Sonothrombolysis in ST Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention: Final Results from the First Randomized Study in Humans

Wilson Mathias, Jr[1], Jeane M Tsutsui[1], Bruno G Tavares[1], Agostina Fava[2], Miguel O D Aguiar[1], Bruno C Borges[1], Mucio T Oliveira Jr[1], Alexandre Soeiro[1], Jose C Nicolau[1], Henrique B Ribeiro[1], Hsu Pochiang[1], João C N Sbano[1], Abdul Morad [2], Andrew Goldsweig[2], Carlos E Rochitte[1], Bernardo B C Lopes[1], José A F Ramirez[1], Roberto Kalil Filho[1], Thomas R Porter[2].

[1] Heart Institute (InCor), The University of São Paulo Medical School, Brazil

[2] Cardiology Department of The University of Nebraska Medical Center, USA

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University of São Paulo Medical School
São Paulo, Brazil

University of Nebraska Medical Center
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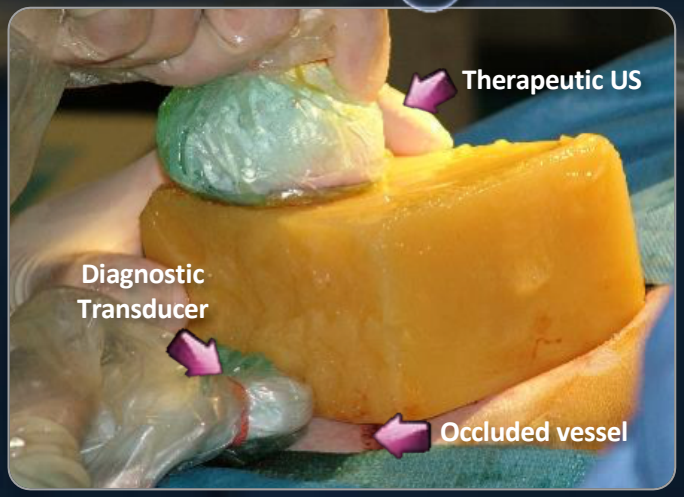
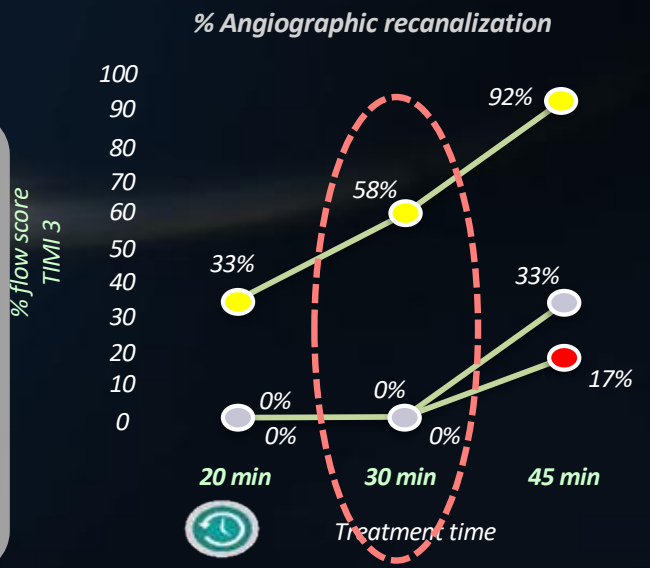
Late Breaking Clinical Trials Session, ACC19, March 17, 2019

BACKGROUND



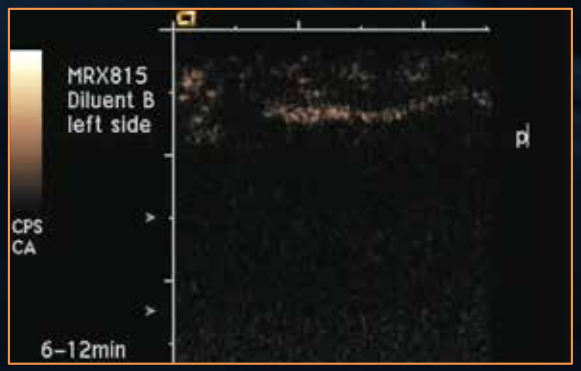
High Energy – IM > 1.0

- 12 Dogs – Thrombotic Occlusions
- Tissue 6 cm
- Therapeutic US1 MHz

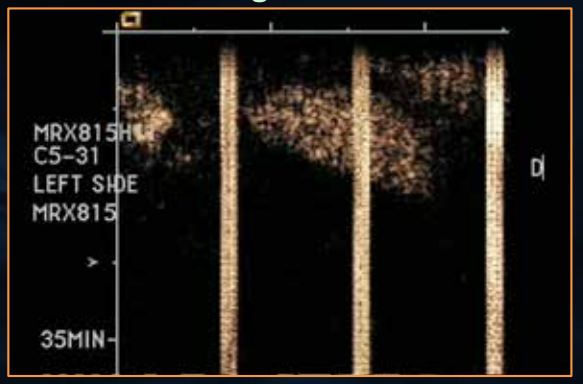


Occluded Graft

Low MI Imaging Small channels despite Graft Occlusion



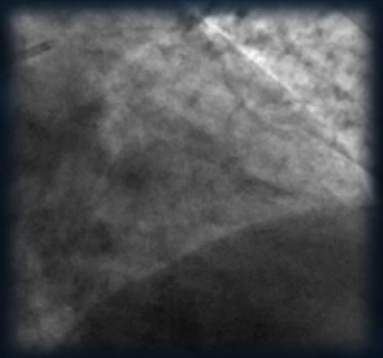
Increase in Channels size After Intermitent High MI US



Tsutsui JM et al. *Treatment of Deeply Located Acute Intravascular Thrombi With Therapeutic Ultrasound Guided by Diagnostic Ultrasound and Intravenous Microbubbles. J Ultrasound Med. 2006 Sep;25(9):1161-8.*

Coronary Reperfusion Therapies in 2019
Drawbacks

- Fibrinolysis: Major Haemorragic Complications in ~ 17%
- Recanalization rates ~ 60% cases when patients present within 4h of pain
- Fibrinolysis and PCI are Available in Brazil to only ~40% of patients



Even with PCI, microvascular occurs in ~35 % of Cases

Aggarwal S et.al. J Am Soc Echocardiogr 2018;31:674-82
Nicoli G et al. Am Coll Cardiol 54:281-92, 2009
Nicolau JC et al. Arq Bras Cardiol. 105(2):1-105, 2015

Study Design

- *Prospective, single-center, two arm randomized study*
- *Patients with 1st ST elevation AMI*
- *May 2014 – July 2018*

