



CHAMPION PHOENIX

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Disclosures

Dr. Bhatt – Advisory Board: Medscape Cardiology; Board of Directors: Boston VA Research Institute, Society of Chest Pain Centers; Chair: American Heart Association Get With The Guidelines Science Subcommittee; Honoraria: American College of Cardiology (Editor, Clinical Trials, Cardiosource), Duke Clinical Research Institute (clinical trial steering committees), Slack Publications (Chief Medical Editor, Cardiology Today Intervention), WebMD (CME steering committees); Other: Senior Associate Editor, Journal of Invasive Cardiology; Research Grants: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company; Unfunded Research: FlowCo, PLx Pharma, Takeda.

This presentation includes off-label and/or investigational uses of drugs, including clopidogrel and cangrelor.

The CHAMPION PHOENIX trial was funded by The Medicines Company.



Antiplatelet Therapy

- ▶ Antiplatelet therapy is a critical part of contemporary PCI.
- ▶ In the era of aspirin and unfractionated heparin, intravenous glycoprotein IIb/IIIa inhibition significantly reduced important periprocedural ischemic events, but significantly increased bleeding.
- ▶ ADP receptor antagonism with oral agents was also shown to reduce ischemic events in PCI and especially ACS.
- ▶ However, available oral agents are limited by their relatively long duration of action and bioavailability, which might be a liability:
 - if given prior to coronary angiography and urgent or emergent CABG is deemed necessary,
 - in situations where absorption may be problematic, such as with rapid times to PCI,
 - in patients who are intubated, nauseated, with STEMI, or shock.

Harrington RA, et al. PURSUIT. NEJM 1998

Desai N and Bhatt DL. Periprocedural Antiplatelet Therapy. JACC Intervention 2010



Cangrelor

- ▶ Cangrelor is an intravenous ADP receptor antagonist that is rapidly acting, potent, and reversible, with return of normal platelet function within an hour.
- ▶ Cangrelor was studied previously in two large Phase 3 PCI trials, CHAMPION PCI and CHAMPION PLATFORM. Neither study met its primary endpoint, but the secondary endpoint of stent thrombosis at 48 hours was significantly reduced in CHAMPION PLATFORM and in a prespecified pooled analysis of the two trials. There was no excess in severe bleeding.
- ▶ The potential efficacy signal prompted us to launch the CHAMPION PHOENIX trial.

Harrington RA, et al. CHAMPION PCI. NEJM 2009

Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009

White HD, et al. Meta-Analysis of CHAMPION PCI and PLATFORM. AHJ 2012



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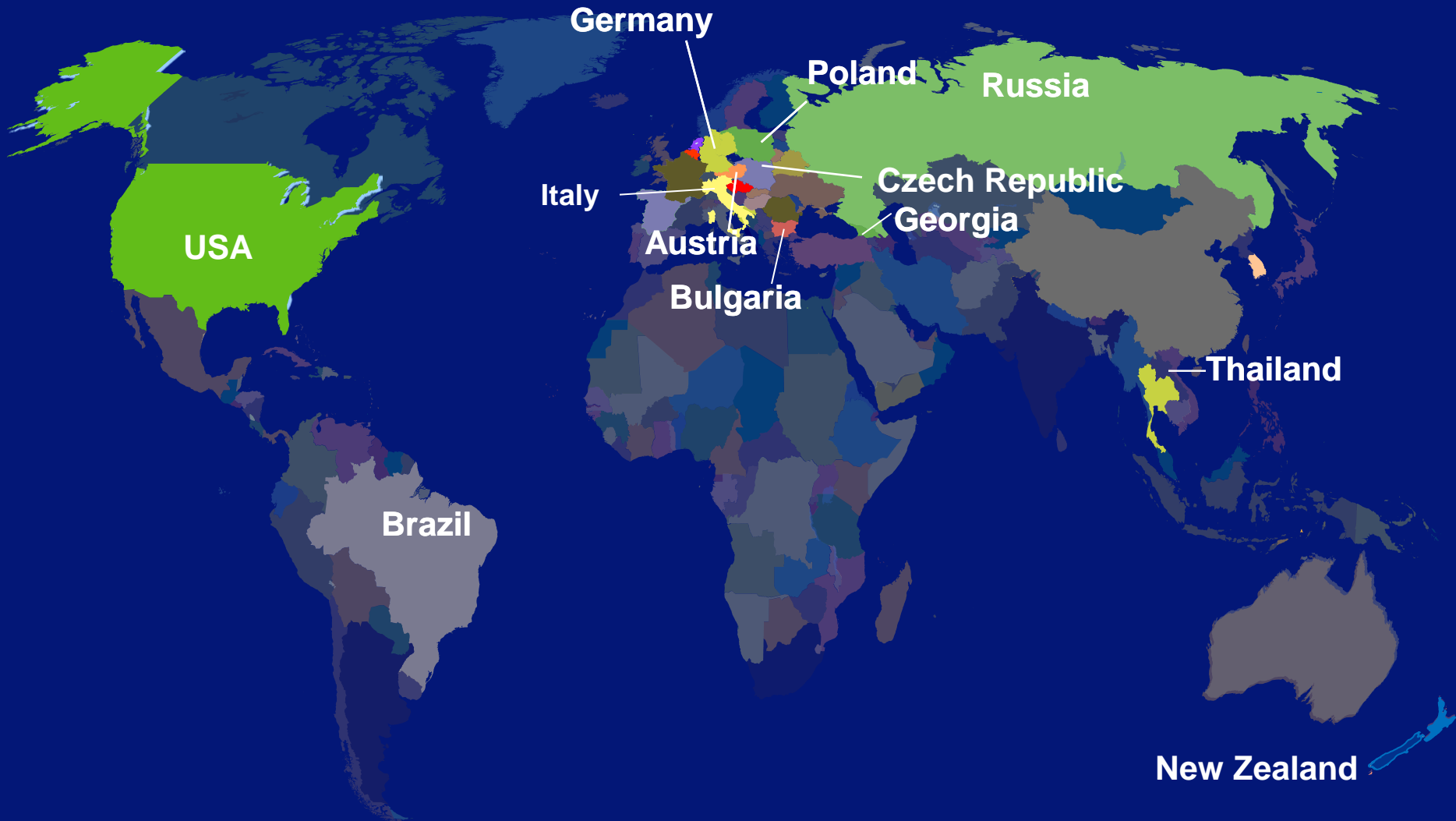
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CHAMPION PHOENIX – A Global Trial



