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Research Article

Tirofiban on Fully Recanalized Stroke with Thrombectomy: A Propensity Score Matching Analysis

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Background and Objective. Approximately 50% of acute ischemic stroke (AIS) patients who achieve complete recanalization after endovascular therapy (EVT) experience unfavorable outcomes that are potentially partially attributed to incomplete microvascular reperfusion, which can possibly be improved by antiplatelet treatment. This study aimed to evaluate the effect of periprocedural tirofiban on AIS patients who achieved complete recanalization with EVT. *Methods*. Anterior circulation large-vessel occlusion stroke patients who achieved complete recanalization after EVT were retrospectively analyzed. Patients were dichotomized into tirofiban and nontirofiban groups and compared. Propensity score matching (PSM) was used to balance baseline confounders. 3-month functional independence (modified Rankin scale: 0–2), any intracranial hemorrhage (ICH), symptomatic ICH (sICH), arterial reocclusion, in-hospital mortality, and 3-month mortality were evaluated. *Results*. This study included 303 patients with 118 and 185 in the nontirofiban and tirofiban groups, respectively. After PSM, 85 couples with balanced baseline characteristics were generated. 49 (57.6%) and 36 patients (42.4%) in the tirofiban and nontirofiban groups achieved functional independence at 3 months with a significant difference (risk ratio: 1.361, 95% confidence interval: 1.001–1.852, $P = 0.046$). However, there was no significant difference between the tirofiban and nontirofiban groups in terms of the other outcomes (all $P > 0.05$). *Conclusions*. In anterior circulation, large-vessel occlusion AIS patients who achieved complete recanalization with EVT, periprocedural tirofiban may improve the functional outcomes and does not appear to increase the rate of ICH and sICH.

1. Introduction

Recent randomized trials have demonstrated the beneficial effect of endovascular therapy (EVT) for acute ischemic stroke (AIS) secondary to large-vessel occlusion in the anterior circulation [1, 2]. However, approximately 50% of patients remain to experience unfavorable outcomes despite timely and complete recanalization with EVT [3–5]. Such unfavorable outcomes may be partially attributed to incomplete microvascular reperfusion (IMR) [6]. Furthermore, recent imaging studies have found that over 30% of patients who achieved a modified thrombolysis in cerebral ischemia (mTICI) score of 3 post-EVT still had areas of hypoperfusion or microvascular no-reflow, which was associated with larger infarct volumes and unfavorable outcomes [7, 8]. Microthrombus, embolization from the proximal thrombus or formation in situ via local platelet and leukocyte aggregation following endothelial damage induced

by EVT procedures, is one of the most important causes of IMR [6]. More recently, antithrombotic therapy that counteracts the formation of microthrombi has been investigated and found to reduce the infarct volume and improve the functional outcomes [6, 9].

Tirofiban, a platelet glycoprotein IIb/IIIa receptor antagonist, has been shown to prevent the aggregation of local platelets and the subsequent formation of thrombi [10]; it has been recommended as a bail-out therapy in patients with acute myocardial infarction with no-reflow or slow-reflow phenomenon during primary percutaneous coronary intervention [11, 12]. Recently, tirofiban has also been widely investigated as an adjunct therapy to EVT in patients with AIS and has been suggested to be safe and potentially effective when used at a low dose [13–16]. We hypothesized that tirofiban could reduce the rate of IMR in patients with AIS who have achieved complete recanalization and improve their functional outcomes. In this study, we aimed to evaluate the efficacy and safety of periprocedural tirofiban in patients with AIS who achieved complete recanalization with EVT.

2. Methods

2.1. Study Participants. We retrospectively analyzed patients with AIS who achieved complete recanalization with EVT at Xuanwu Hospital between January 2013 and June 2021. The inclusion criteria of this study included the following: (1) age of ≥18 years, (2) AIS caused by large-vessel occlusion in the anterior circulation, and (3) complete recanalization after EVT, defined as an mTICI score of 3 [17]. The exclusion criteria were as follows: (1) modified Rankin scale (mRS) before stroke of >2, (2) absence of assessment for early arterial reocclusion, and (3) lack of 3-month follow-up. This study was approved by the Ethics Committee of Xuanwu Hospital (No. [2017]030), and written informed consent was obtained from all patients.

