TREAT TRIAL

Administration of Ticagrelor in Patients with ST elevation myocardial infarction treated with pharmacological Thrombolysis.

“A Phase III, Randomized, International, Multicenter, Open label, with Blinded Adjudication of Outcomes, Non-Inferiority Clinical Trial to Explore the Safety and Efficacy of Ticagrelor Compared with Clopidogrel in Patients with Acute Coronary Syndrome with ST Elevation Treated with Pharmacological Thrombolysis”.

Executive Committee: Prof. Otávio Berwanger (Co-chair)
Prof. Hélio Penna Guimarães (Co-chair)
Prof. Leopoldo Soares Piegas (Co-chair)

Steering Committee:
Prof. Otávio Berwanger (Brazil – Chair); Prof. Leopoldo Soares Piegas (Brazil); Prof. Carlos José Nicolau (Brazil); Prof. Renato Lopes (Brazil); Prof. Hélio Penna Guimarães (Brazil); Prof. Antônio Carlos Carvalho (Brazil); Prof. Francisco Fonseca (Brazil); Prof. José Carlos Saraiva (Brazil); Prof. Chris Granger (USA); Prof. Harvey White (NZ); Prof. Shaun Goodman (Canada); Prof. Stephen Nicholls (Australia); Prof. Lixin Jiang (China); Prof. Alexandr Parkhomenko (Ukraine); Prof. Oleg Averkov (Russia); Prog. German Malaga (Peru) e Prof. Carlos Tajer (Argentina)

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Global Version History

Version 3.0 dated March 23, 2014
Version 4.0 dated October 30, 2017 (Brazilian Version)
Changes: Review, adequacy of the DMC meeting, Outcome adjudication process and inclusion of Participating Countries, correction of spelling errors.
Follow-up treatment with acetylsalicylic acid will be recommended for all patients at hospitalization and continue at discharge.

Ticagrelor:
- 180 mg as early as possible after the index event and not >24 h post event
- 90 mg twice daily for 12 months

Clopidogrel:
- 300 mg as early as possible after the index event and not >24 h post event
- 75 mg/day for 12 months

Follow up visit in 30 days
Follow up visit in 6 months
Follow up visit in 12 months
<table>
<thead>
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<th><strong>Title</strong></th>
<th>Administration of TicagRElor in pAtients with ST elevation myocardial infarction treated with pharmacological Thrombolysis A Phase III, International, Randomized, Multicenter, Open label, with Blinded Adjudication of Outcomes, Non-Inferiority Clinical Trial to Explore the Safety and Efficacy of Ticagrelor Compared with Clopidogrel in Patients with Acute Coronary Syndrome with ST Elevation Treated with Pharmacological Thrombolysis</th>
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</table>
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| **Countries** | About 170 sites from 10 countries (Argentina, Australia, Brazil, Canada, China, Colombia, New Zealand, Peru, Russia, and Ukraine) will participate |
| **Executive Committee** | Prof. Otávio Berwanger (Co-chair)  
Prof. Hélio Penna Guimarães (Co-chair)  
Prof. Leopoldo Soares Piegas (Co-chair) |
| **Steering Committee** | Prof. Otávio Berwanger (Brazil – Chair); Prof. Leopoldo Soares Piegas (Brazil); Prof. Carlos José Nicolau (Brazil); Prof. Renato Lopes (Brazil); Prof. Hélio Penna Guimarães (Brazil); Prof. Antônio Carlos Carvalho (Brazil); Prof. Francisco Fonseca (Brazil); Prof. José Carlos Saraiva (Brazil); Prof. Chris Granger (USA); Prof. Harvey White (NZ); Prof. Shaun Goodman (Canada); Prof. Stephen Nicholls (Australia); Prof. Lixin Jiang (China); Prof. Alexandr Parkhomenko (Ukraine); Prof. Oleg Averkov (Russia); Prog. German Malaga (Peru) e Prof. Carlos Tajer (Argentina) |
| **Study design** | Randomized, Phase III, multicenter, international, with blinded adjudication of outcomes, and intention-to-treat analysis |
| **Methodological quality** | Central Web-based randomization and allocation concealment;  
Blind outcome assessment adjudication committee;  
Intention-to-treat analysis. |
<p>| <strong>Primary safety Objective</strong> | To evaluate the safety (Major Bleeding: TIMI Definition) of Ticagrelor as compared to clopidogrel at 30 days in patients with ST elevation myocardial infarction treated with pharmacological thrombolysis. |
| <strong>Secondary safety Objectives</strong> | To evaluate the safety (Total bleeding according to TIMI, PLATO and BARC definitions, minor bleeding according to TIMI definition and major bleeding according to PLATO definition) of ticagrelor as compared to clopidogrel at 12 months treatment in patients with ST elevation myocardial infarction treated with pharmacological thrombolysis. |
| <strong>Secondary efficacy Objectives</strong> | To evaluate the efficacy of ticagrelor as compared to clopidogrel with regards to major cardiovascular events at 30 days and at 12 months in patients with ST elevation myocardial infarction treated with pharmacological thrombolysis. |</p>
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<tr>
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<td>Male and female patients (aged ≥ 18 years and &lt; 75 years)</td>
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<td>With a diagnosis of ST elevation myocardial infarction with onset during the previous 24 hours treated with fibrinolytic therapy.</td>
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<td>Agreement to sign an informed consent form</td>
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<td>Exclusion criteria:</td>
<td>• 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);</td>
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<td>• Increased risk of bradyarrhythmias</td>
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<td>• Dialysis required</td>
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<td>• Known clinically important thrombocytopenia</td>
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<td>• Any other condition that may put the patient at risk or influence study results in the investigators' opinion (i.e. cardiogenic shock, severe hemodynamic instability, active cancer)</td>
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<td></td>
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<td><strong>Treatment Regimen</strong></td>
<td>Ticagrelor 180mg as early as possible after the index event and not &gt; 24 h post event, followed by 90 mg BID. Clopidogrel 300mg as early as possible after the index event and not &gt; 24h post event, followed by 75mg/day. Follow-up 12 months</td>
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<tr>
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</tr>
<tr>
<td><strong>Study Size</strong></td>
<td>1897 patients per group to assess safety of Ticagrelor compared to Clopidogrel (primary outcome).</td>
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LIST OF ACRONYMS AND ABBREVIATIONS

ACS – Acute Coronary Syndrome
ASA – acetylsalicylic acid
CEC – Clinical Endpoints Committee
CRFs – Case report forms
CVD - Cardiovascular disease
EDC – Electronic Data Capture
GCP – Good Clinical Practice
GDP - gross domestic product
ICH – Harmonized Tripartite Guidelines
LEC – Local Ethical Committees
MI – Myocardium infarct
RRR – Relative risk reduction
PI – Principal Investigator
STEMI – ST segment elevation myocardium infarct
WHO - World Health Organization
ICF – Inform Consent Form
1 BACKGROUND AND RATIONALE

1.1 The Burden of Cardiovascular Diseases

The World Health Organization (WHO) has provided consistent estimates of deaths by sex, age, and causes in different countries and regions, based on systematic reviews of large-scale observational studies. According to these data, cardiovascular diseases (CVDs) in general and acute myocardial infarction (AMI) in particular represent the leading causes of death and disability globally. Moreover, currently, about 80% of the burden on CVDs occur in low and middle income countries, and the exponential grown of such diseases has become a major public health issue in these settings.1,2 Accordingly, The Global Burden of Diseases Study by Murray and Lopez3, suggests that, by the year 2020, CVDs will not only remain as the leading cause of death, but it will also become the leading cause of disability globally. Therefore, there is a continuous need for interventions with proven benefits in reducing the incidence of major cardiovascular events.

