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Ticagrelor versus Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction: Rationale and Design of the TicagRElor in pAtients with ST elevation myocardial infarction treated with Thrombolysis (TREAT) trial



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Ticagrelor versus Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction: Rationale and Design of the TicagRElor in pAtients with ST elevation myocardial infarction treated with Thrombolysis (TREAT) trial

Short title: TREAT Trial: Rationale and Design

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Abstract

BACKGROUND: The safety and efficacy of ticagrelor in patients with ST-elevation myocardial infarction (STEMI) treated with fibrinolytic therapy remain uncertain.

OBJECTIVES: The primary objective of the TicagRElor in pAtients with ST elevation myocardial infarction treated with Thrombolysis (TREAT) trial is to evaluate the short-term safety of ticagrelor when compared with clopidogrel in STEMI patients treated with fibrinolytic therapy. Key secondary objectives are to assess the safety and efficacy of ticagrelor compared with clopidogrel at 12-months.

DESIGN: The TREAT trial is a multicenter, randomized, phase III, Prospective randomized open blinded end-point (PROBE) study that enrolled 3,799 patients in 152 sites from 10 countries. Following administration of fibrinolytic therapy patients were randomized to a loading dose of ticagrelor 180 mg or clopidogrel 300 mg followed by a maintenance dose of ticagrelor 90 mg twice daily or clopidogrel 75 mg/day for 12-months. The primary outcome is the rate of TIMI major bleeding at 30-days and will be assessed for non-inferiority using an intention-to-treat analysis. Co-treatments include aspirin and anticoagulants. Other evidence based therapies are also recommended. Secondary efficacy outcome include a composite of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, transient ischemic attack or other arterial thrombotic event. All-cause mortality as well as individual components of the combined efficacy endpoint will also be ascertained.

SUMMARY: TREAT is an international randomized controlled trial comparing ticagrelor with clopidogrel in STEMI patients treated with fibrinolytic therapy. The results of this trial will inform clinical practice and international guidelines.

Keywords: Myocardial Infarction; Ticagrelor; Fibrinolysis, Bleeding.

INTRODUCTION

Although current guidelines for patients with acute ST-segment elevation myocardial infarction (STEMI) recommend timely primary percutaneous coronary intervention (PCI) as the preferred reperfusion strategy, however, this emergency therapy is often not available.¹⁻⁴ Thus, a large proportion of patients with STEMI receive fibrinolytic therapy as the initial reperfusion strategy¹⁻⁴. In addition, dual antiplatelet therapy (DAPT) traditionally consisting of aspirin plus clopidogrel has been established as the standard treatment in pharmacological reperfusion therapy^{1,2}.

Currently, in STEMI patients managed with fibrinolytic therapy, clopidogrel represents the only P2Y₁₂ receptor inhibitor recommended in the acute phase by guidelines^{1,2}. The preferred recommendation of clopidogrel for this patient population is based on 2 large-scale randomized trials.^{5,6} The CLOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)⁵ randomized 45,852 patients with acute MI (87% had STEMI) within 24 hours of evolution and not treated with primary PCI (54% received fibrinolysis) to receive clopidogrel 75 mg daily or matching placebo in addition to aspirin 162 mg daily. This trial⁵ showed that clopidogrel produced a significant 9% (95% CI 3–14) proportional reduction in death, reinfarction, or stroke (9.2% clopidogrel vs 10.1% placebo; $p=0.002$). The trial also showed that the clopidogrel group had a significant reduction in total mortality (7.5% vs 8.1%; $p=0.03$). Similarly, the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)⁶ randomized 3,491 patients with STEMI (age up to 75 years) treated with fibrinolytic therapy to receive clopidogrel (300-mg loading dose, followed by 75 mg once daily) or placebo. This study demonstrated a 6.7% absolute and a 36% relative reduction in major cardiovascular events with clopidogrel ($p<0.001$). Both studies (COMMIT and CLARITY) also showed similar rates of major bleeding and intracranial hemorrhage between treatment groups up to 30-days. However, despite its safety and efficacy, clopidogrel has a relatively slow onset of effect since it is a prodrug that requires 2-step metabolism for conversion to its active metabolite.^{7,8} The steady-state platelet inhibition is achieved in some patients 4 hours after a loading dose of clopidogrel.^{7,8} Moreover, genetic variability in enzyme function is known to cause the medication to be less effective in individuals who cannot

convert the drug to its active form^{7,8}.

