Addenda to Briefing Document

FDA Advisory Committee for Ticagrelor

July 28, 2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 19, 2010

From: Thomas A. Marciniak, M.D.
Medical Team Leader

Subject: Ticagrelor for acute coronary syndromes, NDA 22-433, changes from original version to amended version

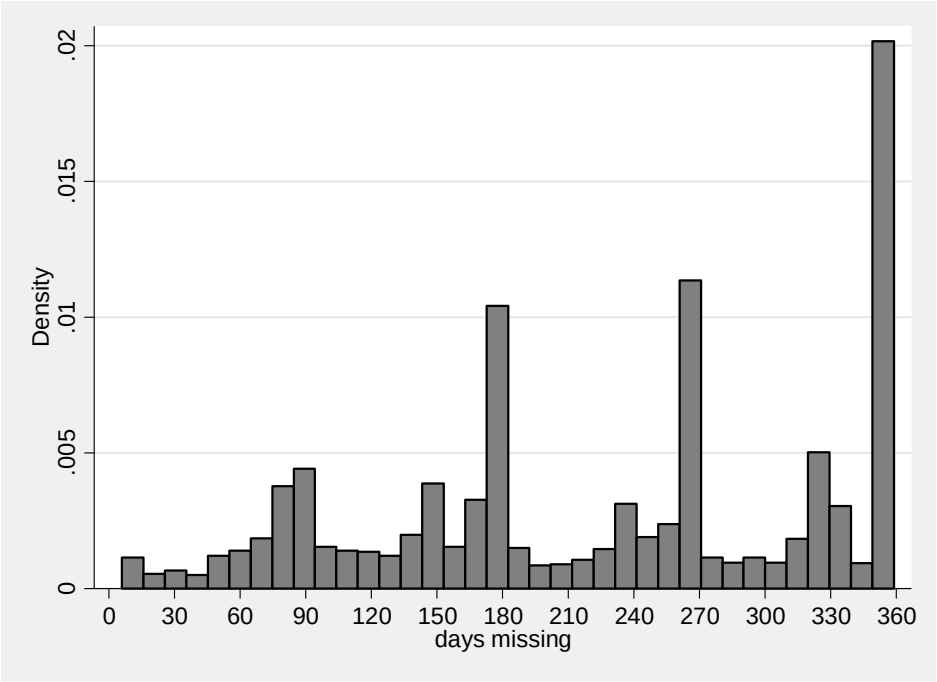
To: Advisory Committee Members

This memo details the changes from the original, June 29, 2010, version of my memo to the amended, July 16, 2010, version. I have provided the page numbers of the changes with a leading "O" for original version page numbers and leading "A" for amended version page numbers, e.g., "O1 A1" below. I have provided, when needed, paragraph numbers following the page numbers and preceded by a hyphen.

O1-2 A1-2. Added sentence: "This amended version provides alternative estimates of follow-up that are more consistent with the study conduct, adds a discussion of efficacy complexity, and corrects slightly some safety statistics quoted from the primary safety review."

O3. Replaced: "For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significant more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). The distributions of days of missing follow-up were similar in both arms, with the overall distribution shown in Figure 1.

Figure 1: Distribution of Days of CV Follow-up Missing in PLATO



The peaks at 180, 270, and 360 days are due to patients withdrawing shortly after randomization, allowing for the rolling phase-out. The median days of CV follow-up missing were 241 days.

I analyzed vital status follow-up similarly, counting vital status follow-up as good if the patient died or had a last visit or contact on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria 6.5% of ticagrelor and 5.2% of clopidogrel patients had incomplete vital status follow-up. The median days of vital status follow-up missing were 179 days in both arms."

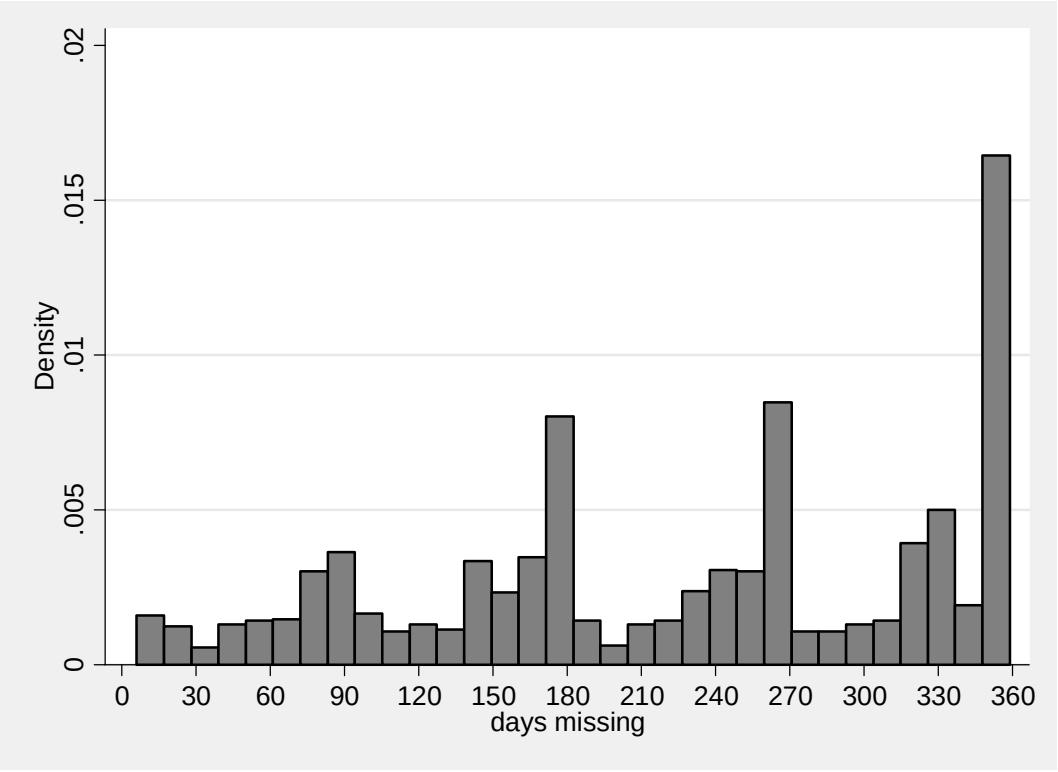
A3. Replaced with: "For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I initially counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit (with vital signs measured) on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significant more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). However, in PLATO patients did not always come in for a visit but may have had follow-up by another route such as a hospital visit or an adverse event report. Trying to account for all possible follow-up in PLATO is complex as shown by Figure 1, the program I used.

Figure 1: Program for Determining CV Follow-up in PLATO

```
gen byte cvfutyp = cond(adjresl==1, 1, 2) if cvfudt!=.
  /* adjresl==1 death so 2 for all other adjudications */
gen int cvfudt = adjdtl /* adjudication date */
replace cvfutyp = 3 if cvfudt==. | (lstcldtn>cvfudt & lstcldtn!=.)
  /* last clinic visit with vital signs */
replace cvfudt =  lstcldtn if cvfudt==. | (lstcldtn> cvfudt &  lstcldtn!=.)
replace cvfutyp = 4 if cvfudt==. (cvvisdtl> cvfudt & cvvisdtl!=.)
  /* visit or phone contact with CV event checkboxes */
replace cvfudt =  cvvisdtl if cvfudt==. | (cvvisdtl>cvfudt & cvvisdtl!=.)
replace cvfutyp = 5 if cvfudt==. | (ciedtl> cvfudt & ciedtl!=.)
  /* cie = cardiac ischemic event */
replace cvfudt =  ciedtl if cvfudt==. | (ciedtl> cvfudt & ciedtl!=.)
replace cvfutyp = 6 if cvfudt==. | (hospdtl> cvfudt & hospdtl!=.) /* hospitalization */
replace cvfudt =  hospdtl if cvfudt==. | (hospdtl> cvfudt & hospdtl!=.)
replace cvfutyp = 7 if cvfudt==. | (aedtl> cvfudt & aedtl!=.) /* adverse event */
replace cvfudt =  aedtl if cvfudt==. | (aedtl> cvfudt & aedtl!=.)
replace cvfutyp = 8 if termreas==1 | termreas==7 | termreas==8  /* bad-wd consent-lost */
replace cvfudt =  termdt if termreas==1 | termreas==7 | termreas==8
```

Figure 1 is frightening. It should not be this difficult to determine what the last date of follow-up is in a one year study. Preferably patients come in for a last study visit unless they are dead, the simpler approach I initially used. By the complex determinations in Figure 1 incomplete CV follow-up is better but still concerning, about 8.6% in each arm. For the primary endpoint (counting any primary endpoint event as good follow-up) the incomplete PEP follow-up is slightly better, 7.8%. The distributions of days of missing CV follow-up were similar in both arms, with the overall distribution shown in Figure 2.

