

Background:

At the time of the initiation of the TRITON trial on November 5, 2004, there were no uniform criteria to define stent thrombosis. However, concerns about late stent thrombosis with drug eluting stents arose at the European Congress of Cardiology in 2006, and the Steering Committee of the TRITON-TIMI 38 trial convened at this meeting and felt that TRITON could provide helpful information about this public health issue. This reviewer queried the sponsor about stent thrombosis in the TRITON trial in the Fall of 2006 and provided the sponsor with a list of data points that should be collected to further evaluate stent thrombosis in the TRITON trial. On December 7-8, 2006, the FDA Circulatory System Devices Panel met to discuss the safety of drug eluting stents, and the TRITON-TIMI 38 Steering Committee decided to incorporate stent thrombosis as the seventh secondary endpoint in the clinical trial. 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: the risk of definite or probable stent thrombosis per ARC definition at study end.

The TIMI Study Group developed a plan to formally evaluate stent thrombosis in TRITON. The TIMI Study Group decided to adjudicate these events on a clinical basis consistent with the ARC definitions by using information from source documents including discharge summaries, autopsy reports, and cardiac catheterization reports. The TIMI Study group identified subjects for adjudication with potential stent thrombosis if:

- a. The site investigator reported stent thrombosis on the case record form
- b. The subject had experienced a previously adjudicated cardiac ischemic event (MI, urgent target vessel revascularization, or cardiovascular death [including sudden/unwitnessed death]. Enzyme triggered periprocedural MI cases were not reviewed.
- c. The subject was undergoing CEC evaluation for a cardiac ischemic event or death

The physician CEC reviewers were trained by the CEC chairman to evaluate cases for stent thrombosis and to seek specific mention in the catheterization reports of terms such as “stent thrombosis, thrombus, clot, hazy lesions, fresh occlusion (early after percutaneous coronary intervention (PCI), etc.)” Many of the physician reviewers were also reviewers for the Harvard Clinical Research Institute which was instrumental in implementing the ARC stent thrombosis criteria.

Reason for FDA Request:

While reviewing some of the catheterization and PCI reports for patients who were adjudicated by the CEC as having definite or probable stent thrombosis, I realized some of these cases were not consistent with stent thrombosis at all.

TRITON CEC:

The CEC adjudicated a total of 174 events of “definite or probable stent thrombosis (ARC criteria)” during the efficacy period, including 116 events in the clopidogrel treatment group and 58 events in the prasugrel treatment group. These numbers are slightly different than those found in the sponsor’s Table TAAL.11.6 entitled “Number and Percentage of Subjects Reaching the Secondary Composite Endpoints—CEC Adjudicated (All Randomized Subjects)” under “Definite or Probable Stent Thrombosis through Study End.” In Table TAAL 11.6, 178 events of definite or probable stent thrombosis were reported, including 120 events in the clopidogrel treatment group and 58 events in the prasugrel treatment group. The additional 4 events in the clopidogrel treatment group occurred outside of the efficacy period.

The 174 events detailed above refer to all acute coronary syndrome subjects with a stent placed at the index PCI (N=6422 in both the prasugrel and clopidogrel treatment groups).

FDA Review and Request:

I reviewed the catheterization and percutaneous coronary intervention (PCI) reports from a random sample of 57 out of 174 subjects in Study TAAL (TRITON) who were reported to have definite or probable stent thrombosis by the TRITON CEC. Additionally, I reviewed the catheterization and PCI reports for 6 patients who were thought by the investigator to have stent thrombosis, but the cases were inadvertently NOT sent to the TRITON CEC for adjudication of stent thrombosis. The sponsor never referred these 6 cases to the CEC for adjudication because they believed there was a significant reduction of stent thrombosis with prasugrel, and they did not think these events would impact the study conclusions. No angiograms were available for my review.

Out of the 57 cases which were adjudicated by the TRITON CEC as definite or probable stent thrombosis (ARC criteria), I agreed with 45 of the interpretations. However, I classified the remaining 12 cases as follows:

- 6 cases: no stent thrombosis (although angiography would be needed in two of these cases for a final decision)
- 1 case: definite stent thrombosis
- 5 cases: likely definite stent thrombosis

Out of the 6 investigator reported cases of stent thrombosis which were never referred to the TRITON CEC for adjudication, I thought 3 of these cases were not consistent with stent thrombosis.

On August 29, 2008, I asked the sponsor to have an angiographic core laboratory perform a blinded review of the angiograms for the 18 subjects listed below. Additionally, the sponsor was asked to submit angiograms to the core laboratory for 18 "control subjects," matched by age, sex, vessel (and if possible, lesion), who were readmitted for anginal symptoms post the index procedure, underwent repeat cardiac catheterization that did NOT demonstrate stent thrombosis, and required revascularization."