Rationale to Test Ticagrelor after administration of Fibrinolytic therapy

Ticagrelor is a direct and reversible inhibitor of the platelet P2Y₁₂ receptor and therefore does not require metabolic activation^{7,8}. Also, unlike thienopyridines, ticagrelor binds reversibly to the P2Y₁₂ receptor^{7,8}. The distinctive characteristics of ticagrelor have been shown to result in significantly faster onset and offset of antiplatelet activity compared with clopidogrel in subjects with acute and chronic coronary disease^{9,10}. Reducing the delay in platelet inhibition is a potential advantage that may be more relevant in patients at higher risk of mortality and recurrent events such as those with STEMI. Ticagrelor was evaluated in the Platelet Inhibition and Patient Outcomes (PLATO) study, a phase III multicenter randomized, double-blind, parallel-group, event-driven, international trial of 18,624 patients hospitalized because of acute coronary syndrome (ACS)⁹. Patients were randomized to receive ticagrelor or clopidogrel in a 1:1 ratio within 24 hours of onset of the most recent cardiac ischemic symptoms and before any planned or urgent PCI. PLATO trial showed that ticagrelor (180 mg loading dose followed by 90 mg twice daily [BID]) was superior to clopidogrel (300-600 mg loading dose followed by 75 mg daily) in 18,624 patients with acute coronary syndrome. Compared with clopidogrel, ticagrelor significantly reduced the rate of the primary composite end point (death from vascular causes, MI, or stroke) at 12-months (9.8% with ticagrelor vs 11.7% with clopidogrel; $P < .001$), and in the short term (days 1-30) (4.8% vs 5.4%, respectively; $P = .045$). In a subgroup of 7,544 patients with STEMI or left bundle-branch block with planned primary PCI¹¹, a trend for a reduction in the 12-month primary end point (cardiovascular death, MI, or stroke) was observed with ticagrelor, consistent with the overall trial results. Compared with clopidogrel, ticagrelor achieved significant reductions in the secondary end points of MI alone ($P = .03$) and definite stent thrombosis ($P = .03$) and a trend for a reduction in total mortality ($P = .05$). Moreover the ticagrelor and clopidogrel groups did not differ significantly with regard to the rates of major bleeding as defined in the trial (11.6% and 11.2%, respectively; $P = 0.43$).

Despite the benefits observed in the PLATO trial, patients who received

fibrinolytic therapy during the previous 24 hours were excluded and no large-scale international trial evaluating the safety and efficacy of ticagrelor in this population has been completed to date. One of the main concerns regarding the use of ticagrelor in this scenario is related to the risk of major bleeding, especially intracranial or fatal bleeding.

In summary: (1) fibrinolytic therapy still plays a significant role in the treatment of STEMI; (2) studies in STEMI patients treated with fibrinolytic therapy have demonstrated the benefit of clopidogrel vs. placebo; (3) the superiority of ticagrelor vs. clopidogrel excluded patients who received fibrinolysis within 24 hours of randomization; and, (4) the more potent ticagrelor also leads to increased non-CABG related bleeding vs. clopidogrel. Thus, the uncertainty around the safety of ticagrelor in fibrinolytic-treated patients with STEMI relative to clopidogrel was the main rationale for the design of the TicagRElor in pAtients with ST elevation myocardial infarction treated with pharmacological Thrombolysis (TREAT) trial.

