CHAMPION PHOENIX

Deepak L. Bhatt, MD, MPH, Gregg W. Stone, MD, Kenneth W. Mahaffey, MD, C. Michael Gibson, MS, MD, Ph. Gabriel Steg, MD, Christian Hamm, MD, Matthew Price, MD, Sergio Leonardi, MD, Dianne Gallup, MS, Meredith Todd, Simona Skerjanec, PharmD, Harvey D. White, DSc, and Robert A. Harrington, MD, on behalf of the CHAMPION PHOENIX Investigators

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

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
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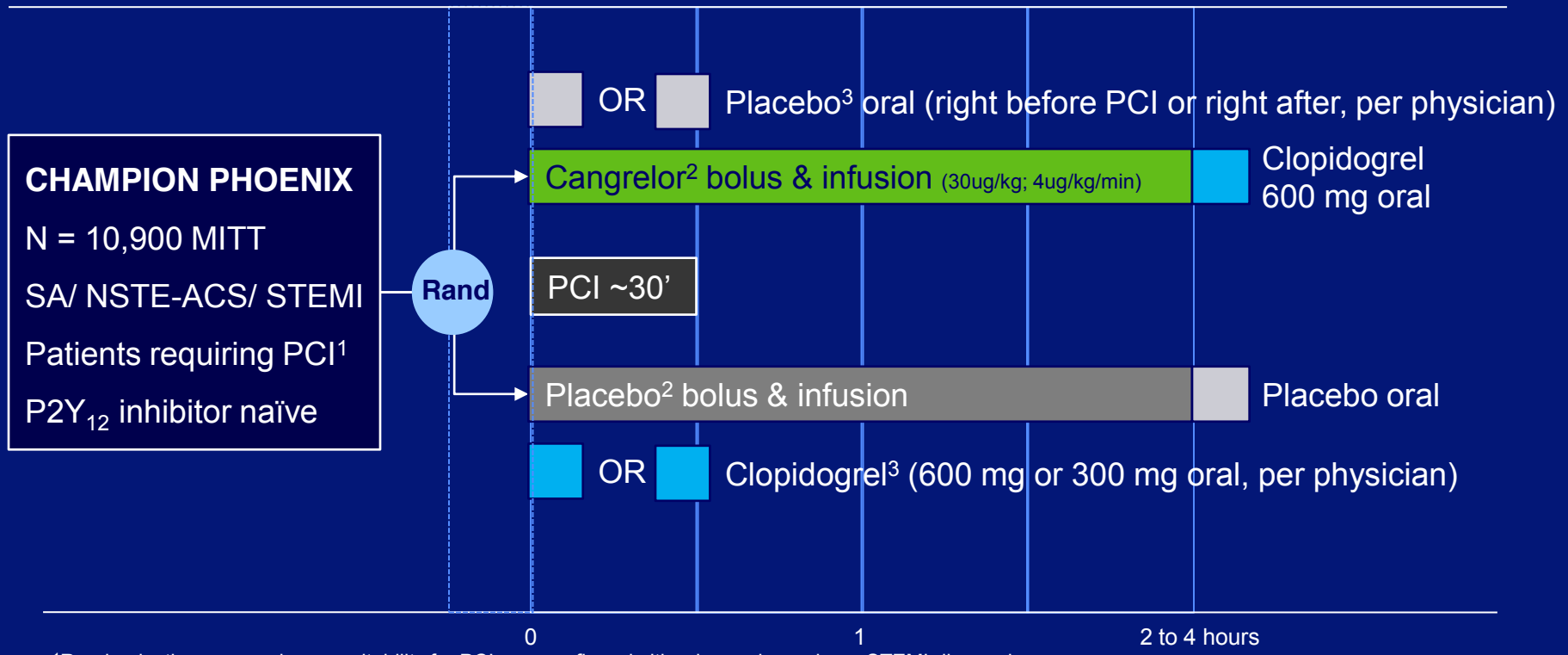
CHAMPION PHOENIX Study Design



[1]Randomization occurred once suitability for PCI was confirmed either by angiography or STEMI diagnosis. Double blind study medication was administered as soon as possible following randomization.

[2]Study drug Infusion (cangrelor or matching placebo) was continued for 2-4 hours at the discretion of the treating physician. At the end of the infusion patients received a loading dose of clopidogrel or matching placebo and were transitioned to maintenance clopidogrel therapy.

[3]Clopidogrel loading dose (or matching placebo) was administered as directed by the investigator. At the time of patient randomization, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

MITT=modified intent-to-treat; NSTE-ACS=non-ST-elevation acute coronary syndrome; PCI=percutaneous coronary intervention; SA=stable angina; STEMI=ST-elevation MI.

