

In summary, in TAAL there was a significantly increased rate of new cancers in the prasugrel treatment group, compared to clopidogrel ($p=0.006$ by log rank). The sponsor argued that the cancer rate was higher in the prasugrel-treated subjects because more cancers were being identified through bleeding adverse events. However, when we performed an analysis eliminating all the subjects in both treatment groups who had bleeding in the particular organ system that subsequently developed cancer, there was still a significant difference in the incidence of cancer between treatment groups ($p = 0.0218$).

7.1.2.3 Additional Serious Adverse Events

In TAAL, the incidence of the following serious adverse events was significantly higher in subjects treated with prasugrel compared to clopidogrel:

- Atrial flutter (All ACS: 0.18% prasugrel versus 0.06% clopidogrel; $p = 0.046$)
- Respiratory failure (All ACS: 0.22% prasugrel versus 0.09% clopidogrel; $p = 0.050$)
- Hypotension (All ACS: 0.21% prasugrel versus 0.06% clopidogrel; $p = 0.019$)

Several of the events of respiratory failure occurred in the setting of TIMI bleeding.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In both the prasugrel and clopidogrel treatment groups, a greater percentage of subjects with the following characteristics discontinued study drug:

- Increased age (≥ 65 , ≥ 70 , ≥ 75 y)
- Female sex
- Low body weight (< 70 kg STEMI and All ACS; < 50 kg UA/NSTEMI)
- Increased Thrombolysis In Myocardial Infarction (TIMI) risk score
- Diabetes mellitus
- Hepatic impairment based on pre-existing conditions (UA/NSTEMI and All ACS)
- Prior transient ischemic attack (TIA) or stroke
- Atrial fibrillation
- Congestive heart failure
- Peripheral arterial disease

A lower percentage of subjects discontinued study drug in eastern Europe, compared to other geographic regions.

In the UA/NSTEMI, STEMI, and All ACS populations, the overall incidence of study drug discontinuation due to adverse events was higher in subjects treated with prasugrel, compared to clopidogrel. In the All ACS population, discontinuations were primarily due to hemorrhagic events in the prasugrel treatment group.

7.1.3.2 Adverse events associated with dropouts

There were significantly more adverse events leading to discontinuation in the prasugrel treatment group, compared to clopidogrel. The most common hemorrhagic treatment emergent adverse events (TEAEs) leading to discontinuation of study drug included gastrointestinal hemorrhage, epistaxis, contusion, and hematuria.

The most common nonhemorrhagic TEAEs leading to study drug discontinuation were atrial fibrillation, intracardiac thrombus, atrial flutter, rash, coronary artery bypass, and deep vein thrombosis.

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A summary of the primary reason for premature study drug discontinuation in the All ACS population is displayed in Table 31. The prasugrel treatment group had significantly more discontinuations related to serious and non-serious hemorrhagic adverse events, compared to clopidogrel.

Table 31. Primary Reason for Premature Study Drug Discontinuation (All ACS) (TAAL)

	Prasugrel		Clopidogrel		Total		OR	(95% CI) ^b	p-value ^b
	n	(%) ^a	n	(%) ^a	n	(%) ^a			
Treated	6741		6716		13457				
Total	1207	(17.91)	1163	(17.32)	2370	(17.61)	1.042	(0.953, 1.138)	0.369
Entry Criteria Violation	25	(0.37)	27	(0.40)	52	(0.39)	0.922	(0.535, 1.591)	0.771
Adverse Event	485	(7.19)	424	(6.31)	909	(6.75)	1.150	(1.005, 1.317)	0.042
Hemorrhagic	169	(2.51)	91	(1.35)	260	(1.93)	1.872	(1.448, 2.421)	<0.001
Serious	106	(1.57)	61	(0.91)	167	(1.24)	1.743	(1.270, 2.393)	<0.001
Non-Serious	64	(0.95)	31	(0.46)	95	(0.71)	2.067	(1.344, 3.179)	<0.001
Non-Hemorrhagic	316	(4.69)	333	(4.96)	649	(4.82)	0.943	(0.805, 1.104)	0.464
Serious	125	(1.85)	111	(1.65)	236	(1.75)	1.124	1.124 (0.869, 1.455)	0.373
Non-Serious	196	(2.91)	232	(3.45)	428	(3.18)	0.837	(0.690, 1.015)	0.071
Other	0		2	(0.03)	2	(0.01)			NE
Investigator Decision	99	(1.47)	95	(1.41)	194	(1.44)	1.039	(0.782, 1.380)	0.791
Subject Decision	598	(8.87)	613	(9.13)	1211	(9.00)	0.969	(0.861, 1.091)	0.604
Study Drug Unblinded	0		2	(0.03)	2	(0.01)			NE