In low and middle-income countries, CVDs also represent a major health problem. In Brazil, an upper middle-income country, for instance, the prevalence of coronary artery disease (CAD) in the adult population is estimated to be 5 to 8% 4,5, and cardiovascular diseases constituted the third cause of hospitalization in Brazil (210,046 hospitalizations for ischemic heart disease in 2010). The cumulative incidence of myocardial infarction in Brazil is estimated to 400,000 new cases per year. Despite recent advances in the management of CVDs, about 29% of deaths, out of a total of 1,133,761, were associated with ischemic heart disease (99,408 deaths or 52.11 deaths/100 000 inhabitants) 3. According to current Brazilian registries 4, ST elevation myocardial infarction (STEMI) is associated with high mortality rates (about 8.10% in all regions, increasing up to 15% in poorer regions of the country).
1.2 Use of Reperfusion Therapies in ST Elevation Myocardial Infarction

In several settings, immediate access to a 24-hour cath lab capable of performing primary angioplasty or transfer to a hospital capable of performing such procedure in a timely fashion is not available. In this regard, a large proportion of STEMI patients ended up receiving chemical thrombolysis, and such patients are typically treated with dual antiplatelet therapy with clopidogrel and aspirin in clinical practice. Moreover, the Brazilian Ministry of Health have launched a National Program for STEMI providing tenectaplaste for ambulances and hospitals in all regions of the country, so it is likely that the proportion of patients treated with thrombolysis will increase.

According to the recent BRIDGE-ACS trial, 20% of STEMI patients were submitted to pharmacological thrombolysis and 15% of these patients died in 30 days. In previous data of a Brazilian Registry of Acute Coronary Syndrome with a total of 2,693 patient recruited, 35% has STEMI and 28,4% of these patient were treated with fibrinolitic therapy. Similarly, in ACCEPT (Acute Coronary Care Evaluation of Practice registry), the largest registry of acute coronary syndromes ever conducted in Brazil, with a total 4200 patient recruited, 35% has STEMI and 12,9% of were treated with fibrinolysis, despite the fact that most of participating sites were cardiology institutes with access to cath lab available 24 hours. A recent registry conducted in Chile enrolled 528 patients (53,1%) with STEMI and demonstrated that 14,1% of them were submitted to pharmacological thrombolysis. Similar findings were reported by registries conducted in other countries and settings.

1.3 Dual-antiplatelet therapy

In the context of ACS treatment, dual antiplatelet therapy traditionally consisting of aspirin plus clopidogrel (a P2Y12 receptor inhibitor) has been established as an important adjunct to reperfusion therapy.

Clopidogrel is a prodrug that is activated in the liver by cytochrome P450 enzymes and 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. This therapy
reduces rates of harmful cardiac events such as cardiovascular causes of death, myocardial infarction, and stroke\(^9\). According to COMMITT trial,\(^{10}\) that randomized 45,852 patients to receive clopidogrel 75 mg daily or matching placebo in addition to aspirin 162 mg daily, clopidogrel produced a highly significant 9% (95% CI 3–14) proportional reduction in death, reinfarction, or stroke (2121 [9·2%] clopidogrel vs 2310 [10·1%] placebo; \(p=0·002\)). The trial also confirmed that clopidogrel group had significant proportional reduction in total mortality (1726 [7·5%] vs 1845 [8·1%]; \(p=0·03\)).

In this way, CLARITY trial\(^{11}\) randomized 3491 patients with ST-elevation myocardial infarction to receive clopidogrel (300-mg loading dose, followed by 75 mg once daily) or placebo. This study demonstrated an absolute reduction of 6.7% in the rate and a 36% reduction in the odds of the end point with clopidogrel therapy (95% IC, 24-47; \(p<0.001\)). In addition, in 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1 to 11.6%, \(p=0.03\)). And also, concluded the rates of major bleeding and intracranial hemorrhage were similar in the two groups.

However, new agents as prasugrel and ticagrelor undergoing evaluation in large clinical trials, acute care providers need to know if the new P2Y12 receptor inhibitor antiplatelet agents are clinically superior to the current standard clopidogrel in STEAMI as they had been proved to be superior in NSTACS. It has been established that a defined percentage of the population exhibits high platelet activity despite the use of clopidogrel. This phenomenon occurs anywhere from 5% to 44% of patients studied depending on the clopidogrel dose and patient population. It is uncertain what level of platelet activity during ACS is related to harmful cardiovascular outcomes such as cardiovascular death, myocardial infarction, and stroke. Ticagrelor and prasugrel have been demonstrated to reduce levels of platelet activation when compared to clopidogrel which could lead to reduced risk of thrombosis and improved artery or stent patency. However, there is debate as to which patients will gain the most clinical benefit from
these costly and potentially harmful agents, especially in undefined contexts such as pharmacological thrombolysis.

1.4 Ticagrelor

Ticagrelor have been demonstrated to reduce levels of platelet activation when compared to clopidogrel, which could lead to reduced risk of thrombosis and improved artery or stent patency. However, there is uncertain as to which patients will gain the most clinical benefit from these costly and potentially harmful agents in pharmacological thrombolysis scenario.

The 2009 focused update of the American College of Cardiology/American Heart Association guidelines for the management of STEMI incorporates one of the newer oral antiplatelet agents, prasugrel, as a component of DAPT, and the latest European revascularization guidelines incorporate both prasugrel and ticagrelor. The new American College of Chest Physicians guidelines for the use of antithrombotic therapy also recommends DAPT for the first year after PCI with stent placement, consisting of Low-dose aspirin plus ticagrelor, clopidogrel, or prasugrel. However, the optimal timing of DAPT in STEMI using ticagrelor remains uncertain in thrombolytic pharmacological treatment.

In contrast to thienopyridines, ticagrelor is a direct and reversible inhibitor of the platelet P2Y12 receptor and therefore does not require metabolic activation. Also, unlike thienopyridines, ticagrelor binds reversibly to the P2Y12 receptor and at a site that is independent of adenosine diphosphate (ADP) but still results in suppression of ADP induced platelet activation by temporarily “locking” the receptor in an inactive state until it dissociates. 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 stable coronary artery disease or acute coronary syndromes.

Ticagrelor has also been shown to overcome non responsiveness to clopidogrel, with similar antiplatelet effects in clopidogrel responders and non-responders alike. All these findings suggest that ticagrelor has the potential to improve reperfusion and potentially prognosis in patients with STEMI undergoing pharmacological thrombolysis.
1.5 The PLATO Trial

The PLATO study \(^{13, 14}\) was a phase III multicenter randomized, double-blind, double-dummy, parallel-group, event-driven, international trial of patients hospitalized because of ACS. Patients are randomized to receive ticagrelor or clopidogrel in a 1:1 ratio using a randomization schedule blocked by site. Randomization occurred within 24 hours of onset of the most recent cardiac ischemic symptoms and before any planned or urgent PCI. Initial background assessments include demographics, cardiovascular risk factors, relevant medical and surgical histories, clinical characteristics, and laboratory data included in risk scores for ACS.

