Disbalance between mortality and non-fatal vascular events in the CHAMPION-PHOENIX trial: The cangrelor efficacy challenge

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Summary
The recently published, largest trial with cangrelor, the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION)-PHOENIX, suggested that the experimental agent significantly reduced the rate of stent thrombosis (ST) and myocardial infarction (MI) during PCI at 48 hours (h) and 30 days. However, the declared impressive cangrelor vascular non-fatal benefit was contradicted by identical deaths at 48 h, and a trend toward excess mortality at 30 days. We analysed the mismatch between outcomes in the CHAMPION-PHOENIX trial. The trial reported identical mortality (18 death in each arm; odds ratio [OR] 1.00 (0.52–1.92); p>0.999) at 48 h, but more deaths, 60 vs 55, after cangrelor at 30 days. There was a significant reduction of ST from 0.8% (n=46) of the patients in the cangrelor group versus 1.4% (n=74) in the clopidogrel group (odds ratio, 0.62; 95% CI, 0.43 to 0.90; p= 0.01) at 48 h, and a persistent but less impressive ST prevention benefit OR of 0.68 (0.50=0.92, p = 0.01) at 30 days. There were also 48 less MI's following cangrelor usage enforced by a significant difference (odds ratio 0.80 (0.67–0.97) p = 0.02), which was also less prevalent at 30 days (OR 0.82 (0.68–0.98), p = 0.03). The reported ST/MI advantage should result in at least a trend towards numerically less deaths after cangrelor at 30 days follow-up, which was opposite of the results reported in CHAMPION-PHOENIX trial. Efficacy of cangrelor is challenged by the disproportional "reduction" of ST and MI conflicting with identical mortality at 48 h and worsened at day 30 fatalities. The dissociation between vascular mortality and non-fatal vascular ischemic occlusions, unless compensated by some other unreported cause(s) of death, should be explored and explained. Unadjudicated 30-day outcomes, and all ST types should be fully disclosed. The ongoing FDA cangrelor review should focus on appropriate event count and/or possible mismatch between site-reported and extra adjudicated events in the CHAMPION-PHOENIX trial.

Keywords
Cangrelor, stent thrombosis, myocardial infarction, efficacy, mortality, clinical trials

Introduction
Cangrelor (AR-C69931MX) is an experimental intravenous antiplatelet agent, and a nonthienopyridine adenosine triphosphate analogue, which is currently under regulatory scope in the USA for approval in percutaneous coronary intervention (PCI) patients based predominantly on the results of the CHAMPION-PHOENIX trial. This viewpoint article summarises several concerns based on the reassessment of cangrelor development including the CHAMPION-PHOENIX trial results. This paper represents the findings of a report issued for the FDA on July 18, 2013 but solely reflects the viewpoint of the authors and has been subjected to peer-review. The article does not necessarily reflect the views of the editors or publishers. The cangrelor New Drug Application has been submitted for the Food and Drug Administration (FDA) secondary review in July, 2013.

One of the largest controversies of modern antiplatelet strategies is the uncertain relation among their potency, associated degree of platelet inhibition, bleeding risks, and prevention of thrombotic occlusions. There are consistent ongoing, yet controversial and mostly unsuccessful, attempts to improve vascular outcomes by applying more aggressive and/or potent antiplatelet regimens. Cangrelor, an experimental nonthienopyridine adenosine triphosphate analogue, is an intravenous antagonist of the P2Y12 receptor characterised by potent and reversible platelet inhibition with presumably rapid offset of action (1). One small, elegant study suggested that bolus and infusion of cangrelor provided immediate and almost complete inhibition of platelet aggregation and activation. Moreover, this profound inhibition is rapidly reversed upon termination of the infusion. Importantly, however, when cangrelor and clopidogrel were administered simultaneously clopidogrel was unable to impact further platelet activity (2). It has been hypothesised that in the presence of a reversible platelet inhibitor, such as cangrelor, active, short-lived, irreversible clopidogrel thiol metabolite is incapable of competing for the P2Y12 receptor binding site until the cangrelor offset of action expires. It
seems cangrelor’s high affinity for the P2Y12 receptor prohibits clopidogrel’s active metabolite from forming the necessary disul-fide bridge with cysteine residues in the extracellular domain of this receptor (2, 3).

There is solid clinical evidence yielded from four randomised trials with cangrelor, namely BRIDGE (4), CHAMPION-PCI (5), CHAMPION-PLATFORM (6), and finally the largest outcome-driven trial CHAMPION-PHOENIX (7).

