BivaliRudin for Acute Myocardial Infarction versus heparin and GPI plus Heparin Trial (BRIGHT)

Study Protocol

Version：V1.03

Version date：2012-04-09

Statement: any information regarding to this trial is prohibited to be disclosed to any other party beyond the scope specified in this protocol without prior written consent of sponsor.

21 **Protocol Synopsis**

Title of study	BivaliRudin for Acute Myocardial Infarction versus heparin and GPI plus Heparin Trial （BRIGHT）
Sponsor	General Hospital of Shenyang Military Region
Principal investigator	Yaling Han
Primary study center	General Hospital of Shenyang Military Region
Study centers	Approximately 82 centers in China
Time frame of study	First patient in：August, 2012
	Last patient in：December, 2013
Objectives	To investigate safety and efficacy of bivalirudin for patients with AMI undergoing primary PCI.
Study design	Prospective, multicenter, randomized, open-label, active controlled study.
Study medication	Bivalirudin
Control medications	(1) Heparin; (2) heparin plus tirofiban
Treatment	Patients were randomly assigned to receive bivalirudin alone, heparin alone, or heparin plus tirofiban in a 1:1:1 ratio. (1) Bivalirudin alone arm：Bivalirudin was given before coronary angiography in the catheterization laboratory, initialized with a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/hr during the PCI procedure and for at least 30 minutes but no more than 4 hours after procedure. Following this mandatory infusion, a reduced dose infusion (0.2 mg/kg/hr) for up to 20 hours could be administered at physician discretion. An additional bivalirudin bolus of 0.3 mg/kg was given if the activated clotting time (ACT) five minutes after the initial bolus (measured with the Hemotec assay) was <225 seconds. (2) Heparin alone arm: A bolus dose (100 U/kg) of heparin was given before coronary angiography in the catheterization laboratory. Additional heparin bolus (20U/kg) was administered if the post-bolus ACT was <225 seconds. **NOTE:** Provisional (bailout) tirofiban use was allowed in the bivalirudin and heparin alone groups for no-reflow, slow flow, visible thrombus or other thrombotic complications. According to Chinese experts consensus, intra-coronary tirofiban should be initialized as 500-750μg, and can be repeated after 3-5min, with a total dose no more than 1500-2250μg. Intra-venous tirofiban administration should be initialized with a bolus of

	10μg/kg (within 3min) and followed by a 0.15μg/kg/min infusion for 18-36 hours. (3) Heparin plus tirofiban arm: Study medications were started before coronary angiography in the catheterization laboratory. Heparin 60 U/kg and tirofiban 10 μg/kg boluses (administrated within 3 min) were given followed by a 0.15 μg/kg/min tirofiban infusion for 18-36 hours. Additional heparin bolus (20U/kg) was administered if the post-bolus ACT was <200 seconds.
Study endpoints	Primary endpoint： Net adverse clinical events (NACE) at 30 days, defined as a composite of major adverse cardiac and cerebral events (MACCE, all-cause death, re-infarction, ischemia-driven target vessel revascularization or stroke) and any bleeding events.
	Secondary endpoints： • NACE at 12 months; • MACCE at 30 days and 12 months; • Any bleeding events (evaluated by BARC classification) at 30 days and 12 months.
	Safety endpoints: • Stent thrombosis (definite or probable by ARC definition) at 30 days and 12 months； • Thrombocytopenia at 30 days; • Any other abnormal symptoms, signs or laboratory test results with clinical significance.
Number of patients	Approximately 2100 patients.
	700 patients in bivalirudin arm; 700 patients in heparin arm; 700 patients in heparin plus tirofiban arm
Follow-up	12 months
Eligible patients	Patients with AMI in whom an emergency PCI is planned
Inclusion criteria	(1) Patients aged from 18~80 years, male or female； (2) AMI (STEMI or NSTEMI) patients with planned emergency PCI. •STEMI within 12 hours after symptom onset or within 12~24 hours with ongoing chest pain, continuous ST segment elevation or new left bundle block. •NSTEMI within 72 hours after symptom onset. (3) Staged revascularization for non-culprit vessel should be performed after 30 days. (4) Antiplatelet agents (aspirin and clopidogrel, both loading and maintenance dose) are given before PCI per guidelines. (5) Subjects or legal representatives voluntarily participated and signed

	informed consent, willing to accept study medications and clinical follow-ups.
Exclusion criteria	(1) Patients not suitable for PCI; thrombolytic therapy administered before randomization; cardiogenic shock; (2) Any anticoagulant (heparin/LMWH, fondaparinux, warfarin or bivalirudin) or tirofiban administered within 48 hours before randomization; (3) Active or recent major bleeding or bleeding predisposition, including retinal or vitreous hemorrhage within one month, GI or urinary track hemorrhage within 3 months, intracranial hemorrhage within 6 months or cerebral infarction within 3 months; (4) Patients at high risk of secondary bleeding, including active gastric ulcer, ulcerative colitis, intracranial aneurysm, etc.; (5) Major surgery (including ophthalmologic operation or neurosurgery) within 1 month; (6) Clinical syndrome suspicious for aortic dissection, pericarditis or endocarditis; (7) Uncontrolled blood pressure (>180/110 mmHg); (8) Known hemoglobin <10 g/dL or platelet count $<100 \times 10^9$/L; (9) Aminotransferase level >3x the upper limit of normal; 10) Severe renal insufficiency (eGFR<30 mL/min/1.73m^2); (11) History of heparin induced thrombocytopenia; (12) Known allergy to study medications or device (heparin, bivalirudin, tirofiban, aspirin, clopidogrel, stainless steel, contrast medium or hirudin) or allergic constitution; (13) Patient pregnant or lactating, or planned pregnant within 1 year; (14) Study subjects with poor compliance judged by investigators or patient ever participated in another clinical trial and has not completed the follow-up to the primary endpoint.
Study timelines	Start of the study：August, 2012. First patient enrolled: August, 2012 Last patient finished: December, 2013
Statistical method	All primary and major secondary endpoints will be analyzed both on an intent-to-treat basis (all patients analyzed as part of their assigned treatment group) and on a per protocol basis (patients analyzed as part of their assigned treatment group only if they actually received their assigned treatment). The primary statistical analyses will be by intent-to-treat.
Version/date	V1.03/2012-04-09

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1. Background

It is an important issue to balance the benefits of antithrombotic therapy and risk of bleeding in patients with acute myocardial infarction (AMI, including ST-segment elevation MI [STEMI] and non- ST-segment elevation MI [NSTEMI]) undergoing an invasive primary angioplasty strategy. The aim of the study is to investigate the efficacy and safety of domestic bivalirudin in patients with AMI during primary PCI, thus to optimize antithrombotic therapy.