In PLATO trial, 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, myocardial infarction [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 PCI, 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 (\(P = .05\)).

1.6 Why do we need a large randomized trial to assess the efficacy and safety of ticagrelor in patients with STEMI treated with thrombolysis?

Several reasons justify the need for a robust ticagrelor RCT in patients with STEMI treated with thrombolysis with adequate methodology and statistical power in order to inform clinical practice, namely:
• To date, no large-scale trial evaluating the safety and efficacy of ticagrelor in STEMI patients have been published. The recently published 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction Guideline recommends Antiplatelet Therapy to Support Primary PCI STEMI using ticagrelor (Class I, evidence level B), but due to the lack of sound evidence, such recommendation cannot be extended to STEMI patients treated with pharmacological thrombolysis.

• The PLATO trial have demonstrated that in patients with Non ST elevation ACS as well as STEMI patients treated with primary PCI, treatment with ticagrelor as compared to clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding. It is very likely that the results are also true in patients with STEMI treated with thrombolysis; however such an answer awaits the results from a well-designed and adequately powered clinical trial.

• Given the fact that pharmacological thrombolysis still has a fundamental role in Brazil and in several others countries, widespread adoption of ticagrelor as the antiplatelet agent of choice in STEMI patients by the public and private healthcare system requires reliable data from a high quality trial.
2  TRIAL OBJECTIVES

2.1  Primary Safety Objectives

The primary safety objective is to evaluate the safety (Major Bleeding according to the TIMI Definition) of Ticagrelor as compared to clopidogrel at 30 days in patients with ST elevation myocardial infarction treated with pharmacological thrombolysis.

2.2  Secondary Safety Objectives

To evaluate the safety (total bleeding – major and minor - according to PLATO, TIMI and BARC definitions, minor bleeding according to the TIMI definition and major bleeding as individual endpoint according to the PLATO definition) of ticagrelor as compared to clopidogrel at 6 months and 12 months treatment in patients with ST elevation myocardial infarction treated with pharmacological thrombolysis. Others safety variables will include: dyspnea, arrhythmia, bradycardia and laboratory safety tests.

2.3  Secondary Efficacy Objectives

To evaluate the efficacy of ticagrelor as compared to clopidogrel with regards to major cardiovascular events (death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event) at 30 days, 6 months, and 12 months in patients with ST elevation myocardial infarction treated with pharmacological thrombolysis.

- Death from vascular causes includes cardiovascular deaths, cerebrovascular deaths, and any other death for which there was no clearly documented nonvascular cause.
- Recurrent MI within 18 hours of a previous MI is defined as recurrent cardiac ischemic symptoms and a new ST elevation. Recurrent MI after 18 hours but before cardiac markers have returned to normal is defined as
symptoms and re-elevation of troponin or CK-MB of at least 50% over a previous value that was decreasing. Myocardial infarction after cardiac biomarkers have returned to normal is defined as elevation of biochemical markers above the upper limit of normal with either ischemic symptoms at rest, ECG changes or pathological findings of an acute MI.

A stroke is defined as a focal loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 hours after onset or leading to death.
3 METHODS

3.1 Study design

Phase III, international, multicenter, open label, randomized clinical trial, with concealed allocation, blinded assessment of outcomes, and intention-to-treat analysis.

3.2 Inclusion criteria

- 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: ≥ 0.1mV in all leads other than leads V2-V3, where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years; ≥ 0.25 mV in men < 40 years, or ≥0.15 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).

The patient (or legal representative) must be able to give informed consent in accordance with ICH GCP guidelines and local legislation and/or regulations.

3.3 Exclusion criteria

Exclusion criteria are:

- 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);
- Need for oral anticoagulation therapy or aspirin doses per day more than 100mg/day.
- 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 CYP3Ainducers (rifampin/rifampicin, phenytoin, carbamazepine)
- Increased risk of bradycardia events
- Dialysis required
- Known clinically important thrombocytopenia
- Known clinically important anemia
- 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)
- Participant in another investigational drug or device study within 30 d
- Pregnancy or lactation
- Any condition that increases the risk for noncompliance or being lost to follow-up
- Involvement in the planning or conduct of the study
- Previous enrollment or randomization in this study
- Contraindications to fibrinolytic therapy including: 15
  - 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: the higher the INR, the higher the risk of bleeding

3.4 Randomization Method and Allocation Concealment

The randomization list will be generated using validated software and blocks of variable sizes. Patients will be stratified by center and previous treatment with clopidogrel. In order to include a patient in the trial, the investigator will have to access the TREAT Trial web site and fill in a simple case report form (CRF) in order to complete randomization.

Our Clinical Trial System https://secure.eclinicalos.com (IBM – Clinical Development) is a central randomization system that ensures allocation concealment.
In other words, the investigators who include patients in the study will not be able to predict to which group each patient was allocated. Proper randomization rests on adequate allocation concealment. An allocation concealment process keeps clinicians and participants unaware of upcoming assignments. Without it, even properly developed random allocation sequences can be subverted. In this regard, by allocation concealment we mean that we will use a central automated randomization system, so that the allocation sequence will be totally unpredictable to investigators who are including the patients in the trial.

3.5 Blinding

This is an open label trial and, as such, treatment allocation will not be blinded from Investigators and patients. All outcomes will be validated by blinded Adjudication Committee using standardized definitions.

3.6 Trial Interventions

Patients will be randomized (1:1) to Ticagrelor or Clopidogrel.

Ticagrelor 180 mg

Patients assigned to Ticagrelor will receive oral Ticagrelor, 180 mg as early as possible after the index event and not >24 h post event followed by 90 mg twice daily for 12 months.

Clopidogrel

Patients assigned to Clopidogrel will receive 300 mg as early as possible after the index event and not > 24h post event, followed by 75mg/day for 12 months.

Drug accountability

Drug supplies must be kept in a secure, limited access storage area under the appropriate storage conditions. A temperature log must be maintained at the study site to make certain that the drug supplies are stored at the correct temperature.
### Co-Interventions

**Medical**

**Adjunctive Antiplatelet Therapy With Fibrinolysis**

1. Aspirin (162- to 325-mg loading dose, and 75 to 100mg as maintenance dose) should be administered to patients with STEMI who receive fibrinolytic therapy.$^{16}$

#### Table 1. Antiplatelet therapy

<table>
<thead>
<tr>
<th>Antiplatelet therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin:</td>
<td></td>
</tr>
<tr>
<td>162 to 325mg loading dose</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose will be 75 to 100mg/day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulant therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH:</td>
<td></td>
</tr>
<tr>
<td>- Weight based IV bolus and infusion adjusted to obtain a PTT of 1.5 to 2.0 times control for 48 h or until revascularization. IV bolus of 60 U/Kg (maximum 4000U) followed by an infusion of 12 U/Kg/h (maximum 1000 U) initially, adjusted to maintain aPTTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48h or until revascularization</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enoxaparin:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- If age&lt; 75 y: 30 mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12h (maximum 100 mg for the first 2 doses)</td>
<td></td>
</tr>
<tr>
<td>- If age ≥75 y: no bolus, 0.75mg/Kg subcutaneously every 12 h (maximum 75mg for the first 2 doses)</td>
<td></td>
</tr>
<tr>
<td>- Regardless of age, if CrCl &lt; 30mL/min: 1 mg/kg subcutaneously every 24h</td>
<td></td>
</tr>
</tbody>
</table>
- **DURATION**: For the index hospitalization, up to 8 d or until revascularization

