Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Central Adjudication Identified Additional and Prognostically Important Myocardial Infarctions in Patients Undergoing Percutaneous Coronary Intervention

Results From CHAMPION PHOENIX

BACKGROUND: In the CHAMPION PHOENIX trial, cangrelor reduced the primary composite end point of death, myocardial infarction (MI), ischemia-driven revascularization, or stent thrombosis at 48 hours. This study aimed to explore the impact of event adjudication and the prognostic importance of MI reported by a clinical events committee (CEC) or site investigators (SIs).

METHODS AND RESULTS: Data from the CHAMPION PHOENIX trial of patients undergoing elective or nonelective percutaneous coronary intervention were analyzed. A CEC systematically identified and adjudicated MI using predefined criteria, a computer algorithm to identify suspected events, and semilogarithmic plots to review biomarker changes. Thirty-day death was modeled using baseline characteristics. Of 10 942 patients, 462 (4.2%) patients had at least 1 MI by 48 hours identified by the CEC (207 [3.8%] cangrelor; 255 [4.7%] clopidogrel; odds ratio [OR] 0.80; 95% CI, 0.67–0.97; *P*=0.022), and 143 patients had at least 1 MI by 48 hours reported by the SI (60 [1.1%] cangrelor; 83 [1.5%] clopidogrel; OR, 0.72; 95% CI, 0.52–1.01; *P*=0.053). Of the 462 MIs identified by the CEC, 92 (20%) were reported by SI, and 370 (80%) were not. Of the 143 MI reported by the SI, 51 (36%) were not confirmed by CEC. All categories were associated with an increased adjusted risk for 30-day death (CEC: OR, 5.35; 95% CI, 2.56–11.2; *P*<0.001; SI: 9.08 [4.01–20.5]; *P*<0.001; CEC and SI: 10.9 [3.23–36.6]; *P*<0.001; CEC but not SI: 4.69 [1.94–11.3]; *P*<0.001; SI but not CEC: 15.4 [5.26–44.9]; *P*<0.001).

CONCLUSIONS: In patients undergoing percutaneous coronary intervention, CEC procedures identified 3 times as many MIs as the SI reported. Compared with clopidogrel, cangrelor significantly reduced MIs identified by the CEC with a qualitatively similar relative risk reduction in MIs reported by the SI. MIs identified by CEC or reported by SI were independently associated with worse 30-day death. Central adjudication identified additional, prognostically important events.

VISUAL OVERVIEW: A visual overview is available for this article.

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WHAT IS KNOWN

- In the CHAMPION PHOENIX trial, cangrelor reduced the primary composite end point of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours.
- Previous reports have shown that in similar patient populations, a clinical events committee identified more myocardial infarction events than site investigators.

WHAT THE STUDY ADDS

- Central adjudication identifies additional, prognostically important events.
- The use of strategies to screen patients for possible periprocedural myocardial infarction is an efficient operational approach to identify important events.

In the CHAMPION PHOENIX trial (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition), cangrelor reduced the primary composite end point of death, myocardial infarction (MI), stroke, ischemia-driven revascularization, or stent thrombosis at 48 hours compared with clopidogrel in patients undergoing either urgent or elective percutaneous coronary intervention (PCI) without increased risk of severe or life-threatening bleeding.[1] A reduction in MI was observed with cangrelor.[1,2]

A clinical events committee (CEC) systematically identified and adjudicated the components of the primary composite end point including MI. Previous reports have shown that in similar populations a CEC identified more MIs than site investigators (SI)—particularly PCI-related MIs.[3]

In this report, we investigate the type of MI events that occurred in the CHAMPION PHOENIX trial to explore the effect of cangrelor on MI outcomes including different types of MI, the impact of event adjudication and the prognostic importance of events identified by the CEC or reported by SIs.