Intensified dual anti-platelet therapy is the cornerstone of antithrombotic therapy in patients with AMI undergoing primary angioplasty strategy, and GP IIb/IIIa inhibitor (GPI) is superior to placebo when they are added to dual anti-platelet therapy. Strengthening anti-platelet therapy is a key strategy in high-risk patients undergoing PCI. However, routine addition of GPI may increase risk of bleeding, and recent studies showed that bleeding could lead to higher mortality. Therefore, the balance between benefits and bleeding risk should be fully evaluated during anti-thrombotic therapy. Recent studies demonstrated that bivalirudin could reduce thrombotic events to a degree comparable to standard anticoagulation therapy, but resulted in less bleeding events. The ACCF/AHA/SCAI 2009 guidelines recommended it as anticoagulation therapy for STEMI emergency PCI at the highest level (I/B). However, little clinical research of bivalirudin in Asian patient population has been performed. The aim of the study is to investigate the efficacy and safety of domestic bivalirudin in patients with AMI during primary PCI, and to provide more evidence for optimizing anticoagulation therapy.

Bivalirudin is a direct thrombin inhibitor, and a synthetic congener of hirudin. By highly specific inhibition of thrombin, it can prolong activated clotting time to prevent thrombus during catheterization. The reversible inhibition of thrombin is short, resulting in infrequent bleeding events, therefore, it is safer than traditional anticoagulation drug, heparin. Thrombin can activate platelet, leading to platelet aggregation and release of platelet-derived micro-particles. Bivalirudin can prevent platelet activation indirectly by inhibiting thrombin.

Bivalirudin is superior to heparin in following aspects: (1) Anticoagulation effects of bivalirudin are achieved by direct and specific inhibition of thrombin, and are independent of antithrombin III; (2) It has a highly predictable dose-response curve, and no routine blood monitoring is needed; (3) It has a short plasma half-life,

and is reversible. This feature is very important when hemorrhagic complications occur. In previous studies of anticoagulation therapy during PCI, bivalirudin was superior to heparin, and GPI did not show any benefits when added to bivalirudin; in studies enrolling patients at various risk, bivalirudin resulted in better clinical outcomes compared to heparin when used during PCI. Considering the benefits of oral anti-platelet therapy, it is important to investigate effects of bivalirudin on clinical prognosis in high-risk AMI patients undergoing PCI after 300-600mg loading dose of clopidogrel.

2. Objectives

The study is a large-scale, prospective, multicenter, active-control, parallel-group, open-label randomized trial. Bivalirudin will be used in patients with AMI undergoing an invasive primary angioplasty strategy, and approximately 2100 patients will be enrolled. The control therapies include heparin and heparin plus tirofiban. Efficacy and safety of domestic bivalirudin will be evaluated in those patients at 30 days, 6 months and 12 months after the procedure.

3. Introduction of study drugs

3.1 Bivalirudin

3.1.1 Pharmacology

Bivalirudin is a direct, specific, reversible inhibitor of thrombin, and its anticoagulation effect is independent of antithrombin III. It inhibits thrombin irrespective of whether the thrombin is free in solution or bound to fibrin, and inhibits thrombin activity directly. Following cleavage at Arg3-Pro4, bivalirudin no longer binds to thrombin, thus allowing thrombin to resume its pro-hemostatic functions, therefore, its effects is short and reversible. *Ex vitro* study from healthy participants showed that, the prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) all rose in a linear fashion with increasing doses of bivalirudin. Binding of bivalirudin to free thrombin or thrombin bound to fibrin is independent of platelet-derived micro-particles. The same level of anticoagulation effects could be achieved in patients undergoing PCI as healthy participants. Bivalirudin is administered by intravenous route, and produces a rapid anticoagulant effect. The half-life of bivalirudin is 25 minutes, and patients'

coagulation system becomes normal 1h after cessation of treatment. There is no specific antidote for bivalirudin.

3.1.2 Drug interactions

Bivalirudin does not bind to plasma protein or red blood cells. Co-administration of bivalirudin with heparin, warfarin, or thrombolytic agents has not been associated with increased risks of major bleeding events.

3.1.3 Adverse reactions

One of common adverse reactions of bivalirudin is bleeding, usually occurring at the puncture site of the artery, or other body part. Bleeding should be highly suspected when abrupt hypotension, volume loss, or other unclear symptoms occur, and bivalirudin should be stopped. Other rare adverse reactions include thrombocytopenia, anemia, allergy, ventricular tachycardia, chest pain, bradycardia, dyspepsia, rash, back pain, headache and hypotension.

3.2 Heparin

3.2.1 Pharmacology

Heparin is a polymer with a molecular weight ranging from 3 to 30 kDa, and the average molecular weight of most commercial heparin preparations is in the range of 12 to 15 kDa. Heparin binds to the enzyme inhibitor antithrombin III (AT), and the activated AT then inactivates thrombin and other proteases involved in blood clotting, including factor Xa, IXa, Xia and XIIa, which is the main mechanism of action of heparin. Heparin has a more potent effect on thrombin than on factor Xa, with an anti-IIa/anti-Xa activity ratio of approximately ten.

Heparin is extensively bound to plasma proteins. Heparin does not cross the placental barrier and is not distributed into breast milk. Heparin is not removed by hemodialysis. The dose-response relationship of heparin is not linear. Anticoagulant effect increases disproportionately in intensity and duration as the dose is increased. The plasma half-life of heparin increases from approximately 60 minutes with a 100 unit/kg dose to about 150 minutes with a 400 unit/kg dose. After bolus intravenous injection of low doses, heparin disappears from the blood exponentially with a dose-dependent half-life; at higher doses, heparin disappears with a concave-convex

pattern. Under continuous intravenous infusion there is a non-linear relationship between the dose of heparin injected and the steady-state plasma concentration. After subcutaneous injection, the bioavailability of the anti-factor Xa activity increases with the dose delivered and tends toward 100% at high doses.

3.2.2 Drug interactions

Oral anticoagulants: Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose should elapse before blood is drawn if a valid prothrombin time is to be obtained.

Platelet inhibitors: Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other interactions: Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium.

3.2.3 Adverse reactions

Hemorrhage is the chief complication that may result from heparin therapy. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug. Generalized hypersensitivity reactions have been reported, with chills, fever and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting and anaphylactoid reactions. Osteoporosis following long-term administration of high doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism and rebound hyperlipidemia on discontinuation of heparin sodium have also been reported.

3.3 Tirofiban

3.3.1 Pharmacology

Tirofiban is an intravenously administered nonpeptide glycoprotein IIb/IIIa receptor antagonist which specifically inhibits fibrinogen-dependent platelet

aggregation and prolongs bleeding times in patients with acute coronary syndromes. When administered intravenously, tirofiban inhibits ex vivo platelet aggregation in a dose- and concentration-dependent manner. When given according to the recommended regimen, >90% inhibition is attained by the end of the 30-minute infusion. It is cleared from the plasma largely by renal excretion, with about 65% of an administered dose appearing in urine and about 25% in feces, both largely as unchanged tirofiban. Its half-life is 1.5~2h.

3.3.2 Drug interactions

Use of thrombolytics, anticoagulants, and other antiplatelet agents and co-administration of antiplatelet agents, thrombolytics, heparin, and aspirin increase the risk of bleeding.

