VELOCITY

A Prospective, Randomized Trial of Peritoneal Hypothermia in Patients with Acute STEMI Undergoing PCI

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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
• Consultant	• Velomedix

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Background

- Systemic hypothermia (≤34.9°C) may reduce infarct size if established before reperfusion
- Peritoneal lavage has a well-established safety profile for diagnosis of blunt abdominal injury in patients with trauma, and for treatment of accidental hypothermia, end-stage renal disease, and cancer
- The large surface area of the bowel may facilitate rapid hypothermia, safely reducing infarct size

Objective

- We therefore sought to assess the feasibility, safety and efficacy of systemic hypothermia induced by peritoneal lavage in patients with STEMI prior to primary PCI

Velocity Trial Design

Symptoms of STEMI between 30 minutes and 6 hours
ST-segment elevation ≥2 mm in ≥2 continuous ECG leads
Intended for primary PCI
Maximum 60 patients

Randomize 1:1

Cardiac catheterization/PCI

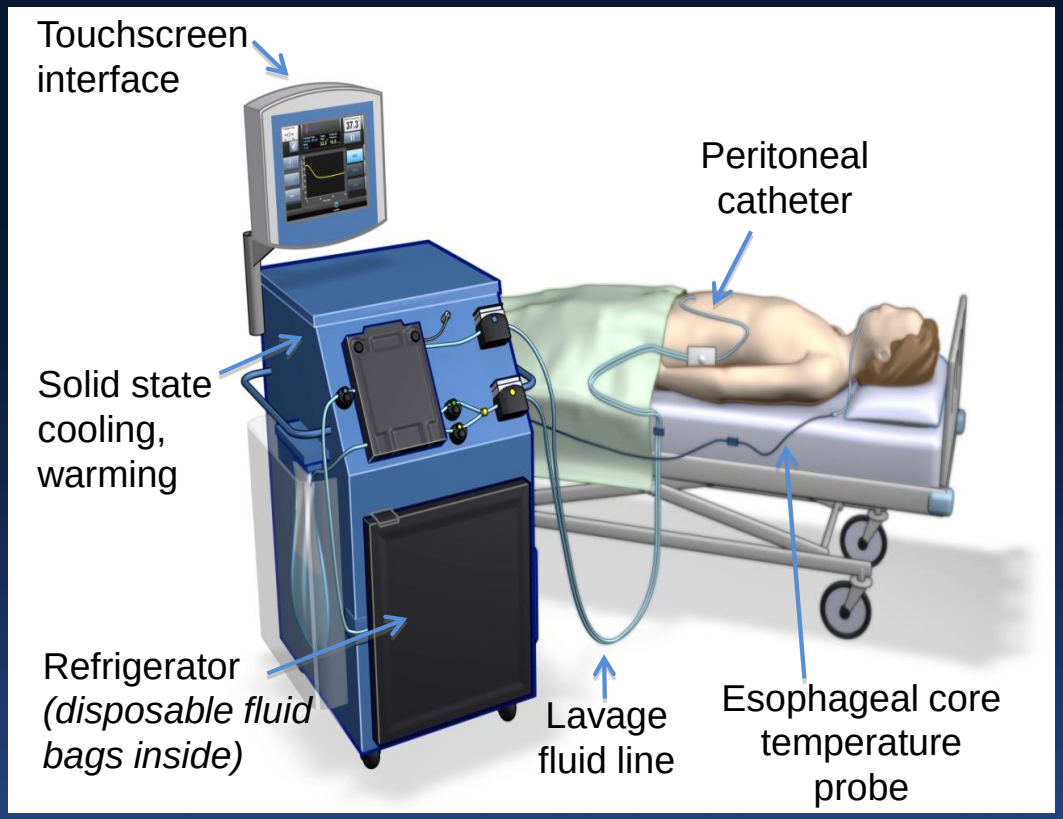
Peritoneal hypothermia followed by cardiac catheterization/PCI

