Conoscere e Curare il Cuore 2019

VENERDI' 1 MARZO

LA PROVOCAZIONE DELLO STUDIO ORBITA: L'ANGIOPLASTICA NON SERVE.

Leonardo Bolognese

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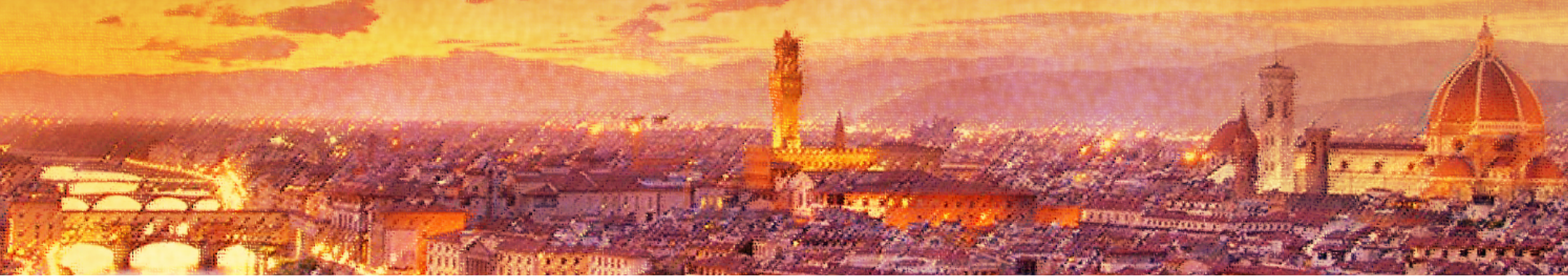

Endpoints to Assess Success of Therapy in Stable CAD Patients

- "Hard Endpoints"
  - (i.e. death, MI)
- Endpoints related to the pathophysiological mechanism
  - Relief of Ischemia
- "Soft Endpoints"
  - Symptoms and quality of life

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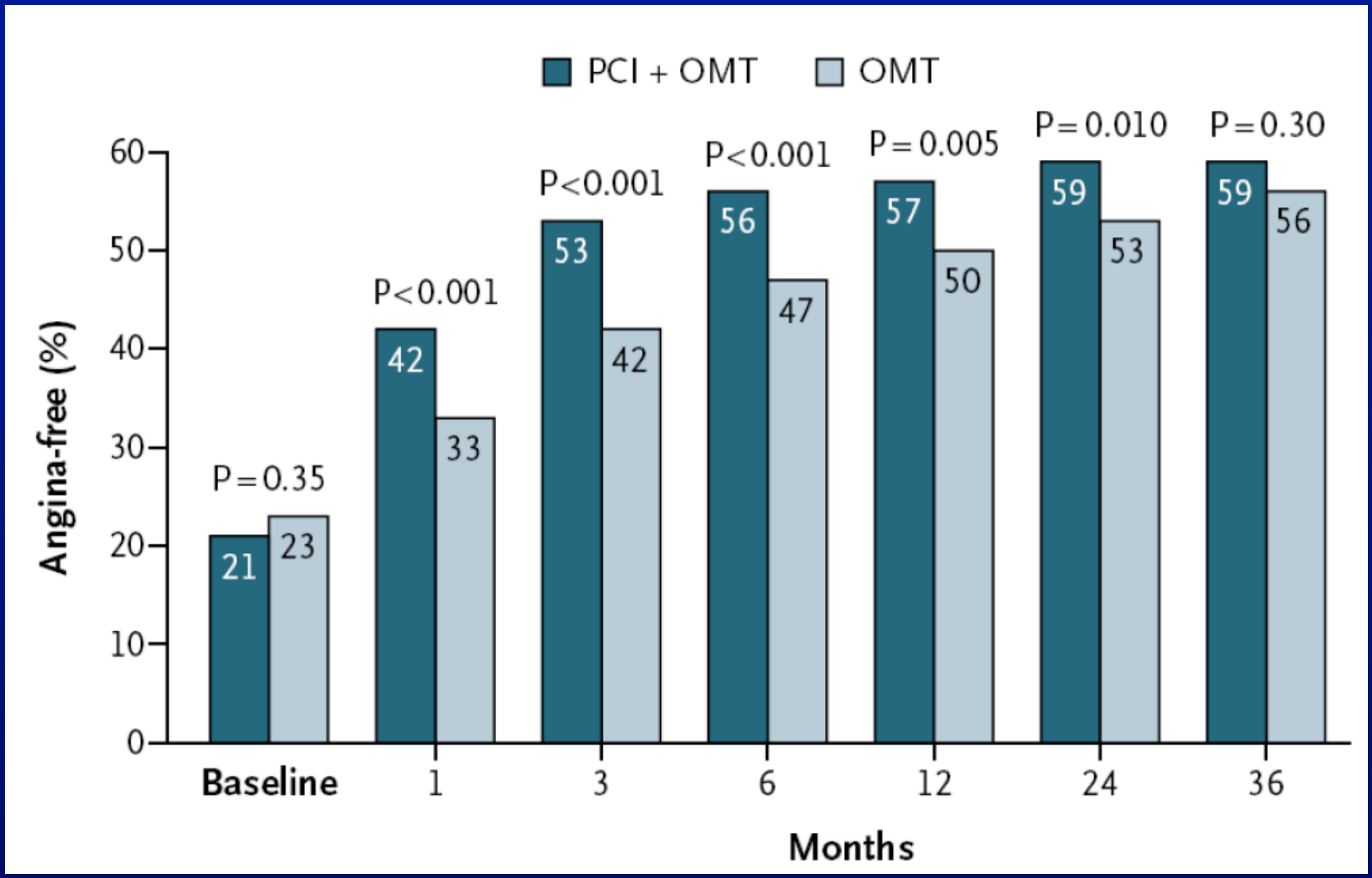
Freedom from Angina in COURAGE



