Table 37. TIMI Hemorrhage Criteria[a]

	ICH	Clinically Overt (including imaging)	Hgb Drop[b,c] (g/dL)
Major Bleeding	X	X	≥ 5
Minor Bleeding	-	X	3 to < 5
Minimal Bleeding	-	X	<3

Hgb=hemoglobin; ICH=intracranial hemorrhage; TIMI=The TIMI Study Group
[a]Accounting for the effect of transfusions on change in hemoglobin (Hgb) as described in footnote b.
[b]One unit packed red blood cells = 1 g Hgb = 3% hematocrit (Hct)
[c]Hgb drop must be associated with clinically overt bleeding
Reproduced from Sponsor, Protocol dated August 10, 2004, page 63.

9.1.5 Inclusion/Exclusion Criteria

Inclusion Criteria (Must be present) (Reproduced from Sponsor)

1. Presented with acute coronary syndrome (ACS) based on the disease diagnostic criteria and were to undergo percutaneous coronary intervention (PCI)
2. Were of a legal age (and at least 18 years of age) and competent mental condition to provide written informed consent before entering the study. Informed consent must have been signed by the study participant or authorized representative, according to local rules and regulations
3. For women of child-bearing potential only (that is, women who were not surgically or chemically sterilized and who were between menarche and 1 year postmenopause), test negative for pregnancy between ACS presentation and enrollment (based on a urine or serum pregnancy test) and agreed to use a reliable method of birth control during the study

Disease Diagnostic Criteria
For TAAL, ACS included 1) moderate to high risk unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) and 2) ST-segment elevation myocardial infarction [STEMI] as follows:

- Moderate to high risk unstable angina (UA) was defined as a history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization, with persistent or transient ST-segment deviation ≥ 1 mm in one or more electrocardiographic leads without elevation of creatine kinase-myocardial bands (CK-MB) or troponin T or I but with a TIMI Study Group (TIMI) risk score ≥ 3.

- Moderate to high-risk non-ST-segment elevation myocardial infarction (NSTEMI) was defined as a history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization with no evidence of persistent ST-segment elevation. Subjects must also have CK-MB or troponin T or I greater than the upper limit of normal (ULN) and a TIMI risk score ≥ 3. If CK-MB or troponin are not available, total CK greater than 2 times ULN is acceptable.

- ST-segment elevation myocardial infarction (STEMI) was defined as a history of chest discomfort or ischemic symptoms of > 20 minutes duration at rest ≤ 14 days prior to randomization with one of the following present on at least one ECG prior to randomization:
  a. ST-segment elevation ≥ 1 mm in two or more contiguous ECG leads
  b. New or presumably new left bundle branch block (LBBB)
  c. ST-segment depression ≥ 1 mm in two anterior precordial leads (V1 through V4) with clinical history and evidence suggestive of true posterior infarction

- Subjects receiving fibrin-specific fibrinolytic therapy (for example, alteplase, reteplase, tenecteplase) could be randomized ≥ 24 hours after completion of infusion of the fibrinolytic for the index STEMI event. Subjects receiving nonfibrin-specific fibrinolytic therapy (for example, streptokinase) could be randomized ≥ 48 hours after completion of infusion of the fibrinolytic for the index STEMI.

TIMI Risk score for unstable angina and non-ST-segment elevation myocardial infarction is described in Table 38.

Table 38. TIMI Risk Score for UA/NSTEMI

			Risk of Cardiac Events (%) by 14 Days in TIMI 11B*	
Parameters	**Points**	**Risk Score**	**Death or MI**	**Death, MI, or Urgent Revascularization**
Historical				
Age ≥ 65	1	0/1	3	5
≥ 3 CAD risk factors (Family History, HTN, HLP, DM, active smoker)	1	2	3	8
Known CAD (stenosis ≥ 50%)	1	3	5	13
ASA use in past 7 days	1	4	7	20
Presentation		5	12	26
Recent (≤ 24 h) severe angina	1	6/7	19	41
Increased cardiac markers	1			
ST deviation ≥ 0.5 mm	1			
RISK SCORE = Total Points	(0-7)			
***Entry criteria: unstable angina or NSTEMI defined as ischemic pain at rest within past 24 hours, with evidence of coronary artery disease (ST segment deviation or +marker)**				
Reproduced from Sponsor, Protocol dated August 10, 2004, page 70.				