**Fondaparinux:**

- Initial dose 2.5mg IV, then 2.5mg subcutaneously daily starting the following day, for the index hospitalization up to 8 d or until revascularization
- Contraindication if CrCl < 30 mL/min

**Adjunctive Anticoagulant Therapy with Fibrynolysis**

1. Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the index hospitalization, up to 8 days or until revascularization if performed.17, 18

   Recommended regimens include

   a. UFH administered as a weight-adjusted intravenous bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization;

   b. Enoxaparin administered according to age, weight, and creatinine clearance, given as an intravenous bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to 8 days or until revascularization; or

   c. Fondaparinux administered with initial intravenous dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to 8 days or until revascularization

**Transfer of Patients With STEMI to a PCI-Capable Hospital for Coronary Angiography After Fibrinolytic Therapy**

   Some participating sites will not have PCI capabilities. In these situations, urgent transfer to a PCI-capable hospital for coronary angiography is reasonable for patients with STEMI who demonstrate evidence of failed reperfusion or reocclusion after fibrinolytic therapy.16
Transfer to a PCI-capable hospital or performance of coronary angiography is also reasonable for patients with STEMI who have received fibrinolytic therapy even when hemodynamically stables and with clinical evidence of successful reperfusion. Angiography can be performed as soon as logistically feasible at the receiving hospital, and ideally within 24 hours, but should not be performed within the first 6 hours after administration of fibrinolytic therapy unless in presence of signs of unsuccessful reperfusion. Patients transferred for intended PCI, including those pre-loaded with clopidogrel, will receive an additional 90mg dose of ticagrelor at procedures 24 hours after randomization at the discretion of the investigator, or an additional 300mg of clopidogrel at anytime relative to randomization.

Other Recommendations

Other management decisions will be according to local guidelines and at the discretion of the Investigator. The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies that may occur during the study.

3.8 OUTCOMES

Outcome Adjudication Process

The analysis of the events occurring in the TREAT Study will be conducted by an independent committee, which will carefully evaluate if these events correspond to the outcomes predefined by the protocol, every two (2) months, according to the established definitions. For the outcome evaluation process, we will consider the following source documents: official reports from physicians regarding the event, official reports of electrocardiograms, echocardiograms signed by responsible physicians, and other tests considered relevant to the reported event, such as troponin values and CK-MB for diagnosis of new myocardial infarction, tomography or magnetic resonance imaging for the diagnosis of stroke, etc.

✓ The documentation submitted must be blinded in order not to compromise the identity of the patient;
The documents must present the patient’s initials and their respective identification number;

- The dates and times in which the procedures were performed cannot be deleted. If the document does not present this information, the research center can enter this data manually;

- Check if reference values are present in laboratory test reports.

The subject personal identity as well the study arm should de-identification in order to maintain the privacy and confidentiality of the research participant, as well as the blinding of outcome adjudicators.

**CEC Members Responsibilities**

The clinical events validation group is composed by trained physicians with extensive experience in clinical practice of Internal Medicine, Neurology and Cardiology. Also an operational team will be responsible for the entire organization and logistics of the process. Documentation of qualifications of the medical reviewers will be filed in IP-HCOR from summarized curriculums of them.

The reviewers will validate and classify suspicious events blinded to the study treatment given to the patient. Any identification of the patient or the treatment present in the documents will be hidden by the site coordinator and checked by the operational team.

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renato Delascio Lopes</td>
<td>CEC Chair</td>
<td><a href="mailto:renato.lopes@duke.edu">renato.lopes@duke.edu</a></td>
</tr>
<tr>
<td>Pedro Gabriel Melo de Barros e Silva</td>
<td>CEC Medical Coordinator</td>
<td><a href="mailto:pedro.barros@bcri.org.br">pedro.barros@bcri.org.br</a></td>
</tr>
<tr>
<td>Diogo Duarte Fagundes Moia</td>
<td>Project Leader</td>
<td><a href="mailto:dfmoia@hcor.com.br">dfmoia@hcor.com.br</a></td>
</tr>
<tr>
<td>Camila Maximo Lasagno</td>
<td>CEC Operational Team</td>
<td><a href="mailto:clasagno@hcor.com.br">clasagno@hcor.com.br</a></td>
</tr>
<tr>
<td>Carolina Trovarelli Candido</td>
<td>CEC Operational Team</td>
<td><a href="mailto:ccandido@hcor.com.br">ccandido@hcor.com.br</a></td>
</tr>
</tbody>
</table>

**Research Institute HCor - IP-HCOR**

Rua Abílio Soares, 250 - 11º andar - Paraiso - São Paulo - SP - Tel.: 55 11 3053-6611

**Periodicity and Evaluation Process**

The evaluation of the outcomes is a continuous process during the project and will occur every two months according to the flow chart below. Thus, the study's
researchers collect data on the electronic case report form (CRF) platform of the study, where there are issues in the predefined visits in the protocol of the study on whether the patient suffered or not (binary question) the outcomes pre-specified by the study. If the investigator marks, yes, he must also fill in the date and time of occurrence of the event, and the electronic system will automatically direct the investigator to the specific CRF of each outcome, where details are asked. For example, in the case of a re-infarction, information on symptoms (chest pain, shortness of breath, etc.), cardiac enzymes (troponin, CK-MB) and electrocardiogram (ST segment change, ninth wave Q, new left bundle branch block, etc.).

The Data Management team hosted at the Coordinating Center weekly identifies all CRFs as completed by researchers in the system (which meets all confidentiality and privacy criteria required) and contacts the research centers requesting copy anonymised as a template above the source documents that bought the information filled out by the investigator in the CRFs. Once these documents have been received by the Coordinating Center and they are complete, they (documents) are sent to the members of the CAE (Event Adjudication Committee) that initiates the evaluation. The evaluation always occurs every 2 months in parallel, simultaneous and independent. If there is consensus, the outcome is validated and confirmed by the CAE members in the specific event award CRF. If there is no consensus, a meeting is scheduled to discuss the events that need definition. After this meeting, the consensus is reached and the analysis of the outcome is completed (yes or no).
3.8.1 Primary Outcome

The primary safety endpoint is time to TIMI-defined and adjudicated first total major bleeding event (including major life-threatening bleeding and other major bleeding) at 30 days.

Bleeding TIMI Definition

Major:
Any intracranial hemorrhage (ICH)*, OR
Clinically significant overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥ 5 g/dL (or, when Hgb is not available, an absolute drop in hematocrit (Hct) of ≥ 15%).

An independent blinded central adjudication committee will adjudicate all suspected primary endpoints.

