INFUSE-AMI

A 2x2 Factorial, Multicenter, Prospective, Randomized Evaluation of Intracoronary Abciximab and Aspiration Thrombectomy in Patients Undergoing Primary PCI for Anterior STEMI

Gregg W. Stone, MD

Columbia University Medical Center
NewYork-Presbyterian Hospital
Cardiovascular Research Foundation

ClinicalTrials.gov number:
NCT00976521

Disclosure Statement of Financial Interest

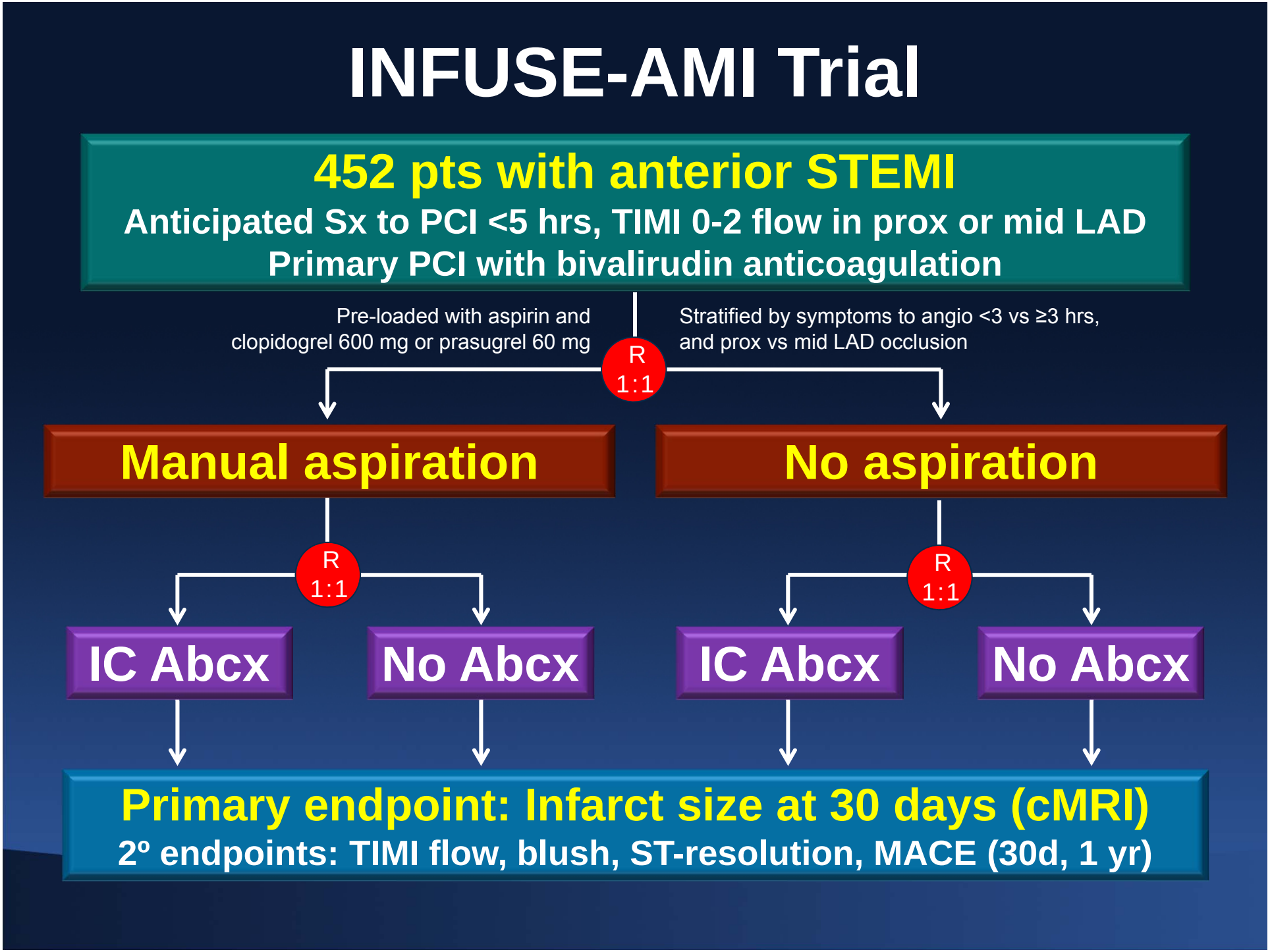
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Consulting Fees/Honoraria	• Abbott Vascular, Boston Scientific, Medtronic, Atrium, BMS-Sanofi, Merck, Janssen, Eli Lilly, Daiichi Sankyo, The Medicines Company, Astra Zeneca

INFUSE-AMI: Background

- Myocardial recovery after primary PCI is often suboptimal despite restoration of TIMI 3 flow, in part due to thrombus embolization which results in impaired microvascular perfusion and increased infarct size
- Two strategies proposed to reduce embolization after primary PCI are bolus IC abciximab and manual thrombus aspiration
- However, prior studies have reported conflicting results as to whether IC abciximab or manual aspiration reduce infarct size or improve clinical outcomes, in part due to enrollment of a high proportion of small infarcts (e.g. non-anterior and/or with TIMI 3 flow), and/or pts presenting late (>4-6 hrs)
- Single center thrombectomy trials have mostly been positive, whereas multicenter trials have mostly been negative

INFUSE-AMI Trial



INFUSE-AMI: Unique aspects

- Randomized only anterior MIs with TIMI 0-2 flow in prox/mid LAD → large MIs (greatest clinical need)
- Required symptom onset to PCI <5 hrs → reperfusion within the time window for potential myocardial salvage
- Aspiration performed with 6F Export (same as in TAPAS)
- IC bolus abciximab delivered by the ClearWay Rx catheter directly to the site of the infarct lesion
- Bivalirudin anticoagulation w/o 12° IV abcx in either arm → bolus only IC abcx vs. no abcx (and less bleeding)
- Infarct size by cMRI at 30 days, after edema has ↓'d

INFUSE-AMI: Devices

ClearWay RX Catheter
(Atrium Medical)

- Microporous PTFE balloon mounted on a 2.7Fr Rx catheter
- Fluid weeps through the pores – no high pressure jets
- Vessel occlusion → site-specific infusion without systemic drug dilution from preferential flow to the LCX or aorta (blowback)
- FDA approved for localized infusion of diagnostic and therapeutic agents

Export Catheter
(Medtronic)

- Guide catheter compatibility: 6F (min ID 0.070")
- Crossing profile: 0.068”
- Aspiration lumen: 0.041”
- FDA approved for removal/aspiration of embolic material (thrombus/debris) from vessels
- In the single center TAPAS trial → improved MBG, STR, survival

INFUSE-AMI: Inclusion criteria

- **Clinical**
  - ≥18 years old with symptoms consistent with STEMI >30 minutes duration
  - ≥1 mm ST-segment elevation in ≥2 contiguous leads in V1-V4, or new left bundle branch block
  - Anticipated symptom onset to device time ≤5 hours (i.e. symptom to presentation ≤3.5 - 4 hours)
- **Angiographic**
  - Infarct lesion in the proximal or mid LAD with visually-assessed TIMI 0-2 flow

