Rationale and design of the Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS-ACS 2 TIMI 51) trial: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome

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Background Although therapy with aspirin or aspirin plus a thienopyridine reduces the incidence of long-term adverse cardiovascular events among patients with acute coronary syndrome (ACS), there remains a significant residual risk of cardiovascular death, recurrent myocardial infarction (MI), and stroke. In a phase 2 trial (ClinicalTrials.gov NCT00402597) in which the addition of the factor Xa inhibitor rivaroxaban was compared with placebo, among ACS patients receiving either aspirin alone or dual-antiplatelet therapy with aspirin and a thienopyridine, the end point of death, MI, or stroke compared with placebo was reduced (87/2331 [3.9%] vs 62/1160 [5.5%]; hazard ratio 0.69, [95% CI 0.50-0.96], $P = .027$). Two candidate doses of rivaroxaban were selected for further evaluation in a pivotal phase 3.

Design The second ATLAS-ACS 2 TIMI 51 Trial is an international, randomized, double-blind, event-driven (n = 983) phase 3 trial involving more than 15,570 patients hospitalized with ACS (ClinicalTrials.gov NCT00809965). All patients are treated with a background of standard therapy including low-dose aspirin, and patients are stratified by the administration of a thienopyridine (clopidogrel or ticlopidine; stratum 2) or not (stratum 1). Within each stratum, patients are randomly assigned in a 1:1:1 ratio to receive rivaroxaban 2.5 mg twice daily, or rivaroxaban 5 mg twice daily, or placebo twice daily. The primary efficacy end point is the composite of cardiovascular death, MI, or stroke. The primary safety end point is thrombolysis in MI major bleeding not associated with coronary artery bypass graft surgery.

Summary The ATLAS-ACS 2 TIMI 51 is testing the hypothesis that anticoagulation with the oral factor Xa inhibitor rivaroxaban reduces cardiovascular death, MI, and stroke among patients with ACS treated with guideline-based therapies for ACS. (Am Heart J 2011;161:815-821.e6.)

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Background

Among patients with acute coronary syndrome (ACS), aggressive antiplatelet therapy with aspirin and a thienopyridine reduces both short- and long-term adverse cardiovascular events.[1-3] There remains, however, an unacceptably high rate of residual recurrent ischemic events among such patients.[3] It is reasonable to consider antithrombotic therapy as effective agents in so far as coronary thrombosis is known to be composed of both platelets and fibrin.[4] Long-term oral anticoagulation has been associated with a reduction in major adverse cardiovascular events after myocardial infarction (MI),

but the clinical use of warfarin and other coumarin derivatives has been hindered by an increased risk of hemorrhagic events, a high rate of drug discontinuation, the need for frequent monitoring, and multiple food and drug interactions.[5,6]

Rivaroxaban, an oral factor Xa inhibitor, is an attractive alternative to coumarin derivatives.[7-11] It has a high degree of bioavailability, predictable pharmacokinetics/pharmacodynamics, and a half-life of 5 to 9 hours and 11 to 13 hours in older patients.[12] There is a close correlation between the plasma level of rivaroxaban and factor Xa inhibition. Rivaroxaban's clinical efficacy as an anticoagulant in the management of venous thromboembolism has been demonstrated among subjects undergoing major lower extremity orthopedic surgery. When compared with subcutaneous enoxaparin, it led to a reduction in thromboembolic events and similar rates of bleeding.[7-11]

Rivaroxaban has been studied in a phase 2 dose-finding and safety study among patients presenting with ACS treated with aspirin alone or aspirin plus a thienopyridine in addition to standard medical therapy in the first ATLAS-ACS 1 TIMI 46 study[13] (ClinicalTrials.gov NCT00402597). Compared with placebo, rivaroxaban was associated with a trend toward a reduction in the incidence of the primary end point, the composite of death, MI, stroke, or severe recurrent ischemia requiring revascularization (7.0% vs 5.6%, $P = .10$) and a significant reduction in the secondary end point, the composite of death, MI, or stroke (5.5% vs 3.9%, $P = .03$) as well as a dose-dependent increase in bleeding events.[13]

The 2 lowest doses of rivaroxiban (2.5 and 5.0 mg orally twice a day) were associated with a trend toward improved efficacy. Among patients treated with aspirin alone, rivaroxaban in these doses reduced the risk of death, MI, or stroke from 11.9% to 6.6% (hazard ratio [HR] 0.54 [0.27-1.08], $P = .08$) and among patients treated with both aspirin plus clopidogrel, rivaroxaban reduced the risk of death, MI, and stroke from 3.8% to 2.0% (HR 0.55 [0.27-1.11], $P = .09$) when compared to placebo. Among patients treated with these doses of rivaroxaban along with aspirin alone, the risk of TIMI major bleeding increased from 0.0% to 1.2% ($P = .17$), and among patients treated with both aspirin plus clopidogrel, TIMI major bleeding increased from 0.2% to 1.2% ($P = .03$) compared with placebo. In an exploratory net clinical benefit analysis of death, MI, stroke, or TIMI major bleeding, rivaroxaban (2.5 mg twice daily or 5 mg twice daily) as compared with placebo resulted in an HR of 0.72 (0.46-1.12) in the entire cohort, 0.59 (0.30-1.16) in stratum 1, and 0.85 (0.47-1.54) in stratum 2.

