Rationale and design of the RIGHT trial: A multicenter, randomized, double-blind, placebo-controlled trial of anticoagulation prolongation versus no anticoagulation after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

Yan Yan, Xiao Wang, Jincheng Guo, Yongjun Li, Hui Ai, Wei Gong, Bin Que, Lei Zhen, Jiapeng Lu, Changsheng Ma, et al.

Rationale and design of the RIGHT trial: a multicenter, randomized, double-blind, placebo-controlled trial of anticoagulation prolongation vs. no anticoagulation after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

Yan Yan, MD[1,2], Xiao Wang, MD[1,2], Jincheng Guo, MD, PhD[3], Yongjun Li, MD, PhD[4], Hui Ai,MD[1,2], Wei Gong,MD[1,2], Bin Que,MD[1,2], Lei Zhen,MD[1,2], Jiapeng Lu, PhD[5], Changsheng Ma, MD, PhD[6], Gilles Montalescot, MD, PhD[7] and Shaoping Nie, MD, PhD[1,2]

[1]Emergency & Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

[2] Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, China

[3] Beijing Luhe Hospital, Capital Medical University, Beijing, China

[4] The Second Hospital of Hebei Medical University, Shijiazhuang, China

[5] National Clinical Research Center of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

[6] Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

[7] Sorbonne University, ACTION Study Group, INSERM UMRS 1166, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France

Corresponding authors:

Shaoping Nie, MD, PhD
Emergency & Critical Care Center
Beijing Anzhen Hospital, Capital Medical University
2 Anzhen Road, Chaoyang District
Beijing, China, 100029
Email: spnie@ccmu.edu.cn

Gilles Montalescot, MD, PhD
ACTION Study Group, Institut de Cardiologie,
Hôpital Pitié-Salpêtrière, Paris, France,
75013
E-mail: gilles.montalescot@aphp.fr

ABSTRACT

BACKGROUD Current guidelines recommend anticoagulation therapy during primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI). However, whether anticoagulation should be continued after pPCI has not been well investigated.

METHODS/DESIGN The RIGHT trial is a prospective, multicenter, randomized, double-blind, placebo-controlled trial in STEMI patients treated with pPCI evaluating the prolongation of anticoagulation after the procedure. Patients are randomized in a 1:1 fashion to receive either prolonged anticoagulant or matching placebo (no anticoagulation) for at least 48 hours after the procedure. When randomized to anticoagulation prolongation, the patient is assigned to intravenous unfractionated heparin (UFH) or subcutaneous enoxaparin or intravenous bivalirudin (same drug and same regimen at each center). The primary efficacy endpoint is the composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, stent thrombosis (definite) or urgent revascularization (any vessel) at 30 days. The primary safety endpoint is major bleeding (BARC 3 to 5) at 30 days. Based on a superiority design and assuming a 35% relative risk reduction (from 7% to 4.5%), 2,856 patients will be enrolled, accounting for a 5% drop-out rate ($\alpha = 0.05$ and power = 80%).

CONCLUSION The RIGHT trial tests the hypothesis that post-procedural anticoagulation is superior to no anticoagulation in reducing ischemic events in STEMI patients undergoing pPCI.

BACKGROUND

Anticoagulant therapy is a mandatory treatment during primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI). STEMI patients remain at risk of ischemic events after the procedure, and post-procedure anticoagulation (PPAC) has been used in clinical practice.[1] However, data regarding the efficacy and safety of PPAC are limited. The MATRIX trial showed that prolonging bivalirudin infusion after PCI did not improve outcomes when compared with interruption of bivalirudin infusion at the end of the PCI procedure. However a subgroup analysis suggested a dose effect as a post-PCI full dose (≤4 hours) was associated with improved outcomes when compared with no or low-dose bivalirudin after PCI.[2,3] This post-hoc analysis remains hypothesis-generating. The current guidelines do not provide clear or consistent recommendations (Table 1).[4-6] Whether anticoagulation should be continued in STEMI after pPCI remains unclear.

Previous studies suggested that acute thrombotic complications of pPCI occur mostly within the first 48 hours after the procedure, while major bleeding events (1% to 2%) occur more steadily over 30 days after procedure.[2,3,7] The delayed effect of oral $P2Y_{12}$ inhibitor and residual thrombosis after stenting may explain the early ischemic complications. Whether a short duration of PPAC (up to ≥48 hours or intensive cardiac care unit discharge) could provide better protection against ischemic event has not been evaluated in a randomized fashion.[8-11]

To test this hypothesis, we designed the randomized comparison of anticoagulation after primary percutaneous coronary intervention using enoxaparin, ACT-guided unfractionated heparin or bivalirudin prolongation vs. no anticoagulation to improve clinical outcome (RIGHT) trial to examine the efficacy and safety of prolonged versus interrupted anticoagulation therapy after pPCI of STEMI patients.

METHODS

Study design

The RIGHT study (clinicaltrial.gov NCT 03664180) is an investigator initiated, nationwide, multicenter, randomized, double-blind, placebo-controlled trial comparing anticoagulation prolongation (experimental group) versus no anticoagulation (control group) after pPCI in approximately 2,856 STEMI patient recruited from ≥40 interventional cardiology sites across China. The trial was designed by Prof. Shaoping Nie and Dr. Yan Yan in conjunction with the scientific director Prof. Gilles Montalescot and the steering committee and scientific review committee (listed in the Appendix 1).

The trial evaluates the comparative efficacy and safety of a strategy of post-procedure anticoagulation versus interruption immediately after pPCI performed in STEMI patients (Figure 1). Randomization allocates the patient to a strategy of anticoagulation or of no anticoagulation but in the anticoagulation group the type of anticoagulant is not randomized but prespecified by center. The steering committee provides scientific direction for the trial and meet periodically to assess its operational progress. The study is conducted according to globally accepted standards of Good Clinical Practice (GCP guidelines) with full adherence to the ethical principles laid down in the Declaration of Helsinki and in keeping with applicable local regulations.

Study objectives

The primary efficacy objective is to demonstrate superiority of a strategy of post-procedure anticoagulation using intravenous unfractionated heparin (with dose adjustment according to ACT measurement) or subcutaneous enoxaparin (fixed dose without anticoagulation monitoring) or intravenous bivalirudin (without anticoagulation monitoring) as compared to their respective placebo to prevent any event of the composite endpoint of all-cause death, non-fatal myocardial infarction, non-fatal stroke, stent thrombosis (definite) or urgent revascularization (any vessel) over 30 days of follow-up. The type of anticoagulation in the prolonged anticoagulation arm was the same for all patients of the same center and decided before the start of the trial according to the current practice of this center.

The primary safety objective is to evaluate major bleeding (BARC 3 to 5) through 30 days from randomization.

The key secondary objective is to evaluate the benefit of each specific anticoagulation regimen (bivalirudin, enoxaparin or unfractionated heparin) on the composite ischemic endpoint of all-cause death, non-fatal myocardial infarction, non-fatal stroke, stent thrombosis (definite) or urgent revascularization (any vessel) through 30 days from randomization. These non-randomized evaluations will be provided only for descriptive information and the results considered only as hypothesis generating.