INFUSE-AMI: Exclusion criteria

- **Clinical**
  - Contraindications to study meds, contrast or cMRI
  - Prior MI, CABG or LAD stenting
  - Known CrCl <30 ml/min/1.73m^2, dialysis, platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, hemoglobin <10g/dL
  - Recent major bleeding, bleeding diathesis, current warfarin use, h/o intracranial ds, ischemic CVA or TIA w/i 6 months, or any permanent neurologic defect
  - Pre-randomization cardiogenic shock, CPR, fibrinolysis, GPI
  - Planned surgery necessitating anti-plat agent interruption, or co-morbid ds likely to interfere with compliance or $\rightarrow$ <1-yr survival
- **Angiographic**
  - Excessive tortuosity, diffuse ds, heavy calc or significant LM ds
  - PCI in non-LAD required during index procedure or w/i 30 days

INFUSE-AMI: Principal endpoints

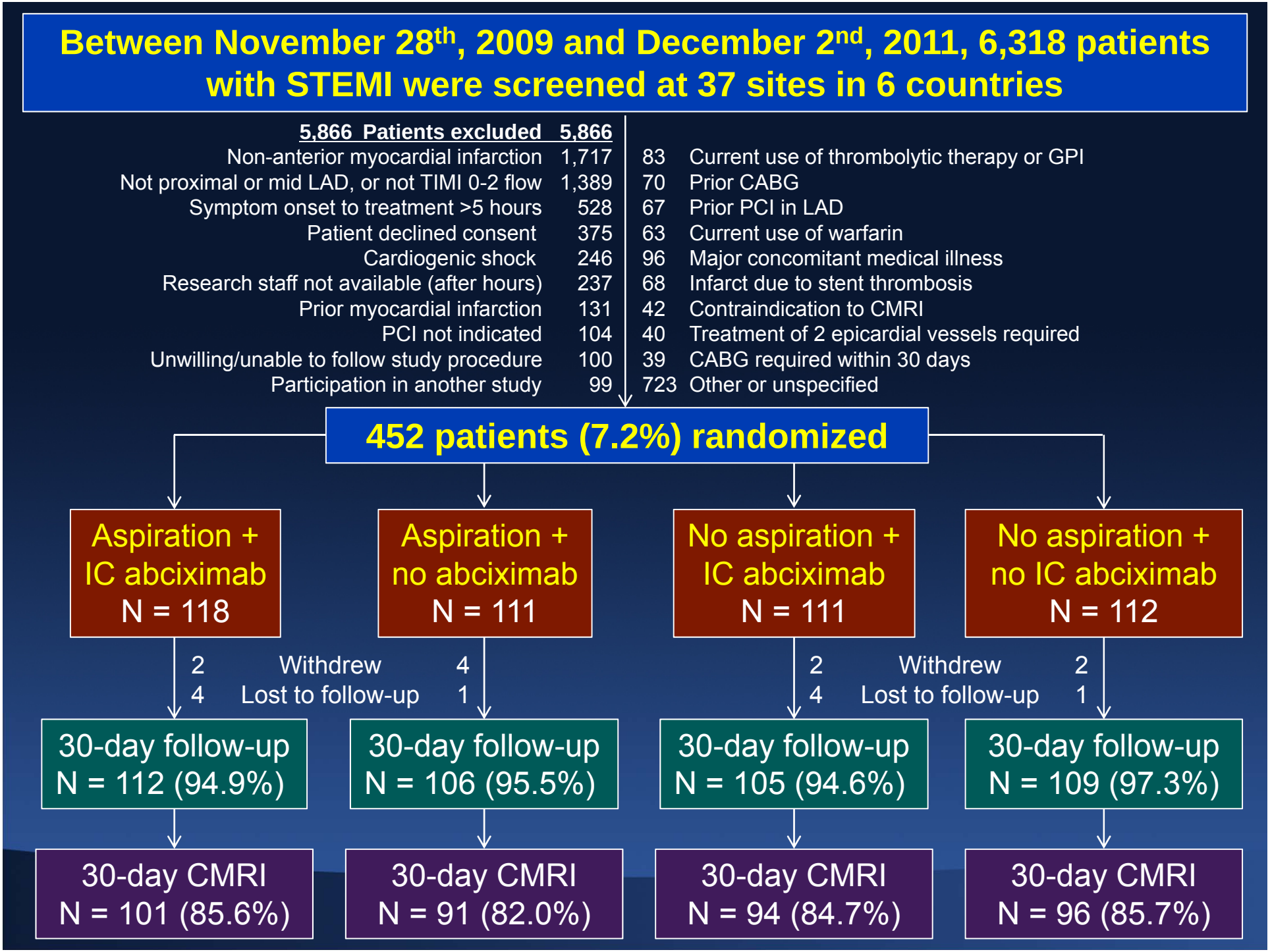
- Primary endpoint (powered):
  - Infarct size (% total LV mass by cMRI) at 30 days in pts assigned to IC abciximab vs. no abciximab (pooled across the aspiration randomization)
- Major secondary endpoint:
  - Infarct size (% total LV mass by cMRI) at 30 days in pts assigned to aspiration vs. no aspiration (pooled across the abciximab randomization)
- Addition endpoints:
  - Post PCI TIMI flow, cTFC and myocardial blush
  - ST-segment resolution at 60 mins
  - MACE at 30 days and 1 year

INFUSE-AMI: Power analysis

- Evaluating 408 subjects randomized to IC abciximab vs. no abciximab would provide 80% power to demonstrate a relative 25% reduction in infarct size from 24% to 18% (with a standard deviation [SD] of 21%, conservatively estimated from prior tc-99m-sestamibi studies)
- Enrollment was planned for 452 pts to account for loss to follow-up and suboptimal CMRI

INFUSE-AMI: Study organization

Principal investigator:	Gregg W. Stone
Co-principal investigator:	C. Michael Gibson
Executive committee:	GW Stone, CM Gibson, DA Cox, R Dave, D Dudek, CL Grines, AJ Lansky, G Steg, T Stuckey, J Wöhrle
EU country leaders:	T Neunteufl, Austria; J Wöhrle, Germany; J Koolen, Netherlands; D Dudek, Poland; A Gershlick, UK
Data monitoring:	Genae Associates, Krakow Cardiovascular Research Institute, Bailer Research, Inc.
Event adjudication:	Cardiovascular Research Foundation C Wong (Chair)
MRI, STR and angio core labs:	Cardiovascular Research Foundation S Wolff, A Maehara, E Cristea and J Dizon (Directors)
Data management: and analysis	Cardiovascular Research Foundation Roxana Mehran (Director), Helen Parise (Biostatistics)
DSMB:	B Gersh (Chair), D Faxon, T Collier
Sponsor and funding:	Atrium Medical (principal), Medtronic, The Medicines Co.