Based on the trend for efficacy and the relative safety of these 2 lowest doses in the phase 2 study, a phase 3 pivotal trial was designed. We describe here the design of ATLAS-ACS 2 TIMI 51 (ClinicalTrials.gov NCT00809965), a randomized, placebo-controlled, multicenter event-driven clinical trial comparing 2 different doses of rivaroxaban with placebo among patients with ACS. The 2 most promising doses of rivaroxaban from the phase 2 trial (2.5 mg and 5.0 mg twice a day) were selected.[15]

Study operations

The trial is funded by Johnson and Johnson and Bayer. The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final contents. The study conduct is overseen by an executive committee that is chaired by Dr Eugene Braunwald, the Chairman of the TIMI Study Group. The executive committee consists of members of the academic leadership of the trial and members from each sponsoring company. The executive committee provides oversight of trial conduct and data analysis, oversees publication of the trial results, appoints members of the steering committee, appoints the Independent Data Monitoring Committee (IDMC) chair, identifies the IDMC members, creates the IDMC charter, and receives recommendations from the IDMC regarding possible additional analysis or modifications to the trial.

Study objectives

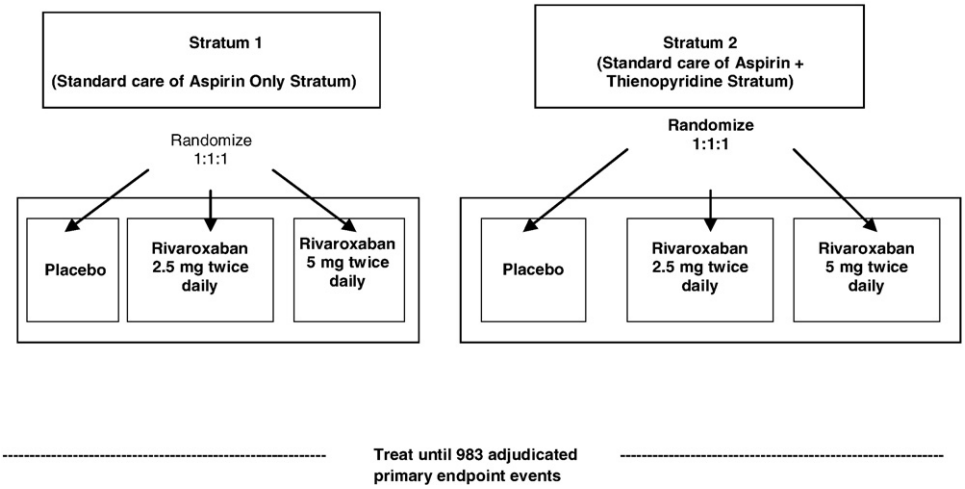
The primary objective of the ATLAS-ACS 2 TIMI 51 study is to determine whether rivaroxaban, when added to standard care, is safe and reduces the risk of the composite of cardiovascular (CV) death, MI, or stroke in subjects with ACS compared with placebo.

Study population and patient selection

Approximately 15,570 men or women 18 years or older hospitalized for symptoms suggestive of ACS with chest discomfort typical of myocardial ischemia that persists for at least 10 minutes at rest and occurs within 48 hours of hospital presentation or who develop ACS while being hospitalized for an indication other than ACS are being enrolled. Subjects must have a diagnosis of (1) ST-segment elevation MI (STEMI), defined as elevation of ST-segment more than 0.1 mV in 2 or more contiguous ECG leads, or new left bundle-branch block, or ST-segment depression 0.1 mV or greater in 2 of the precordial leads V1-V4 with evidence suggestive of true posterior infarction, all with elevated biomarkers of myocardial necrosis; (2) or non-STEMI, defined as elevated biomarkers of myocardial necrosis with one of the following: (*a*) transient ST-segment elevation, or ST-segment depression, or T-wave changes consistent with myocardial ischemia or (*b*) identification of a culprit lesion at coronary angiography demonstrating recent, active intracoronary atherothrombosis; or (3)unstable angina with at least one of the following: (*a*) transient or persistent ST-segment deviation 0.1 mV or greater in 1 or more ECG leads or (*b*) a TIMI risk score ≥ 4.[14]

Subjects who are 18 to 54 years of age must also have either diabetes mellitus or a prior MI in addition to the

Figure 1



Study design of ATLAS 2 TIMI 51.

presenting ACS event. Subjects provided written informed consent before randomization.

Major exclusion criteria include increased bleeding risk, such as but not limited to, active internal bleeding, clinically significant bleeding, bleeding at a noncompressible site, or bleeding diathesis within 30 days of randomization; platelet count less than 90,000/□L at screening; intracranial hemorrhage; major surgery, biopsy of a parenchymal organ, or serious trauma within 30 days before randomization; clinically significant gastrointestinal bleeding within 12 months before randomization; an international normalized ratio known to be > 1.5 at the time of screening; abciximab bolus or infusion within the preceding 8 hours, or an eptifibatide or tirofiban bolus or infusion within the past 2 hours preceding randomization; or any other condition known to increase the risk of bleeding. Other exclusion criteria are shown in Table 1 of the online supplement.

Randomization and treatment protocol

Subjects are randomly assigned to study drug from 24 hours up to 7 days after the subject has been hospitalized for the index ACS event and after parenteral anticoagulant therapy has been discontinued. Enrollment occurs as soon as possible after the initial treatments, including revascularization procedures, for the index ACS event.

