Rationale and design of a prospective multi-center randomized trial of EARLY treatment by rivaroxaban versus warfarin in ST-segment elevation MYOcardial infarction with Left Ventricular Thrombus (EARLY-MYO-LVT trial)

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Background: Left ventricular thrombus (LVT), a common complication of acute ST-segment elevation myocardial infarction (STEMI), is associated with increased risk of systemic embolism and high mortality. Current STEMI guidelines recommend adding anticoagulant therapy to dual antiplatelet therapy (DAPT) if early-formulated LVT were detected, for which vitamin K antagonist (VKA) is the standard anticoagulant agent. The role of non-VKA oral anticoagulants (NOACs) in this scenario is uncertain.

Methods: The EARLY-MYO-LVT study will be a prospective, multi-center and randomized trial designed to investigate the efficacy and safety of rivaroxaban versus warfarin in the treatment of post-STEMI LVT. It will enroll 280 patients with STEMI who have developed LVT within the first month of symptom onset. They will be randomized at 1:1 ratio into the group of rivaroxaban 15 mg daily or VKA treatment (with targeted INR 2–2.5) on the basis of standard DAPT (100 mg daily aspirin plus 75 mg daily clopidogrel) for 3–6 months. The primary efficacy endpoint will be the probability of LVT resolution after 3-month triple therapy, and the principal safety outcome will be the incidence of major bleeding events during the treatment.

Discussion: The described study will systemically assess the efficacy and safety of NOACs-based anticoagulant therapy in the treatment of LVT subsequent to STEMI.

Trial registration: The EARLY-MYO-LVT trial (Clinical trial number: NCT03764241).

Keywords: Bleeding; embolism and thrombosis; myocardial infarction; rivaroxaban

Introduction

Despite advances in reperfusion and adjunctive medical therapy, complications of ST-segment elevation myocardial infarction (STEMI) remain crucial causes of worse prognosis (1,2). The formation of left ventricular thrombus (LVT) subsequent to STEMI is not rare, with an incidence as high as 31–57% when thrombolysis is used as the main method of reperfusion (3-5). In the era of mechanical reperfusion, the risk of LVT is lower, but can still be around 15% (6). The existence of LVT is clearly associated with
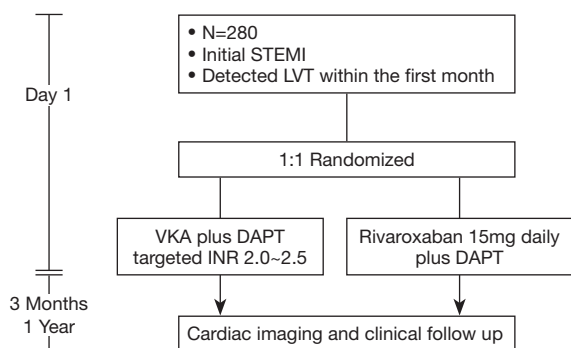
Figure 1 Study flowchart. STEMI, ST-elevation myocardial infarction; VKA, vitamin K antagonist; DAPT, dual antiplatelet therapy (DAPT is composed of 100 mg daily aspirin and 75 mg daily clopidogrel).

increased risks of embolic events and mortality (7-9). In a meta-analysis published in 2019, the rate of embolic events in STEMI patients with LVT was 3.97 times higher (95% CI, 2.68–5.89) than in those without LVT (10).

Current STEMI guidelines recommend additional anticoagulation on the basis of antiplatelet treatment in patients developing LVT, with vitamin K antagonist (VKA) as the standard anticoagulant agent. The 2013 ACC/AHA guideline for STEMI management suggested adding VKA to a dual antiplatelet therapy (DAPT) in patients with LVT for at least 3 months (11). Similarly, the 2014 American Stroke Association (ASA) guideline for primary prevention of stroke gives a IIa recommendation for using VKA adjunctive to DAPT in STEMI patients with LVT (12). The addition of VKA seems effective in both resolving LVT and reducing embolic events (13,14). However, it is restricted by the requirement of frequent monitoring of international normalized ratios (INRs), especially for patients who have difficulty in accessing medical services regularly, and by INR variability resulting in either decreased effects or increasing risk of bleeding.