METHODS

The CHAMPION PHOENIX trial design, patient population, protocol procedures, outcome definitions, and results have been published.[1,4] The protocol was approved by the national and institutional regulatory authorities and ethics committees. All patients provided written informed consent. Patients with stable angina or acute coronary syndrome were randomly assigned to receive cangrelor or clopidogrel before PCI in a double-dummy, double-blind manner. Patients randomized to cangrelor received placebo capsules and cangrelor as a bolus of 30 μg/kg and infusion with 4 μg/kg per minute for the procedure duration (but at least 2 hours) followed by 600 mg clopidogrel. Patients randomized to clopidogrel received 600 or 300 mg clopidogrel before or after the procedure at the discretion of the SI followed by a placebo infusion and capsules after the procedure. Decisions about coronary angiography, revascularization procedures, and pharmacotherapy were left to the discretion of the treating physician. All patients received aspirin and clopidogrel maintenance dose for the first 48 hours.

MIs were identified by a comprehensive strategy. A computer program queried key data elements on the electronic case report form and identified suspected events. These data elements included specific yes/no questions about MI occurrence as well as information that could suggest a possible event such as electrocardiographic changes or urgent catheterizations. Cardiac biomarkers before and after the procedure were interrogated by a computer algorithm to identify elevations possibly related to the PCI or to a postrandomization event separate from the index event. To assess periprocedural MI, each patient was classified by baseline status based on a combination of troponin, ischemic symptoms, and electrocardiographic changes (Table I in the Data Supplement). If patients had missing or elevated baseline values, data were summarized on a plot (examples in Figure I in the Data Supplement). Two physicians (Drs Mahaffey and Leonardi) who were blinded to the treatment independently reviewed each plot of centrally assessed CK-MB (creatine kinase-MB) and troponin values in relation to time of randomization and PCI or coronary artery bypass graft. They identified patients with stable or falling biomarkers before revascularization and those with postrandomization CK-MB elevations. If there was an alteration suggesting an MI indicated by either physician, the data were sent to the CEC for further adjudication. The definition of periprocedural MI (type 4a) is shown in Table II in the Data Supplement. MIs unrelated to PCI were defined based on the Universal Definition of MI.[4,5] Two physicians of the CEC independently adjudicated the events. If both agreed, the adjudication was completed. If the physicians disagreed, a committee of at least 3 physicians reevaluated the event and determined a final result by consensus. SIs completed standard case report forms that collected information about each event. Yes/no questions were asked for each event and if Yes was recorded for a particular event then more information was requested. Report by SI did not include type of MI.

The individual data will not be made available to other researchers for purposes of reproducing the results.

We analyzed the modified-intention to treat population of patients who underwent PCI and received study drug. We determined the odds ratios (OR) and 95% CI of treatment effect (cangrelor compared with clopidogrel) by type and category of identification (CEC) or reporting (SI) of MI at 48 hours using logistic regression. We calculated the unadjusted ORs and 95% CI of 30-day events between patients with and without CEC MI at 48 hours. For multivariate modeling of 30-day mortality, variables (Table III in the Data Supplement) were selected based on statistical significance of univariate analyses and clinical importance including information from prior studies in which these variables have been associated with 30-day mortality.[6]

Categorical variables are expressed as frequencies and percentages and continuous variables as medians and quartiles. ORs and 95% CI between randomized treatments data were calculated with SAS (version 9.2, SAS Institute, Cary, NC). Significance levels were not adjusted for multiplicity.

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RESULTS

Reporting of MI

Of 10 942, 462 patients had at least 1 MI at 48 hours identified by the CEC and 143 patients had at least 1 MI reported by the SIs. In 92 (19.9%) of the 462 CEC-identified MIs, the SIs also reported an MI and in 370 (80.1%) not. Of the 143 MI events reported by the SIs, CEC confirmed MI in 92 (64.3%) patients and did not confirm in 51 (35.7%) patients. Figure II in the Data Supplement illustrates the distribution of MIs identified by the CEC or reported by the SIs according to assigned treatment. The baseline and procedural characteristics by CEC-identified or SI-reported MI at 48 hours are shown in Table IV in the Data Supplement.