3.3.3 Adverse reactions

Bleeding is the most commonly reported adverse reaction. Patients treated with tirofiban plus heparin were more likely to experience decreases in platelet counts than were those on heparin alone. Severe allergic reactions including anaphylactic reactions have occurred during the first day of infusion

4. Previous clinical research

In the early phase, bivalirudin was evaluated in patients undergoing PCI in the Hirulog Angioplasty study (NEJM, 1995,333:764-9). The double-blind, randomized trial enrolled 4098 patients undergoing angioplasty for unstable or post-infarction angina. The results showed that bivalirudin did not significantly reduce the incidence of the primary end point (11.4%, vs. 12.2% for heparin) but did result in a lower incidence of bleeding (3.8% vs. 9.8%, $P<0.001$). In the prospectively stratified subgroup of 704 patients with post-infarction angina, bivalirudin therapy resulted in a lower incidence of the primary end point (9.1% vs. 14.2%, $P=0.04$) and a lower incidence of bleeding (3.0% vs. 11.1%, $P<0.001$).

The ACUITY study (NEJM, 2006,355:2203-16) investigated the role of thrombin-specific anticoagulation with bivalirudin in patients with high-risk acute coronary syndromes. 13,819 patients with acute coronary syndromes were assigned

to one of three antithrombotic regimens: unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin alone. The results showed that bivalirudin plus a glycoprotein IIb/IIIa inhibitor, as compared with heparin plus a glycoprotein IIb/IIIa inhibitor, was associated with noninferior 30-day rates of the composite ischemia end point (7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%), and the net clinical outcome end point (11.8% and 11.7%). Bivalirudin alone, as compared with heparin plus a glycoprotein IIb/IIIa inhibitor, was associated with a noninferior rate of the composite ischemia end point (7.8% and 7.3%, respectively; P=0.32; relative risk, 1.08; 95% confidence interval [CI], 0.93 to 1.24) and significantly reduced rates of major bleeding (3.0% vs. 5.7%; P<0.001; relative risk, 0.53; 95% CI, 0.43 to 0.65) and the net clinical outcome end point (10.1% vs. 11.7%; P=0.02; relative risk, 0.86; 95% CI, 0.77 to 0.97).

The HORIZONS-AMI study（NEJM, 2008,358:2218-30）evaluated the safety and efficacy of bivalirudin in patients with ST-segment elevation myocardial infarction who were undergoing primary PCI. 3602 patients were assigned to treatment with heparin plus a glycoprotein IIb/IIIa inhibitor or to treatment with bivalirudin alone. The two primary end points of the study were major bleeding and combined adverse clinical events, defined as the combination of major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke (hereinafter referred to as net adverse clinical events) within 30 days. The results showed that anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, resulted in a reduced 30-day rate of net adverse clinical events (9.2% vs. 12.1%; relative risk, 0.76; 95% confidence interval [CI] 0.63 to 0.92; P=0.005), owing to a lower rate of major bleeding (4.9% vs. 8.3%; relative risk, 0.60; 95% CI, 0.46 to 0.77; P<0.001). Treatment with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, resulted in significantly lower 30-day rates of death from cardiac causes (1.8% vs. 2.9%; relative risk, 0.62; 95% CI, 0.40 to 0.95; P=0.03) and death from all causes (2.1% vs. 3.1%; relative risk, 0.66; 95% CI, 0.44

to 1.00; P=0.047). One-year outcomes in the HORIZONS-AMI trial continued to show that bivalirudin is associated with a lower rate of major bleeding (15.6% versus 18.3%, p=0.0001) and mortality (3.5% versus 4.8%, p=0.037). In HORIZONS-AMI, there was an increased risk of acute stent thrombosis within 24 hours in the bivalirudin group, which might due to delayed onset of pharmacodynamic effects of clopidogrel.

5. Study design, randomization and blinding

5.1 Study design

This study is a prospective, multicenter, randomized, active controlled, open-label, superiority trial.

5.2 Study procedure

Patients meet ALL the inclusion criteria and NONE of the exclusion criteria will be randomly assigned to 3 arms after informed consent is signed. Study medications will be given in the cath lab before angiography. Activated clotting time (ACT) will be measured 5 min after heparin or bivalirudin administration. Repeat bivalirudin or heparin bolus will be given if ACT is less than standard level according to protocol. Bailout tirofiban can be used in patients allocated in the bivalirudin arm or heparin arm if there is significant thrombus in the culprit vessel. Patients will be visited at 30 days, 6 months and 12 months via telephone or clinic. Detailed study procedures are listed in table 1.

5.3 Randomization

Patients meeting ALL the inclusion criteria and NONE of the exclusion criteria will be enrolled. Randomization will be performed in catheterization laboratory immediately after informed consent is signed, using computer-generated block randomization sequence sealed in an envelope.

5.4 Blinding

Study medications are known by both investigators and subjects. However, independent clinical events committee is blinded to the treatment allocation.

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232 Table 1：Study procedure table

	Baseline	Visit 1 30 days	Visit 2 6 months	Visit 3 12 months
window		±7d	±14d	±30d
Informed consent	X			
Inclusion/exclusion criteria	X			
Randomization	X			
Medical history/demographic features	X			
Vital signs	X			
Routine blood and urine test	X			
Biochemical test	X			
CK/CKMB and troponin T	X			
Activated clotting time	X			
12- leader electrocardiogram	X			
Important clinical symptoms	X	X	X	X
Clinical evaluation	X	X	X	X
Adjunctive medications	X	X	X	X
Coronary angiography	X			
Adverse cardiac events recording		X	X	X
Adverse events recording		X	X	X

6. Study population：

6.1 Target population：

2100 patients who meet the inclusion criteria and receive study medications before coronary angiography.

6.2 Inclusion criteria

(1) Patients aged from 18~80 years, male or female；

(2) AMI (STEMI or NSTEMI) patients with planned emergency PCI.

- STEMI within 12 hours after symptom onset or within 12~24 hours with ongoing chest pain, continuous ST segment elevation or new left bundle block.
- NSTEMI within 72 hours after symptom onset.

(3) Staged revascularization for non-culprit vessel should be performed after 30 days.

(4) Antiplatelet agents (aspirin and clopidogrel, both loading and maintenance dose) are given before PCI per guidelines.

(5) Subjects or legal representatives voluntarily participated and signed informed consent, willing to accept study medications and clinical follow-ups.

6.3 Exclusion criteria：

(1) Patients not suitable for PCI; thrombolytic therapy administered before randomization; cardiogenic shock;

(2) Any anticoagulant (heparin/LMWH, fondaparinux, warfarin or bivalirudin) or tirofiban administered within 48 hours before randomization;

(3) Active or recent major bleeding or bleeding predisposition, including retinal or vitreous hemorrhage within one month, GI or urinary track hemorrhage within 3 months, intracranial hemorrhage within 6 months or cerebral infarction within 3 months;

(4) Patients at high risk of secondary bleeding, including active gastric ulcer, ulcerative colitis, intracranial aneurysm, etc.;

(5) Major surgery (including ophthalmologic operation or neurosurgery) within 1 month;

(6) Clinical syndrome suspicious for aortic dissection, pericarditis or endocarditis;

(7) Uncontrolled blood pressure (>180/110 mmHg);

(8) Known hemoglobin <10 g/dL or platelet count $<100 \times 10^9$/L;

(9) Aminotransferase level >3x the upper limit of normal;

10) Severe renal insufficiency (eGFR<30 mL/min/1.73m2);

(11) History of heparin induced thrombocytopenia;

(12) Known allergy to study medications or device (heparin, bivalirudin, tirofiban, aspirin, clopidogrel, stainless steel, contrast medium or hirudin) or allergic constitution;

(13) Patient pregnant or lactating, or planned pregnant within 1 year;

(14) Study subjects with poor compliance judged by investigators or patient ever participated in another clinical trial and has not completed the follow-up to the primary endpoint.