Figure 2: Distribution of Days of CV Follow-up Missing in PLATO



The peaks at 180, 270, and 360 days are due to patients withdrawing shortly after randomization, allowing for the rolling phase-out. The median days of CV follow-up missing were 241 days.

I analyzed vital status follow-up similarly, counting vital status follow-up as good if the patient died or had a last visit or contact on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria 3.1% of ticagrelor and 2.6% of clopidogrel patients had incomplete vital status follow-up. The median days of vital status follow-up missing were 262 days for ticagrelor and 255 days for clopidogrel."

NOTE: Because I added one additional, initial figure to my amended review, all subsequent figure numbers are increased by one.

O10-1 A11-1. Added: "Attempting to analyze timing of study drug administration is complicated by the usual problems of inaccuracies with dates and times in clinical trials, e.g., I count 725 cases for which the study drug was administered prior to randomization. It is also confounded by another factor: 48% of the ticagrelor patients were on clopidogrel or received clopidogrel within the first 24 hours and the timing of administration of the clopidogrel was not captured."

O12 A13. Added before *Safety*: "*Efficacy Evaluation Complexity*
The previous sections should be convincing that efficacy evaluation in PLATO is extremely complex. I could argue that PLATO tried to do too much: *A priori* it attempted to evaluate three different conditions (i.e., STEMI, NSTEMI, and UA), two different management approaches (invasive and non-invasive), and two different pre-treatments (prior antiplatelet and no prior antiplatelet use). The complexity, e.g., 3 x 2 x 2 x 2 (study drug) = 24 different treatment cells was then increased 4 to 8-fold by the US vs. OUS discrepancies, with the issues of aspirin dosage and study drug timing, and the short term vs. long term effects. The evaluation is complicated further at least qualitatively by the issues of statin exposure and completeness of follow-up. As of the date of this review we have not successfully identified clear patterns among this complexity."

O12-4 A14-1. Replaced "The FDA primary clinical safety reviewer commented that most major bleeds were CABG-related (~ 75%) and most CABG bleeds were major (~85%)" with "The FDA primary clinical safety reviewer commented that most patients with major bleeds had major CABG-related bleeds (~ 67%) and most CABG bleeds were major (~80%)."

O13-1 A14-2. Replaced "While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) minimize any concerns that I have about strokes" with "While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) mitigate any concerns that I have about strokes."

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS A MARCINIAK
07/19/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 16, 2010

From: Thomas A. Marciniak, M.D.
Medical Team Leader

Subject: Ticagrelor for acute coronary syndromes, NDA 22-433 (Amended)

To: Advisory Committee Members

Ticagrelor (Brilinta™) is a novel $P2Y_{12}$ platelet receptor inhibitor submitted for approval for the indication of reducing the rate of thrombotic events in patients with acute coronary syndromes (ACS, including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI)). Two other drugs (clopidogrel, prasugrel) are approved for similar indications and a third (ticlopidine) is approved for related indications. All three have both common and individual limitations: The common limitations are that the approved drugs are all members of the thienopyridine structural class administered as pro-drugs requiring metabolic activation for effect and binding irreversibly to the $P2Y_{12}$ receptor. Ticagrelor does not require metabolic activation and binds reversibly. The individual limitations are that ticlopidine is rarely used because of a higher rate of neutropenia, clopidogrel may be less effective in some patients because of reduced activation due to genetic or drug-interaction factors, and prasugrel is associated with higher rates of bleeding and a question of cancer promotion. A novel drug without these limitations would be a therapeutic advance.

We have provided detailed primary reviews of clinical efficacy and of clinical safety in the FDA briefing package. In this memo I will highlight the significant clinical efficacy and safety questions that we have identified, referencing the preclinical and clinical pharmacological findings when relevant. This amended version provides alternative estimates of follow-up that are more consistent with the study conduct, adds a discussion of efficacy complexity, and corrects slightly some safety statistics quoted from the primary safety review.

PLATO Study Design

The substantial evidence submitted to support the approval of ticagrelor comes from PLATO, a large, international, multi-center, randomized, double-blind, active-controlled trial. The primary reviews summarize well the details of protocol and study design. In general the trial was well-designed. In retrospect I have identified the following issues:

- Ticagrelor is a moderate inhibitor of cytochrome P450 CYP3A. Because several statins are metabolized by CYP3A and statins are commonly administered to ACS patients, the sponsor proposed at the end-of-phase 2 meeting in December 2005 that concomitant therapy with either simvastatin or lovastatin at doses higher than 40-mg should be avoided. We accepted this proposal as reasonable. The protocol states that "As simvastatin has recommended restrictions for concomitant therapy with inhibitors of CYP3A due to increased reporting of myopathy, concomitant study therapy with simvastatin or lovastatin (which is very similar pharmacokinetically to simvastatin) at doses higher than 40mg should be avoided." In hindsight this restriction on a class of drugs with a mortality benefit appears inappropriate. There is no reason to restrict statin dosage in the clopidogrel arm.

  Simvastatin was the most frequently used statin in PLATO—about 54% of patients took it at some time. Atorvastatin usage was very similar. Rosuvastatin usage was a distant third at about 9%. Note that ticagrelor also affects atorvastatin pharmacokinetics, increasing its AUC by a mean of 36%. These changes in statin exposure may be relevant to the time course of the presumed ticagrelor benefit that I discuss below.

  Because of the restriction of simvastatin dosage the protocol should have specified collecting the dosages of statins used in the trial. Unfortunately the protocol failed to do so. The protocol did specify measuring blood lipid levels.

- PLATO was double-blinded but it was trivial to break the blind at the sites. The clopidogrel formulation used was a clopidogrel tablet cut into two and stuffed into a capsule. The dummy was identical in appearance. However, the sites could unblind any patient by breaking one of the patient's clopidogrel/dummy capsules and examining its contents. The protocol submitted in August 2006 described this clopidogrel formulation but the reviewing FDA medical officer did not identify the formulation as problematic. The sponsor did not submit the protocol for a Special Protocol Assessment. In 2006 we might have complained about but accepted the clopidogrel formulation even if we had identified it as problematic. Because of bad experiences with open label trials since 2006, we should be more cautious about such formulations today.

PLATO Study Conduct

Most aspects of the PLATO study conduct also appear to be good. The structure and processes of the trial, e.g., randomization by interactive voice or web response system, unblinded DSMB, blinded event adjudication committee, etc., are ones that we favor. The trial documentation submitted appears to be well-prepared and complete. The CRFs submitted are computer printouts from a data capture computer system. They are highly legible and appear complete but are difficult to read because of the computer formatting. However, we requested and the sponsor provided quickly the audit trail of all changes to the CRF data base—a 16.5GB file. We could analyze this file with standard statistical packages; I found it helpful in understanding changes in CRF data. The sponsor also submitted adjudication packages that were predominantly in an easier to read document format. These adjudication packages included investigator notes, hospital discharge summaries, ECG tracings, etc., that were helpful in understanding the adjudications.

