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ORIGINAL ARTICLE

Ischemic Events Occur Early in Patients Undergoing Percutaneous Coronary Intervention and Are Reduced With Cangrelor: Findings From CHAMPION PHOENIX

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BACKGROUND: Thrombotic events are reduced with cangrelor, an intravenous $P2Y_{12}$ inhibitor. We sought to characterize the timing, number, and type of early events (within 2 hours of randomization) in CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention).

METHODS: CHAMPION PHOENIX was a double-blind, placebo-controlled trial that randomized patients undergoing percutaneous coronary intervention to cangrelor or clopidogrel. For this analysis, we evaluated the efficacy of cangrelor in the first 2 hours postrandomization with regards to the primary end point (death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis). Sensitivity analyses were performed evaluating a secondary, post hoc end point (death, Society of Coronary Angiography and Intervention myocardial infarction, ischemia-driven revascularization, or Academic Research Consortium definite stent thrombosis).

RESULTS: The majority of events (63%) that occurred in the trial occurred within 2 hours of randomization. The most common early event was myocardial infarction; next were stent thrombosis, ischemia driven revascularization, and death. In the first 2 hours after randomization, cangrelor significantly decreased the primary composite end point compared with clopidogrel (4.1% versus 5.4%; hazard ratio, 0.76 [95% CI, 0.64–0.90], *P*=0.002). Similar findings were seen for the composite end point of death, Society of Coronary Angiography and Intervention myocardial infarction, ischemia-driven revascularization, or Academic Research Consortium stent thrombosis at 2 hours (0.9% versus 1.6%; hazard ratio, 0.57 [95% CI, 0.40–0.80], *P*=0.001). Between 2 and 48 hours, there was no difference in the primary composite end point (0.6% versus 0.5%; odds ratio, 1.17 [95% CI, 0.71–1.93]; *P*=0.53). Early (≤2 hours of randomization) GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) moderate or severe bleeding events were infrequent, and there was no significant difference with cangrelor compared with clopidogrel (0.2% [n=10] versus 0.1% [n=4]; adjusted odds ratio, 1.41 [95% CI, 0.37–5.40]; *P*=0.62).

CONCLUSIONS: The reductions in ischemic events and overall efficacy seen with cangrelor in CHAMPION PHOENIX occurred early and during the period of time in which patients were being actively treated with cangrelor. These findings provide evidence that supports the importance of potent platelet inhibition during percutaneous coronary intervention.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary artery disease ■ myocardial infarction ■ percutaneous coronary intervention ■ $P2Y_{12}$ receptor antagonist ■ thrombosis

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WHAT IS KNOWN

- Patients undergoing percutaneous coronary intervention are at risk of thrombotic complications including stent thrombosis and myocardial infarction.
- Cangrelor, an intravenous $P2Y_{12}$ inhibitor, has been shown to reduce major adverse cardiovascular events at 48 hours in the CHAMPION PHOENIX trial (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention).

WHAT THE STUDY ADDS

- Cardiovascular events that occurred in the CHAMPION PHOENIX trial were most commonly ischemic in nature (myocardial infarction, stent thrombosis); and, while the primary end point of the trial was at 48 hours, the majority of cardiovascular events occurred in the first 2 hours after the start of percutaneous coronary intervention.
- Treatment with cangrelor reduced these ischemic events in the first 2 hours after randomization.
- There was no rebound increase in cardiovascular events during the period of time in which patients were being transitioned from cangrelor to an oral $P2Y_{12}$ inhibitor.

Nonstandard Abbreviations and Acronyms

ARC	Academic Research Consortium
CANTIC	Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention
GPI	glycoprotein IIb/IIIa inhibitor
MI	myocardial infarction
NSTEMI	non–ST-segment–elevation myocardial infarction
PCI	percutaneous coronary intervention
SCAI	Society of Coronary Angiography and Intervention
STEMI	ST-segment–elevation myocardial infarction
ST	stent thrombosis

Patients undergoing percutaneous coronary intervention (PCI) are at risk of activation of the clotting process, formation of intravascular thrombus, and subsequent myocardial infarction (MI).[1] These periprocedural thrombotic events can occur due to injury of the vascular wall secondary to the intervention or from the formation of thrombus on equipment used to perform the PCI.[2] These periprocedural MI events are associated with high morbidity and mortality.[3] As such, adjunctive pharmacology used at the time of PCI is designed to prevent thrombus formation by inhibiting both platelet activation and thrombin formation.

The CHAMPION PHOENIX trial (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention) was part of a clinical development program that established the efficacy and safety profile of cangrelor.[4–7] The CHAMPION PHOENIX trial randomized 11 145 patients undergoing PCI to either intravenous cangrelor, an intravenous platelet $P2Y_{12}$ inhibitor, or clopidogrel, an oral $P2Y_{12}$ inhibitor. In this trial, cangrelor reduced the primary composite end point of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours in patients undergoing PCI, as well as the key secondary end point of stent thrombosis.[6] In the trial, cangrelor was given for 2 hours or for the duration of the procedure (whichever was longer). It would be expected that the majority of benefit with cangrelor would be seen during the time in which cangrelor was being administered. Thus, in this analysis, we sought to further characterize the timing, number, and type of events that occurred during the cangrelor infusion.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Design

The full design of the CHAMPION PHOENIX trial has been previously described.[6,8] The trial was a double-blind, placebo-controlled trial that included patients undergoing PCI for ST-segment–elevation myocardial infarction (STEMI), non–ST-segment–elevation myocardial infarction (NSTEMI), or stable angina. Patients treated previously with platelet inhibitors were excluded. After angiography confirmed eligibility for the study, patients were randomized to either cangrelor followed by clopidogrel after the infusion of cangrelor was complete or clopidogrel alone. Patients randomized to cangrelor received an infusion of cangrelor (30 μg per kilogram followed by an infusion of 4 μg per kilogram per minute) as well as placebo capsules. Cangrelor was to be continued for at least 2 hours from randomization or for the duration of the procedure (if the procedure lasted >2 hours). At the conclusion of the infusion of cangrelor, patients received a second set of capsules that contained 600 mg of clopidogrel. Patients randomized to clopidogrel received either 300 or 600 mg of clopidogrel (based on the discretion of the investigator). Randomization was stratified by intended loading dose of clopidogrel (300 versus 600 mg) and normal or abnormal status at baseline (status based on cardiac biomarkers, changes in the ECG, and symptoms).