Weintraub et al. NEJM 2008;359:677-87

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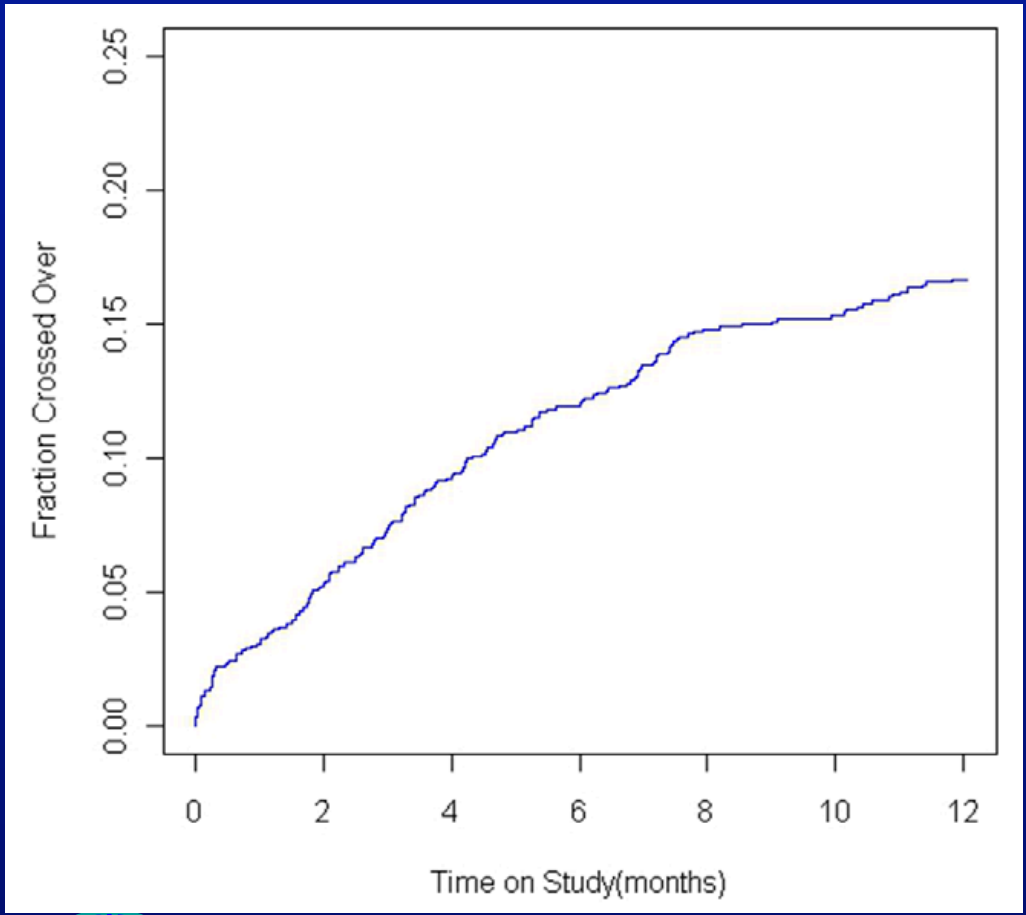
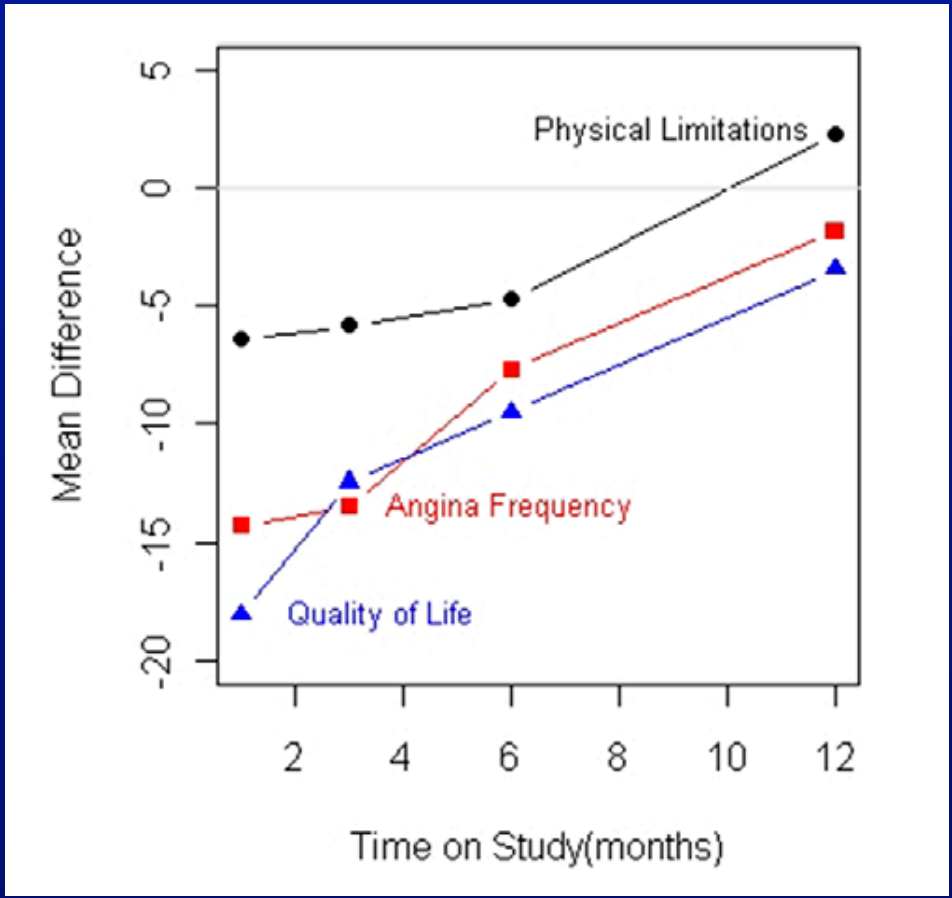
Frequency and Predictors of Crossing Over in COURAGE