Types of MI and Treatment Effect

Of the 462 MIs identified by the CEC, 29 (6.3%) were nonprocedural and 433 (93.7%) were procedural related. Twenty-four (5.2%) were associated with stent thrombosis. The incidence of different types of MI and the effect of treatment are shown in Table 1. Fewer MI was identified by CEC for patients receiving cangrelor compared with clopidogrel (207/5472 [3.8%] cangrelor; 255/5470 [4.7%] clopidogrel; OR, 0.80; 95% CI [0.67–0.97]; *P*=0.022). SIs reported an MI in 60 of 5472 patients (1.1%) randomized to cangrelor and in 83 of 5470 patients (1.5%) randomized to clopidogrel (OR, 0.72; 95% CI [0.52–1.01]; *P*=0.053).

Table 1. Treatment Effect by Category and Type of MI at 48 Hours

Category and Type of MI	Cangrelor, N=5472	Clopidogrel, N=5470	OR (95% CI)
CEC-identified			
Any MI	207 (3.8)	255 (4.7)	0.80 (0.67–0.97)
Nonprocedure-related	13 (0.2)	16 (0.3)	0.81 (0.39–1.69)
Procedure-related	194 (3.5)	239 (4.4)	0.80 (0.66–0.98)
Associated with stent thrombosis	9 (0.2)	15 (0.3)	0.60 (0.26–1.37)
STEMI	24 (0.4)	34 (0.6)	0.70 (0.42–1.19)
NSTEMI	172 (3.1)	202 (3.7)	0.85 (0.69–1.04)
ST-segment elevation not evaluable	11 (0.2)	19 (0.3)	0.58 (0.27–1.22)
Q wave	11 (0.2)	18 (0.3)	0.61 (0.29–1.29)
Non-Q wave	184 (3.4)	218 (4.0)	0.84 (0.69–1.02)
Q wave not evaluable	12 (0.2)	19 (0.3)	0.63 (0.31–1.30)
SI-reported			
Any MI	60 (1.1)	83 (1.5)	0.72 (0.52, 1.01)

Values represent n (%). Type of MI was not collected from SIs. CEC indicates clinical events committee; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation MI; OR, odds ratio; SI, site investigator; and STEMI, ST-elevation MI.

Table 2. Unadjusted Odds of 30-Day Events in Patients With and Without CEC-Identified MI at 48 Hours

30-Day Event	CEC MI at 48 Hours		OR (95% CI)
	Yes, N=462	No, N=10 477	
Death	15 (3.2)	100 (1.0)	3.48 (2.00–6.03)
Cardiovascular death	14 (3.0)	80 (0.8)	4.05 (2.28–7.21)
Ischemia-driven revascularization	46 (10.0)	76 (0.7)	15.1 (10.3–22.1)
PCI	42 (9.1)	67 (0.6)	15.5 (10.4–23.1)
CABG	4 (0.9)	9 (0.1)	10.1 (3.11–33.0)
Stent thrombosis	53 (11.5)	122 (1.2)	11.0 (7.84–15.4)
Intraprocedural	23 (5.0)	66 (0.6)	8.25 (5.08–13.4)
Definite	29 (6.3)	36 (0.3)	19.4 (11.8–31.9)
Probable	4 (0.9)	23 (0.2)	3.96 (1.36–11.5)
Possible	0 (0.0)	0 (0.0)	…

Values represent n (%). CABG indicates coronary artery bypass graft; CEC, clinical events committee; MI, myocardial infarction; OR, odds ratio; and PCI, percutaneous coronary intervention.