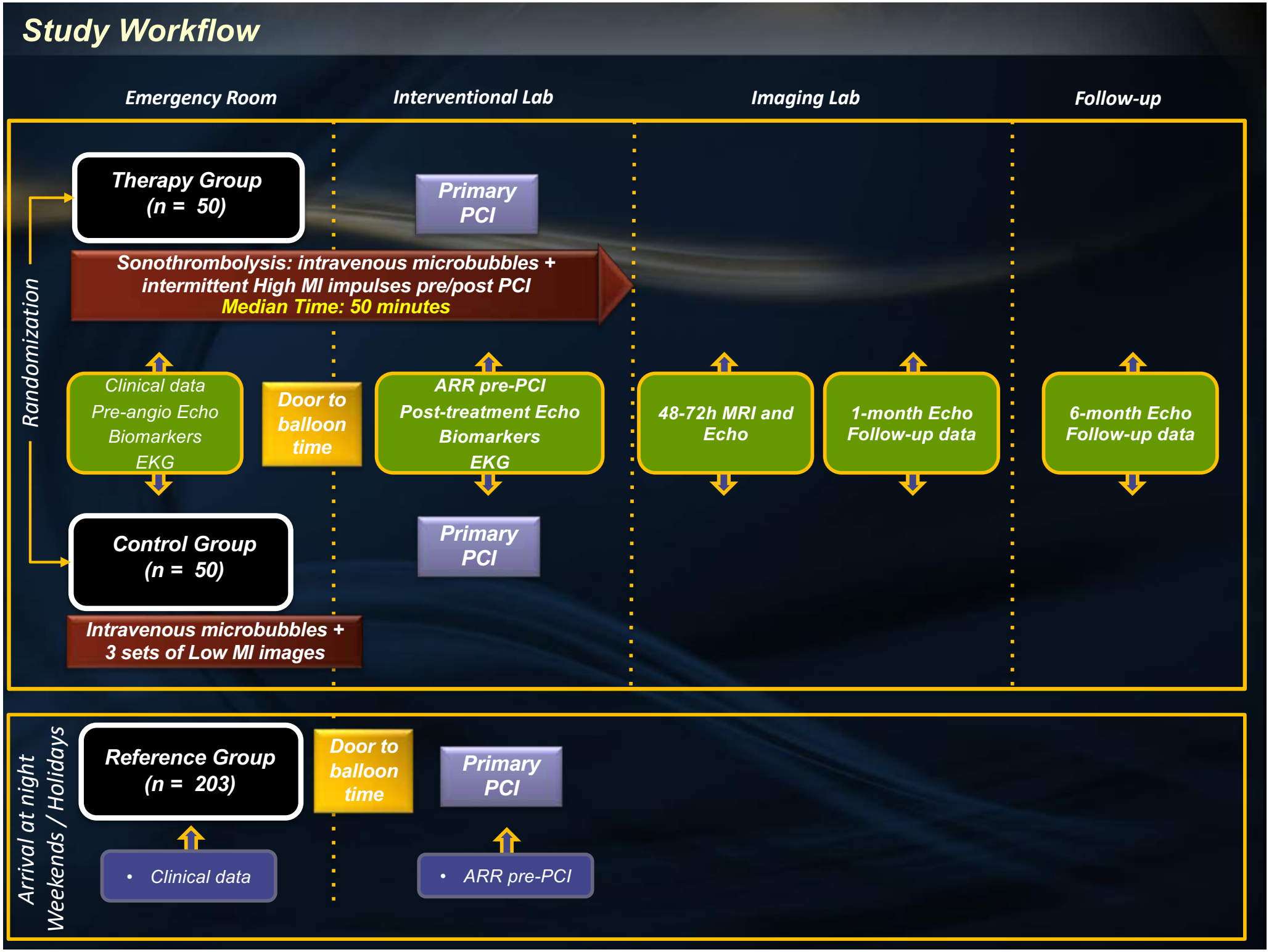
Research Project *# 2010/52114-1*
Final IRB Approval *# 342.799 (07/08/2013)*
Clinical Trials.gov *# NCT02410330*

OBJECTIVES

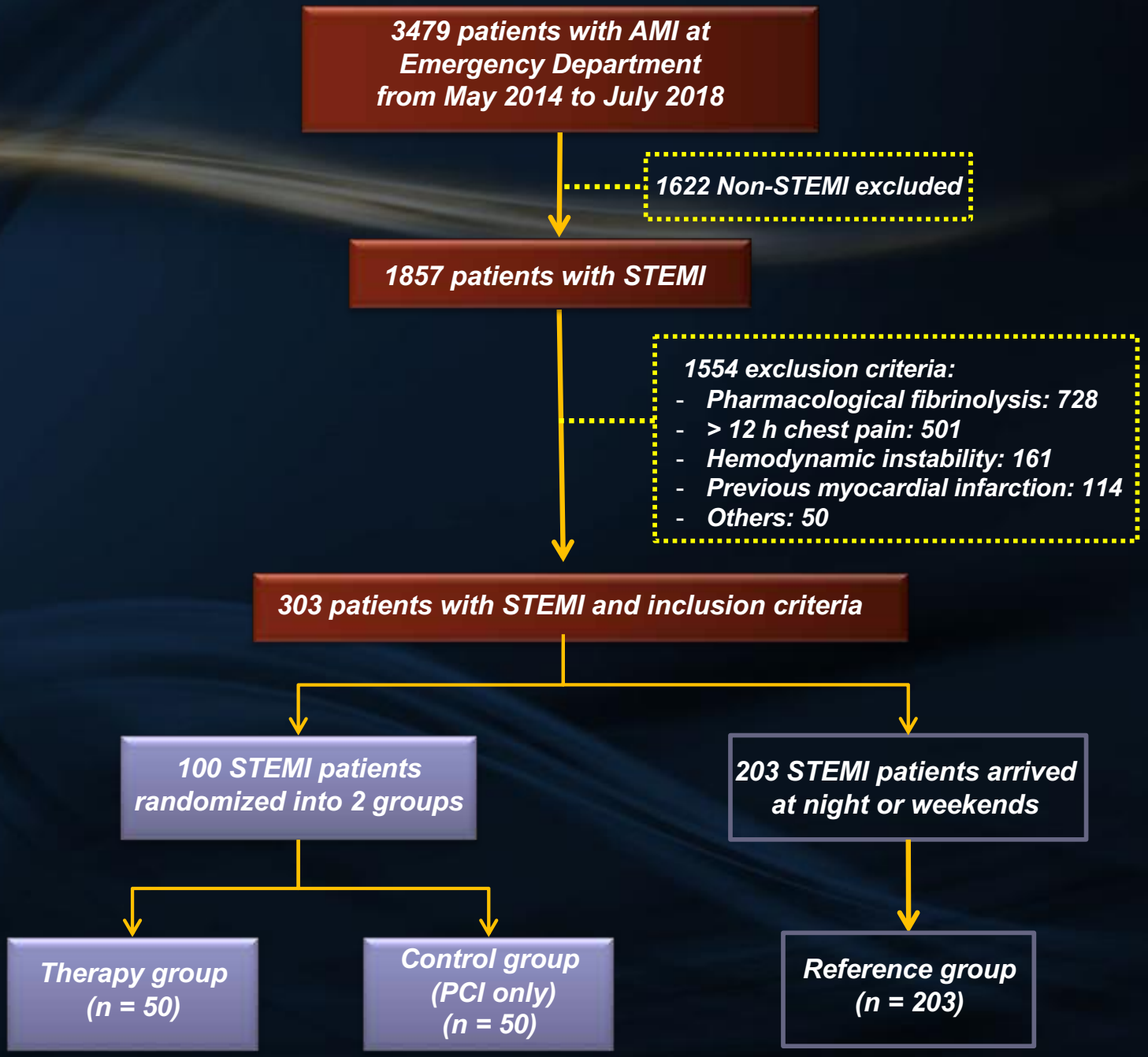
1 *– To determine the safety and feasibility of sonothrombolysis in humans during acute STEMI in 100 patients*

2 *– To determine the potential efficacy of sonothrombolysis in achieving early infarct vessel patency and restoring left ventricular systolic function by reducing MI size*

Study Workflow

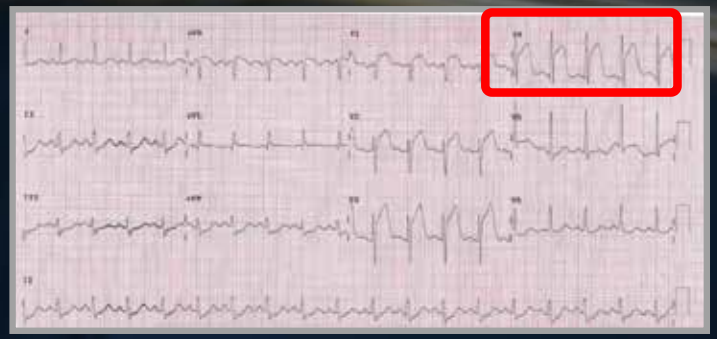


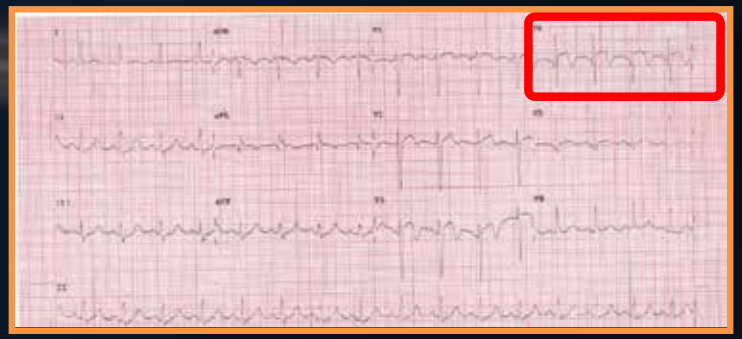
Patient Selection



Elektrocardiogram, Biomarkers and Angiography

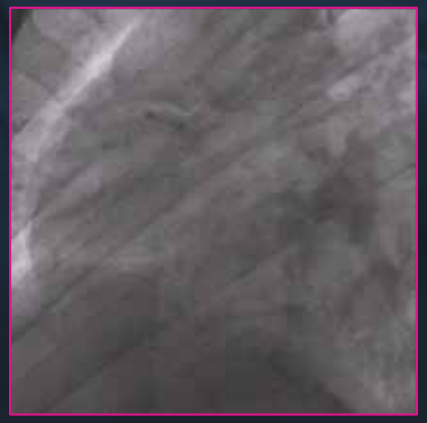
- ✓ *ST segment resolution as a % or ≥50% ST resolution from baseline to Post sonolysis pre PCI and at the and of the second sonolysis (*).*