End Points

All components of the primary and secondary efficacy end points were adjudicated by a clinical events committee at the Duke Clinical Research Institute. The original primary efficacy end point was a composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours. In the primary article, MI was defined based on the second Universal Definition of MI, and stent thrombosis included both definite stent thrombosis (as defined by the Academic Research Consortium [ARC]) and intraprocedural stent thrombosis (angiographically confirmed new or worsening

thrombus related to the placement of the coronary stent).[9–11] Timing of the events was determined and based on the timing of the onset of symptoms/ECG changes, evidence of intraprocedural complications by the angiographic core laboratory, or elevation in biomarkers.

For these analyses, we also present a post hoc secondary composite end point including only those MIs that satisfied the Society of Coronary Angiography and Intervention [SCAI] definition, and stent thrombosis that included only ARC definite stent thrombosis events. These additional end points were included to reflect the Food and Drug Administration's review and approval of the drug. The primary safety end point was severe, noncoronary artery bypass grafting bleeding as defined by the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) criteria.[12] The primary safety end point was not adjudicated independently but was reported by blinded investigators according to prespecified definitions.[13] All outcomes reported are at 48 hours unless otherwise noted.

An academic executive committee and The Medicines Company designed the trial. The Medicines Company funded the trial. At the conclusion of the trial, the database was transferred to the Baim Clinical Research Institute who had full access to the data and worked with The Medicines Company to perform and validate the analyses included in this article. The Institutional Review Board or Ethics Committee for each participating institution reviewed and approved the trial. All patients provided written informed consent.

Statistical Analysis

The modified-intention to treat population of patients who underwent PCI and were treated with study drug was used for these analyses (n=10 942). We performed a post hoc landmark analysis at 2 hours to reflect a comparison before the administration of the clopidogrel 600 mg transition dose in the cangrelor group. Comparisons between patients treated with cangrelor or clopidogrel at 2 hours were made using logistic regression and Cox proportional hazard models. In those patients without an event in the first 2 hours following randomization, a landmark analysis was performed from the second hour to 48 hours. Logistic regression and Cox proportional hazard models were developed to evaluate the factors associated with death, MI (SCAI definition), ischemia driven revascularization, or ARC stent thrombosis (ST) at 2 hours which included the following variables: sex, race, weight, tobacco use, medical history (prior MI, peripheral artery disease, heart failure, diabetes, prior cerebrovascular accident, prior PCI/coronary artery bypass grafting), geography, extent of coronary artery disease, index diagnosis/biomarker elevation, vessel(s) treated, use of drug-eluting stents, treatment allocation, duration of therapy, procedural anti-thrombotic regimen (aspirin dose, clopidogrel loading dose/timing, GPI [glycoprotein IIb/IIIa inhibitor], bivalirudin), and procedural characteristics (duration of procedure, number/length of stents placed). A 2-sided significance level of 0.05 was used. There were no corrections for multiple comparisons due to the exploratory nature of this analysis. Event curves were developed using Kaplan-Meier estimations. Analyses were performed using SAS version 9.3.

RESULTS

The median duration of PCI in the trial was 17 minutes (interquartile range, 10–30), and the median duration of the infusion was 129 minutes. The vast majority of patients randomized to cangrelor received the infusion for >2 hours (n=3805; 69.6%) while 30.4% (n=1662) had an infusion of ≤2 hours.

In the first 2 hours after randomization, cangrelor significantly decreased the events of the primary composite end point of death, MI, ischemia-driven revascularization, or stent thrombosis by 25% when compared with clopidogrel (5.4% [n=293] versus 4.1% [n=223]; hazard ratio, 0.76 [95% CI, 0.64–0.90], *P*=0.002; Table 1, Figure 1A). Similar findings were seen when evaluating the composite end point of death, MI (SCAI), ischemia-driven revascularization, or ARC stent thrombosis at 2 hours (1.6% [n=88] versus 0.9% [n=50]; hazard ratio, 0.57 [95% CI, 0.40–0.80], *P*=0.001; Figure 1B). Compared with clopidogrel the benefit of cangrelor was driven by significant early reductions in MI (SCAI definition) at 2 hours (1.4% [n=75] versus 0.8% [n=44]; hazard ratio, 0.59 [95% CI, 0.40–0.85]; *P*=0.004; Figure 2A) and ST (n=70 [1.3%] versus n=37 [0.7%]; hazard ratio, 0.53 [95% CI, 0.35–0.79], *P*=0.001 [Figure 2B]). As a sensitivity analysis because SCAI-MI and ARC-ST occur post procedurally, we also counted events beginning post-PCI. Of the 270 ischemic events from the secondary composite that occurred post-PCI, the majority occurred during the first two hours (63.3% [n=171]). MI (SCAI definition) was the most common event (44%, n=120); 7% (n=19) were ARC-ST, 7% (n=19) ischemia driven revascularization, and 5% (n=14) death (Figure 3). There was no excess of events (16 versus 15; *P*=0.86) in the cangrelor arm during the 2 to 6 hours transition period to oral clopidogrel when compared with patients given clopidogrel at the time of PCI. Between 2 and 48 hours, there was no difference in the primary composite end point of death, MI, ischemia driven revascularization, or stent thrombosis between patients randomized to either cangrelor or clopidogrel (0.6% [n=34] versus 0.5% [n=29]; odds ratio, 1.17 [95% CI, 0.71–1.93]; *P*=0.53). In the period from 2 to 6 hours compared with the first 2 periprocedural hours, overall number of events decreased by 73%. When stratifying early and late outcomes by the loading dose of clopidogrel, the odds ratio of the primary end point at 2 hours in patients treated with cangrelor compared with clopidogrel was 0.79 (95% CI, 0.57–1.09; *P*=0.15) in the cohort loaded with 300 mg of clopidogrel and 0.74 (95% CI, 0.59–0.91; *P*=0.01) for patients loaded with 600 mg of clopidogrel. There were no differences in late outcomes in both the 300 and 600 mg loading dose cohorts (Tables S1 and S2).