2.2. Tirofiban Intervention. As described in previous studies [13, 18], when there was no sign of intracranial hemorrhage (ICH), tirofiban was prescribed by interventionists considering one or one more of the following cases: (1) successful recanalization with three or more passes of a stent retriever with potential endothelial damage, (2) rescue treatment using permanent stenting or balloon angioplasty for severe residual stenosis, or (3) severe in situ atherosclerosis with a high possibility of arterial reocclusion. Briefly, a low-dose bolus of tirofiban was administered intra-arterially or intravenously at a rate of 1 mL/min with the dose ranging from 0.25 to 0.5 mg; thereafter, it was administered intravenously at a rate of 4–8 mL/h (i.e., 0.2–0.4 mg/h) for 12–24 h and bridged with dual antiplatelet agents.

2.3. Data Collection. The data collected from the database in this study were as follows: age, sex, vascular risk factors, prestroke drug use, admission blood pressure, admission National Institutes of Health Stroke Scale (NIHSS), admission Alberta Stroke Program Early Computed Tomography Score (ASPECTS), vessel occlusion site, stroke etiology, intravenous thrombolysis (IVT), general anesthesia, time interval from symptom onset to puncture (OTP), time interval from symptom onset to recanalization (OTR), additional intra-arterial thrombolysis, ICH, symptomatic ICH (sICH), arterial reocclusion, in-hospital mortality, and clinical outcomes assessed by mRS at the 3-month follow-up.

2.4. Outcomes Assessment. The primary outcome was functional independence at the 3-month follow-up, defined as an mRS score of 0–2. The secondary outcomes included (1) any ICH prior to discharge according to the definition of the Heidelberg bleeding classification; [19] (2) sICH assessed according to the definition of the European Cooperative Acute Stroke Study III, namely, any apparent extravascular blood in the brain or within the cranium identified as the predominant cause of neurological deterioration (defined as an increase of ≥ 4 in the NIHSS score or an increase that led to death); [20] (3) arterial reocclusion; (4) in-hospital mortality; and (5) 3-month mortality. All the safety and efficacy outcomes were evaluated blindly to the treatment by qualified neurologists and trained staffs.

2.5. Statistical Analysis. All data were analyzed using the SPSS (version 25.0) and R statistical software (version 4.1.2). P values of <0.05 (two-sided) were considered significant. Descriptive statistics were used to summarize the baseline characteristics and outcomes of the patients in the tirofiban and nontirofiban groups. Categorical variables were expressed as numbers (percentages) and continuous variables as mean ± standard deviation or medians (interquartile range). Differences in the baseline characteristics and outcomes between the two groups were analyzed using the chi-square test or Fisher's exact test for categorical data and the independent samples t-test or Mann–Whitney U test for continuous data.

Propensity score matching (PSM) analysis was always used to balance confounding variables in observational studies to achieve an estimation of treatment effects with minimal bias. Principally, variables used for PSM should not be influenced by tirofiban. Meanwhile, they should be variables imbalanced between tirofiban and nontirofiban groups. Therefore, baseline variates with statistically significant differences among the two groups (sex, diabetes, current drinking, atrial fibrillation, coronary heart disease, prestroke anticoagulation, admission diastolic blood pressure (DBP), admission NIHSS score, vessel occlusion site, stroke etiology, and OTP time) would be matched. All patients in the two groups were matched according to the above-mentioned baseline variables at 1 : 1 ratio (using nearest-neighbor matching with a caliper size of 0.1). After PSM, baseline characteristics would be analyzed again, and an evaluation of the effects of tirofiban on the clinical outcomes would be performed. The risk ratio (RR) and 95% confidence interval (CI) were calculated.

3. Results

Between January 2013 and June 2021, 303 patients with anterior circulation stroke (mean age: 63.9 ± 12.9 years and proportion of men: 65%) who achieved complete recanalization were recruited, including 118 and 185 in the nontirofiban and tirofiban groups, respectively (Figure 1).