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

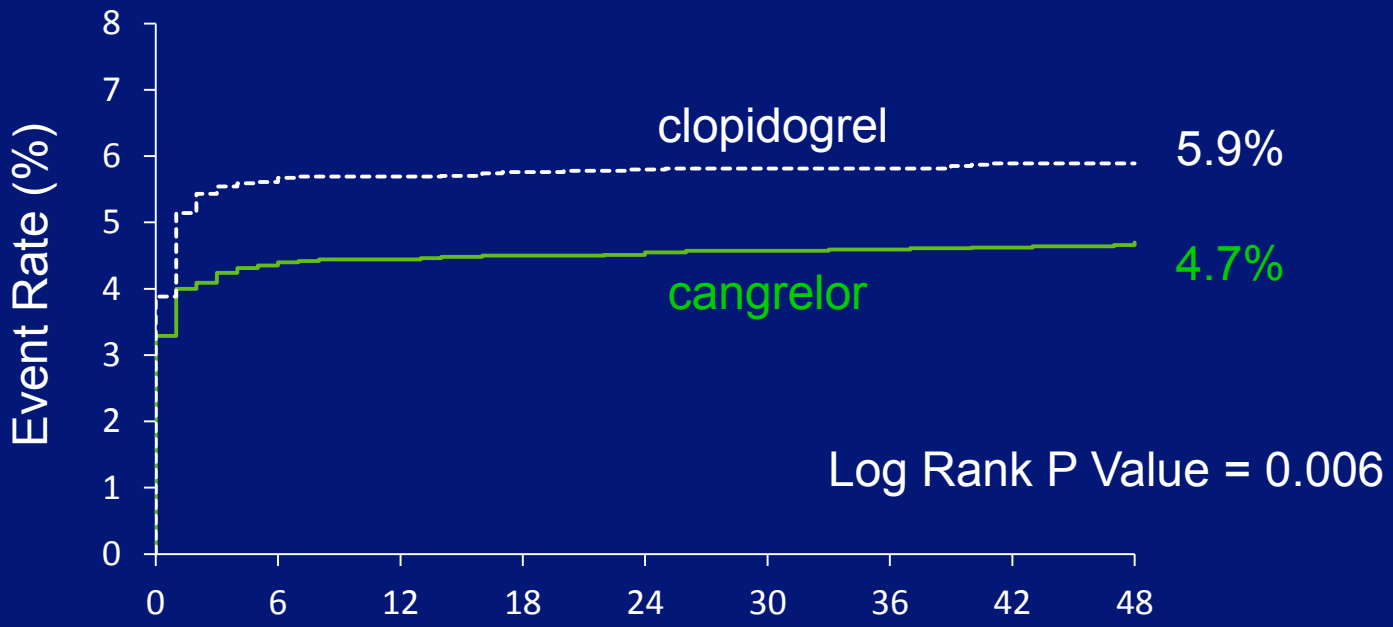
Secondary Efficacy Outcomes at 48 Hours, MITT

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.

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

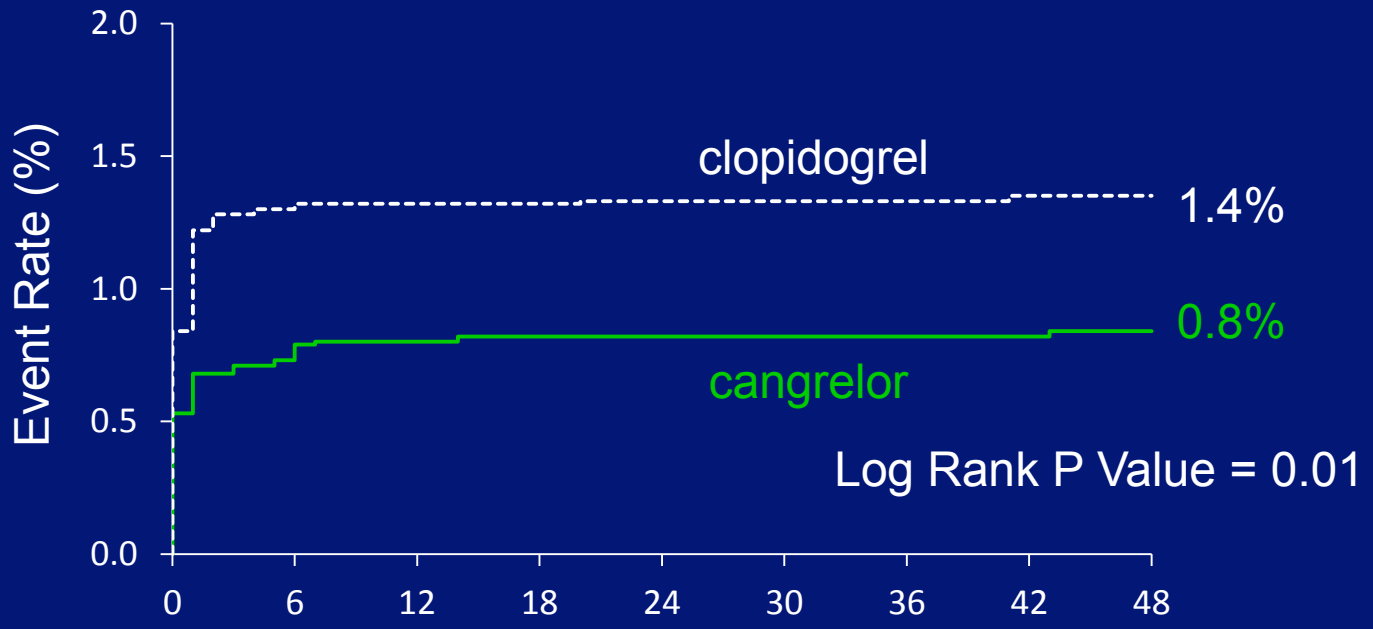
Death/ MI/ IDR/ Stent Thrombosis within 48 Hours



Patient at Risk									
Cangrelor:	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel:	5470	5162	5159	5155	5152	5151	5151	5147	5147

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Stent Thrombosis within 48 Hours



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

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

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

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

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.

For Full Details, Please Go to www.NEJM.org

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events

Deepak L. Bhatt, M.D., M.P.H., Gregg W. Stone, M.D., Kenneth W. Mahaffey, M.D., C. Michael Gibson, M.D., P. Gabriel Steg, M.D., Christian W. Hamm, M.D., Matthew J. Price, M.D., Sergio Leonardi, M.D., Dianne Gallup, M.S., Ezio Bramucci, M.D., Peter W. Radke, M.D., Petr Widimský, M.D., D.Sc., Frantisek Tousek, M.D., Jeffrey Tauth, M.D., Douglas Spriggs, M.D., Brent T. McLaurin, M.D., Dominick J. Angiolillo, M.D., Ph.D., Philippe Généreux, M.D., Tiepu Liu, M.D., Ph.D., Jayne Prats, Ph.D., Meredith Todd, B.Sc., Simona Skerjanec, Pharm.D., Harvey D. White, D.Sc., and Robert A. Harrington, M.D., for the CHAMPION PHOENIX Investigators*

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

THANK YOU!

