

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

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**(We have no financial conflicts of interest)**

# Major Comments

- We strongly oppose approval of cangrelor for the 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 oppose approval of cangrelor for the bridge-to-surgery indication because the single, small phase II trial lacked sufficient clinical data and failed to provide any efficacy data regarding a clinically significant outcome.
- We are disturbed by the ethical lapses in the conduct of the CHAMPION pivotal clinical trials.

# CHAMPION PCI and CHAMPION PLATFORM Trials

## CHAMPION PCI Primary Endpoint Data (mITT)

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

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

## CHAMPION PLATFORM Primary Endpoint Data (mITT)

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

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

# The CHAMPION PHOENIX Trial: Subject Type at Enrollment

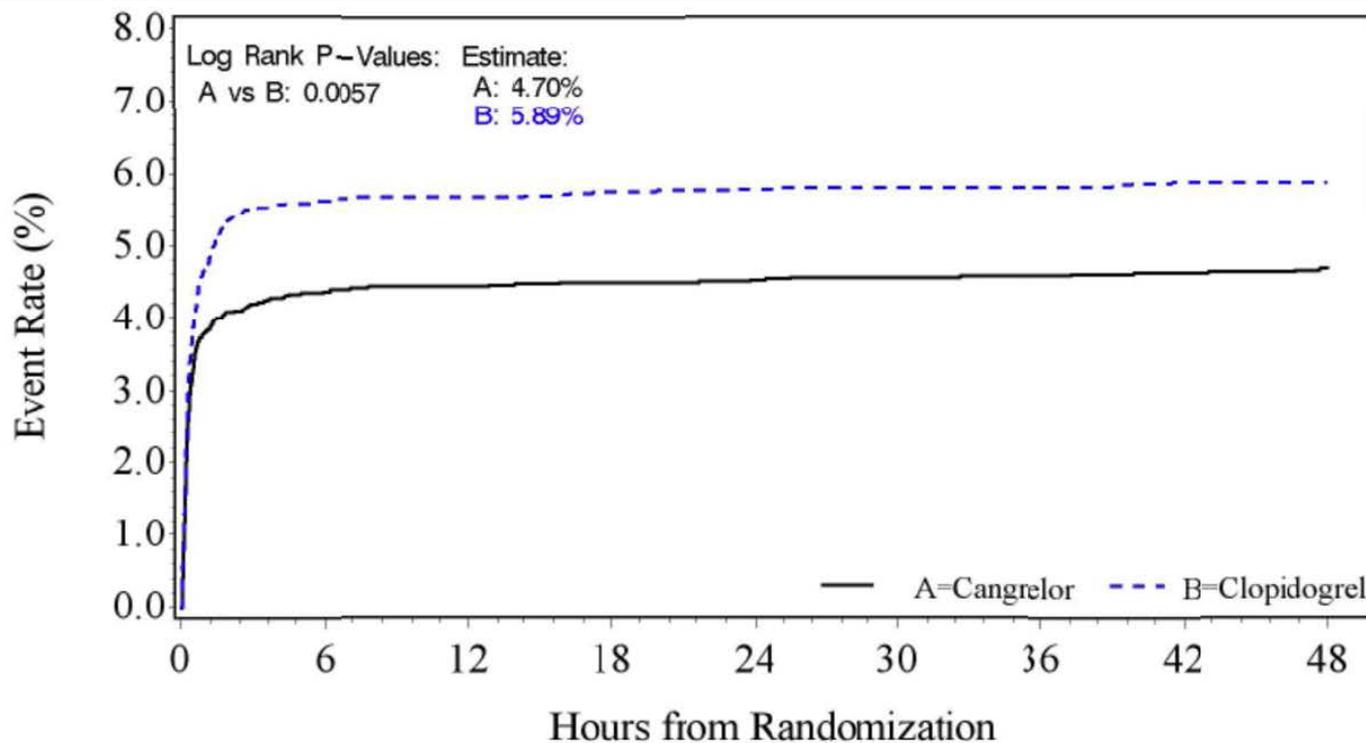
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- **Adults undergoing percutaneous PCI for:**
  - **Stable angina (56%)**
  - **Non-ST-segment elevation acute coronary syndrome (25%)**
  - **ST-segment elevation myocardial infarction (19%).**