12 Countries | 153 Sites





CHAMPION PHOENIX Study Design

- ▶ Randomized, double-blind, double-dummy, superiority
- ▶ Primary efficacy endpoint: **Death/MI/IDR/ST at 48 hours**
 - Adjusted for 600 mg versus 300 mg clopidogrel use
 - Modified Intent-to-Treat (MITT) analysis (patients actually got study drug and PCI)
- ▶ Key secondary endpoint: Stent Thrombosis at 48 hours
- ▶ Efficacy endpoints also examined at 30 days
- ▶ Primary safety endpoint: GUSTO Severe Bleeding at 48 hours

MI, myocardial infarction; IDR, ischemia-driven revascularization; ST, stent thrombosis

Harrington RA, et al. CHAMPION PCI. NEJM 2009

Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009

White HD, et al. Meta-Analysis of CHAMPION PCI and PLATFORM. AHJ 2012

Demographics, MITT



	Cangrelor (N= 5472)	Clopidogrel (N= 5470)
Age, years	64	64
Female	28%	27%
Diabetes mellitus	28%	28%
Patient Type		
Stable angina	57%	55%
NSTE-ACS	25%	26%
STEMI	18%	19%
Loading Dose		
300 mg clopidogrel	26%	26%
600 mg clopidogrel	74%	74%
Region		
United States	37%	37%
Other countries	63%	63%

Primary Efficacy Outcomes at 48 Hours, MITT



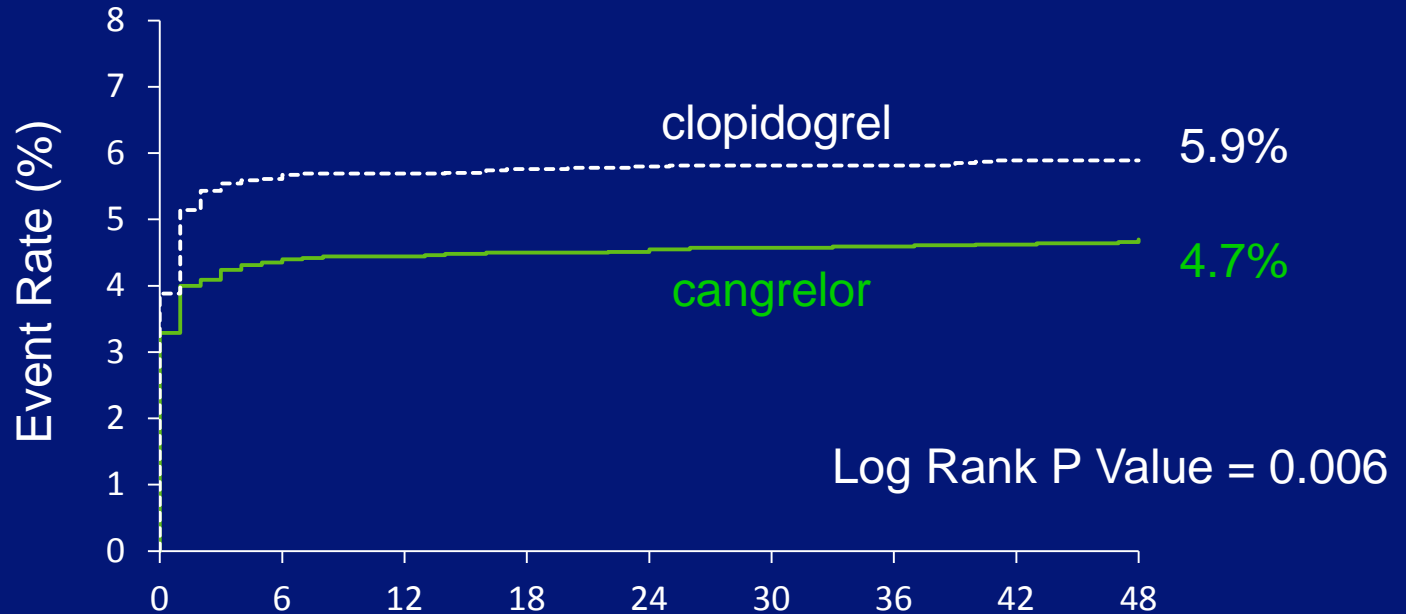
	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P-value
Primary Analysis Adjusted ¹				
Death/MI/IDR/ST	257/5470 (4.7%)	322/5469 (5.9%)	0.78 (0.66, 0.93)	0.005

Secondary Efficacy Outcomes at 48 Hours, MITT

Stent thrombosis (key secondary endpoint)	46/5470 (0.8%)	74/5469 (1.4%)	0.62 (0.43,0.90)	0.01
MI	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67,0.97)	0.02
Q-wave MI	11/5470 (0.2)	18/5469 (0.3)	0.61 (0.29,1.29)	0.19
IDR	28/5470 (0.5)	38/5469 (0.7)	0.74 (0.45,1.20)	0.22
Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99
CV Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99

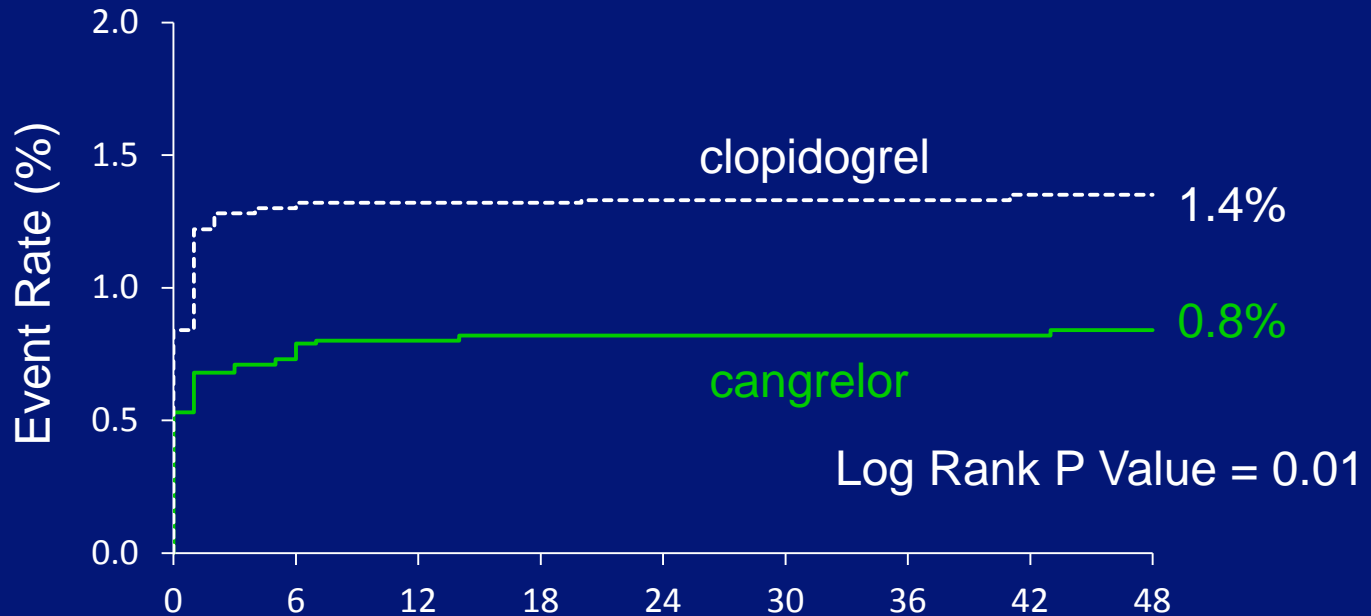
¹ The logistic model was adjusted for baseline status and clopidogrel dose. P value of 0.006 shown on the KM curve is log rank p value.