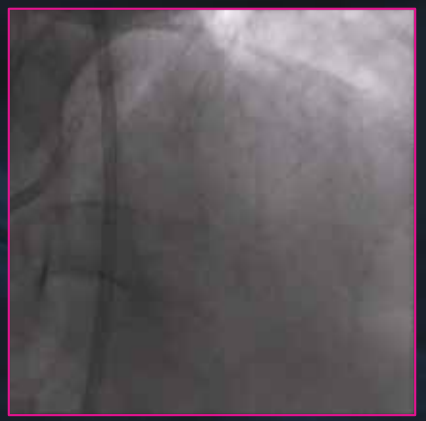
- ✓ *Cardiac specific troponin and creatinine kinase MB fraction (MB-CK) every 3 hours for 18 hours.*

Closed artery – TIMI 0 and 1



Interpretation: UNMC, Nebraska

Opened artery – TIMI 2 and 3

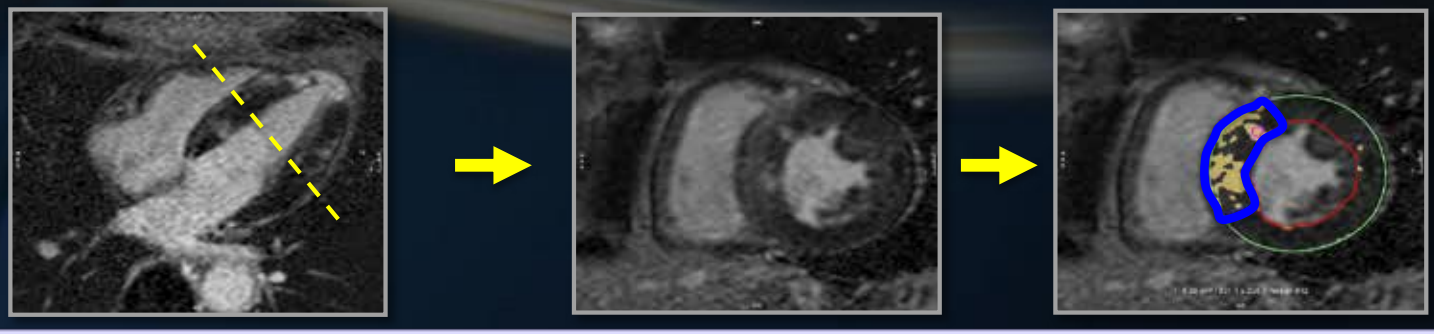


** Spitaleri G at al. . Am J Cardiol 121:1039-1045, 2018.*

Echocardiography and cMRI

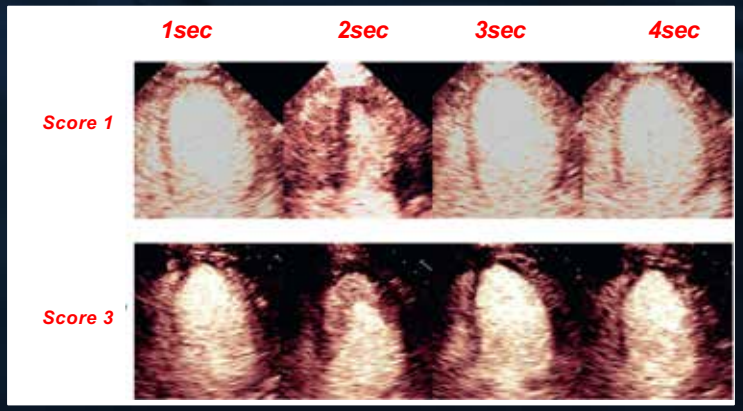
cMRI by Achieva 1.5T Scanner

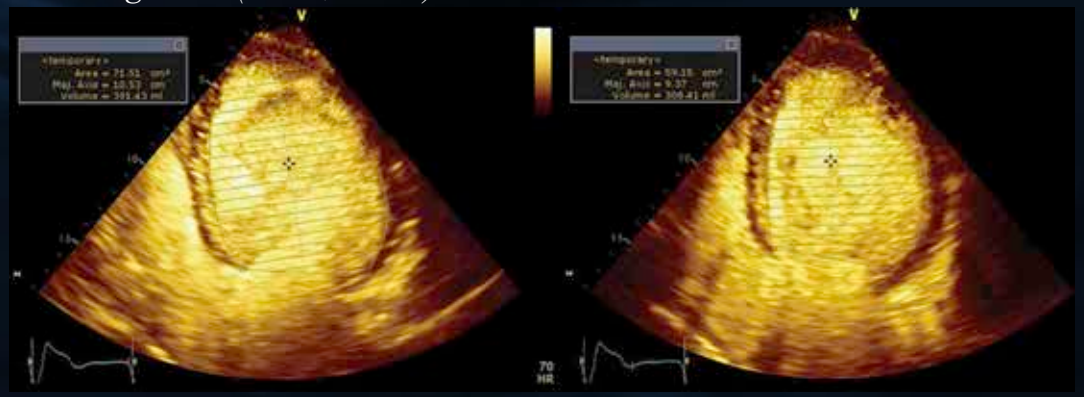
- ✓ *Early (EGE) and Late gadolinium enhancement (LGE) images were obtained at 2 and 10 minutes following injection of 0.2 mmol/Kg Gadolinium. Interpretation: UNMC - Nebraska*



Echocardiography by IE33 – Philips Medical Systems

- ✓ *A score of 1: normal perfusion; 2: >4 second delay; 3: absent replenishment at 10 seconds post high MI impulse (MVO).*
- ✓ *EDV, ESV and Ejection Fraction were computed by contrast images using Simpson's Rule.*
- ✓ *Interpretation: two experienced cardiologists blinded to treatment assignment (InCor, Brazil)*

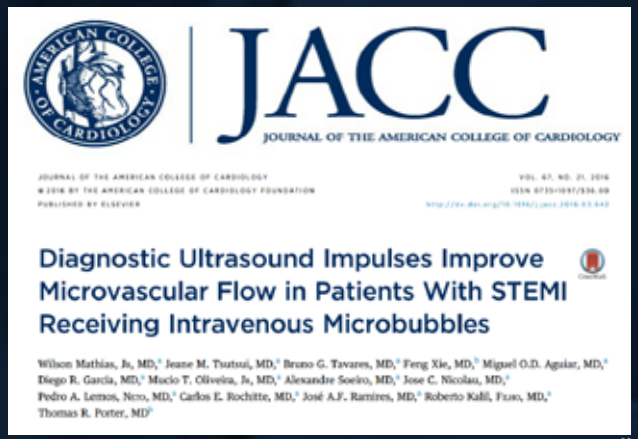


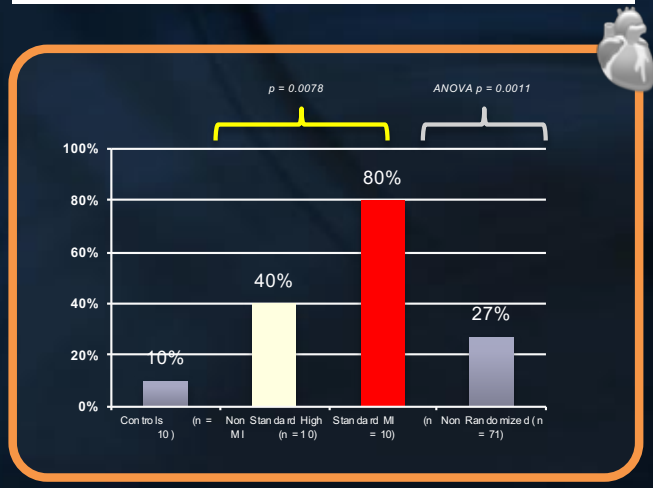


Botker HE et al. J Cardiovas Magn Reson., 14;68, 2012.
Lang RM et al. J Am Soc Echocardiogr 28:1–39, 2015.
Porter TR et al. 31, 241-274, 2018.