BACKUP SLIDES

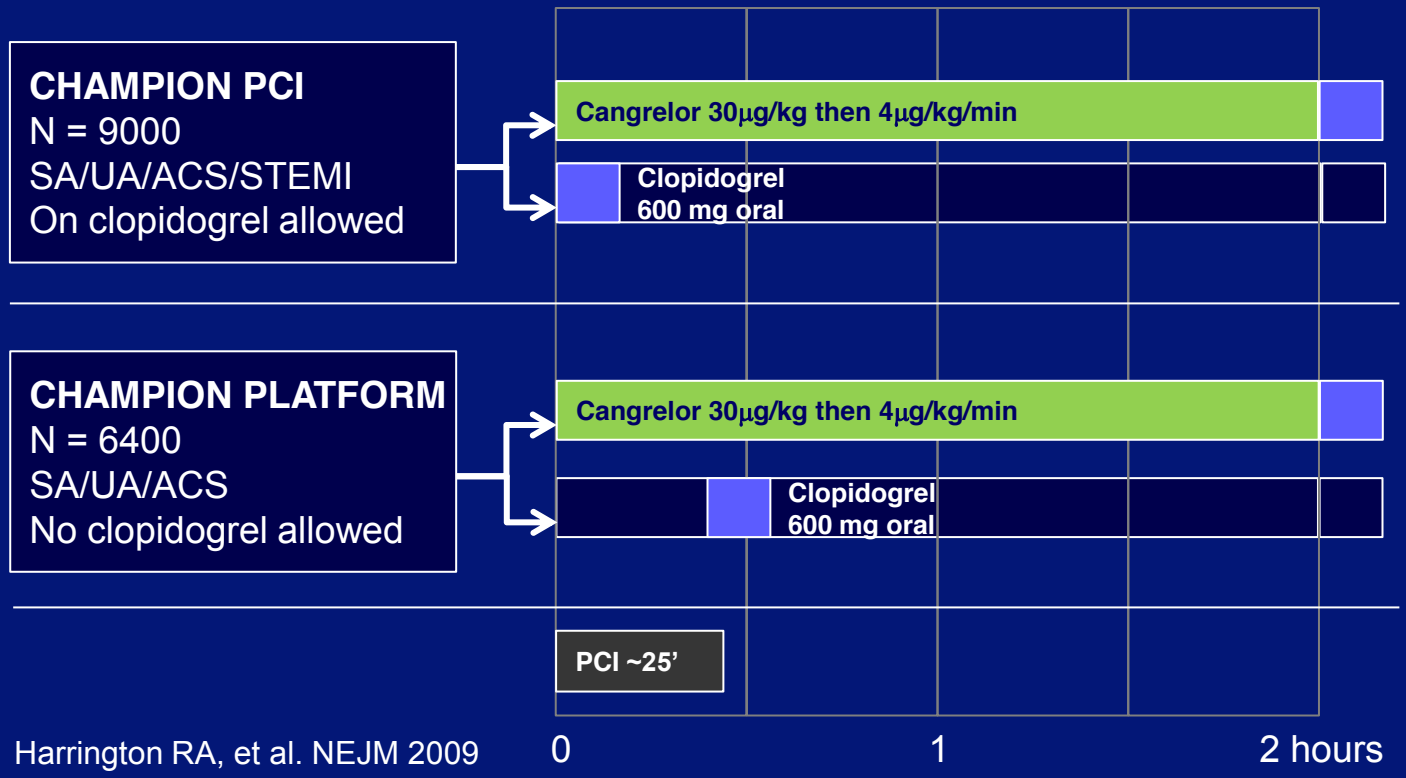
Cangrelor

- Direct platelet $P2Y_{12}$ 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.

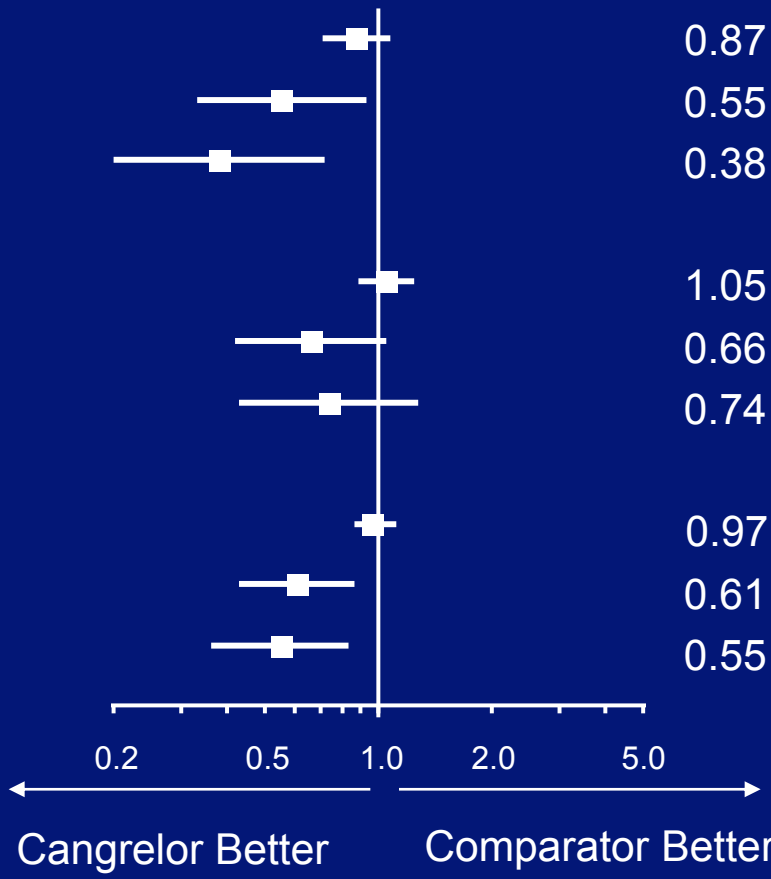
CHAMPION PCI I PLATFORM

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



Harrington RA, et al. NEJM 2009
Bhatt DL, et al. NEJM 2009

Summary of Clinical Efficacy



48-Hour Events	OR [95% CI]	P value
PLATFORM		
Death/MI/IDR	0.87 (0.71,1.07)	0.17
Death/Q-MI/IDR	0.55 (0.33,0.93)	0.02
Death/Q-MI/ST	0.38 (0.20,0.72)	0.003
PCI		
Death/MI/IDR	1.05 (0.89,1.24)	0.57
Death/Q-MI/IDR	0.66 (0.42,1.05)	0.08
Death/Q-MI/ST	0.74 (0.43,1.27)	0.27
POOLED		
Death/MI/IDR	0.97 (0.86,1.11)	0.68
Death/Q-MI/IDR	0.61 (0.43,0.86)	0.005
Death/Q-MI/ST	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 O_2 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

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.