3.1. Baseline Characteristics before PSM. The baseline characteristics of the patients in the tirofiban and non-tirofiban groups are shown in Table 1. The tirofiban group had a higher proportion of men (72.4% vs. 53.4%, $P = 0.001$) and those who were drinking (34.2% vs. 22.9%, $P = 0.038$), higher incidence of diabetes (34.1% vs. 22.9%, $P = 0.038$), lower incidence of atrial fibrillation (31.9% vs. 54.2%, $P < 0.001$), and coronary heart disease (18.9% vs. 31.4%, $P = 0.013$) than the nontirofiban group. Of the patients in the nontirofiban and tirofiban groups, 15.3% and only 7.0% used anticoagulants before stroke, respectively ($P = 0.021$). The tirofiban group also had a higher admission DBP (84.4 ± 13.7 vs. 81.0 ± 14.4 mmHg, $P = 0.040$), lower median NIHSS score (14 vs. 15, $P = 0.026$), higher incidence of internal carotid arterial occlusion (44.9% vs. 28.0%, $P = 0.003$), and longer median OTP time (394 vs. 329 min, $P = 0.003$) and OTR time (455 vs. 405 min, $P = 0.005$) than the non-tirofiban group. In addition, the incidence of large arterial atherosclerotic occlusion stroke was higher in the tirofiban group than in the nontirofiban group (59.5% vs. 29.7%, $P = 0.003$).

3.2. Baseline Characteristics after PSM. PSM conducted to match the significantly imbalanced variables at baseline generated 85 couples of patients. After PSM, comparisons of the baseline characteristics between the two matched groups are shown in Table 1; all baseline variables were well balanced between the two groups (all $P > 0.05$).

3.3. Outcomes. The outcomes after PSM are summarized in Table 2. Functional independence at 3 months was achieved in 36 patients (42.4%) in the nontirofiban group and 49 patients (57.6%) in the tirofiban group (Figure 2). The use of tirofiban was significantly associated with a higher rate of functional independence at 3 months (RR: 1.361, 95% CI: 1.001–1.852, $P = 0.046$).

Seven patients (8.2%) in the nontirofiban group died in the hospital, which was similar to the mortality rate in the tirofiban group (7.1%, RR: 0.987, 95% CI: 0.905–1.077, $P = 0.773$). The 3-month mortality was 17.6% in the nontirofiban group and 10.6% in the tirofiban group. There was no significant difference in the 3-month mortality between the two groups (RR: 0.921, 95% CI: 0.815–1.041, $P = 0.186$). There was also no significant difference in the incidence of reocclusion between the nontirofiban and tirofiban groups (5.9% vs. 3.5%, RR: 0.976, 95% CI: 0.912–1.043, $P = 0.469$).

3.4. ICH and sICH. A total of 29 patients (34.1%) in the tirofiban group and 39 patients (45.9%) in the non-tirofiban group experienced ICH. Meanwhile, 8 patients (9.4%) in the tirofiban group and 11 patients (12.9%) in the non-tirofiban group experienced sICH. The use of tirofiban was not found to be associated with ICH (RR: 0.821, 95% CI: 0.641–1.053, $P = 0.117$) or sICH (RR: 0.961, 95% CI: 0.864–1.069, $P = 0.465$).

4. Discussion

In this study, we found that in patients with anterior circulation AIS who achieved complete recanalization after EVT, periprocedural tirofiban appeared to be associated with a higher rate of functional independence at 3 months after EVT and did not increase the rate of sICH and ICH. However, tirofiban was not associated with reduced reocclusion, in-hospital mortality, and 3-month mortality rates.

In the modern thrombectomy era, IMR induced by microthrombi has been regarded as one of the key factors that cause poor outcomes in patients with AIS who have achieved complete recanalization [7, 8, 21]. Theoretically, periprocedural antithrombotic therapy may be helpful in improving the clinical outcomes of these patients [6]. The CHOICE trial has shown that intra-arterial alteplase therapy following thrombectomy improved the functional outcomes of patients with large-vessel occlusion stroke who achieved successful recanalization [9]. This study also provides evidence to support this hypothesis: tirofiban after thrombectomy improved the 3-month functional outcomes in the patients with large-vessel occlusion AIS who achieved complete recanalization after EVT. However, the RESCUE BT trial found no significant difference in functional prognosis between tirofiban and no-tirofiban groups for patients with large-vessel occlusion stroke undergoing EVT [22]. The discrepancy may result from the differences in the study population (RESCUE BT enrolled some of the AIS patients without recanalization after EVT), the timing of tirofiban (RESCUE BT trial used tirofiban before EVT), and the dose of tirofiban (the RESCUE BT trial used a larger dosage of tirofiban). Moreover, the large-vessel reocclusion rate was not significantly reduced by tirofiban in this study, which may further support the finding that the beneficial effect of tirofiban in completely recanalized patients with AIS may be related to their improved microvascular reperfusion.