There was one aspect of PLATO study conduct that was not good: the follow-up rate. By the sponsor's statistics, about 5% of the patients died while about 82% had a final study visit ("completers" per the sponsor's terminology). Hence about 13% of the patients (100% - 5% - 82%) had incomplete follow-up for determining the primary endpoint of CV death, myocardial infarction (MI), or stroke by the sponsor's tallying.

For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I initially counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit (with vital signs measured) on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significant more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). However, in PLATO patients did not always come in for a visit but may have had follow-up by another route such as a hospital visit or an adverse event report. Trying to account for all possible follow-up in PLATO is complex as shown by Figure 1, the program I used.

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  /* last clinic visit with vital signs */
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replace cvfutyp = 4 if cvfudt==. (cvvisdtl> cvfudt & cvvisdtl!=.)
  /* visit or phone contact with CV event checkboxes */
replace cvfudt =  cvvisdtl if cvfudt==. | (cvvisdtl>cvfudt & cvvisdtl!=.)
replace cvfutyp = 5 if cvfudt==. | (ciedtl> cvfudt & ciedtl!=.)
  /* cie = cardiac ischemic event */
replace cvfudt =  ciedtl if cvfudt==. | (ciedtl> cvfudt & ciedtl!=.)
replace cvfutyp = 6 if cvfudt==. | (hospdtl> cvfudt & hospdtl!=.) /* hospitalization */
replace cvfudt =  hospdtl if cvfudt==. | (hospdtl> cvfudt & hospdtl!=.)
replace cvfutyp = 7 if cvfudt==. | (aedtl> cvfudt & aedtl!=.) /* adverse event */
replace cvfudt =  aedtl if cvfudt==. | (aedtl> cvfudt & aedtl!=.)
replace cvfutyp = 8 if termreas==1 | termreas==7 | termreas==8  /* bad-wd consent-lost */
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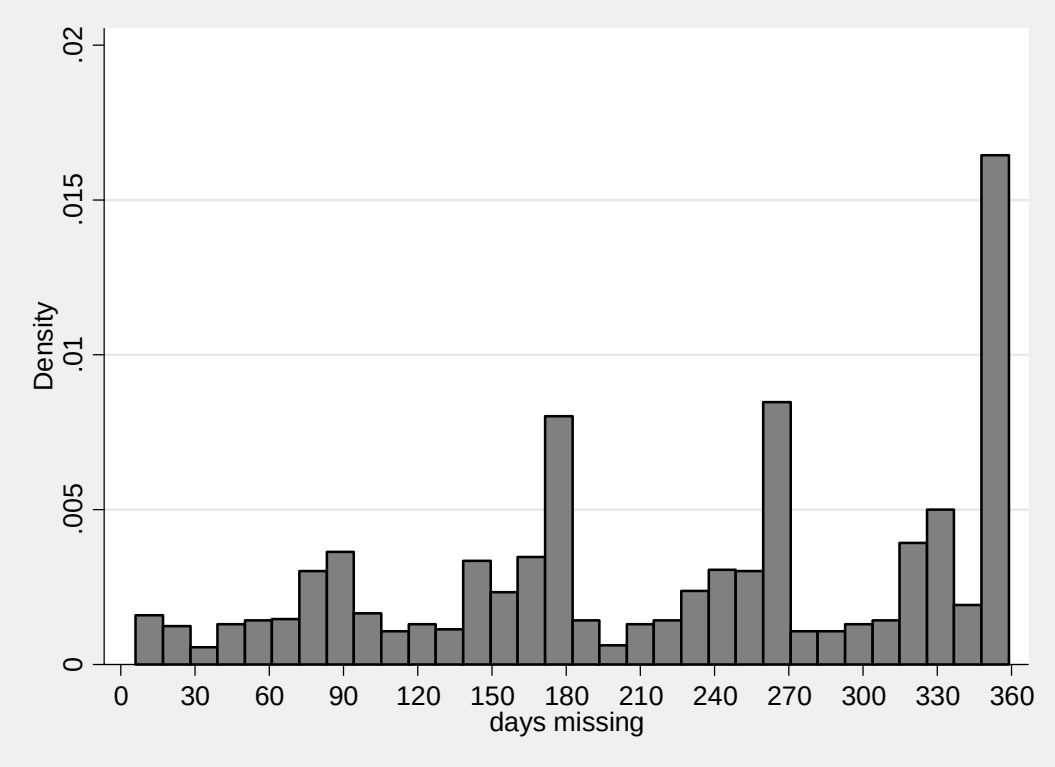
Figure 1 is frightening. It should not be this difficult to determine what the last date of follow-up is in a one year study. Preferably patients come in for a last study visit unless they are dead, the simpler approach I initially used. By the complex determinations in Figure 1 incomplete CV follow-up is better but still concerning, about 8.6% in each arm. For the primary endpoint (counting any primary endpoint event as good follow-up) the incomplete PEP follow-up is slightly better, 7.8%. The distributions of days of missing CV follow-up were similar in both arms, with the overall distribution shown in Figure 2.

Figure 2: Distribution of Days of CV Follow-up Missing in PLATO



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These rates of incomplete follow-up are concerning. They greatly exceed the differences between arms in rates for any of the endpoints. If the endpoint results were consistent, then we would be less concerned about the follow-up rates. However, the efficacy results are inconsistent by region and the time course of the effects are inconsistent with those from the thienopyridine ACS trials.

This problem with incomplete follow-up rates has been an issue for other recent CV outcome trials. While we are sympathetic to the difficulties of performing outcome trials in the modern era of increased patient awareness of medical treatments and mounting privacy concerns, if this trend continues we will not be able to interpret CV outcome trial results. This problem is the number one study conduct problem today threatening the integrity of CV outcome trials.

Efficacy

The PLATO efficacy analyses are time-to-first-event analyses. Before presenting my analyses, I have one analytic issue to discuss. The sponsor, for its time-to-event analyses, used censoring dates for patients without the event of interest based on the last study visit date for the "completers" but projected based on either a future planned visit date plus 30 days for withdrawals or upon the last dispense date plus 90 days for patients who continued on study medication after a "last" visit. While the use of these strange censoring rules does not change the statistics greatly, I can not see the validity of projecting follow-up. I censored patients at the time of an event or the time of the last study visit (for CV events) or the last vital status follow-up (for all-cause mortality).

Sponsor's Primary Adjudicated Results

The sponsor contracted with an academic center to perform blinded adjudications of CV and bleeding events. The sponsor named this adjudication group the Independent Central Adjudication Committee (ICAC). While the use of a blinded adjudication process is good, it does not guarantee that the adjudications are unbiased. Someone still has to decide what events to refer and what documents to include in the adjudication packages. All of these processes are subject to surreptitious unblinding. For example, besides the DSMB the sponsor reported in Serial 008 that four groups within its organization had treatment codes as well as two contractors, i.e., "Quintiles had access to a password protected list of the randomization code which was known to only named personnel. This was used for the identification of PK samples . . ." and a second contractor had treatment codes for the IVRS system. With so many groups having access to treatment codes I am not reassured that the blind was properly maintained.

I show the Kaplan-Meier (K-M) plot for the sponsor's first primary endpoint event (CV death, MI, or stroke - MACE) in Figure 3 and for death in Figure 4.