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)

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

CHAMPION PHOENIX Executive Committee

Deepak L. Bhatt, M.D., M.P.H. (Co-Principal Investigator)
VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School Boston, MA

Robert A. Harrington, M.D. (Co-Principal Investigator)
Department of Medicine, Stanford University, Stanford, CA

C. Michael Gibson, M.S., M.D.
Beth Israel Deaconess Medical Center, Division of Cardiology, Boston, MA

Christian W. Hamm, M.D.
Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany

Kenneth W. Mahaffey, M.D.
Duke Clinical Research Institute, Durham, NC

Matthew J. Price, M.D.
Scripps Clinic and Scripps Translational Science Institute, La Jolla, CA

Ph. Gabriel Steg, M.D.
INSERM U-698, Université Paris-Diderot, and Hôpital Bichat, Assistance-Publique-Hôpitaux de Paris, Paris, France

Gregg W. Stone, M.D.
Columbia University Medical Center and the Cardiovascular Research Foundation, New York, NY

Harvey D. White, D.Sc.
Auckland City Hospital, Auckland, New Zealand

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Universitair Ziekenhuis Gasthuisberg, Belgium

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Brigham & Women's Hospital, Dept. of Medicine, Boston, MA

E. Magnus Ohman, M.D.
Duke University Medical Center, Durham, NC

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Heartcenter University Medical Center, Amsterdam

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Henry Ford Hospital, Detroit, MI

Jan G.P. Tijssen, Ph.D. (Statistician)
Department of Cardiology, Academic Medical Center-University of Amsterdam, The Netherlands

CHAMPION PHOENIX CEC

Duke Clinical Research Institute

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Kenneth W. Mahaffey (Chair)

Sergio Leonardi (co-Chair)

Dianne Gallup (Lead Statistician)

Matthew D. Wilson (Project Leader)

OPERATIONS

Stacey Mangum (Coordinator)

Linda Dowd (Lead CDA)

Dimitrios Stournaras (Lead CDS)

Sachin Vyas (Lead CTA)

REVIEWERS

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Luciana Amaganijan Brazil

Monique Anderson NC

Akshay Bagai NC

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Pedro G. Melo de Barros E Silva Brazil

Phase 2

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Renato D. Lopes NC

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CHAMPION PHOENIX Angiographic Core Lab

Cardiovascular Research Foundation

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Laura Lasalle

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MDCO Clinical + Data Operations

LEADERSHIP

Jenna Bisch (Project Lead)

Tracy Survill (Data Lead)

Tiepu Liu (Statistician)

Steve Elkin (Programming)

Markus Dietrich (Medical)

PROJECT MANAGEMENT

Denise Evans

Tara Richardson

Nita Whyte

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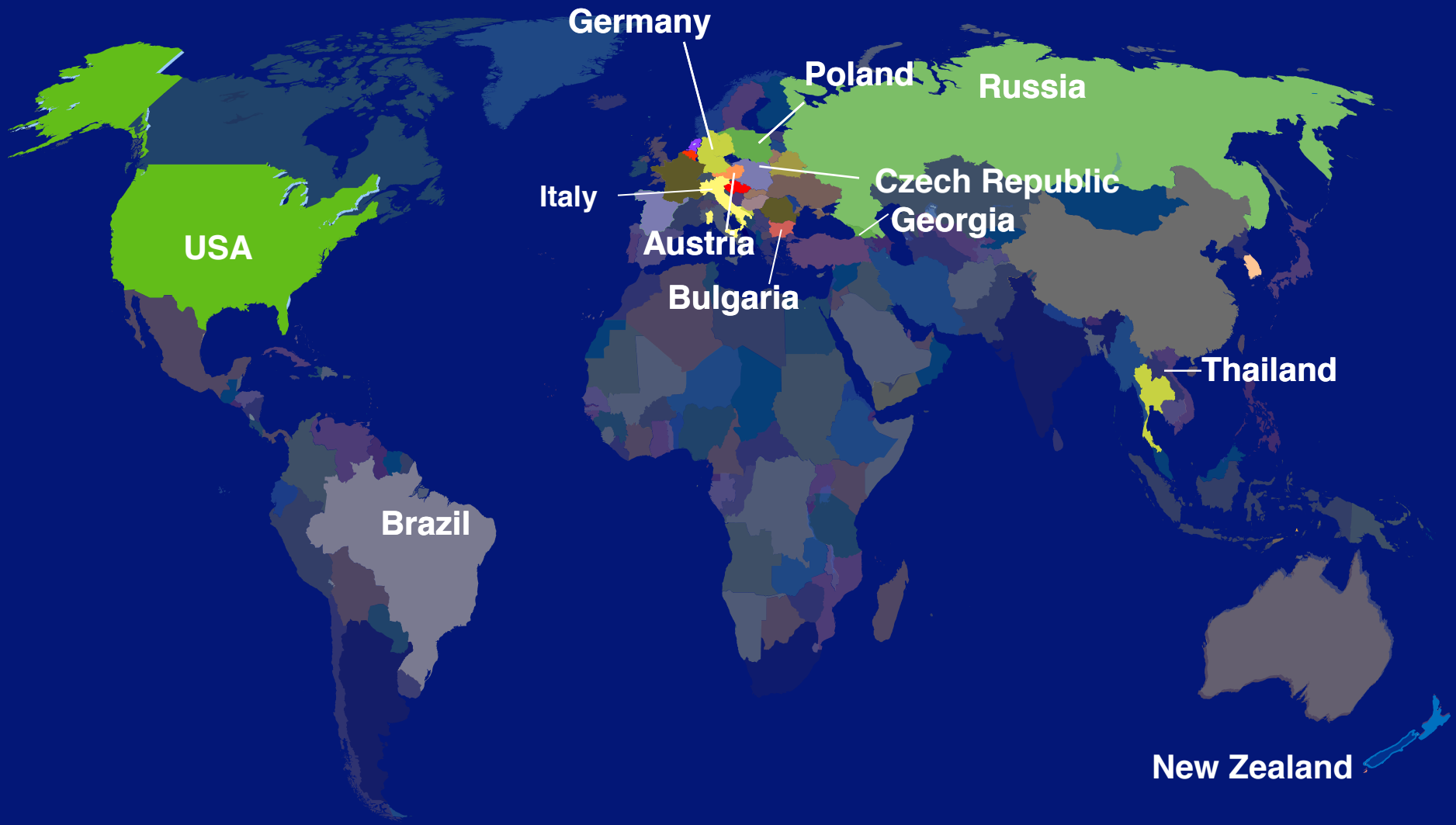
CHAMPION PHOENIX AROs and CROs