Death/ MI/ IDR/ Stent Thrombosis within 48 Hours



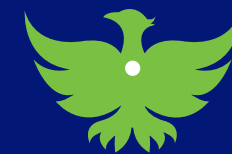
Patient at Risk	Hours from Randomization								
	0	6	12	18	24	30	36	42	48
Cangrelor:	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel:	5470	5162	5159	5155	5152	5151	5151	5147	5147

Stent Thrombosis within 48 Hours



Patient at Risk	Hours from Randomization								
Cangrelor:	5472	5426	5421	5419	5419	5418	5417	5416	5414
Clopidogrel:	5470	5392	5389	5388	5386	5385	5385	5383	5383

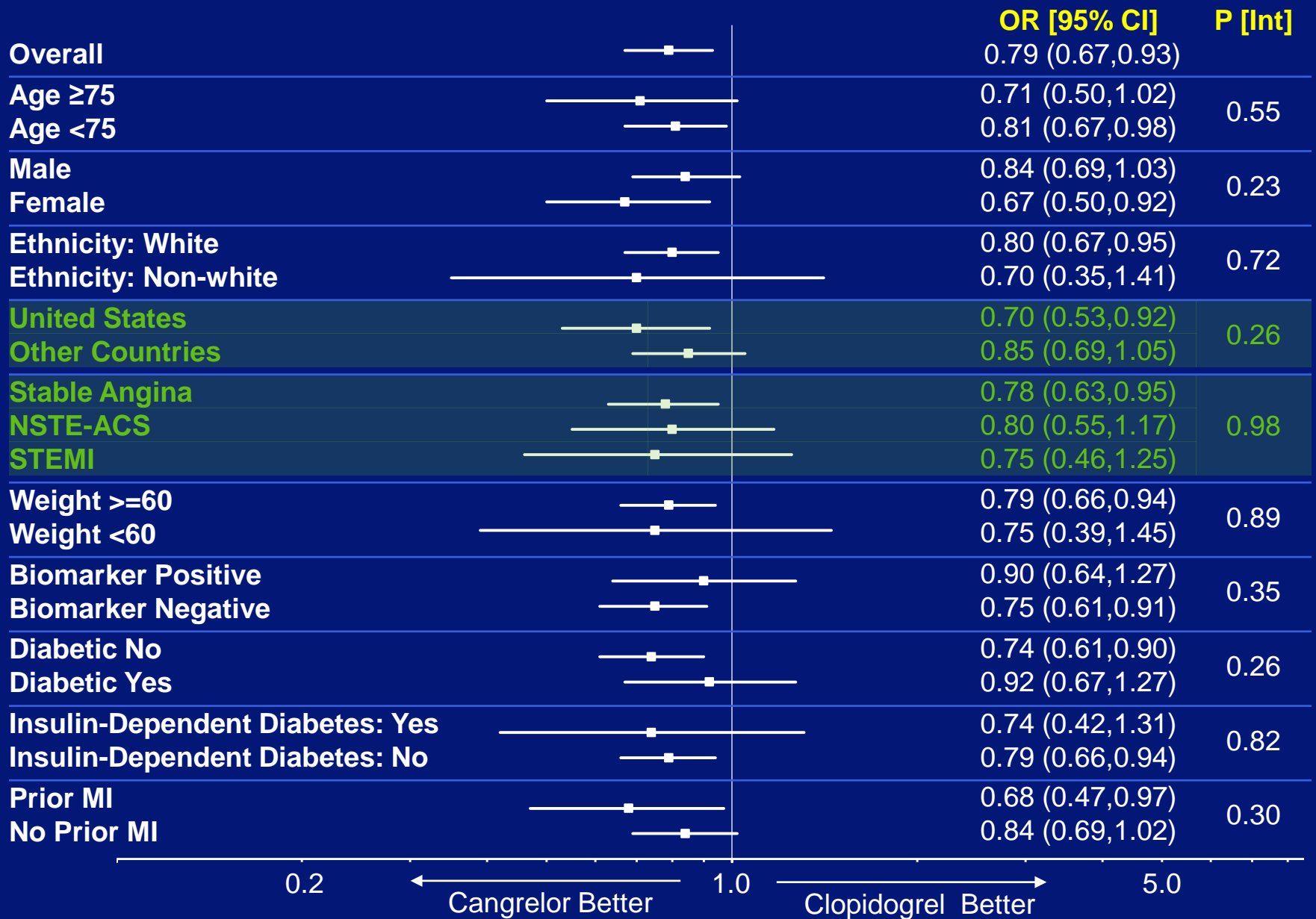
Efficacy Outcomes at 30 Days, MITT



	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P Value
Death/MI/IDR/ST (primary endpoint, adjusted)	326/5462 (6.0%)	380/5457 (7.0%)	0.85 (0.73,0.99)	0.03
Stent thrombosis	71/5462 (1.3%)	104/5457 (1.9%)	0.68 (0.50,0.92)	0.01
MI	225/5462 (4.1%)	272/5457 (5.0%)	0.82 (0.68,0.98)	0.03
Q-wave MI	14/5462 (0.3%)	22/5457 (0.4%)	0.63 (0.32,1.24)	0.18
IDR	56/5462 (1.0%)	66/5457 (1.2%)	0.85 (0.59,1.21)	0.36
Death	60/5462 (1.1%)	55/5457 (1.0%)	1.09 (0.76,1.58)	0.64
CV Death	48/5462 (0.9%)	46/5457 (0.8%)	1.04 (0.69,1.57)	0.84