Subjects who experience a primary or secondary efficacy end point event (other than death) continue to receive blinded study drug and complete all assessments at all scheduled visits, if possible. Subjects return to the study center every 12 weeks (± 6 days of the target visit date) until the prespecified number of primary efficacy end point events and 30 days of active treatment in the last patient enrolled are reached (the global end date). An end-of-treatment visit will be conducted, followed by 24 to 30 days later by an end-of-study visit. Subjects who permanently discontinue the study drug complete an early withdrawal visit at the time of treatment discontinuation. These subjects continue to be contacted every 12 weeks thereafter until the study end to capture efficacy and safety end point data.

Subjects are stratified by the investigator's intention to administer a thienopyridine (clopidogrel or ticlopidine only; stratum 2) or not (stratum 1) at the time of enrollment (Figure 1). Administration of a thienopyridine is at investigator discretion and is not randomized. Within each stratum, subjects are randomly assigned in a 1:1:1 ratio to receive rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily, or placebo.

All study drug or placebo is taken orally, twice daily, in the morning and evening (approximately 12 hours apart). Low-dose aspirin therapy (75-100 mg/day) is administered throughout the study to all patients. The length of the treatment period is not fixed, because the study is event-driven, and subjects will continue the treatment for at least 30 days and until the required number of primary efficacy end point events is reached.

Primary and secondary efficacy end points

The primary efficacy end point is the incidence of the composite of CV death, MI, or stroke in both strata and with both doses combined compared with placebo. The secondary end points are defined below. The universal definition of MI is applied.[15] The definitions of the efficacy outcomes are shown in Table 2 of the online supplement.

An additional efficacy end point includes quality of life as measured using the EQ-5D,[16] a patient-reported outcome measure, which comprises 5 questions assessing

Table I. Data sets

Efficacy analysis data sets			
	Randomized subjects		
Efficacy analysis sets	**Randomized but not treated**	**Early discontinuation (stop treatment before global treatment end date)**	**Treated per protocol (stop treatment on or after global treatment end date)**
mITT observational period	All data from randomization up to the earlier date of 30 d after randomization and the global treatment end date	All data from randomization up to the earlier date of 30 d after last dose and the global treatment end date	All data from randomization up to the global treatment end date
ITT total and ITT observational period	All data from randomization up to the last contact date for each subject; a separate analysis will be done up until the global study end date	All data from randomization up to the last contact date for each subject; a separate analysis will be done up until the global study end date	All data from randomization up to the last contact date for each subject; a separate analysis will be done up until the global study end date

Safety analysis data sets		
	Randomized subjects who take at least one dose of study drug (ie, treated subjects)	
Safety analysis sets	**Early discontinuation (stop treatment before global treatment end date)**	**Treated per protocol (stop treatment on or after global treatment end date)**
Treatment-emergent safety observational period (primary)	All data from first dose up to the last dose date plus 2 d for each subject	All data from first dose up to the last dose date plus 2 d for each subject
mITT approach safety (align with efficacy)	All data from first dose up to the earlier date of 30 d after last dose and global treatment end date	All data from first dose up to the global treatment end date
Safety observational period (postbaseline; includes all events)	All data from first dose up to the last contact date for each subject	All data from first dose up to the last contact date for each subject

the current state of health in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The descriptive part of the questionnaire is used to generate utility scores by applying weights derived from the general UK population. The visual analog scale, which is a graphic representation that is similar to a thermometer that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state), follows the descriptive questions.

Safety outcomes and definitions

The primary safety end point is the incidence of TIMI major bleeding events not associated with coronary artery bypass graft (CABG) surgery. Secondary safety end points include the incidence of other bleeding events (see Table 3 of the online supplement), serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest (eg, any liver-related adverse event, including alanine aminotransferase [ALT] > 3 times the upper limit of normal [ULN; and normal baseline] with confirmation by retesting [within 5 days]; any bleeding event that does not meet serious adverse event; any event occurring within 30 days before a permanent discontinuation).

Three bleeding event scales are used to assess bleeding events in the study. The TIMI scale includes categories of TIMI major bleeding, TIMI minor bleeding, bleeding requiring medical attention, and insignificant bleeding events. The incidence of non-CABG TIMI major bleeding is the primary safety end point.

The second scale, therivaroxaban program scale, includes categories of major bleeding, clinically relevant nonmajor bleeding, and minimal bleeding events used in other trials of rivaroxaban.[8] Bleeding events that meet the criteria in Table 3 of the online supplement for major (TIMI or International Society on Thrombosis and Haemostasis) bleeding, but are associated with CABG, are considered separately from other bleeding events.

The third bleeding scale is the GUSTO classification. This scale will capture severe bleeding events, moderate bleeding events, and mild bleeding events.