Figure 3: Time to Sponsor's First Primary Endpoint Event (MACE)

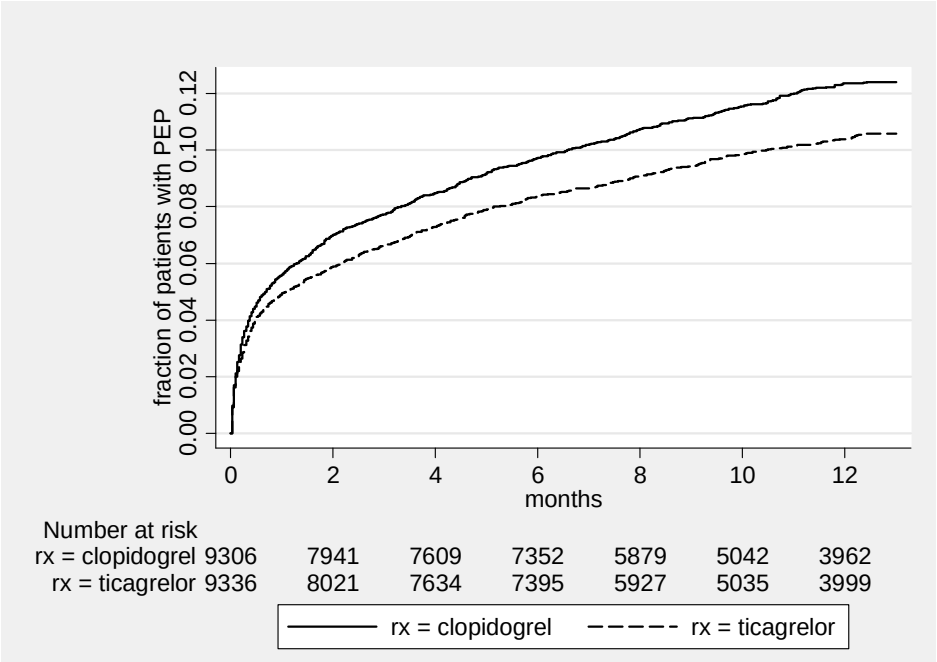
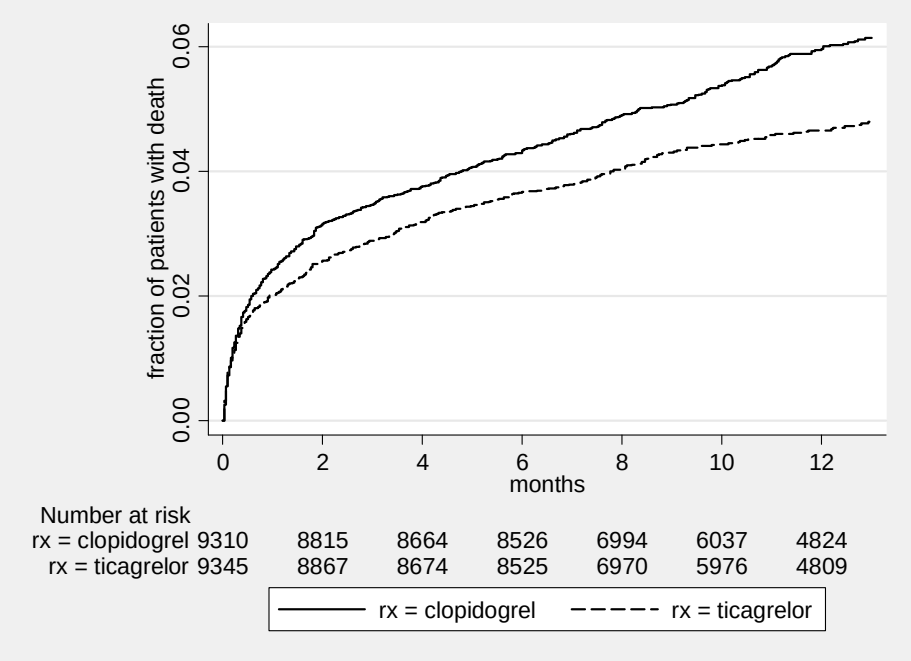


Figure 4: Time to Death from Any Cause

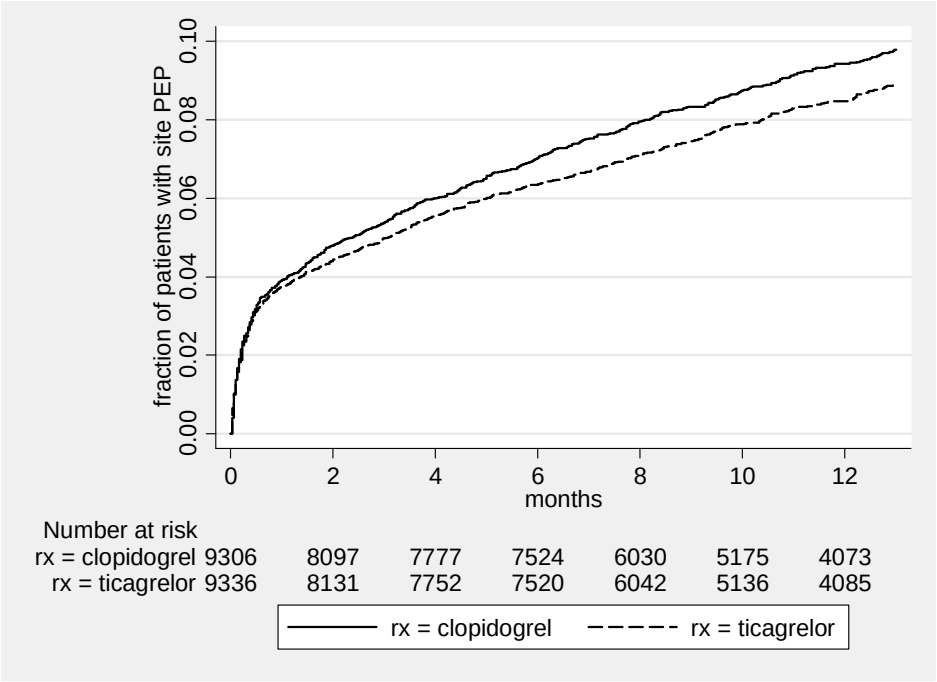


Both time-to-first event analyses are highly statistically significant by the log rank test. One relevant question is that, given the incompleteness of follow-up, are the results real?

Site-Reported MACE

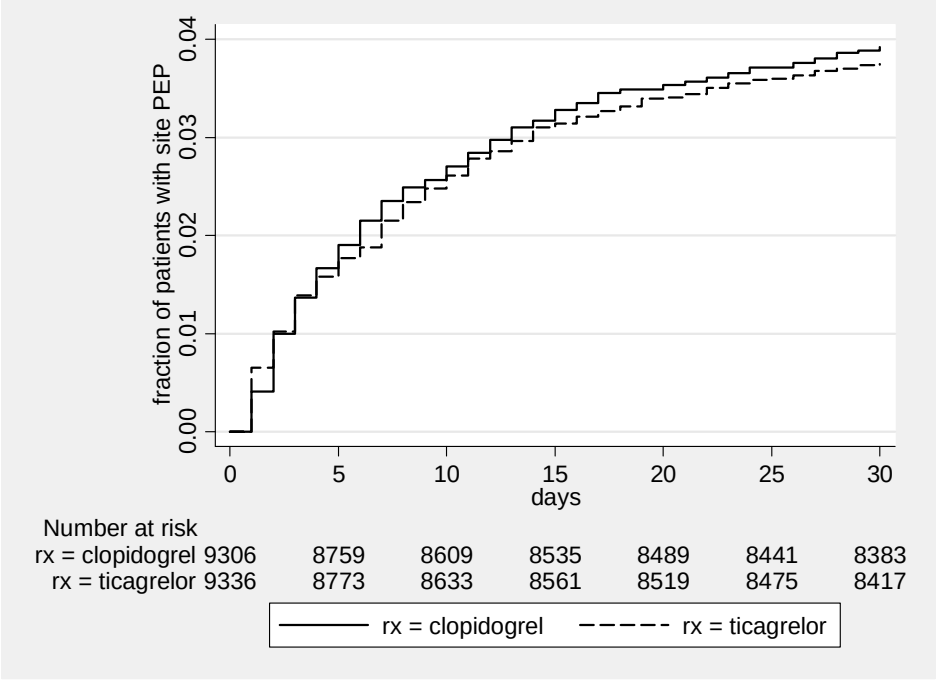
As a check I counted CV death, MI, and stroke events (MACE) as reported by the sites without the ICAC adjudication. For these site-reported statistics I also implemented two variations from the sponsor's classification of CV deaths: (1) The sponsor counted bleeding deaths as CV deaths. While that is reasonable for the primary endpoint (PEP) to estimate a net benefit, for an endpoint to explore efficacy effects alone I believe that it is preferable to exclude bleeding events not related to a cardiovascular or cerebrovascular event. Hence I excluded gastrointestinal bleeds but included non-traumatic intracranial hemorrhages. (2) The sponsor counted all unknown deaths as CV deaths, again reasonable for a PEP for net benefit. I counted sudden unknown deaths as CV deaths but excluded completely unknown deaths. I show the K-M plot for this site-reported MACE in Figure 5.