CI=confidence interval; n=number of subjects, OR=odds ratio, NE=not evaluated due to insufficient data.
^a% is percent of treated subjects
^bTwo-sided p-value based on Pearson chi-square test. The two-sided p-value and odds ratio for All ACS were adjusted for clinical presentation as a stratification factor using Cochran-Mantel-Haenszel method.
 Reproduced from Sponsor, Clinical Study Report, Table TAAL.12.2, page 490.

7.1.3.3 Other significant adverse events

The number of treatment emergent adverse events, serious adverse events, and clinically significant treatment emergent adverse events (CSTEAEs) between treatment groups were similar in the UA/NSTEMI, STEMI, and All ACS populations. In the All ACS population, however, prasugrel subjects had significantly more CSTEAEs than clopidogrel subjects, as seen in .

Clinically significant TEAEs included bleeding events adjudicated as TIMI Major or TIMI Minor, thrombotic thrombocytopenic purpura, and the following reported as a serious adverse event or abnormal laboratory value: hematologic adverse events (thrombocytopenia, pancytopenia, agranulocytosis, neutropenia), abnormal hepatic function, allergic reactions, torsade de pointes, and any TEAE leading to permanent discontinuation of study drug.

Table 32. Overview of Treatment-Emergent Adverse Events Through Study End (All ACS Population) (TAAL)

Adverse Event Type ^a	Prasugrel			Clopidogrel			Total			OR ^b	p-value ^b
	N	n	(%)	N	n	(%)	N	n	(%)		
TEAE	6741	5441	(80.72)	6716	5403	(80.45)	13457	10844	(80.58)	1.017	0.696
SAE	6741	1665	(24.70)	6716	1629	(24.26)	13457	3294	(24.48)	1.024	0.549
Clinically Significant TEAE	6741	925	(13.72)	6716	842	(12.54)	13457	1767	(13.13)	1.110	0.042

SAE=serious adverse event; TEAE=treatment emergent adverse event
^aSubjects may be counted in more than one category
^bThe p-value is obtained from a 2-sided Chi-Square test. Odds ratio (OR) is based on the frequency procedure.
 Reproduced from Sponsor, Table TAAL.14.89, page 1850.

7.1.4 Common Adverse Events

7.1.4.1 Incidence of common adverse events

TAAL

Common adverse events in the prasugrel treatment group were primarily hemorrhagic. Please see Section 7.1.2 for further details.

Rash was reported in 2.8% of prasugrel and 2.4% of clopidogrel subjects.

Anemia was reported in 2.2% of prasugrel and 2.0% of clopidogrel subjects.

Pyrexia and increased tendency to bruise were reported in at least 1% of prasugrel subjects and the incidence of these adverse events was significantly higher than that in the clopidogrel treatment group.

ABT

In the Clinical Pharmacology dataset, post-procedural hemorrhage, headache, contusion, dizziness, nausea, and epistaxis were reported by at least 5% of prasugrel-treated subjects.

7.1.5 Less Common Adverse Events

TAAL

There were 4 reported cases (0.06%) of neutropenia in the prasugrel treatment group, compared to 21 cases (0.31%) in the clopidogrel treatment group.

There were no reported cases of thrombotic thrombocytopenia purpura (TTP) in prasugrel subjects, compared to one case in a clopidogrel subject.

There was no significant difference in the incidence of thrombocytopenia between the prasugrel and clopidogrel treatment groups. In most of the cases of thrombocytopenia, subjects were also receiving a glycoprotein IIb/IIIa inhibitor.

Leukopenia ($< 4 \times 10^9/L$) occurred in 187 (2.77%) of prasugrel subjects and 236 (3.51%) of clopidogrel subjects.

No events of pancytopenia were reported in subjects receiving either prasugrel or clopidogrel.