6.4 Criteria of patient removal, treatment discontinuation and drop out

6.4.1 Criteria of removal

Patient should be removed if:

- Misdiagnosis.
- Without any record of physical or laboratory test results.
- Do not meet the inclusion criteria or meet at least one exlusion criteria.

The reason of removal should be written down and the case report form (CRF) should be preserved for audit check. Removal patients will not be included in the efficacy analysis but could be included in the safety analysis if there are any records regarding efficacy or safety.

6.4.2 Criteria of treatment discontinuation

Discontiuation of any study medication is defined as stopping experimental treatment. The reason of discontinuation should be clearly noted in the original medical records and CRF.

Treatment should be discontinued if:

- Patient withdrawal of informed consent.
- Intolerable side effects of study medications

- Severe allergy that cannot be relieved by anti-allergic therapy
- Adverse events or abnormal laboratory test results indicating that continuation of treatment would be inappropriate.
- Patient suffered from severe complications which necessitated withdrawing study medications.
- Major deviation of the study protocol.
- Severe adverse event that threaten the patient's health.

6.4.3 Criteria for drop out

All patients enrolled in the trial shall be retained until completion of follow-up. Patients have the right to withdraw from the study at any time without penalty, and would not lose any benefits. The reasons that patients drop out may include but are not limited to:

- Severe adverse events causing termination of the study.
- Unexpected illness for which further treatment would be inappropriate.
- Lost to follow-up.
- Patient withdrew informed consent.
- Other reasons causing termination of the study.
- Poor patient compliance which might affect efficacy or safety.

If patients met the above criteria and stop participating in the study, the "completion of study" page in their case reports should be completed. Investigators must report to their respective ethics committees when and why patients stopped participating in the study (according to the procedures specified in each test body). If patient withdrawal was caused by an AE/SAE, clinical follow-up should be performed until the AE/SAE is resolved or stabilized.

7. Methods

7.1 Study medications：

- Bivalirudin for injection：250mg per ampoule, manufactured by Salubris

Pharmaceutical Co. Ltd, Shenzhen, China

- Heparin Sodium injection： 100mg per ampule
- Tirofiban hydrochloride Sodium Chloride Injection: 100mg per package

7.2 Follow-up：

Clinical follow-up will be performed at 30 days, 6 months and 12 months after randomization.

7.3 Treatment

Patients enrolled will be randomly assigned to receive bivalirudin alone, heparin alone or heparin plus tirofiban in a 1:1:1 ratio. Treatments for 3 arms are as follows:

7.3.1 Bivalirudin alone arm：

Bivalirudin is given before coronary angiography in the catheterization laboratory, initialized with a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/hr during the PCI procedure and for at least 30 minutes but no more than 4 hours after procedure. Following this mandatory infusion, a reduced dose infusion (0.2 mg/kg/hr) for up to 20 hours may be administered at physician discretion. An additional bivalirudin bolus of 0.3 mg/kg is given if the activated clotting time (ACT) five minutes after the initial bolus (measured with the Hemotec assay) is <225 seconds.

7.3.2 Heparin alone arm:

A bolus dose (100 U/kg) of heparin is given before coronary angiography in the catheterization laboratory. Additional heparin bolus (20U/kg) is administered if the post-bolus ACT was <225 seconds.

NOTE: Provisional (bailout) tirofiban use is allowed in the bivalirudin and heparin alone arms for no-reflow, slow flow, visible thrombus or other thrombotic complications. According to Chinese experts consensus, intra-coronary tirofiban should be initialized as 500-750μg, and can be repeated after every 3-5 min, with a total dose no more than 1500-2250μg. Intravenous tirofiban administration should be initialized with a bolus of 10μg/kg (within 3min) and followed by a 0.15μg/kg/min infusion for 18-36 hours.

7.3.3 Heparin plus tirofiban arm:

Study medications are started before coronary angiography in the catheterization laboratory. Heparin 60 U/kg and tirofiban 10 μg/kg boluses (administrated within 3 min) are given followed by a 0.15 μg/kg/min tirofiban infusion for 18-36 hours. Additional heparin bolus (20U/kg) is administered if the post-bolus ACT was <200 seconds.

7.3.4 Adjunctive medications during perioperative period

- Dual antiplatelet therapy shall be given before randomization:

(1) Aspirin: 300mg loading followed by 100mg/d maintenance dose definitely.

(2) Clopidogrel: 300mg or 600 mg loading followed by 75mg/d maintenance dose for 12 months. If a maintenance dose of clopidogrel (75mg/d) was given for at least 5 days before randomization, loading dose can be omitted.

- Anticoagulant agent：Anticoagulant agent (heparin, LMWH, etc.) post procedure is not recommended other than in patients who are at high risk of thrombosis. LMWH administration is at physician's discretion for patients undergoing IABP or temporary pacemaker implantation.

8. Endpoints

8.1 Primary endpoint

Primary endpoint is net adverse clinical events (NACE) at 30 days. NACE is defined as a composite of major adverse cardiac and cerebral events (MACCE, all-cause death, re-infarction, ischemia-driven target vessel revascularization or stroke) and any bleeding events.

8.2 Secondary endpoints：

- NACE at 12 months;
- MACCE at 30 days and 12 months;
- Any bleeding events (evaluated by BARC classification) at 30 days and 12 months.

8.3 Safety endpoints

- Stent thrombosis (definite or probable by ARC definition) at 30 days and 12 months;

- Thrombocytopenia at 30 days;
- Any other abnormal symptoms, signs or laboratory test results with clinical significant.

9. Study flowchart:

See Figure 1.