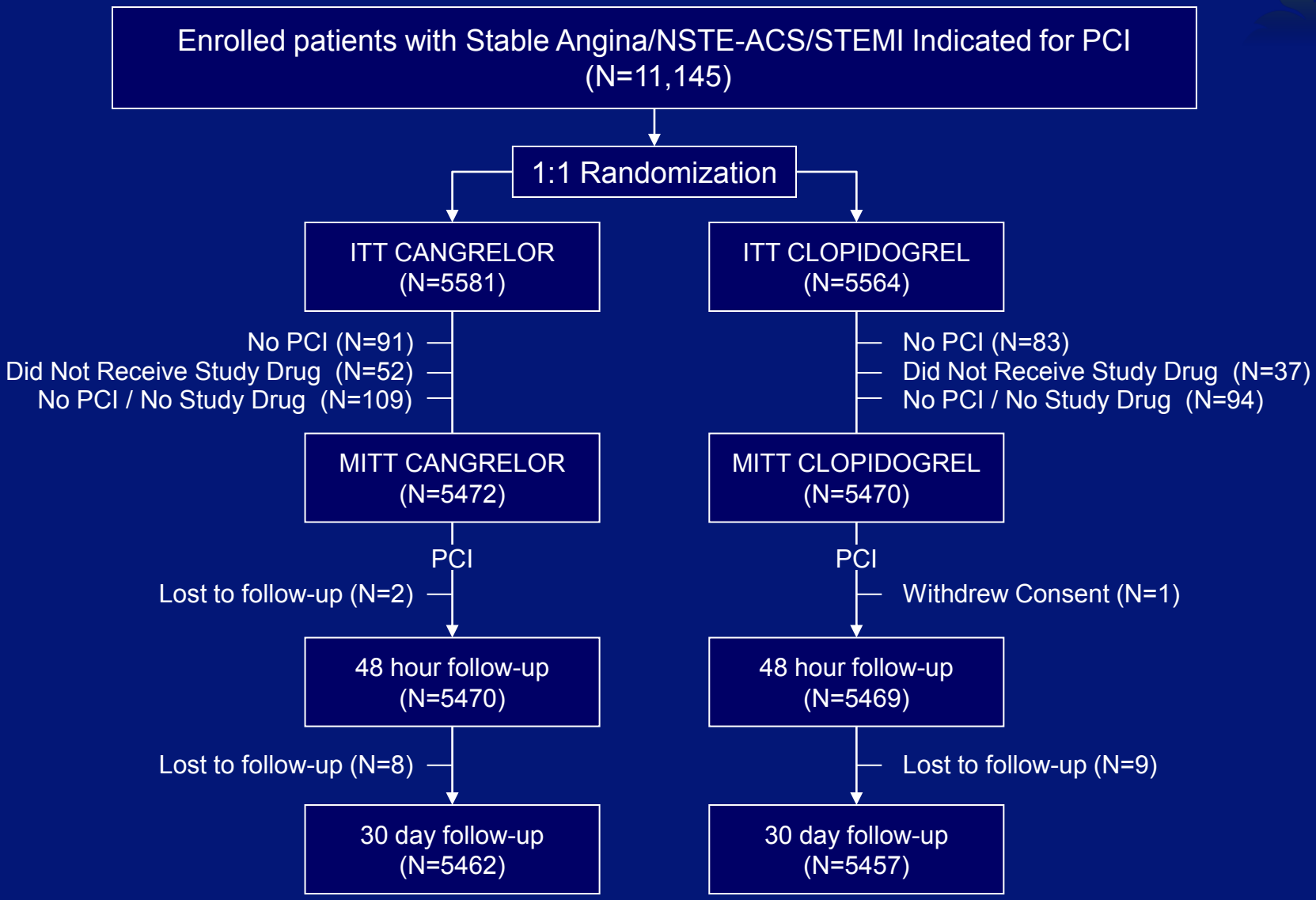
Partners	Role
Almac	IVRS/IWRS
Merge	eCRF
Quest	CKMB central lab
Bioclinica	Web portal for angiographic film uploads
Cardiovascular Research Foundation	Angiographic Core Lab
Duke Clinical Research Institute	CEC
Green Lane Coordinating Center	Site Management – New Zealand
Worldwide Clinical Trials	Site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

CHAMPION PHOENIX – A Global Trial

12 Countries | 153 Sites



Patient Disposition



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 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