Exclusion Criteria (Cannot be present) (Reproduced from Sponsor)
Cardiovascular Exclusion Criteria

1. Have cardiogenic shock at the time of randomization (systolic blood pressure < 90 mm Hg associated with clinical evidence of end-organ hypoperfusion, or subjects requiring vasopressors to maintain systolic blood pressure over 90 mm Hg and associated with clinical evidence of end-organ hypoperfusion)
2. Have refractory ventricular arrhythmias
3. Have New York Heart Association (NYHA) Class IV congestive heart failure

NYHA classifications for congestive heart failure are displayed in Table 39.

Table 39. New York Heart Association Congestive Heart Failure (NYHA CHF) Classifications

Class I	Patients with no limitation of activities; they suffer no symptoms from ordinary activities
Class II	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion
Class III	Patients with marked limitation of activity; they are comfortable only at rest
Class IV	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest
New York Heart Association, 1994.	

Bleeding Risk Exclusion Criteria

4. Have received fibrin-specific fibrinolytic therapy < 24 hours prior to randomization
5. Have received nonfibrin-specific fibrinolytic therapy < 48 hours prior to randomization
6. Have active internal bleeding or history of bleeding diathesis
7. Have clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding.
8. Have any of the following
   a. Prior history of hemorrhagic stroke
   b. Intracranial neoplasm, arteriovenous malformation, or aneurysm
   c. Ischemic stroke ≤ 3 months prior to screening
9. Have an International Normalized Ratio (INR) known to be > 1.5 at the time of evaluation
10. Have a platelet count of ≤ 100,000/mm^3 at the time of screening
11. Have anemia (hemoglobin [Hgb] < 10 gm/dl) at the time of screening

Prior/Concomitant Therapy Exclusion Criteria

12. Have received one or more doses of a thienopyridine (ticlopidine or clopidogrel) ≤ 5 days prior to PCI
13. Are receiving or will receive oral anticoagulation or other antiplatelet therapy that cannot be safely discontinued for the duration of the study
14. Are receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDS) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require > 2 weeks of daily treatment with NSAID or COX2 inhibitors during the study

General Exclusion Criteria

15. Are investigator site personnel directly affiliated with the study or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
16. Are employed by Eli Lilly & Company, Ube Industries Limited, Sankyo Company Limited, The TIMI Study Group, or the contract research organization (CRO) (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
17. Have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry or are presently enrolled in another drug or device study
18. Have previously completed or withdrawn from this study or any other study investigating CS-747
19. Are women who are known to be pregnant, who have given birth within the past 90 days, or who are breastfeeding
20. Have a concomitant medical illness (for example, terminal malignancy) that in the opinion of the investigator is associated with reduced survival over the expected treatment period (maximum of 15 months)
21. Have known severe hepatic dysfunction (that is, with cirrhosis or portal hypertension)
22. Have a condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence
23. Have a history of intolerance or allergy to aspirin or approved thienopyridines (ticlopidine or clopidogrel)
24. May be unable to cooperate with protocol requirements and follow-up procedures

9.1.6 Study Plan

The TAAL study design is displayed in Figure 23.

Following screening and informed consent, subjects were randomized as follows:

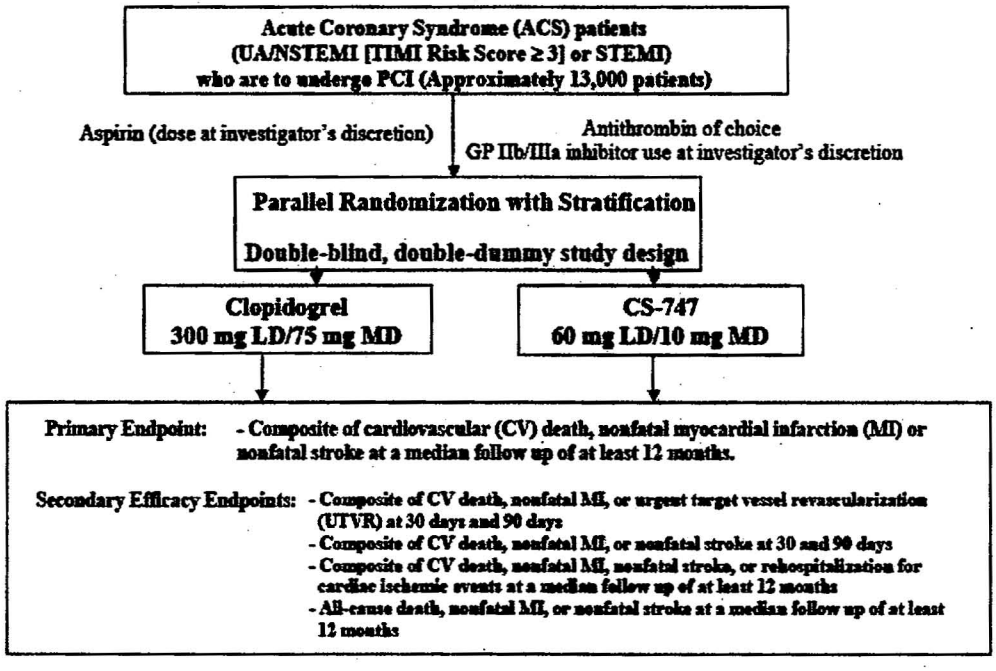
- Subjects presenting with UA/NSTEMI and those presenting with STEMI > 12 hours after symptom onset were randomized and loaded with study drug after diagnostic angiography confirmed anatomy suitable for PCI only
- Subjects presenting with STEMI ≤ 12 hours after symptom onset (those undergoing primary PCI) were randomized and loaded with study drug at the time of diagnosis and prior to diagnostic angiography