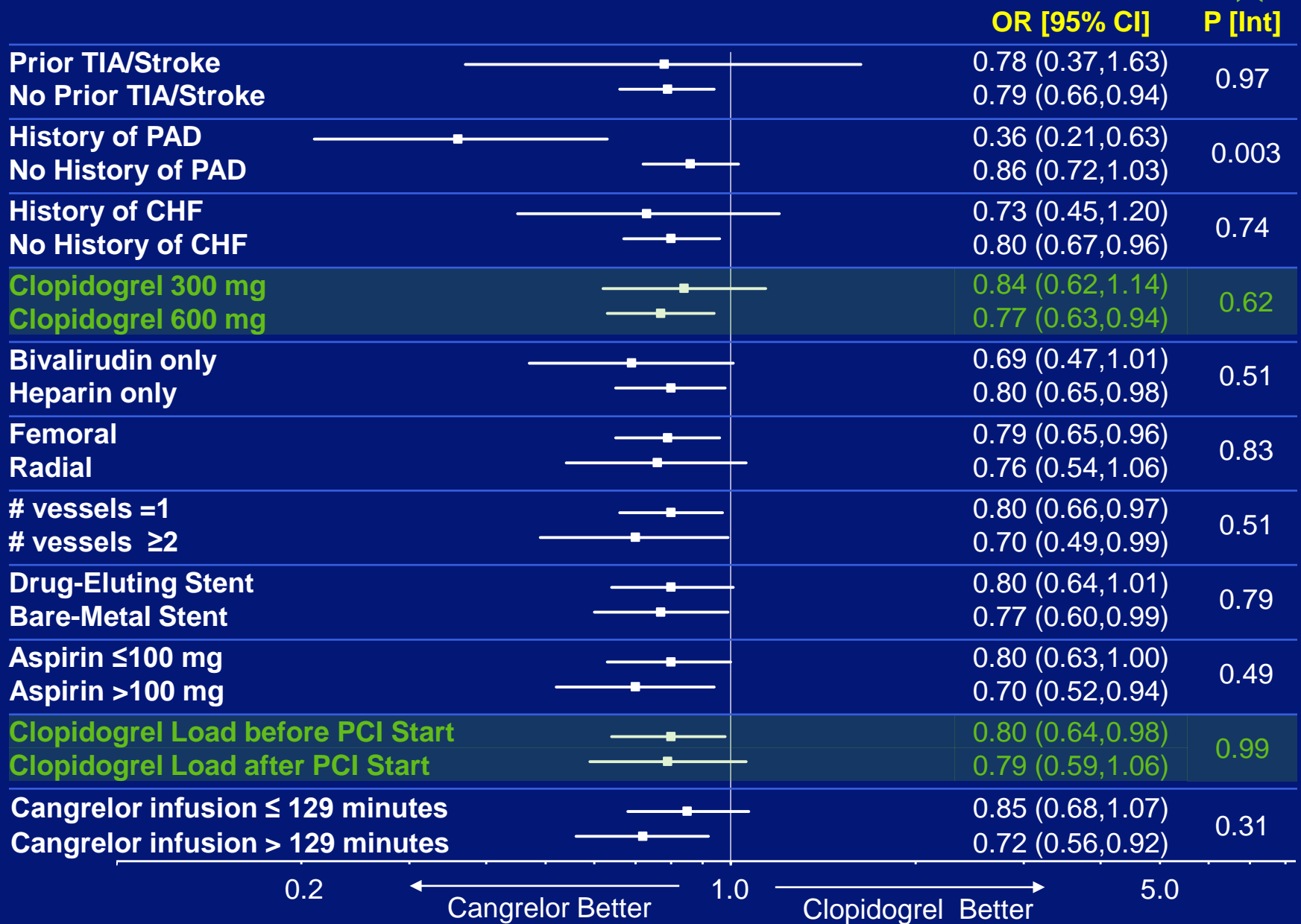


Subgroups: Death/MI/IDR/ST at 48 Hours





Subgroups: Death/MI/IDR/ST at 48 Hours (continued)