Association of MI With 30-Day Mortality

Table 2 summarizes the occurrence of 30-day events and the unadjusted risk for patients with CEC-identified MI compared with patients without CEC-identified MI. The risk for 30-day death was 3.2% in patients with CEC-identified MI compared with 1.0% in patients without CEC-identified MI (OR, 3.48; 95% CI [2.00–6.03]).

The association of MI with 30-day mortality is shown in Table 3. After multivariable adjustment, CEC-identified MI was associated with an increased risk for 30-day death (OR, 5.35; [2.56–11.17]; *P*<0.001). All categories were significantly associated with an increased risk for 30-day death (SI-reported MI: OR, 9.08; [4.01–20.5]; *P*<0.001; CEC-identified and SI-reported MI: OR, 10.9; [3.23–36.6]; *P*<0.001; CEC-identified but not SI-reported MI: OR, 4.69; [1.94–11.3]; *P*<0.001; SI-reported but not CEC-identified MI: OR, 15.4; [5.26–44.9]; *P*<0.001).

DISCUSSION

The main findings of this analysis are that (1) the CEC identified more MIs than the SIs reported, (2) cangrelor reduced MI identified by CEC compared with clopidogrel, (3) CEC adjudication in ACS and PCI population adds sensitivity and specificity to MI assessment, and (4) CEC-identified and SI-reported MIs were independently associated with an increased mortality at 30 days.

More MIs Identified by CEC

CEC identified more MIs than the SIs (462 versus 143) which is consistent with previous reports.[3,7,8] In CHAMPION PHOENIX, biomarkers were assessed

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Table 3. Adjusted Odds of Death at 30 Days by CEC Identification or SI Reporting of MI at 48 Hours

Identified/reported by	30-Day Death		Adjusted OR (95% CI)	*P* Value
	Patients With MI at 48 Hours	Patients Without MI at 48 Hours		
CEC	15/462 (3.2)	100/10457 (1.0)	5.35 (2.56–11.2)	<0.001
PCI-related MI	8/433 (1.8)	107/10486 (1.0)	3.97 (1.65–9.52)	0.002
By biomarker elevation		107/10486 (1.0)		
3–5×ULN	0/196 (0.0)		<0.01–>999	0.99
5–10×ULN	4/135 (3.0)		6.17 (1.86–20.5)	0.003
>10×ULN	4/98 (4.1)		5.66 (1.67–19.2)	0.005
SI	10/142 (7.0)	105/10777 (1.0)	9.08 (4.01–20.5)	<0.001
CEC and SI	5/92 (5.4)	95/10407 (0.9)	10.9 (3.23–36.6)	<0.001
CEC but not SI	10/370 (2.7)	95/10407 (0.9)*	4.69 (1.94–11.3)	<0.001
SI but not CEC	5/50 (10.0)	95/10407 (0.9)*	15.4 (5.26–44.9)	<0.001

Values represent n/N (%). CEC indicates clinical events committee; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; SI, site investigator; and ULN, upper limit of normal.

*Patients without CEC-identified and without SI-reported MI at 48 hours.

systematically. A computer algorithm identified suspected events, and a novel approach was implemented to review plots of biomarkers to detect MI.[9] This enabled the CEC to identify many events not reported by the SIs. The majority of the CEC-identified MIs were classified as periprocedural. Although data from SIs about the type of MI were not collected, we hypothesize that SIs underreported many of the periprocedural MIs that were triggered for CEC review through biomarker elevations missed by the SIs. Often periprocedural biomarkers are not assessed routinely after procedures. However, periprocedural MI is an important complication as it is significantly associated with an increased long-term mortality.[10]