Figure 5: Time to Site-Reported First MACE



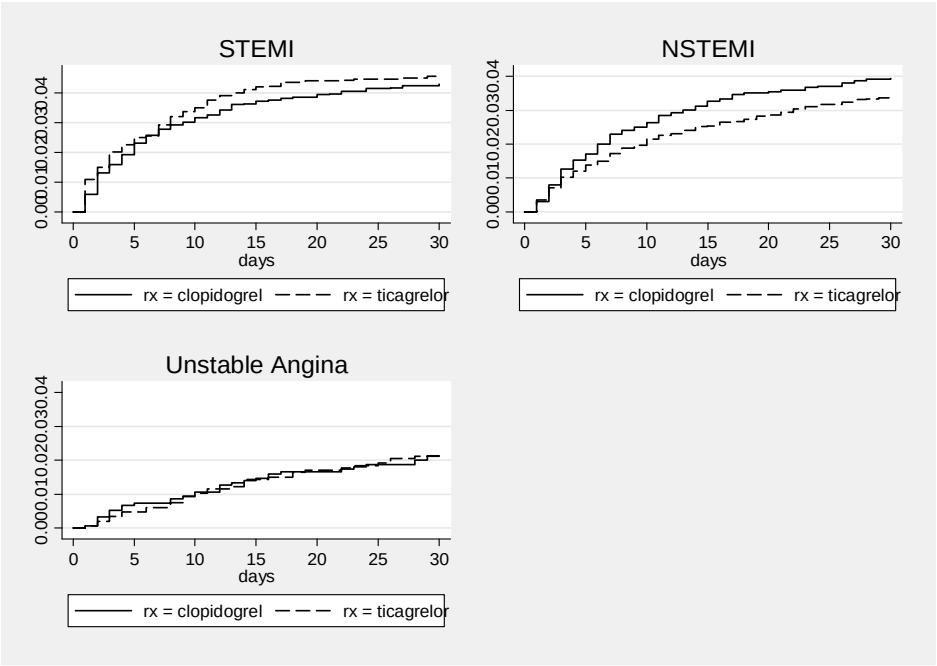
The possible benefit of ticagrelor is much less impressive for site-reported events and not statistically significant (p about 0.095 by log rank). For site-reported events there is only a slight benefit regarding MIs (relative risk (RR) about 0.94), a detriment regarding strokes (RR about 1.2), with the best benefit regarding CV deaths (RR 0.85). Note that the curves do not diverge early. In fact, there is little divergence for the first 30 days as shown in Figure 6.

Figure 6: Time to Site-Reported First MACE – 30 Days



The time course in Figure 5 and Figure 6 is quite different from what we have seen with the thienopyridines in ACS. Typically there has been an almost immediate benefit that rapidly accrues during the early days. The benefit beyond 30 days is harder to establish. For ticagrelor there appears to be little variation early by type of index event as shown in Figure 7.

Figure 7: Time to Site-Reported First MACE by Index Event Type



For all three types of index event ticagrelor appears to show beneficial effects longer term. The short term effects for ticagrelor are the opposite of what we've seen with prasugrel compared to clopidogrel: For prasugrel there was an immediate and dramatic benefit in STEMI patients in the TRITON trial but, at least for site-reported events, modest benefit for NSTEMI patients. There are three significant differences of TRITON compared to PLATO: (1) TRITON excluded patients with prior thienopyridine use; PLATO included them. (2) In TRITON all patients underwent percutaneous coronary intervention (PCI); in PLATO about 55% of patients had a PCI within the first 7 days after study drug administration. (3) In TRITON administration of study drug was delayed until after coronary angiography in all but the STEMI patients who presented within 12 hours of symptom onset; in PLATO the investigator was to give study drug immediately after randomization regardless of angiography having being done and prior to PCI. However, the investigator could delay randomization until after angiography at his or her discretion.

Relationship to Subsequent Percutaneous Coronary Intervention (PCI)
About 61% of PLATO patients had at least one PCI after study drug administration at some time during the study, virtually identical rates in both arms. I examined MACE rates in patients who did or did not have a subsequent PCI but did not find any discernible differences. However, about 43% of the patients had a PCI on the day of randomization and only 25% had a first or subsequent PCI after the day of randomization. Analyzing MACE rates by PCIs after day 1 produces some interesting results. I show the MACE rates by PCI anytime after day 1 in Figure 8, by PCI days 2 to 7 in Figure 9, and by PCI or death day 1 without a subsequent PCI with 30 days in Figure 10 .

Figure 8: Time to Site-Reported First MACE by PCI Anytime after Day 1

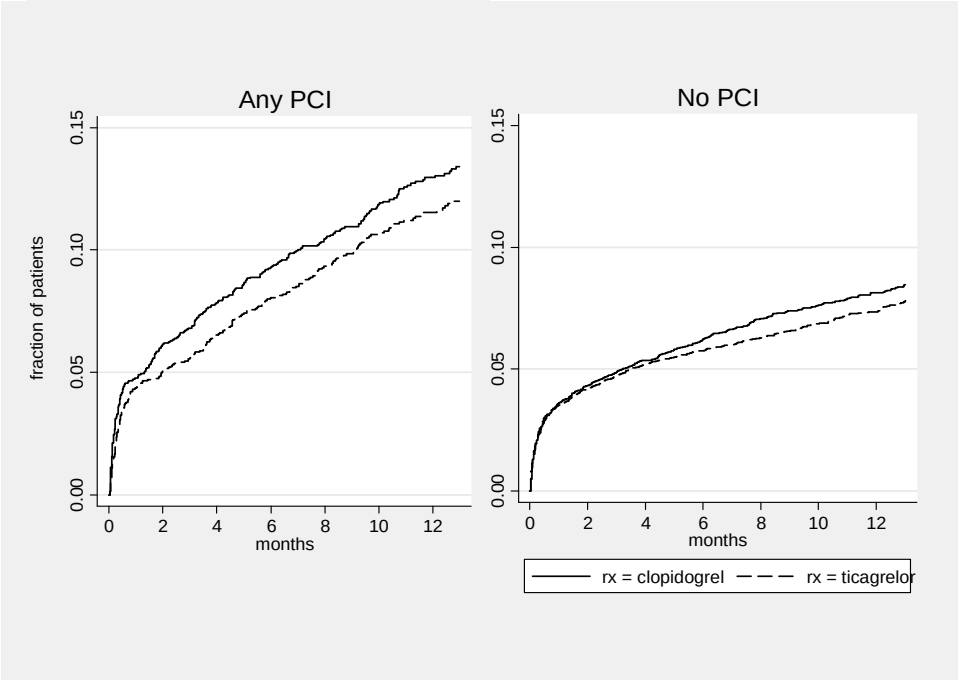


Figure 9: Time to Site-Reported First MACE by PCI Days 2 to 7

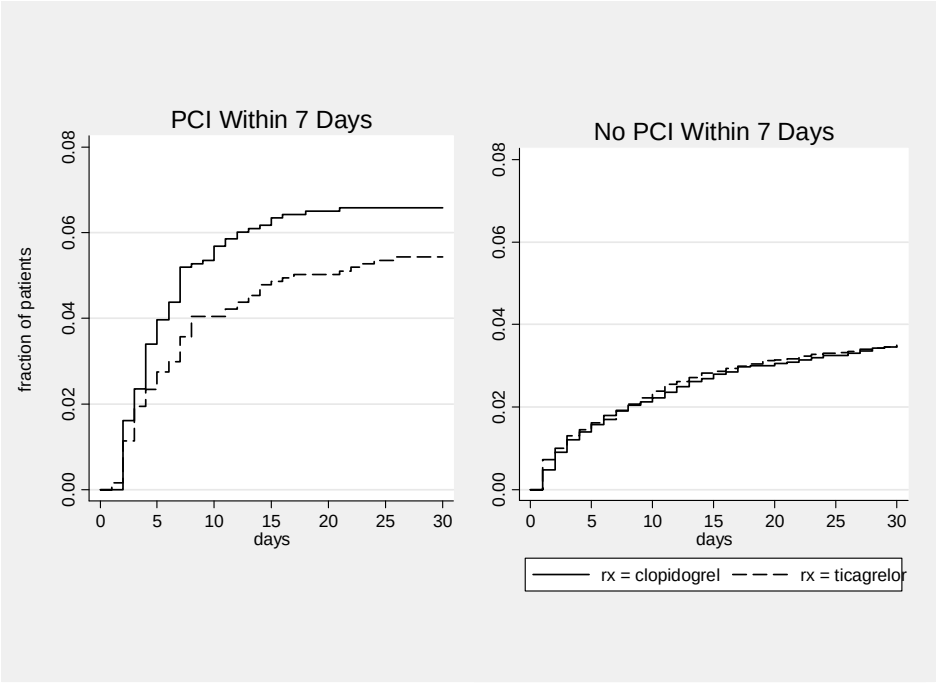
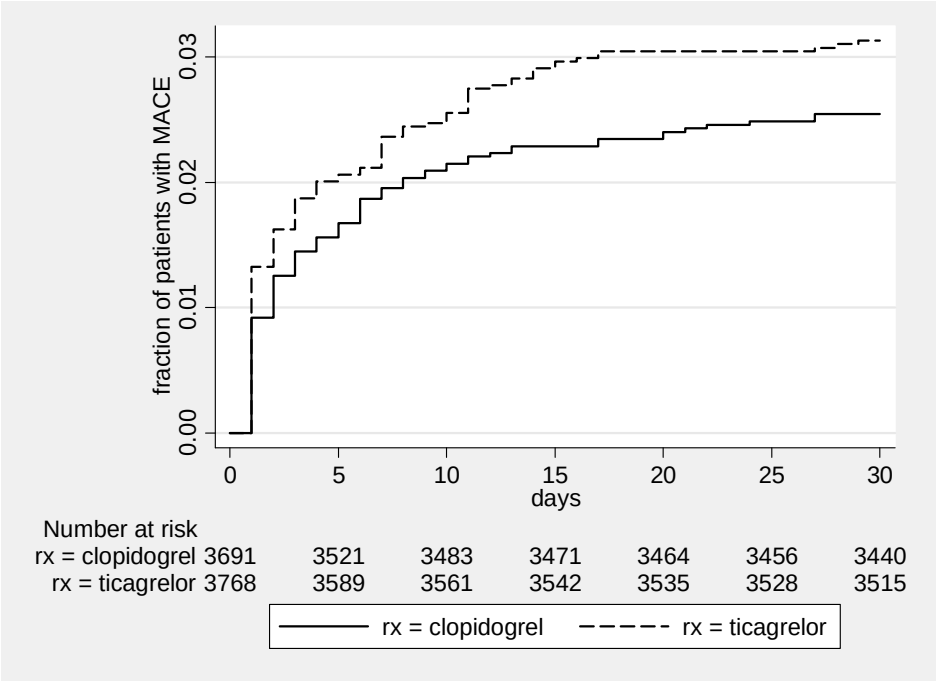


Figure 10: Time to Site-Reported First MACE in Patients with a PCI or Death Day 1 but No Subsequent PCI through Day 30



There appears to be no short term and limited long term benefit of ticagrelor in patients who did not have a subsequent PCI, while there is an apparent good benefit in patients who needed a subsequent PCI within 2 to 7 days of randomization. These findings alone might be interpreted

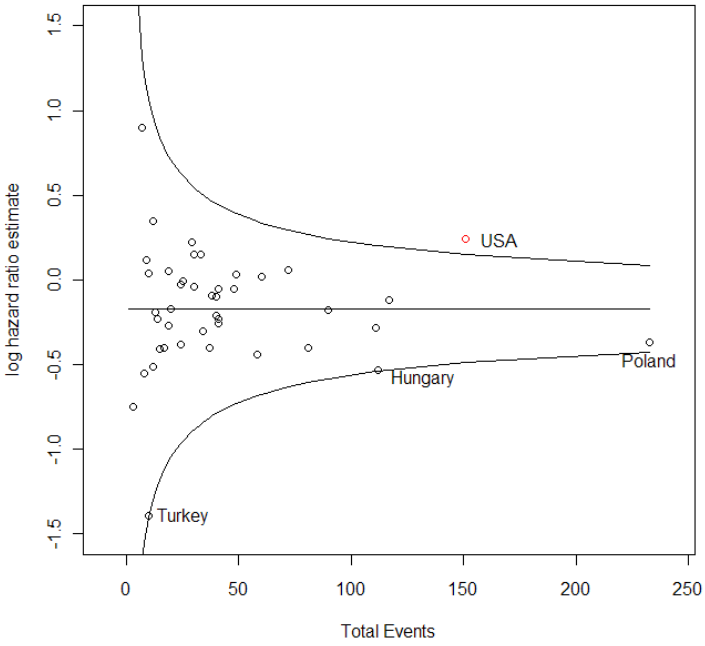
as that ticagrelor shows greater benefit in the sicker patients requiring PCI. Furthermore, the determination of the need for PCI is a post-randomization decision subject to biases—and PCI itself can be considered to be a CV endpoint. However, that ticagrelor may show a detrimental effect in patients with PCIs on day 1 suggests an alternative explanation: Ticagrelor may have a delayed onset of platelet inhibition compared to clopidogrel. Attempting to analyze timing of study drug administration is complicated by the usual problems of inaccuracies with dates and times in clinical trials, e.g., I count 725 cases for which the study drug was administered prior to randomization. It is also confounded by another factor: 48% of the ticagrelor patients were on clopidogrel or received clopidogrel within the first 24 hours and the timing of administration of the clopidogrel was not captured.

The measured pharmacokinetics (PK) and pharmacodynamics of ticagrelor do not provide a consistent explanation for a delayed onset. Per the FDA clinical pharmacology review, the median T_{max} for ticagrelor levels after oral administration is 2.65 hours. This number suggests that some patients could be at risk for delayed effect. Furthermore, ticagrelor is >99% bound to plasma protein and total (not free) ticagrelor levels were measured in most PK studies, representing another source of variation between patients. However, the clinical pharmacology review notes that "The rate of offset of pharmacodynamic effect (%IPA [inhibition of platelet aggregation]) of ticagrelor is faster than that in clopidogrel in CAD patients on aspirin. However, given the higher antiplatelet activity and longer half-life of ticagrelor and its active metabolite, the time to conduct surgery following stopping of ticagrelor and clopidogrel may not be much different (5 days)." The half-life of ticagrelor is about 8 hours so that its half-life does not explain the delayed offset. Because we do not understand the delayed offset I question whether we really understand the timing of onset as well.

United States (US) vs. Outside United States (OUS) Efficacy

Another issue regarding the efficacy of ticagrelor is the quandary of the unfavorable results in the US that are inconsistent with the results in most other countries represented in PLATO. The funnel plot from the FDA Statistical Review reproduced in Figure 11 depicts the inconsistency well.

Figure 11: Funnel Plot of Log Hazard Ratio by Events per Country (from FDA Statistical Review)



The US has worse results with ticagrelor for all efficacy measures, including MACE, MI, stroke, CV death, and all-cause mortality and is an outlier for all of them except stroke. Stroke rates are at least numerically higher with ticagrelor in all regions.

The sponsor has proposed one mechanism for explaining the disparate US vs. OUS results: aspirin dosage. Aspirin dosages in the US were split between 325 mg and 82 mg while OUS the vast majority of the dosing was 75 or 100 mg. The sponsor proposes that ticagrelor patients did worse with the high 325 mg dosage. Please see the FDA primary clinical efficacy and statistical reviews for exhaustive analyses of the aspirin dosage. I agree with those reviews' conclusions that, because of multiple problems with the analyses (aspirin dosage and region are highly correlated, the sponsor's analyses are sensitive to reclassification of small numbers of cases regarding loading vs. maintenance aspirin dosing and events in high dose aspirin OUS, biologic plausibility, etc.) aspirin dosing does not explain the disparate results.

Because I identified the issue of a delayed onset for ticagrelor effect after the primary reviewers had finished their reviews, we have not yet incorporated parameters relevant to delayed onset into any of our US vs. OUS analyses. These parameters include ones such as all clopidogrel use prior to PCI, timing of study drug administration relative to PCI, and early PCI vs. no early PCI. We will complete these analyses and forward them to advisory committee members when available or present them at the meeting. I do have the following quick observation: From prior ACS studies we have observed that there are practice differences between the US and Europe regarding antiplatelet drug use in ACS. Many US practitioners prefer to delay giving antiplatelet drugs until after angiography to determine whether the coronary anatomy is suitable for PCI or for coronary artery bypass surgery. European practitioners prefer to administer the antiplatelet drugs early so that platelet inhibition is maximal at the time of PCI. If US investigators delayed

study drug administration and if ticagrelor does have a delayed onset relative to clopidogrel, I would expect to see the results that PLATO has produced including the US-OUS disparity.

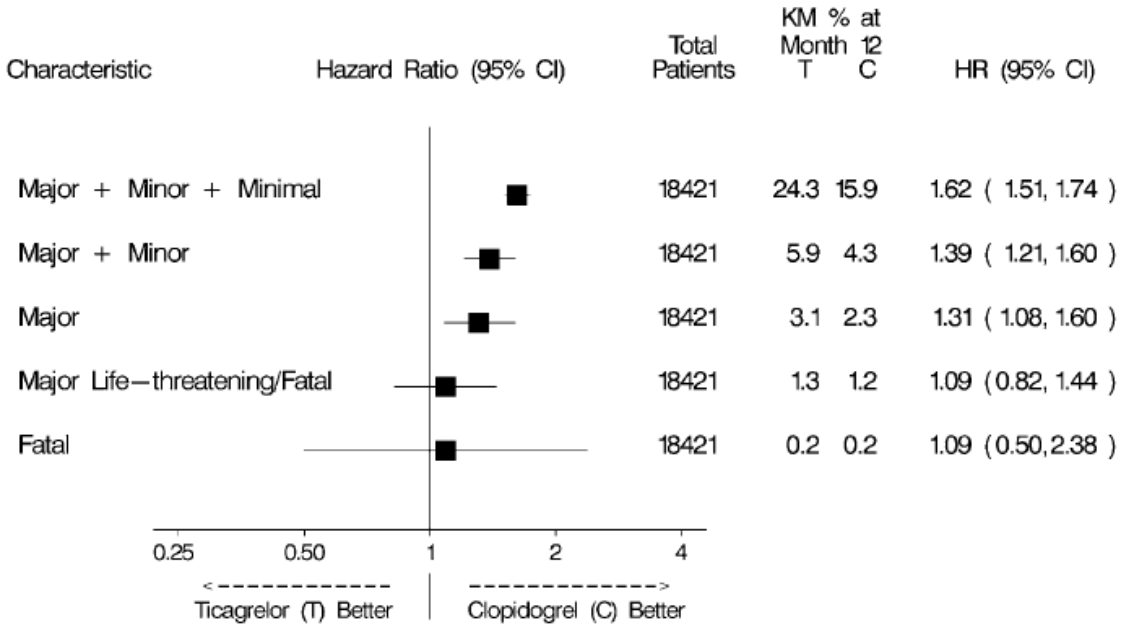
Long Term Benefit
The late divergence of the curves in Figure 5 and Figure 8 do suggest that ticagrelor may have a long term benefit and one that tracks differently than for the thienopyridines. Ticagrelor by *in vitro* testing does appear to produce greater platelet inhibition than clopidogrel at the dosages used in PLATO. The greater bleeding rates with ticagrelor in PLATO (see Safety below) confirm the greater platelet inhibition clinically. Hence greater platelet inhibition could explain the long term benefit. However, there are at least two other alternative or contributory mechanisms: (1) Ticagrelor is a moderate CYP3A inhibitor and increases the exposures of both simvastatin and atorvastatin, which account for the majority of the statin use in PLATO. PLATO did not capture statin dosages so we are unable to analyze them. We have not yet finished our analyses of lipid levels, which were captured. The one indication I have now that ticagrelor may have increased statin exposure is that rhabdomyolysis/myopathy AEs were greater with ticagrelor (8 vs. 2), although there was only one rhabdomyolysis SAE in each arm. (2) Ticagrelor blocks the uptake of adenosine into erythrocytes, potentially increasing local concentrations of endogenous adenosine and prolonging its effects. The sponsor has proposed this mechanism as a possible cause of the ventricular pauses seen with ticagrelor administration. Because adenosine also depresses ventricular automaticity and attenuates the cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals, this mechanism could also have a beneficial impact upon ventricular arrhythmias. I examine ventricular arrhythmia rates in Safety below.

Efficacy Evaluation Complexity
The previous sections should be convincing that efficacy evaluation in PLATO is extremely complex. I could argue that PLATO tried to do too much: *A priori* it attempted to evaluate three different conditions (i.e., STEMI, NSTEMI, and UA), two different management approaches (invasive and non-invasive), and two different pre-treatments (prior antiplatelet and no prior antiplatelet use). The complexity, e.g., 3 x 2 x 2 x 2 (study drug) = 24 different treatment cells was then increased 4 to 8-fold by the US vs. OUS discrepancies, with the issues of aspirin dosage and study drug timing, and the short term vs. long term effects. The evaluation is complicated further at least qualitatively by the issues of statin exposure and completeness of follow-up. As of the date of this review we have not successfully identified clear patterns among this complexity.

Safety
The major approvability issues for ticagrelor appear to be efficacy related. However, there are some common and some unique safety issues that warrant discussion.

Bleeding
The safety issue common to platelet inhibitors is bleeding. Ticagrelor did produce more bleeding than clopidogrel as shown by the sponsor's statistics in Figure 12.

Figure 12: Sponsor's Hazard Ratio Estimates of Non-procedural Bleeds



CI Confidence interval; HR Hazard ratio; KM% Kaplan-Meier estimate of % of patients with an event at 12 months.

While major bleeds and less serious bleeds were substantially increased with ticagrelor, life-threatening and fatal bleeds were not significantly increased. The FDA primary clinical safety reviewer commented that most patients with major bleeds had major CABG-related bleeds (~ 67%) and most CABG bleeds were major (~80%). The risk of CABG-bleeding was increased in ticagrelor patients who did not wait until day 5 after stopping treatment to have CABG. Besides confirming that the offset for ticagrelor is substantially longer than the pharmacokinetics predict, these statistics suggest that delaying CABG and other major surgery for five days or more after stopping ticagrelor is the most important management principle for dealing with the increased bleeding risk of ticagrelor.

Strokes, Intracerebral Hemorrhages, and Embolism

Strokes were included in the sponsor's primary efficacy endpoint but, because rates of stroke were higher with ticagrelor, they are also safety issues. Site-reported stroke rates were higher, but not significantly higher, with ticagrelor (1.5% vs. 1.2%). One possibility is that higher platelet inhibition could convert a small, subclinical ischemic stroke into a clinically apparent hemorrhagic one. The sponsor reported that with ticagrelor more patients had non-procedural intracranial hemorrhage (ICH, 26 vs. 14) and fatal ICH (11 vs. 2). The FDA primary clinical safety reviewer has raised the possibility of another mechanism: Pulmonary embolism and embolic events in general were slightly more frequent with ticagrelor. She also observes that strokes and pulmonary emboli were very slightly more frequent with prasugrel than clopidogrel in the TRITON trial. She hypothesizes that higher platelet inhibition might lead to clots that are more friable and likely to embolize. While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) mitigate any concerns that I have about strokes.

Dyspnea
Dyspnea events in PLATO were reported more frequently in ticagrelor patients than in clopidogrel patients, about 14% vs. 8% by the sponsor's statistics. Dyspnea leading to discontinuation was uncommon but more frequent with ticagrelor (0.9% vs. 0.1%) as were dyspnea serious adverse events (SAEs, 0.7% vs. 0.4%). About half of the dyspnea AEs resolved within one week while a third were continuing at study termination. PLATO included a pulmonary function substudy that did not reveal any differences between treatment groups, although the FDA primary clinical safety reviewer questions that it was designed, conducted and analyzed in such ways that might have obscured differences if they existed. The sponsor hypothesizes that dyspnea may be another AE, like ventricular pauses, potentially related to adenosine. The sponsor proposes that if a patient reports dyspnea, physicians should evaluate the patient for underlying causes of dyspnea. If no cause is identified, patients should continue on ticagrelor treatment unless they cannot tolerate the dyspnea. I agree that this proposal is reasonable.

Ventricular Pauses and Ventricular Arrhythmias
Phase 2 studies suggested ticagrelor increased slightly the rate of sinus pauses. Because of this observation PLATO included a Holter monitoring substudy. The Holter monitoring confirmed that more ticagrelor patients had ventricular pauses ≥3 seconds and ≥5 seconds compared to clopidogrel; this difference was statistically significant for ventricular pauses ≥3 seconds at visit 1 only (relative risk 1.7, 95% confidence limits 1.15 to 2.64).

Reported AEs also do not suggest a clinical problem from ventricular pauses or bradycardia. Sinus pause AEs were uncommon and only slightly more frequent with ticagrelor (20 vs. 17). Bradycardia was similarly slightly more frequent (4.3% vs. 4.0%). Because of the slightly higher rate of stroke with ticagrelor, I recoded all atrial fibrillation events. By my recoding patients with atrial fibrillation events were virtually perfectly balanced between the two arms (both 5.2%). (My rates of atrial fibrillation are higher than those coded by the sponsor because I included reports of "absolute arrhythmia" and "arrhythmia", European terms for atrial fibrillation, as well as the reports of atrial fibrillation.)

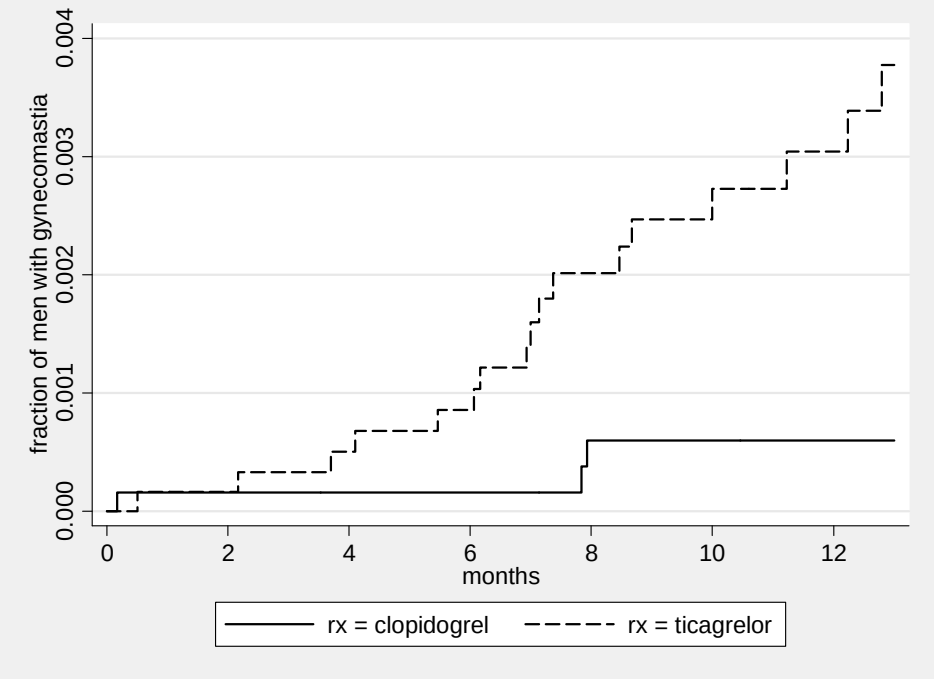
I also recoded ventricular tachycardia and ventricular fibrillation events. Both types of serious ventricular arrhythmias appear to be less frequent with ticagrelor, combined about 1.5% of ticagrelor patients and 1.8% of clopidogrel patients. Only about 13% of these arrhythmias were reported in patients who also suffered an MI, so the slightly lower rate of MIs with ticagrelor may not explain the difference. The lower rate of ventricular arrhythmias may be another adenosine-related effect of ticagrelor and one that could contribute to the long term benefit.

Sex Hormonal Adverse Effects
Ticagrelor has signals of sex hormonal activity from its pre-clinical animal studies. The short summary from the FDA pharmacology and toxicology review is the following: There were reported drug-related effects on the reproductive organs of both sexes. In male mice, very high doses caused seminiferous epithelial degeneration of the testes. Female mice had an absence of corpora lutea at very high doses. In rats, endocrine effects were manifested as dose-related decreases in regular estrus cycles at relatively low doses ≥10 mg/kg. The relatively non-specific

finding of irregular estrus cycles became more important in light of the carcinogenicity study where female rats showed statistically significant incidences of uterine adenocarcinoma and uterine squamous cell carcinoma.

Because of these findings we scrutinized all adverse effects that could be related to sex hormonal activity, including malignancies of sexual organs. The one signal we found was regarding gynecomastia. For more details see the FDA primary clinical safety review, but the K-M plot of time to first gynecomastia is striking, as shown in Figure 13.

Figure 13: Time to First Gynecomastia in Men



Note that the absolute rate of gynecomastia is low, about 3 per 1,000 men at one year. The sponsor has commented that the use of other drugs associated with gynecomastia, such as spironolactone, confounds some of these cases. However, this is still a randomized comparison and, that ticagrelor may potentiate gynecomastia effects of other drugs, is not reassuring.

On the other hand, in this relatively short study we did not find any evidence for effects upon rates of sex organ malignancies. One testicular cancer was reported in a ticagrelor patient while prostate cancer was evenly balanced (13 vs. 12). Breast cancer events favored ticagrelor (4 vs. 10) while ovarian cancer was relatively balanced (2 vs. 1) and no uterine or cervical cancer events were reported. Given an observed favorable overall impact of ticagrelor upon CV events and total mortality, a potential increased risk of some sex hormone-related adverse effects is acceptable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

THOMAS A MARCINIAK
07/16/2010