Statistics

- ✓ *Based on pilot data (*), we anticipated randomizing 100 patients to achieve statistical significance ($p<0.05$ using unpaired one-tailed t testing for continuous variables.*
- ✓ *Data were analyzed for possible confounders*





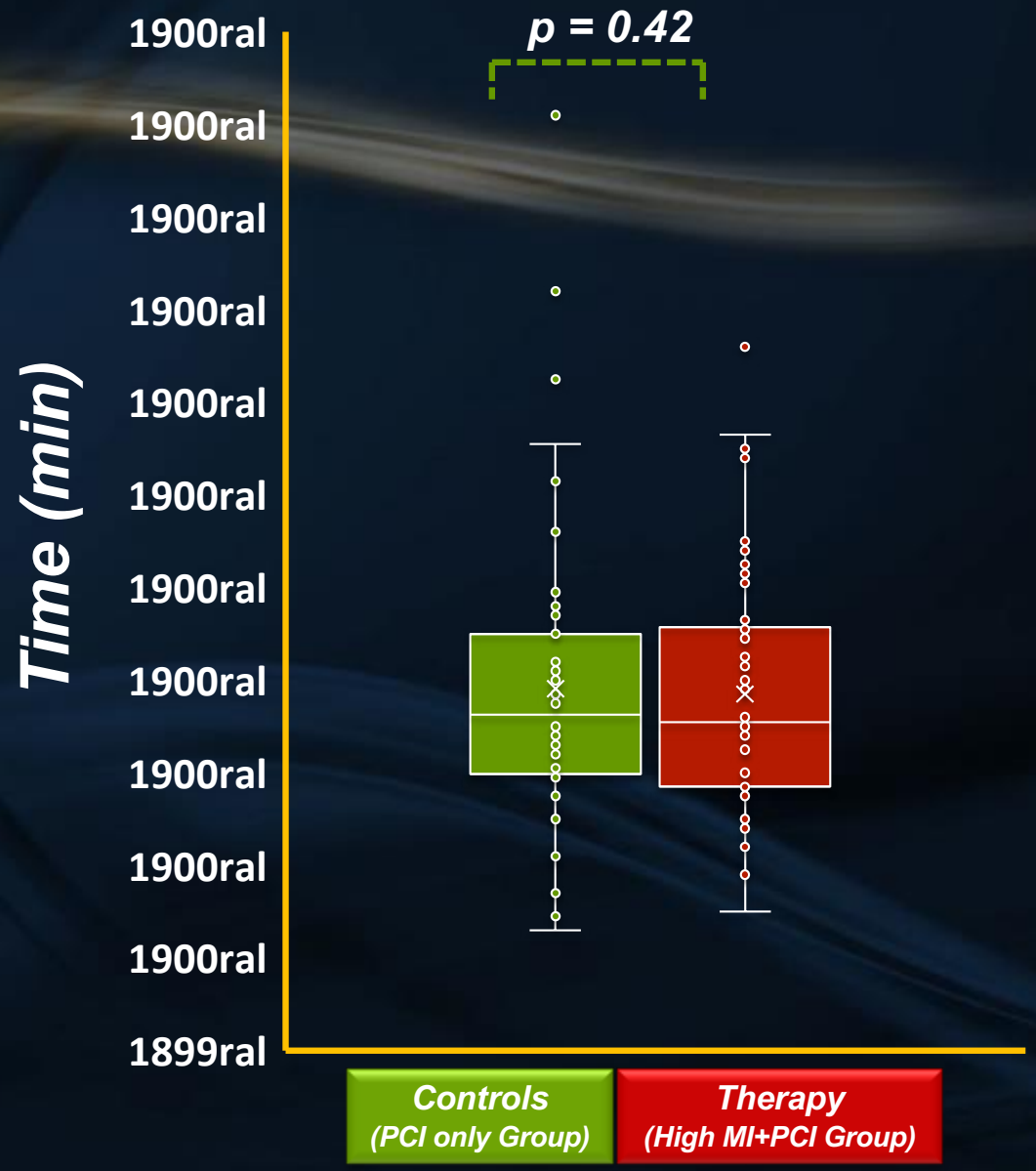
- ✓ *Primary outcomes: rate of ST segment resolution and angiographic patency prior to PCI as continuous and dichotomous variable.*
- ✓ *Secondary outcomes: Infarct size by CMRI and microvascular flow, LVEF and Myocardial Perfusion post PCI, one week and six months.*
- ✓ *Differences were compared between groups at specific time points, and no adjustments were made for multiple comparisons over time.*

Demographic Variables

Variable	Control Group n= 50	Therapy Group n = 50	Reference Group n = 203	p Value
Age (years)	59±11	59±10	59+11	0.96(1)
Gender (male)	40 (80%)	32 (64%)	148 (73%)	0.20(2)
Weight (kg)	77±16	74±16	76+13	0.65(1)
BSA (m^2)	1.86 + 0.22	1.82 + 0.22	1.82 + 0.19	0.41(1)
Diabetes	11 (22%)	21 (42%)	67 (33%)	0.10(2)
Hypertension	28 (56%)	28 (56%)	118 (58%)	0.95(2)
Hyperlipidemia	15 (30%)	20 (40%)	55 (27%)	0.20(2)
Smoking	20 (40%)	24 (48%)	70 (34%)	0.20(2)
Medication in use				
Statin	14 (28%)	19 (38%)	21 (10%)	<0.001(2)
Beta blocker	5 (10%)	14 (28%)	27 (13%)	0.019(2)
Aspirin	50 (100%)	48 (96%)	202 (99%)	0.14(3)
Nitrate	25 (50%)	27 (54%)	95 (47%)	0.64(2)
Calcium channel Blocker	4 (8%)	5 (10%)	14 (7%)	0.72(3)
STEMI arterial territory				
LAD	26 (52%)	26 (52%)	90 (44%)	0.83(2)
RCA	14 (28%)	17 (34%)	84 (41%)	
LCX	10 (20%)	7 (14%)	29 (14%)	