12 Subjects: (Cases that were TRITON CEC Adjudicated as Definite Stent Thrombosis and that the Reviewer thought were Suspicious)

- 01000613703
- 01003315389
- 01004923223
- 01005723228
- 01006510171
- 01010721034
- 01021921998
- 01022421407
- 01023010665
- 54044022962
- 55084522273
- 61051219720

6 Subjects: (Investigator-Reported Stent Thrombosis Cases that were NOT Adjudicated by the TRITON CEC and that the Reviewer thought were Suspicious)

- 49060714838
- 55085522276
- 01005013384
- 01035513961
- 39069114674
- 97098913056

Methods:

A. Case-Matched Control Pool

The case-matched control pool was identified using the following steps as agreed upon by the FDA:

1. Subjects were identified who had an investigator reported ischemic event (post index event) with cardiac ischemic symptoms at rest and who had a revascularization in response to the cardiac ischemic event. (All these events had been sent to the TRITON CEC for adjudication of the cardiac ischemic event and to assess for stent thrombosis).
2. Cases were removed that had a revascularization event reported as non-urgent.
3. Cases were removed that had been adjudicated by the TRITON CEC as definite or probable stent thrombosis as well as those reported by the investigator as stent thrombosis and subsequently downgraded by the TRITON CEC.
4. Cases were removed if the cardiac ischemic event and the PCI were more than 7 days apart

B. Angiographic Analysis of Stent thrombosis in the TRITON Trial: PERFUSE Core Lab:

1. Data Collection Tools
 - a. PERFUSE developed a case report form to render an opinion as to whether stent thrombosis was present on the angiogram.
 - b. PERFUSE received films from the sponsor in a binder. Each film was associated with a unique ID number which was recorded at the top of the case report form. **No clinical information was provided.**
2. Personnel
 - a. A panel of 4 readers reviewed the angiograms. A consensus by two readers was required. If no consensus was reached, a third over reader rendered the final opinion. The director of the angiographic core laboratory (C. Michael Gibson, M.S., M.D.) was present for the analysis of all films. Per PERFUSE, his role as director was "to answer questions regarding the process and to ensure the integrity of the over reading."
3. Film Review Process
 - a. The index procedure was reviewed first. The location and the length of the stent was carefully evaluated. The placement of the stent had to be clear on the film. If no stent was seen (some stents are not radio opaque), the analysis could not be undertaken and verification from the clinical record of stent placement was required.
 - b. The follow-up procedure was then reviewed to assess whether thrombus was present. The location of the culprit lesion was recorded. If thrombus was present, the location and size of the thrombus was characterized.
 - c. PERFUSE assessed flow in the epicardial artery using the TIMI Flow Grade system and the corrected TIMI Frame Count.
 - d. PERFUSE assessed myocardial perfusion using the TIMI Myocardial Perfusion Grade.
 - e. PERFUSE prespecified criteria to determine if the presence of thrombus constituted stent thrombosis.

C. Adjudication of Stent Thrombosis in the TRITON Trial: Harvard Clinical Research Institute (HCRI)

1. Adjudication Process

Three interventional cardiologists comprised the committee. This committee reviewed the cases in a face-to-face meeting and provided interpretation by consensus. Final adjudication case and specific interpretation of the angiogram was reported on an adjudication case report form for each case.
2. Identification of Events

Events were selected based on prior adjudication status by FDA and matched with a control patient by study Sponsor.

3. Case Review

The Committee reviewed the clinical data and made a preliminary adjudication. The angiogram, if available, was then reviewed to confirm or reverse the preliminary decision. If the angiogram was not available, the Committee would comment on the potential impact on the adjudication decision.

4. Quorum and Decision Methods

All 3 members of the Committee were required to attend and participate in review of each case. Discussion was held with intent of unanimous decision whenever possible. In cases with discordance, decision was based on agreement of 2 members. All cases coming to vote were detailed in meeting minutes with specific reasons provided.

5. Reporting of Results

The Committee entered results of preliminary adjudication, angiogram review, and final adjudication on the case report form.

Results:

The TRITON Clinical Endpoints Committee (CEC) adjudicated a total of 335 investigator-identified events, which included 135 (135/6422 or 2.10%) events in the prasugrel group and 200 (200/6422 or 3.11%) events in the clopidogrel group. Of these events, 43% of the events in the prasugrel group (58/135) and 58% of the events in the clopidogrel group (116/200) were classified as ARC definite or probable stent thrombosis. The CEC downgraded 60% of the investigator reported events of stent thrombosis in the prasugrel group (81/135) and 44% of the investigator reported events of stent thrombosis in the clopidogrel group (88/200). Therefore, the CEC downgraded a greater percentage of prasugrel than clopidogrel cases of investigator reported stent thrombosis. The 16% absolute difference in the downgrades between treatment groups was a concern. This imbalance suggested there could have been a particular clinical presentation that occurred more commonly in the prasugrel group that tended to be downgraded by the CEC as not conclusive of stent thrombosis. However, in TRITON, investigators did not specify the criteria they used for reporting an event as stent thrombosis.

