Cyclosporin, Dronedarone, Erythromycin, Ketoconazole	Increase edoxaban plasma level: amiodarone, quinidine, verapamil, itraconazole, ketoconazole, posaconazole, voriconazole, tacrolimus, imatinib, crizotinib, nilotinib, lapatinib, abiraterone, enzalutamide, tamoxifen Reduce edoxaban plasma level: ritonavir, carbamazepine, phenytoin, phenobarbital, St. John's wort, dexamethasone, vinblastine, sunitinib, doxorubicin, vandetanib

CrCl, creatinine clearance; *more drug-drug interaction information come from the reference [Expert Rev Clin Pharmacol. 2017, 10(11):1191-1202].

of NOACs in patients with AF; and the prevalence and factors associated with OAC underuse. If sufficient data are available, further subgroup analyses will be performed based on antithrombotic regimen, anticoagulation status, age, weight, renal function, clinical setting (inpatient *vs.* outpatient), and geographic region.

Sample size calculation

This study is designed as a multicenter cross-sectional study. Assuming a response rate of 80% with a 2% margin of error and 95% confidence intervals and considering a 10% dropout rate, the required sample size was calculated to be 1,750 patients. The sample size was calculated using PASS software version 15.

Statistical analyses

Statistical analyses will be performed with the SPSS software, version 22.0 (SPSS Inc., Chicago, Illinois, USA). Categorical variables will be presented as numbers and percentages, and the chi-square test will be used for

categorical variables. Continuous variables will be presented as the means ± standard deviations. Descriptive analyses will be performed to assess the CHA2DS2-VASc, HAS-BLED, and SAMe-TT_2R_2 scores. A univariate logistic regression analysis will be performed to identify possible factors associated with inappropriate antithrombotic therapy and NOAC prescription. All variables with P values <0.1 in univariate analysis will be used for multivariate logistic regression analysis. A P value <0.05 will be considered statistically significant.

Discussion

The benefits of OACs for stroke prevention may not be realised if antithrombotic therapies are prescribed inappropriately. According to existing Chinese registries, the adherence to OAC guidelines is currently poor, and there is much room for improvement and the implementation of new interventions (26-28). The use of NOACs for stroke prevention in patients with AF is increasing rapidly and is also driven by guidelines recommending NOACs as the first line of treatment. However, the underuse or improper use of NOACs is quite common in real-world clinical practice, especially in many Asian countries (29).

There have been many problematic medical practices related to guideline adherence in China, such as using aspirin instead of OACs for stroke prevention, as well as the overuse of OACs in patients with a low stroke risk. In 2012, the CRAF registry showed that 61.2% of patients received antiplatelet treatment instead of anticoagulation treatment, and the underuse of anticoagulants were also common in China. NOACs were not available in China at the time that the CRAF registry was conducted (30). A recent cross-sectional study in China showed that 90.2% of AF patients required OACs, whereas only 4.1% actually received them. Nevertheless, the study did not describe and analyze anticoagulant usage in patients with AF (31). An ongoing registry (ChiOTEAF) will recruit 5,000 patients with AF in China, aiming to explore contemporary antithrombotic strategies among the elderly Chinese population and to compare the clinical characteristics and outcomes between Chinese and European AF populations. Regrettably, the study is limited to elderly patients and lacks the evaluation of NOAC prescriptions (32).

Prior studies have reported that NOAC dosing in clinical practice deviates from the label's information by rates of 17–33% (33,34). Off-label dosing of NOACs was reported to be associated with increased risk of adverse events, including major bleeding, recurrence of venous thromboembolism, and death (33,35). Asian physicians are concerned about the risk of bleeding with OAC use and therefore, prefer to prescribe a reduced NOAC dose (36,37). The results on the inappropriate use of reduced NOAC doses are controversial. Although 15 mg of rivaroxaban was recommended as a standard dose in patients with normal renal function in an exclusively Japanese population, as per the findings of the J-ROCKET-AF trial, the number of enrolled patients was too small to generalise this dose to all Asian patients (38). In a Taiwanese cohort, reduced doses of dabigatran and rivaroxaban showed better effectiveness and safety than a real-world warfarin dose (36). Another study in Taiwan showed that off-label underdosing of rivaroxaban should be avoided in Asian patients with AF; this was because of the higher risk of ischaemic stroke without any reduction in the risk of intracranial haemorrhage associated with this approach (17).

There is a paucity of information on the real-world practice pattern of OACs and label adherence of NOACs in the Chinese mainland. Pharmacists could assist in the prescription process to reduce drug-related problems. They are experts in pharmacology and pharmacokinetics and are able to increase the safety of NOAC use through many aspects. They can aid in drug selection, NOAC dosing, transition of anticoagulant and periprocedural planning, and identification of drug-drug interactions.

Strengths and limitations

The major strength of this study will be that it will include a large and nationally representative sample, which will provide strong evidence for the appropriateness of NOAC prescriptions in patients with AF in China. A large sample from different regions will be representative of the Chinese general population. Second, most studies evaluating the appropriateness of NOAC prescriptions mainly focus on dosage and administration, while our study will evaluate the appropriateness of NOAC decision-making based on guideline recommendations and labels. To our knowledge, this will be the first study conducted by pharmacists in China to evaluate the current state of NOAC prescription patterns. Inevitably, there are some limitations in this study. First, this study will be limited by its cross-sectional design, which might not allow for evaluation of causality. Therefore, the outcomes of patients with AF treated with inappropriate anticoagulation treatments will not be evaluated. Second, participants will be recruited from tertiary care centers,

which may lead to a certain selection bias. Finally, some centers do not have access to certain anticoagulants, which can also have an impact on the outcomes.

Conclusions

This study will be the first national, prospective, multicenter study performed by pharmacists in China to provide real-world data on the appropriateness of antithrombotic therapy and NOAC prescription in patients with AF.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6893). The authors have no conflicts of interest to declare. ZCG serves as an unpaid editorial board member of *Annals of Translational Medicine*.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study will be conducted according to the principles of the Declaration of Helsinki (as revised in 2013). Ethics committee of Fuwai Hospital of Chinese Academy of Medical Sciences has approved the study protocol on July 21, 2020 (Approval number: 2020-1356). All participants will sign written informed consent.

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