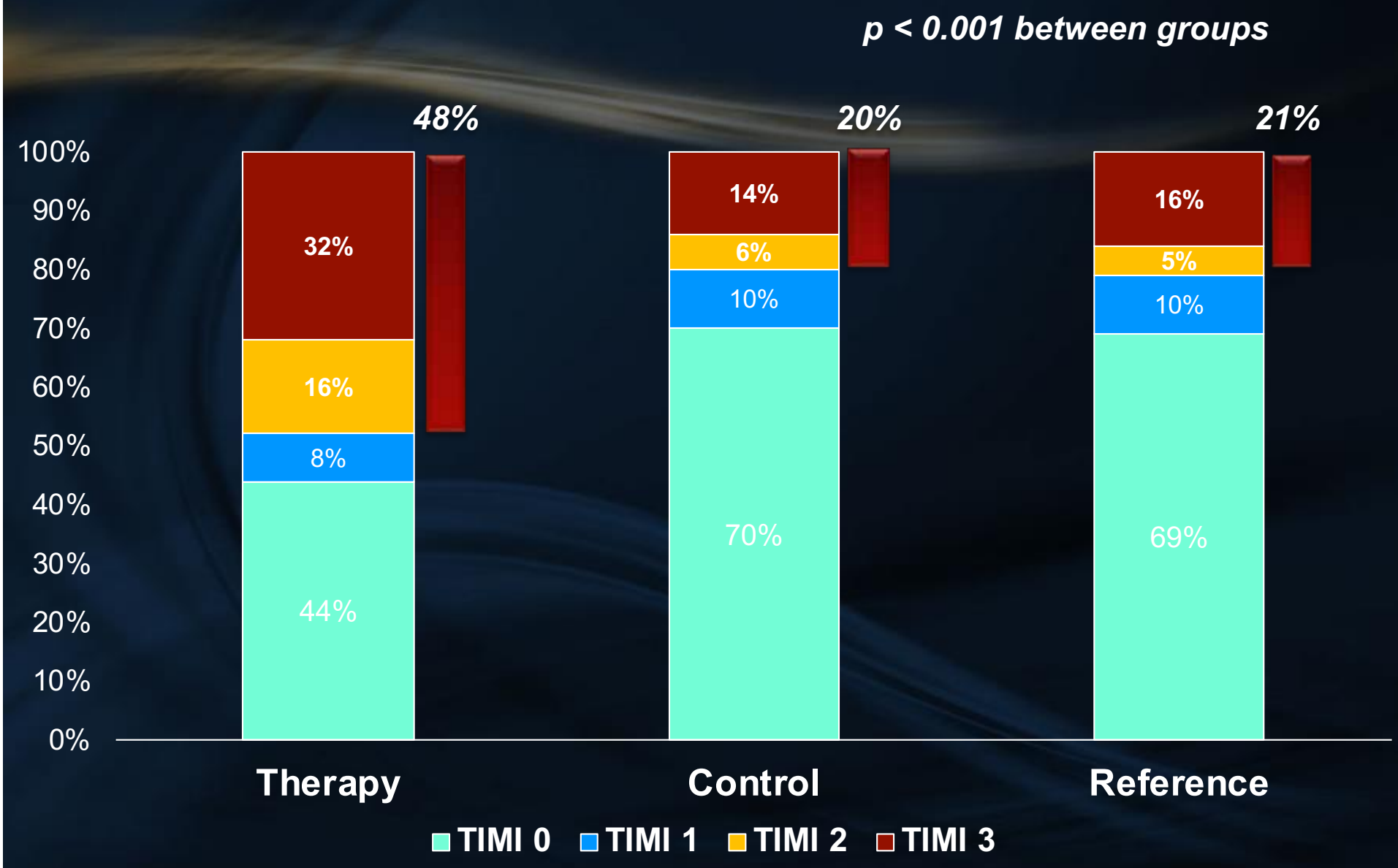
Variables expressed as mean ± standard deviation or number (%). (1) Analysis of variance; (2) Chi- square test; (3) Fisher Exact test.