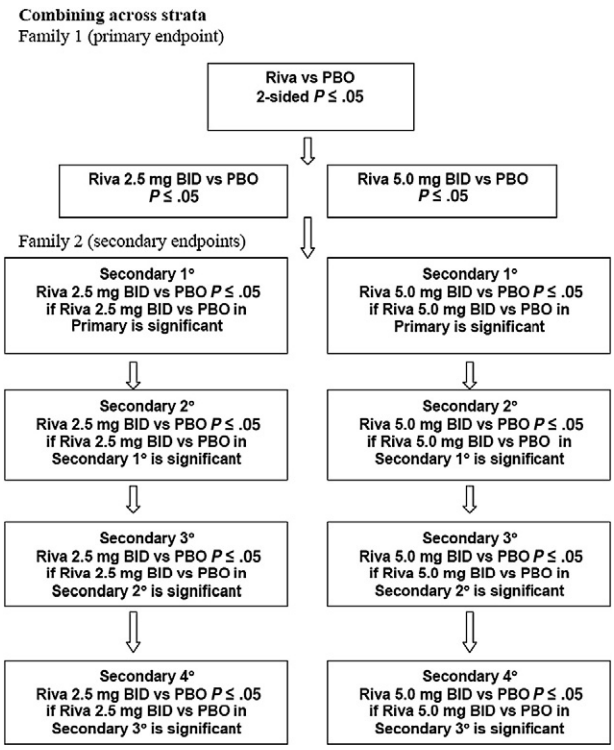
To account for transfusion, hemoglobin measurements are adjusted for any packed red blood cells or whole blood transfused between the prebleeding and post-bleeding hemoglobin measurements. The numbers of

units of packed red blood cells and whole blood combined are added to the change in hemoglobin. If only a hematocrit value is known, the corresponding hemoglobin value is assumed to be one third of the hematocrit value (in g/dL). Detailed bleeding definitions are shown in Table 3 of the online supplement.

Other adverse events of special interest include any liver-related adverse event, including ALT > 3 times the ULN (with normal baseline) with confirmation (within 5 days). The incidence of Hy's law is also assessed. Hy's law cases have the following 3 components[17]:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or aspartate aminotransferase than the (nonhepatotoxic) control agent or placebo.
2. Among subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3× the ULN, some subjects also show elevation of serum total bilirubin to > 2× ULN, without initial findings of cholestasis (serum alkaline phosphatase activity > 2× ULN).
3. No other reason can be found to explain the combination of increased aminotransferase and total bilirubin such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Figure 2



Sequence of statistical analyses in ATLAS 2 TIMI 51.

Statistical considerations

Study subjects, investigators, and sponsors are blinded throughout the trial. The trial will stop (ie, the global treatment end date will be reached) when the number of adjudicated primary efficacy end point events reaches approximately 983 events across both randomization strata and at least approximately 728 primary efficacy end points in stratum 2, and all patients have been treated with at least 30 days of study drug. Events that occur after this time will not be included as part of the primary analyses but will be analyzed as part of a supportive analysis. There is approximately 96% power to detect a 22.5% relative reduction (ie, hazard ratio 0.775) between pooled doses of rivaroxaban and placebo arms pooled across strata 1 and 2, with a 2-sided type I error rate of 0.05, based on a log-rank statistic with 2:1 allocation (rivaroxaban/placebo). Three analysis sets will be used: modified intent-to-treat (mITT), intent-to-treat (ITT), and safety. There are 2 ITT populations: one that ends with the global treatment end date (ITT observational data set, and an ITT analysis that censored at the time of last patient contact (ITT total data set). Efficacy summaries and analyses will be based on the treatment group assigned by the Interactive Voice Response System, regardless of treatment actually received. Events post-randomization will be included in the efficacy analyses irrespective of whether the patient ingested study medication. Additional details of the statistical considerations can be found in Table 2 of the online Appendix.

Primary efficacy analysis data set

The primary efficacy analysis will be based on the mITT approach. The mITT analysis set for efficacy analyses consists of all randomized subjects and end point events, which are observed from randomization up to the earliest date of the completion of the treatment period (ie, global treatment end date), or 30 days after early discontinuation of the study drug, or 30 days after randomization for those subjects who were randomly assigned to treatment but not treated. The evaluable events from this approach will be counted for the expected primary efficacy end point for interim and final analyses.

Secondary efficacy analysis data set

The ITT data set for efficacy analyses will be based on all randomized subjects, regardless of treatment exposure, and all end point events occurring on or after randomization through the global treatment end data (ITT observational data set). A second ITT analysis includes data until the last contact with the patient (ITT total data set). The efficacy analysis data set are summarized in Table I.

Safety analysis data set(s)

The safety analysis sets will consist of all randomized subjects who received any amount of study medication and analyzed according to the treatment as randomized. The safety analysis data sets are summarized in Table I.

Censoring of time-to-event end points

Table 6 of the online supplement presents the details of the time-to-event censoring.

Methods of analysis

Two simultaneous evaluation strategies, based on data combined across both strata and on data for stratum 2 only, for the primary end point analysis will be conducted. The primary evaluation strategy based on data combined across both strata is summarized below. A second evaluation strategy will be carried out based on data in stratum 2 only.

Statistical hypotheses for trial objectives

To reasonably control multiplicity, the multiple closed testing procedure described below is used:

Primary efficacy end point in combined strata (based on mITT efficacy analysis set in both strata). Rivaroxaban is superior to placebo, in addition to standard care, in the reduction of the primary efficacy end point. The primary efficacy analysis is performed between all rivaroxaban and all placebo arms at $\alpha = .05$, based on the log-rank test, stratified by the intention to use a thienopyridine. If this achieves statistical significance in favor of rivaroxaban, the study is considered to have met the primary efficacy end point.

If the above superiority is declared, the treatment effect following hypothesis is then simultaneously tested in each dose of the combined strata.