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

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

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

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

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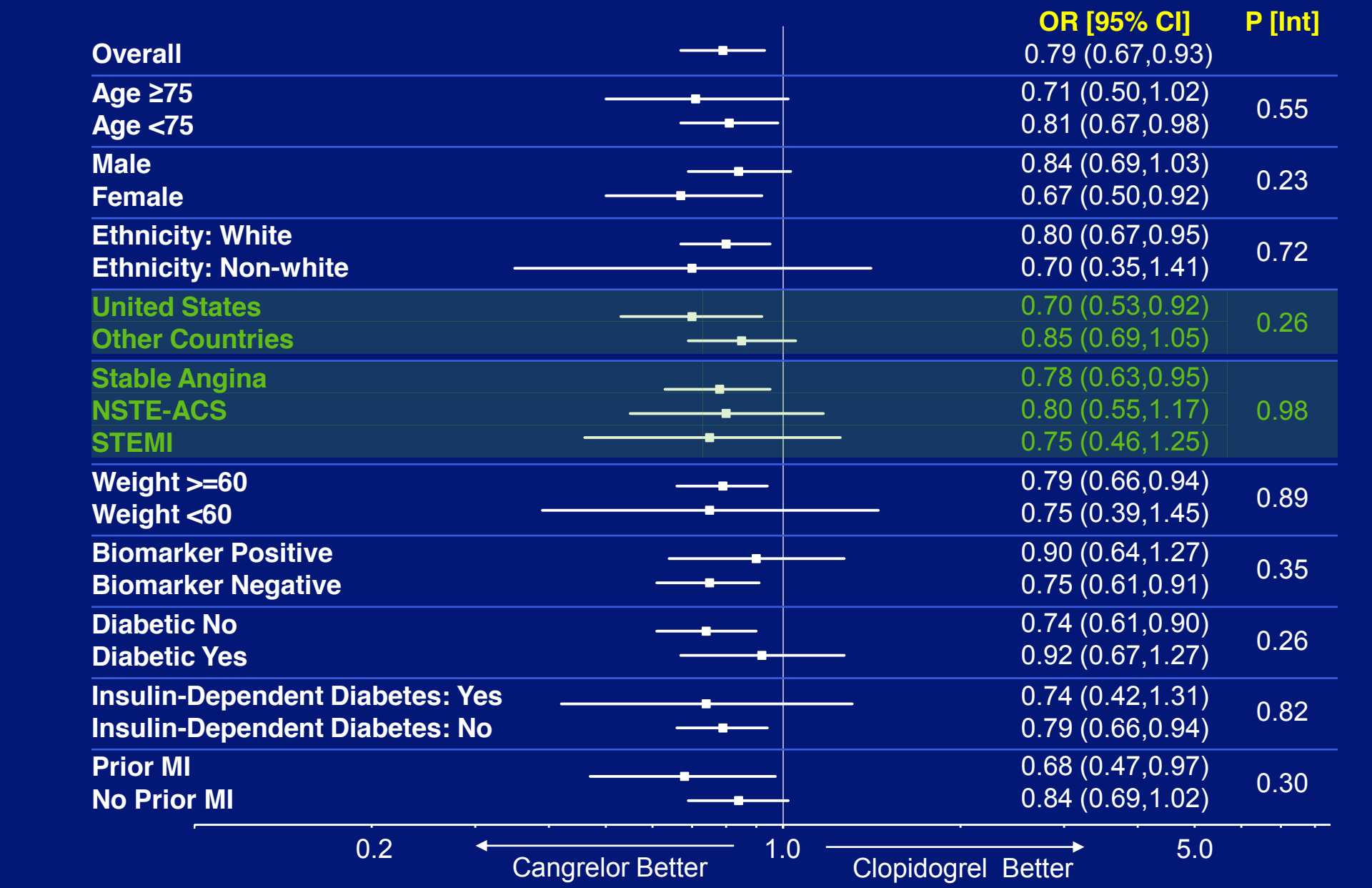
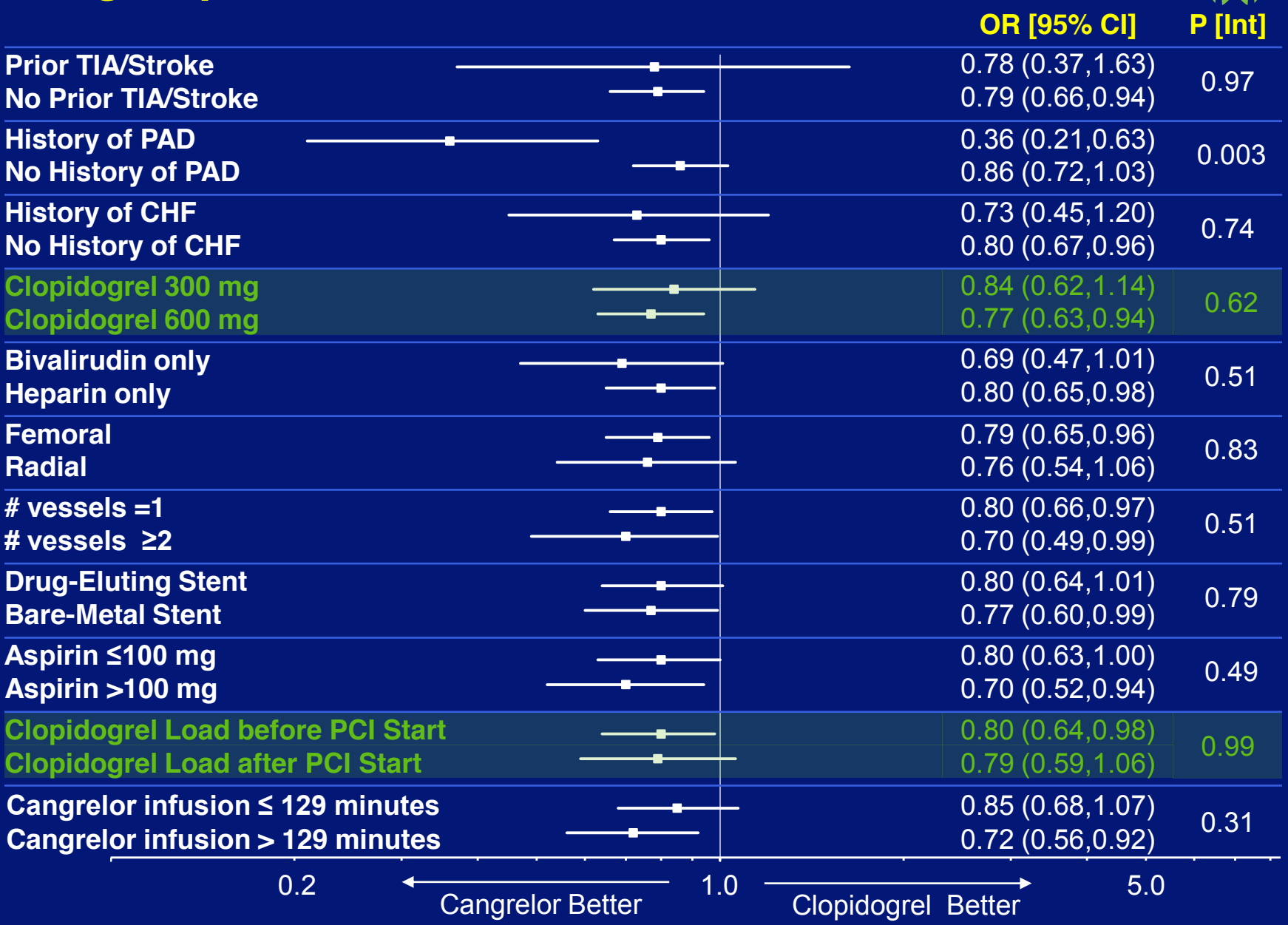
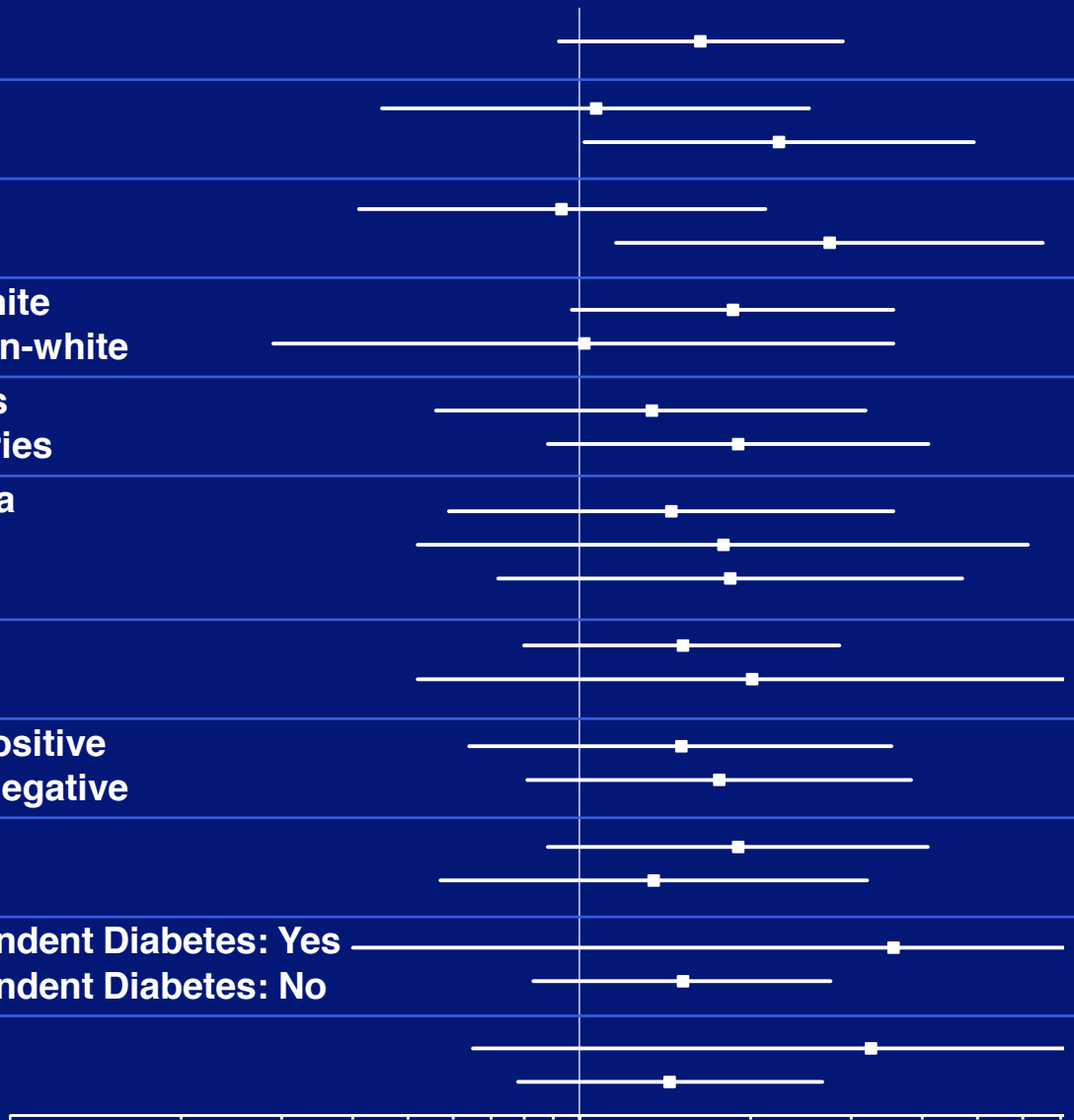
Subgroups: Death/MI/IDR/ST at 48 Hours