Door to Balloon Time



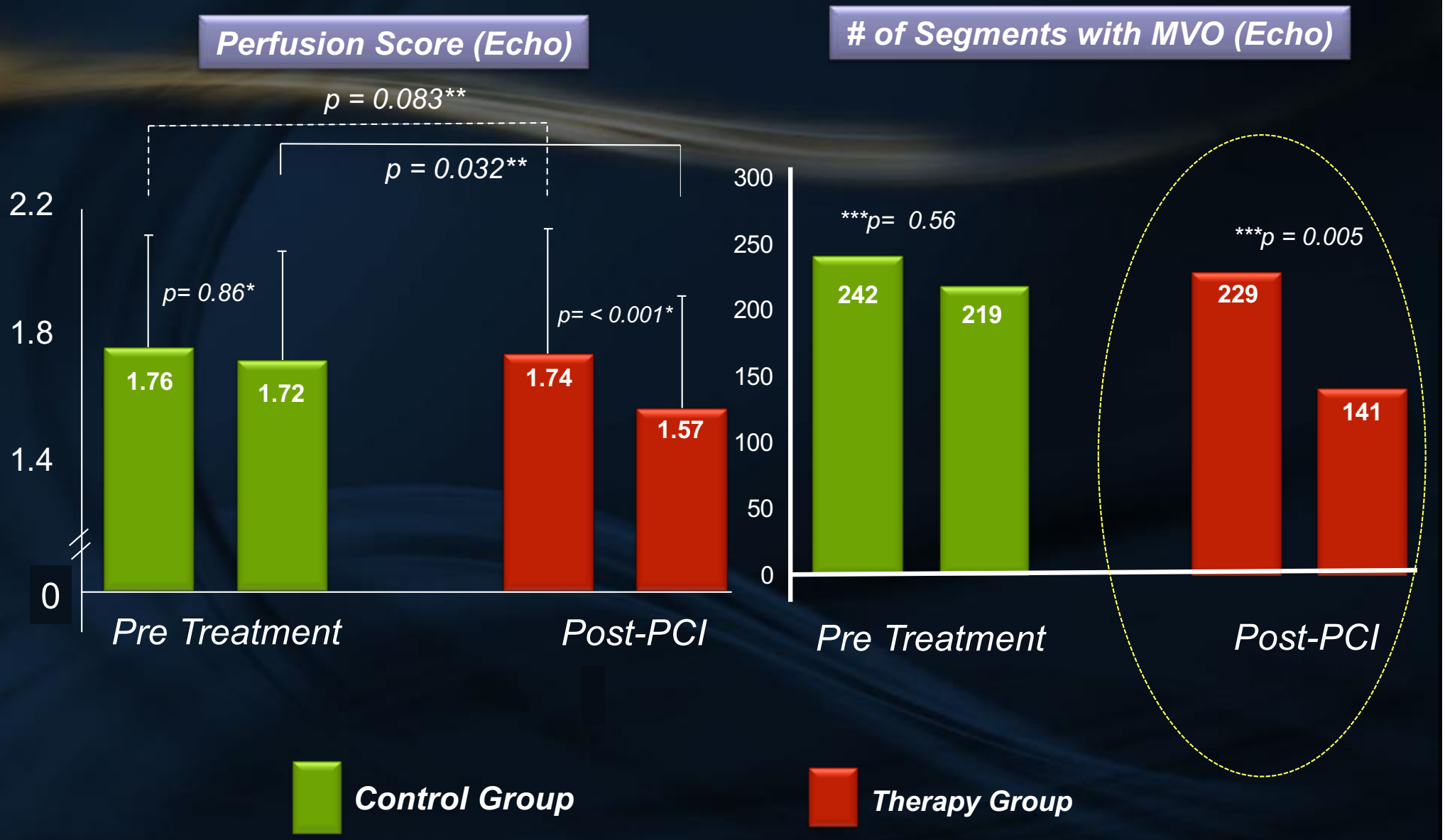
Fisher Exact test

Angiographic Recanalization Rate Pre PCI



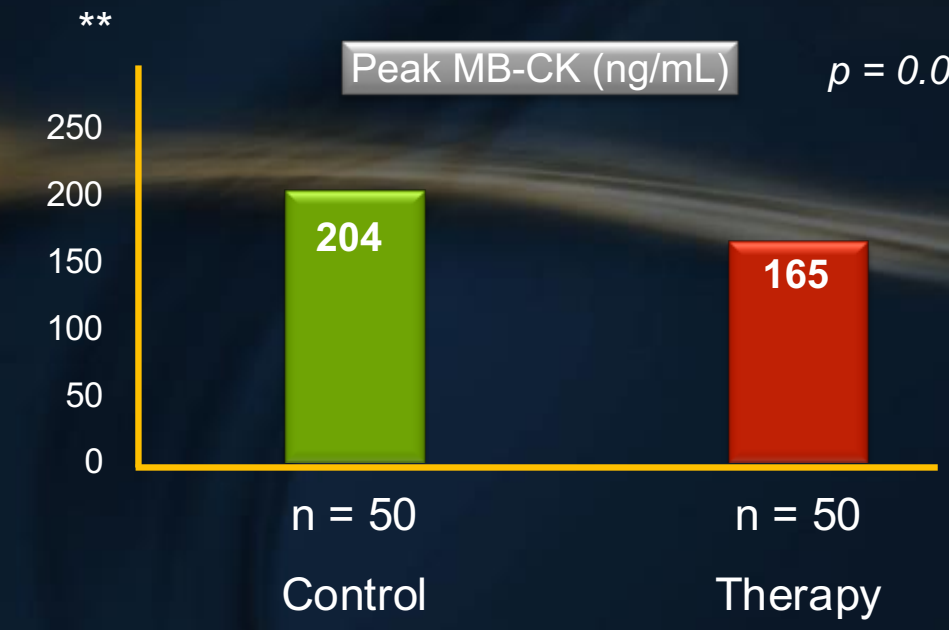
Chi Square X2 test

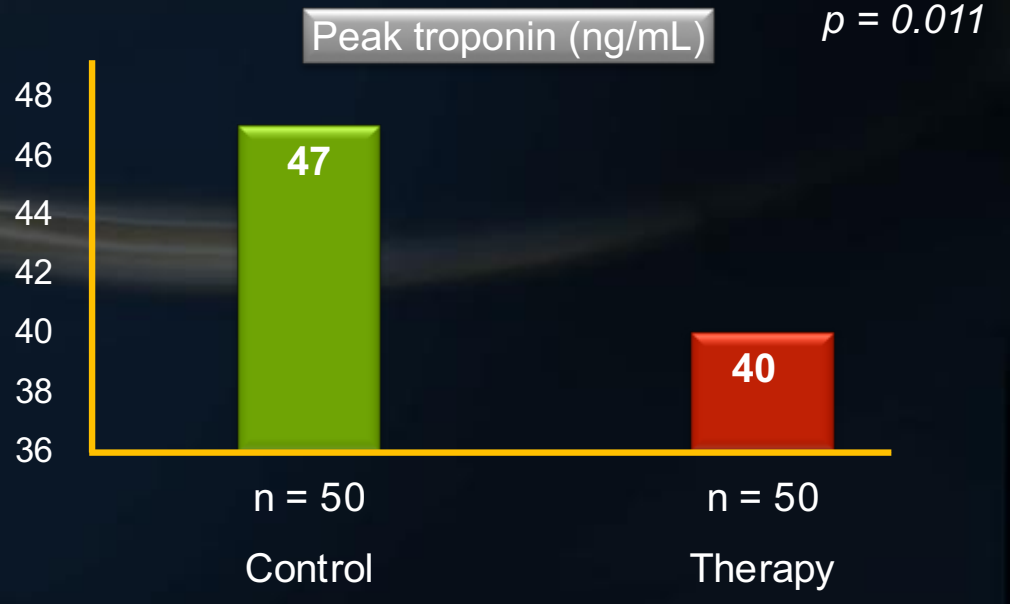
Change in Perfusion Score # Segs MVO (Baseline - Post PCI)

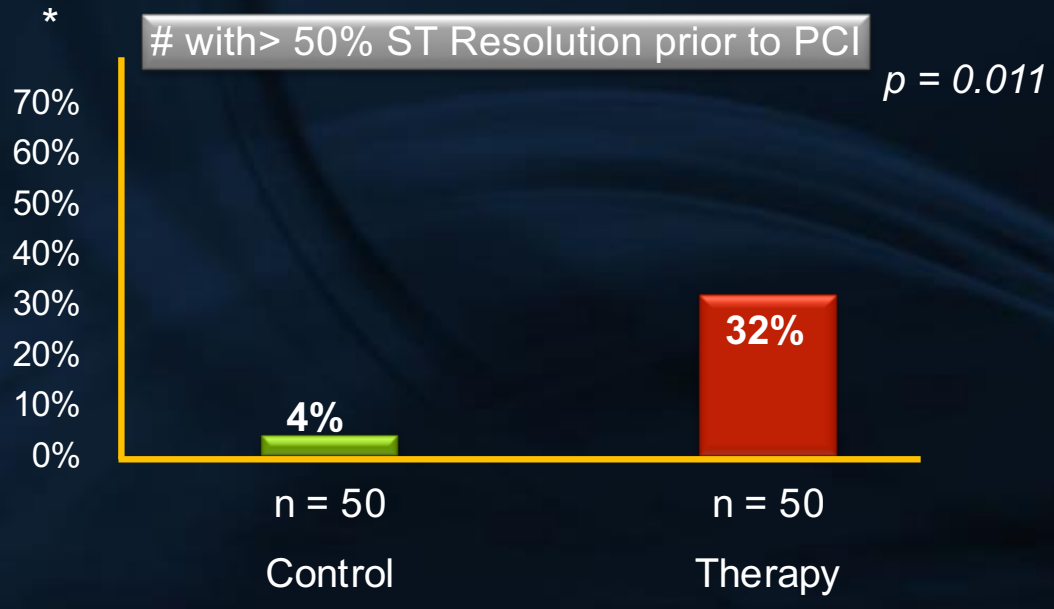


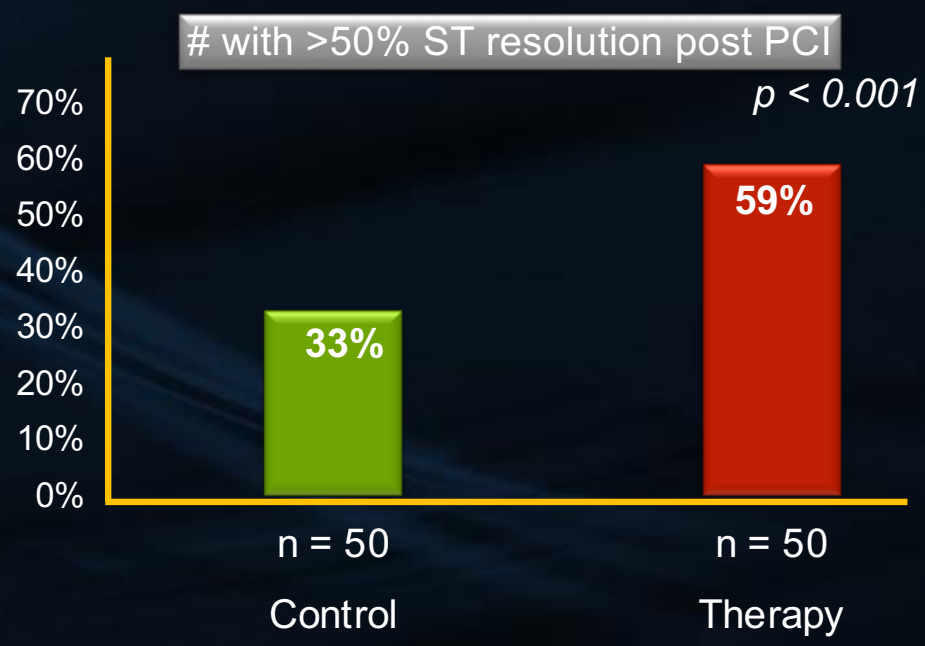
* Paired Student T test ** Unpaired Student T test *** Chi Square test

ST Segment Resolution and Peak Troponin/MB-CK Values









(*) Mann- Whitney test; (**) Student T test.