Study population

All patients are screened for the RIGHT trial has a confirmed diagnosis of STEMI and an indication for pPCI. Patients may have, or not received anticoagulation before pPCI. pPCI is defined as an emergent percutaneous coronary intervention (PCI) performed in the same setting as the coronary angiogram, on the identified infarct-related artery, without any

previous administration of a fibrinolytic treatment before access to the catheterization laboratory. Enrollment into the study requires a written informed consent and a pPCI always performed with the same anticoagulation regimen of bivalirudin. Patients meeting all of the inclusion criteria but none of the exclusion criteria (Table 2) are eligible for randomization.

Randomization and blindness

Randomization occurs after the procedure and prior to the end of the PCI bivalirudin infusion in eligible patients. The PCI bivalirudin infusion dose (1.75 mg/kg/h) is continued up to 4 hours after sheath removal.

All eligible patients are randomized via Interactive Web Response System (IWRS) in 1:1 fashion in blocks of six, to one of the two study arms (prolongation vs. interruption of anticoagulation after procedure). When randomized to the anticoagulation arm, the patient is assigned (regimen is prechosen by center) to unfractionated heparin (UFH), enoxaparin or bivalirudin prolongation for at least 48 hours at each site. In the no anticoagulation arm, the patient receives the matching placebo.

The study has a double-blind design with UFH, enoxaparin or bivalirudin and their matching placebo. The randomization number assigned by IWRS to the patient is linked to a treatment arm and specifies a unique medication number. Investigator dispenses study medication according to the medication number. The patients, investigators, academic research center staff, and study site research personnel involved in the treatment and/or clinical evaluation of the patients are not aware of the treatment received. To maintain the double-blind in the UFH group, the monitoring ACT values cannot be revealed to the investigator nor to the patient. Only the designated unblinded medical professional knows the assignment to UFH or placebo. They provide true ACT values for patients on UFH or mock values for patients assigned to placebo. Investigators adjust the infusion rate according to a pre-established nomogram not knowing if the values are real or mock values (double dummy). The mock values are kept in a blinded envelop with a prefilled list of 10 ACT values corresponding to likely variations under UFH treatment. A total of 40 prefilled lists were prepared for the whole study. No ACT and no other coagulation measurements are performed in the other two groups (bivalirudin and enoxaparin) during the administration of study medication.

Study medication preparation

UFH and its placebo are manufactured and packaged by Changzhou Qianhong Bio-pharma Co., Ltd and distributed using Qianhong products distribution procedures. UFH is

presented as a sterile, clear, colorless liquid. Each ampoule is for single use only. Placebo is presented in identical containers as a clear, colorless, sterile liquid.

Enoxaparin sodium injection (Clexane, Sanofi) is purchased and distributed from the commercial way. Enoxaparin is presented in prefilled syringe as a sterile, clear, colorless liquid as well as its placebo. A designated unblinded medical professional is in charge of preparing study medication after randomization on site. He/she transfers the prefilled syringes in a blinder manner to the medical personnel in charge of the patient.

Bivalirudin concentrated powder and placebo is donated by Jiangsu Hansoh Pharmaceutical Group Co., Ltd. and distributed using Hansoh products distribution procedures. Bivalirudin is presented as a concentrated powder. Each vial is for single use only. Placebo is presented in identical containers as a concentrated powder.

All the study medications are stored according to the storage and expiration information according to the industry requirements. Damaged product is not administered. The box number of study medication (active drug or placebo) is recorded on electronic case report form (eCRF).

Study treatment

Double-blind study medication is administered within 30 minutes before the end of the PCI bivalirudin infusion. After PCI the transition from bivalirudin infusion to prolonged anticoagulation over a 30 minute period prevents accumulation of the drugs. The anticoagulation strategy was prechosen by center. Each center can use only one anticoagulant in all patients randomized at this center, either UFH or enoxaparin or bivalirudin (Figure 1). Thus, each subject is assigned to one of the following study groups: 1) UFH group 2) Enoxaparin group 3) Bivalirudin group or 4) placebo.

Study medication is given immediately after randomization. All study medications are used with reduced doses to provide reduced anticoagulation levels compared to what is done during the procedure. The recommended dose of UFH is 10 IU/kg/h initially, adjusted to maintain ACT between 150 to and 220 seconds. The dose of enoxaparin is 40 mg/day s.c. once daily; The dose of bivalirudin is 0.2 mg/kg/h (low-dose). Study medication is administered for at least 48 hours after the procedure or until discharge from CCU if it occurs later. Study medication will be stopped rapidly (within 48 hours) if eGFR <15 L/min/1.73m^2 in the enoxaparin and bivalirudin group. After randomization, the patients can only receive the drug allocated by randomization. If a new indication for chronic anticoagulation occurs during the follow-up period of the patient (e.g. new AF), full anticoagulation is provided to the patient and the choice of the drug left to the discretion of the investigator. The patient

will be censored in the final analysis at this date corresponding to the start of the new anticoagulant treatment. An independent data safety monitoring board (DSMB) is appointed to monitor the progress of the trial and to ensure that the safety of the patients enrolled in the trial is not compromised.

Follow-up

All randomized subjects are followed for 30 days after the procedure. All randomized subjects have a follow-up telephone contact or office visit (preferred) at 48 hours and 30 days after randomization. The follow-up is continued for a total of 1 year, with data collected by telephone contact or office visits at 6 months and 1 year.

Endpoint

The primary efficacy endpoint is a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, stent thrombosis (definite) or urgent revascularization (any vessel) at 30 days. The definition of MI is based on the fourth universal definition of myocardial infarction criteria and is dependent on the clinical timing of the event in relation to PCI and randomization corresponding to start of anticoagulation therapy. [12] The event "MI" corresponds in our study to a "reinfarction" within 30 days of the index MI. The classification of MI (type 1, 2, 3, 4 or 5) is adjudicated according to the fourth universal definition of MI.[12] MI events considered by the CEC include type 1, 2 and 4b. Type 3 MI is adjudicated as cardiovascular death.

The primary safety endpoint of bleeding includes BARC types 3 to 5 within the first 30 days after randomization.[13] Secondary endpoints include a composite of all-cause death, non-fatal myocardial infarction, or non-fatal stroke at 30 days, individual events of the primary endpoint at 30 days, cardiovascular death at 30 days, stent thrombosis (ARC definite) at 30 days, bleeding events (TIMI, STEEPLE and GUSTO definition) and thrombocytopenia (a platelet count <50 000 cells per µL) at 30 days.[13-15]

An independent Clinical Events Committee (CEC) will adjudicate all ischemic and bleeding events. The committee members and the CEC management team will be completely blinded to the randomized therapy, as well as any patient identifying information. The CEC will adjudicate the events based on pre-determined definitions outlined in the CEC Charter. The CEC members will not be study investigators (Appendix 1).