Notably, the use of tirofiban was not associated with the risk of ICH and sICH in our study, which appears to be different from several previous findings [23–25]. This discrepancy with regard to the safety of tirofiban among different studies may be attributed to the following reasons. The patients in a previous study [23] had a more severe stroke (median NIHSS score in the tirofiban group, 18 vs. 15) and a higher proportion of IVT before EVT (proportion in the tirofiban group, 70% vs. 35.3%) than those in this study, which may be associated with a higher risk of ICH and sICH. Conversely, tirofiban has a dose-dependent effect on ICH or sICH, and a medium-to-full dose of tirofiban has been reported to increase the hemorrhagic risk [24, 25]. In this study, we used the protocol of intra-arterial or

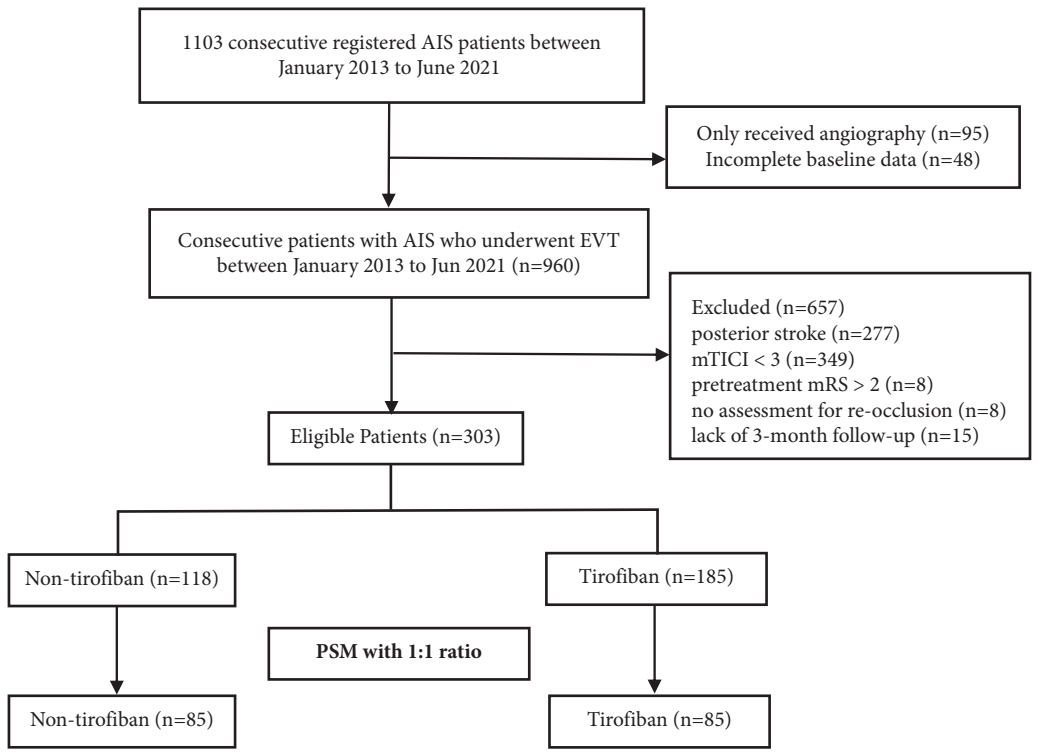

Figure 1: Flowchart of this study. AIS, acute ischemic stroke; EVT, endovascular therapy; mTICI, modified thrombolysis in cerebral ischemia; mRS, modified Rankin scale.

Table 1: Baseline characteristics of patients before and after PSM.