### 3.8.2 Secondary Safety Outcome

Secondary safety endpoints: Total bleeding (major and minor) according to PLATO, TIMI and BARC definitions, minor bleeding according to the TIMI definition and major bleeding as individual endpoint according to the PLATO definition. Others safety variables will include: dyspnea, arrhythmia, bradycardia and laboratory safety tests.

**PLATO bleeding definition:**

**Major bleed—life threatening;** meets any of these criteria:

Fatal or intracranial or intrapericardial with cardiac tamponade or hypovolemic shock or severe hypotension requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells.

<table>
<thead>
<tr>
<th>Term</th>
<th>Associated decrease in hemoglobin</th>
<th>Transfusion of whole blood or PRBCs for bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed—life threatening; meets any of these criteria:</td>
<td>Fatal or intracranial or intrapericardial with cardiac tamponade or hypovolemic shock or severe hypotension requiring pressors or surgery</td>
<td>≥50 g/L (3.1 mmol/L)</td>
</tr>
<tr>
<td>Major bleed—other; meets any of these criteria:</td>
<td>Significantly disabling (eg, intraocular with permanent vision loss)</td>
<td>30-50 g/L (1.9-3.1 mmol/L)</td>
</tr>
</tbody>
</table>
### Other major bleeding

We define other major bleeding as bleeding that led to clinically significant disability (i.e., intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the hemoglobin level of at least 30 g per liter but less than or equal 50 g per liter or requiring transfusion of 2 to 3 units of red cells.

### Bleeding TIMI Definition

**Minor:**

Any clinically significant overt sign of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL (or, when Hgb is not available, a fall in Hct of 9 to < 15%).

To account for transfusions, Hgb and Hct measurements will be adjusted for any PRBCs or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be assumed to result in an increase by 1 mg/dL in Hgb or by 3% in Hct. Thus, to calculate the true change in hemoglobin or hematocrit, if there has been an intervening transfusion between two blood measurements, the following calculations should be performed:

\[
\Delta \text{Hgb} = [\text{Baseline Hgb} - \text{Post transfusion Hgb}] + [\text{number of transfused units}] \\
\Delta \text{Hct} = [\text{Baseline Hct} - \text{Post transfusion Hct}] + [\text{number of transfused units} \times 3]
\]

**Bleeding requiring medical attention:**

<table>
<thead>
<tr>
<th>Minor bleed</th>
<th>Requires medical intervention to stop or treat bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal bleed</td>
<td>All others not requiring intervention or treatment</td>
</tr>
</tbody>
</table>

If the bleeding event fulfills criteria in N1 category, the event will be assigned to the most severe category. PRBCs, Packed red blood cells.
Any clinically overt bleeding that requires unplanned medical treatment, surgical treatment, or laboratory evaluation, and does not meet criteria for major or minor bleeding, as defined above.

**TIMI Clinically significant Bleeding:**
The presence of either TIMI major or TIMI minor bleeding, or bleeding requiring medical attention.

For patients experiencing a hemorrhage that occurs as a result of CABG, the following criteria will be used:

**Major:** Any hemorrhage that meets any of the following criteria:

a. Fatal bleeding (i.e., bleeding that directly results in death), or
b. Peri-operative intracranial bleeding*, or
c. Re-operation following closure of the sternotomy incision for the purpose of controlling bleeding, or
d. Transfusion** of ≥ 5 units of whole blood or PRBC’s within a 48 hour period, or
e. Chest tube output >2 liters within a 24 hour period.

* In light of the increased sensitivity of brain imaging for microhemorrhages of uncertain clinical significance, brain imaging with an incidental finding of microhemorrhage in the absence of attributable clinical symptoms/findings will not be considered to meet the protocol definition of intracranial hemorrhage. Intracerebral microhemorrhages will rather be classified in a separate category for analysis.

** Cell saver transfusion will not be counted in calculations of blood products.

None: Not qualifying as a major bleed in setting of CABG.

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**Bleeding BARC Definition**

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Type 0: no evidence of 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 clinically overt sign of hemorrhage that is actionable but does not meet criteria for type 3, 4 or 5. Must meet at least 1 of following criteria:

- Requires intervention
  - Defined as a healthcare professional– guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug
  - Examples include coiling, compression, use of reversal agents (Vit. K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy

- Leads to hospitalization
  - Defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care

- Prompts evaluation
  - Defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, hematocrit testing, hemoccult testing, endoscopy, colonoscopy, computed tomography scanning, or urinalysis

Type 3: clinical, laboratory, and/or imaging evidence of bleeding, with healthcare provider responses:

- BARC type 3a
  - Any transfusion with overt bleeding
  - Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL
- **BARC type 3b**
  - Overt bleeding plus hemoglobin drop >5 g/dL
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  - Bleeding requiring intravenous vasoactive drugs

- **BARC type 3c**
  - Intracranial hemorrhage, subcategories confirmed by autopsy, imaging or lumbar puncture
  - Intraocular bleed compromising vision

**Type 4: Coronary Artery Bypass Graft–related bleeding**
- Perioperative intracranial bleeding within 48 hours
- 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-hour period
- Chest tube output 2 L within a 24-hour period

  Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

**Type 5: Fatal bleeding**
- Probable fatal bleeding (type 5a)
- Bleeding that is clinically *suspicious* as the cause of death, but the bleeding is *not directly observed* and there is no autopsy or confirmatory imaging.
- Definite fatal bleeding (type 5b)
• Bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy
• BARC fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed

3.8.3 Secondary Efficacy Outcome (NET Benefit):

Secondary efficacy combined endpoint: death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event.

We will also measure the individual outcomes all-cause mortality and need for rescue PCI, as well as individual components of the combined efficacy endpoint.

The definitions for the individual efficacy outcomes are presented below:

Myocardial infarction

Recurrent MI within 18 hours of a previous MI is defined as recurrent cardiac ischemic symptoms and a new ST elevation. Recurrent MI after 18 hours but before cardiac markers have returned to normal is defined as symptoms and re-elevation of troponin or CK-MB of at least 50% over a previous value that was decreasing. Myocardial infarction after cardiac biomarkers have returned to normal is defined as elevation of biochemical markers above the upper limit of normal with either ischemic symptoms at rest, ECG changes or pathological findings of an acute MI.

Stroke

Defined as a sudden, focal neurologic deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause, such as a tumor or seizure. An event matching this definition that lasts <24 hours is considered a transient ischemic attack (TIA).
Advanced brain imaging is sought in each case to help distinguish hemorrhagic from ischemic stroke. The outcome of all strokes is classified according to the modified Rankin scale at hospital discharge. Subjects dying from any cause within 30 days of the onset of stroke are regarded as having fatal stroke.

**Vascular Death**

Deaths are adjudicated as having been caused by vascular causes (eg, stroke, embolism, or acute MI) or nonvascular due to conditions such as malignancy or hemorrhage.

**Recurrent ischemia,**

Defined as ischemic discomfort or equivalent meeting the following criteria:

- Lasting ≥ 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, considered to be myocardial ischemia upon final diagnosis

**Severe recurrent Ischemia**

Defined as ischemic discomfort or equivalent meeting the following criteria:

a) Lasting ≥ 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, considered to be myocardial ischemia upon final diagnosis

**AND**

b) Prompting coronary revascularization performed during an unscheduled visit to healthcare facility or during an unplanned hospitalization for these symptoms, or revascularization which was either done emergently or not previously planned during the course of the hospitalization.