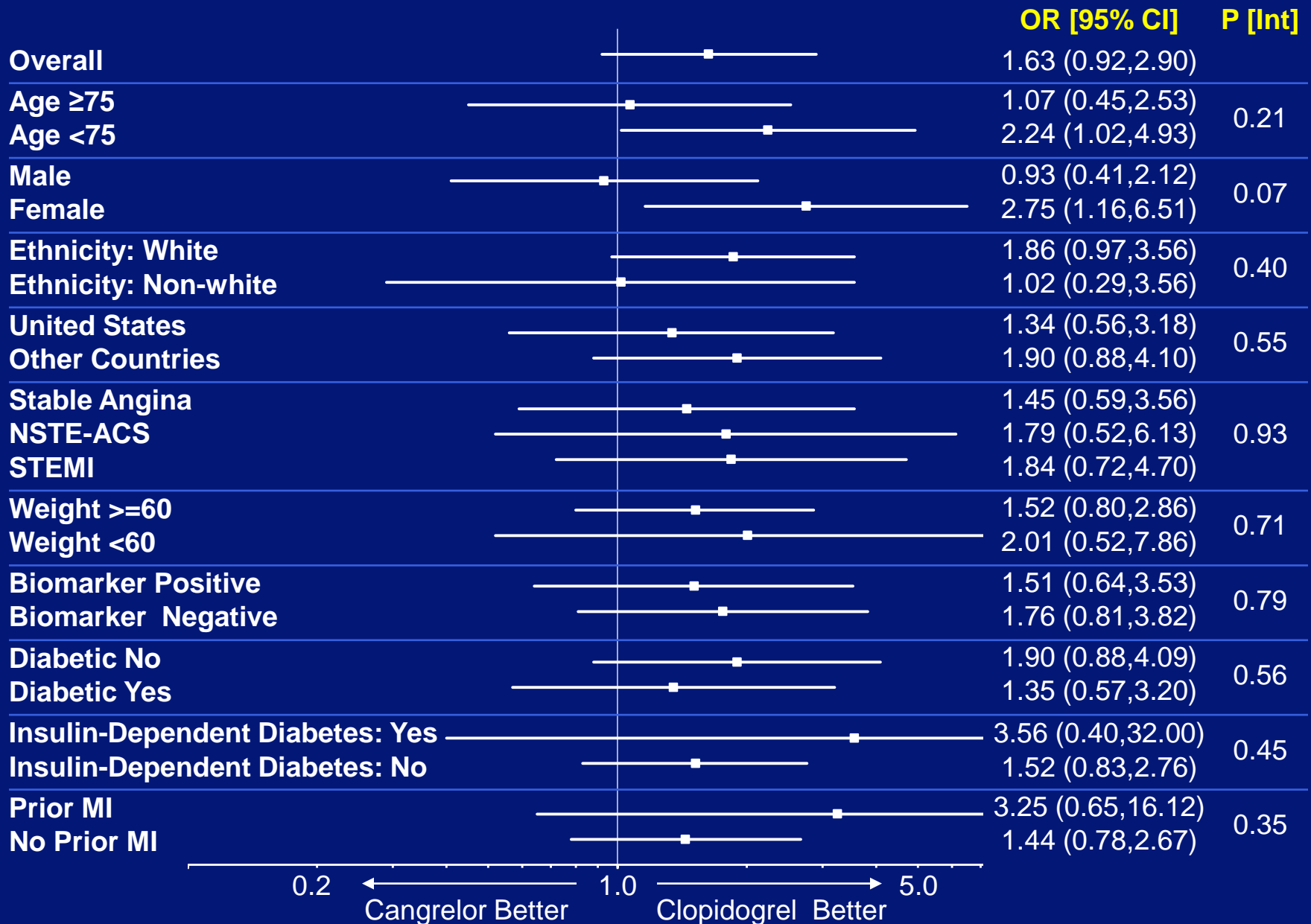
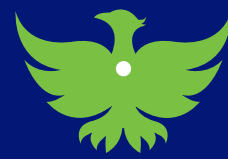


Non-CABG Bleeding at 48 Hours, Safety

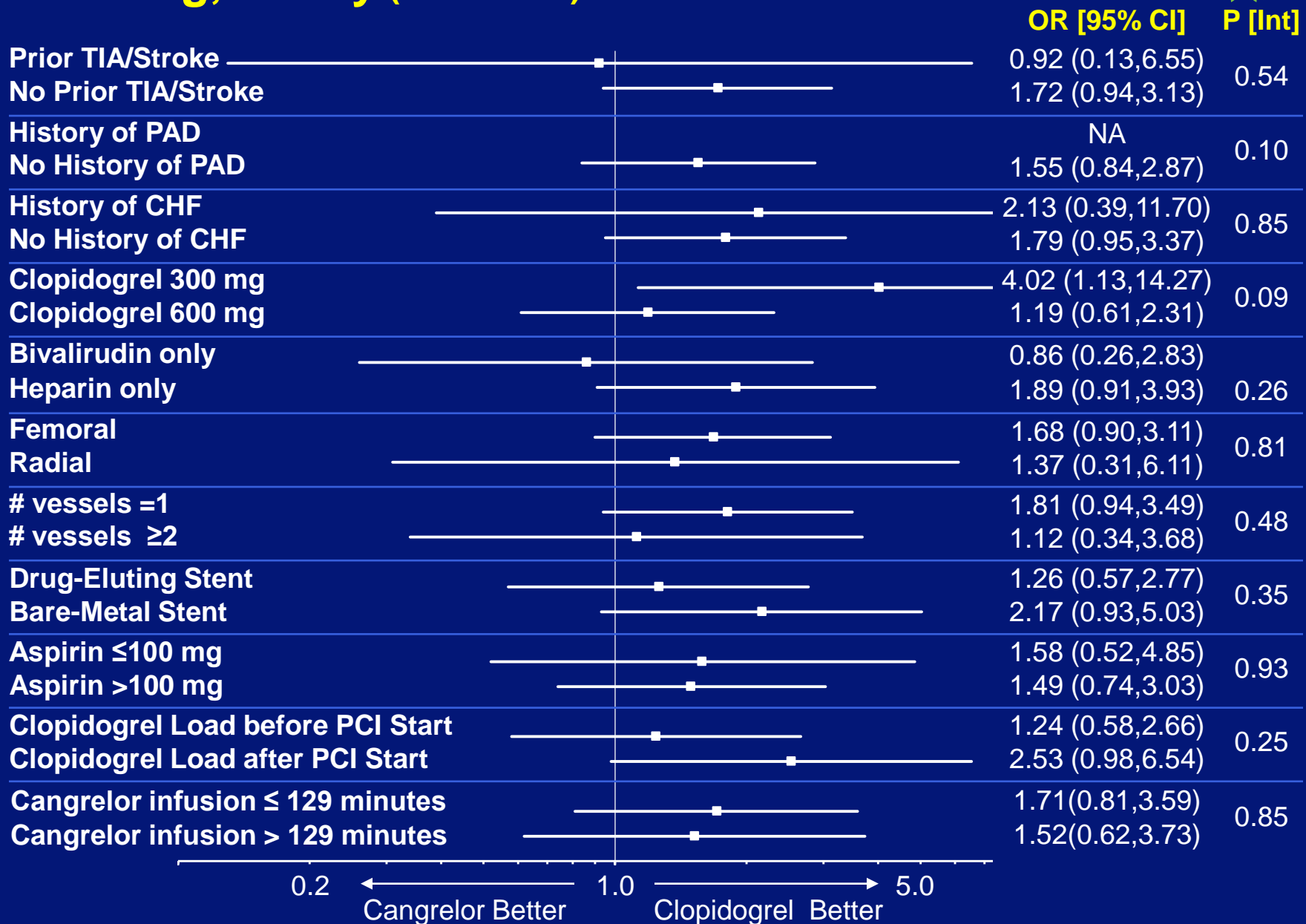
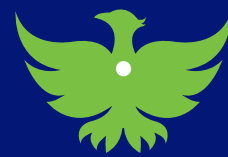