Statistical consideration

The event rate (primary endpoint) taken here is based on similar pPCI studies (see table 3): 7% at one month in the control arm.[2,16-20] A sample size of 2720 patients randomized to anticoagulation vs no anticoagulation will have 80% power to detect a 35% reduction in the

relative risk (4.5%) with a survival analysis at a two-sided alpha level of 5%. With a dropout rate of 5% we calculated that 1428 patients /group will be required (total of 2856 patients).

All the statistical procedures will be made with blinded treatment arms. A detailed statistical analysis plan will be finalized before database locking. The primary and secondary efficacy endpoints will be analyzed using the intent-to-treat (ITT) population, which is defined as all subjects who are randomized regardless of whether they have received study drug. The safety endpoints observed or derived in the study will be analyzed using the safety population, which is defined as all subjects who are randomized and have been treated with study drug (at least one dose).

Baseline characteristics will be tabulated and comparability/differences between the study groups will be tested by t test or nonparametric test for continuous variables or chi-square or Fisher exact test for categorical variables. For each primary and secondary endpoint, Kaplan-Meier methods will be used to estimate 30-days event rates in each arm, and comparisons between study groups will be performed using log-rank test. And the hazard ratios (HRs) with 95% CIs will be estimated for the primary and secondary efficacy endpoints with Cox proportional-hazards method. In addition, subgroup analysis will be performed to assess the consistency of treatment effects of post-procedure anticoagulation compared with placebo on primary efficacy endpoint using tests for interactions. The pre-defined subgroups are shown in table 4. No interim analysis will be performed.

Missing data at baseline will not be imputed. Missing data for the primary endpoint will be censored at the time of the last information available. All missing patient will be searched for mortality. All tests will be two-sided at a 5% significance level. All data analysis will be conducted with SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

Current status

Currently, 36 investigation sites are recruiting patients. The first patient was recruited on Jan 11, 2019, and 1159 patients have already been enrolled on Jan 31, 2020 (Table 5). The duration of this study is expected to be 24 months of recruitment with the expectation ending in the fourth quarter of 2020. The last patient 30-day visit is expected to occur in the first quarter of 2021. The current enrollment in the RIGHT study is shown in Figure 2. With a number of 1168 patients enrolled at the time of writing, the mean duration of study medication was 2.4 days.

CMR Substudy

The effect of prolonged anticoagulation after pPCI on myocardial injury remains unclear.

In a post-hoc analysis of the INNOVATION trial, there was a nominal but non-significant reduction in infarct size by cardiac magnetic resonance (CMR) between the prolonged anticoagulation group and brief anticoagulation group at 30 days after pPCI.[21] The RIGHT CMR substudy aims at determining whether post-procedure anticoagulation therapy, as compared with no anticoagulation, reduces infarct size measured by CMR in STEMI patients undergoing pPCI. The secondary objective is to evaluate the effect of different anticoagulation regimen used (bivalirudin, enoxaparin or UFH) on infarct size.

CMR scanning will be performed in 318 consecutive patients recruited from hospitals with onsite CMR at 3 to 7 days after pPCI. Patients with contraindications to CMR (e.g. claustrophobia) will be excluded. The primary endpoint is infarct size (percent infarcted myocardium relative to left ventricular [LV] mass). Secondary endpoints include the incidence of microvascular obstruction (MVO), the mass of MVO and intramyocardial hemorrhage (IMH), myocardial salvage index (MSI), and LV structure and function parameters. All CMR studies will be performed blindly to treatment allocation and according to a unique centralized protocol.

A total of 318 patients are to be enrolled to have 80% power to detect a 4% difference in infarct size in the two groups, assuming that infarct size will be 24.5±12% of LV mass in the no anticoagulation group ($\alpha = 0.05$ and power = 80%), accounting for 10% drop-out.

Organization and funding

The RIGHT study is led by the Academic Research Organization CREATE (China REsearch Allies for Thrombosis & Embolism), the coordinating center being the China National Clinical Research Center for Cardiovascular Disease, Beijing Anzhen Hospital. The study design and study protocol as well as the study management were discussed with the ACTION Study Group (www.action-coeur.org, Paris, France). The protocol was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University on October 18, 2018 (2018019). It is sponsored by Beijing Anzhen hospital, a member of the CREATE group. Site monitoring of all patient medical records is to be performed. Data management and analysis are performed under the responsibility of National Clinical Research Center of Cardiovascular Diseases.

The trial is supported by Jiangsu Hengrui Medicine Co., Ltd. through a research grant to the Beijing United Heart Foundation and partially funded by unrestricted grants from Beijing Anzhen hospital, Capital Medical University. No other extramural funding was used to support this work. Study medications have been obtained from Changzhou Qianhong Bio-pharma, Sanofi and Jiangsu Hansoh Pharmaceutical Group. The funders have no role in

study design, study conduct, data management, interpretation of the results, or decisions for publication. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Data Safety & Monitoring Board (DSMB)

An independent DSMB has been appointed to monitor the progress of the trial and to ensure that the safety of the patients enrolled in the trial is not compromised. DSMB members will not participate to any other aspect of the trial. A specific charter will be written to define the role of the DSMB and its interaction with the study chair and the study sponsor (Appendix 1).

DISCUSSION

Current guidelines recommend anticoagulant therapy during pPCI for STEMI.[5,6,22] Various anticoagulant options including UFH, enoxaparin, and bivalirudin, have been used for pPCI (Table 1).[23-25] Their utility for the prevention of ischemic event before and during procedure have been widely accepted.[2,16,17,20,23] However, whether anticoagulation should be continued after pPCI, has not been clearly investigated, casting doubt on the clinical utility of PPAC in daily practice. For example, in the Italian cath lab registry, anticoagulant therapy was used approximately in 10% of patients after procedure for STEMI.[1] In the pooled analysis of EUROMAX and HORIZON-AMI trials, 16.6% of patients received PPAC in the USA, 49.8% in the Europe and 18.8% in the rest of the world.[26] The reasons for these variations are complex, possibly due to local practice patterns, complications, and physician's choice but not really with evidence.[27]

Current guidelines in the management of STEMI recommend discharge at 48-72 hours in the low-risk patients with successful primary PCI (Class IIa, Level of Evidence: A).[5] The basis for this recommendation, however, stems from old trials or observational studies.[28] Currently with more effective and rapid reperfusion therapies, the low frequency of acute thrombotic complications and arrhythmias have decreased, and we recognize that some patients may be discharged earlier than 48 hours in some areas.[29] However, the median length of in-hospital stay is around 3 days in the national and regional reports, including the CathPCI registry in the United states.[30,31] Furthermore, whilst the benefits of complete revascularization over culprit-lesion PCI are now proven, meeting the requirement of staged PCI for full revascularization of several coronary arteries during the index of hospitalization may be more difficult to reach with very short hospital stay.[32]