Treatment Effect—Sensitivity and Specificity of CEC Adjudication

Cangrelor significantly reduced the occurrence of MI compared with clopidogrel using data from the CEC. A qualitatively similar, statistically non-significant effect was observed when analyses were performed using only SI-reported MIs. This suggests that CEC adjudication adds sensitivity in the assessment of MI capturing more events with potential treatment effect signal such as small MIs and thus increasing the power to detect such effect.[11] In the case of periprocedural MI, specificity is limited by the capability to differentiate the periprocedural MI from the index MI.[9] The repeated measurements of troponin before PCI enabled the detection of rising levels of biomarkers. The thorough assessment of cardiac biomarkers along with an independent review of the summarized data in a semilogarithmic plot allowed the CEC to maximize the discrimination between periprocedural MI and the index MI.[4,9]

CEC-Identified and SI-Reported MI Predictive of 30-Day Outcomes

Studies showed that events identified by CECs are associated with subsequent events.[8,12,13] In the present study, all MIs whether reported by the SIs or identified by the CEC were associated with an increased risk for death at 30 days. The mortality of patients with SI-reported MIs was higher compared with the CEC-identified MI group (7.0% versus 3.2%). This might be explained by the higher sensitivity of the CEC ascertainment of MIs, which detected even small MIs. The prognostic importance of these periprocedural MI particularly if defined by smaller magnitudes of biomarker elevation has been controversial.[14,15] This study showed that the events that were additionally identified through CEC are prognostically important.

Implications for Future Research

Some have suggested that CEC efforts might be overly complex and associated with lower cost-efficiency.[16] It has been shown that CEC procedures do not delay end point ascertainment[17] and are responsible for only 3% to 6% of trial costs.[18] Our results highlight the need to account for methods of event identification as well as MI definitions in the design of trials. To avoid bias, systematic standardized approaches to MI identification and adjudication should be used. The use of strategies to screen patients for possible periprocedural MI is an efficient operational approach and should be considered for future programs to increase sensitivity of MI detection. Rigorous application of definitions that may not be universally agreed on is needed with CEC processing of MI events, particularly post-PCI.

Electronic health records could add efficiency to CEC processes. Hlatky et al[19] showed that

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administrative data may reliably identify MIs and similar treatment effects. This might be particularly helpful for pragmatic trials designs and extended follow-up of participants. Periprocedural MI, however, was less frequently coded and events might be missed. Some events were missed by the standard procedures since they did not rely on claims data. This indicates that a combination of both methods might be the preferred choice to increase accuracy.

Our analyses focused on periprocedural MI. CEC efforts for other end points, however, have also been evaluated.[20] If specific causes of death are included in an end point in cardiovascular trials, 16% are because of undetermined causes.[21] A CEC may reduce the rate of undetermined deaths. End points in trials of congestive heart failure are often difficult to differentiate from renal events in dialysis population, and more work is needed to understand the necessity of a CEC to discriminate these events.

Clinical Implications

Systematic collection of biomarkers and interpretation with clinical context by experienced personnel like that used in CHAMPION PHOENIX is important to support a thorough CEC process. This supports the assessment of biomarkers in clinical practice before and after PCI to identify periprocedural MI associated with worse outcome.

Limitations

The CHAMPION PHOENIX trial was not powered to detect treatment effect on subtypes of MI. We did not collect systematically information to objectively differentiate the types of MI reported by the CEC and the SIs. We do know that CEC-identified MIs met the protocol criteria for symptoms, procedural complications, biomarker elevations, and electrocardiographic changes. Our insights might help to refine the SI reporting of MI events in future trials to potentially improve our understanding of the differences observed between CEC and SIs.

Conclusions

In CHAMPION PHOENIX, patients undergoing PCI had a 20% relative reduction in the odds of an MI with cangrelor with consistent results for procedural- and nonprocedural-related MI. SIs reported less 48-hour MI end points in this population of patients treated with PCI than the CEC process identified. Treatment effects observed using the CEC-identified MI and the SI-reported MI end points were consistent. MIs identified by the CEC or reported by the SIs were independently associated with worse 30-day death. Central adjudication identifies additional, prognostically important events.

ARTICLE INFORMATION

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*A list of all CHAMPION PHOENIX investigators has been published.[1]

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