# **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)**
- **Imbalance in the loading dose of clopidogrel between the two study groups.**

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

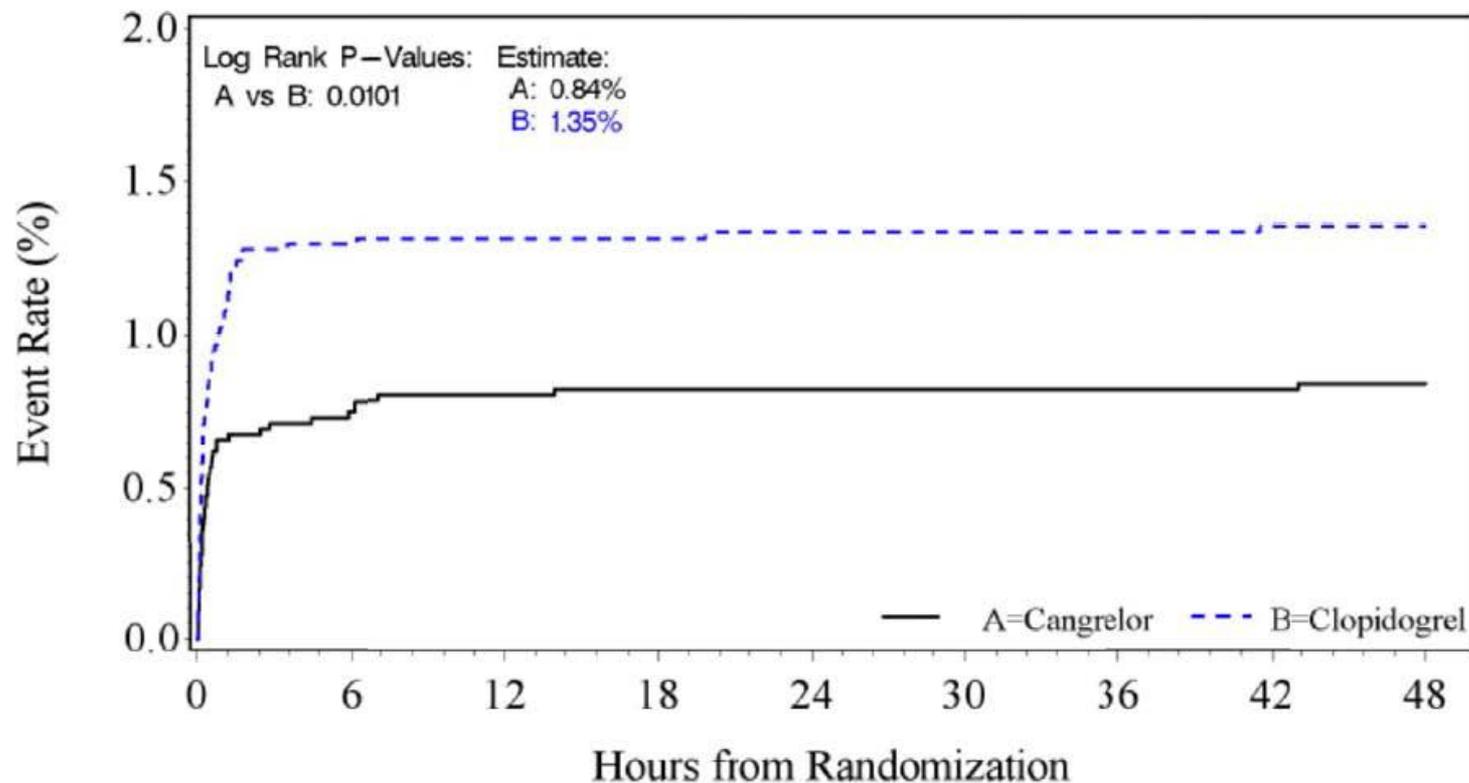


Patients at Risk

|    |      |      |      |      |      |      |      |      |      |
|----|------|------|------|------|------|------|------|------|------|
| A: | 5472 | 5233 | 5229 | 5225 | 5223 | 5221 | 5220 | 5217 | 5213 |
| B: | 5470 | 5162 | 5159 | 5155 | 5152 | 5151 | 5151 | 5147 | 5147 |

Source: Section 14.2, Figure 5.11.1.1.

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



Patients at Risk

|    |      |      |      |      |      |      |      |      |      |
|----|------|------|------|------|------|------|------|------|------|
| A: | 5472 | 5426 | 5421 | 5419 | 5419 | 5418 | 5417 | 5416 | 5414 |
| B: | 5470 | 5392 | 5389 | 5388 | 5386 | 5385 | 5385 | 5383 | 5383 |