The TIMI CEC evaluated more than 1500 cases of death, MI, or urgent target vessel revascularization for the possibility of stent thrombosis that were not identified as such by local investigators. Ultimately, the TIMI Study Group downgraded 195 subjects (92 prasugrel, 103 clopidogrel) and upgraded 65 subjects (24 prasugrel, 41 clopidogrel). Nevertheless, the 195 downgrades by the TIMI Study Group appeared to be reasonable, as did the 65 upgrades, and TIMI Study Group worst case analyses with downgrades and upgrades still demonstrated a statistically significant reduction in stent thrombosis with prasugrel. Nevertheless, central adjudication from raw data was requested to evaluate the trial for potential bias.

Following blinded PERFUSE angiographic core laboratory review, the Harvard Clinical Research Institute (HCRI) assessed the 12 FDA selected cases previously adjudicated as definite or probable stent thrombosis (ARC criteria) by the TRITON CEC. Additionally, the 6 cases of investigator reported stent thrombosis that had not been sent to the TRITON CEC for adjudication were similarly assessed, as were the 18 case-matched control subjects.

At both PERFUSE and HCRI, cases were not reviewed independently. At PERFUSE, a consensus panel consisted of four physicians, and a consensus by two readers was required. If no consensus was reached, a third overreader provided the final opinion. The director of the angiographic core laboratory (C. Michael Gibson, M.S., M.D.) was present for the analysis of all films. Dr. Gibson's role was to answer questions regarding the process and to ensure the integrity of the review only. No clinical information was provided to PERFUSE. The index procedure was reviewed first, and the follow-up procedure was subsequently reviewed.

At HCRI, a committee of 3 interventional cardiologists reviewed the cases in a face-to-face meeting and provided interpretation by consensus. HCRI had access to baseline clinical and stent procedure data and event data as previously available to the TIMI study group CEC as well as coronary angiography from the baseline procedure and suspect event.

- **Six Cases of Investigator Reported Stent Thrombosis Cases that were NOT Adjudicated by the TRITON CEC and the Reviewer Thought were Suspicious:**

PERFUSE and HCRI adjudicated 3 out of the 6 cases of investigator reported stent thrombosis as “no stent thrombosis” and 3 cases as “definite stent thrombosis,” as shown in Table 1. My review was consistent with these results. Both subjects who received prasugrel did not have stent thrombosis whereas three out of the four subjects who received clopidogrel had definite stent thrombosis.

Table 1. Investigator-Reported Stent Thrombosis Cases Not Sent to TRITON CEC for Adjudication

Subject ID	Treatment Assignment	KAH Review	PERFUSE: Definite/Probable Stent Thrombosis?	HCRI	Primary TRITON CEC Event Adjudicated
TAAL-490607-14838	Prasugrel	No stent thrombosis	No	No stent thrombosis	Positively adjudicated as MI
TAAL-550855-22276	Prasugrel	No stent thrombosis	No	No stent thrombosis	Positively adjudicated as MI
TAAL-010050-13384	Clopidogrel	Definite Stent thrombosis	Yes	Definite stent thrombosis	Positively adjudicated as MI
TAAL-010355-13961	Clopidogrel	Definite stent thrombosis	Yes. Assessment Comments: “Dates are different! Info paper reads 17.09.2005. Film reads 19.09.2005.”	Definite stent thrombosis	Positively adjudicated as MI
TAAL-390691-14674	Clopidogrel	No stent thrombosis	No	No stent thrombosis	Positively adjudicated as MI
TAAL-970989-13056	Clopidogrel	Definite stent thrombosis	Yes	Definite stent thrombosis	Two positively adjudicated MIs

KAH: Karen A. Hicks, M.D. (reviewer); MI: myocardial infarction; PERFUSE: angiographic core laboratory; HCRI: Harvard Clinical Research Institute (CEC adjudication)

- **12 Cases that were TRITON CEC Adjudicated as Definite Stent Thrombosis (and that the Reviewer Thought were Suspicious):**

Stent thrombosis adjudication for these 12 cases is summarized in Table 2. PERFUSE adjudicated 7 cases as having angiographic evidence of stent thrombosis and 5 cases as not having angiographic evidence of stent thrombosis. HCRI adjudicated 7 cases as definite (3 prasugrel, 4 clopidogrel), 1 case as probable (clopidogrel), and 4 cases as no stent thrombosis (3 clopidogrel, 1 prasugrel). In the case of Subject 01022421407, PERFUSE did not see angiographic evidence of thrombus or total occlusion involving the stent, but the clinical report documented the presence of thrombus likely involving the stent; therefore, HCRI adjudicated this case as probable stent thrombosis.