METHODS

Study Design

The TREAT trial is an academically-led, investigator-initiated, phase III international, multicenter, randomized, open-label, blinded-endpoint assessment (PROBE) study of 3,799 patients hospitalized due to a STEMI and treated with fibrinolytic therapy. The TREAT trial has involved 152 sites that included patients in 10 countries (Australia, Argentina, Brazil, Canada, China, Colombia, Russia, New Zealand, Peru, and Ukraine). Recruitment was competitive with no maximum limit for patients from each center.

Primary objective

To determine in patients with STEMI treated with fibrinolytic therapy whether the use of ticagrelor is non-inferior in terms of safety compared to clopidogrel. The primary outcome is the rate of major bleeding according to the TIMI definition¹² at 30-days.

Secondary objectives

To compare the effect of ticagrelor vs clopidogrel on rates of major or minor bleeding according to the PLATO⁹ and BARC definitions¹², and clinically relevant non-major bleeding or minor bleeding according to the TIMI definition¹² at 30-days and at 12-months. Also, key secondary efficacy outcomes included the composite endpoint of death from vascular causes, myocardial infarction, stroke, recurrent ischemia, transient ischemic attack, or other arterial thrombotic events at 30-days and at 12-months.

Eligibility

Male and female patients aged ≥ 18 years and < 75 years with STEMI in the 24 hours before randomization and who were treated with fibrinolytic therapy were eligible for this trial. Patients already under use of clopidogrel were not excluded from the trial. Contra-indication of study drugs (clopidogrel or ticagrelor) and/or to fibrinolytic therapy were the main exclusion criteria. All the inclusion and exclusion criteria are shown in Tables I and II.

Randomization and Allocation Concealment

Patients were randomized to receive ticagrelor or clopidogrel in a 1:1 ratio in permuted blocks of four, stratified according to site using a central concealed randomization system (e-ClinicalTrials OS, Merge Healthcare, IBM).

Trial Interventions

Patients received a loading dose of 180 mg (two 90 mg tablets) of ticagrelor or a 300 mg loading dose of clopidogrel according to randomization. The clopidogrel dose was chosen based on current evidence-based guideline recommendations for STEMI patients treated with fibrinolytic therapy^{1, 2} while ticagrelor was used according to the current dose recommended in STEMI patients treated with primary PCI^{1, 2}. Patients pretreated with clopidogrel before randomization were still eligible and, if randomized to ticagrelor, the trial loading dose was recommended, and, if randomized to clopidogrel, could receive an additional 300 mg of clopidogrel, at the discretion of the investigator and in accordance to local guidelines if undergoing PCI. The randomized maintenance therapy for ticagrelor was 90 mg twice daily and for clopidogrel was 75 mg once daily.

Early discontinuation will be documented and reported with the trial results.

Concomitant Therapies

Since TREAT is a pragmatic study, the types of fibrinolytic agents are used according to the local practice following international guidelines^{1,2}. Details around different types of fibrinolytic therapies will be reported in the publication of the results.

All patients were to receive acetylsalicylic acid (ASA) 75 to 100 mg daily unless intolerant. For patients not previously receiving ASA, a loading dose of 162 to 325 mg was recommended. Oral anticoagulant drugs were exclusion criteria but if required after randomization, continuation of study drug was determined by the investigator. All other evidence-based therapies recommended by guidelines and not contra-indicated (e.g. high-intensity statin, beta-blockers, ACE inhibitors, etc) were to be used in all patients during index hospitalization and also during follow-up^{1,2}.

Study treatment compliance was assessed by the return of all unused investigational products and empty packages at each visit. Patients who took study medication for $\geq 80\%$ of days between each visit were regarded as compliant.

Procedures

Initial background assessments include demographics, cardiovascular risk factors, relevant medical and surgical histories, clinical characteristics, and laboratory data included in risk scores for ACS. Study visits assessing endpoints were planned to occur at discharge or 7th day, 30-days, 6 months and 12-months after the index event. The trial flowchart is presented in Figure 1 and the detailed information collected in each study visit is provided in the supplementary appendix.