**CHAMPION-PHOENIX design**

One thing is certain, the CHAMPION-PHOENIX study is not a true trial of cangrelor vs clopidogrel. In fact, only the CHAMPION-PCI study has the closest design to be considered a true cangrelor vs clopidogrel trial which, to the contrary, yielded entirely negative results (5). In the CHAMPION-PHOENIX, every patient received cangrelor during the percutaneous coronary intervention (PCI) followed by a 600 mg load of clopidogrel at the end of the cangrelor infusion in the treatment arm. In the control arm, patients received a clopidogrel load of either 300 mg or 600 mg directly before or after the PCI procedure. Since we know the benefit of a peri-PCI clopidogrel loading is time dependent (the earlier the better), none of the patients were essentially treated effectively with clopidogrel at the time of PCI in the control arm. Thus from a practical standpoint, the CHAMPION-PHOENIX study was more closely designed as a trial of cangrelor vs placebo than cangrelor vs clopidogrel, especially considering that not only all patients received clopidogrel, but overall patients randomised to cangrelor received more clopidogrel (mandatory 600 mg) than controls (n=1,405 or (25.7%) received 300mg clopidogrel loading) (7). The results of the CHAMPION-PHOENIX trial, based upon a 11,145 patient Phase 3 randomised, double-blind clinical trial in patients undergoing PCI, were reported in March of 2013 and suggested that patients treated with cangrelor had a 22% (p=0.005) reduced odds of experiencing the primary endpoint, which was a composite incidence of death, myocardial infarction (MI), ischaemia-driven revascularisation, and stent thrombosis (ST) at 48 hours (h) and 30 days after randomisation.

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Cangrelor (N=5470)</th>
<th>Clopidogrel (N=5470)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint*</td>
<td>257/5470 (4.7)</td>
<td>322/5469 (5.9)</td>
<td>0.78 (0.66–0.93)</td>
<td>0.005</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>46/5470 (0.8)</td>
<td>74/5469 (1.4)</td>
<td>0.62 (0.43–0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>207/5470 (3.8)</td>
<td>255/5469 (4.7)</td>
<td>0.80 (0.67–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mortality**</td>
<td>18/5470 (0.3)</td>
<td>18/5469 (0.3)</td>
<td>1.00 (0.52–1.92)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Table 1: Efficacy outcomes at 48 hours after randomisation in CHAMPION-PHOENIX trial.

Outcomes at 48 hours

Cangrelor use was associated with a 38% reduction in the odds of the key secondary endpoint, namely incidence of ST at 48 h. Increases in the frequency of access site bleeding and transient dyspnea were observed with cangrelor. However, the trial reported identical mortality (18 deaths in each arm; odds ratio [OR] 1.00, 95% confidence interval [CI] 0.52 to 1.92; p > 0.999) but significant excess of ST with 0.8% (n=46) of the patients in the cangrelor group vs 1.4% (n=74) of patients in the control group (OR 0.62; 95% CI, 0.43 to 0.90; p = 0.01). There were also 48 less MIs after cangrelor usage, and this difference was significant (OR 0.80, 95% CI, 0.67 to 0.97; p = 0.02). The efficacy of cangrelor in the CHAMPION-PHOENIX trial is presented in Table 1.

Outcomes at 30 days

The design paper clearly indicates that the outcomes at 30 days were integral, pre-specified aspects of the trial (8). However, the data from the 30 days study are seldom and limited only to the overall “remained” endpoint-, and “persistent” ST benefits of cangrelor (7). It is entirely unclear why the efficacy and safety data of the full 30 days trial was not reported in the primary publication, despite 15 extra pages of supplementary materials (7). These data are available and were retrieved from the latest American College of Cardiology 2013 late-breaking trials presentation (9). Importantly, at 30 days, the benefit looks slightly less impressive, especially since there were five more deaths after cangrelor (Table 2). Again, the differences in mortality are quite small and are probably due to the “play of chance”; however, the unadjusted verified 30 days outcomes are needed to better assess this pivotal issue. Analysing unadjusted numbers is especially important since the non fatal outcomes at 30 days are not that impressive as at 48 h.

Moreover, considering that the difference in definite ST was not significant (p = 0.09), full disclosure of all ST data at 48 h and 30 days should be presented, especially assuming that the position paper provides detailed ST definitions and applied classifications for both time points (8). Without that pivotal data there is a bothersome sense that the ST numbers in the CHAMPION-PHOENIX trial were artificially inflated since there is no difference in ischaemia-driven revascularisation or death at 30 days. Any “real” acute and/or subacute ST which was plenty (at least 35%), excluding intraprocedural ST, would more likely lead to more deaths or an urgent revascularisation benefiting cangrelor.
Stent thrombosis and mortality