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

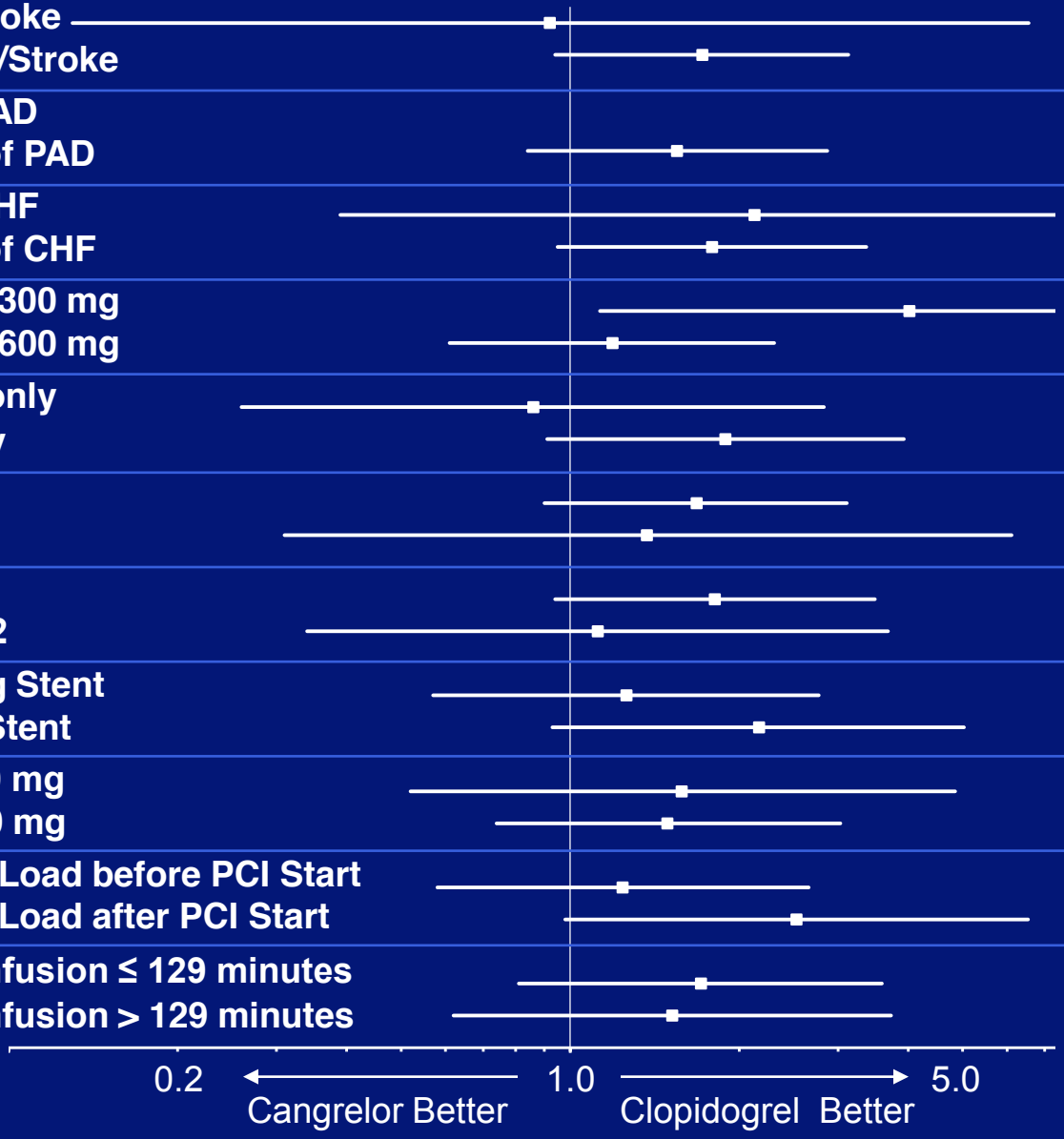


Subgroups: GUSTO Severe/Moderate Bleeding, Safety



	OR [95% CI]	P [Int]
Overall	1.63 (0.92,2.90)	
Age ≥75	1.07 (0.45,2.53)	0.21
Age <75	2.24 (1.02,4.93)	
Male	0.93 (0.41,2.12)	0.07
Female	2.75 (1.16,6.51)	
Ethnicity: White	1.86 (0.97,3.56)	0.40
Ethnicity: Non-white	1.02 (0.29,3.56)	
United States	1.34 (0.56,3.18)	0.55
Other Countries	1.90 (0.88,4.10)	
Stable Angina	1.45 (0.59,3.56)	0.93
NSTE-ACS	1.79 (0.52,6.13)	
STEMI	1.84 (0.72,4.70)	
Weight >=60	1.52 (0.80,2.86)	0.71
Weight <60	2.01 (0.52,7.86)	
Biomarker Positive	1.51 (0.64,3.53)	0.79
Biomarker Negative	1.76 (0.81,3.82)	
Diabetic No	1.90 (0.88,4.09)	0.56
Diabetic Yes	1.35 (0.57,3.20)	
Insulin-Dependent Diabetes: Yes	3.56 (0.40,32.00)	0.45
Insulin-Dependent Diabetes: No	1.52 (0.83,2.76)	
Prior MI	3.25 (0.65,16.12)	0.35
No Prior MI	1.44 (0.78,2.67)	

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



	OR [95% CI]	P [Int]
Prior TIA/Stroke	0.92 (0.13,6.55)	0.54
No Prior TIA/Stroke	1.72 (0.94,3.13)	
History of PAD	NA	0.10
No History of PAD	1.55 (0.84,2.87)	
History of CHF	2.13 (0.39,11.70)	0.85
No History of CHF	1.79 (0.95,3.37)	
Clopidogrel 300 mg	4.02 (1.13,14.27)	0.09
Clopidogrel 600 mg	1.19 (0.61,2.31)	
Bivalirudin only	0.86 (0.26,2.83)	
Heparin only	1.89 (0.91,3.93)	0.26
Femoral	1.68 (0.90,3.11)	0.81
Radial	1.37 (0.31,6.11)	
# vessels =1	1.81 (0.94,3.49)	0.48
# vessels ≥2	1.12 (0.34,3.68)	
Drug-Eluting Stent	1.26 (0.57,2.77)	0.35
Bare-Metal Stent	2.17 (0.93,5.03)	
Aspirin ≤100 mg	1.58 (0.52,4.85)	0.93
Aspirin >100 mg	1.49 (0.74,3.03)	
Clopidogrel Load before PCI Start	1.24 (0.58,2.66)	0.25
Clopidogrel Load after PCI Start	2.53 (0.98,6.54)	
Cangrelor infusion ≤ 129 minutes	1.71(0.81,3.59)	0.85
Cangrelor infusion > 129 minutes	1.52(0.62,3.73)	

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

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

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.