Clinical Outcomes

An independent blinded central adjudication committee adjudicated all suspected primary and key secondary outcomes.

The bleeding events were classified according to TIMI¹², BARC¹² and PLATO definitions^{9, 11}. The detailed definitions of the bleeding outcomes are described in the supplementary appendix. Additional safety variables including dyspnea, arrhythmia and other laboratory safety results were collected on the CRF and reported as non-adjudicated secondary safety endpoints (assessed also at 30-days and 12-months).

Key secondary efficacy endpoints included the composite endpoint of death from vascular causes, myocardial infarction, stroke, recurrent ischemia, transient ischemic attack, or other arterial thrombotic events at 30-days and at 12-months and also a composite endpoint of death from vascular causes, myocardial infarction, or stroke also 30-days and at 12-months. We will also evaluate individual components of the composite efficacy endpoints and all-cause mortality at 30-days and at 12-months. The detailed definitions of the efficacy outcomes are described in the supplementary appendix.

Sample size calculation

The event rate of the primary outcome was initially estimated based on the results from previous trials with ticagrelor in STEMI patients^{9,11} and also according to the characteristics of the study. In the first version of the protocol the event rate was expected to be 6% with a non-inferiority margin of 2.5%. Considering a one-tailed alpha of 2.5% with 80% statistical power, these assumptions led to a total sample size of 3794 patients. During the enrollment period and according to data management standards it was found that the aggregated adjudicated event rate for TIMI major bleeding at 30-days was close to 1%. Similar rates were seen in the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) Trial¹³, where TIMI major bleeding occurred at 30-days in 1.3% in both pre hospital and in hospital ticagrelor groups.

Despite the lower than expected event rate for the primary endpoint, the original sample of 3794 patients was maintained as the final target trial population. Thus, this sample size will provide 90% statistical power, considering a non-inferiority margin of 1.0% (absolute margin), a one-sided alpha of 2.5%, and assuming a 1:1 allocation ratio.¹⁴

All decisions were made by the trial leadership, who were blinded to the study treatment assignments until the database lock.

In addition, and as stated in the first version of the protocol, this sample size will also enable us to test the superiority of ticagrelor as compared to clopidogrel for the key secondary efficacy outcome (death from vascular causes, myocardial infarction, stroke, recurrent ischemia, TIA, or other arterial thrombotic event) at 12-months. For this outcome, considering a control group event rate of 16% for the key secondary efficacy endpoint at 12-months (based on previous trials)^{9,11,15}, and a two-tailed alpha of 5%, a sample size of 1897 patients per group will provide over 90% statistical power to detect a relative risk reduction (RRR) of 25% and 80% statistical power to detect a RRR of 20%.

Statistical Analysis

In order to maintain the benefits of randomization, the primary analysis will follow the intention-to-treat principle. The primary non-inferiority endpoint test for bleeding in 30-days will be performed by comparing proportions considering 1.0% non-inferiority margin. The other bleeding evaluations (secondary events) will only be presented with 95% confidence intervals for the estimated relative and absolute risks.

Secondary efficacy endpoints will be assessed using a log-rank test for Cox proportional hazards model considering null equivalence hypothesis to evaluate the efficacy of the outcomes in a combined form (at least one of the events) and in isolation: death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other thrombotic arterial events within 12-months.

The results will be presented with the respective confidence intervals for the measure of estimated effect (hazard ratio). In addition, Kaplan-Meier curves will be presented for efficacy outcomes up to 30-days and 12-months.

As a sensitivity analysis, we will perform analysis according to protocol and "as-treated" analyzes, adjusting Cox proportional hazards models according to the groups.

Subgroup analyzes for the outcomes will be evaluated by adjustments of

regression models considering interaction of the variable in question with the group. Multivariable adjustments will be made for sex, age, diabetes mellitus, time from index event to randomization, Killip class, concomitant anticoagulant treatment, use and timing of aspirin and clopidogrel pre-randomization.