The RIGHT trial evaluates whether prolonged anticoagulation is beneficial in patients with STEMI undergoing pPCI without any other indication for anticoagulation. Prior trials have evaluated PPAC in PCI with different designs.[33] The TETAMI trial enrolled 1,224 STEMI patients ineligible for reperfusion.[34] It confirmed that perioperative use with UFH or enoxaparin for at least 2 and up to 8 days had comparable safety and efficacy. [35] But patients in this trial did not receive timely revascularization, which is the gold standard for treating STEMI nowadays. ATLAS ACS 2–TIMI 51 randomized 15,526 stented ACS patients treated with daily dual antiplatelet therapy without an anticoagulation indication. Rivaroxaban reduced the incidence of ischemic event with increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding.[36] Further analysis on optimal dosage showed low-dose rivaroxaban had a better risk/benefit ratio on stent thrombosis than the full-dose.[37] In the recent MATRIX trial including 7213 patients with ACS, prolonging bivalirudin infusion after PCI did not improve the outcomes compared with bivalirudin infusion confined to the duration of PCI.[2] However, a post hoc analysis suggested that prolonging bivalirudin with a full-PCI dose after PCI was associated with the lowest risk of ischemic and bleeding events, which is in accordance with the current label of the drug.[3,26,27,38,39]

Considering the limited and discordant information on this topic, the RIGHT trial will complement the previous trials in several ways. First, it is the largest trial in the field and it is placebo-controlled providing an opportunity to show reductions in hard outcomes. Second, adjudication will use the fourth universal definition of myocardial infarction (MI) allowing a better characterization of reinfarction during the acute phase of STEMI. Third, RIGHT may clarify the optimal risk/benefit of anticoagulation duration in these patients. Fourth, RIGHT offers an opportunity of evaluating different anticoagulation strategies prechosen by center. As there is no randomization for the type of anticoagulant, the three anticoagulation regimens will not be directly compared. The information collected will be descriptive and hypothesis generating, in terms of efficacy and safety for post-procedure anticoagulation. Fifth, RIGHT use cardiac MR to assess MI size and microvascular obstruction, which are prognostic factors after reperfusion therapy.[21,40,41] Finally, the trial is national in scope and includes centers in Chinese mainland, allowing broad generalizability.

CONCLUSIONS

The RIGHT trial is the first multicenter, randomized, double-blind, placebo-controlled trial to address the utility of post procedural anticoagulation after successful pPCI for STEMI patients in the contemporary era.

CONTRIBUTION

YY, XW, GM and SN contributed to the trial design; YY, XW, JG, HA, WG, BQ, LZ, JL, GM and SN contributed to protocol development; YY, JG, YL and SN contributed to study conduct; YY, XW, GM and SN contributed to writing of the manuscript; JL contributed to the statistical analysis and actively participated in the writing of the statistical sections of the manuscript; all authors critically reviewed the manuscript and approved the final version.

DECLARATIONS OF INTEREST

Dr. Yan was funded by CS Optimizing Antithrombotic Research Fund (BJUHFCSOARF201801-14), the Fund for Beijing Science & Technology Development of TCM (QN2018-01) and Beijing Municipal Administration of Hospitals Incubating Program (PZ2019005). Dr. Wang was funded by National Natural Science Foundation of Chin (81870322) and Beijing Municipal Science and Technology Commission (Z181100001718060). Dr. Gong was funded by grants from the National Natural Science Foundation of China (81970292, 81600213), Beijing Hospitals Authority Youth Program (QML20190603), CS Optimizing Antithrombotic Research Fund (BJUHFCSOARF201901-08). Dr. Montalescot reports research Grants to the Institution or Consulting/Lecture Fees from Abbott, Amgen, Actelion, American College of Cardiology Foundation, AstraZeneca, Axis-Santé, Bayer, Boston-Scientific, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, China heart House, Daiichi-Sankyo, Idorsia, Elsevier, Europa, Fédération Française de Cardiologie, ICAN, Lead-Up, Medtronic, Menarini, MSD, Novo-Nordisk, Partners, Pfizer, Quantum Genomics, Sanofi, Servier, WebMD. Dr. Nie was funded by National Natural Science Foundation of China (81670222), Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX201710), Beijing Municipal Administration of Hospitals' Ascent Plan (DFL20180601), Natural Science Foundation of Beijing, China (7191003), and the Capital Health Research and Development of Special Fund (2018-1-2061). The other authors have no conflicts of interest to declare.