Variables	Before PSM			After PSM		
	Nontirofiban ($n = 118$)	Tirofiban ($n = 185$)	P value	Nontirofiban ($n = 85$)	Tirofiban ($n = 85$)	P value
Demography						
Age (y), mean (SD)	65.1 ± 13.7	63.2 ± 12.4	0.202	64.6 ± 13.1	64.4 ± 11.9	0.922
Male, *n* (%)	63 (53.4%)	134 (72.4%)	**0.001**	50 (58.8%)	53 (62.4%)	0.638
Vascular risk factors						
Hypertension	77 (65.3%)	123 (66.5%)	0.825	57 (67.1%)	54 (63.5%)	0.629
Diabetes	27 (22.9%)	63 (34.1%)	**0.038**	24 (28.2%)	23 (27.1%)	0.864
Hyperlipidemia	62 (52.5%)	110 (59.5%)	0.236	47 (55.3%)	43 (50.6%)	0.539
Current smoking	34 (28.8%)	72 (38.9%)	0.072	29 (34.1%)	31 (36.5%)	0.748
Current drinking	27 (22.9%)	63 (34.1%)	**0.038**	23 (27.1%)	24 (28.2%)	0.864
Atrial fibrillation	64 (54.2%)	59 (31.9%)	**<0.001**	37 (43.5%)	38 (44.7%)	0.877
Previous stroke	28 (23.7%)	28 (15.1%)	0.060	21 (24.7%)	17 (20.0%)	0.461
Coronary heart disease	37 (31.4%)	35 (18.9%)	**0.013**	22 (25.9%)	20 (23.5%)	0.722
Drug use prestroke						
Anticoagulation, *n* (%)	18 (15.3%)	13 (7.0%)	**0.021**	12 (14.1%)	12 (14.1%)	0.099
Antiplatelet, *n* (%)	42 (35.6%)	56 (30.3%)	0.334	27 (31.8%)	29 (34.1%)	0.744
Admission characteristics						
SBP (mmHg), mean (SD)	141.2 ± 21.8	145.8 ± 23.4	0.089	144.1 ± 21.8	142.5 ± 23.0	0.674
DBP (mmHg), mean (SD)	81.0 ± 14.4	84.4 ± 13.7	**0.040**	82.5 ± 15.0	83.1 ± 14.2	0.822
NIHSS, median (IQR)	15 (7)	14 (7)	**0.026**	15 (7)	15 (6)	0.794
ASPECTS, median (IQR)	9 (3)	9 (2)	0.674	9 (3)	9 (2)	0.595
Vessel occlusion site						
ICA occlusion	33 (28.0%)	83 (44.9%)	**0.003**	30 (35.3%)	30 (35.3%)	0.999
MCA occlusion	85 (72.0%)	102 (55.1%)		55 (64.7%)	55 (64.7%)	
Stroke etiology						
LAA	35 (29.7%)	110 (59.5%)	**<0.001**	34 (40.0%)	35 (41.2%)	0.799
CE	73 (61.8%)	66 (35.6%)		46 (54.1%)	43 (50.6%)	
Others	10 (8.5%)	9 (4.9%)		5 (5.9%)	7 (8.2%)	

Table 1: Continued.

Variables	Before PSM			After PSM		
	Nontirofiban ($n = 118$)	Tirofiban ($n = 185$)	P value	Nontirofiban ($n = 85$)	Tirofiban ($n = 85$)	P value
Treatment information						
IVT, n (%)	52 (44.1%)	72 (38.9%)	0.374	38 (44.7%)	30 (35.3%)	0.210
General anesthesia, n (%)	35 (29.7%)	42 (22.7%)	0.175	25 (29.4%)	18 (21.2%)	0.217
OTP (min), median (IQR)	329 (223)	394 (261)	**0.003**	365 (235)	394 (259)	0.385
OTR (min), median (IQR)	405 (203)	455 (246)	**0.005**	436 (227)	450 (268)	0.608
Additional intra-arterial thrombolysis, n (%)	1 (0.8%)	2 (1.1%)	0.999	0 (0%)	1 (1.2%)	0.999

SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta stroke program early computed tomography score; ICA, internal carotid artery; MCA, middle cerebral artery; LAA, large artery atherosclerosis; CE, cardioembolism; IVT, intravenous thrombolysis; OTP, time interval from symptom onset to puncture; OTR, time interval from symptom onset to recanalization. The bold values mean $P < 0.05$.

Table 2: Outcomes of patients after PSM.

Outcomes	Nontirofiban	Tirofiban	RR (95% CI)	P value
3-month mRS 0~2	36 (42.4%)	49 (57.6%)	1.361 (1.001–1.852)	**0.046**
Reocclusion	5 (5.9%)	3 (3.5%)	0.976 (0.912–1.043)	0.469
Any ICH	39 (45.9%)	29 (34.1%)	0.821 (0.641–1.053)	0.117
sICH	11 (12.9%)	8 (9.4%)	0.961 (0.864–1.069)	0.465
In-hospital mortality	7 (8.2%)	6 (7.1%)	0.987 (0.905–1.077)	0.773
3-month mortality	15 (17.6%)	9 (10.6%)	0.921 (0.815–1.041)	0.186

ICH, intracranial hemorrhage; sICH, systematic ICH; mRS, modified Rankin scale. The bold values mean $P < 0.05$.

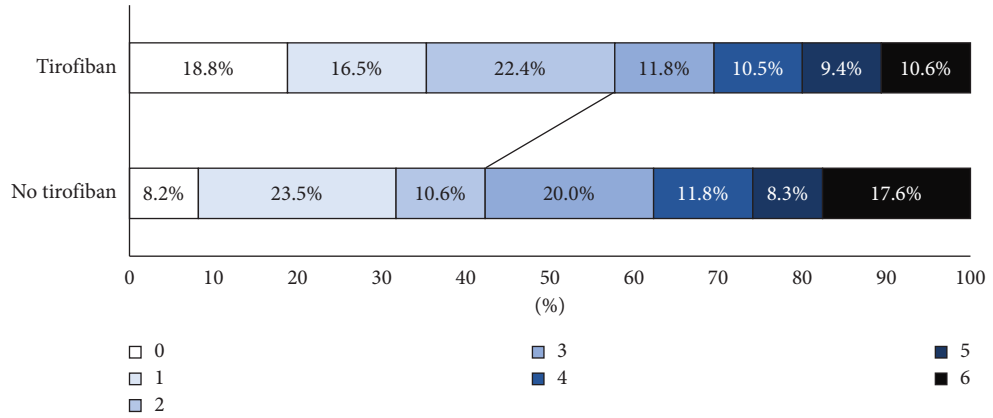

Figure 2: Distribution of modified Rankin scale at 3-month follow-up.

intravenous bolus injection of a low dose of tirofiban (0.25–0.5 mg), followed by a continuous intravenous injection of a low dose of tirofiban (0.2–0.4 mg/h) for 12–24 h; the dose is lower than that used in previous studies, which might have also contributed to the lower incidence of sICH and ICH.

Our study had several limitations. First, although we used PSM to reduce data bias, the inherent limitations of the observational study design may still cause potential confounders that cannot be ruled out. Second, since tirofiban was administered intra-arterially or intravenously in our study, the different administration routes of tirofiban might influence its effect. Thus, the optimal protocol requires further investigation. In addition, our study could not directly demonstrate whether tirofiban improves the functional outcomes of completely recanalized patients with AIS by improving microvascular reperfusion. Further imaging studies are warranted to explore the effect of periprocedural antiplatelet therapy on microcirculatory impairment in patients with AIS who have undergone EVT. Finally, our results were based on a single-center study with a relatively small sample size, which should be confirmed in future multicenter prospective studies.

5. Conclusions

In summary, our study suggests that in large-vessel occlusion AIS patients who achieved complete recanalization after EVT, periprocedural tirofiban may improve the rate of functional independence at 3 months and does not appear to

increase the rate of sICH or ICH. Further investigations are urgently needed to clarify the underlying mechanisms and their association with IMR.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

WTG conceived of the study idea, collected and analyzed the data, and drafted the manuscript. NL collected and analyzed the data and drafted and modified the manuscript. JLX, WBH, and JM participated in the data collection. SJL, CHR, JC, JGD, QFM, HQS, WBZ, and XMJ participated in the coordination of the study. WBZ and XMJ helped to modify the manuscript. All authors read and approved the final manuscript. WG and NL contributed equally to this article.

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Supplementary Materials

This study is in accordance with the STROBE checklist. (*Supplementary Materials*)

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