All analyzes will be performed using the R software in its most current version.¹⁷

ORGANIZATIONAL STRUCTURE

Funding and Trial Oversight

This is an investigator-initiated study with financial support from AstraZeneca (Mölndal, Sweden). The funding source had no role in the study design, conduct, analysis, interpretation of data, or decision to publish the results. The Steering Committee designed the TREAT trial independently and, together with an Operations Committee located at the Research Institute - Heart Hospital (HCor) from Sao Paulo-SP, Brazil, oversees the medical, scientific, and operational conduct of the study. The Research Institute - HCor coordinates data management where information from the electronic clinical report form and the clinical event committee is entered into separate databases. Source data verification, validation, and consistency checks are performed also by Research Institute HCor. After data lock, the database will be available for analysis also by the statisticians at the Research Institute HCor. The Steering Committee members are responsible for the reporting of the results and the drafting and editing of this and forthcoming manuscripts.

An independent and external Data Monitoring Committee (DMC) monitors safety data on an ongoing basis and has access to unblinded data. An independent central adjudication committee adjudicates all potential primary and secondary end points in blinded fashion to the study drug.

The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

Ethical Aspects

The study adheres fully to the ethical principles of the Declaration of Helsinki, to

specifications of the International Conference of Harmonization, and to Good Clinical Practice. The study protocol was approved by an Independent Ethics Committee or Institutional Review Board at each site. The protocol required each subject's informed consent before initiating any study procedure.

DISCUSSION

The use of aspirin plus a P2Y₁₂ inhibitor is routinely recommended for STEMI patients. Currently, clopidogrel is the only P2Y₁₂ inhibitor recommended by evidence-based guidelines for patients managed with fibrinolytic therapy^{1,2}. This recommendation reflects the lack of robust evidence regarding the safety of more potent oral antiplatelets (e.g. ticagrelor) in this scenario⁹.

The TREAT trial was designed to test the safety of a strategy of DAPT using ticagrelor in comparison to clopidogrel on a background of aspirin among patients with STEMI that received fibrinolytic therapy. The primary objective of TREAT trial is to determine whether ticagrelor is non-inferior in terms of safety when compared to clopidogrel in this scenario. The non-inferiority margin used in TREAT trial is in accordance with assumptions used in other trials of antithrombotic therapy in ACS patients^{11,13, 18} and was chosen also in accordance with expert opinion (query opinion of the Steering Committee). Nevertheless, this non-inferiority margin is 1% should be taken into consideration when interpreting the study results, especially if the differences between groups is close to the non-inferiority margin.

Considering that this study was designed to evaluate primarily the safety of the intervention, groups with higher risk of major bleeding were not included (as patients aged above 75 years old). This approach was used also in the CLARITY trial⁶ that evaluated the use of clopidogrel versus placebo in a similar clinical setting. Importantly, similar to PLATO trial, TREAT will include also patients not naïve to P2Y₁₂ inhibitor. This aspect should be carefully assessed at the time of the publication of the results since differences between groups that started with the loading dose of ticagrelor or patients who switched from clopidogrel to ticagrelor may impact the applicability of the results in clinical practice.

The time-frame of 30-days for the primary safety outcome was chosen, since this is the most vulnerable period for bleeding events related to fibrinolytic therapy. This length of follow-up is also consistent with previous trials in STEMI patients managed with fibrinolytic therapy such as CLARITY and COMMIT.^{5,6} On the other hand, these trials were conducted more than a decade ago, and more recent trials of DAPT in ACS patients have followed patients up to 12-months^{9,19}. In addition, current guidelines also recommend 12-months of DAPT as Class I for STEMI patients treated with fibrinolytic therapy^{1,2}. Thus, in our study, we decided to treat patients with DAPT up to 12-months but we have kept the primary safety outcome at 30-days since the risk of bleeding related to fibrinolytic therapy is higher in the first days. However, even if the result of the primary outcome TREAT trial shows that the intervention is safe, we believe that the information about efficacy is warranted to allow a more robust recommendation of ticagrelor in this clinical setting. The 12-month outcome data will provide more statistical power for efficacy analysis and will be published as a secondary analysis of the trial. The 12-month data will also allow a potential indirect comparison of the findings of the TREAT and PLATO studies. A meta-analysis combining data from TREAT and from the PLATO STEMI subgroup analysis¹¹ is being also planned. Due to the increased statistical power, this meta-analysis can potentially provide additional relevant information on the efficacy and safety of ticagrelor in a broader spectrum of STEMI patients.