Timing of crossover in COURAGE



Health status over time



Spertus JA et al. Circ Cardiovasc Qual Outcomes 2013; 06:409-418

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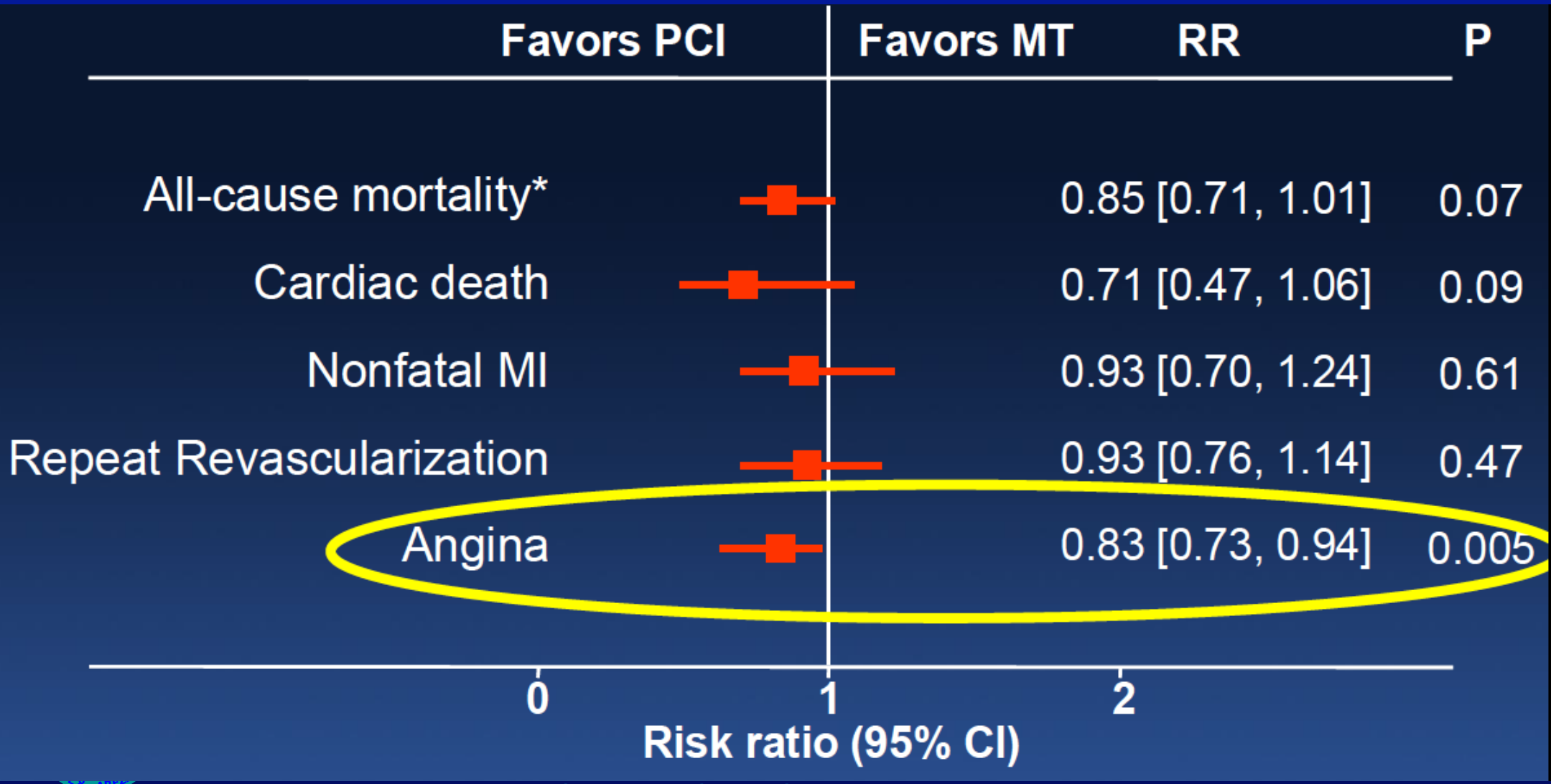
PCI vs. Medical Therapy for Stable CAD

12 RCTs enrolling 7182 participants



Pursnani S et al. Circ Cardiovasc Interv. 2012;5:476-490

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PCI vs. Medical Therapy for Stable CAD

12 RCTs enrolling 7182 participants

Angina Recurrence

	PCI (n=3584)	GDMT (n=3593)	RR (95%CI)	P value
Angina, any	53.0%	58.0%	0.83 (0.73, 0.94)	0.005
- ≤1 year*	45.8%	57.1%	0.76 (0.65, 0.88)	0.0006
- 1-5 years*	39.2%	59.2%	0.64 (0.43, 0.94)	0.02
- ≥5 years*	54.0%	58.0%	0.85 (0.72, 1.00)	0.05