Subjects were randomized via an interactive voice response system (IVRS) in a 1:1 fashion to receive either CS-747 (prasugrel: 60 mg oral loading dose followed by 10 mg daily oral maintenance dose) or clopidogrel (300 mg oral loading dose followed by 75 mg daily oral maintenance dose) using a double-dummy design. Subjects received active formulation of one drug and placebo formulation of the other drug for the loading and maintenance doses, as shown in Figure 24.

Additionally, subjects were to receive ASA during the 24 hours prior to PCI (75 to 325 mg oral or 250 to 500 mg intravenous) and for the duration of the study (between 75 mg and 325 mg oral).

The study was to continue until all of the following conditions were met:
1. Median treatment period of at least 12 months
2. Completion of at least 6 months of follow-up
3. Achievement of the primary endpoint in at least 875 UA/NSTEMI subjects

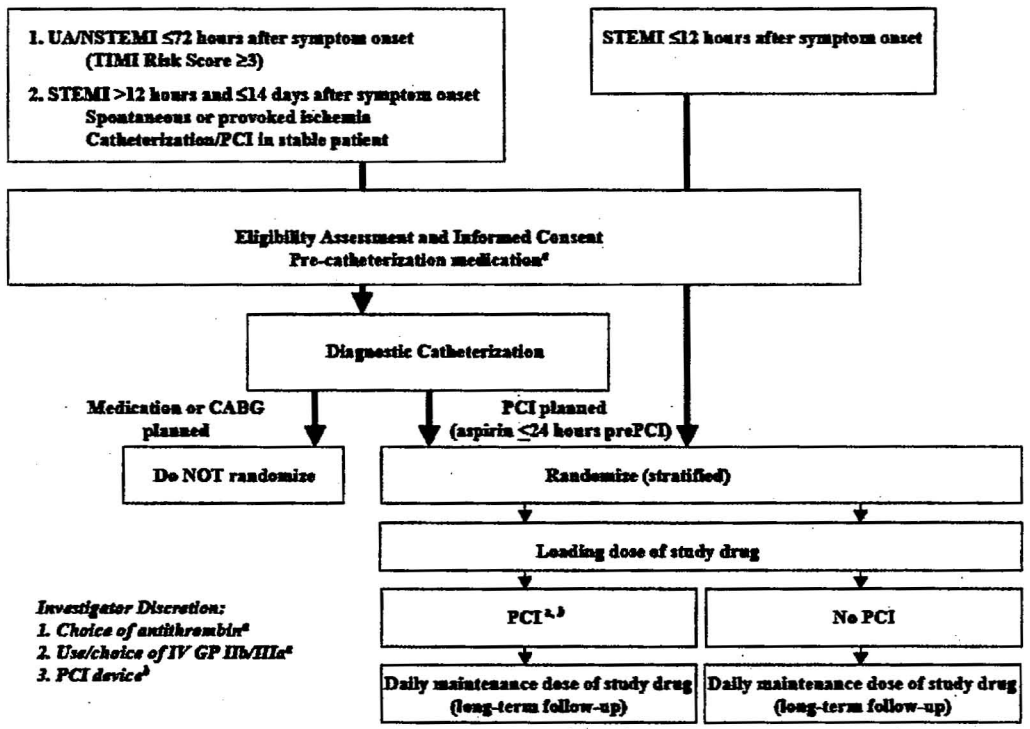
Figure 23. Study H7T-MC-TAAL Study Design



Abbreviations: ACS = acute coronary syndrome; CV = cardiovascular; GP = glycoprotein; LD = loading dose; MD = maintenance dose; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = The TIMI Study Group; UA = unstable angina; UTVR = urgent target vessel revascularization.