I concurred with the four cases of no stent thrombosis (Subjects 01000613703 (clopidogrel), 01010721034 (clopidogrel), 55084522273 (clopidogrel), and 61051219720 (prasugrel)).

In the case of Subject 01003315389 (prasugrel) which I did not think was stent thrombosis because by the catheterization report, the vessel appeared to be totally occluded at the mid right coronary artery percutaneous transluminal coronary angioplasty (PTCA) site and not the proximal stent site, PERFUSE noted that “no revascularization [was] filmed after stent thrombosis. Thrombosis occurred at the edge of [the] stent. It is possible that it could be thrombosis of a distal PTCA site.” However, HCRI adjudicated this case as definite stent thrombosis.

In the case of Subject 54044022962 (prasugrel) which I did not think was stent thrombosis because the catheterization report stated the patient had “instent restenosis,” PERFUSE saw angiographic evidence of thrombus and HCRI adjudicated the case as definite stent thrombosis.

Lastly, I thought Subject 01022421407 was likely a stent thrombosis, but per HCRI, the case was adjudicated as “probable.” Please see the detailed explanation above.

- **18 Case-Matched Control Subjects:** All cases were adjudicated by PERFUSE and HCRI as no stent thrombosis.

Table 2. Stent Thrombosis Adjudication (12 FDA Selected Cases)

Subject # from FDA Request	Subject ID	Tx	TRITON CEC Result: Definite/ Probable ST?		PERFUSE Assessment Comments, if Present	HCRI: Was Independent Core Lab Angiogram Report Available for Review	HCRI: If angiogram report available, did it confirm clinical report of ST	HCRI: If report did not confirm clinical report of ST, specify reason	HCRI: Based on Clinical Review and Angiographic Data, did ST occur (defined by ARC definite/probable criteria)		Investigator Reported Stent Thrombosis?	CEC Adjudicated MI at time of event
1	01000613703	C	Yes	No		Yes	Yes		No	No	No	Yes
2	01003315389	P	Yes		No revascularization filmed after stent thrombosis. Thrombosis occurred at the edge of stent. It is possible that it could be thrombosis of a distal PTCA site.	Yes	Yes		Yes		No	Yes
3	01004923223	C	Yes			Yes	Yes		Yes		Yes	No
4	01005723228	C	Yes			Yes	Yes		Yes		Yes	Yes
5	01006510171	C	Yes			Yes	Yes		Yes		Yes	Yes
6	01010721034	C	Yes	No	New thrombus distal to stent at site of untreated ulcer	Yes	No	2	No	No	Yes	No
7	01021921998	P	Yes			Yes	Yes		Yes		Yes	

Subject # from FDA Request	Subject ID	Tx	TRITON CEC Result: Definite/ Probable ST?		PERFUSE Assessment Comments, if Present	HCRI: Was Independent Core Lab Angiogram Report Available for Review	HCRI: If angiogram report available, did it confirm clinical report of ST	HCRI: If report did not confirm clinical report of ST, specify reason	HCRI: Based on Clinical Review and Angiographic Data, did ST occur (defined by ARC definite/probable criteria)			Investigator Reported Stent Thrombosis?	CEC Adjudicated MI at time of event
8	01022421407	C	Yes	No		Yes	No	2	Yes	Probable	Likely a Definite	Yes	Yes
9	01023010665	C	Yes			Yes	Yes		Yes			No	Yes
10	54044022962	P	Yes			Yes	Yes		Yes			No	Yes

Subject # from FDA Request	Subject ID	Tx	TRITON CEC Result: Definite/Probable ST?		PERFUSE Assessment Comments, if Present	HCRI: Was Independent Core Lab Angiogram Report Available for Review	HCRI: If angiogram report available, did it confirm clinical report of ST	HCRI: If report did not confirm clinical report of ST, specify reason	HCRI: Based on Clinical Review and Angiographic Data, did ST occur (defined by ARC definite/probable criteria)		Investigator Reported Stent Thrombosis?	CEC Adjudicated MI at time of event
11	55084522273	C	■	No	Edge dissection distal to the OM stent is present. On previous analysis, no stent was seen to be placed, and it was felt that this was a balloon angioplasty reocclusion.	Yes	Yes		No	No	Yes	Yes
12	61051219720	P	■	No		Yes	Yes		No	No	No	No

ARC: Academic Research Consortium; C: clopidogrel; P: prasugrel; HCRI: Harvard Clinical Research Institute; OM: obtuse marginal; PCI: percutaneous coronary intervention; PDA: posterior descending artery; PLB: posterolateral branch; PTCA: percutaneous transluminal coronary angioplasty; RCA: right coronary artery; SVG: saphenous vein graft; Tx: treatment.