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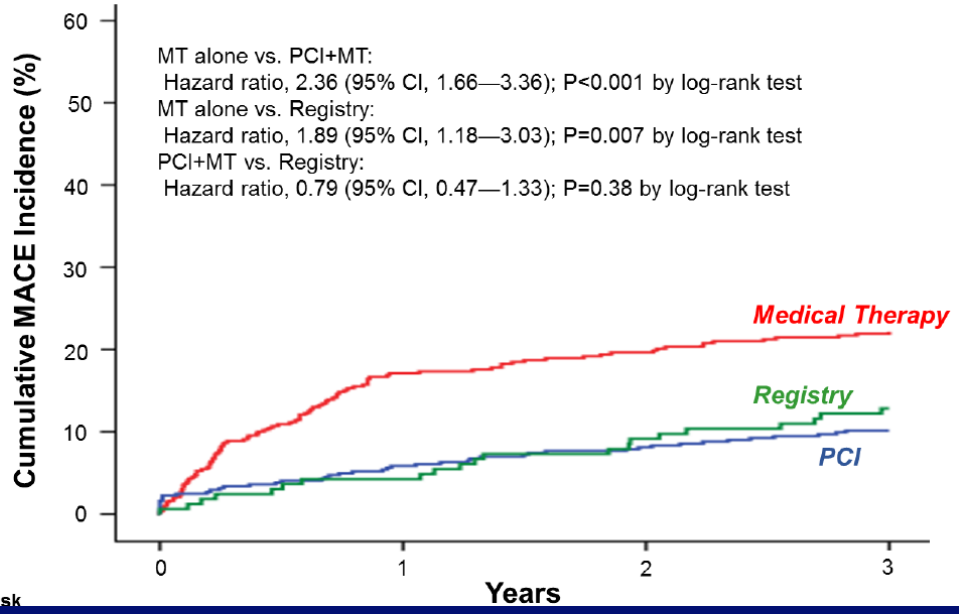
Pursnani S et al. Circ Cardiovasc Interv. 2012;5:476-490

FAME – 2 Trial

3 Year Clinical Outcome and Cost-effectiveness

Results: Clinical Outcome

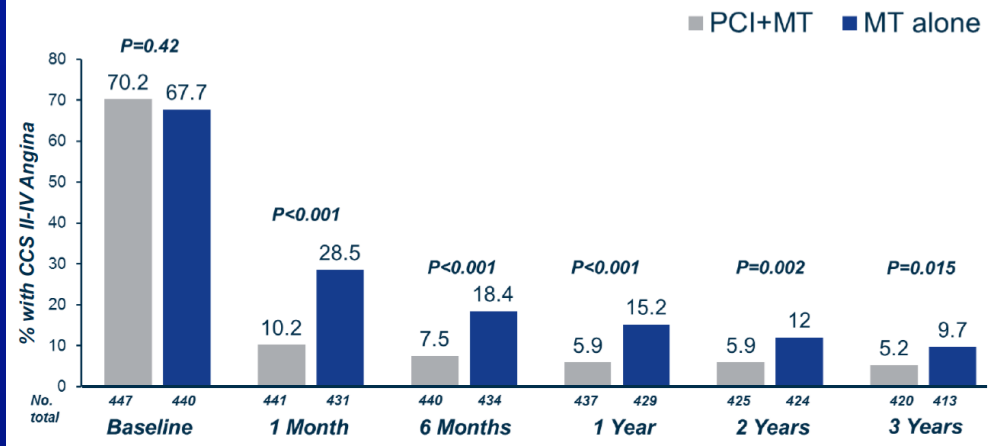
Three Year Rate of Death, MI, or Urgent Revascularization



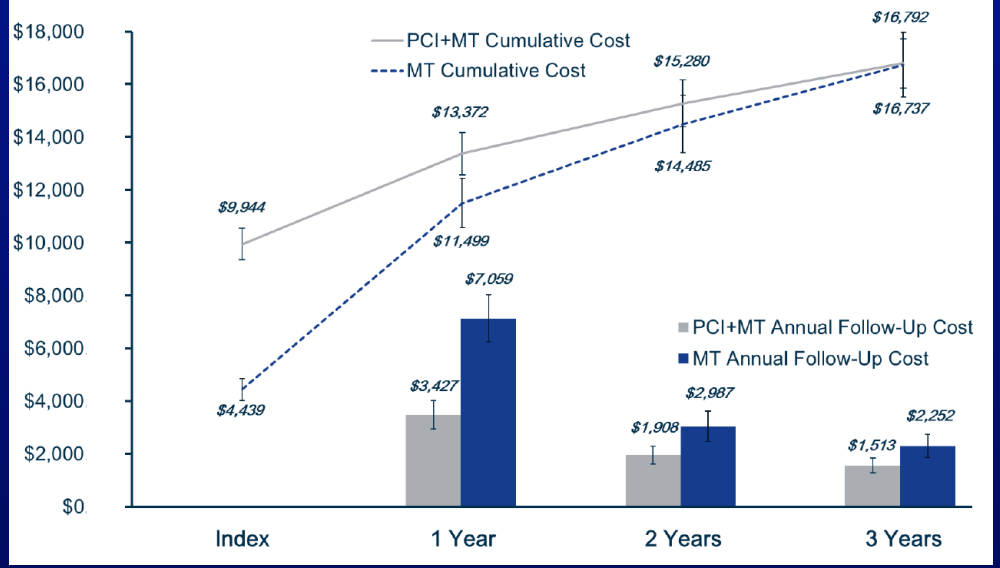
Fearon WF et al. Circulation 2018;137:480–487.