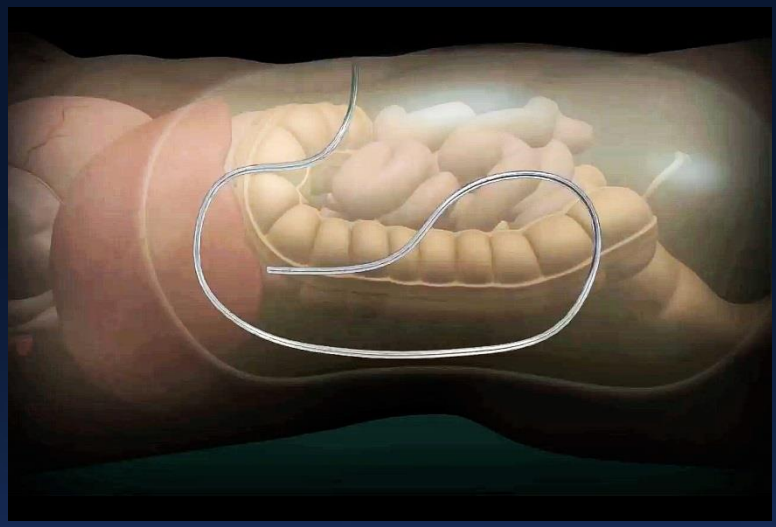
Cardiac MRI at 3-5 days and at 30 (±7) days
Clinical follow-up at 30 days and 6 months

Key Exclusion Criteria

- Contraindications to peritoneal lavage (e.g. prior intraperitoneal surgery, profound obesity, abdominal aortic aneurysm, or massive ascites)
- Temperature-sensitive hematological dyscrasias or vasospastic disorders
- Cardiac arrest, pulmonary edema or cardiogenic shock
- Oxygen-dependent COPD
- Prior MI
- Active bleeding, thrombolytic therapy or chronic oral anticoagulant use
- Known hemoglobin <9 mg/dL, platelet count <100,000 or >750,000 cells/mm^3, serum creatinine >2.0 mg/dL, dialysis or abnl liver function
- Allergy or intolerance to contrast or study drugs
- Contraindications for MRI
- Pregnant or nursing
- Comorbidities with life expectancy <1 year
- Inability to provide informed written consent

Velomedix Automated Peritoneal Lavage System





Shivering prophylaxis and treatment

Pre-PCI: Buspirone; meperidine, forced-air warming blanket

If needed: Fentanyl, magnesium, dexmedetomidine

- Hypothermia to 34.9°C is induced before PCI by lavaging the peritoneal cavity with temperature-controlled 2.5 - 4.5 liters of lactated Ringer's solution
- Further cooling occurs to a target temperature of 32.5°C, which is maintained for 3 hours post-PCI, after which the system initiates active re-warming and then fluid drainage

Endpoints

- Device success (hypothermia): Core temperature ≤34.9°C before PCI
- Primary safety endpoint: Composite rate of death, reinfarction, ischemia-driven TVR, major bleeding, sepsis, pneumonia, peritonitis, severe arrhythmias, or renal failure occurring within 30 (±7) days
- Primary efficacy endpoint: Infarct size assessed by cardiac MRI on day 3-5 (%LV mass)
- Other endpoints:
  - MRI: MVO at 3-5 days, and LV volumes and EF at 3-5 and 30 days
  - TIMI flow, ST-segment resolution
  - Clinical: MACE (cardiac death, reinfarction, or ischemia-driven TVR); ARC stent thrombosis

VELOCITY Trial Organization

Principal investigator: Gregg W. Stone, Columbia University Medical Center, New York, NY

Co-principal investigator: Graham Nichol, University of Washington-Harborview Center for Prehospital Emergency Care, Seattle, WA

Sponsor, site management and data monitoring: Velomedix, Inc., Menlo Park, CA; Russell Ivanhoe, Griffeth W. Tully

Data management and analysis: The Cardiovascular Research Foundation (CRF), New York, NY; Ori Ben-Yehuda, Melissa Nichols, Ovidiu Dressler, Rupa Parvataneni

Coronary angiographic core laboratory: CRF; Philippe Genereux

Cardiac MRI core laboratory: CRF; Steven D. Wolff, Akiko Maehara

ECG core laboratory: St. Louis University, St. Louis, MO; Bernard Chaitman, Abhay Laddu