Between November 28th, 2009 and December 2nd, 2011, 6,318 patients with STEMI were screened at 37 sites in 6 countries
5,866 Patients excluded 5,866
Non-anterior myocardial infarction 1,717
Not proximal or mid LAD, or not TIMI 0-2 flow 1,389
Symptom onset to treatment >5 hours 528
Patient declined consent 375
Cardiogenic shock 246
Research staff not available (after hours) 237
Prior myocardial infarction 131
PCI not indicated 104
Unwilling/unable to follow study procedure 100
Participation in another study 99
83 Current use of thrombolytic therapy or GPI
70 Prior CABG
67 Prior PCI in LAD
63 Current use of warfarin
96 Major concomitant medical illness
68 Infarct due to stent thrombosis
42 Contraindication to CMRI
40 Treatment of 2 epicardial vessels required
39 CABG required within 30 days
723 Other or unspecified
452 patients (7.2%) randomized
Aspiration + IC abciximab N = 118
Aspiration + no abciximab N = 111
No aspiration + IC abciximab N = 111
No aspiration + no IC abciximab N = 112
2 Withdrew 4
4 Lost to follow-up 1
2 Withdrew 2
4 Lost to follow-up 1
30-day follow-up N = 112 (94.9%)
30-day follow-up N = 106 (95.5%)
30-day follow-up N = 105 (94.6%)
30-day follow-up N = 109 (97.3%)
30-day CMRI N = 101 (85.6%)
30-day CMRI N = 91 (82.0%)
30-day CMRI N = 94 (84.7%)
30-day CMRI N = 96 (85.7%)

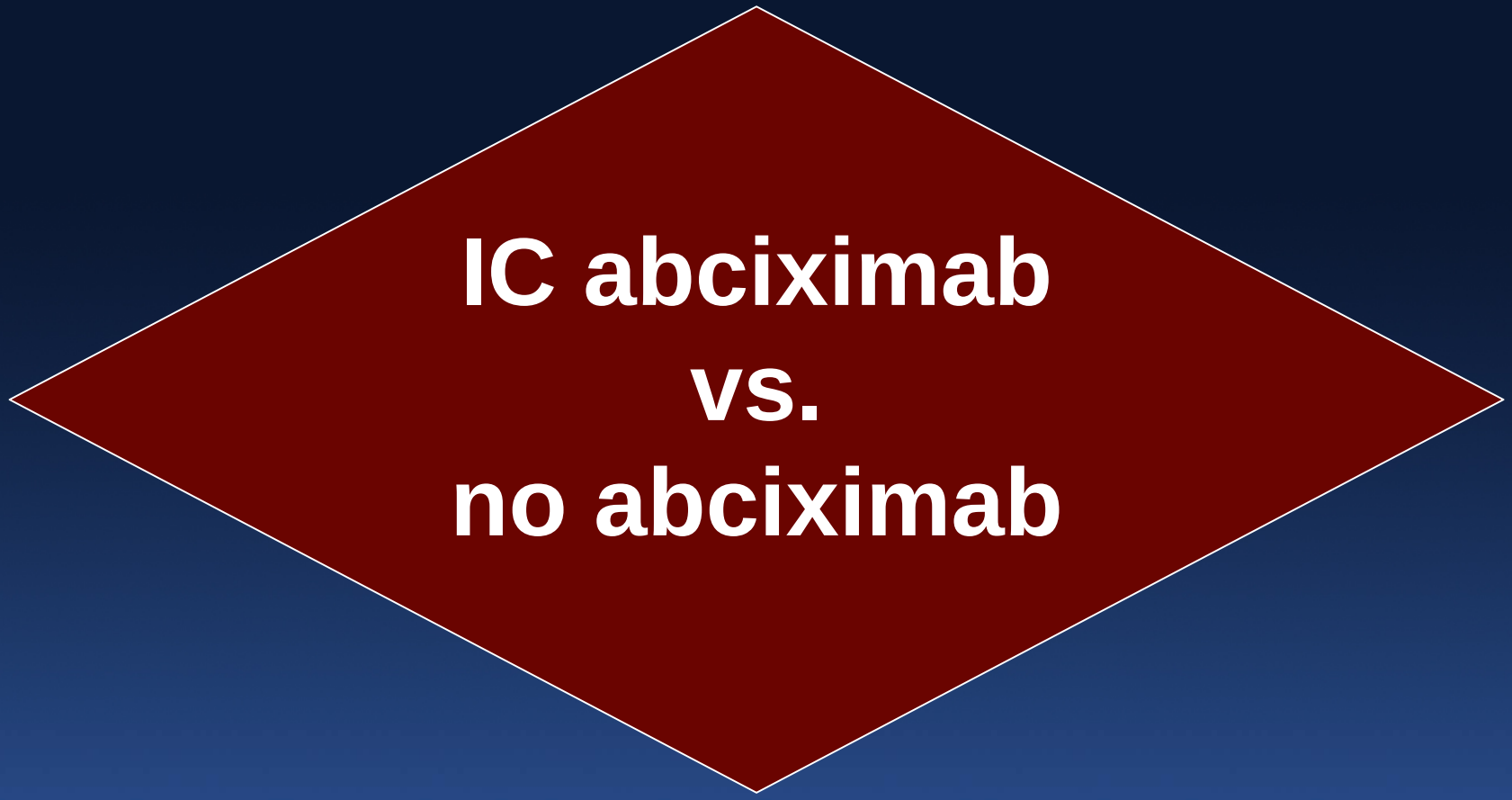
INFUSE-AMI: Top 11 enrollers

Principal Investigator	City, State/Country	N enrolled
Bernhard Witzenbichler	Berlin, Germany	44
Jacek Godlewski	Krakow, Poland	32
Andrzej Ochala	Katowice, Poland	29
Saqib Chowdhary	Manchester, UK	27
Magdi El-Omar	Manchester, UK	27
Jan-Henk E. Dambrink	Zwolle, The Netherlands	27
Thomas Neunteufl	Vienna, Austria	24
Afzar Zaman	Newcastle, UK	21
D. Chris Metzger	Kingsport, TN	20
Keith Oldroyd	Glasgow, UK	18
Dariusz Dudek	Krakow, Poland	18

INFUSE-AMI: Baseline characteristics

	Aspiration + IC abciximab N=118	No aspiration + IC abciximab N=111	Aspiration + no abciximab N=111	No aspiration + no abciximab N=112
Age (years)	60 [52, 66]	56 [49, 68]	62 [53, 73]	62 [53, 71]
Male	71.2%	75.7%	76.6%	72.3%
Hypertension	31.4%	27.0%	35.1%	32.1%
Hyperlipidemia	17.1%	17.1%	16.2%	12.5%
Diabetes mellitus	12.7%	8.1%	17.3%	7.1%
Cig smoking, current	44.4%	48.6%	42.2%	49.1%
Prior MI	0%	2.7%	0.9%	0.0%
Prior PCI	1.7%	1.8%	2.7%	2.7%
Killip class II/III	16.1%	13.5%	25.5%	19.6%
Sx - hosp, mins	93 [65, 152]	101 [75, 158]	107 [67, 153]	98 [67, 136]
Infarct artery				
- Proximal LAD	62.7%	68.5%	61.3%	66.1%
- Mid LAD	41.5%	39.6%	42.3%	42.9%
LVEF, % (site)	40 [35, 49]	40 [35, 48]	40 [38, 50]	40 [31, 50]