The best data that shows that early ST is much less dangerous than later ST comes from the HORIZONS–AMI trial. Acute ST is indeed infrequent, even without additional heparin (10). Regardless, it is important to prevent since more than one-third of all ST events during three-year follow-ups occurred during the index hospital phase. Mortality and major bleeding were significantly higher after in-hospital ST compared with out-of-hospital ST (11). Based on the ACUITY and HORIZON-AMI trials, recent post-hoc analyses show that intraprocedural ST is a relatively rare complication of PCI, but is strongly associated with subsequent out-of-lab ST and mortality (12). However, these retrospective data are severely challenged by the randomised evidence yielded by the CHAMPION-PHOENIX trial (7) discussed in this paper. Indeed, most of the ST in the CHAMPION–PHOENIX report was intraprocedural and increasingly prevented by cangrelor, but mortality surges. Moreover, intraprocedural ST might also be related to an insufficient level of anticoagulation at the time point of the PCI (underdosed heparin etc.) and might not necessarily be directly associated with the level of P2Y12 platelet inhibition.

Mismatch between mortality and non-fatal events

The outcome data suggests that most cangrelor early advantage stated in the CHAMPION-PHOENIX (7) is yielded from ST reduction (hazard ratio [HR] = 0.62), with 28 extra events prevented by the experimental agent. There were also 48 fewer MI (HR = 0.80) reported after cangrelor usage. Importantly, the CHAMPION-PHOENIX position paper clearly states that ST, as part of the primary endpoint, consisted of events from intraprocedural up to 48 h postrandomisation by angiography core laboratory (8). The adjudicated ST at 30 days was made according to the Academic Research Consortium definition (10) taking into account intraprocedural ST, acute ST (< 24 h post procedure), and subacute ST (> 24 h and ≤ 30 days) and discriminating against definite, probable, and possible ST. In addition and expansion to the Academic Research Consortium definition, intraprocedural ST was defined as any new or worsened procedural thrombus related to the stent (8). However, the reported impressive ST/MI advantage of 76 non-fatal, hard vascular events should translate in at least a trend towards less deaths after cangrelor, which was entirely lacking in the CHAMPION-PHOENIX trial. Indeed, it is highly unusual to include intraprocedural ST, and hardly any previous large trial relied on such outcomes as a part of the “key secondary endpoint” as was done in the CHAMPION-PHOENIX study. The reason for skepticism with regard to intraprocedural ST is because such acute closures are not unusual and when it occurs it can be treated effectively within seconds to minutes making it very unlikely to have any long-term, adverse outcomes. Granted it is better to avoid, but it seems the clinical significance of such ST should not be overstated and has been now proven to be negligible by distribution of fatalities in the CHAMPION-PHOENIX trial, especially at 30 days. In fact, the very early outcome cut-off time-point of 48 h following PCI indicates that “intraprocedural stent thrombosis” constituted apparently the majority of ST types in the CHAMPION-PHOENIX report. It is reasonable to assume that the associated mortality is low because it is happening in the catheterisation laboratory, and can be fixed immediately. What is confusing is that diagnosis of ST is very obvious in the first 48 h after PCI. It is hard to understand how the non-significant difference in definite ST (0.2% vs 0.4%; p = 0.09) for the numbers intended to treat population became 0.8% and 1.4% (p = 0.01) when intraprocedural ST was included. It is not so much the significance aspect, but rather the fact that for what is typically defined as ST there was no significant benefit of cangrelor. Finally, the administration of cangrelor on top of aspirin or/and clopidogrel consistently increases the risk for early bleeding events after PCI in all four trials including CHAMPION-PHOENIX (4–7). However, bleeding hazards were largely dependent on the definition used, and how this excess risk of bleeding was captured. The details and meta-analyses for cangrelor trials are available elsewhere (13). In fairness, early in-hospital bleeding events are rarely fatal, in contrast to the delayed outpatient catastrophic haemorrhages associated with high mortality. This was confirmed In CHAMPION-PHOENIX because extra bleeding complications after cangrelor were not associated with early deaths since all 48 h fatal events in the trial were of cardiovascular causes (7).

**STEMI mismatch**

The advantage of cangrelor in preventing non-fatal vascular events is somewhat challenged by the disbalance in the baseline trial with
regard to STEMI cohorts. In fact, there were more STEMI patients in the clopidogrel arm, 18.8% (n=1,030) vs only 17.6% (n=962) treated with cangrelor in the CHAMPION-PHOENIX report (7). The extra 68 STEMI patients who received less potent antiplatelet protection with only clopidogrel on board will ultimately result in some interprocedural ST and early reinfections reported in the CHAMPION-PHOENIX trial, artificially inflating the cangrelor benefit. Also, it seems important to note that clopidogrel pretreatment was not allowed in the CHAMPION-PHOENIX study, making the trial design somewhat similar to that of the TRITON study (14). In contrast, however, prevention of early periprocedural MI resulted in a mortality advantage of prasugrel in STEMI cohort of the TRITON trial (15), which was not reported in the CHAMPION-PHOENIX report (7).