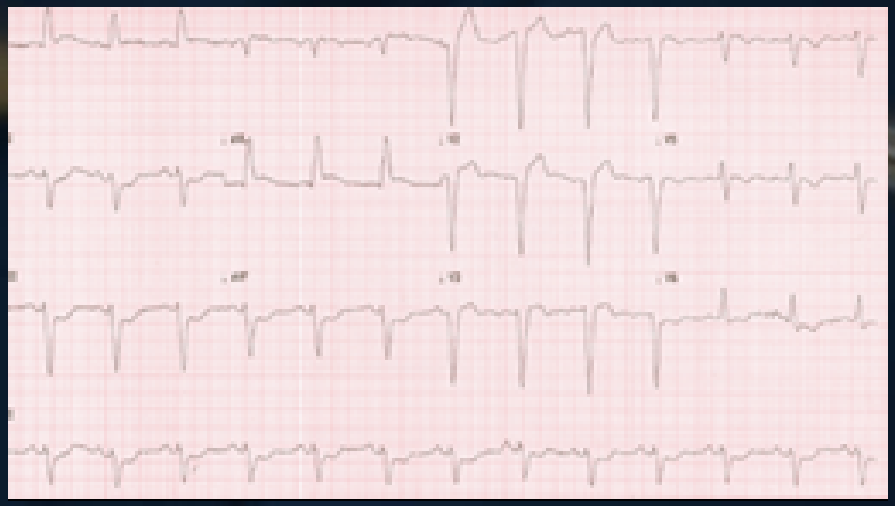
Clinical Case # 76

Randomized to Therapy Group

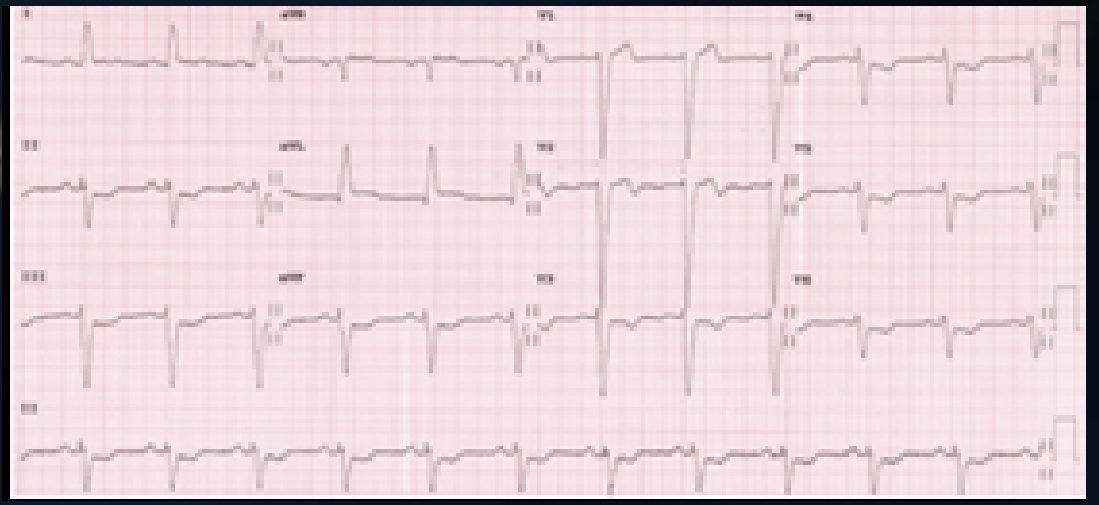
- *CAF, 52y/o Male*
- *Hypertensive*
- *Dyslipidemia*
- *Continuous chest pain (9/10 Scale) for ~1:45h*