Attempted revascularization procedures, even if not successful, will be counted. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as urgent coronary revascularization.

**Transient ischemic attack is defined by:**
a. an acute focal neurological deficit ending lasting <24 hours, and not due to an identifiable non-vascular cause (e.g. brain tumor, trauma), AND
b. absence of new infarct on brain imaging (if obtained).

3.9 Definitions of adverse events

Adverse event

An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily need to have a causal relationship with this treatment.

Serious adverse event

The outcomes (defined above) that fulfill the criteria of an SAE will not be reported as SAEs, but as OEs. An SAE is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

The intensity of the AE should be judged based on the following:

- Mild: Awareness of signs or symptoms which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or
re-challenge. Only unexpected and not previously described serious adverse events that are believed with a reasonable level of certainty to be related to the trial medication need to be reported immediately (i.e., within 24 hours of knowledge of the event) to the TREAT Project Office. For such events research personnel should complete an SAE CRF and immediately enter it into the e-CRF. The Project Office will then inform ANVISA (Brazilian national Regulatory Agency) in a timely manner according to the SAE Management Plan.

**Reporting of serious adverse events**

The Investigator is responsible for informing the local authorities and Local Ethical Committees, of any serious adverse events as per local requirements, and concurrently AstraZeneca.

Serious adverse events that do not require expedited reporting need to be reported to AstraZeneca quarterly either as individual case reports or as line-listings. When reporting to AstraZeneca, a cover page should accompany the SAE form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator’s name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications.

Send SAE report and accompanying cover page by way of fax to AstraZeneca’s designated fax line: +55 11 4702-2481

### 3.10 Follow-up

Patients will be followed-up for 12 months. After being randomized, all patients will be observed for the duration of the study to ascertain clinical events. Patients will be seen at hospital discharge or 7th day, 30 days, 6 months, and 12 months.
3.11 Sample Size

In order to test non-inferiority of Ticagrelor to Clopidogrel for bleeding over 30 days according to the TIMI criterion, it was estimated that 1897 patients per group would be required. The following parameters were considered for the calculations: bleeding rate of 1.22% \(^{21}\); non-inferiority margin of 1.0%; level of monocular significance of 2.5%; allocation ratio 1:1.

Also, evaluating the test power scenario for the secondary efficacy endpoint, which is to test the superiority of Ticagrelor compared to Clopidogrel (death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or another thrombotic arterial event), a control event rate of 16% was used \(^{22,14}\) at 12 months, a 5% two-tailed alpha, a relative risk reduction of 25.0%, and a statistical power of 90% estimating a sample of 1592 patients per group.

Thus, we established our minimum sample size in 1897 patients per group (total of 3794) to have adequate statistical power to test non-inferiority over severe bleeding and the hypothesis of superiority that explores plausible moderate effects of Ticagrelor versus Clopidogrel in the reduction of such combined outcome. We also emphasize that the sample size of 3794 provides more than 90% statistical power to detect a relative risk reduction of 25%, plus 80% statistical power to detect a reduction of 22.5% and just under 80% of statistical power to detect a 20% reduction in efficacy outcome.

Recruitment will be competitive in about 170 sites from 10 countries (Argentina, Australia, Brazil, Canada, China, Colombia, New Zealand, Peru, Russia and Ukraine) with no maximum limit for patients from each center.

Rationale for the evaluation interval of the primary and secondary efficacy endpoints

The bleeding rate was initially defined at 12 months, but we preferred to replace the primary endpoint within 30 days, since all recent and large studies in the area, i.e. involving patients with myocardial infarction with supra-leveling of the Segment ST treated with thrombolytic, reported their primary outcomes within 30 days.\(^{23}\) Other recent large-scale randomized studies in patients with supra ST-treated MI treated with
fibrinolytic also define their primary outcomes within 30 days. In this sense, to maintain greater consistency and comparability with the literature, we consider that 30 days is an adequate interval for the primary outcome. Already studies involving patients with infarcts treated primarily with angioplasty / percutaneous coronary intervention (which is not the case with the TREAT Study) have more recently reported 12-month outcomes, as was the case with the PLATO Study. Anyway, to allow comparability with the PLATO Study, 12-month follow-up will be maintained and all secondary outcomes will also be reported in this period. Additionally, we will conduct a meta-analysis where we will analyze the TREAT data in 12 months combined with that of the PLATO Study in 12 months (subgroup of patients with infarction with supra ST). This meta-analysis will allow comparing the results of both studies and will also provide important additional information with adequate statistical power.

**Rationale for non-inferiority margin**

There is no data in the literature comparing non-inferiority and defining the non-inferiority margin of Ticagrelor versus Clopidogrel for major bleeding in patients with MI. The most current reference of a randomized study in patients with ST-segment elevation MI comparing two types of antithrombotics is the HORIZONS-AMI Study. This study had as its primary outcome the non-inferiority in relation to major bleeding and also the absolute margin of 1% was proposed. Thus, based on the current literature and the technical opinion of the researchers who have experience in cardiology, this margin would be relevant.

The absolute 1% bleeding rate is equivalent to a non-inferiority limit of 1.77 for the estimated Hazard Ratio according to the Cox proportional hazards model. This margin is more stringent than the non-inferiority limit used by the GEMINI-ACS study, for example, which used Hazard Ratio of 2.0 as the non-inferiority limit for bleeding.

**Rationale for choosing the bleeding rate in the control group**

The best estimate of the literature for major TIMI bleeding in 30 days in patients with MI with supra ST and who receive Ticagrelor comes from the ATLANTIC study.
this study, the incidence in 30 days was 1.3%. The initial sample size of the study was calculated assuming this event rate, however, an interim analysis performed with 1300 patients indicated that the bleeding rate awarded according to TIMI criteria in up to 30 days was less than 1%. If the overall bleeding rate is up to 1.22% in 30 days a total sample size of 3794 patients guarantees at least 80% of power for a non-inferiority margin of 1%.

**Rationale for choosing the rate of events in the control group**

The combined major cardiovascular event rate of 16% is based on recent randomized studies of patients with MI with Supra from ST, most of which involve patients treated with fibrinolytic, as shown in the table below. In these studies, the rate of major cardiovascular events ranged from 12.4% to 17.2%, although the definition was slightly different between studies. Thus, we judge that 16% is the expected event rate for our population, coincident with the event rate of the control group of the PLATO global study27 (comparison between Ticagrelor and Clopidogrel).

<table>
<thead>
<tr>
<th>Study</th>
<th>REFERENCES</th>
<th>Outcomes</th>
<th>Event Rates in Patients with MI treated with Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO - Global</td>
<td>New Engl J Med 2009; 361:1045-57</td>
<td>Major Cardiovascular Events</td>
<td>16,0%</td>
</tr>
</tbody>
</table>
### Rationale for choosing the relative risk reduction (RRR)

The relative risk reduction estimate is also based on several recent randomized studies of patients with AMI with Supra ST, as shown in the table below. In these clinical trials, the RRR used in the calculation of sample size in these studies varied between 24% and 40%.