(Reproduced from Sponsor, Protocol dated August 10, 2004, page 19)

Figure 24. Study H7T-MC-TAAL Treatment Plan



Abbreviations: CABG = coronary artery bypass graft surgery; GP = glycoprotein; IV = intravenous; NSTEMI = Non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = The TIMI Study Group; UA=unstable angina.

(Reproduced from Sponsor, Protocol dated January 10, 2006, page 2676)

Subjects were to receive the loading dose of study drug at any time between randomization and the completion of the PCI procedure, defined as ≤ 1 hour of the subject leaving the cardiac catheterization laboratory.

The first maintenance dose was to be administered 20 to 28 hours after the loading dose and subsequent maintenance doses were to be taken in a fed or fasting state.

PCI was to be performed immediately following randomization or at any time within the first 24 hours (maximum of 28 hours) after the loading dose, and prior to the first maintenance dose. At the investigator's discretion, the activated clotting time (ACT) could be used to monitor unfractionated heparin (UFH). If UFH was used with GPIIb/IIIa inhibition, the recommended maximal ACT during PCI was 200 to 250 seconds. If UFH was used with GP IIb/IIIa inhibition, the recommended maximal ACT was 350 seconds.

The first maintenance dose was to be administered 20 to 28 hours after the loading dose and subsequent maintenance doses were to be taken in a fed or fasting state.

If subjects were randomized, but PCI was not performed, they were to continue on study drug, remain in the study, and be evaluated for clinical and adverse events.

The choice of antithrombin and dose administered, use and choice of GP IIb/IIIa inhibitors, and choice of device(s) used for PCI were at the discretion of the investigators. Investigational devices were not to be used during PCI. Use of approved closure devices was permissible. It was recommended that intravenous antithrombin therapy be discontinued on completion of the PCI procedure and not restarted. Specific therapy for bleeding, including transfusion with platelets and/or other blood products or discontinuation of concomitant therapy was also at the investigator's discretion. Although daily doses of ASA ranging from 75 to 162 mg were recommended after discharge, the aspirin dose was left to the investigator's discretion.

Within the first 24 hours after PCI, three blood samples were to be obtained for CK-MB. The first sample was to be obtained 6 hours (± 2 hours) after PCI. The second and third samples were to be obtained 6 hours (6-8 hours recommended) after the first and second samples, respectively.

In STEMI patients who remained hospitalized longer than 24 hours, three additional samples for CK-MB were to be obtained at least 6 hours apart (6-8 hours recommended).

Post PCI CK-MB samples were to be sent to a central laboratory.

If a subject needed to undergo emergency or urgent CABG or other surgical procedure within 5 days of the loading dose, the study drug was to be temporarily discontinued and restarted when thought to be safe.

Subjects were to be followed for a maximum of 15 months. If necessary, the study drug could be temporarily discontinued. For discontinuations > 14 days, consultation with the CRO Helpline was required.

Subjects were to return on Days 30, 90, and 180 for clinic visits and if enrolled in the study over 180 days were also to return on Days 270, 360, and 450. If subjects experienced cardiac symptoms following discharge, CK-MBs were to be checked locally and treatment was left to the investigator's discretion.

Permitted medications included but were not limited to histamine 2 receptor (H2) blockers and proton pump inhibitors (PPIs); oral, sublingual, or intravenous nitrates; calcium channel blockers; beta blockers; Angiotensin converting enzyme inhibitors (ACEIs); Angiotensin receptor blockers (ARBs); 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins); anti-arrhythmic drugs; vasodilators; and intravenous vasopressors agents.

9.1.7 Schedule of Evaluations and Procedures

The schedule of evaluations and procedures is displayed in Table 40.