In the prasugrel treatment group, fifteen (0.22%) subjects developed abnormal hepatic function, 8 (0.12%) subjects had abnormal hepatic function reported as a serious adverse event, and 8 (0.12%) subjects developed ALT $> 3x$ ULN and total bilirubin $> 1.5 \times$ ULN, compared to 18 (0.27%), 15 (0.22%), and 4 (0.06%) subjects, respectively, in the clopidogrel treatment group.

Twenty-four prasugrel (0.36%) and clopidogrel (0.36%) subjects had allergic reactions reported as serious adverse events.

Four (0.06%) prasugrel subjects and 3 (0.04%) clopidogrel subjects had angioedema reported as a serious adverse event. One of the prasugrel subjects was also receiving an angiotensin converting enzyme inhibitor (ACE-I).

Rash was reported in 2.8% of prasugrel and 2.4% of clopidogrel subjects.

ABT

- 1 subject developed angioedema 5 days after starting prasugrel. The subject had also started an ACE-I and herbal preparation 10 days earlier.
- Subject TAAV-115 was a 58 year old healthy male who developed acute liver failure after receiving prasugrel and atorvastatin. The subject participated in 2 treatment periods. In Treatment Period 1, he received prasugrel 60 mg LD on 1/10/2006 and 10 mg MD from 1/11/2006 to 1/20/2006. In Treatment Period 2, he received 80 mg atorvastatin daily from 2/8/2006 (Day -6) until 2/16/2006 (Day 3) with concomitant prasugrel (60 mg LD on 2/14/2006 (Day 1) and 10 mg MD on 2/15 and 2/16/2006 (Days 2 and 3)). He received his final dose of atorvastatin and prasugrel on 2/16/2006 (Day 3). Liver enzymes were mildly elevated on Day -1, compared to Day -7. His liver enzymes continued to increase, and the subject was withdrawn from the study. On _____ Subject 115 was admitted to the hospital with acute liver failure with AST 15 x ULN, ALT 18 x ULN, lactic dehydrogenase 2 x ULN, alkaline phosphatase 3 x ULN, direct bilirubin 7 x ULN, and normal creatinine kinase. He was discharged from the hospital on _____ and as of _____ his liver function enzymes were decreasing.

b(6)

7.1.6 Laboratory Findings

Please see Section 7.1.6.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

In the primary safety database, blood pressure and heart rate were measured at baseline and at visits corresponding to 24 hours post-PCI or hospital discharge (whichever came first) and at the 30-, 90-, 180-, 270-, 360-, and 450-day visits. These vital sign measurements were not standardized and were meant for subject management only. There were no clinically important differences between the prasugrel and clopidogrel treatment groups.

In ABT studies, postbaseline arterial blood pressure and hear rate were systematically measured in Study TAAD and demonstrated no clinically significant differences.

Lastly, there were no clinically significant changes in vital signs noted in the tertiary safety database.

7.1.8 Electrocardiograms (ECGs)

The QT Interdisciplinary Review Team (QTIRT) reviewed the thorough QT(TQT) study entitled, Study H7T-EW-TAAP. Please refer to the QTIRT review for full details.

Study TAAP was a single-centre, randomized, three-period crossover study in 60 healthy male and female subjects who received placebo or an 80-mg single dose of prasugrel. Subjects also received a single oral dose of moxifloxacin 400 mg administered open label. Twelve-lead ECGs were sampled at 1, 2, and 6 hours on Day -1 and at 1, 2, 6, and 24 hours post-dose on Day 1. Each of the three treatment periods was separated by a washout of at least 10 days.

With regard to TQT design, Study TAAP had several limitations:

- The 80-mg single dose was not sufficient to cover worst case scenarios after a 60-mg loading dose. However, this dose does cover the expected high exposure scenario for the 5- or 10-mg maintenance dose.
- The ECG sampling times were not adequate to capture T_{max} for three of the metabolites

- The time-matched baseline (1, 2, and 6 hours only) was captured prior to period 1 only and was used for all periods in double-delta analysis. Therefore, the present double-delta analysis (change from placebo adjusted for baseline) was equivalent to a single-delta analysis (change from placebo)

Despite the limitations, Study TAAP was performed adequately and was considered to be a negative QT study. The results are displayed in Table 33. The largest upper limit of the two-sided 90% CI for the mean difference between prasugrel and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guideline.