Bleeding Scale	Cangrelor (N=5529)	Clopidogrel (N=5527)	OR (95% CI)	P Value
GUSTO Severe	9 (0.16%)	6 (0.11%)	1.50 (0.53,4.22)	0.44
GUSTO Moderate	22 (0.4%)	13 (0.2%)	1.69 (0.85,3.37)	0.13
GUSTO Severe + Moderate	31 (0.6%)	19 (0.3%)	1.63 (0.92,2.90)	0.09
TIMI Major	5 (0.1%)	5 (0.1%)	1.00 (0.29,3.45)	>0.999
TIMI Minor	9 (0.2%)	3 (0.1%)	3.00 (0.81,11.10)	0.08
TIMI Major + Minor	14 (0.3%)	8 (0.1%)	1.75 (0.73,4.18)	0.2
Any Blood Transfusion	25 (0.5%)	16 (0.3%)	1.56 (0.83,2.93)	0.16
ACUITY Major	235 (4.3%)	139 (2.5%)	1.72 (1.39,2.13)	<0.001
ACUITY w/out hematoma	42 (0.8%)	26 (0.5%)	1.62 (0.99,2.64)	0.05

Subgroups: GUSTO Severe/Moderate Bleeding, Safety



Subgroups: GUSTO Severe/Moderate Bleeding, Safety (continued)



Summary of Treatment Emergent Adverse Events



Adverse Event	Cangrelor (N=5529)	Clopidogrel (N=5527)	P Value
Patients with at least one AE	20.2%	19.1%	0.13
Patients with at least one AE causing study drug discontinuation	0.5%	0.4%	0.21
Transient dyspnea	1.2%	0.3%	<0.001



Limitations

- ▶ A loading dose of 600 mg has become more common than 300 mg
 - However, in the three quarters of patients who received 600 mg, the benefit of cangrelor remained statistically significant and was not attenuated.
- ▶ It is possible the benefits we saw here would have been attenuated with a longer duration of pretreatment.
 - Of note, the clopidogrel pretreatment was given “on the table” as is consistent with many practices around the world and in particular in the United States.
 - Importantly, prospective randomized clinical trials, namely CREDO and PRAGUE-8, did not find a significant benefit for clopidogrel pretreatment.
- ▶ The benefits seen here may also have been attenuated had prasugrel or ticagrelor been used in the control arm.
 - However, to date, the largest trial of prasugrel pretreatment, ACCOAST, was terminated by the DSMB for lack of efficacy and excess bleeding.
 - Thus, oral pretreatment, while biologically appealing and intuitive, remains unproven in prospective randomized clinical trials.



Conclusions

- ▶ In CHAMPION PHOENIX, intravenous ADP receptor antagonism with cangrelor significantly ($p=0.005$) reduced the composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours, with a 22% odds reduction.
- ▶ The key secondary endpoint of stent thrombosis was also significantly reduced, with a 38% odds reduction.
- ▶ The benefit was sustained through 30 days.
- ▶ There was no excess in severe bleeding or transfusions.
- ▶ Intravenous cangrelor may be an attractive option across the full spectrum of PCI, including stable angina, NSTEMI, and STEMI.



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events

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and Robert A. Harrington, M.D., for the CHAMPION PHOENIX Investigators*



THANK YOU!



BACKUP SLIDES



Cangrelor

- ▶ Direct platelet P2Y₁₂ receptor antagonist
- ▶ ATP analogue MW=800 Daltons
- ▶ Parenteral administration
- ▶ T1/2 = 3 to 6 minutes
- ▶ Offset = 60 minutes

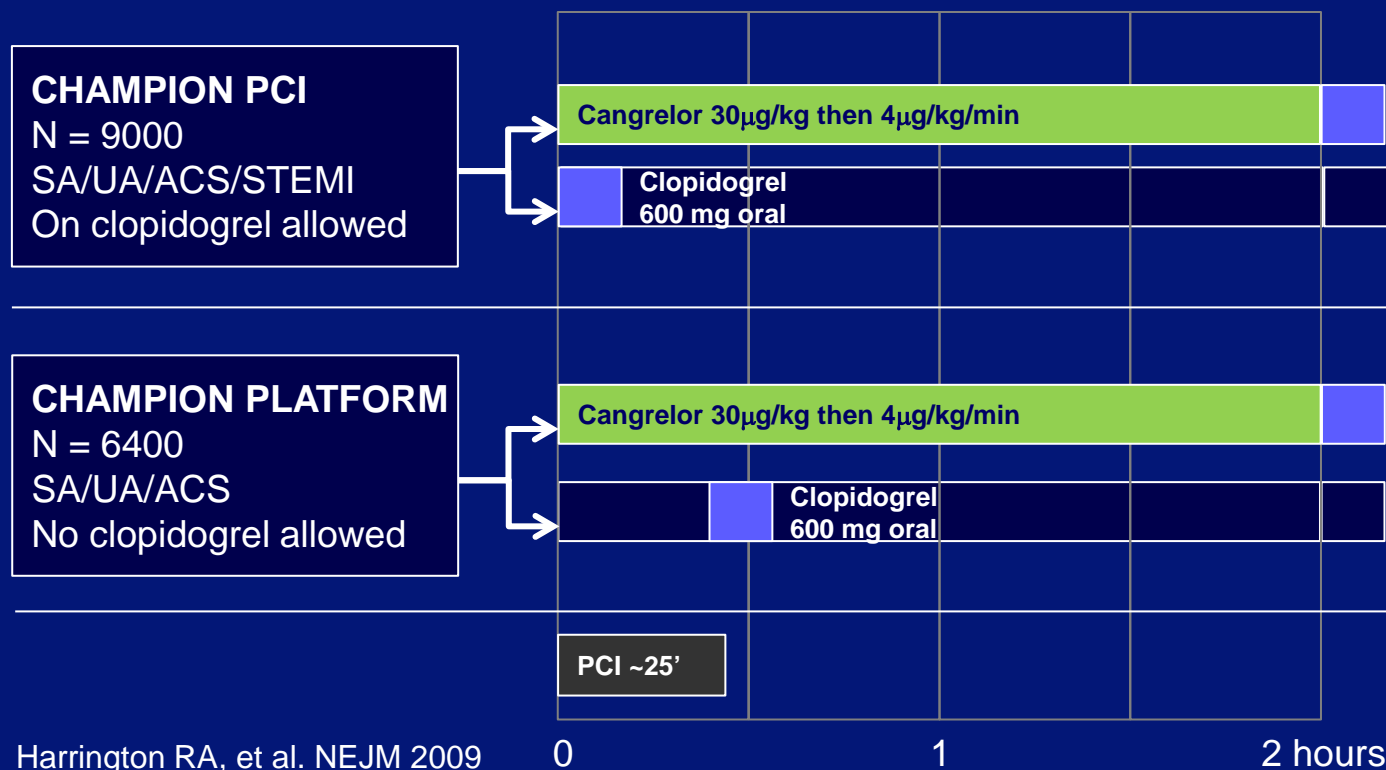


Angiolillo DJ, Schneider DJ, Bhatt DL, et al. Pharmacodynamic effects of cangrelor and clopidogrel: the platelet function substudy from the cangrelor versus standard therapy to achieve optimal management of platelet inhibition (CHAMPION) trials. *J Thromb Thrombolysis* 2012;34:44-55.