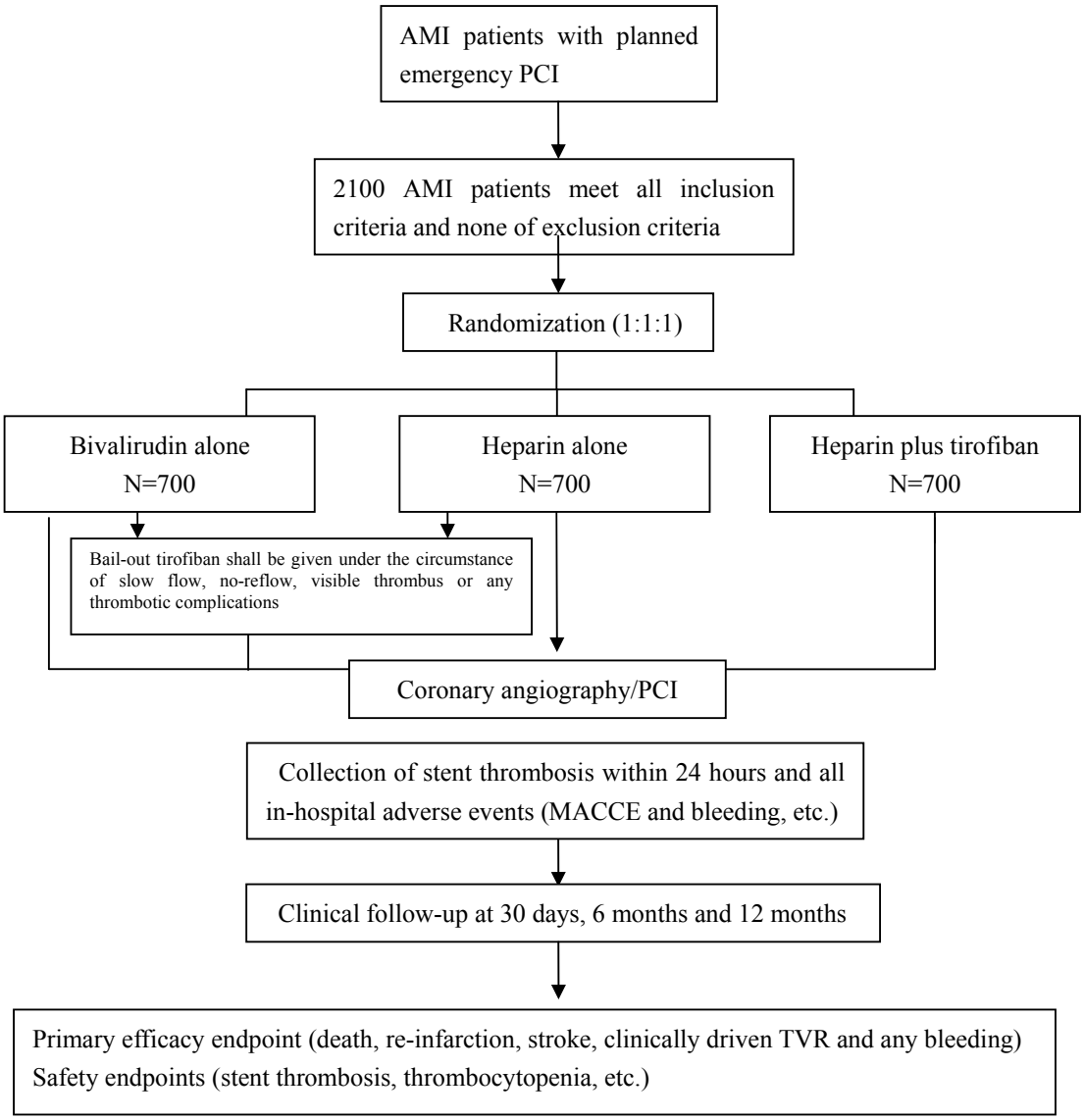

Figure 1. Study flowchart

10. AE/SAE reporting

There are two classifications of adverse events: adverse event (AE), and serious adverse event (SAE). Adverse events must be monitored until resolved or adequately explained. All serious and unanticipated adverse events must be reported, regardless of the cause. They should be reported to the local IRB/EC and Sponsor within 24 hours of knowledge of the event.

10.1 Definition of AE / SAE

- **AE**

Any adverse medical events occurring in a clinical trial, not necessarily having a causal relationship with the study treatments. Adverse events could be any signs (including abnormal laboratory values), symptom, or temporary disease, whether related or unrelated to the study drug use. An adverse event may be categorized as the following:

- Mild – signs or symptoms that do not interfere with the patients' usual activities or is transient and resolves without treatment of sequelae.
- Moderate – interferes with the patients' usual activities and/or requires symptomatic treatment.
- Severe – symptoms causing severe discomfort and significant impact the patient's usual activities and requires treatment.

- **SAE**

A study-related event that is fatal, life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, requires intervention to prevent permanent impairment/damage, or results in persistent or significant disability.

10.2 Observation and recording of AEs

Investigators should collect and record all AEs occurring from the time of signing informed consent for each subject to end of the follow-up in the clinical study.

For AEs, only medical events with clinical worsening compared to baseline are recorded. Abnormal evaluation results at screening or baseline examination are not

considered AEs.

For any AEs required to be recorded and described in the raw data, investigators must determine their type, date, measures taken, outcomes, as well as their relevance to study medications.

Subjects with AEs should receive clinical follow-up until the adverse event has subsided (to a normal state or to baseline condition), or the patients achieves a stable condition, or investigators believe the patients has reached a reasonable condition. If the AEs did not subside to the above conditions, the investigators should continue to provide the necessary treatment, and report and record the patient's progress. For special circumstances, AEs should be treated in accordance with the instructions of relevant administrative departments.

10.3 Procedure of SAE reporting

The Investigator must complete the SAE form for each SAE, whether related or not to study drug. The event should be reported to the Investigational Review Board (IRB)/ Ethics Committee (EC), national regulatory authority, sponsor and CRO within 24 hours (from the point in time when the SAE is identified by the site). The information provided must be sufficient to allow for independent medical assessment of the event. The Investigator should provide any additional follow-up information regarding the event to the sponsor as soon as it becomes available.

11. Data collection

11.1 Filling in case report form (CRF)

- Principal investigator shall authorize personnel to fill in CRF.
- Investigators shall fill in the CRF in accordance to GCP principles and CRF instructions to ensure that true, accurate and complete examination results are transcribed into the CRF in a timely and standardized manner.
- Data recorded in the CRF should be verified with source medical recordings.
- Any change in the CRF should be marked with a deletion line. The correction should be written down beside with the investigator's signature and date.
- Any abnormal data (great deviation from normal or clinically unacceptable)

should be verified and illustrated by the investigator.

- CRF data will be maintained by the sponsor and clinical research institutions.

11.2 CRF auditing

Monitors should audit patient consents and enrolment periodically in each participating center:

- To ensure that data in the CRF are correct and are consistent with the original medical records.
- To ensure all errors and missing data are corrected or illustrated and signed by the investigator.
- To ensure each therapeutic change, concomitant medication and complication is recorded accurately.
- To ensure that all patient withdrawals or loss of follow-up are recorded in the CRF.
- To ensure that all AEs are recorded and all SAEs are reported per standard procedure.
- To ensure that the delivery, storage and recycling of study drugs abide to regulatory requirements and are recorded.

12. Statistical analysis

BRIGHT is a prospective, multicenter, randomized, open label, active controlled trial. AMI patients with planned emergency PCI will be enrolled and randomly assigned to be treated with bivalirudin, heparin alone or heparin plus tirofiban. Analysis for primary endpoint will be performed at the time that 30 day follow-up for all subjects are completed. Analysis for secondary endpoints will be performed when 12-month follow-up are completed.

12.1 Sample size calculation

The primary endpoint is 30-day NACE, a composite of all-cause death, reinfarction, ischemia driven TVR, stroke or any bleeding. Incidence of primary endpoint will be compared between bivalirudin group and two control groups sequentially. Only when both p values of two step tests (bivalirudin versus heparin alone and bivalirudin versus heparin plus tirofiban) are less than 0.05, then the

conclusions of bivalirudin being superior to controls will be accepted.

The study hypothesis is that bivalirudin is superior to both heparin alone and heparin plus tirofiban on 30-day NACE.