Table 33. QTIRT Analysis: The Point Estimates and the 90% Cis Corresponding to the Largest Upper Bounds for Prasugrel 80 mg and the Largest Lower Bounds for Moxifloxacin (H7t-EW-TAAP)

Treatment	Time (h)	Δ QTcF (ms)	90% CI
Prasugrel 80 mg	24	2.1	(-1.3, 5.40)
Moxifloxacin 400 mg	1	10.7	(8.3, 13.0)*

*After Bonferroni correction.

The lack of positive signal from the concentration-QT modeling together with comparable levels of at least two metabolites in TAAP and TAAL suggest that prasugrel may not prolong QT at clinically relevant exposures.

7.1.9 Immunogenicity N/A

7.1.10 Human Carcinogenicity (Please see Section 7.1.2.2 for further details)

7.1.11 Special Safety Studies N/A

7.1.12 Withdrawal Phenomena and/or Abuse Potential N/A

7.1.13 Human Reproduction and Pregnancy Data

Prasugrel has not been studied in pregnant or lactating women. There are no pregnancies reported in the prasugrel clinical program.

7.1.14 Assessment of Effect on Growth N/A

7.1.15 Overdose Experience

To date, there are no reports of subjects who experienced a prasugrel overdose.

7.1.16 Postmarketing Experience

Prasugrel has not been approved for marketing in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

In Study TAAL, 4088 subjects were exposed to prasugrel for at least 1 year, and 2,656 subjects were exposed for at least 15 months. A summary of exposure for the primary and secondary safety databases is presented in Table 34.

Table 34. Exposure to Prasugrel (by Days) in Subjects with Atherosclerosis in the Primary and Secondary Safety Databases

Primary Safety Database: All ACS subjects treated with prasugrel in Study TAAL (N=6741)		
Days of Exposure	Subjects	Subject-Years ^a
LD (60 mg)	6718	NA
MD (10 mg)	6672	6464.60
1 - 3	77	0.38
>3 - 30	216	8.29
>30 - 90	232	34.88
>90 - 180	365	146.37
>180 - 270	876	518.11
>270 - 360	753	651.87
>360 - 450	1497	1725.31
>450	2656	3379.40
Secondary Safety Database: All subjects treated with prasugrel in ABT studies (N=940)		
Days of Exposure	Subjects	Subject-Years ^a
Any LD ^b	885	NA
Any MD ^c	880	71.28
1 - 3	6	0.04
>3-30	287	17.05
>30	587	54.19

Abbreviations: ABT = All but TAAL (Studies TAAD, TAAH, TABL, and TABR); ACS = acute coronary syndrome; LD = loading dose; MD = maintenance dose; NA = not applicable.

Subject exposure = Last dose date - First maintenance dose date + 1.

^a Subject-years = Mean exposure in days times number of treated subjects/365.25.

^b Either 40 or 60 mg prasugrel.

^c Either 5, 7.5, 10, or 15 mg prasugrel.

Exposure by days for the 2 populations (UA/NSTEMI and STEMI) in the primary safety database is located in Table APP.2.7.4.36 and Table APP.2.7.4.37, respectively.

Source: Q3055, Q3060.

(Reproduced from Sponsor, Integrated Summary of Safety (ISS), Table 2.7.4.5., page 33)

Prasugrel exposure in hepatically and renally impaired subjects was limited, as shown in Table 35.

Table 35. Prasugrel Exposure in Clinical Pharmacology Studies

Tertiary Database: Prasugrel Subjects in Clinical Pharmacology Studies (N=898)			
Subjects	# of Subjects	# of Subject Doses	
		(Single Dose or Loading Dose)	(Multiple Dose Studies)
Healthy ^a	839	1194	5885
Hepatically-impaired ^b	22	29	85
Renally-impaired ^c	37	37	0
Total	898	1260	5970

^a Studies in healthy subjects included single loading dose studies with multiple phases for dosing and appropriate wash-out periods (2.5-, 5-, 10-, 15-, 20-, 25-, 30-, 40-, 60-, 75-, and 80-mg prasugrel) and multiple dose (maintenance dose) studies (2.5-, 5-, 7.5-, 10-, 15-, and 20-mg prasugrel).

^b Studies in hepatically-impaired subjects included single loading dose studies with multiple phases for dosing and appropriate wash-out periods (60-mg prasugrel) and multiple-dose (maintenance dose) studies (10-mg prasugrel).

^c Studies in renally-impaired subjects included single loading-dose studies with multiple phases for dosing and appropriate wash-out periods (5-, 10-, 30-, and 60-mg prasugrel) and no multiple-dose studies.