Non-VKA oral anticoagulants (NOACs) have shown confirmed advantages compared with VKA in the prevention of embolic events derived from the thrombus in venous system. Nevertheless, their roles in the treatment of LVT remain unclear. Recently, NOACs have been reported in several case reports to effectively resolve post-STEMI LVT together with DAPT, suggesting they could also be promising alternatives to VKA in this clinical scenario.

Therefore, the EARLY-MYO-LVT study has been designed to systemically evaluate the efficacy and safety of rivaroxaban, a potent Xa factor inhibitor, in comparison to VKA in STEMI patients who are in the early phase of LVT after symptom onset.

Methods

Study design and setting

The EARLY-MYO-LVT trial (Clinical trial number: NCT03764241) will be a prospective, multicenter, randomized, open-label, parallel-group, noninferiority trial to evaluate the efficacy and safety of rivaroxaban- versus VKA-based triple antithrombotic therapy in the treatment of early developed LVT after STEMI.

Patients with STEMI will undergo cardiac imaging examinations within 1st month. Those developing LVT will be treated with different antithrombotic regimens for 3 months, during which patients will receive repeated imaging examinations and clinical follow-up. The trial will enroll 280 patients at 10 centers in China. The patient safety and scientific conduct in this study will be supervised by an independent Data and Safety Monitoring Board (DSMB). The flowchart of the trial is illustrated in *Figure 1*.

Patient population

Consecutive patients aged 18–75 years who undergo first-time STEMI and develop LVT in the first month of symptom onset are eligible for study participation. Major exclusion criteria are contraindications to anticoagulation and current anticoagulant therapy. Complete inclusion and exclusion criteria are listed in *Table 1*.

Randomization

The enrolled patients will be assigned to rivaroxaban or VKA group at 1:1 ratio in 24 hours after the confirmation of LVT. A central computer-generated randomization will be used for all participant centers.

Study treatments

All patients will start DAPT therapy right after the diagnosis of STEMI according to the current guidelines (11,15). Enrolled patients will start dedicated treatments for LVT on the same day of randomization. Patients assigned to the rivaroxaban (Bayer Co. XARELTO) group will take 15 mg daily rivaroxaban on the basis of 100 mg daily aspirin and 75 mg daily clopidogrel. Patients assigned to the VKA

Table 1 Inclusion and exclusion criteria

Inclusion criteria

   1. Age: 18–75 years old

   2. Acute ST-segment elevation myocardial infarction diagnosed by

      1) Typical ischemic symptom

      2) Elevated ST segment at the J-point in two contiguous leads (ST elevation should be ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age in leads V2 and V3; and ≥1 mm in leads other than V2 and V3

      3) Elevated cardiac troponin value with at least one value above 99th percentile UPL

   3. Evidenced LVT confirmed by CMR in the first month after symptom onset

Exclusion criteria

   1. Bleeding risk

      1) Active bleeding

      2) History of intracranial hemorrhage

      3) Clinically significant gastrointestinal bleeding within 12 months before randomization

      4) Severe thrombocytopenia (<50×10^9/L), or Anemia (i.e., hemoglobin <90 g/L) at screening or pre-randomization

      5) Liver function Child-Pugh B or C

      6) Untreated arterial aneurysm, arterial or venous malformation and aorta dissection

      7) Body weight <40 kg

   2. Undergoing anticoagulant therapy before STEMI onset

   3. Cardiovascular condition

      1) Cardiac shock

      2) Uncontrolled blood pressure (SBP ≥180 mmHg);

      3) Planned CABG within 3months

      4) Suspicious Pseudo-ventricular aneurysm

   4. Concomitant diseases

      1) Severe chronic or acute renal failure (CrCl <50 mL/min at screening or pre-randomization)

      2) Significantly liver disease

      3) Current substance abuse (drug or alcohol) problem

      4) Life expectancy to less than 12 months

      5) Known allergies, or intolerance to rivaroxaban

      6) Woman who is currently pregnant, or breastfeeding

      7) Other hypercoagulable state, such as malignant tumor, SLE

   5. Other conditions adjudicated by investigators to be unsuitable to anticoagulation

UPL, upper reference limit; LVT, left ventricular thrombus; CABG, coronary artery bypass graft; SBP, systolic blood pressure; CrCl, creatine clearance; CMR cardiac magnetic resonance; SLE, systemic lupus erythematosus.