Clinical events committee, and data safety and monitoring board: David Beiser, Joseph P Carrozza Jr., Sam Tisherman, Kyle D. Rudser

VELOCITY Trial Participating Hospitals and Principal Investigators

Huntsville Hospital, Huntsville, AL; Warren Strickland

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Vanderbilt Medical Center, Nashville, TN; John McPherson

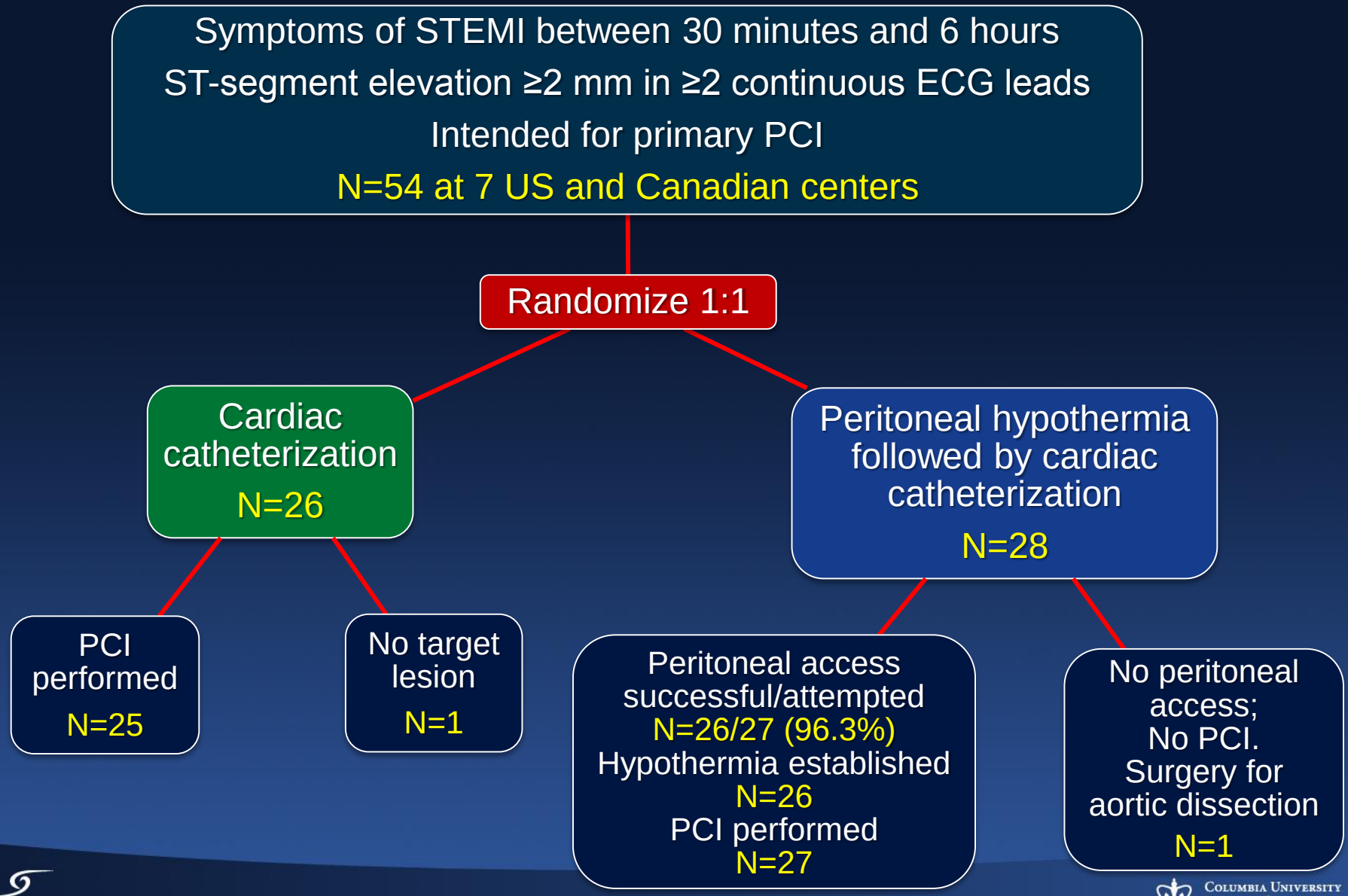
Hospital Laval, Laval, Quebec City, Canada; Gérald Barbeau