Results: Quality of Life

% of Patients with Class II-IV Angina at each Time Point



Results: Costs



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Are symptom control and quality of life appropriate endpoints to assess PCI success?

The problem is that these outcomes are rather subjective and prone to placebo and nocebo effects

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Sham Controlled Trials Shuold be the New Standard for Device Trials *A Story about Mark Twain*

Twain was convinced that he could only sleep in well ventilated rooms. Finding himself in a small hotel room with a window that was stuck shut, he tried in vain to fall asleep

Finally unable to bear any longer, he reached under his bed, picked up a shoe, and heaved it at window. The ensuing crash relieved him and quickly fell aspleep.

He awoke refreshed, only to find that he had missed the window and shattered a mirror instead

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Fred Leavitt Drugs and Behavior Sage Publications 1994

Historical precedents

- Sham-controlled trials of internal mammary artery ligation for severe angina (1959 and 1960)
- Sham-controlled trial for stable angina using laser transmyocardial revascularization (2005)

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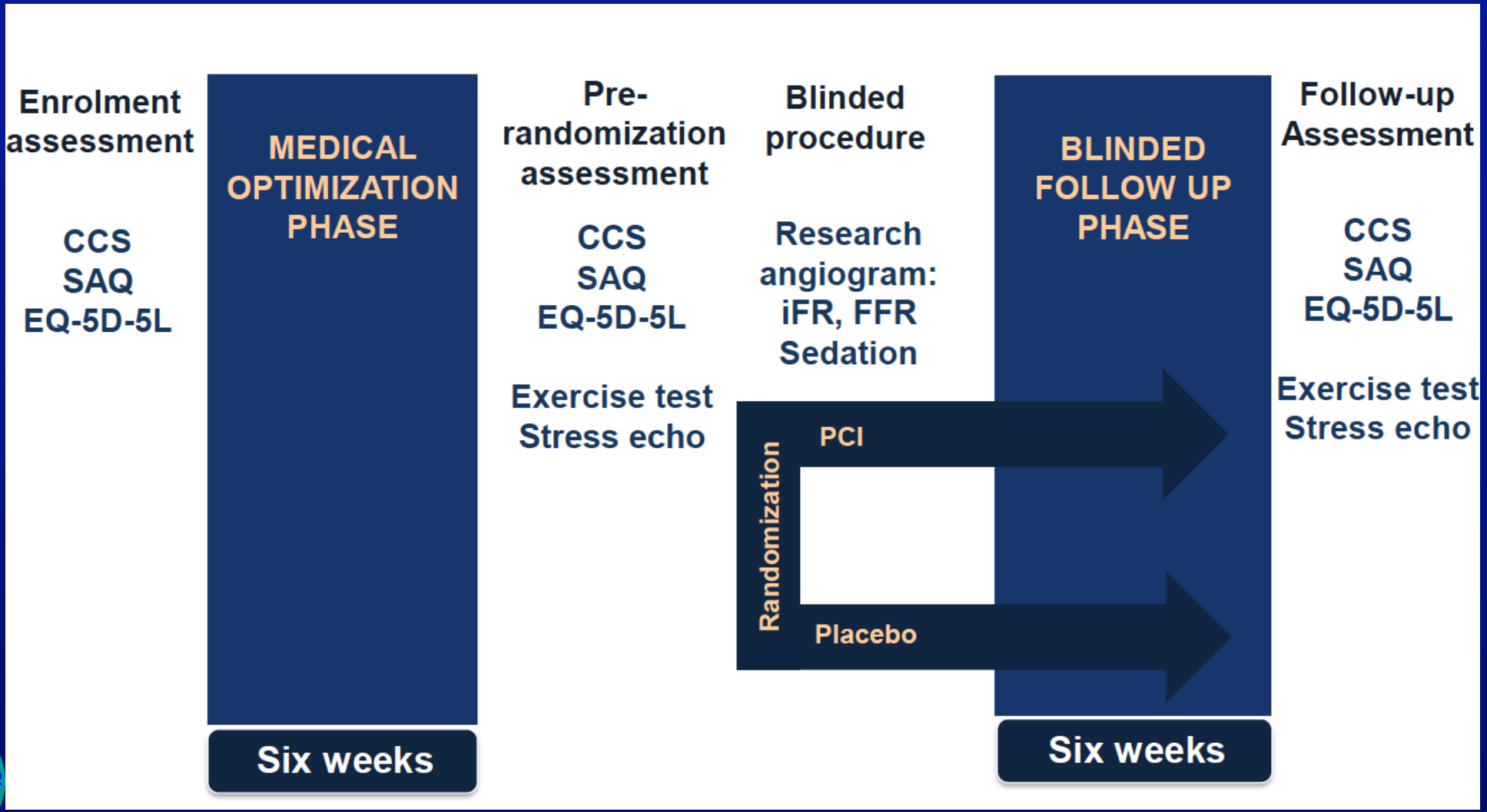
ORBITA Trial:
The world's first placebo-controlled trial of PCI