In a multivariable analysis, factors associated with the increased risk of the composite of death, MI (SCAI), ischemia-driven revascularization, or ARC-ST at 2 hours included intent to use a 300 mg loading dose of clopidogrel, being randomized from a site in the United States treatment with a GPI, longer PCI duration, and infusion of cangrelor for <120 minutes. In contrast, factors associated with a lower risk of the composite of death, MI

Table 1. Event Rates and Odds Ratios for Early (≤2 Hours) and Late (>2 Hours) Events

	Cangrelor (N=5470)	Clopidogrel (N=5469)	OR (95% CI)	*P* value
Early events (≤2 h)				
Death, MI, IDR, ST (protocol)	223 (4.1%)	293 (5.4%)	0.75 (0.63–0.90)	0.002
Death, MI (SCAI), IDR, ST	80 (1.5%)	134 (2.5%)	0.59 (0.45–0.78)	<0.001
Death, MI (SCAI), IDR, ARC-ST	50 (0.9%)	88 (1.6%)	0.56 (0.40–0.80)	0.001
Death	7 (0.1%)	6 (0.1%)	1.17 (0.39–3.47)	0.78
MI (protocol)	191 (3.5%)	243 (4.4%)	0.78 (0.64–0.94)	0.01
MI (SCAI)	44 (0.8%)	75 (1.4%)	0.58 (0.40–0.85)	0.005
IDR	2 (0.1%)	11 (0.2%)	0.18 (0.04–0.82)	0.03
ST	37 (0.7%)	70 (1.3%)	0.53 (0.35–0.78)	0.002
ARC-ST	2 (0.0%)	17 (0.3%)	0.12 (0.03–0.51)	0.004
Late events (>2 to 48 h)				
Death, MI, IDR, ST (protocol)	34 (0.6%)	29 (0.5%)	1.17 (0.71–1.93)	0.53
Death/MI (SCAI)/IDR/ST	29 (0.5%)	24 (0.4%)	1.21 (0.70–2.08)	0.49
Death/MI (SCAI)/IDR/ARC-ST	29 (0.5%)	26 (0.5%)	1.12 (0.66–1.90)	0.69
Death	11 (0.2%)	12 (0.2%)	0.92 (0.40–2.08)	0.83
MI (protocol)	16 (0.3%)	12 (0.2%)	1.33 (0.63–2.82)	0.45
MI (SCAI)	9 (0.2%)	6 (0.1%)	1.50 (0.53–4.22)	0.44
IDR	26 (0.5%)	27 (0.5%)	0.96 (0.56–1.65)	0.89
ST	9 (0.2%)	4 (0.1%)	2.25 (0.69–7.32)	0.18
ARC-ST	10 (0.2%)	5 (0.1%)	2.00 (0.68–5.86)	0.21

ARC indicates Academic Research Consortium; IDR, ischemia driven revascularization; MI, myocardial infarction; OR, odds ratio; SCAI, Society of Angiography and Intervention; and ST, stent thrombosis.

(SCAI), ischemia-driven revascularization, or ARC-ST at 2 hours included treatment with cangrelor, positive cardiac biomarkers at baseline, tobacco use, receipt of a drug-eluting stent (Table 2).

Treatment with cangrelor was associated with lower risk of SCAI MI (adjusted odds ratio, 0.57 [95% CI, 0.35–0.94]; *P*=0.03) while an intended clopidogrel dose of 300 mg was associated with an increased risk of SCAI MI (adjusted odds ratio, 3.20 [95% CI, 1.61–6.36]; *P*=0.009). Other predictors of increased risk of SCAI MI at 2 hours included randomization in the United Sates, 300 mg clopidogrel loading dose, utilization of a GPI, short duration of cangrelor infusion, and an increased duration of PCI. Other predictors of a lower risk of SCAI MI at 2 hours included elevated cardiac biomarkers, tobacco use, and treatment with a drug-eluting stent (Table S3).

Early (≤2 hours of randomization) GUSTO moderate or severe bleeding events were infrequent and there was no significant difference in rates of these events in patients treated with cangrelor compared with clopidogrel (0.2% [n=10] versus 0.1% [n=4]; adjusted odds ratio, 1.41 [95% CI, 0.37–5.40]; *P*=0.62).

DISCUSSION

In this analysis of CHAMPION PHOENIX, we found the majority of cardiovascular events that occurred in the overall trial were ischemic in nature (MI, stent thrombosis), and these events occurred more frequently in the first 2 hours after the start of PCI. The early reduction in the composite cardiovascular end point was evident with both the original protocol-defined end point, as well as with a post hoc composite end point that reflected a more selective definition of MI and ST. The use of SCAI-defined MI and ARC-ST provided further reassurance that cangrelor could reduce ischemic complications of PCI even when using a definition that identified a subset of events which some have thought may be more clinically important.[3]

These early events corresponded with the time in which patients randomized to cangrelor were receiving the intravenous $P2Y_{12}$ inhibitor. Thus, earlier onset of platelet inhibition with an intravenous drug allows for platelet inhibition that is earlier than oral clopidogrel (which must be converted into its active form by the liver). Furthermore, since cangrelor is available in an intravenous formulation which is immediately active, the platelet inhibition is more consistent than clopidogrel and unaffected by differences in genotype.[14]