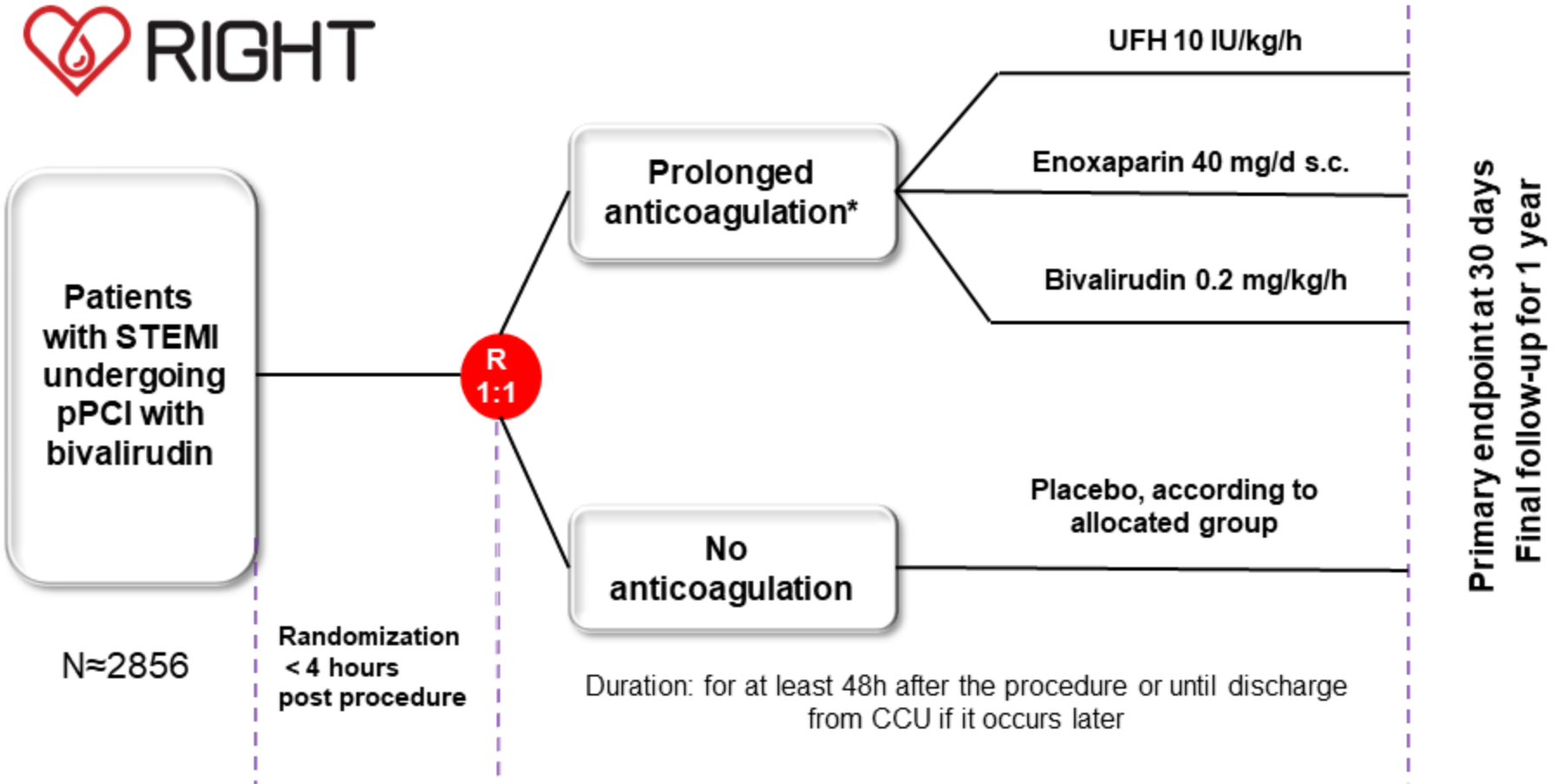
REFERENCE

1. De Luca L, Musumeci G, Leonardi S, et al. Antithrombotic strategies in the catheterization laboratory for patients with acute coronary syndromes undergoing percutaneous coronary interventions: insights from the EmploYEd antithrombotic therapies in patients with acute coronary Syndromes HOspitalized in iTalian cardiac care units Registry. J Cardiovasc Med (Hagerstown) 2017;18:580-9, http://dx.doi.org/10.2459/JCM.0000000000000533.
2. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med 2015;373:997-1009, http://dx.doi.org/10.1056/NEJMoa1507854.
3. Gargiulo G, Carrara G, Frigoli E, et al. Post-Procedural Bivalirudin Infusion at Full or Low Regimen in Patients With Acute Coronary Syndrome. J Am Coll Cardiol 2019;73:758-74, http://dx.doi.org/10.1016/j.jacc.2018.12.023.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165, http://dx.doi.org/10.1093/eurheartj/ehy394.
5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77, http://dx.doi.org/10.1093/eurheartj/ehx393.
6. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-e140, http://dx.doi.org/10.1016/j.jacc.2012.11.019.
7. Zeitouni M, Silvain J, Guedeney P, et al. Periprocedural myocardial infarction and injury in elective coronary stenting. Eur Heart J 2018;39:1100-1109, http://dx.doi.org/10.1093/eurheartj/ehx799.
8. Franchi F, Rollini F, Cho JR, et al. Impact of Escalating Loading Dose Regimens of Ticagrelor in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Results of a Prospective Randomized Pharmacokinetic and Pharmacodynamic Investigation. JACC Cardiovasc Interv 2015;8:1457-67, http://dx.doi.org/10.1016/j.jcin.2015.02.030.
9. Rollini F, Franchi F, Hu J, et al. Crushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Intervention: The CRUSH Study. J Am Coll Cardiol 2016;67:1994-2004, http://dx.doi.org/10.1016/j.jacc.2016.02.045.
10. Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol 2015;65:511-2, http://dx.doi.org/10.1016/j.jacc.2014.08.056.
11. Sumaya W, Parker WAE, Fretwell R, et al. Pharmacodynamic Effects of a 6-Hour Regimen of Enoxaparin in Patients Undergoing Primary Percutaneous Coronary Intervention (PENNY PCI Study). Thromb Haemost 2018;118:1250-6, http://dx.doi.org/10.1055/s-0038-1657768.
12. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237-269, http://dx.doi.org/10.1093/eurheartj/ehy462.
13. Meharn R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47, http://dx.doi.org/10.1161/CIRCULATIONAHA.110.009449.
14. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82, http://dx.doi.org/10.1056/NEJM199309023291001.
15. Montalescot G, White HD, Gallo R, et al. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. N Engl J Med 2006;355:1006-17, http://dx.doi.org/10.1056/NEJMoa052711.
16. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. Lancet 2011;378:693-703, http://dx.doi.org/10.1016/S0140-6736(11)60876-3.
17. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA 2015;313:1336-46, http://dx.doi.org/10.1001/jama.2015.2323.

18. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369:2207-17, http://dx.doi.org/10.1056/NEJMoa1311096.
19. Erlinge D, Omerovic E, Frobert O, et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. N Engl J Med 2017;377:1132-1142, http://dx.doi.org/ 10.1056/NEJMoa1706443.
20. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;384:1849-1858, http://dx.doi.org/10.1016/S0140-6736(14)60924-7.
21. Song PS, Kim MJ, Jeon KH, et al. Efficacy of postprocedural anticoagulation after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: A post-hoc analysis of the randomized INNOVATION trial. Medicine (Baltimore) 2019;98:e15277, http://dx.doi.org/10.1097/MD.0000000000015277.
22. Chinese Society of Cardiology of Chinese Medical Association. 2019 Chinese Society of Cardiology (CSC) guidelines for the diagnosis and management of patients with ST-segment elevation myocardial infarction. Zhonghua xin xue guan bing za zhi 2019;47:766-783, http://dx.doi.org/10.3760/cma.j.issn.0253-3758.2019.10.003.
23. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30, http://dx.doi.org/10.1056/NEJMoa0708191.
24. Montalescot G, Ellis SG, de Belder MA, et al. Enoxaparin in primary and facilitated percutaneous coronary intervention A formal prospective nonrandomized substudy of the FINESSE trial (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events). JACC Cardiovasc Interv 2010;3:203-12, http://dx.doi.org/10.1016/j.jcin.2009.11.012.
25. Tcheng JE, Kandzari DE, Grines CL, et al. Benefits and risks of abciximab use in primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. Circulation 2003;108:1316-23, http://dx.doi.org/10.1161/01.CIR.0000087601.45803.86.
26. Ducrocq G, Steg PG, Van't Hof A, et al. Utility of post-procedural anticoagulation after primary PCI for STEMI: insights from a pooled analysis of the HORIZONS-AMI and EUROMAX trials. Eur Heart J Acute Cardiovasc Care 2017;6:659-665, http://dx.doi.org/10.1177/2048872616650869.
27. Madhavan MV, Genereux P, Kirtane AJ, et al. Postprocedural anticoagulation for specific therapeutic indications after revascularization for ST-segment elevation myocardial infarction (from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction Trial). Am J Cardiol 2014;114:1322-8, http://dx.doi.org/10.1016/j.amjcard.2014.07.061.
28. Gong W, Li A, Ai H, et al. Safety of early discharge after primary angioplasty in low-risk patients with ST-segment elevation myocardial infarction: A meta-analysis of randomised controlled trials. Eur J Prev Cardiol. 2018;25(8):807-815. http://dx.doi.org/10.1177/2047487318763823.
29. Hedong Han, Xin Wei, Qian He, et al. Comparison of In-Hospital Mortality and Length of Stay in Acute ST-Segment-Elevation Myocardial Infarction Among Urban Teaching Hospitals in China and the United States. J Am Heart Assoc. 2019;8(22):e012054. http://dx.doi.org/10.1161/JAHA.119.012054.
30. Swaminathan RV, Rao SV, McCoy LA, et al. Hospital length of stay and clinical outcomes in older STEMI patients after primary PCI: a report from the national cardiovascular data registry. J Am Coll Cardiol. 2015;65(12):1161-1171. http://dx.doi.org/10.1016/j.jacc.2015.01.028.
31. Felipe Díez-Delhoyo, María Jesús Valero-Masa, Jesús Velásquez-Rodríguez, et al. Very Low Risk ST-segment Elevation Myocardial Infarction? It Exists and May Be Easily Identified. Int J Cardiol. 2017;228:615-620. http://dx.doi.org/10.1016/j.ijcard.2016.11.276.
32. Mehta SR, Wood DA, Storey RF,et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2019;381(15):1411-1421. http://dx.doi.org/10.1056/NEJMoa1907775.
33. Montalescot G, Angiolillo DJ. Anticoagulation, the Unknown of the Antithrombotic Equation After Stenting of an Acute Coronary Syndrome. J Am Coll Cardiol 2019;73:775-8, http://dx.doi.org/10.1016/j.jacc.2018.12.022.
34. Cohen M, Maritz F, Gensini GF, et al. The TETAMI trial: the safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and of tirofiban versus placebo in the treatment of acute myocardial infarction for patients not thrombolyzed: methods and design. J Thromb Thrombolysis 2000;10:241-6, http://dx.doi.org/10.1023/a:1026543107533.
35. Cohen M, Gensini GF, Maritz F, et al. The safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and tirofiban versus placebo in the treatment of acute