If the superiority of a dose group is observed, the major secondary efficacy end points will then be tested for that dose group (Figure 2 and Table 2 in the online Appendix).

Subgroup analyses, if identified, will be specified before unblinding of treatment assignment.

Interim Analysis

A formal interim review of efficacy and safety data will be performed when approximately 70% (688) of the required total number (983) of primary efficacy events (based on best available data, which is a blend of events adjudicated by the clinical end point committee and those reported by the local investigator) have occurred, to assess whether the study should be stopped for overwhelming superiority. A conservative Haybittle-Peto boundary (one-sided P value $< .0001$; z-value > 3.09) is used as a stopping boundary for efficacy. The final primary efficacy analyses will then be evaluated using a 2-sided $\alpha = .0499$. Details of the stopping rules are presented in Table 7 of the online supplement.

In addition to this formal interim analysis, throughout the trial, the IDMC chairman reviews unblinded best available data after every 1,000 patients are enrolled. These contain abridged data summarizing all-cause mortality (including fatal bleeding events), serious bleeding events (including intracranial hemorrhage), and liver-related SAEs. The chairman of the IDMC can call for a review by the entire IDMC at his discretion.

In addition to the ongoing safety surveillance review by the IDMC chairman, periodic meetings of the full IDMC occur 4 times during the conduct of the trial: at 25% of enrollment and at 25%, 50%, and 70% of total events.

All-cause mortality, bleeding events, treatment discontinuations, and liver-related adverse events are closely monitored.

Conclusion

ATLAS-ACS 2 TIMI 51 studies a broad population of ACS patients treated with optimal medical therapy including stratification by use of a thienopyridine. It is adequately powered to provide definitive results regarding the efficacy and safety of rivaroxaban when added to current guideline-based medical therapy for ACS.

Disclosures

All authors received research grant support from the sponsors of the trial (Johnson and Johnson and Bayer Inc.). Dr. Gibson reports receiving consulting monies from Johnson and Johnson and Bayer Inc. Dr. Mega reports receiving honoraria from Bayer Inc. Drs. Burton, Plotnikov and Sun are employees of Johnson and Johnson. Dr. Bruns is an employee of Bayer Inc.

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Appendix. Online Supplementary Materials

Online Supplementary Table 1: Additional Exclusion Criteria

1. Severe concomitant condition or disease, such as cardiogenic shock at the time of randomization, ventricular arrhythmia refractory to treatment at the time of randomization, calculated creatinine clearance < 30 mL/min at screening, known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis), or liver function test (LFT) abnormalities (confirmed with repeat testing) which would require study drug discontinuation, i.e., ALT > 5 × ULN or ALT > 3 × ULN plus total bilirubin > 2 × ULN, prior ischemic stroke or transient ischemia attack (TIA) in subjects who are planned to be included in stratum 2 (ASA plus thienopyridine),anemia (i.e., hemoglobin < 10 g/dL) at screening, known clinical history of human immunodeficiency virus (HIV) infection at screening, substance abuse (drug or alcohol) problem within the previous 6 months or any severe condition such as cancer that would limit life expectancy to less than 6 months.
2. Systemic treatment with strong CYP 3A4 and P-glycoprotein inhibitors (e.g., certain azole antimycotics, such as ketoconazole and HIV protease inhibitors, such as ritonavir)
3. Allergy or hypersensitivity to any component of rivaroxaban or placebo excipients (includes lactose, microcrystalline cellulose, magnesium stearate, hypromellose, macrogol, croscarmellose sodium, sodium lauryl sulfate, titanium oxide)
4. Known aspirin allergy
5. Atrial fibrillation excluded except for subjects younger than 60 years of age who have no clinical or echocardiographic evidence of cardiopulmonary disease and who had only a single episode of atrial fibrillation that occurred more than 2 years ago
6. Treatment with an investigational drug or used an investigational medical device within 30 days before the planned start of treatment, or are currently enrolled in an investigational study
7. Anticipated need for chronic (more than 4 weeks) therapy with non-steroidal anti-inflammatory drugs
8. Pregnancy or breastfeeding or plans to become pregnant during the study
9. Previous completion or withdrawal from the study
10. Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements
11. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

Online Supplementary Table 2: Efficacy outcomes, definitions, and details of statistical testing

The primary efficacy endpoint is the composite of CV death, nonfatal MI and stroke. All deaths are assumed to be cardiovascular in nature unless a non-cardiovascular cause can be clearly documented.

An event is counted as an MI whether it occurred spontaneously or as the direct consequence of an investigation/procedure or operation. Indeed, the definition of MI as an endpoint takes into account whether a subject had a recent MI or has undergone revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery, using approved and universal definitions.

In order to meet the criteria for an endpoint, an MI must be distinct from the qualifying event (i.e., re-infarction for a subject who qualified for the study based on recent MI). Detailed criteria for the definition of MI are given in Table 4 of the on line supplement.

Stroke is defined as a new, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible or results in death within 24 hours and is not due to a readily identifiable cause, such as a tumor or seizure. Stroke is subclassified into one of 4 groups as described in Table 5 of the on line supplement.

The following events will not be counted as a primary stroke endpoint: subdural and epidural bleeding events and ischemic cerebrovascular events lasting less than 24 hours (these will be considered transient ischemic attacks). The incidence of micro-hemorrhage will be recorded, but will not be included in the stroke endpoint.