CHAMPION PCI | PLATFORM

- ▶ PCI | all comers PCI | 58% ACS | **on** clopidogrel allowed | clopidogrel 600mg administered at the **start** of PCI in the control arm
- ▶ PLATFORM | all comers PCI | 65% ACS | clopidogrel **naïve** | clopidogrel 600mg administered at the **end** of PCI in the control arm





Summary of Clinical Efficacy

48-Hour Events PLATFORM

Death/MI/IDR
Death/Q-MI/IDR
Death/Q-MI/ST

OR [95% CI] P value

0.87 (0.71,1.07) 0.17
0.55 (0.33,0.93) 0.02
0.38 (0.20,0.72) 0.003

PCI

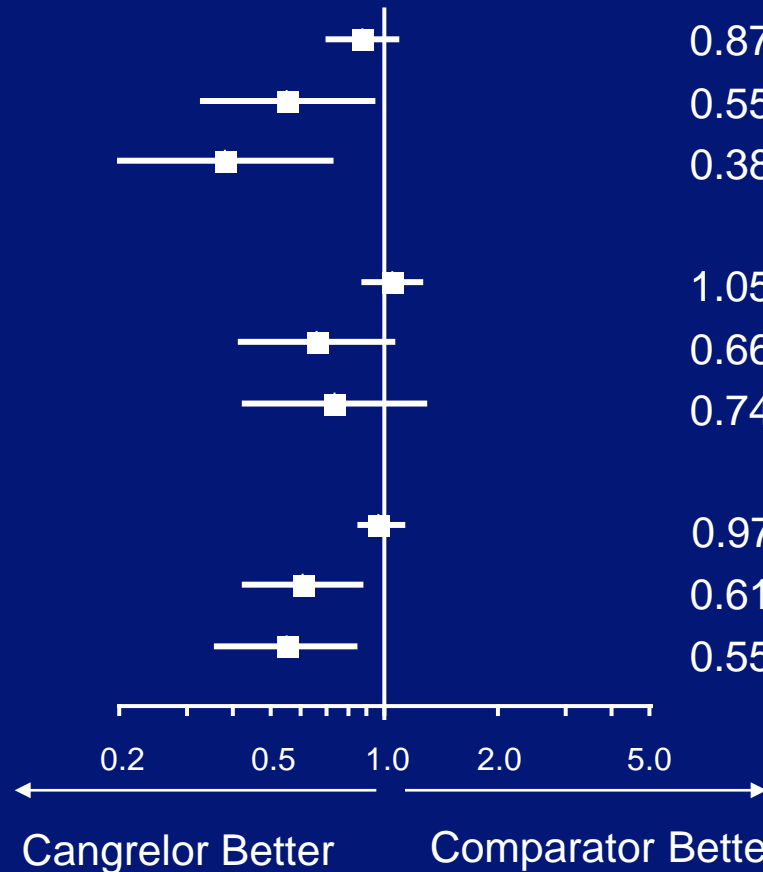
Death/MI/IDR
Death/Q-MI/IDR
Death/Q-MI/ST

1.05 (0.89,1.24) 0.57
0.66 (0.42,1.05) 0.08
0.74 (0.43,1.27) 0.27

POOLED

Death/MI/IDR
Death/Q-MI/IDR
Death/Q-MI/ST

0.97 (0.86,1.11) 0.68
0.61 (0.43,0.86) 0.005
0.55 (0.36,0.83) 0.004



1. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 2009;361:2330-41.
2. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med 2009;361:2318-29.
3. White HD, Chew DP, Dauerman HL, et al. AHJ 2012.

CHAMPION PHOENIX



Lessons from CHAMPION PCI | PLATFORM

Trial Design	Implementation
Patient population	
All comers PCI	Inclusion of patients with normal cardiac markers at baseline est. 65% trial population
P2Y ₁₂ inhibitor naïve	Patients not pre-treated with P2Y ₁₂ inhibitor within 7 days prior to angiogram
Endpoint definitions	
MI definition ¹	UDMI Central lab to assure consistency of CKMB mass assay globally angiographic core lab to consistently assess evidence of ischemia
Stent thrombosis definition ²	ARC Definition includes occurrence associated with IDR Death MI also intra-procedural stent thrombosis measured by angiographic core lab ³

1. Thygesen K, Alpert JS, and White HD, on behalf of the Joint ESC/ACCF/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J. 2007;28:2525-2538.

2. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-2351.

3. Brener SJ, Cristea E, Kirtane AJ, et al. Intra-Procedural Stent Thrombosis. J Am Coll Cardiol Intv 2013;6:36-43.



Universal Definition of MI

Better discrimination of MI with consideration of multiple criteria

CKMB elevations | ischemic symptoms | angiographic evidence |
ECG changes

Diagnosis of MI from various perspectives

Type 1 | spontaneous MI related to ischemia

Type 2 | MI secondary to ischemia | change in O₂
demand/supply

Type 3 | sudden unexpected cardiac death

Type 4 | associated with coronary angioplasty | stents

Type 4a | MI associated with PCI

Type 4b | MI associated with Stent Thrombosis

Type 5 | MI associated with CABG



Definition of ST

Angiographic Evidence:

ARC ST (Academic Research Consortium)¹

- ▶ Acute (<24 hours post-procedure)
- ▶ Subacute stent thrombosis (>24 hours and ≤30 days)
 - Definite from probable stent thrombosis
 - Adjudicated by the CEC

IPST (Intra-procedural stent thrombosis)

- ▶ New or worsening thrombus related to the stent or
- ▶ Abrupt closure due to thrombosis

1. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115(17):2344-2351.