ST-segment elevation myocardial infarction patients ineligible for reperfusion (TETAMI): a randomized trial. J Am Coll Cardiol 2003;42:1348-56, http://dx.doi.org/10.1016/s0735-1097(03)01040-4.
36. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9-19, http://dx.doi.org/10.1056/NEJMoa1112277.
37. Gibson CM, Chakrabarti AK, Mega J, et al. Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51. J Am Coll Cardiol 2013;62:286-90, http://dx.doi.org/10.1016/j.jacc.2013.03.041.
38. Schoos MM, De Luca G, Dangas GD, et al. Impact of time to treatment on the effects of bivalirudin vs. glycoprotein IIb/IIIa inhibitors and heparin in patients undergoing primary percutaneous coronary intervention: insights from the HORIZONS-AMI trial. EuroIntervention 2016;12:1144-1153, http://dx.doi.org/10.4244/EIJV12I9A186.
39. Madhavan MV, Genereux P, Kirtane AJ, et al. Is routine post-procedural anticoagulation warranted after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction? Insights from the HORIZONS-AMI trial. Eur Heart J Acute Cardiovasc Care 2017;6:650-658, http://dx.doi.org/10.1177/2048872615592246.
40. Abbas A, Matthews GH, Brown IW, et al. Cardiac MR assessment of microvascular obstruction. Br J Radiol 2015;88:20140470, http://dx.doi.org/10.1259/bjr.20140470.
41. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet 2012;379:453-60, http://dx.doi.org/10.1016/S0140-6736(11)61335-4.
42. Harker M, Carville S, Henderson R, et al. Key recommendations and evidence from the NICE guideline for the acute management of ST-segment-elevation myocardial infarction. Heart 2014;100:536-43, http://dx.doi.org/10.1136/heartjnl-2013-304717.
43. Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy. Can J Cardiol 2018;34:214-233, http://dx.doi.org/10.1016/j.cjca.2017.12.012.
44. JCS Joint Working Group. Guidelines for Secondary Prevention of Myocardial Infarction (JCS 2011). Circ J 2013;77:231-48, http://dx.doi.org/10.1253/circj.cj-66-0053.
45. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet 2000;355:1936-42, http://dx.doi.org/10.1016/S0140-6736(00)02324-2.
46. Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA 1996;276:811-5.
47. Zhang S, Gao W, Li H, et al. Efficacy and safety of bivalirudin versus heparin in patients undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials. Int J Cardiol 2016;209:87-95, http://dx.doi.org/10.1016/j.ijcard.2016.01.206.
48. Nuhrenberg TG, Hochholzer W, Mashayekhi K, et al. Efficacy and safety of bivalirudin for percutaneous coronary intervention in acute coronary syndromes: a meta-analysis of randomized-controlled trials. Clin Res Cardiol 2018;107:807-15, http://dx.doi.org/10.1007/s00392-018-1251-1.
49. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315, http://dx.doi.org/10.1093/eurheartj/ehv320.
50. Le May MR, Acharya S, Wells GA, et al. Prophylactic warfarin therapy after primary percutaneous coronary intervention for anterior ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2015;8:155-162, http://dx.doi.org/10.1016/j.jcin.2014.07.018.
51. Shavadia JS, Youngson E, Bainey KR, et al. Outcomes and Prognostic Impact of Prophylactic Oral Anticoagulation in Anterior ST-Segment Elevation Myocardial Infarction Patients With Left Ventricular Dysfunction. J Am Heart Assoc. 2017;6: e006054, http://dx.doi.org/10.1161/JAHA.117.006054.
52. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e531S-e575S, http://dx.doi.org/10.1378/chest.11-2304.

53. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e637S-e668S, http://dx.doi.org/10.1378/chest.11-2306.
54. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44-122, http://dx.doi.org/10.1016/j.jacc.2011.08.007
55. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74, http://dx.doi.org/10.1056/NEJMoa020496.
56. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895-903, http://dx.doi.org/10.1056/NEJM200106213442503.
57. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605-13, http://dx.doi.org/10.1016/S0140-6736(01)05775-0.
58. Le May MR, Wells GA, Glover CA, et al. Primary percutaneous coronary angioplasty with and without eptifibatide in ST-segment elevation myocardial infarction: a safety and efficacy study of integrilin-facilitated versus primary percutaneous coronary intervention in ST-segment elevation myocardial infarction (ASSIST). Circ Cardiovasc Interv 2009;2:330-8, http://dx.doi.org/10.1161/CIRCINTERVENTIONS.108.847582.108.847582.
59. Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J 2014;35:2285-94, http://dx.doi.org/10.1093/eurheartj/ehu182.
60. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957-66, http://dx.doi.org/10.1056/NEJMoa013404.
61. Yusuf S, Mehta SR, Xie C, et al. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. JAMA 2005;293:427-35, http://dx.doi.org/10.1001/jama.293.4.427.
62. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med 2006;354:1477-88, http://dx.doi.org/10.1056/NEJMoa060898.
63. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205-17, http://dx.doi.org/10.1056/NEJMoa0706816.
64. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA 2006;295:1519-30, http://dx.doi.org/10.1001/jama.295.13.joc60038.
65. Van't Hof AW, Ten Berg J, Heestermans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-46, http://dx.doi.org/10.1016/S0140-6736(08)61235-0.