INFUSE-AMI



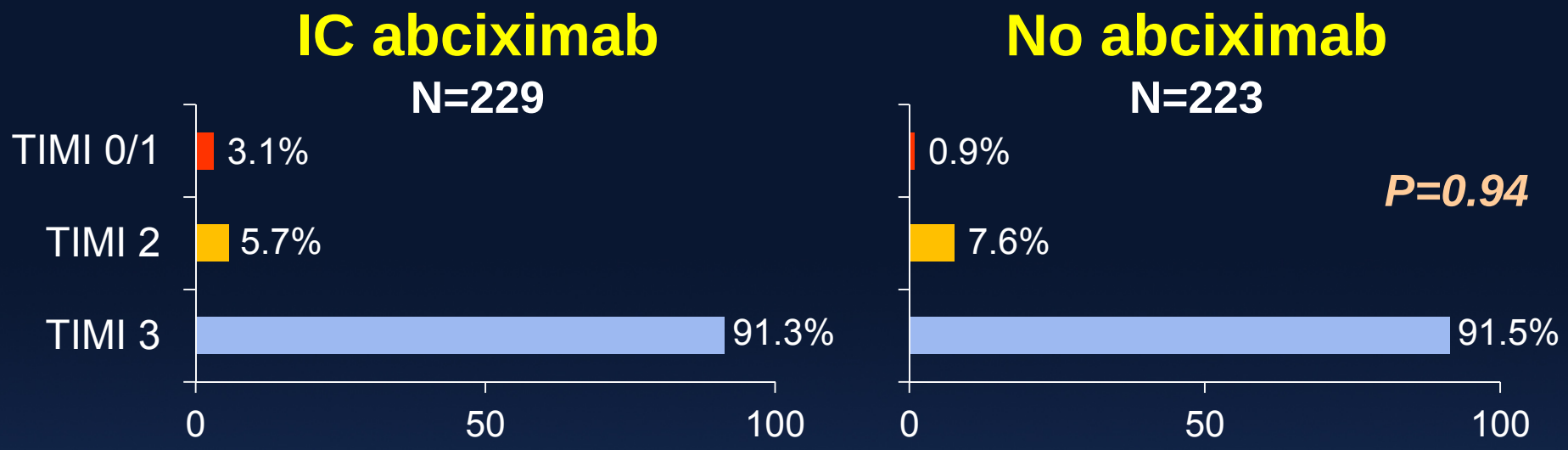
Pooled across the aspiration randomization

INFUSE-AMI: Meds and procedures

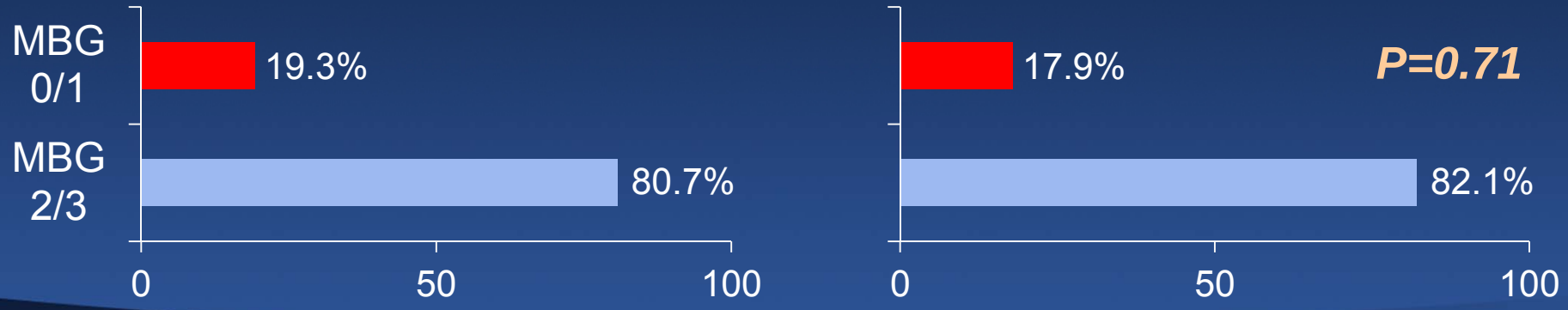
	Intracoronary abciximab N=229	No intracoronary abciximab N=223	P value
TIMI flow pre-PCI 0/1*	72.5%	70.9%	0.70
Blush pre-PCI 0/1*	84.2%	83.8%	0.90
Hospital - 1st device, mins	45 [35, 66]	45 [32, 67]	0.84
Aspiration performed	52.0%	51.6%	0.93
Abciximab administered	97.4%**	2.2%	<0.001
N lesions treated	1.1 ± 0.4	1.2 ± 0.4	0.28
DES implanted	74.7%	70.4%	0.31
Stent length (mm)	24 [18, 34]	23 [17, 33]	0.13
Max stent diameter (mm)	3.0 [3.0, 3.5]	3.0 [3.0, 3.5]	0.75

*Core laboratory assessed; **Bolus via ClearWay Rx in all but one case

INFUSE-AMI: Reperfusion post-PCI*

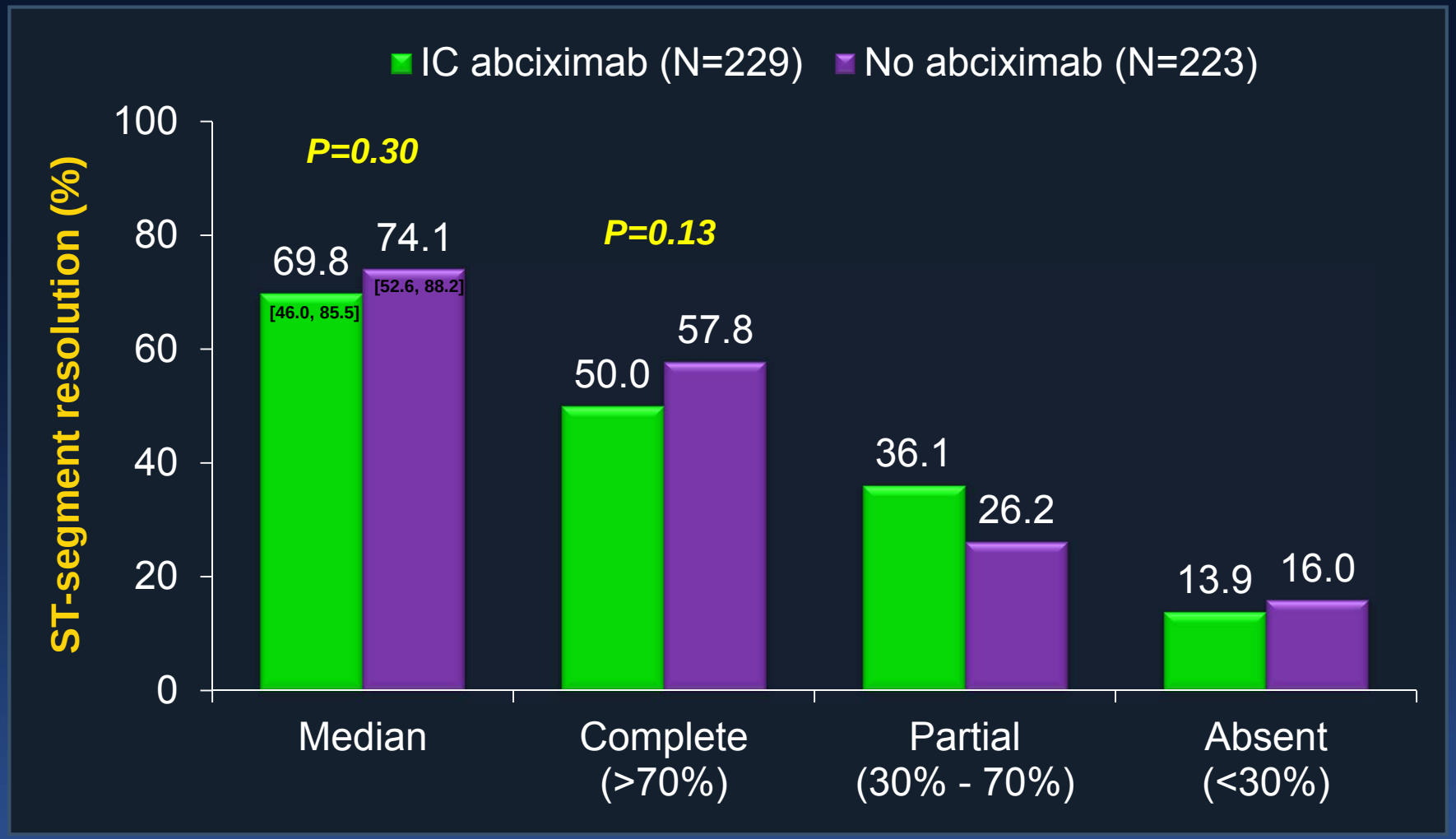


Corrected TIMI frame counts: **20 [16, 26]** **vs.** **20 [16, 26]** ***P=0.62***