Northeast Georgia Heart Center Gainesville, GA; Allison Dupont

Ochsner Medical Center, New Orleans, LA; Steve Jenkins

Royal Jubilee Hospital, Victoria, BC, Canada; Eric Fretz

Patient Flow



Baseline Features

	Control (n=26)	Hypothermia (n=28)	P value
Age in years	57.5 [52, 63]	57 [47, 65]	0.51
Male gender	21 (80.8%)	25 (89.3%)	0.46
Medical history			
Hypertension	9 (34.6%)	14 (50.0%)	0.25
Hyperlipidemia	6 (23.1%)	10 (35.7%)	0.31
Diabetes	6 (23.1%)	6 (21.4%)	0.88
Current smoking	11/25 (44.0%)	12 (42.9%)	0.93
Prior MI	0	0	-
Anterior infarct (ECG)	12 (46.2%)	13 (46.4%)	0.98

Baseline and Procedural Medications

	Control (n=26)	Hypothermia (n=28)	P value
Medications on admission			
Aspirin	19 (73.1%)	23 (82.1%)	0.42
ADP antagonist	8 (30.8%)	5 (17.9%)	0.27
Beta blocker	4 (15.4%)	7 (25.0%)	0.38
ACEI/ARB	0	0	-
Statin	1 (3.8%)	0	0.48
Medications prior to and/or during PCI			
Heparin	16 (61.5%)	14 (50.0%)	0.39
Bivalirudin	21 (80.8%)	21 (75.0%)	0.61
Aspirin	18 (69.2%)	22 (78.6%)	0.43
ADP antagonist, any	20 (76.9%)	20 (71.4%)	0.65
Clopidogrel	9 (34.6%)	11 (39.3%)	0.72
Prasugrel	10 (38.5%)	3 (10.7%)	0.02
Ticagrelor	2 (7.7%)	6 (21.4%)	0.25
GP IIb/IIIa inhibitor	10 (38.5%)	13 (46.4%)	0.55

Temperature and Time Measures

	Control (n=26)	Hypothermia (n=28)	P value
Temperature measures (°C)			
Emergency room arrival	36.4 [36.1, 36.7]	36.5 [36.3, 36.9]	0.17
At time of first balloon	36.2 [35.9, 36.7]	34.7 [34.0, 34.9]*	<0.0001
Min temp (PCI pts, n=27)	-	34.0 [33.2, 34.8]	-
Time intervals (minutes)			
Symptom onset-to-hospital	118 [52, 164]	102 [80, 165]	0.72
Hospital-to-cath lab	19 [1, 29]	12 [1, 40]	0.51
Cath lab-to-arterial access	13 [11, 17]	27 [17, 31]	<0.0001
Door-to-balloon	47 [37, 55]	62 [51, 81]	0.007
Symptom onset-to-balloon	167 [104, 217]	172.5 [152, 247]	0.17
PCI procedure duration	33 [25, 48]	32 [24, 58]	0.56

*Goal temperature of ≤34.9°C before PCI was achieved in 24/27 hypothermia pts (88.9%) at median 17.0 [13.5, 28.5] minutes after cooling onset.

Angiographic Outcomes (core lab)

	Control	Hypothermia	P value
Angiography, baseline	n=25	n=26	
Target vessel			
LAD	10 (40.0%)	11/25 (44.0%)	0.77
LCX	2 (8.0%)	3/25 (12.0%)	>0.99
RCA	12 (48.0%)	11/25 (44.0%)	0.78
SVG	1 (4.0%)	0/25 (0%)	>0.99
TIMI flow			
0/1	18 (72.0%)	21 (80.8%)	0.46
2	6 (24.0%)	1 (3.8%)	0.05
3	1 (4.0%)	4 (15.4%)	0.35
Angiography, post-PCI	n=24	n=26	
TIMI flow			
0/1	0 (0%)	0 (0%)	-
2	2 (8.3%)	5 (19.2%)	0.42
3	22 (91.7%)	21 (80.8%)	0.42
TIMI frame count	28 [20, 36]	26 [23, 34]	0.77