- **Primary efficacy endpoint** Death, MI, stroke, stent thrombosis or urgent revascularization at 30 days
- **Primary safety endpoint** Major bleeding (BARC 3 to 5) at 30 days

* **Each center will use only one anticoagulant in all patients randomized at this center**

Figure 2. Enrollment curve of the RIGHT study

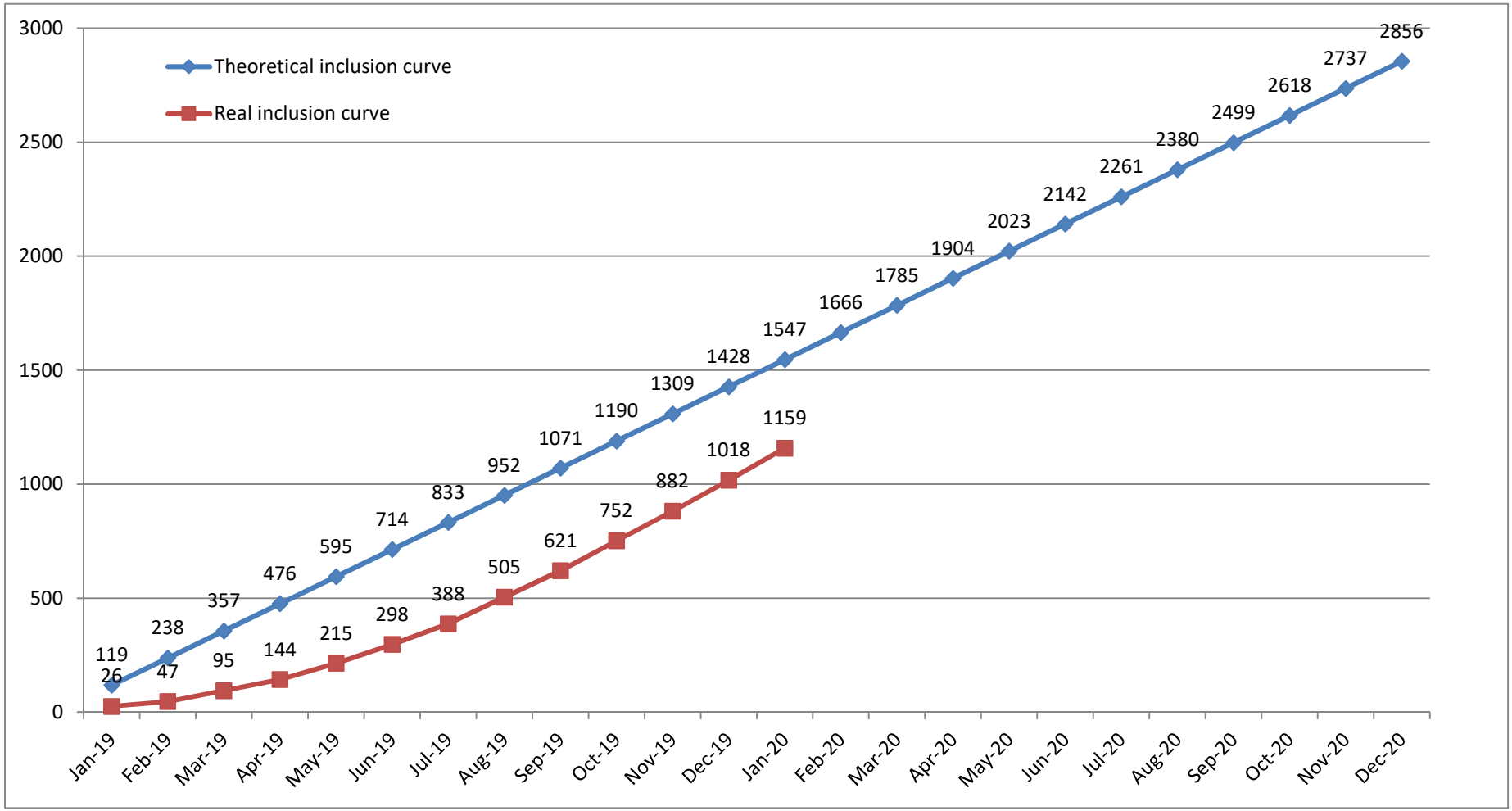


Table 1. Guideline recommendations on periprocedural parenteral anticoagulation in primary PCI for STEMI

Phase	Recommendations	ESC/EACTS[4,5]	ACCF/AHA[6]	NICE[42]	CCS/CAIC[43]	CSC[22]	JCS[44]	Reference
		COR/LOE	COR/LOE	COR/LOE	COR/LOE	COR/LOE	COR/LOE	
Per-procedural AC	Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I/A	NSER	NM	NM	I/A	NM	45,46
	Routine use of UFH is recommended.	I/C	I/C	Strong	NM	I/C	NM	N/A
	Routine use of enoxaparin should be considered.	IIa/B	NSER	Strong	NM	IIa/A	NM	16
	Routine use of bivalirudin may be considered.	IIb/A	I/B	Strong	NM	IIa/B	NM	2,18,20,23,47,48
Post procedural AC	Routine post-procedural anticoagulant therapy is not indicated after primary PCI, except when there is a separate indication for either full-dose anticoagulation [due, for instance, to atrial fibrillation (AF), mechanical valves, or LV thrombus) or prophylactic doses for the prevention of venous thromboembolism in patients requiring prolonged bed rest.	NSER	NM	NM	NESR	NM	NM	49
	Anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis.	NSER	IIb/C	NM	Not recommend	NM	I/A	50-55

ESC/EACTS= European Society of Cardiology/European Association for Cardio-Thoracic Surgery, ACCF/AHA= American College of Cardiology Foundation/ American Heart Association, NICE=

National Institute for Health and Care Excellence, CCS/CAIC=Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology, CSC= Chinese Society of Cardiology, JCS= Japanese Circulation Society, COR=Class of recommendation, LOE=Level of evidence, AC=anticoagulation , NSER=No specific equivalent recommendation, NM= Not mentioned, N/A= not applicable

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. ST-segment elevation myocardial infarction with primary PCI of culprit lesion (as defined above), regardless of the regime of thienopyridines administered before randomization.
2. Undergoing bivalirudin therapy during primary PCI.
3. Age ≥ 18 years.
4. Ability to understand and to comply with the study protocol.
5. Signed informed consent form.