Al-Lamee R et al. Lancet 2 November 2017

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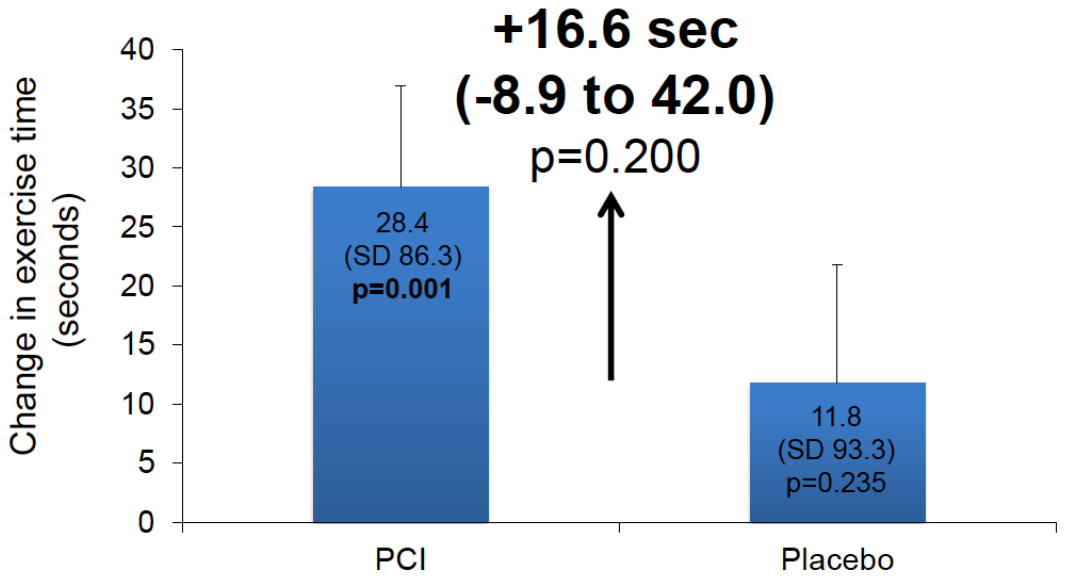
ORBITA Trial: Results

Primary endpoint result

Change in total exercise time



Secondary endpoint results

No difference in symptom improvement or quality of life

Physical limitation score (SAQ)	
Difference in Δ between arms	2.4 (-3.5 to 8.3) p=0.420
Angina frequency score (SAQ)	
Difference in Δ between arms	4.4 (-3.3 to 12.0) p=0.260
Quality of life (EQ-5D-5L)	
Difference in Δ between arms	0.00 (-0.04 to 0.04) p=0.994

Secondary endpoint results

Blinded evaluation of ischaemia reduction

Peak stress wall motion index score	PCI n = 80	Placebo n = 57
Pre-randomization	1.11 (0.18)	1.11 (0.18)
Follow-up	1.03 (0.06)	1.13 (0.19)
Δ (Pre-randomization to follow-up)	-0.08 (0.17)	0.02 (0.16)
	p<0.0001	p=0.433
Difference in Δ between arms	-0.09 (-0.15 to -0.04) **p=0.0011**	

Al-Lamee R et al.
Lancet 2 November 2017

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"KOL" Reactions to ORBITA Trial

Polarity of opinions

Some overextrapolated the results to undermine PCI as a whole for stable angina

Others were just as quick to undermine the trial

"Exchange on social media – vitriolic (both pro and con)
1716 Tweets and 200 patients Feb 25 2018

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Last nail in the coffin for PCI in stable angina?

Interventional cardiology began in Switzerland in 1977, when Andreas Gruentzig performed the first successful percutaneous transluminal coronary angioplasty (PTCA) on a 38-year-old man with angina and a focal proximal stenosis of the left anterior descending coronary artery. Despite numerous subsequent randomised trials and meta-analyses of these trials, which have shown no reduction in death or myocardial infarction,[1] the use of percutaneous coronary intervention (PCI) has grown exponentially. Some of this growth was driven by data from clinical trials suggesting that PCI was more effective in relieving angina than medical therapy alone. For example, in 1992, the results of the Angioplasty Compared to Medicine (ACME) study,[2] showed that at

Cardiovascular Data Registry showed that less than half of patients undergoing PCI were receiving optimal medical therapy, with no increase following the publication of COURAGE.[7] More importantly, despite the known placebo power of invasive procedures, until now, there had not been a blinded clinical trial of PCI in its entire 40 year history.[8]

In a landmark new study in *The Lancet*, the investigators of the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) group[9] have filled this important gap. We commend them for challenging the existing dogma around a procedure that has become routine, ingrained, and profitable. The results of ORBITA show (once again) why regulatory

BSIP/Getty Images

Published Online
November 2, 2017
http://dx.doi.org/10.1016/
S0140-6736(17)32757-5

See Articles page 31

"ORBITA (shows) unequivocally that there are no benefits for PCI compared with medical therapy for stable angina, even when angina is refractory to medical therapy."

"...all cardiology guidelines should be revised to downgrade the recommendation for PCI in patients with angina despite use of medical therapy."

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ORBITA investigators should be commended!

- Appropriate hypothesis
- Appropriate primary endpoint
- Sham control
- Successful blinding procedures
- Appropriate PCI technique
- Independent funding
- Transparent reporting
  - Protocol
  - Coronary angiograms of all patients

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The ORBITA Trial: internal validity

	PCI	Placebo
Exercise time (s)		
Patients assessed	104	90
Pre-randomisation	528·0 (178·7)	490·0 (195·0)
Follow-up	556·3 (178·7)	501·8 (190·9)
Increment (pre-randomisation to follow-up)	28·4 (95% CI 11·6 to 45·1)	11·8 (95% CI −7·8 to 31·3)
Difference in increment between groups	16·6 (95% CI −8·9 to 42·0)	..
p value	0·200	..