*Core laboratory assessed

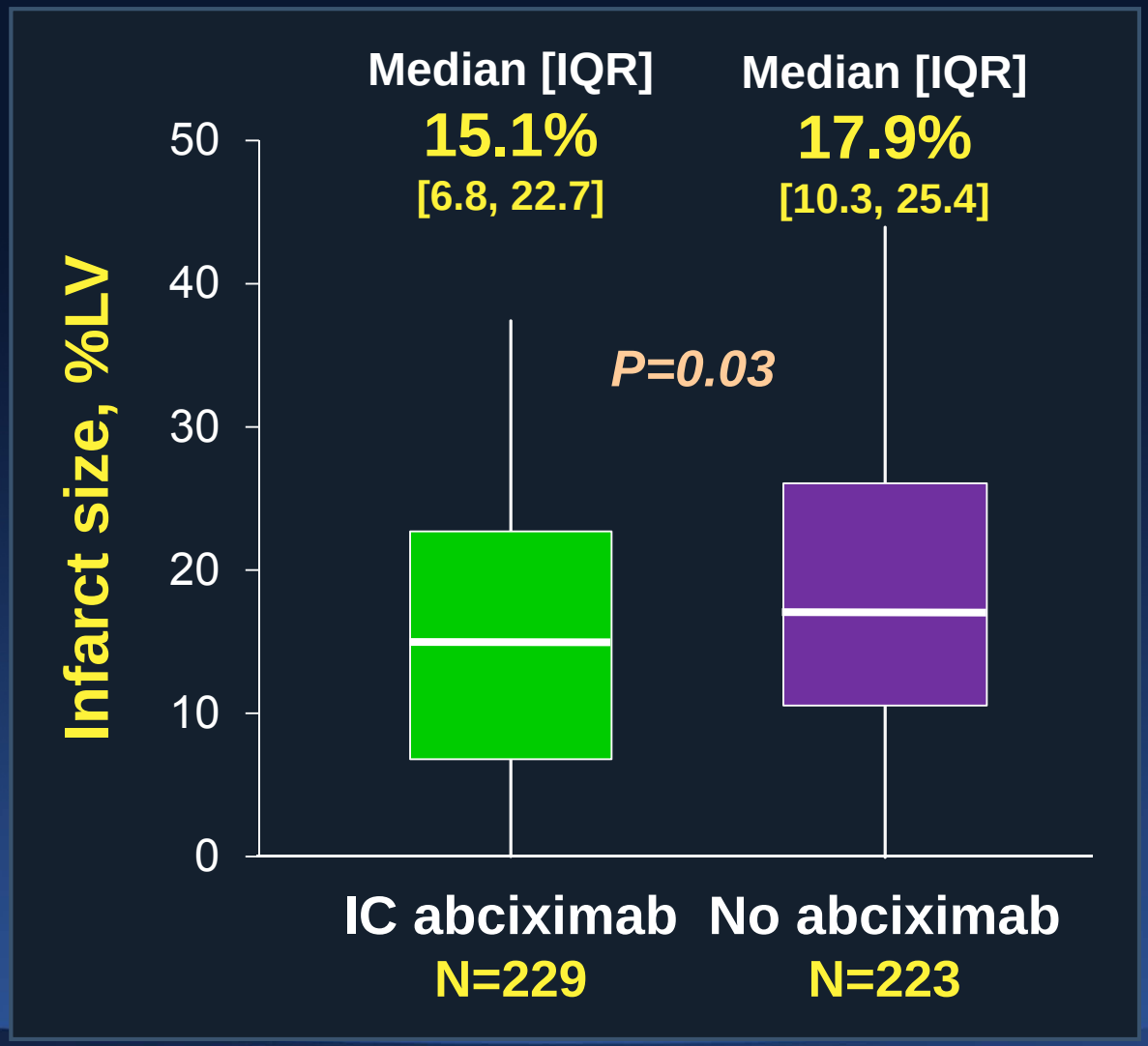
INFUSE-AMI: STR 60 minutes post-PCI*



*Core laboratory assessed

INFUSE-AMI: Infarct size at 30 days*

- Primary endpoint -



*Core laboratory assessed

INFUSE-AMI: cMRI at 30 days*

	Intracoronary abciximab N=188	No intracoronary abciximab N=184	P value
Total LV mass, grams	128.6 [106.6, 152.4]	130.4 [109.9, 155.9]	0.55
Infarct mass, grams	18.7 [7.4, 31.3]	24.0 [12.1, 34.2]	0.03
Infarct mass (% of total LV mass)	15.1 [6.8, 22.7]	17.9 [10.3, 25.4]	0.03
Total abnormal wall motion score	7.0 [2.0, 10.0]	8.0 [3.0, 10.0]	0.08
LVEF (%)	50.2 [44.2, 57.9]	48.9 [42.3, 56.7]	0.22

*Core laboratory assessed

INFUSE-AMI: 30-day clinical efficacy

	Intracoronary abciximab N=229	No intracoronary abciximab N=223	P value
Death	3.5% (8)	2.3% (5)	0.42
Reinfarction	0.5% (1)	0.9% (2)	0.56
New onset severe HF	3.1% (7)	4.5% (10)	0.44
Rehospitalization for HF	0.0% (0)	0.9% (2)	0.15
Stroke	0.4% (1)	0.0% (0)	0.32
Clinically-driven TVR	0.9% (2)	1.4% (3)	0.65
Stent thrombosis, def/prob*	0.9% (2)	0.9% (2)	0.99
MACCE	4.8% (11)	3.2% (7)	0.36
MACE	7.0% (16)	6.8% (15)	0.91

Data are Kaplan-Meier estimates (n of events). *No cases of acute (<24 hr) stent thrombosis occurred. MACE = death, reinfarction, new onset severe heart failure (HF) or rehospitalization for HF; MACCE = death, reinfarction, stroke or clinically-driven TVR

INFUSE-AMI: 30-day clinical safety

	Intracoronary abciximab N=229	No intracoronary abciximab N=223	P value
HORIZONS-AMI major bleeding	4.9% (11)	3.6% (8)	0.50
TIMI major or minor bleeding	2.2% (5)	1.8% (4)	0.75
- TIMI major	2.2% (5)	0.5% (1)	0.11
- TIMI minor	0.0% (0)	1.4% (3)	0.08
GUSTO bleeding, any	6.7% (15)	5.5% (12)	0.58
- GUSTO severe	4.4% (10)	4.1% (9)	0.84
- GUSTO moderate	1.3% (3)	0.0% (0)	0.09
- GUSTO mild	0.9% (2)	1.4% (3)	0.64
Any blood product transfusion	1.8% (4)	0.5% (1)	0.18
Thrombocytopenia (in-hospital)*	2/196 (1.0%)	2/179 (1.1%)	0.99