Exclusion criteria

1. Patients with a formal indication for anticoagulation after pPCI (e.g. atrial fibrillation, left-ventricular thrombus, intra-aortic balloon pump, pulmonary embolism, mechanical heart valve).
2. Patients with any indication for chronic anticoagulation.
3. Patients with previous lytic treatment.
4. Patients with previous coronary artery bypass graft surgery (CABG).
5. Cardiogenic shock, malignant ventricular arrhythmia, or mechanical complications.
6. Any anticoagulation other than bivalirudin started after the procedure before randomization
7. Estimated body weight of >120 kg or <45kg.
8. BP≥180/110mmHg at randomization.
9. Any bleeding diathesis or severe hematologic disease or history of intracerebral mass, aneurysm, arteriovenous malformation, recent (<6months) ischemic stroke or TIA, recent (<6months) intracranial haemorrhage or, gastrointestinal or genitourinary bleeding within the past 2 weeks.
10. History of heparin-induced thrombocytopenia.
11. Suspected acute aortic dissection (AAD).
12. Major surgery within 1 month.
13. A planned elective surgical procedure that would necessitate an interruption in treatment with P2Y12 inhibitors in the next 6 months after enrolment.
14. Known PLT≤100×10^9 or HGB≤10g/L.
15. Known transaminase >3-fold upper limit of normal ULN, or CCr<30ml/min.
16. Known allergy to any study drug.
17. Pregnancy or lactation.
18. Noncardiac coexisting conditions that could limit life expectancy to less than 1 year.
19. Currently participating in an investigational drug or another device trial.

Table 3. Studies analyzed for the estimation of the primary end point.

Study	Total Patients	Therapies	STEMI (%)	PEP	FU	Rate	Bleed definition	FU	Rate
ADMIRAL[56]	300	A+H v H	100	D,MI,uR	30 days	6.0 vs 14.6	TIMI major	30 days	0.7 vs 0
ASSENT-3(fibrinolysis)[57]	6095	Enox v H	100	D,MI	30 days	11.4 vs 15.4	Study definition (severe)	in-hospital	3 vs 2.2
ASSIST[58]	400	E v H	100	D,MI,uR	30 days	6.47 vs 5.53	TIMI major	in-hospital	9.5 vs 5.5
ATOLL[16]	910	Enox v H	100	MACE	30 days	8 vs 12	STEEPLE	30 days	5 vs 5
BRAVE 4[59]	548	B v H	100	D,MI,ST,stroke, uR	30 days	4.8 vs 5.5	TIMI	30 days	2.6 vs 2.9
BRIGHT[17]	1464	B v H	87	D,MI,uR,stroke	30 days	5 vs 5.8	BARC 3-5	30 days	0.5 vs 1.5
CADILLAC[25,60]	2082	H v A+H	88	D,MI,uR,stroke	30 days	4.6 vs 7	Study definition (severe)	30 days	0.4 vs 0.6
CREATE[61]	15570	R v P	77.5	D,MI or stroke	30 days	11.8 vs 13.6	Major or life-threating	30 days	0.9 vs 0.4
EUROMAX[18]	2218	B v H+Enox	100	MACE	30 days	6 vs 5.5	TIMI major	30 days	1.3 vs 2.1
ExTRACT-TIMI 25(fibrinolysis)[62]	20560	Enox v H	100	D,MI	30 days	9.9 vs 12	TIMI major (incluing ICH)	30 days	2.1 vs 1.4
FINESSE Enoxaparin[63]	2452	H v Enox	100	D,MI,uR	30 days	6 vs 4.4	TIMI major	7 days	4.4 vs 2.6
HEAT PPCI[20]	1812	B v H	100	MACE	30 days	12 vs 7	BARC 3-5	30 days	3.5 vs 3.1
HORIZONS-AMI[23]	3602	H+GPI v B	100	MACE	30 days	5.5 vs 5.4	Major bleeding, non-CABG	30 days	8.3 vs 4.9
MATRIX[2]	7213	B v H	56	MACE	30 days	10.3 vs 10.9	BARC 3 or 5	30 days	1.4 vs 2.5
OASIS 6[64]	12092	H or P v F	100	D,MI	30 days	11.2 vs 9.7	OASIS 5 major bleeding	9 days	2.1 vs 1.8
ON-TIME 2[65]	1398	H v T+H	100	D,MI,uR	30 days	8.2 vs 7	TIMI major	30 days	2.9 vs 4.0
VALIDATE-SWEDEHEART[19]	6006	B v H	50	D,MI or stroke	180 days	2.4 vs 2.8	BARC 2,3 or 5	180 days	5.1 vs 5.6

PEP=primary end point, FU=follow up, A= abciximab, H=heparin, E= eptifibatide, Enox=enoxaparin, B=bivalirudin, R= reviparin, P=placebo, F= fondaparinux, T= tirofiban, D=death, MI=myocardial infarction, uR=urgent revascularization, ICH= intracerebral hemorrhage. The marked studies were used to estimate the primary end point.

Table 4. Subgroups of interest

Major Subgroups of interest

1. Female
2. Elderly (>75 years)
3. Diabetes
4. Prior Cancer
5. weight < 60 kg
6. Creatinine Clearance <30mL/min
7. Location of MI (anterior vs. non-anterior)
8. Prior revascularized coronary artery disease (CAD)
9. Anticoagulation therapy cross-over before randomization
10. Glycoprotein IIb/IIIa antagonists
11. Prior stroke
12. Type of stent
13. Length of stent
14. Duration of anticoagulation (below versus above median)
15. Successful PCI (Stent implanted and TIMI3 after procedure) vs others

Other subgroups of interest

1. Patients on Ticagrelor
2. Patients on Clopidogrel
3. Patients on intensive lipid-lowering therapy before procedure
4. Aspirin dose
5. Left ventricle ejection fraction <50% before discharge
6. Stent vs. no stent implanted
7. TIMI 3 flow vs. no TIMI 3 flow at the end of procedure
8. Anemia at admission
9. TIMI risk score after procedure

Table 5. Baseline characteristics of the first 1159 enrolled patients.

Variables	Overall (n=1159)
Socio-demographic	
Age, year, mean (SD)	60.08(12.24)
Female sex, n (%)	230(19.84)
Medical history, n (%)	
Current smoking	598(51.6)
Hypertension	618(53.32)
Diabetes	279(24.07)
Insulin	54(4.66)
Oral antidiabetic drugs	171(14.75)
Unknown	68(5.87)
Dyslipidemia	485(41.85)
Prior Myocardial infarction	65(5.61)
Prior PCI	67(5.78)
Cancer	22(1.9)
History of prior bleeding	30(2.59)
Anemia	4(0.35)
Atrial Fibrillation	10(0.86)
Pre-existing Chronic or Acute Liver disease	40(3.45)
Known Peripheral Artery disease	14(1.21)
Prior Stroke/TIA	115(9.92)
Clinical Status at admission	
BMI, kg/m^2, mean (SD) *	24.94(4.29)
Systolic BP, mmHg, mean(SD)	127.21(22.46)
Heart rate, mean (SD)	76.84(15.73)
Killip Stage ≥2, n (%)	139(11.99)
Cardiac arrest at admission	1(0.09)
Location of infarction	
Anterior, n (%)	472(40.72)
Creatinine clearance, ml/min, mean (SD)**	102.54(37.62)
Angiographic and Procedure data, n (%)	
Access site	
Radial	1112(95.94)
Femoral	35(3.02)
Other	12(1.04)
PCI with stent	1067(92.06)
TIMI flow 0/1 at baseline	950(81.97)
TIMI flow 3 at the end of procedure	1130(97.5)

* 2 outliers caused by misleading unit were treated as missing values.

** 6 outliers caused by misleading unit were treated as missing values.