Effect size from invasive PCI of 30 s. Sample size calculation assumed a between-patient SD of change in exercise time of 75 s

The lower exercise time in the control group at baseline is likely due to chance, and the subsequent improvement with repeat testing is an expected phenomenon. Statistically speaking this is known as "regression to the mean"

The power of the study to detect a difference between the groups was lower than planned. The observed between-patient SD was more than twice as high as that assumed, resulting in a power to detect a difference between the groups as low as 20%

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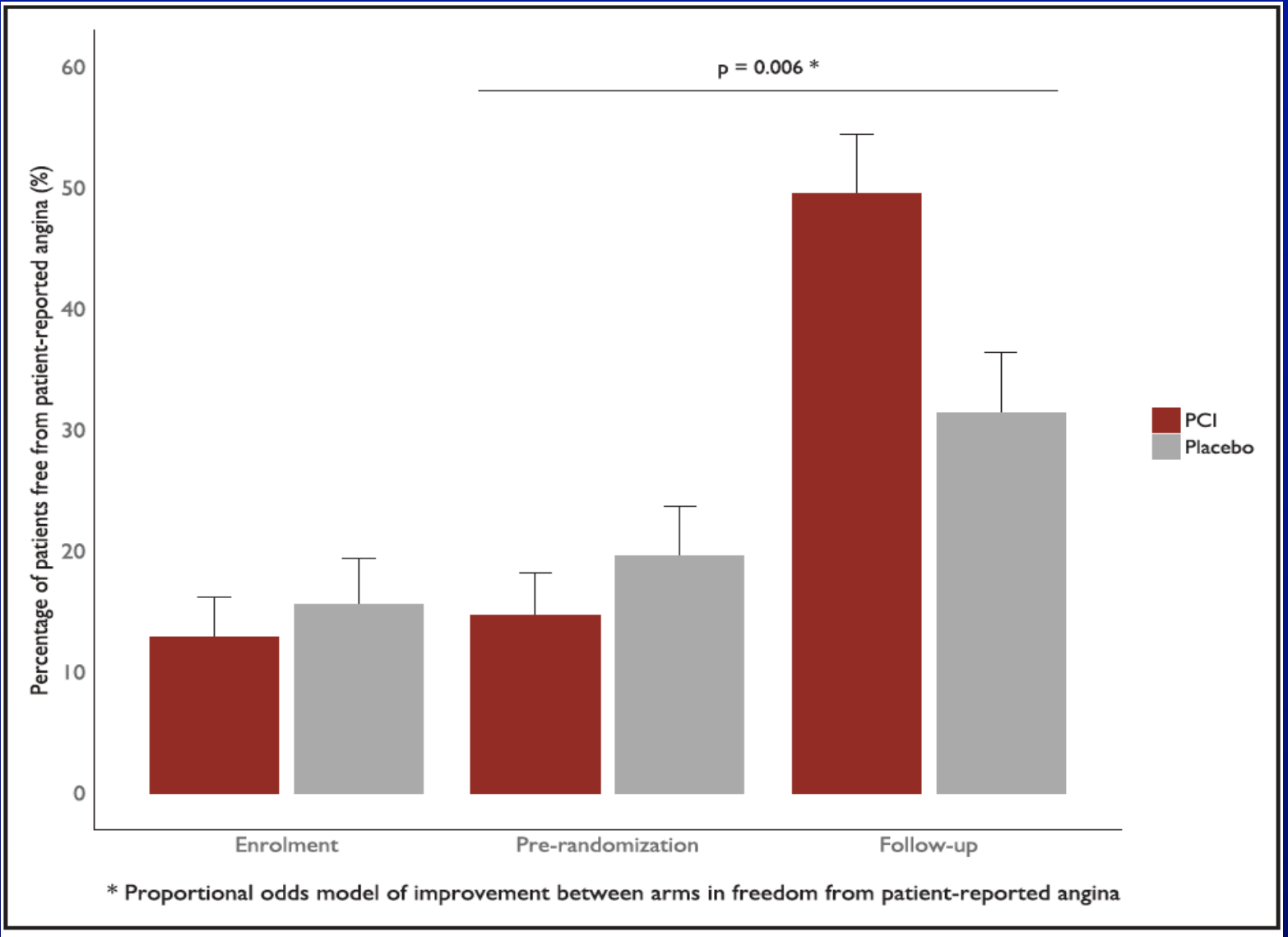
Endpoint analysis for all patients

Endpoint	ANCOVA estimate with the covariate modelled as a restricted cubic spline (PCI over placebo)
Total exercise time	20.7s (95% CI -4.0 to 45.5; p=0.100)
Dobutamine stress echo score	1.07 (95% CI 0.70 to 1.44; p<0.00001)
SAQ physical limitation score	2.59 (95% CI -2.93 to 8.10; p=0.356)
SAQ quality of life score	2.08 (95% CI -3.85 to 8.01; p=0.490)
EQ-5D-5L descriptive system	0.001 (95% CI -0.039 to 0.042; p=0.951)
EQ-5D-5L visual analogue scale	1.22 (95% CI -3.47 to 5.90; p=0.609)

16.6 sec in the primary analysis

Al-Lamee R et al. Circulation 22 May 2018

Patient-reported freedom from angina



Al-Lamee R et al. Circulation 22 May 2018

The ORBITA Trial: external validity

- The FU was very short. The clinical success of this strategy and acceptance from a patient preference standpoint, over a longer time horizon is unclear

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Was the Sham a Sham?