H_0: $P_B=P_C$

H_1:$P_B \neq P_C$, α =0.05 (two-sided)

P_B denotes NACE rate in the bivalirudin group, P_C NACE rate in the control group.

Assuming a 30-day NACE rate of 11.5% in the heparin alone group and 12.1% in the heparin plus tirofiban group, allowing for 5% lost to follow-up, with a two-sided alpha of 0.05, 700 patients per group would provide >90% power to demonstrate a 45% reduction with bivalirudin for each comparison. Enrollment of 2,100 total patients (~700 per group) was therefore planned.

12.2 Analysis populations

All primary and major secondary endpoints will be analyzed both on an intent-to-treat basis (all patients analyzed as part of their assigned treatment group) and on a per protocol basis (patients analyzed as part of their assigned treatment group only if they actually received their assigned treatment). The primary statistical analyses will be by intent-to-treat.

- **Intention-to-treat (ITT) set:** Patients who meet the study inclusion criteria, sign the written informed consent and receive study medications after randomization and have any assessment for the primary endpoint will be included in the ITT set. ITT set will be used as baseline characteristics and endpoint analysis.
- **Per protocol (PP) set:** Patients with a successful procedure and complete follow-up information will be included in the PP set.

12.3 Statistical method

Data will be analyzed using SPSS V19.0 software package. Two sided test with alpha level of 0.05 will be used.

Baseline demographic and clinical variables will be summarized for each of the treatment groups for the ITT set. All continuous variables will be summarized using means, standard deviations, medians, interquartile ranges, minimums and maximum

values and two-sided 95% confidence intervals. Categorical variables will be summarized using frequencies and percentages with two-sided exact 95% confidence intervals. P-values comparing the two treatment groups will be presented for descriptive purposes. Continuous data will be summarized using mean and standard deviation and compared using Student's t-test or one-way ANOVA. Time-to-event data were compared with the log-rank test.

Pre-specified subgroups for analysis include gender, age, type of AMI, heart failure, diabetes, anemia, renal insufficiency, arterial access, multivessel disease, history of cardiovascular events, high bleeding risk, and PCI for left anterior descending coronary artery.

13. Quality Control

Sponsor shall appoint monitors to conduct systematic monitoring for the study in accordance with GCP principles to ensure the study is carried out according to the protocol and the case report form is identical with original data. The monitors should also assess compliance corresponding to the regulations and protocol.

Investigators must ensure the integrity of the medical files. All study files will be reviewed by the sponsor and monitors. Monitors should ensure the following: the rights of the subjects should be protected; original data should comply with GCP and protocol requirements.

14. Clinical Event Committee (CEC)

A Clinical Events Committee (CEC) is organized for this study. The committee is composed of a number of interventional cardiologists who are not participations in this study. The committee shoulders the mission for the classification of clinical events and the development of specific criteria of clinical endpoints used in this study. The CEC will request the original data as necessary. All CEC members are familiar with the protocol of this study. All events are judged based on ARC, BARC and other standard definitions (Appendix 1). The Committee shall regularly make assessments and judgments on death, myocardial infarction, ischemia-driven target vessel revascularization, stent thrombosis, bleeding, stroke and thrombocytopenia events

which occur during the trial.

15. Ethics Committee

Before study initiation, the study director must submit the study protocol, informed consent form and other related study documents to the Ethics Committee to obtain its approval for conducting the clinical trial. After receiving the application, the Ethics Committee will convene a meeting to review, discuss and issue written comments attached with the list of participants, professional information and signature of primary investigator. During the study, the sponsor or contract research organization appointed by the sponsor should promptly report serious adverse events, including risks to subjects and other issues. Any modification to the protocol should be approved and recorded by the Medical Ethics Committee.

16. Study Management

16.1 Modification in the protocol

Any modification in the protocol should be released by sponsor and signed by investigators. The updated protocol should be saved as an annex. Any modification to protocol should be approved and recorded by the Medical Ethics Committee.

If deviations from the protocol are necessary, investigators should inform the sponsor as soon as possible, and discuss the specific situation to reach an agreement. The reason for deviation from the protocol should be recorded.

If the telephone or address is changed during the study, the sponsor will inform investigators in writing without modification to protocol.

16.2 CRF tracking

All CRFs of subjects who signed an informed consent should be turned over regardless of whether the study is completed. Any questions or comments on the case report form must be submitted directly to the sponsors and CRA.

16.3 Training

Sponsor must ensure that all staff involved in the study have been trained by the sponsor or the organization designated by sponsor before the study starts. An investigators' meeting should be convened for all investigators to be familiar with the

protocol as well.

16.4 Replacement of research center

Research centers which are replaced must be documented. The only reasons to replace a research center are slow enrollment and poor compliance.

16.5 Clinical follow-up

All AE/SAE should be followed up; see details in the relevant sections.

17. Responsibilities of each party

17.1 Responsibilities of Sponsor

1) Design the study protocol and sign contracts with the investigators and contract research organization;

2) Provide instruction of the drug used in the study to the investigators and monitors;

3) Provide relevant training to the investigators before study initiation;

4) Collect and keep clinical data and information；

5) Collect and keep relevant information, such as clinical programs, medical records, the ethics committee opinions, adverse event reports, statistical analysis, basic data and final clinical report;

6) Report side effects to the administration;

7) Provide rights and ability to terminate the study.

17.2 Responsibilities of Investigators

1) Be familiar with and strictly follow the study protocol;

2) Complete the clinical study within the stipulated time, including 30-day, 6-month, and 12-month clinic and telephone follow-up;

3) Submit the study protocol to local ethics committee and update progress to sponsor;

4) Be familiar with relevant data (nature, efficacy and safety of the study drug);

5) Conduct the clinical trial in qualified medical institutions capable of handling all kinds of emergency situations to ensure the safety of subjects; laboratory test results should be accurate and reliable;

6) Obtain consent from the medical institutions, and ensure the clinical study is completed within the stipulated time. All stuff members should be familiar with their

responsibilities to ensure a sufficient number of subjects are enrolled;

7) Ensure that subjects signed the informed consent forms prior to study initiation, and ensure their safety;

8) If serious adverse events occur, investigators must immediately take appropriate therapeutic measures for the subjects, and report the events to the Ethics Committee, the sponsor, and the State Food and Drug Administration within 24h after informed of these events. Meanwhile, investigators should ensure the subjects receive appropriate treatment in case of adverse events;

9) Ensure that the data is true, accurate, complete, timely, and legally recorded in the medical files and CRF;

10) Accept the monitoring and auditing of the monitors as well as inspecting of drug supervision and management department so as to ensure the quality of the clinical study;

11) Ensure no conflict exists with other clinical studies；

12) The interests of the subjects are priority in any situation. Protecting subjects from adverse events is consistent with the protocol, but any AEs and deviations from the protocol should be described in the final report;

13) Any modification (for subjects' safety) that deviate from the protocol should be reported to the Ethics Committee and the sponsor;

14) If unexpected events occur, investigators should terminate the clinical study and notify the subjects and their doctors;

15) Take primary responsibility to ensure the validity, clarity and reliability of all documents relating to the study;

16) Any modification to the original data must be signed by an authorized person and dated, and the original records must be retained for future reference;

17) After completion of the follow-up for the study, investigators should submit a final study report to the sponsor;

18) They also should maintain confidentiality obligations regarding information provided by the sponsor during the entire process of the study.