Studies include: S001, S002, S003, S004, TAAA, TAAB, TAAC, TAAE, TAAF, TAAL, TAAJ, TAAK, TAAN, TAAO, TAAP, TAAQ, TAAR, TAAS, TAAT, TAAU, TAAV, TAAW, TAAX, TAAZ, TABF, TABS, TABV, TABW, TABZ, TACF, TACG, TACI, TACK.

Source: Section 2.7.4.7; Table APP.2.7.4.1; Table APP.2.7.4.2; Table APP.2.7.4.3.

(Reproduced from Sponsor, Risk Management Plan, Table 1.5, page 15 of 97)

7.2.1 Demographics

Demographics and baseline characteristics for TAAL are presented in Table 36. For a complete summary of these characteristics, please see Section 9.1. Baseline characteristics appeared to be balanced between treatment groups. Women, the elderly, and subjects with renal impairment were underrepresented.

Table 36. Demographics and Baseline Characteristics (All Randomized All ACS Subjects) (TAAL)

	Prasugrel	Clopidogrel
Clinical Presentation n (%)^a		
UA/NSTEMI	N=5042	N=5027
UA	1271 (25.21)	1257 (25.00)
NSTEMI	3771 (74.79)	3770 (75.00)
STEMI	N=1767	N=1765
STEMI ≤ 12 hours	1203 (68.08%)	1235 (69.97)
STEMI > 12 hours	564 (31.92%)	530 (30.03)
Age (years)	N=6813	N=6795
Mean/SD	60.9/11.2	60.9/11.4
≥ 75 years	901 (13.22)	908 (13.36)
Sex n (%)^a	N=6813	N=6795
Male	5108 (74.97)	4977 (73.25)
Ethnicity	N=6813	N=6795
Caucasian	6263 (91.93)	6274 (92.33)
Geographic Region	N=6813	N=6795
Europe	3436 (50.43)	3439 (50.61)
Eastern Europe	1657 (24.32)	1665 (24.50)
Western Europe	1779 (26.11)	1774 (26.11)
North America	2164 (31.76)	2146 (31.58)
United States	2039 (29.93)	2020 (29.73)

	Prasugrel	Clopidogrel
Tobacco Use n (%)^a	N=6813	N=6795
Any Tobacco Use	4462 (65.49)	4490 (66.08)
Creatinine Clearance (mL/min)	N=6699	N=6681
< 60 mL/min n (%) ^a	717 (10.70)	774 (11.59)
Medical History n (%)^a	N=6813	N=6795
Diabetes ^a	1576 (23.13)	1570 (23.11)
Hypertension ^a	4370 (64.14)	4371 (64.33)
Hypercholesterolemia ^a	3790 (55.63)	3790 (55.78)
Prior MI ^a	1226 (18.00)	1208 (17.78)
Prior PCI ^a	904 (13.27)	926 (13.63)
Prior CABG ^a	541 (7.94)	497 (7.31)
Atrial Fibrillation ^a	211 (3.10)	212 (3.12)
History of Heart Failure ^a	265 (3.89)	247 (3.64)
Prior TIA or Stroke ^a	257 (3.77)	252 (3.71)
Peptic Ulcer Disease ^a	400 (5.87)	415 (6.11)
Peripheral Artery Disease ^a	349 (5.12)	363 (5.34)
ACS=acute coronary syndromes; CABG=coronary artery bypass graft; MI=myocardial infarction; N=number of randomized subjects; n=number of subjects in subcategory; NSTEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction; TIA=transient ischemic attack; UA=unstable angina ^a % is percent of number of subjects with non-missing values for category (Reproduced from Sponsor, Integrated Summary of Safety, Table 2.7.4.7, page 35-37)		

7.2.1.1 Postmarketing experience N/A

7.2.1.2 Literature N/A

7.2.2 Adequacy of Overall Clinical Experience

The overall clinical experience is adequate.

7.2.3 Adequacy of Special Animal and/or In Vitro Testing

The special animal and/or in vitro testing appears to be adequate. Please see the Pharmacology/Toxicology review for full details.

7.2.4 Adequacy of Routine Clinical Testing

Routine clinical testing appears adequate.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

While the metabolic, clearance, and interaction workup appear to be adequate, one should refer to the Clinical Pharmacology/Biopharmaceutics review for further details.