Electrocardiography (core lab)

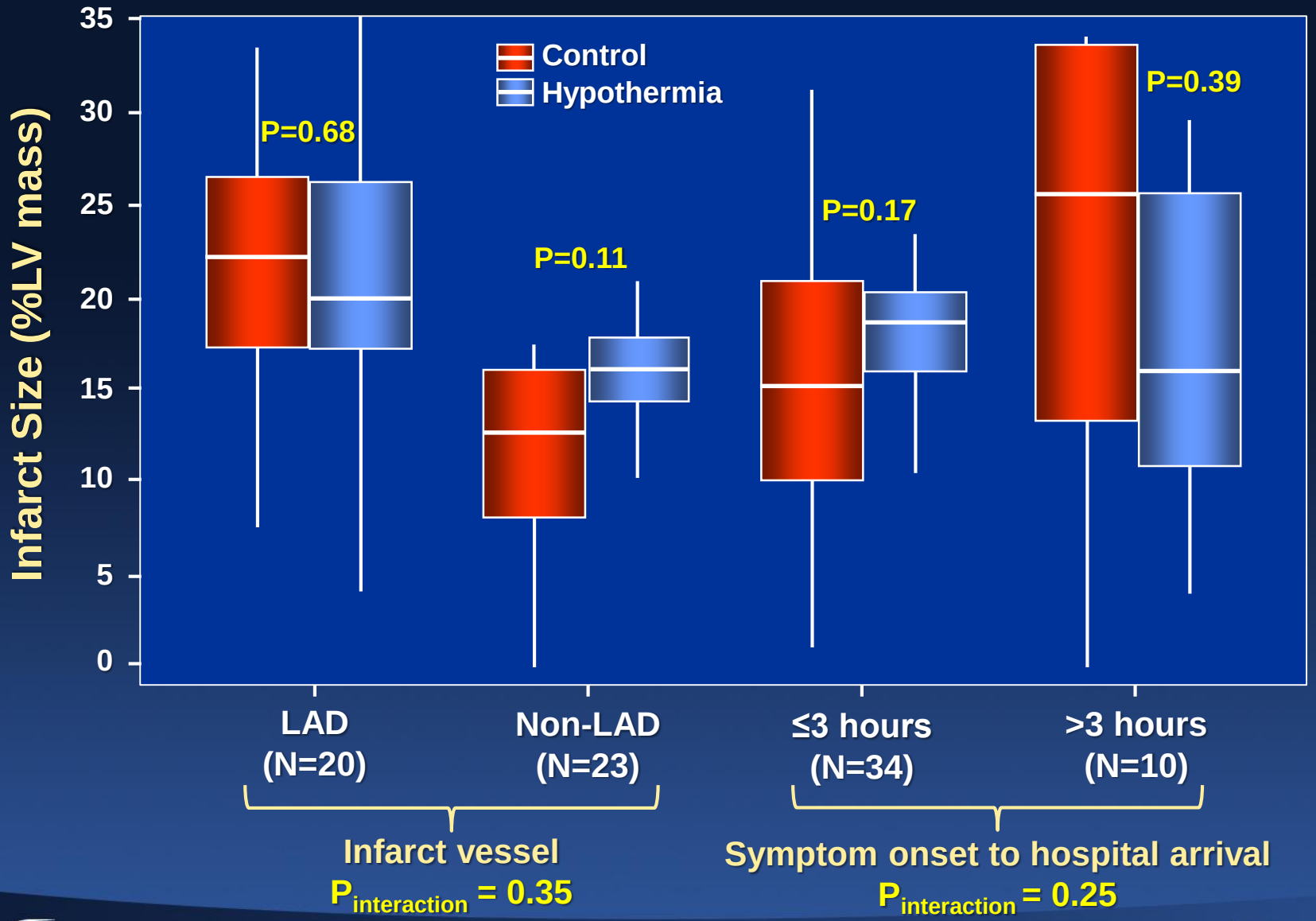
	Control	Hypothermia	P value
Baseline			
ST-segment elevation, mm	N=26	N=28	
Summed	9.1 [6.5, 12.1]	7.8 [6.0, 11.7]	0.48
Maximum lead	2.3 [2.1, 3.6]	2.9 [2.0, 3.5]	0.87
60 mins post-PCI			
ST-segment resolution	N=26	N=26	
Complete (≥70%)[1]	5 (19.2%)	5 (19.2%)	>0.99
Complete (≥70%)[2]	7 (26.9%)	7 (26.9%)	>0.99