Table 40. Study Schedule for Study H7T-MC-TAAL

Procedure	PrePCI	PCI	24 ±4 hrs post-PCI or at hospital discharge, whichever comes first	Day 30[b]	Day 90[b]	Day 180[b]	Day 270[b,c]	Day 360[b,c]	Day 450 or last visit[b,c]
Screening	X								
Informed consent (before study procedures)	X								
Randomization through IVRS[a]	X[a]								
Medical history/preexisting conditions	X								
Concomitant medications recorded (including aspirin)[d]	X		X	X	X	X	X	X	X
Physical exam	X		X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
ECG[a]	X		X	X	X	X	X	X	X
Local laboratory measures									
Urine or serum pregnancy	X[f]								
Hgb/Hct/plt count	X		X						
Central laboratory measures[e,g]									
CBC w/ diff and plt count	X			X	X	X			X
Clinical chemistry	X		X (fasting when possible)	X	X	X			X
CK-MB	X[i]	X[i]	X[j]	as needed (local laboratory)[h]					
Adverse events recorded	X	X	X	X	X	X	X	X	X
Study drug dispensed	X(LD)[l]		X(MD)[m]	X(MD)	X(MD)	X(MD)	X(MD)	X(MD)	
Study drug collected				X	X	X	X	X	X

Abbreviations: CBC w/ diff=complete blood count with differential; CK-MB=creatine kinase-myocardial bands; CRF=case report form; ECG=electrocardiogram; Hgb=hemoglobin; Hct=hematocrit; hrs=hours; IVRS=interactive voice response system; LD=loading dose; MD = maintenance dose; PCI=percutaneous coronary intervention; plt count=platelet count.

a Occurs prePCI after informed consent is signed. UA/NSTEMI, STEMI >12 hours from symptom onset subjects are to be randomized after diagnostic cath. STEMI ≤12 hours from symptom onset subjects may be randomized before diagnostic cath.

b Follow-up may be performed within Day 28 to Day 35 of the Day 30 day timepoint, and within ±2 week of the other timepoints. Window does not apply to dosing.
c Patients will be observed for a minimum follow-up period of 6 months. Maximum follow-up is anticipated to be 15 months. The end of study activities should be completed at the subject's last visit, even if this occurs prior to Day 450.
d Patients will supply their own daily aspirin therapy with the dose determined at the investigator's discretion. The recommended dose after discharge from the index hospitalization is 75 mg to 162 mg.
e See Attachment TAAL.3 for details on all central laboratory measures.
f A urine or serum pregnancy test will be performed locally for women of child bearing potential, and a negative result must be obtained prior to randomization.
g Samples will be sent to a central laboratory for analysis unless otherwise stated.
h CK-MB (and/or troponin) obtained for cardiac ischemic symptoms after discharge from the index hospitalization will be performed locally.
i If informed consent and PCI are more than 1 hour apart, two samples are recommended, one at the time of enrollment and one during the PCI procedure, prior to balloon inflation.
j In all patients, it is required that three blood samples be drawn for CK-MB within the first 24 hours after PCI. The first sample should be 6 hours (±2 hours) after PCI. The second sample should be drawn at least 6 hours later (6 to 8 hours recommended), and the third sample should be drawn at least 6 hours after the second sample (6 to 8 hours recommended). In patients with STEMI who remain hospitalized longer than 24 hours, three additional blood samples should be drawn for CK-MB at least 6 hours apart (6 to 8 hours recommended).
l The loading dose is to occur prior to the completion of the PCI procedure.
m The first maintenance dose should be administered 20 to 28 hours after administration of the loading dose.
n Data acceptable if obtained after the onset of qualifying symptoms and prior to randomization.

Abbreviations: CBC w/ diff=complete blood count with differential; CK-MB=creatine kinase-myocardial bands; CRF=case report form; ECG=electrocardiogram; Hgb=hemoglobin; Hct=hematocrit; hrs=hours; IVRS=interactive voice response system; LD=loading dose; MD = maintenance dose; PCI=percutaneous coronary intervention; plt count=platelet count.

a Occurs prePCI after informed consent is signed.

(Reproduced from Sponsor, Study Schedule for Study H7T-MC-TAAL, Protocol dated January 10, 2006, pages 2720-2721)

Please note that superscript [m] in the initial protocol stated "the once-daily maintenance dose [was] to start after the PCI procedure."

9.1.8 Endpoints

9.1.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was a composite of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a median of 12 months follow-up.

Definitions Per Sponsor:

- **Cardiovascular Death (CV Death):** death due to documented cardiovascular cause. Additionally, death not clearly attributable to noncardiovascular causes was considered to be CV death.