Sample Size Estimation

- ▶ Event rate of 5.1% in the clopidogrel arm and 3.9% in the cangrelor arm (24.5% reduction in odds ratio)
- ▶ N = 10,900 (power of 85% to detect this difference at the one sided significance level of 0.025)



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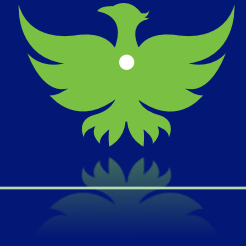
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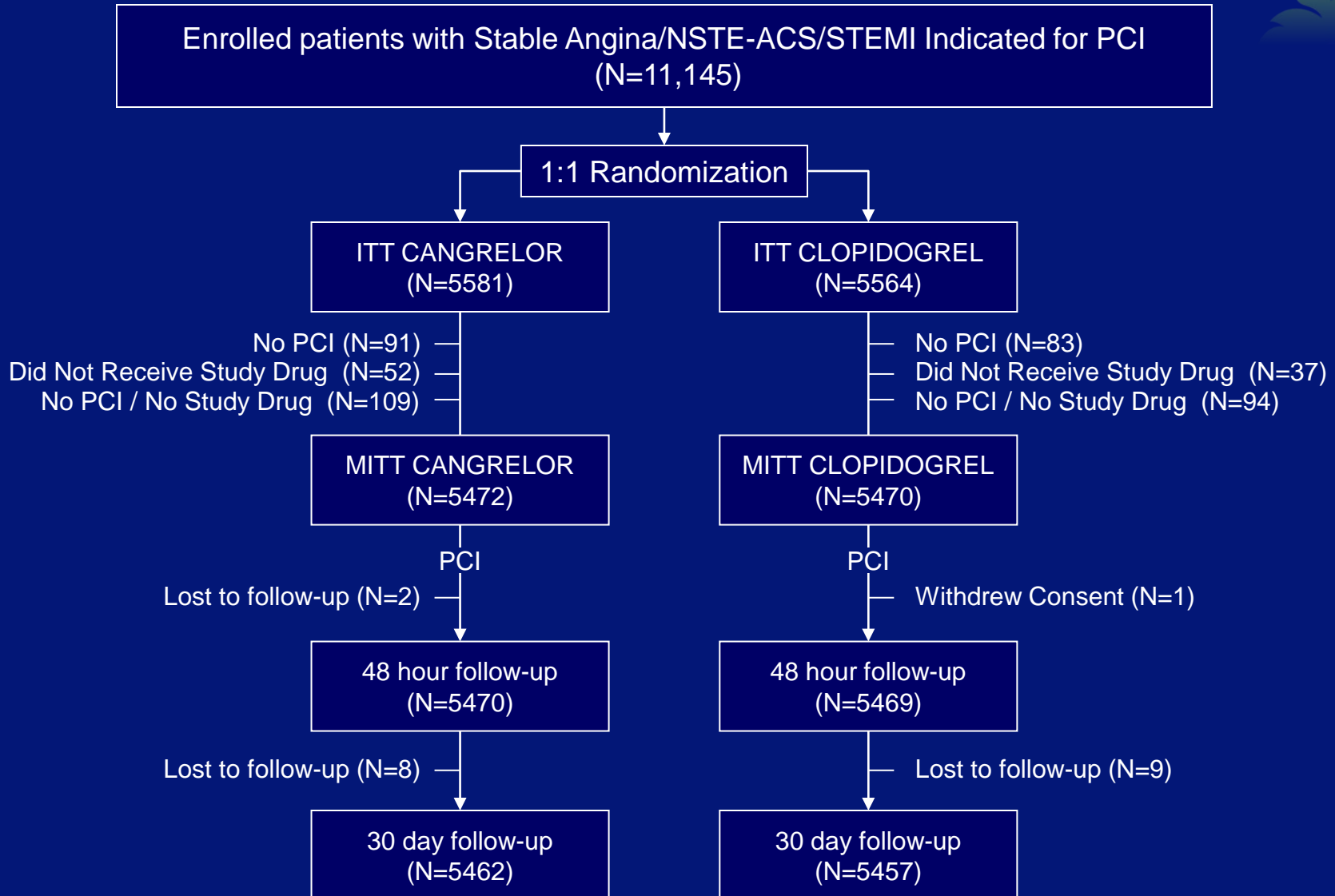
Cindy Lazos

CHAMPION PHOENIX AROs and CROs



Partners	Role
Almac	IVRS/IWRS
Merge	eCRF
Quest	CKMB central lab
Bioclinica	Web portal for angiographic film uploads
Cardiovascular Research Foundation	Angiographic Core Lab
Duke Clinical Research Institute	CEC
Green Lane Coordinating Center	Site Management – New Zealand
Worldwide Clinical Trials	Site Management – ROW excl. US + NZ
MDCO	Site Management - US

Patient Disposition



Primary Efficacy Outcome at 48 Hours, MITT



	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P-value
Primary Analysis Adjusted ¹				
Death/MI/IDR/ST	257/5470 (4.7%)	322/5469 (5.9%)	0.78 (0.66, 0.93)	0.005
Clopidogrel Loading				
300 mg	81/ 1405 (5.8%)	95/ 1401 (6.8%)	0.84 (0.62,1.14)	0.27
600 mg	176/ 4065 (4.3%)	227/ 4068 (5.6%)	0.77 (0.63,0.94)	0.009

¹. The logistic model was adjusted for baseline status and clopidogrel dose. MI, myocardial infarction; IDR, ischemia-driven revascularization; ST, stent thrombosis



Efficacy Outcomes at 48 Hours, ITT

	Cangrelor (N=5581)	Clopidogrel (N=5564)	OR (95% CI)	P Value
Death/MI/IDR/ST (primary endpoint, adjusted)	260/5573 (4.7%)	325/5561 (5.8%)	0.79 (0.67,0.93)	0.005
Stent thrombosis (key secondary endpoint)	46/5573 (0.8%)	74/5561 (1.3%)	0.62 (0.43,0.89)	0.01
MI	207/5573 (3.7)	255/5561 (4.6)	0.80 (0.67,0.97)	0.02
Q-wave MI	11/5573 (0.2)	18/5561 (0.3)	0.61 (0.29,1.29)	0.19
IDR	29/5573 (0.5)	38/5561 (0.7)	0.76 (0.47,1.23)	0.27
Death	20/5573 (0.4)	21/5561 (0.4)	0.95 (0.51,1.75)	0.87
CV Death	20/5573 (0.4)	21/5561 (0.4)	0.95 (0.51,1.75)	0.87

MI, myocardial infarction; IDR, ischemia-driven revascularization; ST, stent thrombosis