group will initially take 5 mg daily warfarin in addition to the same regimen of DAPT. Because VKA initially increases the risk of thrombosis due to temporarily inhibit protein C, S and Z (16), low molecular weight heparin will be overlapped at least five days until the dose of warfarin is titrated to maintain an INR value in the 2–2.5 range (17). In the case of patients on non-clopidogrel P2Y12 antagonists before randomization, the medication will be changed to clopidogrel with a loading dose of 600 mg when the triple therapy starts (18). Replacement of clopidogrel by other P2Y12 antagonists is not allowed during the study period. To prevent gastrointestinal (GI) bleeding, proton pump inhibitor (PPI) use is mandatory for 1 year for all patients. All other concomitant medications will be administrated according to the current STEMI guidelines.

Triple antithrombotic therapy will continue for 3 months in both groups. A forgotten dose of both rivaroxaban and warfarin could be taken up within 12 h of scheduled intake. Otherwise, dose should be skipped and the next scheduled dose should be taken (19). Patients are required to report any interruption of treatments due to personal reasons.

Patients education will be conducted at enrollment to enhance adherence. A day-marked medication box will be delivered to each participant.

Treatment may be discontinued immediately for emergent situations including major bleeding events or urgent invasive procedures. Other situations that may lead to suspension of treatments should be evaluated and determined by the DSMB. Major bleeding will be treated according to the latest practical guide (19).

According to the newest guideline, patients with residual thrombus after 3-month therapy will continue triple anticoagulant treatment until thrombus resolution or up to 6 months unless they are at increased risk of bleeding (15). *Table 2* shows the timeline of the study.

Study endpoints

Study endpoints are summarized in *Table 3*. The primary efficacy endpoint is the rate of LVT resolution assessed by cardiac imaging, such as cardiac magnetic resonance imaging (CMR), after 3 months of triple antithrombotic therapy. The incidence of any systemic embolic events and composite adverse events including all-cause death, recurrent myocardial infarct, systemic embolism within 3 months and 1 year after triple therapy will also be compared between the two regimens.

The primary safety endpoint is the incidence of major

bleeding events during triple therapy. A major bleeding is defined as any of the following situations according to the International Society on Thrombosis and Hemostasis (ISTH) criteria: (I) A ≥20 g/L fall in hemoglobin. (II) A transfusion of ≥2 units of red blood cells or whole blood. (III) Bleeding at critical sites including intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome and retroperitoneal. (IV) Bleeding with a fatal outcome (20,21). The incidence of other non-major bleeding events will also be recorded.

Study procedures

During the screening period (day 1 to 30), patients will undergo echocardiography examination at days 7, 14 and 30. Exclusion of LVT during this period will be determined by imaging experts at each center. Suspicious LVT on echocardiography will be confirmed by CMR in 24 hours. An example of manifestations of LVT by CMR is shown in *Figure 2*. During the treatments, CMR will be repeated at day 30, 60 and 90 (±2 days) to monitor the change of thrombus. All CMR images will be sent to a core lab for off-line analysis as we previously described (1). An independent, double-blinded imaging panel will adjudicate the occurrence and resolution of LVT centrally.

A routine clinical follow-up will be performed each month for 1 year after randomization. Clinical status, including activity tolerance, adverse events, and medical compliance will be documented. Participants and family members are required to report major bleeding and MACEs as soon as possible. Patients assigned to the warfarin group are required to undergo INR testing once every two weeks to measure time in therapeutic range (TTR) during the treatment. Dose adjustment of warfarin will be performed if necessary.

Study data will be documented by certificated medical assistants under DSMB and clinical research associate (CRA) monitoring regulation.

Sample size and statistical analysis

The sample size of the trial was calculated based on the rate of LVT resolution. There was no clinical trial specifically designed to compare the effect of warfarin-based triple therapy versus placebo or other regimen on LVT resolution. Two recent studies mentioned that warfarin-based triple therapy resolved 87.5% and 92.3% of LVT, respectively (13,14). According to the China Clinical Trial Statistics Working Group (CTTS) guideline (22) and the International

Table 2 Study timelines and schedule

Tasks	Screening period	Follow up	
	1 month from STEMI onset	Monthly review from 1st–3rd month	Monthly review from 4th–12th month
Informed consent	√		
Demographic data	√		
Physical examination	√	√	√
Medical history	√		
Cardiac imaging for LVT[†]	√	√	√
Lab test	√	√	√
Evaluation for concomitant treatments	√	√	√
Evaluation for bleeding risk	√	√	√
Treatment compliance	√	√	√
Adverse events	√	√	√
Safety assessment	√	√	√

[†], LVT will be confirmed and followed up by CMR in the 1st–3rd month. After 3 months, residual thrombus will be continually assessed by CMR, while other patients will be followed up by echocardiography to detect recurrent LVT. LVT, left ventricular thrombus; CMR cardiac magnetic resonance.

Table 3 Study endpoints

Efficacy outcome

  Primary: rate of LVT resolution after triple antithrombotic therapy for 3 months

  Secondary: (I) time to LVT resolution. (II) Incidence of any systemic embolic events within 3 months and 1 year after triple therapy. (III) Incidence of composite adverse events including all-cause death, recurrent myocardial infarct, systemic embolism within 3 months and 1 year

Safety outcome

  Primary: incidence of major bleeding as defined by the ISTH criteria during triple antithrombotic therapy and within 1 year

  Secondary: incidence of other non-major bleeding events during triple antithrombotic therapy and within 1 year

LVT, left ventricular thrombus; ISTH, International Society on Thrombosis and Hemostasis.

Council for Harmonisation (ICH) 10 principle (23), an 85–90% preservation of the efficacy of the control agent is reasonable for the non-inferiority test in this situation. Thus, the non-inferiority margin for the rate of LVT resolution by rivaroxaban was set at 76.1% for this trial. With a reported 81–88% of LVT resolution by rivaroxaban-based antithrombotic therapy in case reports, (14,24,25) and an estimated 8% lost of follow-up, the trial will require 280 patients (140 in both arms) to conclude the noninferiority of rivaroxaban to warfarin at a one-side $\alpha=0.025$ level with 80% power. The sample size was calculated by using the PASS software version 15 (NCSS LLC, USA).

Statistical analysis will be conducted based on intention-to-treat analysis. Continuous data will be presented as the mean ± standard deviation or the median with interquartile range. Categorical data will be presented as counts and percentage. The rate of LVT resolution will be compared using the Chi-square test. Time to LVT resolution and adverse events will be expressed by Kaplan-Meier curves and compared by the log-rank test. If the noninferiority of rivaroxaban were observed, a superiority test would be explored. All P values will be two-sided, and the statistical significance will be set at 5% level. The proportion and 95% confidence interval (CI) will be calculated. Analyses
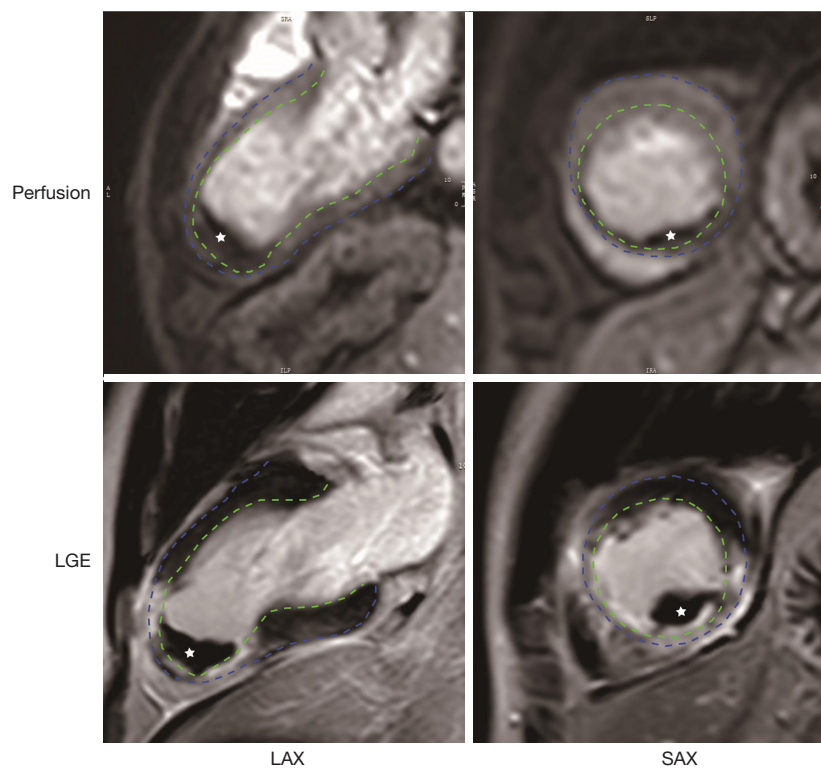
Figure 2 Manifestations of left ventricular thrombus (LVT) on CMR. LVT (white star) appears as a hypo-signal mass in the left ventricular in both the gadolinium perfusion (upper row) and late enhancement (lower row) imaging. Endo- and epi-cardium is delineaed by green and blue dash line, respectively. LGE, late gadolinium enhancement; LAX, long axis; SAX, short axis.