These data demonstrate that the reductions in ischemic events with cangrelor corresponded to the time in which patients were being treated with cangrelor. From 2 hours on, a period of time in which 70% of patients randomized to cangrelor had already been transitioned to oral clopidogrel, the odds of ischemic events were similar in both groups. This demonstrates that the transition period from cangrelor to oral maintenance

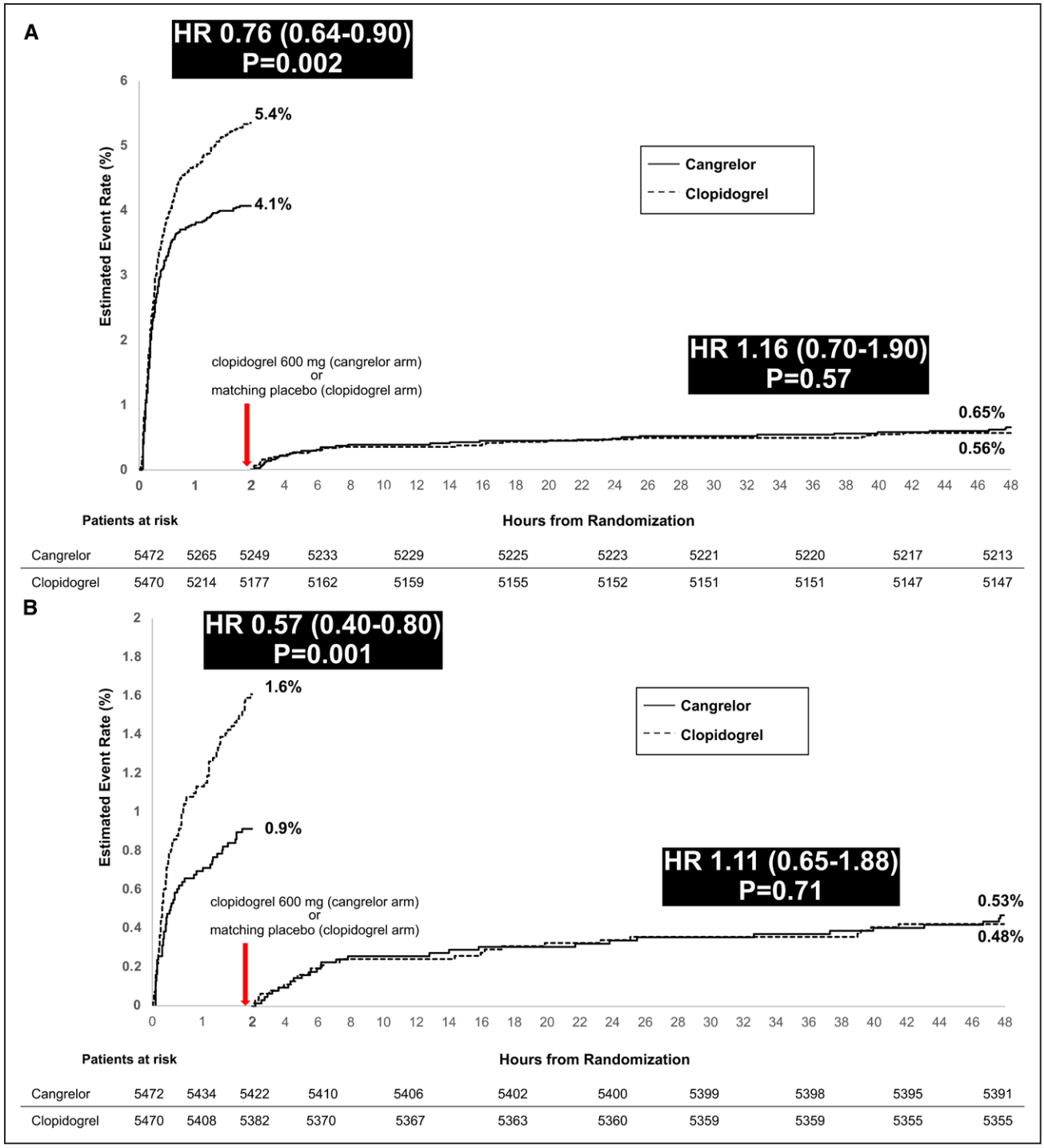

Figure 1. Landmark analyses of composite ischemic end points.
Landmark analysis of the (**A**) incidence of death, myocardial infarction, ischemia driven revascularization, or stent thrombosis at 2 hr following randomization and after 2 hr and (**B**) death, myocardial infarction [Society of Angiography and Intervention], ischemia driven revascularization, or Academic Research Consortium stent thrombosis at 2 hr following randomization and after 2 hr. HR indicates hazard ratio.

therapy (clopidogrel) did not result in adverse ischemic consequences.

These data also support the hypothesis that an effective antiplatelet strategy reduces thrombotic events in patients undergoing PCI. In addition, it supports prior findings of increased risk of ischemic events in the early time period around PCI.[15] Previous analyses from the CHAMPION program support the idea that early periprocedural antiplatelet therapy (beyond aspirin and anticoagulation) does indeed further reduce important ischemic events.[4] However, given the low number of adverse cardiovascular events seen in patients undergoing PCI in the nonacute