Data are Kaplan-Meier estimates (n of events)

* <100,000 cells/mm^3 in patients with a baseline platelet count >150,000 cells/mm^3 (n=384)

INFUSE-AMI

Manual aspiration
vs.
no aspiration

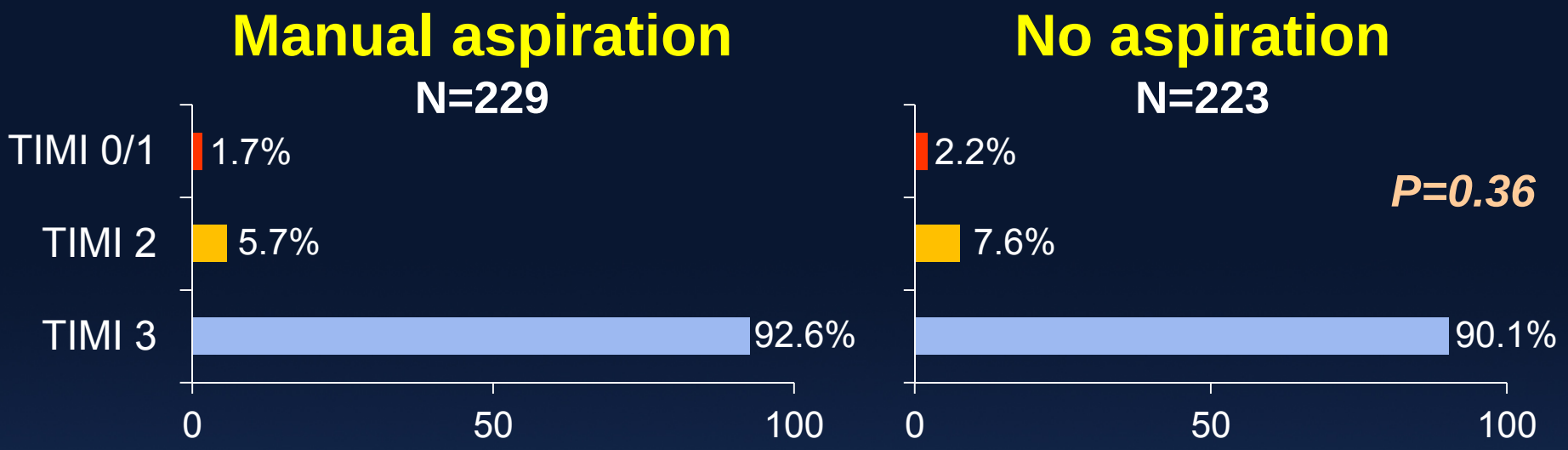
Pooled across the abciximab randomization

INFUSE-AMI: Meds and procedures

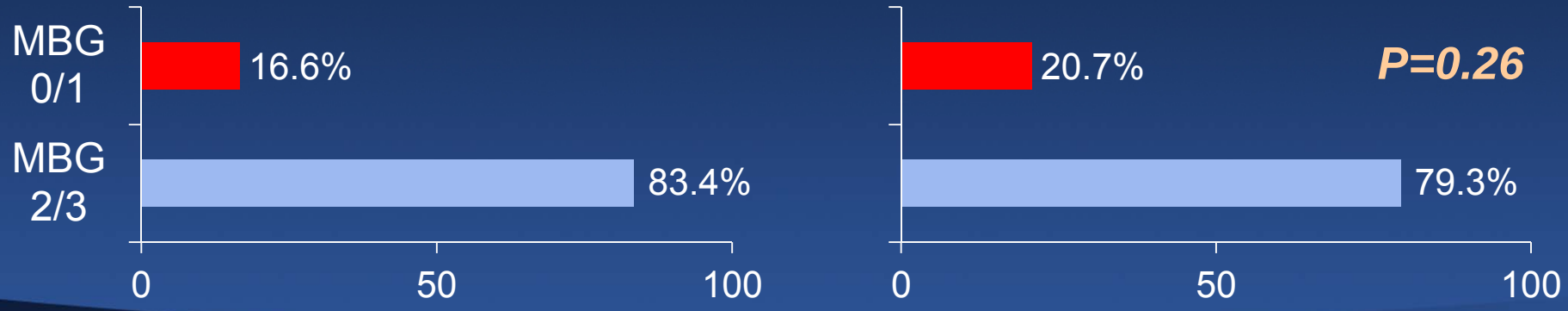
	Manual aspiration N=229	No aspiration N=223	P value
TIMI flow pre-PCI 0/1*	73.4%	70.0%	0.42
Blush pre-PCI 0/1*	85.5%	82.4%	0.37
Hospital - 1st device, mins	43 [30, 63]	48 [35, 70]	0.02
Aspiration performed	98.3%**	4.0%	<0.001
Abciximab administered	50.7%	50.2%	0.93
N lesions treated	1.1 ± 0.4	1.1 ± 0.4	0.46
DES implanted	74.2%	70.9%	0.42
Stent length (mm)	24 [18, 32]	24 [18, 35]	0.30
Max stent diameter (mm)	3.0 [3.0, 3.5]	3.0 [3.0, 3.5]	0.20

*Core laboratory assessed; **6F Export used in all but 3 cases, with thrombus retrieved in 78.9%