Other secondary endpoints will include severe recurrent ischemia, severe recurrent ischemia requiring revascularization and severe recurrent ischemia requiring hospitalization.

Severe recurrent ischemia is defined as ischemic discomfort or equivalent meeting the following criteria:

- Lasting at least 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration, and precipitated by minimal exertion), considered to be myocardial ischemia upon final diagnosis.
- At least one of the following additional criteria for coronary artery disease and/or ischemia:
  - New and/or dynamic ST-depression > 0.05 mV, ST-elevation > 0.1 mV, or symmetric T-wave inversion > 0.2 mV on a resting ECG
  - Definite evidence of ischemia on stress echocardiography, myocardial scintigraphy (e.g. an area of clear reversible ischemia), or ECG-only stress test

(e.g., significant dynamic ST shift, horizontal or downsloping)
– Angiographic evidence of epicardial coronary artery stenosis of > 70% diameter reduction and/or evidence for intraluminal arterial thrombus.

The total number of events was estimated based on the sum of the events required at approximately 90% power in each stratum, to detect a 35% relative reduction in Stratum 1 and a 22.5% relative reduction in Stratum 2 comparing pooled rivaroxaban doses (2.5 mg twice daily and 5 mg twice daily) and placebo arms within each stratum. For the calculations estimating power for individual doses it was assumed that the number of primary efficacy endpoint events available to compare each rivaroxaban dose with the placebo treatment group is two-thirds of the total events required for the three-arm study. Each individual dose arm, pooled across Stratum 1 and 2, is powered at approximately 90% for an overall relative risk reduction of 22.5% (based on 655 primary efficacy endpoint events), within each individual dose arm, and within each individual stratum the study is powered at approximately 80% for the assumed relative risk reduction of 35% in Stratum 1 and 22.5% in Stratum 2.

If the superiority of a dose group is observed, the major secondary efficacy endpoints (see below) will then be tested for that dose group (Figure 2) in the sequential order below. That is, the subsequent ordered secondary endpoint will be tested only for the doses that are significant for the previous endpoints. If an individual test during any step is not statistically significant, further exploratory testing may continue but significance will not be claimed. All tests of secondary endpoints will be based on the mITT analysis set.

Secondary Efficacy Endpoint No. 1: Rivaroxaban is superior to placebo in the reduction of the composite endpoint of all-cause death, MI, or stroke.

Secondary Efficacy Endpoint No. 2: Rivaroxaban is superior to placebo in the reduction of the composite endpoint of CV death, MI, ischemic stroke, or TIMI major bleeding event not associated with CABG surgery.

Secondary Efficacy Endpoint No. 3: Rivaroxaban is superior to placebo in the reduction of the composite endpoint of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization.

Secondary Efficacy Endpoint No. 4: Rivaroxaban is superior to placebo in the reduction of the composite endpoint of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization.

No multiplicity adjustment will be carried out for safety endpoint analyses. Figure 2 summarizes the testing procedures.

Pre-Specified Subgroups for Analysis

The primary efficacy endpoint will be evaluated in the following pre-specified subgroups:

- Intention to use a thienopyridine (yes or no); based on actual stratification group, if errors made at randomization IVR entry. A subgroup analysis based on actual use of at least one dose of a thienopyridine is planned.
- Region (North America, South America, Western Europe including Israel, Eastern Europe including Egypt, Asia Pacific and Others including Australia and New Zealand)
- Index events (STEMI or non-STEMI/UA)
- Sex (male, female)
- Age (< 55, 55 to 75, > 75)
- Race (White or Caucasian, Black or African American, Asian, other)
- Baseline renal function (calculated creatinine clearance < 30, 30-<50, 50-80, ≥ 80 mL/min)
- Baseline diabetes status

A subgroup analysis using subjects on study treatment for > = 1 year may be examined for exploratory purposes. The reduction in second events in each patient and the reduction in multiple events in each patient will be evaluated.

The rate of drop-in to open label thienopyridine therapy in Stratum 1 and the rate of drop-out of thienopyridine in Stratum 2 will be summarized by treatment group over time. The effect of drop-ins and drop-outs will be examined to show the impact on the primary efficacy and safety analyses.

Online Supplementary Table 3: Detailed Bleeding Definitions

A TIMI major bleeding event is defined as any intracranial bleeding or clinically overt bleeding event that is associated with a decrease in hemoglobin of ≥ 5g/dL or an absolute drop in hematocrit of ≥ 15%.TIMI minor bleeding is defined as any clinically overt bleeding event, including bleeding that is evident on imaging studies, that is associated with a decrease in hemoglobin that is ≥ 3 g/dL but is < 5g/dL from baseline hemoglobin value. Bleeding requiring medical attention is defined as any bleeding event that requires medical treatment, surgical treatment, or laboratory evaluation and does not meet criteria for TIMI major or TIMI minor bleeding event, as defined above. Insignificant bleeding is defined as a reported blood loss or bleeding event episode not meeting any of the above criteria. The composite endpoint of TIMI major bleeding, TIMI minor bleeding, or bleeding requiring medical attention event is termed clinically significant bleeding on the TIMI scale.