Adjustment of 30 days outcomes

Failure to report unadjusted data for the 30 days outcomes in the CHAMPION-PHOENIX trial is alarming. In lay terms it means that CHAMPION-PHOENIX statisticians chose not to report the real numbers, but altered them based on identifiable differences in characteristics of the two populations being studied. Adjusted analysis is typically reserved for non-randomised, post-hoc analyses which are difficult if possible to match. However, it is hard to find an instance when adjusted analyses were used in a key endpoint of a large indication seeking, randomised trial. By definition, adequate randomisation should balance out major baseline characteristics, and the sample size of the CHAMPION-PHOENIX trial (n=11,145) was more than sufficient to match the trial arms. Also confusing is a statement that “the logistic model was adjusted for baseline status and clopidogrel dose”. Clopidogrel loading dose was determined randomly by the treating physician, but most importantly there was no difference in the 48-h outcomes based on clopidogrel dose (7). So this adjusting would indicate that there is reason to believe the clopidogrel loading dose impacted later events between 48 h and 30 days, but there is no evidence to support this claim.

Historic perspective

The CHAMPION-PHOENIX trial was not the first to show dissociation between favourable, non-fatal vascular events and lack of mortality advantage. A similar pattern was observed in the CURRENT (OASIS-7) study when double-dose clopidogrel was associated with identical mortality: 1.9% vs 1.9%; CI = 0.96 (0.77-1.19; p = 0.68) despite reported substantial advantage is ST prevention: 1.6% vs 2.3%; CI = 0.71 (0.57-0.89; p = 0.002) (16). It is not surprising that double dose clopidogrel (150 mg/daily) for the first week after PCI as tested in the CURRENT trial is not generally accepted despite the ST reduction claim. One should also be skeptical when significant ST prevention advantage does not result in at least numerical trends towards fewer deaths.

Sponsor site monitoring

Finally, the sponsor was self-monitoring sites in the CHAMPION-PHOENIX trial, which may be similar to the negative experience of sponsor monitoring in the PLATO trial (17). The FDA secondary review (18) and especially complete response documents (19) revealed severe problems with trial conduct, underreporting of adverse events, unblinding, and missing data in PLATO. Therefore, the adequate assessment of potential cangrelor clinical utility should be put on hold until already published numbers are verified, and the missing 30 days unadjusted outcomes data are appropriately disclosed to public.

Impressions

Future cangrelor utilisation, if any, will be tailored to seek “bridging” indication specifically to the patients undergoing heart surgery. It is impossible to comprehend why cangrelor will be added to the conventional pharmacological armamentarium before elective or emergency PCI. Indeed, if the patient will not be considered an appropriate coronary artery bypass grafting (CABG) candidate, cangrelor use cannot be justified, since the drug causes more dyspnea, agitation, bleeding, and numerically worsened mortality at 30 days. Post-CABG usage of cangrelor also represents a heavy challenge, since the only available clinical evidence can be driven from the BRIDGE trial, done in thienopyridine-free patients. However, the BRIDGE study was very small (n=210), with no fatal bleeding, or intracranial haemorrhages, thus the reported numbers may represent a play of chance.

The reported ST/MI advantage should result in at least a trend towards numerically less deaths by cangrelor over no cangrelor at 30 days follow-up, which was reversely reported in the CHAMPION-PHOENIX trial. Efficacy of cangrelor is challenged by the disproportional “reduction” of ST and MI conflicting with identical mortality at 48 h, and worsened at day 30 fatalities. The dissociation between vascular mortality and non-fatal vascular ischaemic occlusions, unless compensated by some other unreported cause(s) of death, should be explored and convincingly explained. Unadjudicated 30 days outcomes, and all ST types should be fully disclosed. The ongoing FDA cangrelor review should focus on appropriateness of ST diagnosis, recovering of day 30 data, and possible mismatch between site-reported and extra adjudicated events in the CHAMPION-PHOENIX trial.

Conflicts of interest

VLS received research grants and consulting fees from Sanofi-Aventis, Bayer and McNeil Consumer Products (the manufacturers of clopidogrel and aspirin). He received funding for research studies with clopidogrel, and consultant fees from the clopidogrel manufacturers. None of these funds were linked to the present publication. ANP, SDF, and JJD have nothing to declare. Special thanks to Dr. D. Angiolillo (BRIDGE) for the trial data clarification.
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