INFUSE-AMI: Reperfusion post-PCI*

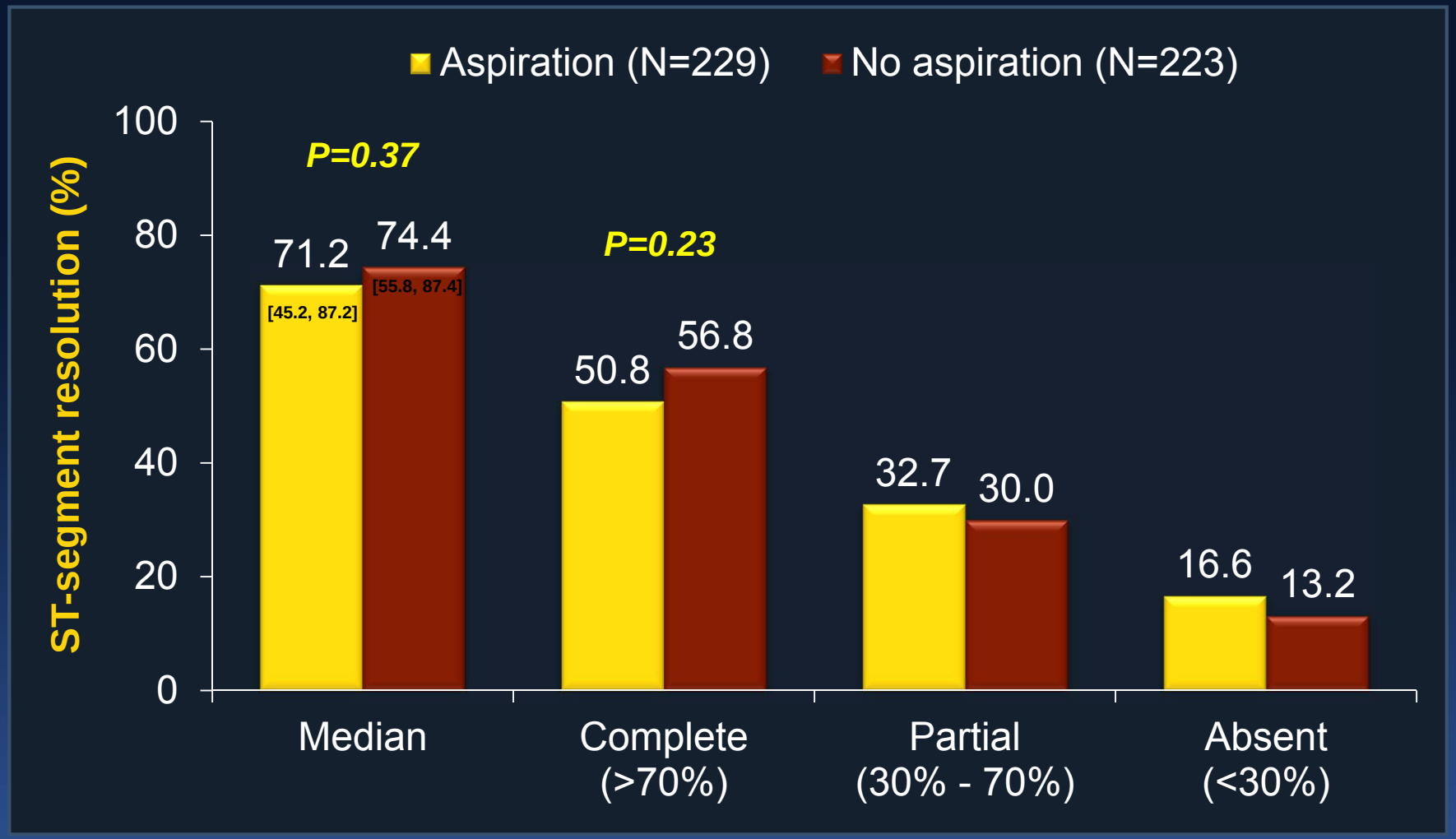


Corrected TIMI frame counts: 20 [16, 26] vs. 20 [16, 26] *P=0.40*



*Core laboratory assessed

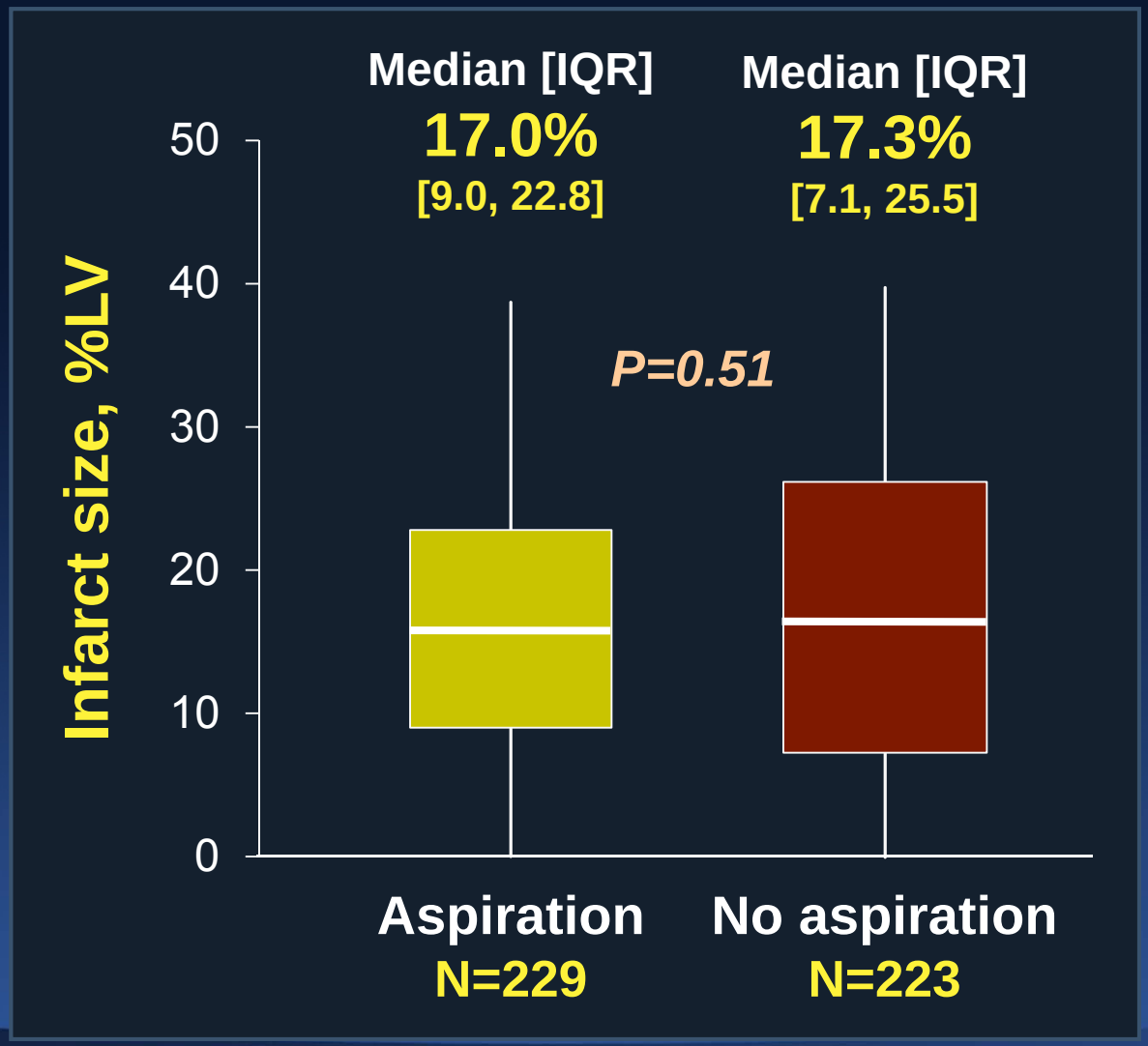
INFUSE-AMI: STR 60 minutes post-PCI*



*Core laboratory assessed

INFUSE-AMI: Infarct size at 30 days*

- Major secondary endpoint -



*Core laboratory assessed. No interaction was present between the 2 randomization groups for the primary 30-day infarct size endpoint (p=0.46)

INFUSE-AMI: cMRI at 30 days*

	Manual aspiration N=186	No aspiration N=186	P value
Total LV mass, grams	128.3 [108.9, 149.8]	132.0 [107.6, 156.1]	0.50
Infarct mass, grams	20.3 [9.7, 31.7]	21.0 [9.1, 34.1]	0.36
Infarct mass (% of total LV mass)	17.0 [9.0, 22.8]	17.3 [7.1, 25.5]	0.51
Total abnormal wall motion score	7.5 [2.0, 10.0]	7.5 [2.0, 10.0]	0.89
LVEF (%)	49.6 [43.3, 56.8]	49.5 [41.8, 57.6]	0.66

*Core laboratory assessed

INFUSE-AMI: 30-day clinical efficacy

	Manual aspiration N=229	No aspiration N=223	P value
Death	3.1% (7)	2.7% (6)	0.81
Reinfarction	0.5% (1)	0.9% (2)	0.55
New onset severe HF	3.5% (8)	4.1% (9)	0.77
Rehospitalization for HF	0.0% (0)	0.9% (2)	0.15
Stroke	0.0% (0)	0.5% (1)	0.31
Clinically-driven TVR	0.5% (1)	1.8% (4)	0.17
Stent thrombosis, def/prob*	1.4% (3)	0.5% (1)	0.33
MACCE	3.1% (7)	5.0% (11)	0.31
MACE	6.6% (15)	7.2% (16)	0.81