17.3 Responsibilities of CRO

1) Monitor the entire process of the study;

2) Promptly update any adverse events or deviations to sponsor and investigators;

3) Follow the protocol and report any variances from the protocol to sponsor in writing;

4) Use study drugs strictly according to the protocol, and report any devaitions to sponsor;

5) Conduct systematic monitoring for the study in accordance with GCP principles;

6) Obtain the informed consent of the subjects;

7) In accordance with national regulations, the case record form should be recorded on time and consistent with the data from the subject；

8) Record and report any adverse events to sponsor;

9) Retain records for subjects, as well as any study terminations;

10) After completion of the follow-up for the study, the CRO should submit a final study report to the sponsor and investigators;

11) They also should maintain confidentiality obligations regarding information provided by the sponsor during the entire process of the study.

Appendix 1. Definitions

Death: Deaths that are not caused by definite non-cardiac factors are deemed as cardiac deaths. Specifically, any unexpected deaths in subject are deemed as cardiac deaths, even if they also have potential fatal non-cardiac diseases (for example, cancer and infection).

Cardiac death: any deaths without known cause, and deaths caused by immediate heart-related factors (such as MI, low cardiac output heart failure or fatal arrhythmia) are deemed as cardiac deaths, including those related to surgery and accompanied treatment.

Vascular death: deaths caused by cerebrovascular diseases, pulmonary embolism, aneurysm rupture or other vascular diseases.

Non-vascular death: any deaths that are not covered in the definitions above, including those caused by infection, pyemia, pulmonary diseases, accident, suicide or injury.

Myocardial infarction. Myocardial infarction is defined according to the third Universal Definition of Myocardial Infarction.

Type 1: Spontaneous myocardial infarction.

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischaemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism,

tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG modification or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG modification or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves

or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Stent thrombosis: Stent thrombosis is defined according to the definite or probable criteria of the Academic Research Consortium (Circulation 2007;115:2344-51).

1. Definite stent thrombosis

Presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion.

2. Probable stent thrombosis

Unexplained death within 30 days after the procedure, or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.

3. Possible stent thrombosis

All unexplained death occurring at least 30 days after the procedure.

Stent thrombosis classification by time frame

1. Acute stent thrombosis

Occurring within 24 hours after the index PCI.

2. Subacute stent thrombosis

Occurring between 24 hours and 30 days after the index PCI.

3. Late stent thrombosis

Occurring between 31 and 360 days after the index PCI.

4. Very late stent thrombosis

Occurring later than 360 days after the index PCI.

Ischemia-driven Target Vessel Revascularization. Ischemia-driven target vessel revascularization is defined as repeat PCI or bypass surgery of the target lesion(s) and any additional lesions in the main epicardial coronary artery or branches containing the target lesion, with one or more of the following conditions:

1. Patient had ischemic symptoms and ECG-changes referable to the target lesion.

2. Diameter stenosis ≥50% at follow-up angiography and a positive functional study corresponding to the area served by the target vessel.

3. Diameter stenosis <50% at follow-up angiography but a markedly positive functional study or ECG-modification corresponding to the territory supplied by target vessel.

4. Diameter stenosis ≥70% at follow-up angiography in absence of documented clinical or functional ischemia.

Stroke. Stroke is defined as an acute event of non-hemorrhagic cerebrovascular origin causing focal or global neurologic dysfunction lasting > 24 hours, which is confirmed by both clinical and radiographic criteria.

Bleeding. Bleeding is defined according to the Bleeding Academic Research Consortium (Circulation 2011;123:2736-47).

Type 0: no bleeding.

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following

criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.

Type 3:

Type 3a: Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed); any transfusion with overt bleeding.

Type 3b: Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); Bleeding requiring intravenous vasoactive agents.

Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); Subcategories confirmed by autopsy or imaging or lumbar puncture; Intraocular bleed compromising vision.

Type 4: CABG-related bleeding: Perioperative intracranial bleeding within 48 h; Reoperation after closure of sternotomy for the purpose of controlling bleeding; Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period; Chest tube output ≥2L within a 24-h period.

Type 5: fatal bleeding.

Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.

Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

Acquired thrombocytopenia. Acquired thrombocytopenia is defined as a platelet count decrease by >50% or by >150×10^9/L from baseline.

Appendix 2. Informed consent

（V2.01）

Title：BivaliRudin in Acute Myocardial Infarction versus Heparin and GPI plus Heparin: a Randomized Controlled Trial.

Research center: _____

1. Research aim and profile

Since you have been confirmed or suspected as being diagnosed with an acute myocardial infarction, you will undergo emergency coronary angiography. If necessary, a percutaneous coronary intervention, PCI (Including the balloon expansion of narrow blood vessels and placing a stent) may be performed. So you are invited to attend the study.

PCI therapy is a conventional treatment in patients with coronary heart disease (CHD). Anticoagulant drugs such as heparin or low molecular heparin must be used as a routine during PCI. Bivalirudin, a new anticoagulant drug, had significantly lower drug related bleeding rates than traditional heparin therapy in large scale clinical studies such as REPLACE-2、ACUITY、HORIZONS-AMI. Bivalirudin was the preferred recommended drug for PCI anticoagulation in the 2011 joint guidelines of the foundation of the American College of Cardiology, the American Heart Association and the American Society for Cardiovascular Angiography and Interventions.

The present study is enrolling AMI patients undergoing PCI to observe whether bivalirudin improves the efficacy and safety compared to traditional heparin or heparin treatment plus tirofiban. Patients participating in this study will be randomly assigned to three treatment groups: bivalirudin alone, or unfractionated heparin alone, or unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor. The care provide for patients treated with each kind of therapy are otherwise equal. Drug therapy would begin before PCI, and depending on the drug a continuous intravenous infusion may be continued for up to 36 h after PCI.

Patients in each group will take antiplatelet drugs as follows: 1) aspirin: 300mg before PCI, 100 mg every day long term after PCI; 2) clopidogrel: 300mg - 600mg before PCI, 75 mg each day for 1 year. Patients who have already used clopidogrel 75mg per day for 5 days need no loading dose. Aspirin and clopidogrel are both the conventional drugs taken around the time of

PCI. You need to take them whether or not you participate in the study.

2. Protocols

2.1 Therapy procedure

Your doctor will determine whether you are eligible to participate in this study according to your clinical history (including any medications you are taking), in-hospital examination, routine tests and ECG. After discharge, you need outpatient follow-up at 30 days, 6 months and 12 months.

Interview 1(0-3 day before PCI)

Patients will be randomized to one of the three groups if suitable for participation in this study and after signing the informed consent. Different drug treatments would be done according to randomization. Other standard drugs (except the study drugs) would be determined by your doctor. You will undergo coronary angiography. In order to observe blood coagulation function, doctors will take 5 ml blood from the arterial sheath for laboratory tests.

Interview 2 (30 days after PCI):

The doctor will ask for your symptoms. When necessary, your doctor will check for vital signs and take blood tests as an outpatient, or you will receive treatment as necessary during any hospital admissions. The doctor will record any therapies provided.