will be performed using SAS software version 9.3 (SAS Institute, USA).

Discussion

The EARLY-MYO-LVT trial aims to be the first randomized clinical trial to evaluate the efficacy and safety of rivaroxaban compared with warfarin in the treatment of early developed LVT after STEMI. The hypothesis is that rivaroxaban will be non-inferior to VKA when used in conjunction with standard DAPT from the perspectives of both the resolution of LVT and the risk of bleeding events.

In a study including 2,911 patients, 93.2% of post-STEMI LVT occurred subsequent to the occlusion of left artery descending (LAD). Large infarction extent, low left ventricular ejection fraction and the formation of ventricular aneurysm are risk factors of LVT (26). LVT greatly increases the incidence of adverse events including systemic embolism and death. The rate of 5-year embolic events could be up to 16.9% in STEMI patients with LVT who did not receive

effective anticoagulant therapy, significantly higher than a rate of 2.9% in patients without LVT (27).

An additional anticoagulant agent is thus essential on the basis of antiplatelet therapy as recommended by the current guidelines (11,12,15). Because the majority of LVT is detected within the first month after STEMI onset (14,28), most patients need combined antithrombotic therapy including DAPT and one anticoagulant agent. Early-developed LVT can be effectively resolved by VKA-based triple therapy, and the incidence of systemic embolism can be reduced to nearly 3% (27). Besides their preventive effects on thrombus formation, NOACs also have been used to resolve existing thrombus in the venous system and atrium. For example, in the X-TRA study, which explored the efficacy of rivaroxaban on the resolution of left atrial thrombus in patients with atrial fibrillation, 15 mg daily rivaroxaban resolved 41% of thrombus. However, current practice using rivaroxaban as well as other NOACs to resolve LVT is empirical. A recent systemic review reported that the rate of LVT resolution by NOACs

Table 4 Summary of case reports of rivaroxaban-based triple antithrombotic treatment of post-AMI LVT

| No. | Author | Etiology | Thrombus | | | HAS-BLED | Regimen | | | Outcome | Adverse event |
			Shape	Location	Size (mm²)		Rivaroxaban (mg)	Duration (month)	Adjunctive antiplatelet agents		
1	Abdelnaby M (24)	NSTEMI	–		10×10	2	15	3	Aspirin 100 mg + clopidogrel 75 mg	Resolved	None
2		STEMI			12×5	2	15	3		Resolved	None
3		STEMI			13×7	2	20	3		Resolved	None
4		STEMI			14×7	2	20	3		Resolved	None
5		STEMI			8×2	1	15	3		Resolved	None
6		STEMI			10×6	2	15	3		Resolved	None
7		NSTEMI			12×10	2	15	3		Residual	None
8		NSTEMI			12×12	1	20	3		Resolved	None
9	Makrides CA (30)	STEMI	–	–	–	1	15	3	Aspirin 100 mg + clopidogrel 75 mg	Resolved	None
10		STEMI	pedunculated	Apex	17×16	2	15	3	Aspirin 75 mg + clopidogrel 75 mg	Resolved	None
11		STEMI	elongated	Apex	–	2	15	3	Aspirin 75 mg + clopidogrel 75 mg	Resolved	None
12	Shokr M (31)	STEMI	Protrusion	Apex	38×18	1	15–20	3	Aspirin 100 mg + clopidogrel 75 mg	Resolved	None
13		STEMI	mural	Septal	12×9	1	20	4		Resolved	None
14		STEMI	–	Apex	18×8	2	20	3		Resolved	None
15		ICM	–	Apex	13×11	3	20	6		Resolved	GI bleeding
16	Seecheran R (32)	STEMI	Protrusion	Apex	25×15	1	20	3	Aspirin 81 mg + ticagrelor 90 twice daily	Resolved	None
17	Summaria F (33)	NSTEMI	Masses	Apex	–	3	15	6	Aspirin 100 mg + clopidogrel 75 mg	Resolved	None
18	Azizi A (34)	STEMI	–	Apex	–	1	20	3	Aspirin 100 mg + clopidogrel 75 mg	Resolved	None
19	Smetana KS (35)	STEMI	mural	Apex	–	–	20	–	Aspirin + clopidogrel	–	–
20		NSTEMI	–	–	10×10		15 twice–20 daily		Aspirin + clopidogrel	Residual	None
21		NSTEMI	Small	Apex	–		15 twice–20 daily		Aspirin + clopidogrel	Resolved	None

STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; ICM, ischemic cardiomyopathy; GI, bleeding gastrointestinal bleeding.

Page 8 of 10

He et al. Trial design of rivaroxaban vs. warfarin in STEMI with LVT

in case reports was around 81–100% (29). *Table 4* summarizes 21 case reports using rivaroxaban to treat post-MI LVT. It is suggested from these cases that ≥15 mg daily rivaroxaban is effective to resolve LVT on the basis of antiplatelet agents.

VKA-based triple antithombotic therapy has been associated with increasing risk of bleeding events. Dr. Maniwa once reported a 2.17% rate of major bleeding in the warfarin-based triple antithrombotic treatment of LVT (27). The incidence was even higher in other larger studies using warfarin-based triple regimen. For example, the WOEST study reported a 5.6% rate of major bleeding (36) and the ISAR-TRIPLE trial reported a 5.3% rate of major bleeding (37). Similarly, although the combination of low-dose rivaroxaban with DAPT has been demonstrated to be safe in STEMI patients with atrial fibrillation by the PIONEER-AF study (38), the ATLAS ACS-TIMI 46 study, in which 5, 10, 15, 20 mg daily rivaroxaban was respectively combined with DAPT in ACS patients with high ischemic risk, showed an apparent dose-dependent bleeding risk. Therefore, 15 mg daily rivaroxaban will be used as the treating dosage in this study to achieve a reasonable efficacy/bleeding risk balance, which was associated with an acceptable 1.79% rate of TIMI major bleeding events in the ATLAS ACS-TIMI 46 study (39).

Currently, echocardiography remains the routine modality to detect LVT in practice. However, recent studies have demonstrated the advantages of CMR compared to echocardiography in visualizing and evaluating LVT (40). Moreover, CMR is the reference method for the volumetric and necrotic assessment of LV. Therefore, CMR will be employed as the confirmatory modality in this trial to achieve more precise detection and follow-up of LVT, as well as functional evaluation of LV.

Rivaroxaban has showed superiority to warfarin in different clinical scenarios that require anticoagulant treatments (25,29,38,39,41-43). Accordingly, the safety and efficacy of rivaroxaban to treat LVT would also be reasonably expected. In the 2017 ESC guidelines for STEMI management, the choice of anticoagulation in patients with LVT is not literally limited to VKA by the first time (15). However, to the best of our best knowledge, there has been no RCT evidence on NOACs versus warfarin in patients with STEMI-related LVT. This trial will use the rate of LVT resolution as the primary efficacy outcome. It is logically conceivable that the resolution of LVT will tightly correlate with the reduction of embolic events. Therefore, the result of the study will provide a solid basis to inform larger RCTs using clinical outcomes as primary endpoints if the hypothesis is proven.

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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. The design and conduct of the study are in accordance with the Declaration of Helsinki and Chinese regulations. Ethics committee of Renji Hospital has approved the study protocol on June 24. 2019 (Approval number: KY-2019-057). All participants will sign written informed consent before randomization.

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