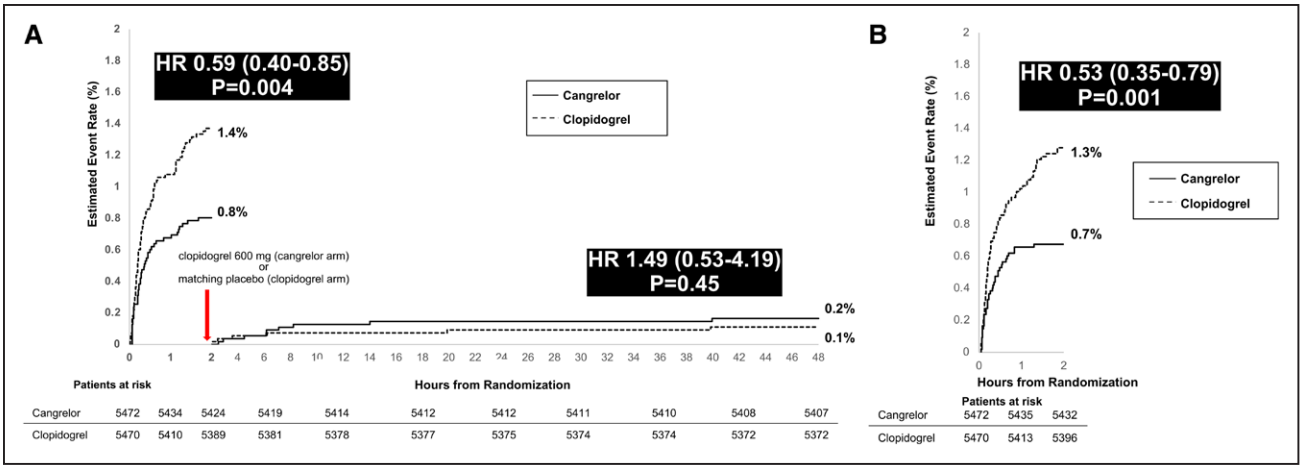

Figure 2. Landmark analyses of individual ischemic end points.
Landmark analysis of the incidence of (**A**) myocardial infarction (Society of Angiography and Intervention Definition) before and after 2 hr postrandomization and (**B**) stent thrombosis at 2 hr. HR indicates hazard ratio.

MI setting, it would require an extremely large randomized clinical trial to prove that more potent antiplatelet therapy reduces mortality in this particular subset of patients, though in the CHAMPION PLATFORM trial of cangrelor versus placebo, there was a significantly lower rate of mortality with cangrelor.[4]

Treatment with cangrelor, when compared with clopidogrel, reduced these early ischemic events without increasing the incidence of early or late severe bleeding events seen with other intravenous therapies, such as GPI.[16,17] The absolute risk reduction seen in early trials with GPIs was similar to the absolute increase in the risk of major bleeding events. However, contemporary randomized trials in patients with non–ST-segment–elevation acute coronary syndrome failed to show a benefit with GPI but did continue to find a significant increase in the risk of bleeding.[18,19]

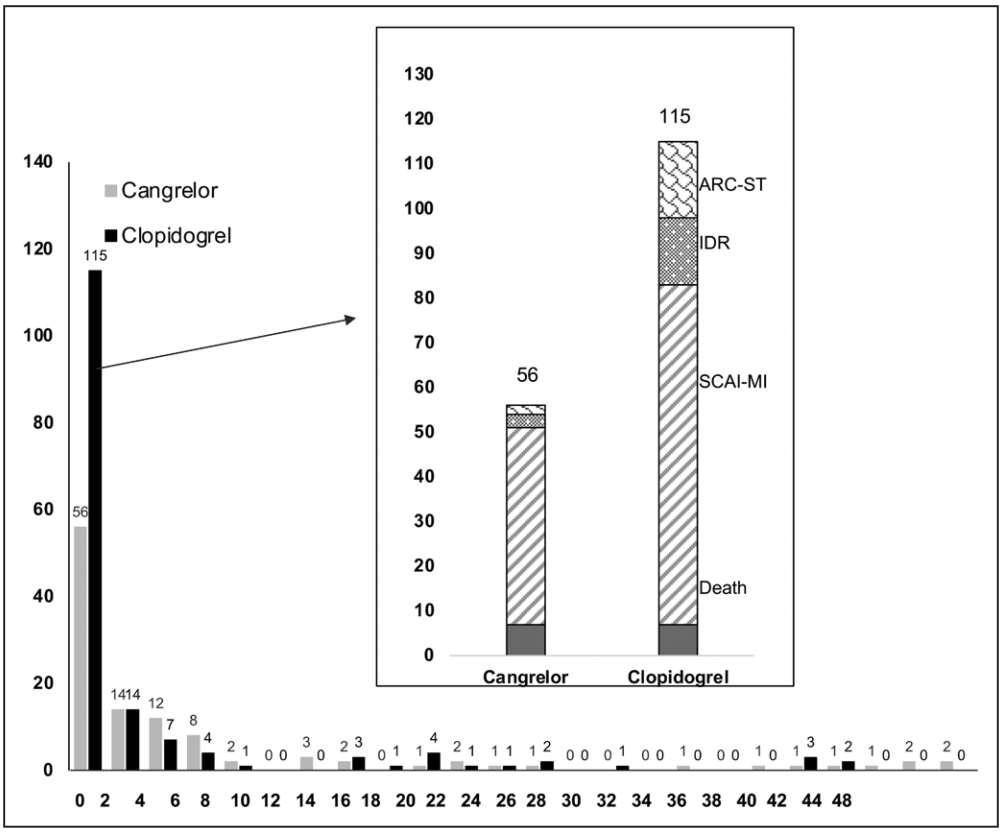

Figure 3. Distribution and type of ischemic events post-percutaneous coronary intervention in CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention).
ARC indicates Academic Research Consortium; IDR, ischemia driven revascularization; MI, myocardial infarction; SCAI, Society of Angiography and Intervention; and ST, stent thrombosis.