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Sample Size Calculation Parameters for Efficacy (Superiority)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Sample Size Calculation Parameters for Efficacy (Superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO – STEMI Patients</td>
<td>Circulation 2010; 122:2131-41</td>
<td>15,0%</td>
</tr>
<tr>
<td>STREAM STEMI patients treated with fibrinolytics</td>
<td>New Engl J Med 2013; 368:1379-87</td>
<td>12,4%</td>
</tr>
<tr>
<td>CLARITY - STEMI patients treated with fibrinolytics</td>
<td>N Engl J Med 2005; 352:1179-89</td>
<td>15,0%</td>
</tr>
</tbody>
</table>
In the PLATO Study, which represents the largest and best comparison available between Ticagrelor and Clopidogrel (in the specific publication in patients with STEMI\(^{22}\)), relative risk reductions for relevant clinical outcomes ranged from 13% to 35%. For example, for endpoint total mortality the RRR was 20% and for the outcome arterial thrombosis was 35% when Ticagrelor and Clopidogrel were compared. Thus, we believe that using 25% relative risk reduction in the calculation of sample size for efficacy is in agreement with the literature. It would also be no different from the parameters used in the calculation of sample size and no other study recently published in the area.

**Form**

The following formulas were used to calculate the sample size.\(^{28}\)

Hypothesis test for proportions between two independent groups (efficacy):

\[
\begin{align*}
    n_c &= \left( \frac{z_{\alpha/2} + z_\beta}{\sqrt{\log\left( \frac{p_c(1-p_c)}{p_t(1-p_t)} \right)}} \right)^2 \left( \frac{1}{(kp_t(1-p_t))} + \frac{1}{(p_c(1-p_c))} \right) \\
    n_c &= n_t
\end{align*}
\]

- \(k = 1 (1:1)\): the allocation ratio of the groups
- \(\alpha\): level of significance (type I error)
- \((1-\beta)\): power of the test
- \(z_\alpha\): percentile of the standard normal distribution.
- \(p_c\) and \(p_t\): expected probability of the events of the control and treatment groups respectively.

\(n_c\) and \(n_t\): estimated sample size for the control and treatment groups respectively.
For the non-inferiority primary event, a test was performed for differences in proportions considering TIMI serious bleeding as an event. The $\delta$ in the formula refers to the absolute non-inferiority margin.

$$n_c = \frac{(z_{\alpha/2} + z_{\beta})^2}{((p_c - p_t) - \delta)^2} \left( \frac{p_t(1-p_t)}{k} + \frac{(p_c(1-p_c))}{1} \right), \quad n_c = n_t$$

### 3.12 Statistical Analysis Plan

Primary analysis will follow the intention-to-treat principle. The primary non-inferiority endpoint for bleeding in 30 days will be performed by comparing proportions test considering non-inferiority margin of 1%. The remainder of the bleed evaluations (secondary events) will only be presented with 95% confidence intervals for the estimated relative 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, infarction myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other thrombotic arterial events within 12 months.

Each of the efficacy outcomes will be consecutively evaluated using sequential hierarchical test method, which consists of performing the hypothesis test for the next outcome if and only if the previous outcome has a significant descriptive level ($p < 0.05$). This method is more robust for detecting possible spurious results. We will use the following hierarchy for the secondary endpoints:

- Combined outcome of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other thrombotic arterial event;
- Combined death outcome due to cardiovascular, AMI or stroke;
- MI
- Cardiovascular death
• AVC
• Death from any cause
• Need for rescue PCI

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.

Initially we will construct the CONSORT flow with the respective inclusions and exclusions of the study patients. This is followed by the characterization table of the collected sample described by absolute and relative frequencies (categorical variables) and descriptive statistics of position and scale (continuous variables).

We will evaluate the treatments and procedures according to the patient's allocation group. Comparisons of the continuous order variables will be assessed compared between groups using t-student tests or Mann-Whitney tests if the normality assumptions required for the first test are not satisfied. Comparisons between qualitative variables will be evaluated by Fisher's exact test. Other variables evaluated by time to event will be evaluated by Cox proportional hazards models, as described for the primary objective, unless the risk proportionality assumption is not maintained, in which case we will use survival models that consider this characteristic.

The document attached to the most complete statistical analysis plan contains the table templates to be used in the main analysis of the study.

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. Adjustments will be made considering gender, age, diabetes mellitus, TIMI score, time from the beginning of the index event until randomization, Killip class and Clopidogrel pre-randomization. The choice of the model will depend on the characteristic of the evaluated variable: Cox proportional hazards models for time-to-event variables, logistic regressions for binary outcomes in predefined time frames, and generalized linear
models for continuous variables, depending on the frequency distribution of the
analyzed variable.

A meta-analysis combining the results of TREAT and sub-study STEMI PLATO will
also be performed, providing additional robust information (more accurate in terms of
statistical power).

It should be emphasized that comparisons of outcomes between groups will only
be assessed when all expected participants complete follow-up.

The analyzes will be performed using the R software in its most current version.\textsuperscript{30}

\subsection*{3.13 Independent Data Monitoring Committee Analysis}

The Independent Data Monitoring Committee will be composed of the President
(President of the DMC - invited by the Steering Committee), who must be a medical
researcher and experienced professor in the area of cardiology, who holds a position of
management in an institution of recognized excellence and:

The.

a. Another medical researcher experienced in the area of cardiology;
b. Clinical Epidemiologist;
c. Statistician with experience in analyzes of randomized studies;
d. Specialist in Bioethics and Good Practices in Clinical Research;

The Committee meetings will be held at three times: 25%, 50% and 75% of data
collected to assess study status, recruitment rate, protocol adherence, data quality,
follow-up losses, specific problems with centers or others aspects that are deemed
relevant. The study is not intended to be discontinued for effectiveness.

\subsection*{3.14 Data Entry System}
Data will be managed using the Electronic Data Capture (EDC) system. Case report forms (CRFs) will be transferred to an electronic record and sent to the Coordinating Center in a validation database.

3.14.1 Data collection form

CRFs will be entirely filled and sent online; they will be signed electronically, and access will require a personal, non-transferable password. The PI may choose to keep print copies of the CRFs (booklets as source documents); these copies should be signed by the investigator/coordinator responsible for data collection or by authorized co-investigators, as determined by the task assignment chart.

4 ETHICAL ASPECTS AND GOOD CLINICAL PRACTICE (GCP)

The TREAT Trial will be conducted in accordance with local and international regulations described in the documents below:

- Helsinki Declaration.
- 215 (R2) ICH Harmonized Tripartite Guidelines for Good Clinical Practice.

4.1 Study approval

Prior to study initiation, the investigator should send a copy of the research protocol, of the ICF, and of other relevant documents to the independent REC of the institution. A covering letter and the REC approval should be sent to the Coordinating Center. Any amendments to the original protocol should also be approved by the REC of each of the participating centers.

4.2 Inform consent form (ICF)

Every patient will be asked to sign the ICF. Whenever a patient is unable to provide consent, their legal representative will be asked to sign the document. The
physician in charge or the study coordinator will ask the patient or legal representative to sign the form and will provide explanations about the study. Both the patient and the professional involved will have to date and sign the two copies of the ICF; one copy will be given to the patient, and the other will be filed with study documents. Subjects will be clearly informed that participation is voluntary, and that refusal to participate at any time will not have any effects on the quality and conduct of subsequent medical treatment. The ICF proposed for the study will be evaluated by each participating center, and any changes to the original text should be approved by the Coordinating Center prior to submission to the REC.