- **Nonfatal Myocardial Infarction (MI):** The definition of MI was adapted from the standard American College of Cardiology (ACC) definition and was dependent on the clinical timing of the event in relation to presenting syndrome and cardiovascular procedures.

  A peri-procedural event must have been distinct from the index event.[10] If an ischemic biomarker was elevated at the onset of the suspected event, there must have been demonstration of a falling biomarker level prior to the onset of the suspected event, and that the subsequent peak was greater than 1.5 times the value prior to the onset of the event (these criteria did not need to be met if the ischemic biomarker was not elevated at the time of the suspected event). The biomarker levels required for the diagnosis of MI were dependent on relationship to cardiac procedures.

  - If the suspected event was within 48 hours of a percutaneous coronary intervention (PCI), the creatine kinase-myocardial bands (CK-MB) value (on at least two samples) must have been > 3x the upper limit of normal (ULN); no symptoms were required. **The Amendment dated January 10, 2006 extended the definition of peri-procedural MI to include a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI.**

  - If the suspected event was within 48 hours of a CABG, the CK-MB value (on a single measure) must have been >10x the upper limit of normal; no symptoms were required.

  - If the suspected event was not within 48 hours of a PCI or CABG, the diagnostic criteria were met if the subject had CK-MB or cardiac troponin > ULN and the presence of either chest pain ≥ 20 minutes in duration or ST-segment deviation ≥ 1mm on the electrocardiogram (ECG).

  In any clinical circumstance, the appearance of new Q-waves on the electrocardiogram distinct from a prior event (including the presenting event) or pathologic evidence (such as autopsy) showing a new myocardial infarction felt to be distinct from a prior event would be considered appropriate evidence for MI, as would ST-segment elevation (meeting enrollment criteria) lasting for at least 20 minutes and accompanied by ischemic chest pain or hemodynamic decompensation.

[10] **A clarification of peri-procedural and index events was added in Amendment 1 dated January 10, 2006.**

There were five major sets of criteria used for the diagnosis of nonfatal MI:

1. ST elevation or re-elevation of ST segment, AND one of the following: ischemic chest pain ≥ 20 minutes in duration or hemodynamic decompensation.

2. Spontaneous CK-MB or troponin > ULN, AND one of the following:

    - Ischemic chest pain (or anginal equivalent) ≥ 20 minutes in duration
      or
    - ST segment deviation ≥ 1 mm in one or more leads

3. CK-MB > 3x ULN on at least two samples following PCI

4. CK-MB > 10x ULN on one sample following CABG

5. New Q waves ≥ 0.04 seconds, or pathology distinct from prior MI

ECGs or other supporting clinical tests or evaluations such as imaging used to identify clinical endpoints would be adjudicated with documents submitted to the Clinical Endpoints Committee (CEC) for evaluation.

- **Nonfatal Stroke:** the rapid onset of new-persistent neurologic deficit lasting more than 24 hours. In the case of clinical diagnosis of nonfatal stroke, computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging was strongly recommended. CT or MRI scans would be considered by the CEC to support the clinical impression. Supplemental information from head CT or MRI scans would determine if there was a demonstrable lesion compatible with an acute nonfatal stroke. Furthermore, nonfatal stroke would be classified as either ischemic or hemorrhagic based on imaging data, if available, or uncertain cause if imaging data was not available.

Prespecified subgroup analyses for the primary endpoint included but were not limited to

- Clinical presentation
- Demographics and Baseline Characteristics
- Medical History
- Index PCI Procedure—culprit lesion and all intervened lesions
- Anti-thrombotics used in support of the index PCI procedure
- Selected concomitant medications
- Aspirin use
- Timing of the Loading Dose Relative to the index PCI

9.1.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints included

1. CV death, nonfatal MI, or nonfatal stroke at 90 days post randomization (Group 1)
2. CV death, nonfatal MI, or nonfatal stroke at 30 days post randomization (Group 1)
3. CV death, nonfatal MI, or UTVR at 90 days post randomization
4. CV death, nonfatal MI, or UTVR at 30 days post randomization
5. All-cause death, nonfatal MI, or nonfatal stroke at study end (after a median follow-up of at least 1 year post randomization)
6. CV death, nonfatal MI, nonfatal stroke, or rehospitalization for CIE at study end

In the Statistical Analysis Plan Amended (b) dated September 18, 2007 and in the Clinical Study Report dated November 28, 2007, the sponsor added the following objective:

7. the risk of definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end