Table 2. Factors Associated With Risk of Death, MI (SCAI), Ischemia Driven Revascularization, or ARC Stent Thrombosis at 2 Hours

Factor	Category	Event (N=138)	No event (N=10801)	Adjusted OR and 95% CI	*P* value for adjusted OR
Treatment	Cangrelor	50/5470 (0.9)	5420/5470 (99.1)	0.51 (0.32–0.81)	0.005
	Clopidogrel	88/5469 (1.6)	5381/5469 (98.4)		
Intended clopidogrel loading dose	300 mg	55/2806 (2.0)	2751/2806 (98.0)	2.93 (1.54–5.57)	0.001
	600 mg	83/8133 (1.0)	8050/8133 (99.0)		
United States	Yes	58/4097 (1.4)	4039/4097 (98.6)	3.98 (1.54–10.33)	0.005
	No	80/6842 (1.2)	6762/6842 (98.8)		
Baseline cardiac marker positive	Yes	33/3980 (0.8)	3947/3980 (99.2)	0.48 (0.27–0.83)	0.009
	No	105/6950 (1.5)	6845/6950 (98.5)		
Smoker	Yes	69/6305 (1.1)	6236/6305 (98.9)	0.57 (0.36–0.92)	0.02
	No	66/4370 (1.5)	4304/4370 (98.5)		
Received eluting stent	Yes	56/5808 (1.0)	5752/5808 (99.0)	0.45 (0.27–0.76)	0.003
	No	75/4651 (1.6)	4576/4651 (98.4)		
GPI used	Yes	25/380 (6.6)	355/380 (93.4)	9.81 (4.90–19.63)	<.0001
	No	113/10559 (1.1)	10446/10559 (98.9)		
Infusion duration	≤120 min	58/3287 (1.8)	3229/3287 (98.2)	2.33 (1.40–3.87)	0.001
	>120 min	80/7641 (1.0)	7561/7641 (99.0)		
PCI duration, mins	N	138	10799	1.01 (1.01–1.02)	0.001
	Mean±SD	35.59±31.23	22.44±19.21		
	Median	26.50	17.00		
	(Q1, Q3)	13.0–43.0	10.0–30.0		
	(min, max)	2.0–205.0	0.0–359.0		

ARC indicates Academic Research Consortium; GPI, glycoprotein IIb/IIIa inhibitor; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; and SCAI, Society of Angiography and Intervention.

In the CHAMPION PHOENIX trial, most patients randomized were undergoing PCI for stable angina (n=6140, 56%). The percentages of patients undergoing PCI for NSTEMI (26%) and STEMI (18%) were lower. Therefore, the majority of ischemic events occurred in patients undergoing PCI for stable angina (n=403), with a lower number of events in patients with NSTEMI (n=111) and STEMI (n=65). In the overall trial, there was no interaction between the benefit with cangrelor and the index indication for PCI (*P* value [interaction]=0.98).[6,20] The angiographic core-lab analysis from CHAMPION PHOENIX (the largest to date) showed that benefits were present in acute coronary syndrome, as well as non-acute coronary syndrome patients, especially when the latter group had high risk angiographic features.[21]

The findings from this study should be interpreted in the context of some limitations. First, these analyses represent a post hoc analysis analyzing the effects of cangrelor at a period of time not designated as the primary duration. We chose 2 hours because this corresponds to a time in which patients were being treated with cangrelor and before the period of time in which they were transitioned to oral clopidogrel. All patients in the comparator arm were treated with clopidogrel, and the timing of clopidogrel administration (either before the start of the PCI or immediately after) was left to the discretion of the individual operator. Both these subgroups showed consistent benefit. Whether the early reduction in events seen with cangrelor would persist when compared with more potent oral $P2Y_{12}$ inhibitors cannot be addressed directly by CHAMPION PHOENIX. However, the CANTIC trial (Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) found a significant degree of additional platelet inhibition in patients with STEMI on top of the antiplatelet effect of ticagrelor.[22] In the CANTIC trial, patients undergoing primary PCI were randomized to either cangrelor or crushed ticagrelor. Those patients randomized to cangrelor had significantly lower $P2Y_{12}$ reaction units compared with patients randomized to crushed ticagrelor.[22] In addition, previous studies have not found more potent, oral $P2Y_{12}$ inhibitors to reduce ischemic events when used before revascularization in patients with acute coronary syndromes, and the most recent European Society of Cardiology guidelines give such routine oral pretreatment a class III recommendation when the coronary anatomy is unknown and an early invasive strategy is planned.[23–25] Furthermore, cangrelor has been shown to have antiplatelet effects which occur more quickly than oral $P2Y_{12}$ inhibitors. In the CHAMPION PHOENIX trial, patients were excluded if they had previously been treated with an intravenous platelet inhibitor since it would have not been possible to assess the effects of cangrelor if patients had already been treated with another agent before randomization in the trial. Finally, the cost effectiveness of therapy with cangrelor has yet to

be fully defined. Prior studies have found intraprocedural thrombotic events and delays to coronary bypass surgery, which were reduced with cangrelor, to be associated with significant health care costs.[26,27]

In conclusion, the reductions in ischemic events, and thus, the overall efficacy seen with cangrelor in this exploratory analysis of CHAMPION PHOENIX occurred early and during the period of time in which patients were being actively treated with cangrelor. These findings affirm the feasibility of the transition strategy for procedural cangrelor to oral maintenance $P2Y_{12}$ inhibition and provide evidence that supports the importance of potent platelet inhibition during PCI.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

APPENDIX

CHAMPION PHOENIX Leadership

Executive Committee: Deepak L. Bhatt, MD, MPH (co-Principal Investigator and co-Chair); Robert A. Harrington, MD (co-Principal Investigator and co-Chair); C. Michael Gibson, MS, MD; Christian W. Hamm, MD; Kenneth W. Mahaffey, MD; Matthew J. Price, MD; Ph. Gabriel Steg, MD; Gregg W. Stone, MD; Harvey D. White, DSc.

National Coordinators: Kurt Huber; MD (Austria); Valter C. Lima, MD, PhD (Brazil); Julia B. Jorgova-Makedonska, MD, PhD (Bulgaria); Petr Widimský, MD, DSc (Czech Republic); Bondo Kobulia, MD, PhD (Georgia); Peter W. Radke, MD (Germany); Ezio Bramucci, MD (Italy); Adam Witkowski, MD, PhD (Poland); Evgeny Shlyakhto, MD, PhD (Russia).