Source: Section 14.2, Figure 5.51.1.1.

# The CHAMPION PHOENIX Trial Efficacy Data

## FDA Clinical Reviewers Observations

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- “The results favoring cangrelor over clopidogrel were driven by ST (OR 0.62, 95%CI [0.43, 0.89],  $p=0.0098$ ) and MI (OR 0.80, 95%CI [0.67, 0.97],  $p=0.0212$ )...”
- “The ST component of the primary composite endpoint was driven by IPST (OR 0.64, 95%CI [0.42, 0.99],  $p=0.0421$ )...”
- “The MI component of the composite primary endpoint was driven by UDMI-type 4a (OR 0.80, 95%CI [0.66, 0.97],  $p=0.0258$ ). There were no other significant differences between cangrelor and clopidogrel for other MI definitions (i.e. QWMI, types 1, 2, 3, 4b, and 5).”

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

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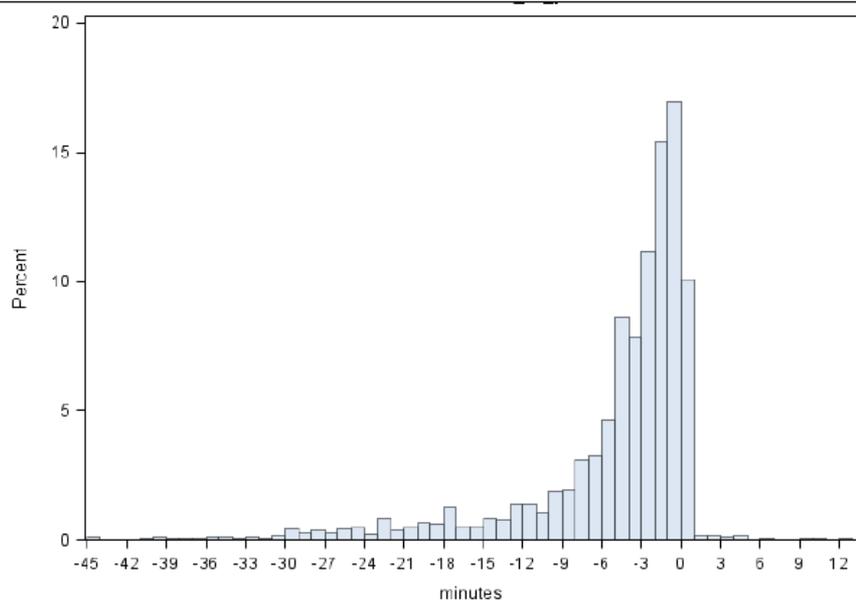
- FDA Medical Team Leader:

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

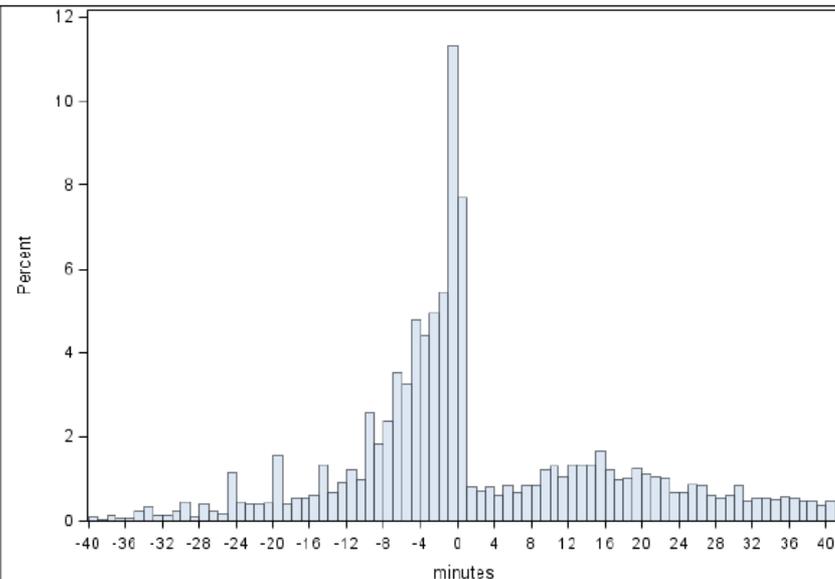
*“COMMENT: Given the PLATFORM results, I find it very disturbing that PHOENIX sites delayed clopidogrel administration until after PCI in a substantial number of patients.”*

# 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

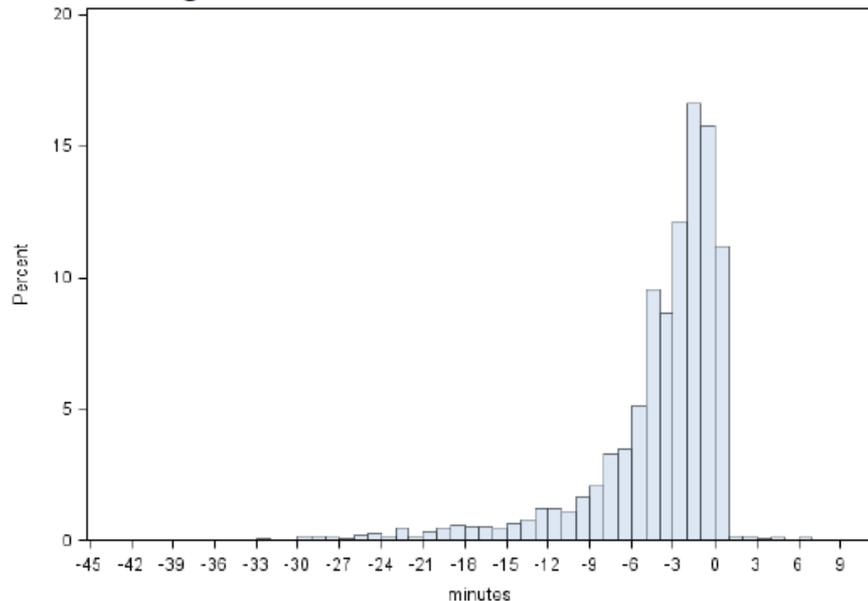


PCI is at time 0. A negative number means subject received drug before PCI.  
Reviewer's analysis: time\time active drug pci, Dataset isd osd dem. X-axis truncated.

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

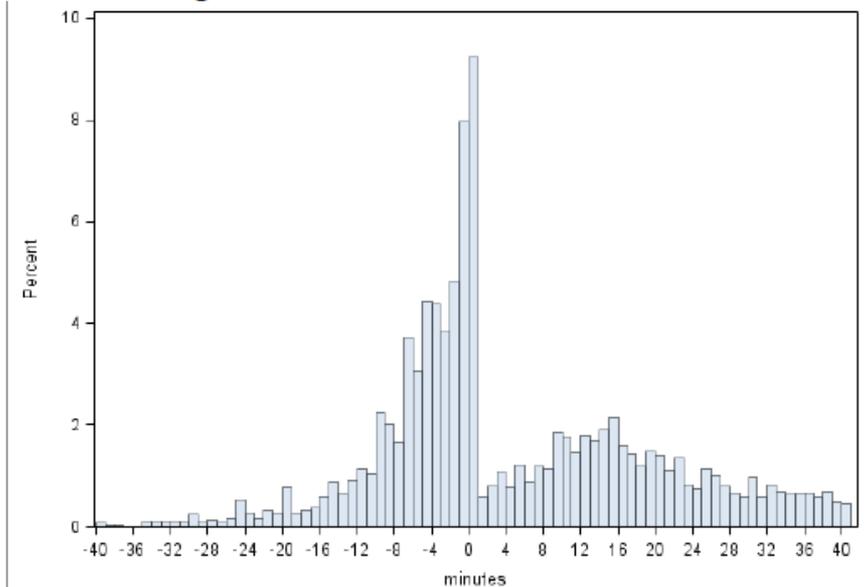
A. Timing of cangrelor infusion start relative to PCI

Stable Angina



B. Timing of clopidogrel dose relative to PCI

Stable Angina



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

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

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# 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.”**

# **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)**

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**“...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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# **The CHAMPION PHOENIX Trial: FDA Medical Team Leader's Conclusions**

**“I conclude that the CHAMPION trials did not show superiority or noninferiority of a cangrelor regimen to a clopidogrel regimen or to standard of care for the following reasons:**

- “Clopidogrel administration was delayed inappropriately [in the control groups] in all of the trials. The trials themselves provide evidence that earlier administration of clopidogrel was better both by cross-trial comparisons and by logistic regressions of the PHOENIX data. Clopidogrel was never consistently administered early enough such that we can not even conclude that cangrelor is noninferior to clopidogrel...”**

# **The CHAMPION PHOENIX Trial: FDA Medical Team Leader's Conclusions**

- **“The “superiority” is only statistically significant in the stable angina subgroup. Yet stable angina is the condition for which cangrelor offers minimal advantages if any: We can easily load clopidogrel in stable angina patients at any desired interval before PCI and we can delay CABG for days to washout the clopidogrel effects if the anatomy elucidated at angiography is unsuitable for PCI and CABG is preferred.”**

# **The CHAMPION PHOENIX Trial: FDA Medical Team Leader's Conclusions**

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- **“The data suggest the possibility of harm with cangrelor for ST segment elevation MI (STEMI) patients.”**
- **“While the trials did not demonstrate convincingly superiority of cangrelor for efficacy, they do demonstrate an increased risk of bleeding with it.”**

# 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.”

# **The CHAMPION PHOENIX Trial: FDA Medical Team Leader's Recommendation**

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- **“I recommend not approving cangrelor at this time for the PCI indication. I recommend not approving cangrelor until another trial succeeds in correcting the flaws that I have documented in this review and in my parallel review on the ethicalness of the cangrelor development program.”**

# Cangrelor and the Bridge-to-Surgery Indication

- **FDA clinical reviewers:**  
**“We recommend a Complete Response to the proposed separate indication to maintain P2Y12 inhibition in patients with acute coronary syndrome or with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 Inhibitor therapy is interrupted due to surgery.”**

# 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.

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

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- 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

- **Public Citizen urges the advisory committee to recommend that the FDA not approve the NDA for cangrelor for either the PCI or bridge-to-surgery proposed indications.**
- **We also call on the FDA Commissioner to investigate the failures in agency oversight that allowed the CHAMPION clinical trials to proceed using a design that exposed many control subjects to substandard antiplatelet interventions.**