7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Please see Section 1.2 for recommendations on postmarketing requirements.

7.2.7 Assessment of Quality and Completeness of Data

Please refer to section 4.4 of this review for additional details on quality and completeness of data.

7.2.8 Additional Submissions, Including Safety Update

I reviewed the 4-month safety update, and there are no new safety issues.

8 ADDITIONAL CLINICAL ISSUES

8.1 Conclusions

Prasugrel significantly reduced the composite of cardiovascular death, nonfatal MI, or nonfatal stroke at the expense of more bleeding. Subjects ≥ 75 years of age, subjects with a history of transient ischemic attack/cerebrovascular accident, and subjects with weight category < 60 kg have an increased risk of bleeding on prasugrel, compared to clopidogrel.

Preliminary analyses from TAAL suggest there is an increased incidence of new cancers in prasugrel subjects, compared to clopidogrel subjects.

9.1.4 Objectives

Primary Objective:

To determine if CS-747 (prasugrel) plus aspirin was superior to clopidogrel plus aspirin in the treatment of subjects with acute coronary syndrome (ACS) who were to undergo percutaneous coronary intervention (PCI), as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a median follow-up of at least 12 months.

Key Secondary Objectives:

Efficacy Objectives:

To compare CS-747 with clopidogrel with respect to:

- the risk of CV death, nonfatal MI, or nonfatal stroke at 90 days
- the risk of CV death, nonfatal MI, or nonfatal stroke at 30 days
- the risk of CV death, nonfatal MI, or urgent target vessel revascularization (UTVR) at 90 days
- the risk of CV death, nonfatal MI, or UTVR at 30 days
- the risk of all-cause death, nonfatal MI, or nonfatal stroke at a median of at least 12 months
- the risk of CV death, nonfatal MI, nonfatal stroke, or rehospitalization for cardiac ischemic events at a median of at least 12 months

In the Clinical Study Report dated November 28, 2007, the sponsor added the following objective:

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

ARC Definitions of Definite, Probable, and Possible Stent Thrombosis⁹

• **Definite Stent Thrombosis**

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathologic confirmation:

- a. Angiographic confirmation of stent thrombosis†
 - i. The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
 1. Acute onset of ischemic symptoms at rest
 2. New ischemic ECG changes that suggest acute ischemia
 3. Typical rise and fall in cardiac biomarkers
 4. Nonocclusive thrombus
 - a. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream
 5. Occlusive thrombus
 - a. TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)
 - b. Pathological confirmation of stent thrombosis
 - i. Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

⁹Cutlip DE, S Windecker, R Mehran, A Boam, DJ Cohen, G-A van Es, PG Steg, M-A Morel, L Mauri, P Vranckx, E McFadden, A Lansky, M Hamon, MW Krucoff, PW Serruys and on behalf of the Academic Research Consortium, 2007, Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions, *Circulation* 115:2344-2351.

- **Probable Stent Thrombosis**

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- a. Any unexplained death within the first 30 days§
- b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- **Possible Stent Thrombosis**

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis

Safety Objectives:

- to evaluate the incidence of non-coronary artery bypass graft (CABG) surgery-related TIMI Study Group (TIMI) major bleeding in subjects receiving prasugrel or clopidogrel
- to evaluate the incidence of life-threatening bleeding (a subset of non-CABG-related TIMI major bleeding) in subjects receiving prasugrel or clopidogrel
- to evaluate the incidence of non-CABG-related TIMI minor bleeding in subjects receiving prasugrel or clopidogrel
- To evaluate the overall safety and tolerability of CS-747 administration based on clinical findings, laboratory values, and the occurrence of treatment-emergent adverse events (TEAEs)

Health Economics Objectives:

- Total 1-year medical care costs for ACS subjects undergoing PCI treated with CS-747 or clopidogrel
- Initial hospitalization costs between the two treatment groups
- Total 30-day costs between the two treatment groups

Other Objectives:

- To repeat all analyses, including the triple composite endpoint of CV death, nonfatal MI, or nonfatal stroke at a median follow-up of at least 12 months, in the STEMI population
- To evaluate the time course of the relative benefit of therapy as measured by hazard ratios
- To evaluate the incidence of TIMI major bleeding reported in subjects who undergo coronary artery bypass graft surgery

TIMI major, minor, and minimal bleeding are described in Table 37.