An ISTH major bleeding event is defined as clinically overt bleeding that is associated with:

- A fall in hemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or

- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

A clinically relevant non-major bleeding event is defined as an overt bleeding event not meeting the criteria for a major bleeding event but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

Examples of nonmajor clinically relevant bleeding events include:

- Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.)
- Gingival bleeding if it occurs spontaneously (i.e., unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes
- Hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent
- Rectal blood loss, if more than a few spots
- Hemoptysis, if more than a few speckles in the sputum, or
- Intramuscular hematoma
- Subcutaneous hematoma if the size is larger than 25 cm^2 or larger than 100 cm^2 if provoked
- Multiple source bleeding events

All other overt bleeding event episodes not meeting the criteria for major or clinically relevant non-major bleeding events will be classified as minimal bleeding events. The composite endpoint of either major or clinically relevant non-major bleeding event is termed clinically significant bleeding on the rivaroxaban program scale.

Online Supplementary Table 4: Criteria for the Definition of MI

All myocardial infarctions will be counted as events whether they represent the reason for the hospitalization or occurred during a hospitalization. In addition, they will be counted as events whether they occurred spontaneously or as the direct consequences of an investigation/procedure or operation.

In order to meet the criteria as an endpoint, an MI must be distinct from the qualifying event (i.e., re-infarction for a subject who qualified for the study based on recent MI). The definition of MI as an endpoint will take into account whether a subject had a recent MI or has undergone revascularization with PCI or CABG surgery. In cases where both cardiac troponin and CK-MB are available (collected at similar time points) and are discordant, clinical judgment will be used to apply the most relevant biomarker data. The definitions of MI are as follows for the 4 clinical settings in which it may occur:

A. For patients with no recent revascularization, criteria (1) and (2) or criterion (3) or criterion (4) must be met:

1. Typical cardiac biomarker rise and fall with the following degrees of elevation accepted as biochemical evidence of myocardial necrosis:
   a. Troponin T or I: maximal concentration greater than the MI decision limit;
   b. CK-MB: maximal concentration greater than the ULN;

AND

2. At least 1 of the following additional supportive criteria:
   a. Ischemic discomfort at rest lasting $\geq$ 10 minutes; or
   b. ECG changes indicative of ischemia (ST elevation $\geq$ 0.1 mV or ST depression $\geq$ 0.05 mV, or new T-wave inversions);

OR

3. Development of new, abnormal Q waves ($\geq$ 30 msec in duration and $\geq$ 1 mm in depth) in $\geq$ 2 contiguous precordial leads or $\geq$ 2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction;

OR

4. Pathologic findings of an acute MI.

B. For patients with no recent revascularization in who biomarkers from a qualifying (or recent) MI remain elevated, criteria (1) and (2), or criterion (3), or criterion (4), or criterion (5) must be met:

1. Cardiac biomarker re-elevation defined as:
   a. Increase by at least 20% of the previous value; and
   b. Documentation that the biomarker assayed was decreasing before the suspected new MI;

AND

2. At least 1 of the following additional supportive criteria:
   a. Ischemic discomfort at rest lasting $\geq$ 10 minutes; or

b. ECG changes indicative of ischemia (ST elevation ≥ 0.1 mV or ST depression ≥ 0.05 mV, or new T-wave inversions);

OR

3. Development of new, abnormal Q waves (≥ 30 msec in duration and ≥ 1 mV in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction;

OR

4. New elevation of ST-segments ≥ 0.1 mV in ≥ 2 contiguous precordial or adjacent limb leads; and
   a. Ischemic discomfort at rest lasting ≥ 20 minutes; or
   b. Ischemia-mediated new hemodynamic decompensation requiring pharmacologic or mechanical support; or
   c. Angiographic evidence of acute coronary occlusion

5. Pathologic findings of an acute MI.

C. Within 24 hours after PCI (or felt to be clinically related to a PCI) a patient must have EITHER:

1. CK-MB > 3 × ULN and, if the pre-PCI CK-MB was >ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing before the suspected recurrent MI;

OR

2. Pathologic finding of an acute MI

Note: Symptoms are not required.

D. Within 24 hours after CABG (or felt to be clinically related to CABG) a patient must have criteria (1) and (2), or criterion (3), or criterion (4):

1. CK-MB > 5 × ULN and, if the pre-CABG CK-MB was above ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing before the suspected recurrent MI;

AND

2. At least one of the following supportive criteria:
   a. Development of new, abnormal Q waves (≥ 30 msec in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction, or
   b. Angiographically documented new graft or native coronary occlusion, or
   c. Imaging evidence of new loss of myocardium

OR

3. CK-MB > 10 × ULN and, if the pre-CABG CK-MB was above ULN, both an increase by at least 20% over the previous value and documentation that CK-MB was decreasing before the suspected recurrent MI;
4. Pathologic findings of an acute MI.

Note: Symptoms are not required.

Note: If cardiac troponin measurements are the only cardiac biomarker data available, they may be used by the CEC, along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularization (PCI or CABG).

If the subject is classified as having an MI, then the clinical classification of the type of MI will be adjudicated as:

Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as a plaque erosion and/or rupture, fissuring, or dissection

Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a: Myocardial infarction associated with PCI

Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5: Myocardial infarction associated with CABG

Online Supplementary Table 5: Criteria Used to Subclassify Stroke

Stroke is defined as a new, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible (or results in death) within 24 hours and is not due to a readily identifiable cause, such as a tumor or seizure. Cerebrovascular event/stroke will be subclassified into 1 of the following 4 groups:

1. Ischemic infarction: Stroke without focal collections of intraparenchymal blood on a brain imaging scan.
2. Ischemic infarction with hemorrhagic conversion: Infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Micro-hemorrhages evident on MRI, whether in the cortex or deep brain structures, are not considered to be consistent with a hemorrhagic conversion endpoint.