Clinical Case # 76

EKG at arrival



EKG post PCI



Beginning of Sonothrombolysis

At 12 minutes of Sonothrombolysis

Echo post PCI

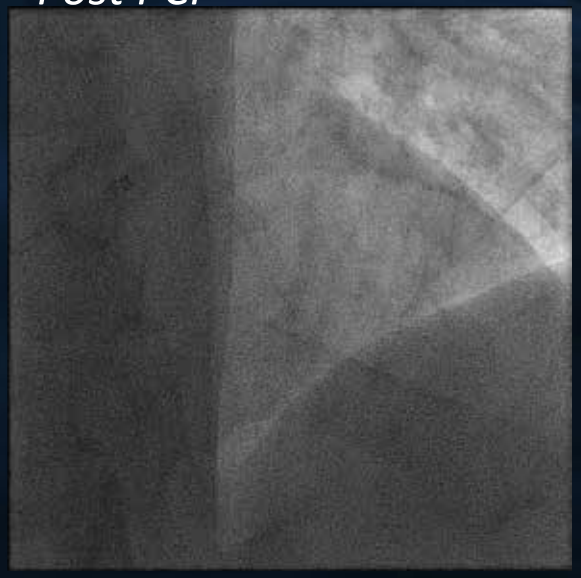
LVEF 29%

Clinical Case # 76

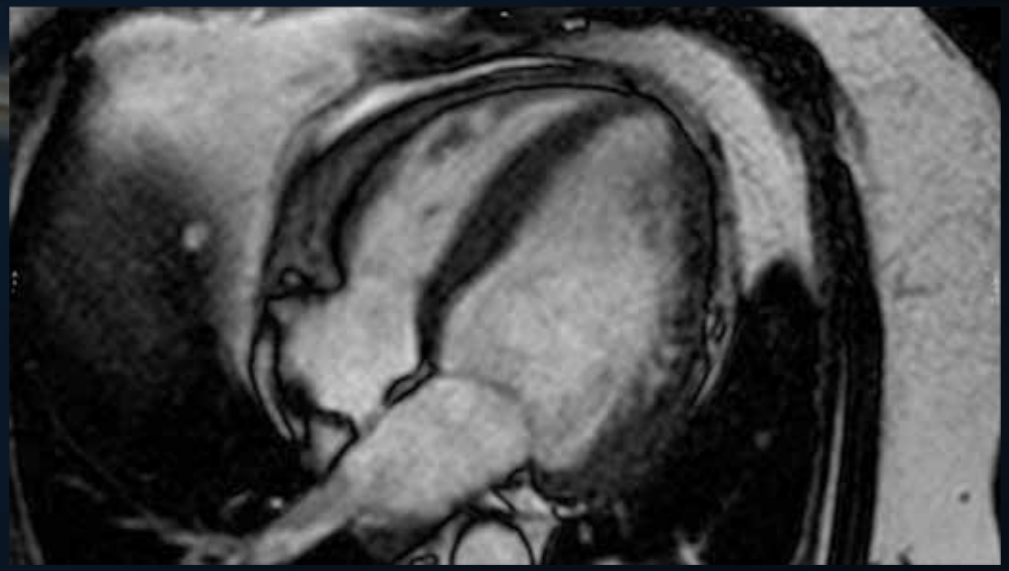
Coronary Angiography

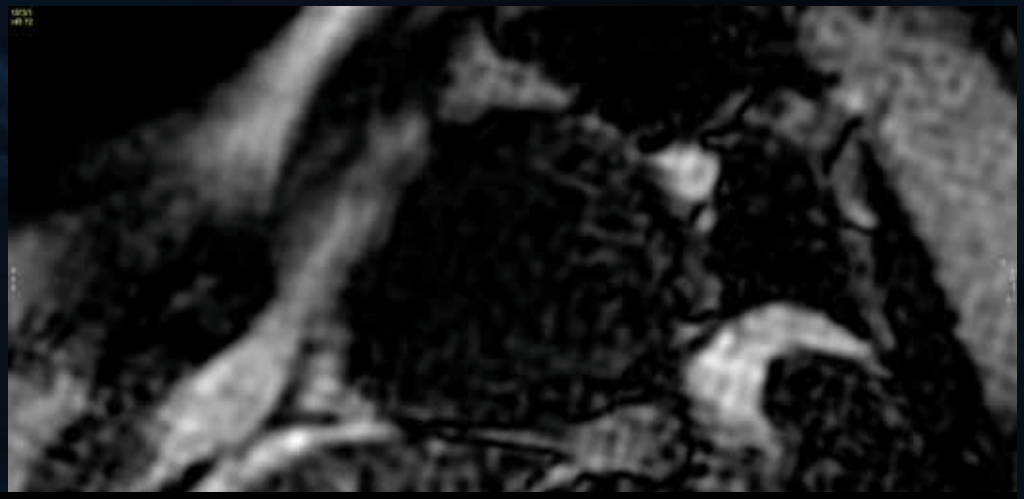
Before PCI

Post PCI



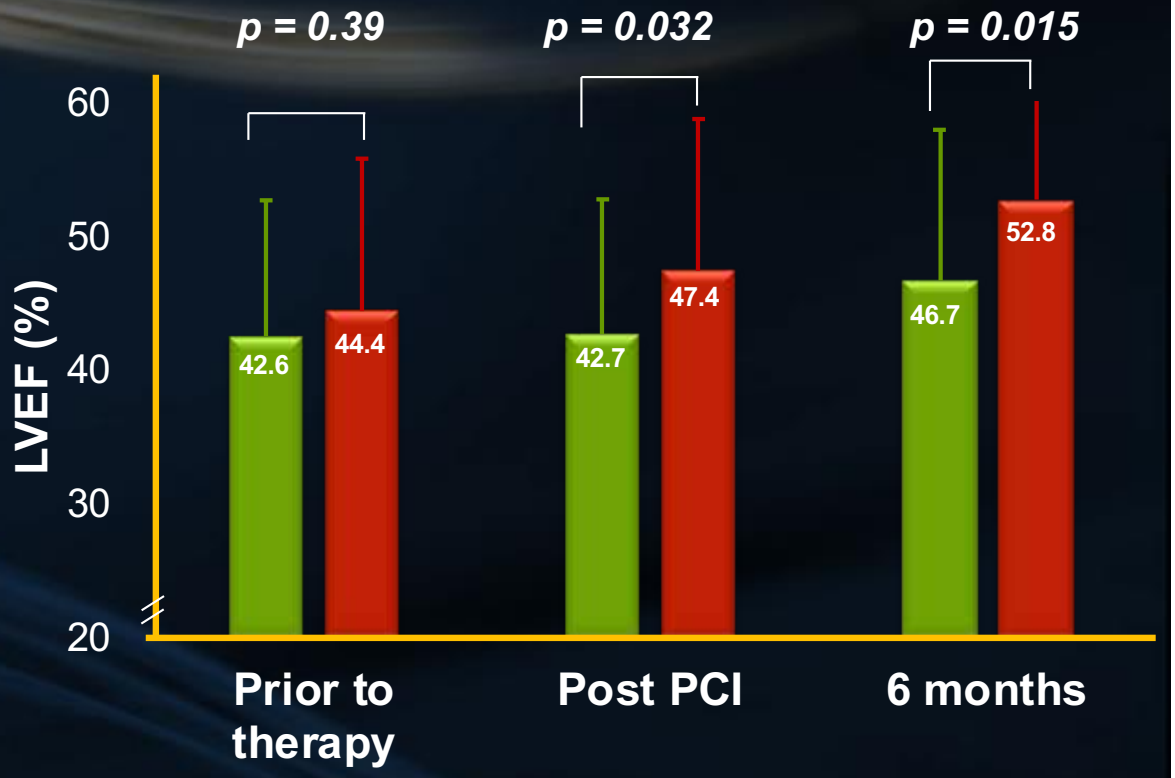
72h cMRI





72h MRI demonstrating 4 Chamber View and a focal perfusion defect on first pass in mid anterior wall segment

Infarct Size by MRI and LVEF by Echo



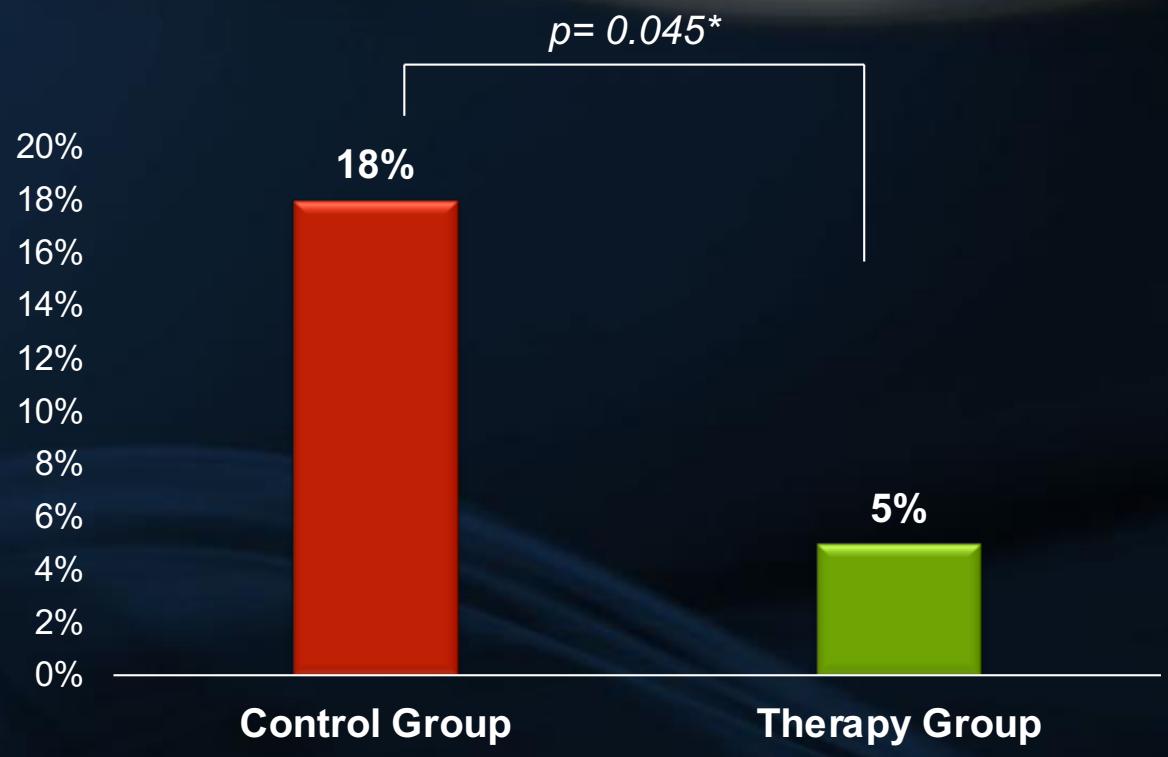
Controls
(PCI only Group)

Therapy
(High MI+PCI Group)

Mann Whitney test

Follow-up – EF < 30%

Qualified for Automatic Implantable Cardioverter Defibrillator



* *Fisher Exact test*

Sonothrombolysis in ST Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention: Final Results from the First Randomized Study in Humans

1 – Sonothrombolysis in humans is safe and feasible in patients with STEMI

2 – Sonothrombolysis is efficacious in achieving early infarct vessel patency, microvascular flow, reducing infarct size and consequently restoring left ventricular systolic function

3- A Phase III multicenter clinical trial is warranted with focus on earlier sonothrombolysis at point of patients care

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Sonothrombolysis in ST-segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND Pre-clinical studies have demonstrated that high mechanical index (MI) impulses from a diagnostic ultrasound transducer (DUS) during an intravenous microbubble infusion (Sonothrombolysis) can restore epicardial and microvascular flow in acute ST-segment elevation myocardial infarction (STEMI).

OBJECTIVE We tested the clinical effectiveness of sonothrombolysis in patients with STEMI.

METHODS Patients with their first STEMI were prospectively randomized to either DUS-guided high MI impulses during an intravenous ultrasound agent infusion prior to, and following, emergent percutaneous coronary intervention (PCI), or to a control group that received PCI only (n=50 in each group). A reference first STEMI group (n=203) who arrived outside the randomization window was also analyzed. Angiographic recanalization prior to PCI, ST-segment resolution, infarct size (IS) by magnetic resonance imaging, and systolic function (LVEF) at six months were compared.

RESULTS ST-segment resolution occurred in 16 (32%) high MI PCI versus 2(4%) PCI only patients *prior* to PCI, and angiographic recanalization was 48% in high/MI PCI versus 20% in PCI only and reference groups ($p<0.001$). IS was reduced (29±22 grams high MI/PCI versus 40±20 grams PCI only; $p=0.026$). LVEF was not different between groups before treatment (44±11% versus 43±10%), but increased immediately after PCI in the high MI/PCI group ($p=0.03$), and remained higher at six months ($p=0.015$). Need for implantable defibrillator (LVEF≤30%) was reduced in the high MI/PCI group (5% versus 18% PCI only; $p=0.045$).

CONCLUSIONS Sonothrombolysis added to PCI improves recanalization rates and reduces infarct size, resulting in sustained improvements in systolic function after STEMI.

TRIAL REGISTRATION Clinical Trials.gov # NCT02410330. (J Am Coll Cardiol 2019) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Email for correspondence: wmathias@incor.usp.br

[a]Heart Institute (InCor)- University of São Paulo, Medical School, São Paulo, Brazil; [b]University of Nebraska Medical Center, Omaha, NE; and the [c]University of Kansas Medical Center, Kansas City, KS. **IRB Approval** # 342.799 (07/08/2013)

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"This is not the end. This is not even the beginning of the end, but perhaps, it is the end of the beginning"

Winston Churchil
2nd Battle of El Alamain