Data and Safety Monitoring Committee: Frans Van de Werf, MD (Chair); David P. Faxon, MD; E. Magnus Ohman, MD; Freek W.A. Verheugt, MD; W. Douglas Weaver, MD; Jan G.P. Tijssen, PhD (statistician).

Clinical Event Committee (Duke Clinical Research Institute): Kenneth W. Mahaffey, MD (Chair); Sergio Leonardi, MD, MHS (co-Chair); Matthew Wilson, RN (Project Leader); Stacey Mangum, RN (Study Coordinator); Reviewers: Renato D. Lopes, MD, PhD, MHS; Chiara Melloni, MD, MHS; Matthew J. Brennan, MD; Pierluigi Tricoci, MD, PhD, MHS; Robert Harrison, MD; Pedro Barros, MD; Luciana Armaganijan, MD; Monique Anderson, MD; Akshay Bagai, MD.

Angiographic Core Lab (Cardiovascular Research Foundation): Philippe Généreux, MD (Director); Sorin J. Brener, MD; Laura LaSalle.

CHAMPION PHOENIX Investigators

Austria (total enrollment=602): Werner Benzer, Landeskrankenhaus Feldkirch; Georg Delle-Karth, Medizinische Universität Wien; Kurt Huber, Wilhelminenspital der Stadt Wien; Franz Leisch, AKH Linz.

Brazil (total enrollment=158): Jamil Abdalla Saad, Hospital Felicio Rocho; Alexandre Abizaid, Instituto Dante Pazzanese de Cardiologia; Carlos Augusto Formiga Areas, Hospital São José; Expedito E. Ribeiro, Instituto do Coracao – INCOR; Fabio Rossi Dos Santos, Loema - Instituto de Pesquisa Clinica & Consultores; Rogerio Tadeu Tumelero, Hospital Sao Vicente de Paulo; Roberto Vieira Botelho, Instituto do Coracao do Triangulo Mineiro.

Bulgaria (total enrollment=336): Borislav Atzev, MHAT 'Puls' AD; Boicho Boichev, MHAT 'Dr Hristo Stambolski' EOOD; Georgi Grigorov, Second MHAT - Sofia AD; Nikolay Penkov, SHATC - Varna, EOOD; Ivo Petrov, MHAT 'Tokuda Hospital Sofia', AD; Boris Zehirov, MHAT 'Sveti Vrach' EOOD.

Czech Republic (total enrollment=1,630): Pavel Cervinka, Krajska zdravotni, a.s. - Masarykova nemocnice Usti nad Labem, o.z.; Zdenek Coufal, Krajska nemocnice T.Bati, a.s.; Petr Hajek, Fakultni nemocnice v Motole; David Horak, Krajska nemocnice Liberec, a.s.; Petr Kala, Fakultni nemocnice Brno; Petr Kmonicek, Nemocnice Na Homolce; Viktor Kocka, Fakultni nemocnice Kralovske Vinohrady; Jan Mrozek, Mestska nemocnice Ostrava; Stanislav Simek, Vseobecna fakultni nemocnice; Jan Sitar, Fakultni nemocnice u sv. Anny v Brne; Josef Stasek, Fakultni nemocnice Hradec Kralove; Frantisek Tousek, Nemocnice Ceske Budejovice, a.s.

Georgia (total enrollment=1,485): Gulnara Chapidze, Emergency Cardiology Center by Academician G.Chapidze LLC; Nodar Emukhvari, EOPL. Tbilisi State Medical University Alexandre Aladashvili University Clinic; George Khabeishvili, Diagnostic Services Clinic LTD; Merab Mamatsashvili, The Clinic of Angiocardiology "ADAPTI" LLC; Tamaz Shaburishvili, Tbilisi Heart and Vascular Clinic LTD.

Germany (total enrollment=494): Steffen Behrens, Vivantes Klinikum Spandau; Harald Darius, Vivantes Klinikum Neukoelln; Martin Dissmann, Vivantes-Humboldt Klinikum; Stephan Fichtlscherer, Universitaetsklinikum Frankfurt; Wolfgang Franz, Klinikum Grosshadern der LMU; Tobias Geisler, Universitaetsklinikum Tuebingen; Sabine Genth-Zotz, Universitätsmedizin der Johannes Gutenberg-Universität Mainz; Britta Goldmann, Universitaetsklinikum Hamburg-Eppendorf; Hubertus Heuer, St. Johannes Hospital – PS; Stefan Hoffmann, Vivantes Klinikum im Friedrichshain; Andreas Mugge, St. Josef-Hospital – PS; Tudor Poerner, Universitaetsklinikum Jena; Peter Radke, Universitaetsklinikum Schleswig-Holstein; Gert Richardt, Segeberger Kliniken GmbH; Christoph Stellbrink, Klinikum Bielefeld; Nikos Werner, Universitaetsklinikum Bonn.

Italy (total enrollment=621): Ezio Bramucci, Fondazione IRCCS Policlinico San Matteo; Stefano De Servi, Ospedale Civile di Legnano; Gennaro Galasso, Azienda Ospedaliera Universitaria "Federico II"; Alberto Menozzi, Azienda Ospedaliero Universitaria di Parma; Giuseppe Musumeci, Ospedali Riuniti di Bergamo; Andrea Picchi, Presidio Ospedaliero della Misericordia; Patrizia Presbitero, Istituto Clinico Humanitas.

New Zealand (total enrollment=45): Gerard Devlin, Waikato Hospital; Alexander Sasse, Wellington Hospital; Douglas Scott, Middlemore Hospital; Ralph Stewart, Auckland City Hospital.