Interview 3 (6 months after PCI):

The doctor will ask for your symptoms. When necessary, your doctor will check for vital signs and take blood tests as an outpatient, or you will receive treatment as necessary during any hospital admissions. The doctor will record any therapies provided.

Interview 4 (12 months after PCI):

The doctor will ask for your symptoms. When necessary, your doctor will check for vital signs and take blood tests as an outpatient, or you will receive treatment as necessary during any hospital admissions. The doctor will record any therapies provided.

2.2 Study time and number of patients

A total of 2400 patients would participate in preliminary screening in the present study. Finally 2100 patients would be enrolled in the study. The approximate time span is 12 months. This study would will be carried out in 80 heart centers.

2.3 Limitations and responsibilities of subjects

If you have any symptoms or discomfort or hear of any lab abnormalities, please inform your

study doctor immediately. Contact information will be listed on the informed consent.

3. Side effects, risks, and discomfort

3.1 Side effects

Adverse reactions of bivalirudin have been studied in about 3000 patients. Results showed that the drug was well tolerated. Bleeding is the most common complication (usually at the arterial puncture site, sometimes from other body parts). Other rare adverse reactions are: thrombocytopenia, anemia, allergic reactions, ventricular tachycardia, angina pectoris, bradycardia, dyspnea, rashes, backache, headaches, low blood pressure.

If you are randomized to a regular treatment group (heparin or heparin plus tirofiban), these drugs can have similar side effects. And every patient whose diagnosis was coronary heart disease (CHD) and in whom PCI was performed would receive anticoagulant therapy, regardless of in this study.

3.2 The possible influence to the fetus

Females:

Participating in the study may be dangerous to the unborn fetus. If you are a pregnant woman or got pregnant during the study, these dangers could affect you or your unborn child. Women should use contraception during study. Acceptable methods including oral contraceptives, intrauterine device and protective screen containing spermicide (diaphragm, condoms). Contraceptives should be approved by the doctor.

Before the study begin, every women of child-bearing potential will undergo a pregnancy test. Pregnancy tests may be performed repeatedly due to the uncertainty of the test. Please inform your doctor if you are pregnant.

Pregnancy is a reason to stop the study. If you become pregnant during study, you must withdraw from the study. If you become pregnancy within 28 days of the use of the study drugs, please contact with your doctor for safety monitoring. You should let your obstetrician know you have participated in this study. Your cardiologist collect pregnancy data from the obstetrician for safety monitoring.

Males:

If your spouse or partner becomes pregnancy when you are participating in the study or within 28

days of use of the study drugs, please let your doctor know. If your spouse or partner has already become pregnancy, she will be asked to sign a consent form to permit your research doctor to collect pregnancy data from her obstetrician just for safety monitoring.

3.3 Discomfort

You may develop discomfort such as pain at the blood collecting site, burning or blood clot, feel dizzy or faint at needling, or allergy to tape.

4. Your potential benefits

In the study protocol, the drugs and dosing regimens in the regular treatment groups (heparin group and heparin plus tirofiban) have been approved by the government, and have been in clinical use for several decades. Bivalirudin, which has been approved by the government, is also used in routine clinical practice. Bivalirudin has been reported to result in lower bleeding and death rates than control groups in some studies. There are other anticoagulant drugs such as low molecular heparin and fondaparinux sodium that are used in clinical practice, although the guideline recommendation levels for these two drugs are lower than bivalirudin, heparin and tirofiban. Patients in the bivalirudin group may benefit from this study, and other patients may be benefit from information obtained from the present study. If you are enrolled in the study, the costs may be lower than routine medicine service. If you are randomized to bivalirudin, the bivalirudin will be free. If you are randomized to regular treatment group (heparin or heparin plus tirofiban), you will get free clopidogrel tablets for 1 month. Your study doctor will pay close attention and you will have careful follow-up so that adverse events may be processed quickly.

5. Compensation

We do not want you to have any health problems due to the study. If you suffer from bleeding which is identified by medical department that is caused by bivalirudin, you will be provided with appropriate free treatment.

6. Withdrawal

You have the right to decide whether to participate in the study. You can choose not to participate in the study or withdraw at any time during the study. Your decision will not affect your medical service at the time of hospitalization. There will be no loss of your entitled benefits. After your dropping out of the study, we will analyze data collected before you dropped out unless you do not agree that we may do so.

In some cases, your doctor will withdraw you from the study. This may occur if you do not follow the study doctor's guidance; if you develop a serious disease that is irrelevant to present study; if the present study is not advantageous to you in your doctor’s opinion; if the study was halted by research group, management agency or Ethics Committee; if pregnancy or planned pregnancy or breastfeeding occurs.

7. Privacy

Your record and health data in present study will be kept secret. But these files will be provided to the Ethics Committee and department of drug supervision and administration.

Signing this consent form indicates that you have agreed to the above mentioned staffing and authority obtaining your data. We will take measures to protect your privacy, and your identity will not appear in any research documents, reports, or published articles, now or in the future. After your withdrawing from the study, we will analyze data collected before unless you do not agree that we may do so.

Finally, the research data will be published as an academic paper. But your identity will not be disclosed in this paper, and no one will be able to guess your identity.

Your participating in the present study (even if you withdraw) means you agree with no limitation of your data being transmitted to the department of drug supervision and administration.

8. Answer questions about the study

Before you sign up, you should ask any and all questions about the study. The research staff will also answer your questions anytime during the study.

Name: ID:

If you have any questions about how the study carrying out or potential side effects please contact:

Research Doctor: Tel:

Research Coordinator: Tel:

The present study has been approved on paper by Ethics Committee of General Hospital of Shenyang Military region. If you have any questions about you rights in the study, please contact:

Ethics Committee of General Hospital of Shenyang Military region

No.83 Wenhua Road, Shenyang, Liaoning Province, 110016, Tel:+86-24-28856472

Informed consent (for signature)

I have read all the words of the above guidelines. I voluntarily agree to participate in the study" BivaliRudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and Heparin: a Randomised Controlled Trial."

1. I have recovered Informed consent with signature and date. I understand the purpose, nature, protocol, potential risk, and benefit of this study, and other standard treatments for my disease. I have had plenty of time to ask any questions. I have been provided satisfactory answers.

2. I agree to cooperate with the research doctor and comply with the requirements of this study.

3. I have been told that I must contact with doctor if illness or symptom arises so I may receive for effective treatment.

4. I understand that this study fully follows the declaration of Helsinki, and Chinese Clinical research regulations and specifications. The present study has been approved on paper by the Ethics Committee of General Hospital of Shenyang Military region.

5. I can choose not to participate in the study or withdraw at any time during the study. My decision will not affect my medical service at the time of hospitalization.

6. My participating in the present study (even if I withdraw) means you agree with no limitation of dealing with my data in clinical research. My privacy will be kept secret and will not appear in any research documents, reports, or published articles.

I agree to participate in the study.

Patient Name (signature): Date:

Tel:

I have detailed introduced the purpose, nature, protocol, potential risks and benefits of this study. The subject has agreed to be enrolled in the study with signature and date.

Investigator (signature) Date:

Tel: