Testimony before the FDA Cardiovascular and Renal Drugs Advisory Committee Regarding KENGREAL (Cangrelor) Injection: Insufficient Evidence of Benefit

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Michael Carome, M.D.
Public Citizen's Health Research Group

(I have no financial conflicts of interest)

Major Coments

- **Public Citizen strongly opposes approval of cangrelor for the newly narrowed PCI indication because many subjects in the control group for the CHAMPION PHOENIX trial received substandard antiplatelet management, and as a result, one cannot conclude that the drug is superior, or even non-inferior, to clopidogrel appropriately administered.**

- **We also remain disturbed by the apparent ethical lapses in the conduct of the CHAMPION trials.**

CHAMPION PCI and CHAMPION PLATFORM Trials

CHAMPION PCI Primary Endpoint Data (mITT)

Cangrelor N=3889	Clopidogrel N=3865	Odds Ratio (95% CI)	P value
290 (7.5%)	276 (7.1%)	1.05 (0.88-1.24)	0.59

Harrington RA, et al. NEJM. 2009;361(24):2318-2329

CHAMPION PLATFORM Primary Endpoint Data (mITT)

Cangrelor N=2654	Clopidogrel N=2641	Odds Ratio (95% CI)	P value
185 (7.0%)	210 (8.0%)	0.87 (0.71-1.07)	0.17

Bhatt DL, et al. NEJM. 2009;361(24):2330-2341

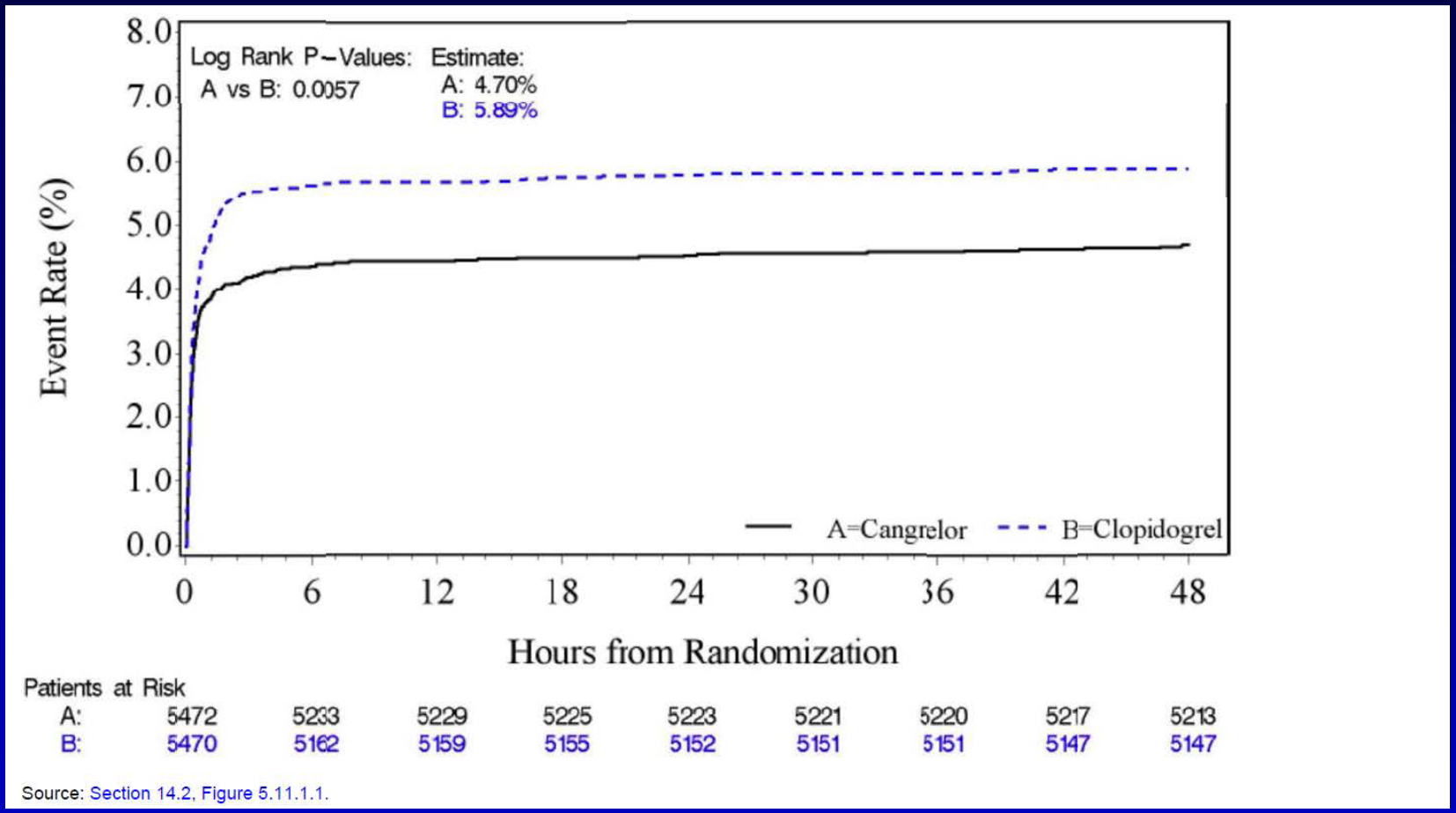
The CHAMPION PHOENIX Trial: Subject Type at Enrollment

- Adults undergoing percutaneous PCI for:
  - Stable angina (58%)
  - Non-ST-segment elevation acute coronary syndrome (26%)
  - ST-segment elevation myocardial infarction (16%).

The CHAMPION PHOENIX Trial: Seriously Flawed

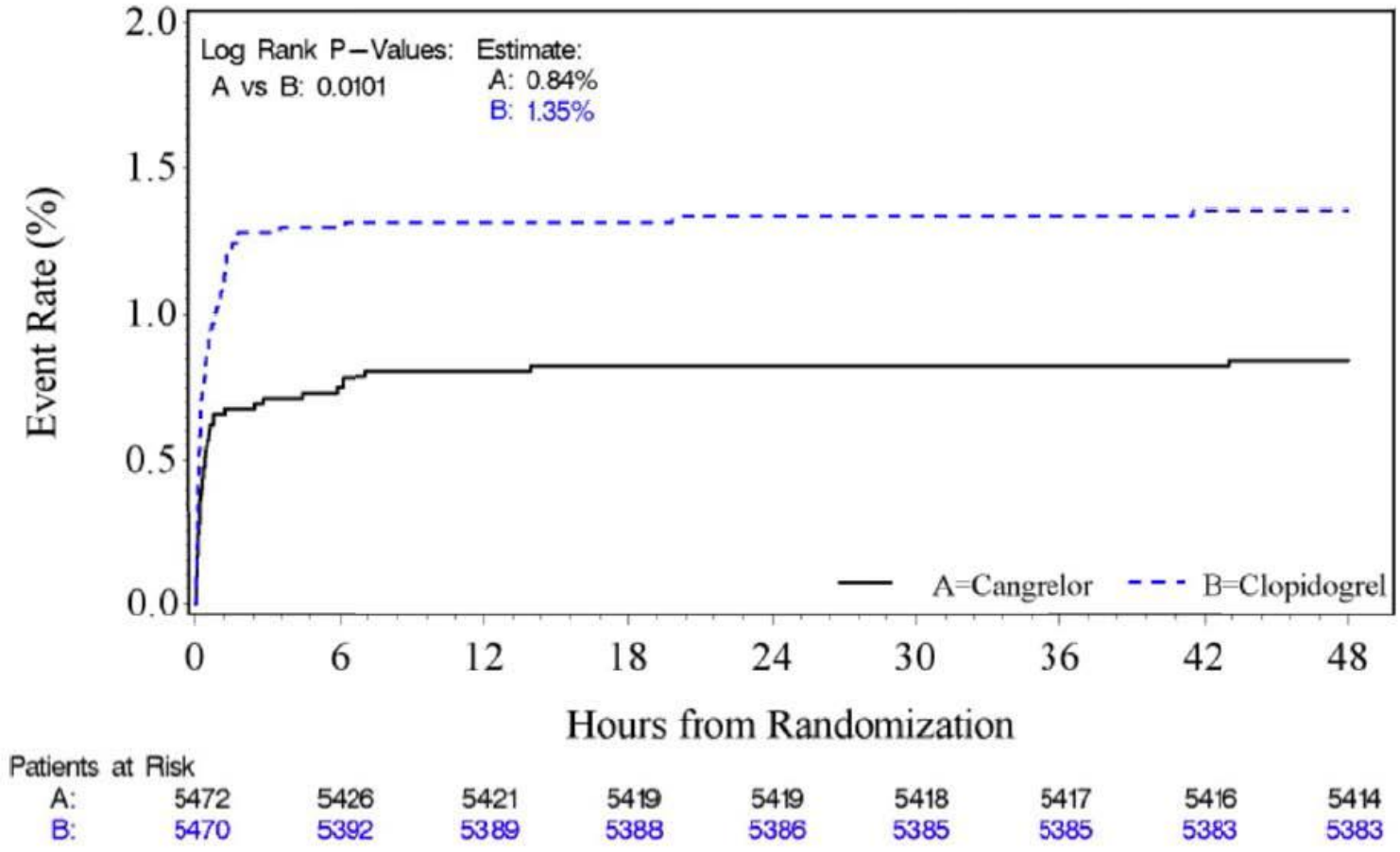
- Deficiencies in the control group intervention included:
  - Inappropriate timing of clopidogrel administration
  - Inappropriate dosing of clopidogrel
  - Protocol-specified prohibition against other antiplatelet drugs known to be superior to clopidogrel in patients with acute coronary syndrome who are undergoing PCI (prasugrel and ticagrelor)
  - protocol-specified restriction on the use of glycoprotein IIb/IIIa inhibitors use to bailout only

CHAMPION PHOENIX Kaplan-Meier Plot to First Occurrence of Primary Endpoint (mITT)



Source: Section 14.2, Figure 5.11.1.1.

CHAMPION PHOENIX Kaplan-Meier Plot to First Occurrence of Stent Thrombosis(mITT)



Source: Section 14.2, Figure 5.51.1.1.

The CHAMPION PHOENIX Trial: Timing of Clopidogrel Intervention in Control Subjects

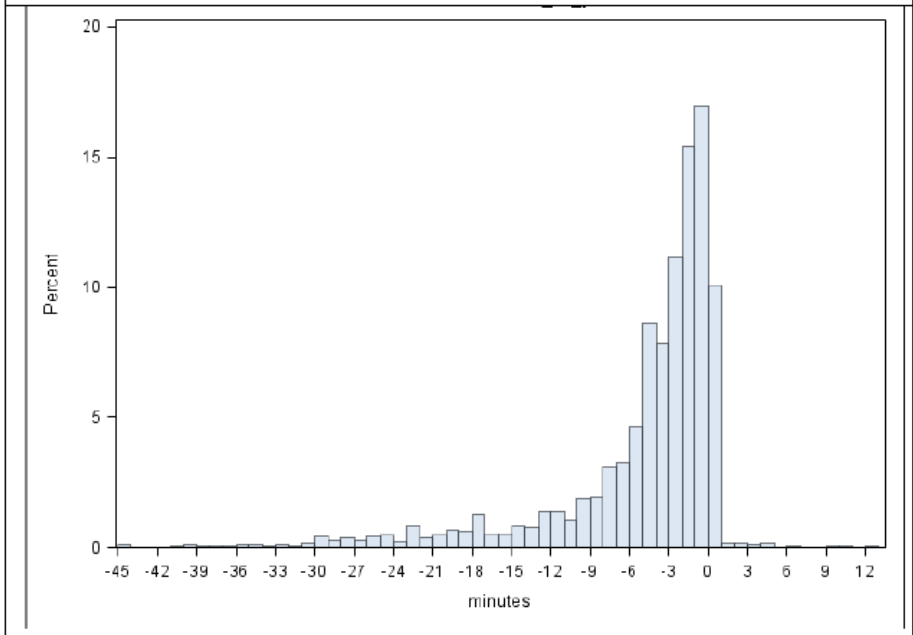
- **FDA Medical Team Leader:**

  "For about 32% of the patients the first oral study drug was administered after the completion of the PCI." [Emphasis added]

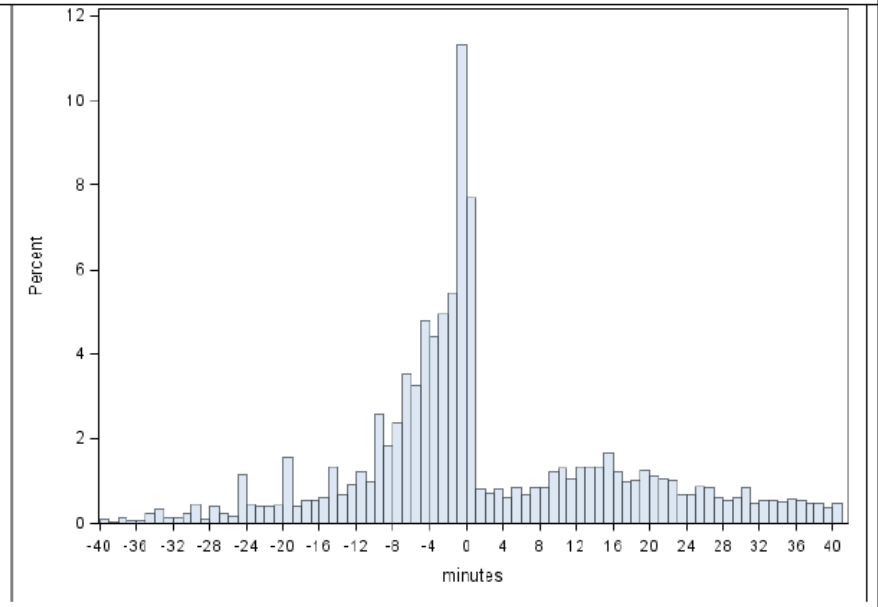
  "COMMENT: Given the PLATFORM results, I find it very disturbing that PHOENIX sites delayed clopidogrel administration until after PCI in a substantial number of patients."

CHAMPION PHOENIX Trial: Start to Active Drug Relative to PCI, All Subjects

A. Timing of cangrelor infusion start relative to PCI



B. Timing of clopidogrel dose relative to PCI

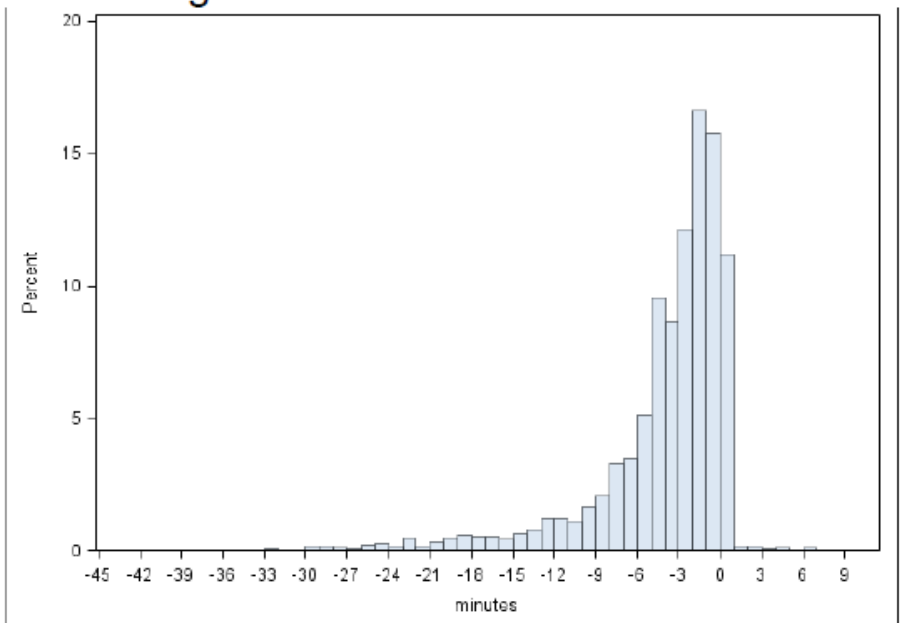


PCI is at time 0. A negative number means subject received drug before PCI.
Reviewer's analysis: time\time active drug pci, Dataset isd osd dem. X-axis truncated.

CHAMPION PHOENIX Trial: Start to Active Drug Relative to PCI, Stable Angina Subjects

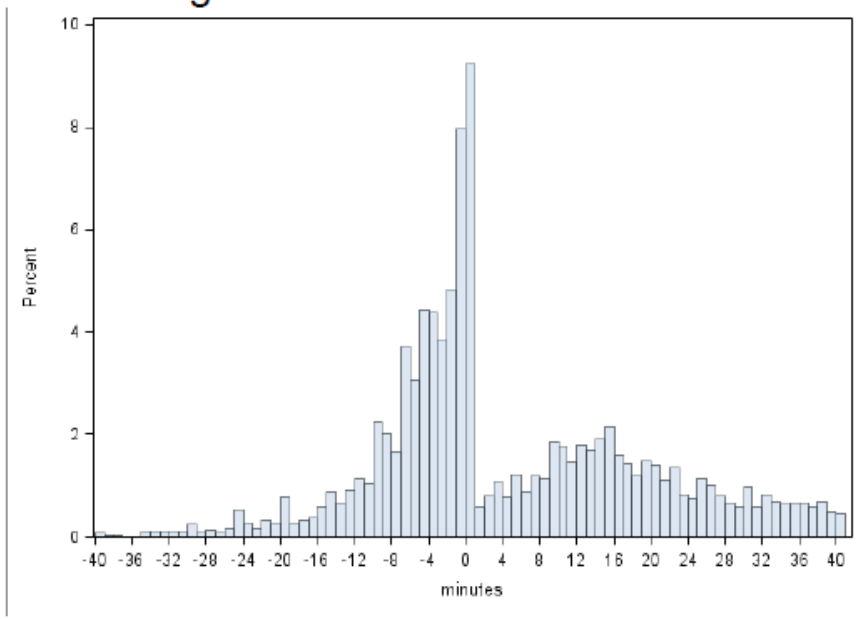
A. Timing of cangrelor infusion start relative to PCI

Stable Angina

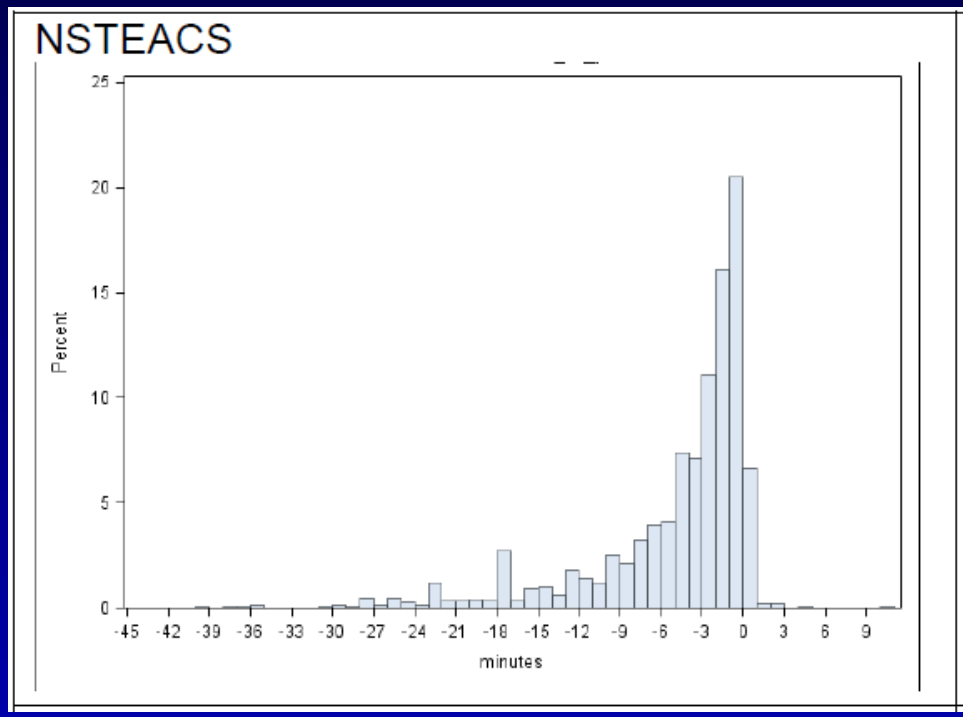


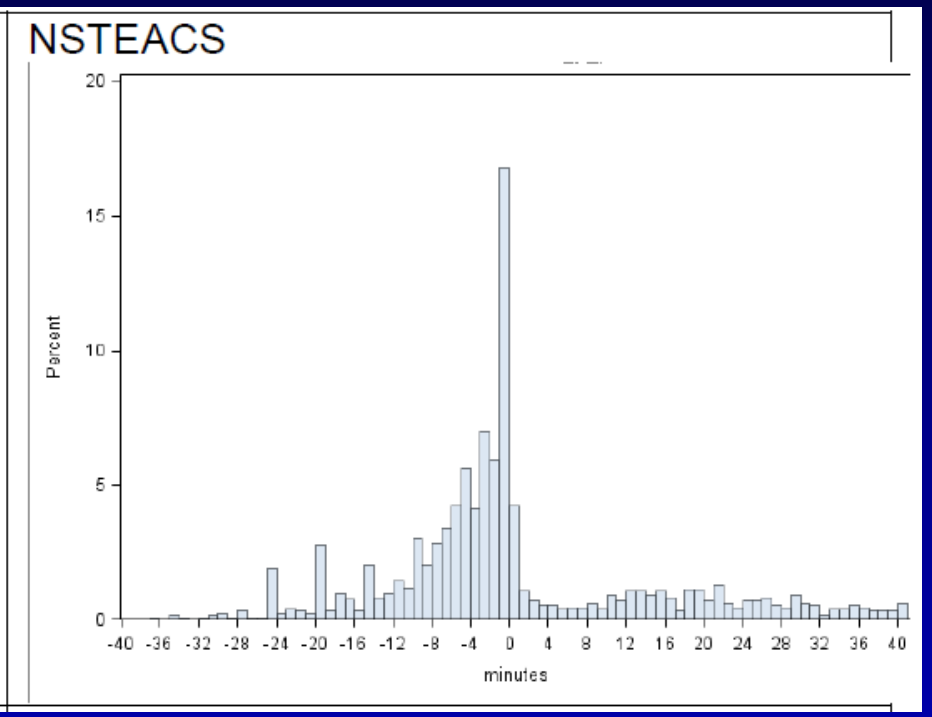
B. Timing of clopidogrel dose relative to PCI

Stable Angina

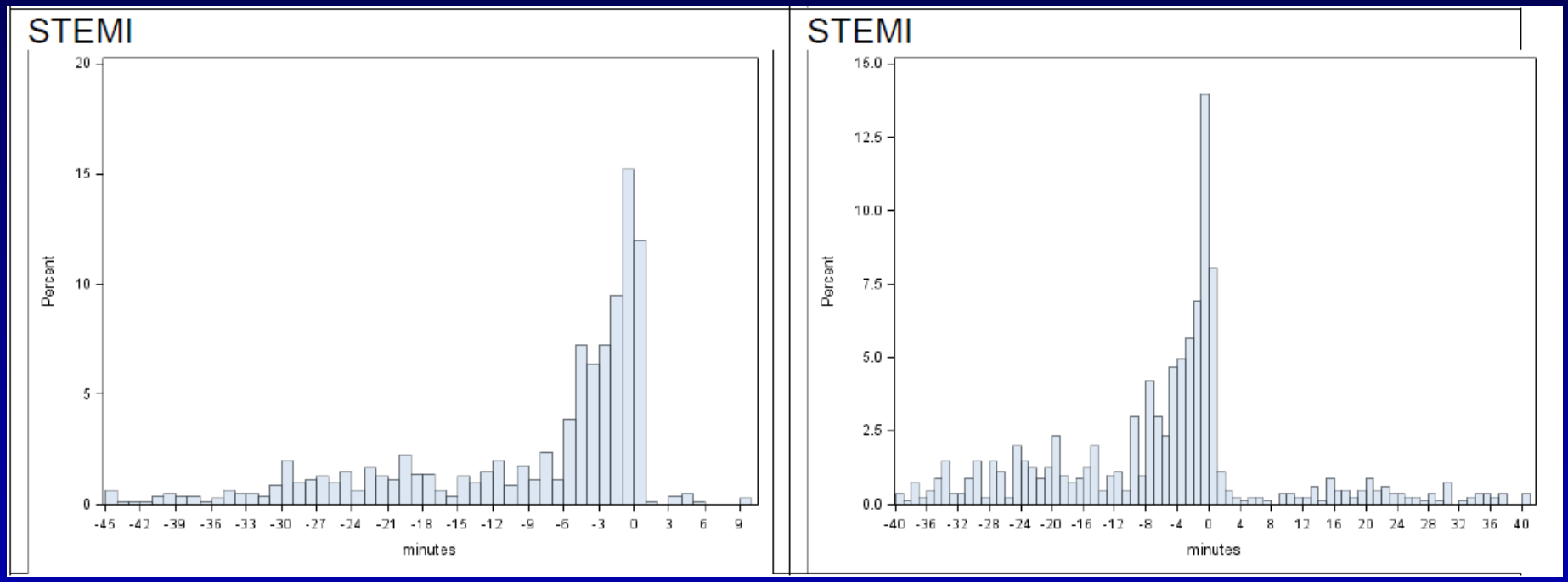


CHAMPION PHOENIX Trial: Start to Active Drug Relative to PCI, NSTEACS Subjects





CHAMPION PHOENIX Trial: Start to Active Drug Relative to PCI, All Subjects



The CHAMPION PHOENIX Trial: Dosing of Clopidogrel

- **FDA clinical reviewers:**

  "In the SA population a substantial number of subjects received clopidogrel after the procedure compared to the NSTEACS and STEMI populations, respectively (Figure 13). While the guidelines (page 105) for P2Y12 inhibitors (clopidogrel, ticagrelor, and prasugrel) are a Class I, Level A for PCI/stent they do not specify the precise timing of these agents relative to the start of PCI. However, practice patterns generally provide for administration before start of PCI. The primary efficacy endpoint favoring cangrelor was driven by the SA population. The data above raises speculation that the delay in clopidogrel in the SA population might have contributed to the positive results of the trial."

The CHAMPION PHOENIX Trial: Dosing of Clopidogrel

- **FDA Statistical Reviewer:**

  "[T]here was an imbalance on the actual loading dose between two treatment groups in the study. … If the intended loading dose in the primary analysis was replaced by the actual loading dose in the model, the treatment effect would not be statistically significant anymore. The p-value increased from 0.005 to 0.088. Although the treatment effect of cangrelor was still trending in the right direction when compared with clopidogrel patients who had 600 mg loading dose, the results seemed to be driven by the comparison with the patients given 300 mg clopidogrel loading dose."

FDA Attempt to Discount Notion that Giving Clopidogrel Before PCI is Better

- FDA was fully aware of the PHOENIX trial design and allowed it to proceed and, therefore, has an interest in defending that the trial design was ethical.
- Some contemporaneous guidelines at the time the trial was conducted recommended administration of P2Y12 therapy as soon as possible in patients with non-ST-elevation ACS.
- The ACCOAST trial findings cannot be extrapolated to the timing of clopidogrel dosing because prasugrel is a faster, better platelet inhibitor than clopidogrel.

Comments Made by Dr. Deepak Bhatt Prior to the Start of the CHAMPION PHOENIX Trial

"… there were significant reductions in death and stent thrombosis in the cangrelor group vs the placebo group in CHAMPION-PLATFORM that I believe are real. This strongly supports the strategy of earlier antiplatelet therapy. It confirms that such therapy should be given before the procedure rather than after."

"But for me, the CHAMPION-PLATFORM trial reinforces that we need to get the antiplatelet therapy on board as soon as possible."

Hughes S. CHAMPION: Negative trials but some positive angles for cangrelor? *Heartwire from Medscape*. November 15, 2009.

Comments Made by Dr. Robert Harrington Prior to the Start of the CHAMPION PHOENIX Trial

"The second important point that I'd like to highlight on this slide is that this is an active-control trial. The clopidogrel, as you've heard, has been given a 1A recommendation, and so we wanted to compare ticagrelor with the standard. And if we were going to compare it with the standard, the steering committee felt very strongly that we needed to give the standard the best chance possible…

"We designed the trial to incorporate all of that, again, to give the comparator a fair test."

Transcript of the July 28, 2010, meeting of the Cardiovascular and Renal Drugs Advisory Committee.

Protocol-Specified Restriction on the Use of Glycoprotein IIb/IIIa Inhibitors

The FDA reviewers for this meeting noted:

- **The data from the antecedent CHAMPION trials suggest that common practice would deploy GPI agents at a much higher incidence than that seen in PHOENIX, …**

- **The concomitant use of cangrelor with a GP IIb/IIIa agent has not been tested, but combination therapy using clopidogrel and a GP IIb/IIIa agent showed a benefit outweighing risk with limited population studies as a guideline for American practice. Based on previous CHAMPION trials, it appears that if patients who might have required GPI therapy were enrolled in PHOENIX, the rate of use probably would have been much higher and the outcome of the trial might have been different.**

NEJM Editorial on the CHAMPION PHOENIX Trial

"Where does cangrelor fit in the armamentarium of dual antiplatelet therapy? Unfortunately, the study by Bhatt et al. does not answer this question definitively. In the patients given cangrelor, a maximal antiplatelet effect was operative before and during PCI; this was not true in the case of the patients treated with clopidogrel. Approximately one fourth of the patients who were randomly assigned to clopidogrel received a 300-mg loading dose, which is inferior to a dose of 600 mg in achieving platelet inhibition and preventing periprocedural ischemic events. Furthermore, 37% of the patients in the clopidogrel group received the drug during or after PCI; as a result, the antiplatelet effects of clopidogrel were suboptimal at the time of PCI…"

NEJM Editorial on the CHAMPION PHOENIX Trial (cont'd)

"…Finally, in many centers, patients with an acute coronary syndrome (which was the diagnosis at presentation in 44% of the patients in this study) receive ticagrelor or prasugrel, since these drugs are superior to clopidogrel at reducing PCI-related complications. Studies comparing cangrelor with these agents are lacking."

Lange and Hillis, NEJM, 2013

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Prior FDA Medical Team Leader's Overall Assessment of the CHAMPION Trials

"My interpretation of the CHAMPION trials is that they demonstrated that a cangrelor regimen including a clopidogrel 600 mg loading dose is slightly more efficacious than a bad clopidogrel regimen with delayed clopidogrel loading. The major limitation of any perceived greater efficacy is that clopidogrel was loaded badly ranging from questionably (after angiography) in [CHAMPION] PCI to horribly (after PCI) in [CHAMPION] PLATFORM. The CHAMPION trials provide evidence that earlier administration of clopidogrel is better by both the cross-trial comparisons and by logistic regressions of the PHOENIX data. If clopidogrel had been administered consistently earlier in the CHAMPION trials it is possible that clopidogrel would be shown superior to cangrelor."

Apparent Ethical Lapses in the Design and Conduct of the CHAMPION Trials

- Many subjects randomized to the control groups received substandard antiplatelet therapy, particularly with respect to timing of clopidogrel, given existing published clinical guidelines and usual clinical practice at the participating hospitals. As a result, risks to control subjects were not minimized.

Apparent Ethical Lapses in the Design and Conduct of the CHAMPION Trials (cont'd)

- It appears that the at least some, and perhaps many, of the consent forms used to enroll subjects in the CHAMPTION PHOENIX trial failed to adequately describe the nature and risks posed by the control group antiplatelet intervention relative to guideline-recommended care provided to subjects undergoing PCI, and alternative courses of treatment that may have been advantageous to the subjects.

Conclusion

- **The Medicines Company obviously is desperate to obtain FDA approval for cangrelor for any indication, knowing that once approved, the drug will no doubt be used extensively off-label. However, because the development plan for cangrelor was poorly conceived and implemented, we have no idea where cangrelor fits in the armamentarium of antiplatelet therapies for the range of patients undergoing PCI or whether it as safe and effective as existing antiplatelet therapies, including prasugrel, ticagrelor, and GP IIb/IIIa inhibitors.**

Conclusion (cont'd)

- **Approving the drug now given the great uncertainty of its benefit-risk profile relative to other products on the market would do a great disservice to public health.**

- **Therefore, Public Citizen urges the advisory committee to recommend that the FDA not approve the NDA for cangrelor for the proposed narrowed PCI indication.**