Poland (total enrollment=702): Szyszka Andrzej, NZOZ Centrum Medyczne HCP; Witold Dubaniewicz, NZOZ Pomorskie Centra Kardiologiczne SA; Zbigniew Gasior, SPSK Nr 7 UM w Katowicach Gornosl CM prof L Gieca; Jaroslaw Kasprzak, Wojewodzki Specjalistyczny Szpital im.dr W.Bieganskiego; Andrzej Kleinrok, SP Szpital Wojewodzki im.Papieza Jana Pawla II; Zdzislawa Kornacewicz-Jach, SPSK nr 2 Pomorskiej Akademii Medycznej w Szczecinie; Andrzej Rynkiewicz, Uniwersyteckie Centrum Kliniczne; Cezary Sosnowski, Instytut Kardiologii im.Prymasa Tysiaclecia St. Kardynala Wyszynskiego; Radoslaw Targonski, NZOZ Pomorskie Centra Kardiologiczne SA; Jaroslaw Trebacz, SPZOZ Krakowski Szpital Specjalistyczny im.Jana Pawla II; Adam Witkowski, Instytut Kardiologii im.Prymasa Tysiaclecia Stefana Kardynala Wyszynskiego; Elzbieta Zinka, Szpital Wojewodzki im. M. Kopernika w Koszalinie.

Russia (total enrollment=582): Olga Barbarash, Municipal Healthcare Institution Kemerovo Cardiology Dispensary; Yakov Dovgalevsky, FSI Saratov Scientific Research Institute of Cardiology of Russian Federation MOH & Social Development; Ivan Gordeev, City Clinical Hospital #15 n.a. O.M. Filatov; Svetlana Kalinina, Ural State Medical Academy, Sverdlovsk Regional Clinical; Elena Kosmachova, State Healthcare Institution, Regional Clinical Hospital #1 n.a. Prof. S.V. Ochapovsky; Kirill Linev, Regional State Budget Healthcare Institution, Regional Clinical Hospital #1 Krasnoyarsk; Valentin Markov, Research Institure of Cardiology SB RAMS; Prokhor Pavlov, Institution of Khanty-Mansi Autonomous Area - Yugra Regional Clinical Hospital; Sergey Shalaev, State-financed Scientific Institution of Tymen Region, Tyumen division of South Ural Scientific Cent; Zaur Shogenov, Moscow State Healthcare Institution, City Clinical Hospital #81; Irina Sukmanova, State Healthcare Institution Regional Clinical Hospital; Elena Vasilieva, State Clinical Hospital #23 MedSanTrud; Alexey Yakovlev, FSBI Federal Center of Heart, Blood and Endocrinology n.a. V.A. Almazov of the MoH and Social Dev.

Thailand (total enrollment=302): Sarana Boonbaichaiyapruck, Ramathibodi Hospital; Noppadol Chamnarnphol, Songklanagarind Hospital; Pinij Kaewsuwanna, Maharat Nakhon Ratchasima Hospital; Srun Kuanprasert, Maharaj Nakorn Chiang Mai Hospital; Dilok Piyayotai, Thammasat University Hospital.

United States (total enrollment=4188): Maged Amine, Tomball Regional Hospital, TX; Dominick Angiolillo, University of Florida Health Science Center, FL; Imran Arif, University of Cincinnati, OH; James Blankenship, Geisinger Medical Center, PA; Emmanouil Brilakis, Dallas VA Medical Center, TX; Michael Chan, St. Joseph Hospital, CA; Joseph Cinderella, Peninsula Regional Medical Center, MD; Brent Davis, Mother Frances Hospital Regional Health Care Center, TX; Chandanreddy Devireddy, Emory University Hospital Midtown, GA; Mark Dorogy, Medical Center of Central Georgia, GA; John Douglas, Emory University Hospital, GA; Norman Ferrier, Black Hills Cardiovascular Research, SD; Daniel Fisher, University of Massachusetts - Worcester, MA; Robert Foster, St. Vincent's East, AL; William French, Harbor-UCLA Medical Center, CA; John Galla, Providence Hospital, AL; Lawrence Gimple, UVA Health System, VA; Harinder Gogia, Western Medical Center Santa Ana, CA; Prospero Gogo, Fletcher Allen Health Care, VT; Raghava Gollapudi, Sharp Memorial Hospital, CA; Luis Gruberg, Stony Brook University Medical Center, NY; James Hermiller, St. Vincent Medical Group, IN; Richard Heuser, St. Luke's Medical Center, AZ; Robert Iwaoka, Presbyterian Hospital, NC; Zubair Jafar, Vassar Brothers Medical Center, NY; Carey Kimmelstiel, Tufts Medical Center, MA; Scott Kinlay, VA Boston Healthcare System, MA; James Leggett, Hope Heart Institute/Overlake Medical Clinics Cardiology, WA; Pierre Leimgruber, Spokane Cardiology, P.S.C, WA; Dustin Letts, Gaston Memorial Hospital, NC; Michael Lipsitt, Saint Joseph's Hospital of Atlanta, Inc., GA; Reginald Low, UC Davis Medical Center, CA; Joaquin Martinez-Arraras, Amarillo Heart Clinical Research Institute, Inc, TX; Marc Mayhew, Wellmont Holston Valley Medical Center, TN; Brent McLaurin, AnMed Health, SC; Paul McWhirter, John Muir Medical Center, Concord Campus, CA; Ayoub Mirza, Carilion Roanoke Memorial Hospital, VA; Brian Negus, The Chattanooga Heart Institute, TN; Thomas Nygaard, Centra Lynchburg General Hospital, VA; William O'Riordan, eStudy Site, La Mesa, CA; Richard Paulus, King's Daughters Medical Center, KY; John Petersen, Swedish Medical Center - Cardiovascular Research, WA; Hector Picon, Redmond Regional Medical Center, GA; Mark Picone, Heart Hospital of Austin, TX; Matthew Price, Scripps Green Hospital, CA; Ernesto Rivera, Amarillo Heart Clinical Research Institute, Inc, TX; David Rizik, Scottsdale Healthcare Osborn, AZ; David Rizik, Scottsdale Healthcare Shea, AZ; Arsenio Rodriguez, Florida Hospital, FL; Jorge Saucedo, University of Oklahoma, OK; J. Christopher Scott, University

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