Conclusion

TREAT is an international randomized trial testing the short-term safety of ticagrelor compared with clopidogrel in STEMI patients who are treated with fibrinolytic therapy. The results of this study will inform clinical practice and international guidelines.

Conflict of interests

OB: Dr Otavio Berwanger received research grants from Astra Zeneca, Bayer, Amgen, and Boehringer-Ingelheim and participated on Advisory Boards for Astra Zeneca, Bayer, Amgen, Sanofi, Novo Nordisk and Boehringer-Ingelheim.

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ACC: Federal University of Sao Paulo: none.

Lixin Jiang: Fuwai Hospital: none.

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Trial Organization

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Table 1. Inclusion criteria for TREAT Trial

1. Male and female patients aged ≥ 18 years and < 75 years with ST segment elevation myocardial infarction (STEMI) with onset during the previous 24 hours, treated with fibrinolytic therapy *For the purpose of the TREAT trial, the definition of STEMI includes: ST segment elevation at the J point in two contiguous leads in electrocardiogram with cut-points: $\geq 0.1\text{mV}$ in all leads other than leads V2-V3, where the following cut points apply: $\geq 0.2\text{ mV}$ in men ≥ 40 years; $\geq 0.25\text{ mV}$ in men < 40 years, or $\geq 0.15\text{ mV}$ in women OR a new left bundle-branch block AND at least 1 of the following criteria: ✓ Angina-like chest pain or ischemic equivalent chest pain; ✓ Abnormalities above the reference value for markers of myocardial necrosis (troponin and/or CK-MB). 2. The patient (or legal representative) must be able to give informed consent in accordance with ICH GCP guidelines and local legislation and/or regulations.

Table 2. Exclusion criteria for TREAT Trial

1. Any contraindication against the use of clopidogrel or ticagrelor (i.e. hypersensitivity, moderate or severe liver disease, active bleeding or recent bleeding history, history of intracranial hemorrhage);
2. Need for oral anticoagulation therapy or aspirin doses per day more than 100mg/day.
3. Concomitant oral or IV therapy with strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice N1 L/d), CYP3A substrates with narrow therapeutic indices (cyclosporine, quinidine), or strong CYP3A inducers (rifampin/rifampicin, phenytoin, carbamazepine)
4. Increased risk of bradycardia events
5. Dialysis required
6. Known clinically important thrombocytopenia
7. Known clinically important anemia
8. Any other condition that may put the patient at risk or influence study results in the investigators' opinion (eg, cardiogenic shock, severe hemodynamic instability, active cancer)
9. Participant in another investigational drug or device study within 30 d
10. Pregnancy or lactation
11. Any condition that increases the risk for noncompliance or being lost to follow-up
12. Involvement in the planning or conduct of the study
13. Previous enrollment or randomization in this study
14. Contraindications to fibrinolytic therapy including:
 - Any prior intracranial hemorrhage
 - Known structural cerebral vascular lesion (eg, Arterial Venous Malformation - AVM)
 - Known malignant intracranial neoplasm (primary or metastatic)
 - Ischemic stroke within 3 months

- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head trauma or facial trauma within 3 months

*Observation: In case of relative contraindications to fibrinolytic therapy, it is reasonable to consider including the patient in TREAT protocol if the investigator decides for fibrinolytic therapy. The relative contraindications are:

- Prior coronary-artery bypass grafting
- Patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR
- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
- History of prior ischemic stroke <3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase/anistreplase: prior exposure (>5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants.