[1]From summed leads; [2]From maximum lead

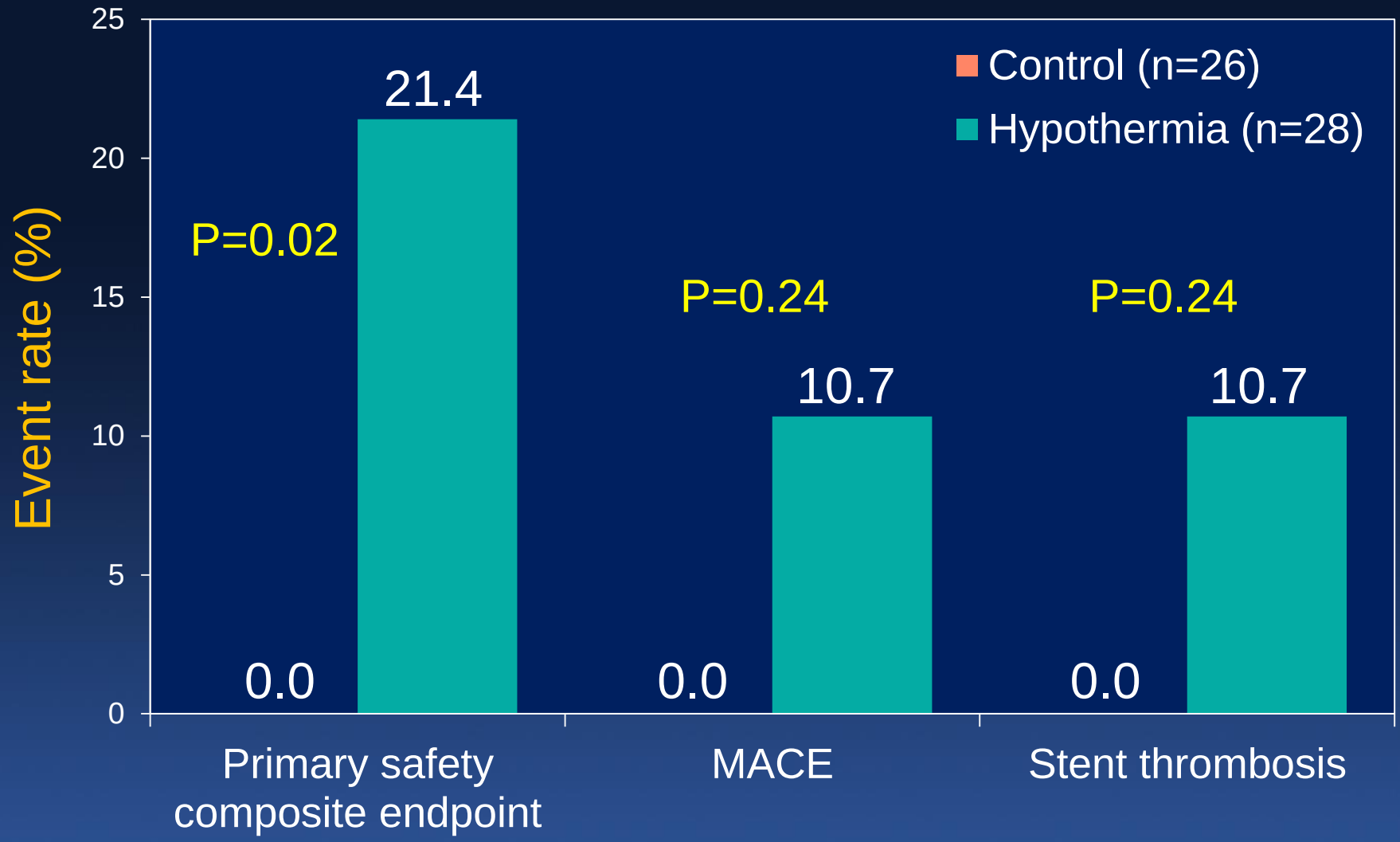
MRI Results at Day 3-5

	Control (n=20)	Hypothermia (n=26)	P value
Time from PCI (days)	4 (3, 4)	4 (3, 5)	0.53
LV myocardial mass (grams)	125.5 (109.5, 135,5)	123 (107, 142)	0.80
Area at risk (grams)	35.1 (20.4, 50.5)	34.2 (26, 51.6)	0.56
Area at risk (% LV mass)	26.8 (16.7, 40.6)	26.1 (22.7, 34.4)	0.69
Infarct mass (grams)	20.8 (10.9, 27.6)	22.2 (15.6, 30.1)	0.44
Infarct mass/area at risk (%)	55.8 (43.8, 67.2)	67.3 (48.9, 73.3)	0.36
Myocardial salvage (%)	44.2 (32.8, 56.2)	32.7 (26.7, 51.1)	0.36
Primary efficacy endpoint: Infarct size (% total LV mass)	16.1 (10.0, 22.2)	17.2 (15.1, 20.6)	0.54
MVO (grams)	0 (0, 0.2)	0 (0, 0.7)	0.57
MVO (% total LV mass)	0 (0, 0.2)	0 (0, 0.5)	0.64
LV end-diastolic volume (mL)	161 (137.5, 172)	159 (125, 191)	0.80
LV end-systolic volume (mL)	83.3 (66.8, 102)	81.9 (71, 119)	0.63
LV stroke volume (mL)	75.2 (61.4, 81.5)	75.4 (61.1, 84)	0.78
LV ejection fraction (%)	46.3 (42.6, 50.6)	43.3 (37.4, 52)	0.37
Abnormal wall motion score	8 (4, 11.5)	8 (6, 10)	0.52

Subgroup Analysis for Infarct Size at Day 3-5



Clinical Events at 30 Days



Primary Safety Composite Endpoint

30-day events	Control (n=26)	Hypothermia (n=28)	P value
Composite rate	0	6 (21.4%)	0.02
Cardiac death	0	1 (3.6%)*	>0.99
Non-cardiac death	0	0	-
Reinfarction	0	1 (3.6%)	>0.99
Ischemia-driven TVR	0	3 (10.7%)	0.24
Major bleeding	0	1 (3.6%)**	>0.99
VT/VF	0	1 (3.6%)	>0.99
Sepsis	0	1 (3.6%)	>0.99
Pneumonia	0	0	-
Renal failure	0	0	-
Peritonitis	0	0	-

*Pt with aortic dissection mimicking STEMI died after surgery (no PCI or hypothermia);
**From femoral artery access site

Major Adverse Cardiac Events

30-day events	Control (n=26)	Hypothermia (n=28)	P value
Composite MACE	0	3 (10.7%)	0.24
Cardiac death	0	1 (3.6%)*	>0.99
Reinfarction	0	1 (3.6%)**	>0.99
Ischemia-driven TVR	0	3 (10.7%)**	0.24
Stent thrombosis	0	3 (10.7%)	0.24
Acute (≤24 hrs)	0	2 (7.1%)	0.49
Subacute (1-30d)	0	1 (3.6%)	>0.99
Definite	0	3 (10.7%)	0.24
Probable	0	0	-

*Pt with aortic dissection mimicking STEMI died after surgery (no PCI or hypothermia);
**Due to stent thrombosis

Limitations

- Modest sample size, not powered for efficacy
- Unblinded
- Non-anterior as well as anterior infarcts
- Level of optimal cooling prior to PCI is unknown
- Long-term follow-up is not available

Conclusions

- Controlled systemic hypothermia through automated peritoneal lavage may be rapidly established in pts with evolving STEMI undergoing primary PCI at the expense of a modest increase in door-to-balloon time
- In the present randomized trial, peritoneal hypothermia was associated with an increased rate of adverse events (including stent thrombosis) without reducing infarct size