3. Primary hemorrhagic: An intraparenchymal hemorrhage, subdural or epidural hematoma:
   - Intraparenchymal hemorrhage: Stroke with focal collections of intraparenchymal blood seen on a brain image (computed tomography [CT] or magnetic resonance imaging [MRI]) or a postmortem examination, not felt to represent hemorrhagic conversion. Subarachnoid hemorrhage should be included in this category. Microhemorrhages discovered on brain imaging in the absence of associated symptoms or not in the relevant part of the brain to account for the symptoms in the absence of other brain lesions will not be considered to be a primary intraparenchymal hemorrhage endpoint.
   - Subdural hematoma: density representing fluid collection in subdural space on brain images or blood in the subdural space on autopsy.
   - Epidural hematoma: density representing fluid collection in epidural space on brain images or blood in the epidural space on autopsy.
4. Uncertain: Any stroke without brain imaging (e.g., CT or MRI), surgical exploration, autopsy, other documentation of type, or if tests are inconclusive.

The following events will not be counted as a primary stroke endpoint:

1. Subdural and epidural bleeding events and ischemic cerebrovascular events lasting less than 24 hours (these will be considered TIAs).
2. Microhemorrhages are defined as rounded foci of < 10 mm that appear hypointense and that are distinct from other causes of signal loss on gradient-echo MRI sequences (e.g., vascular flow voids, leptomeningeal hemasiderosis, or non-hemorrhagic subcortical mineralization). Since epidemiological studies have shown as high as ~40% rate of microhemorrhage in stable asymptomatic elderly patients undergoing gradient-echo MRI (but not other imaging modalities), and the clinical significance of these findings is not clear, findings of a microhemorrhage by itself will not be considered to satisfy the criteria for a stroke or bleeding event. Nonetheless, we will capture the presence of microhemorrhages and note if they are in an anatomical site consistent with the distribution of the clinical stroke findings. In cases when imaging cannot be appropriately evaluated due to poor quality, inappropriate modality, or if not performed, the microhemorrhages will not be assessed.

Online Supplementary Table 6: Censoring Rules for Time-to-Event Endpoints

For any time-to-event endpoint in this study, the following censoring rules will be applied:

- For analyses based on mITT, all randomized subjects without documentation of an evaluable event will be censored at the minimum (earliest) of either the global treatment end date, 30 days after the last dose date for early discontinued subjects, 30 days after randomization for randomized but not treated subjects, or the last date of contact.
- For analyses based on ITT, all randomized subjects without an evaluable event will be censored at the global study end date.
- For treatment-emergent safety analyses, all treated subjects without documentation of an evaluable event will be censored at the Minimum (Earliest) of either the date of the last dose + 2 days, or the last contact date.
- For analyses based on ITT-total, all randomized subjects without an evaluable event will be censored at the last contact date.
- For analyses based on mITT approach safety analysis set, all treated subjects without documentation of an evaluable event will be censored at the Minimum (Earliest) of either the global treatment end date, 30 days after the last dose date for early discontinued subjects, or the last date of contact.
- For analyses based on safety analysis set, all treated subjects without an evaluable event will be censored at the last date of contact.

Online Supplementary Table 7: Stopping Rules

The interim stopping plan implemented to assess "overwhelming" efficacy will be based on both combined strata and stratum 2 primary composite analyses with both doses pooled and individual doses. Additional stopping guidelines will also be considered to confirm the appropriateness of stopping for efficacy:

Both doses are significant or one dose provides compelling evidence of efficacy and there's qualitative interaction for the 2 doses comparing with placebo, across strata and within stratum 2.
None of the components (CV death, MI, or stroke) show a trend in the wrong direction, in combined strata and stratum 2
No major safety concerns including TIMI major/minor bleeds, renal and liver functions, in combined strata and stratum 2
All cause mortality is either neutral or trending in the right direction (hazard ratio point estimate <1.0), in combined strata and stratum 2
Net clinical outcome (composite of the primary efficacy endpoint and non-CABG TIMI major bleed) trend in the right direction
Sufficient information (both efficacy and safety) to adequately assess differences between the 2 active doses

The analyses to be performed for the interim include the primary and secondary efficacy endpoint analyses,

the primary safety endpoint and other safety endpoints analyses, and adverse events of special interest. In addition, exploratory analyses would be performed as necessary to assess the efficacy and safety of rivaroxaban. All endpoint analyses will be based upon the best available or CEC adjudicated endpoint data, where the best available endpoint takes the CEC adjudicated results when available, otherwise, takes investigator reported results. The proposed efficacy boundary is generated by an α-spending function. A conservative Haybittle[2] – Peto[3] boundary (one-sided p-value < 0.0001; z-value > 3.719) will be used as a stopping boundary for pooled rivaroxaban doses and individual rivaroxaban doses vs placebo primary efficacy analyses, and small adjustments will be required only for the final primary efficacy analyses (the final primary efficacy analyses will then be evaluated using a 2-sided $\alpha = 0.0499982$).