4.3 Data confidentiality

No patient data will be disclosed to the data or study management teams. Electronic CRFs will identify patients and centers by numbers. Data from printed medical records will be kept confidential by all participating centers, stored in locked cabinets. Patient anonymity in all provisional and definitive reports will be guaranteed.

4.4 Progress reports

The investigator should submit written summaries of the trial progress to the REC of the institution every six months, as well as a final report upon study completion.

5 STUDY COORDINATION

5.1 Coordinating Center

The Coordinating Center of the TREAT Trial will be the Research Institute –HCor, located at the Heart Hospital (Hospital do Coração) of Sao Paulo, Brazil. The institution is widely experienced in conducting large RCTs. The Research Institute-HCor team will provide guidance and support to the participating centers to ensure adherence to the research protocol. The Research Institute-HCor team has the necessary expertise and
level of knowledge in research methods and biostatistics, and we are assisted by awarded career scientists.

Considering ACS patients, studies coordinated by IP-HCor during the last 5 years have enrolled over 41,000 patients in clinical trials, from which over 10,000 in ACS clinical trials (5040 in ACCEPT Registry, 373 in Phase I and 1,150 in Phase II of BRIDGE-ACS trial, 802 in ACT trial and 4112 in SECURE trial – ongoing trial).

5.2 Executive Committee

Members of the Executive Committee of the TREAT Trial will be responsible for supervising the clinical trial, including the decisions to suspend or modify study procedures as necessary, deal with the challenges involved in implementing the protocol, revise and interpret data, and prepare the final manuscript. Such coordination will be accomplished through in-person or telephone meetings held at least every three months. All other committees of the TREAT Trial will report directly to the Steering Committee.

5.3 Publication Committee

Members of the Executive Committee will be selected to compose a Publication Committee, which will be responsible for writing the final manuscript and submitting it for publication. This committee will also manage the database and will be responsible for evaluating proposals for publications based on TREAT Trial data.

5.4 Adjudication Process

The Clinical Endpoints Committee (CEC) is responsible for adjudicating all the pre-specified endpoints of the study. All suspected events will be entered into the CEC tracking database. There will then be an administrative review of each of the endpoints to check that all necessary documents are available. For the adjudication process, we will consider the following source documents: official physician reports concerning the event, exams signed by physician,
and others exams considered relevant to the related outcome. Electronic records or DVD regarding imaging exams are not necessary, but could be requested if the official reports are not available or in cases of disagreement between adjudicators or between clinical presentation and test results. The Research Institute HCor will print out the necessary documents from the eCRF and include additional supportive information in a completed CEC packet. The Research Institute HCor will forward two copies of each endpoint package to the CEC where they will be randomly assigned to two independent physician reviewers. The physician reviewers will independently review the cases assigned to them, document and provide supporting information for each event’s adjudication directly in the endpoint package. If the two adjudications agree, the event adjudication is considered complete. If there is a discrepancy in an event adjudication between the physician reviewers, or at the discretion of a physician reviewer, the case will be presented for review by at least one additional reviewer to establish a final adjudication. The final adjudication result will be entered into the database by the CEC coordinator. A copy of all signed adjudication forms will be filed in each respective CEC folder and will be stored at the CEC. Additional details of processes specific to each of the 2 branches of the CEC will be detailed in separately maintained documentation of standard procedures at HCor

All adjudications will be documented, within the event review packet, with respect to the supporting endpoint criteria that were met. For any case that sets precedence, the CEC Chair will document the details of the adjudication, and the case will be recorded in a log which will serve as a guide for the reviewers to stay consistent with respect to application of endpoint definitions.

5.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee will comprise at least two established clinical investigators and one biostatistician, and will be independent from study investigators. The primary role of this board will be the continuous independent review of the reports received directly from the Methods Center, concerning: 1) study progress; 2) effectiveness and safety reports, with formal interim analysis.
The Data Safety Monitoring Committee will keep the Executive Committee informed about these issues. It will look after the safety of study participants at all times. The principles of the Data and Safety Monitoring Board (DSMB), of the DAMOCLES study group (Data Monitoring. Committees: Lessons, Ethics, Statistics, 2005), will be adopted for the description of roles, responsibilities, and reports produced by this committee.27

5.6 Data quality management and maintenance

Several procedures will be adopted to guarantee data quality and protocol standardization, thus contributing to minimize bias. Such procedure include: 1) one-day training with all research coordinators before study initiation, so as to guarantee consistency in study procedures; 2) a detailed Operations Manual of the TREAT Trial, describing each step of the protocol; 3) the study coordinator will visit participating centers to revise the protocol and to provide new training sessions, as necessary; 4) an electronic data capture system will validate the data and propose questions or corrections whenever errors are detected during quality control assessments; and 5) the Coordinating Center will prepare detailed monthly reports on patient screening, recruitment, randomization, data quality, adherence to the protocol, consistency and perfection in data entered, in addition to event rates. The team at the Coordinating Center will be available every day to solve problems and provide clarifications to research coordinators and investigators from the participating centers.

5.7 Role of the Study Sponsor

This is a relevant clinical trial, designed and sponsored by the Research Institute HCor with support from AstraZeneca. The aim of the study is exclusively to obtain the best scientific knowledge on daily clinical practice, free from any conflicts of interest. If appropriate, the source of financial support will be acknowledged in presentations and publications. The results of the TREAT Trial will be published irrespective of the positive or negative nature of the data obtained.

5.8 Role of investigators and co investigators of the participating centers
The PI of each center will conduct and/or supervise the daily operations of the project at his/her respective center, assisted by the co-investigator and the research coordinators. Most tasks can be delegated by the PI to individuals on the research team of each center, provided these individuals are qualified for the tasks and the decision to delegate is recorded including the name of the individual and their position. However, the PI will continue to be legally responsible for the tasks. In addition, investigators are responsible for initiating the study at their center, for maintaining study procedures, for guaranteeing protocol improvement or refinement, as well as for data quality and veracity.

5.9 Monitoring for Protocol Compliance

Representatives of TREAT Project Office must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. During on-site visits, they will review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

6 RESULT PUBLICATION

The success of the TREAT Trial will depend on the research team involved, on the efforts and collaboration of all investigators, research coordinators, and patients. Therefore, the main results will be published having as author the team that has participated in the study (not only the study organizers).

7 PROTOCOL AMENDMENTS

Any agreed upon change to the study protocol should be recorded in writing via an amendment signed by the PI.
Approval and recommendation of the changes by the Research Ethics Board is required before their implantation, unless there are safety reasons that superimpose such approval or recommendation.

In some cases, amendments can require changes to the ICF. The investigator should receive the approval or recommendation of the revised form before implementing the changes. In addition, changes to the ICFs, if required, will be incorporated in the amendment. Before proceeding with the changes, the protocol amendment should be submitted to the appropriate regulatory agencies for approval, except in emergency situations.

REFERENCES


32. E Magnus Ohman, Matthew T Roe, P Gabriel Steg, Stefan K James et al for the Gemini-ACS-1 investigators. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in