Data are Kaplan-Meier estimates (n of events). *No cases of acute (<24 hr) stent thrombosis occurred. MACE = death, reinfarction, new onset severe heart failure (HF) or rehospitalization for HF; MACCE = death, reinfarction, stroke or clinically-driven TVR

INFUSE-AMI: 30-day clinical safety

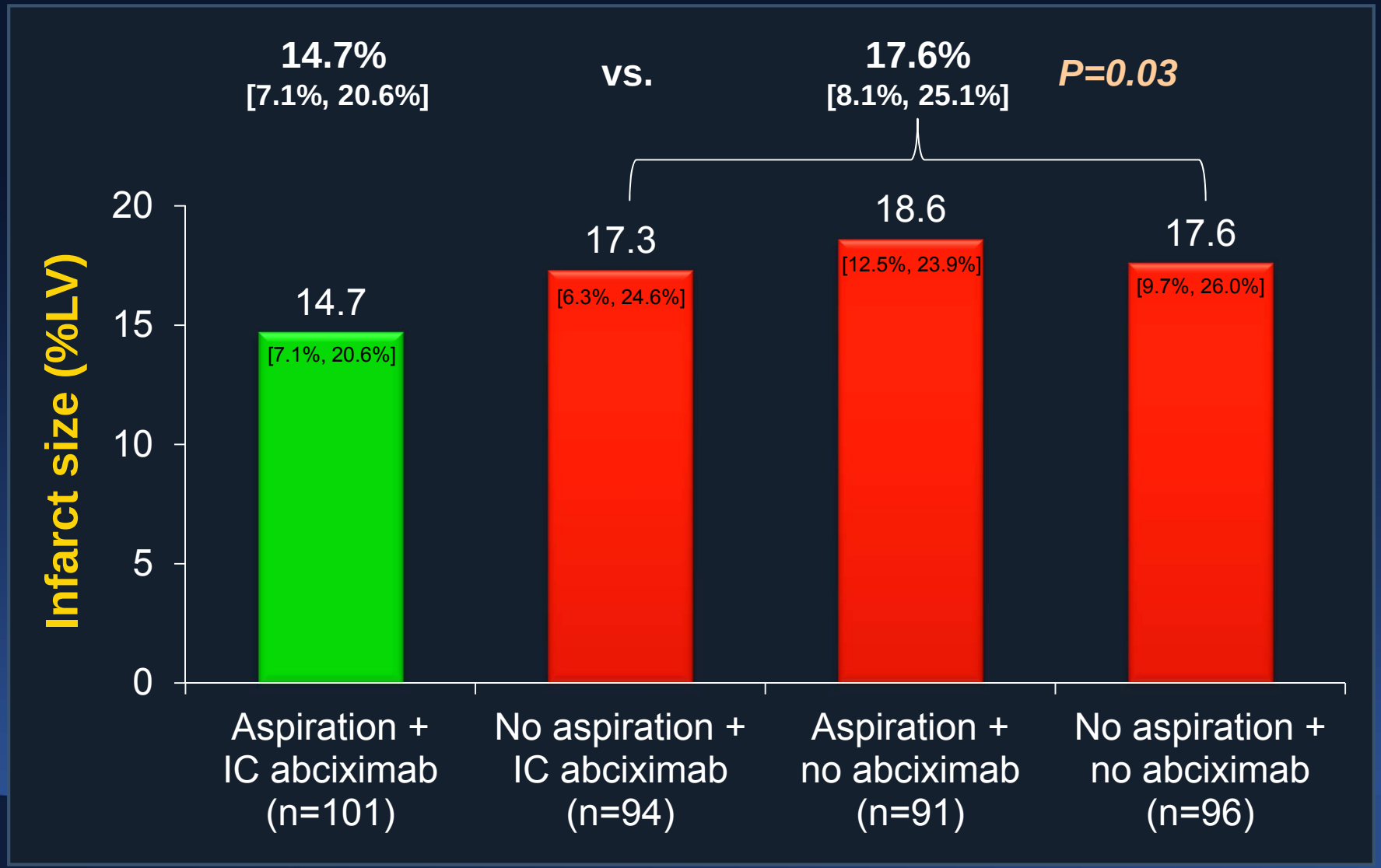
	Manual aspiration N=229	No aspiration N=223	P value
HORIZONS-AMI major bleeding	4.0% (9)	4.6% (10)	0.79
TIMI major or minor bleeding	1.3% (3)	2.8% (6)	0.30
- TIMI major	0.9% (2)	1.8% (4)	0.40
- TIMI minor	0.5% (1)	0.9% (2)	0.55
GUSTO bleeding, any	5.3% (12)	6.8% (15)	0.51
- GUSTO severe	4.0% (9)	4.5% (10)	0.77
- GUSTO moderate	0.9% (2)	0.5% (1)	0.58
- GUSTO mild	0.4% (1)	1.8% (4)	0.17
Any blood product transfusion	0.9% (2)	1.4% (3)	0.64
Thrombocytopenia (in-hospital)*	1/186 (0.5%)	3/189 (1.6%)	0.62

Data are Kaplan-Meier estimates (n of events)

* <100,000 cells/mm^3 in patients with a baseline platelet count >150,000 cells/mm^3 (n=384)

INFUSE-AMI: Infarct size at 30 days*

- 4 group analysis -



INFUSE-AMI: Limitations (1)

- Single-blind trial – but the patient, follow-up personnel, core labs and CEC were blinded
- Highly selected (7.2% STEMIs screened were randomized) – but given the study design it is unlikely that IC abciximab or aspiration would be *more* effective in other groups
- Slightly fewer 30-day cMRIs were available for analysis than planned, but 97% post-hoc power was present to demonstrate the pre-specified 25% relative inter-group reduction in infarct size

INFUSE-AMI: Limitations (2)

- Discordance between immediate biomarkers of reperfusion and 30 day infarct size with IC abciximab is noted – requires further study
- Similar 30-day MACE rates between groups is consistent with the comparable rates of MBG and STR observed; improved 30-day infarct size should correlate with late survival (1-yr FU ongoing)
- INFUSE-AMI was not powered for clinical events; a large RCT is required to determine whether the magnitude of the infarct size reduction seen with IC abciximab in this trial would translate into improved clinical outcomes without excessive bleeding

INFUSE-AMI: Conclusions & Implications

In patients presenting early in the course of a large evolving anterior STEMI undergoing primary PCI with bivalirudin anticoagulation:

1) Bolus IC abciximab delivered to the infarct lesion site via the ClearWay Rx Infusion Catheter resulted in a significant but modest reduction in infarct size at 30 days

   - A RCT powered for clinical and safety endpoints is warranted to determine the role of local abciximab delivery in STEMI

INFUSE-AMI: Conclusions & Implications

In patients presenting early in the course of a large evolving anterior STEMI undergoing primary PCI with bivalirudin anticoagulation:

2) Manual aspiration with the 6F Export Catheter did not reduce infarct size
   - The utility of combined aspiration + local delivery of IC abciximab deserves further study
   - The final word on aspiration in STEMI awaits the ongoing large-scale randomized TOTAL and TASTE trials