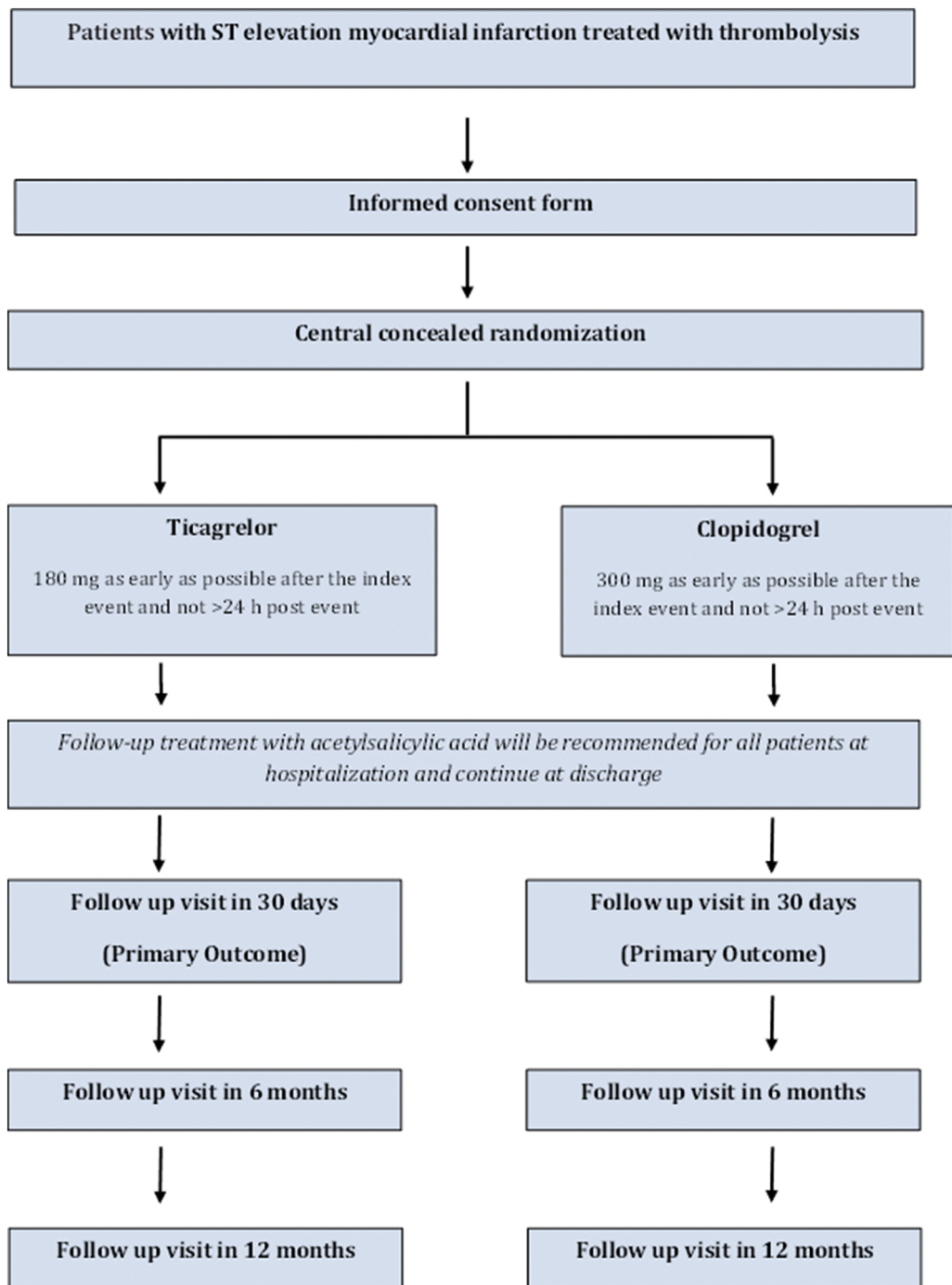


Figure 1