When patients were enrolled into the trial, they were told that when the study was unblinded they would have an in-depth conversation with their physician and decide together what their next step would be, with their preference taken into account

After the 6-week period of the study ended, 85% of patients randomized to the placebo arm underwent PCI

Al-Lamee R et al. Circulation 22 May 2018

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The ORBITA Trial: external validity

- The FU was very short. The clinical success of this strategy and acceptance from a patient preference standpoint, over a longer time horizon is unclear

- The findings apply to selected SV disease pts with only a small minority of patients planned for PCI at five centres over almost four years enrolled in the trial

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The ORBITA Trial: external validity

5 centers in Great Britain 1200 PCIs/yr during the recruitment period of January 6, 2014, to August 11, 2017 = 21,532 PCIs

368 (1.7%) patients
were initially assessed for eligibility

138 excluded

230 entered into the optimal
medical phase of the trial (1%)

30 additional patients
left the study

200 were randomized (0.9% of the entire group)

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The ORBITA Trial: external validity

- The FU was very short. The clinical success of this strategy and acceptance from a patient preference standpoint, over a longer time horizon is unclear
- The findings apply to selected SV disease pts with only a small minority of patients planned for PCI at five centres over almost four years enrolled in the trial
- *The run-in period of optimized antianginal medications meant that a substantial proportion of pts were angina-free going into the randomization; the intensity of medical management was guideline-recommended, but not necessarily something that is common in medical practice today*

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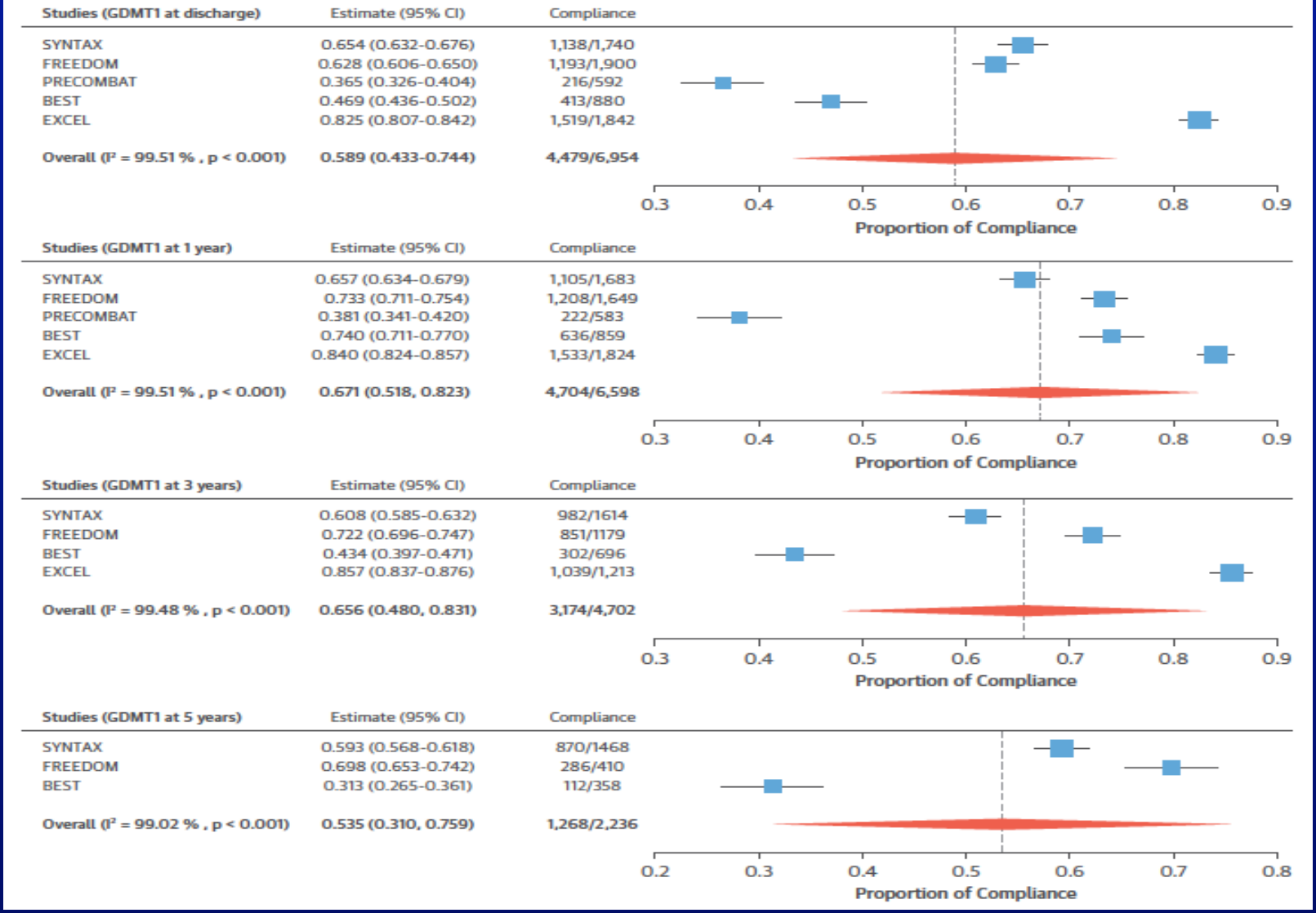
Compliance with guideline-directed medical therapy in contemporary coronary revascularization trials



Pinho-Gomes A-C et al. J Am Coll Cardiol 2018; 71:591–602

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SCAI 2018
Scientific Sessions
SAN DIEGO • APRIL 25-28

SCAI President Kirk Garratt asked Al-Lamee if she had any sense of how many of those patients who elected to have PCI did so because they were tired of taking medical therapy. Noting that it was a reason for some, Al-Lamee offered anecdotal explanations such as a patient who told her the medications were "worse than chemo."

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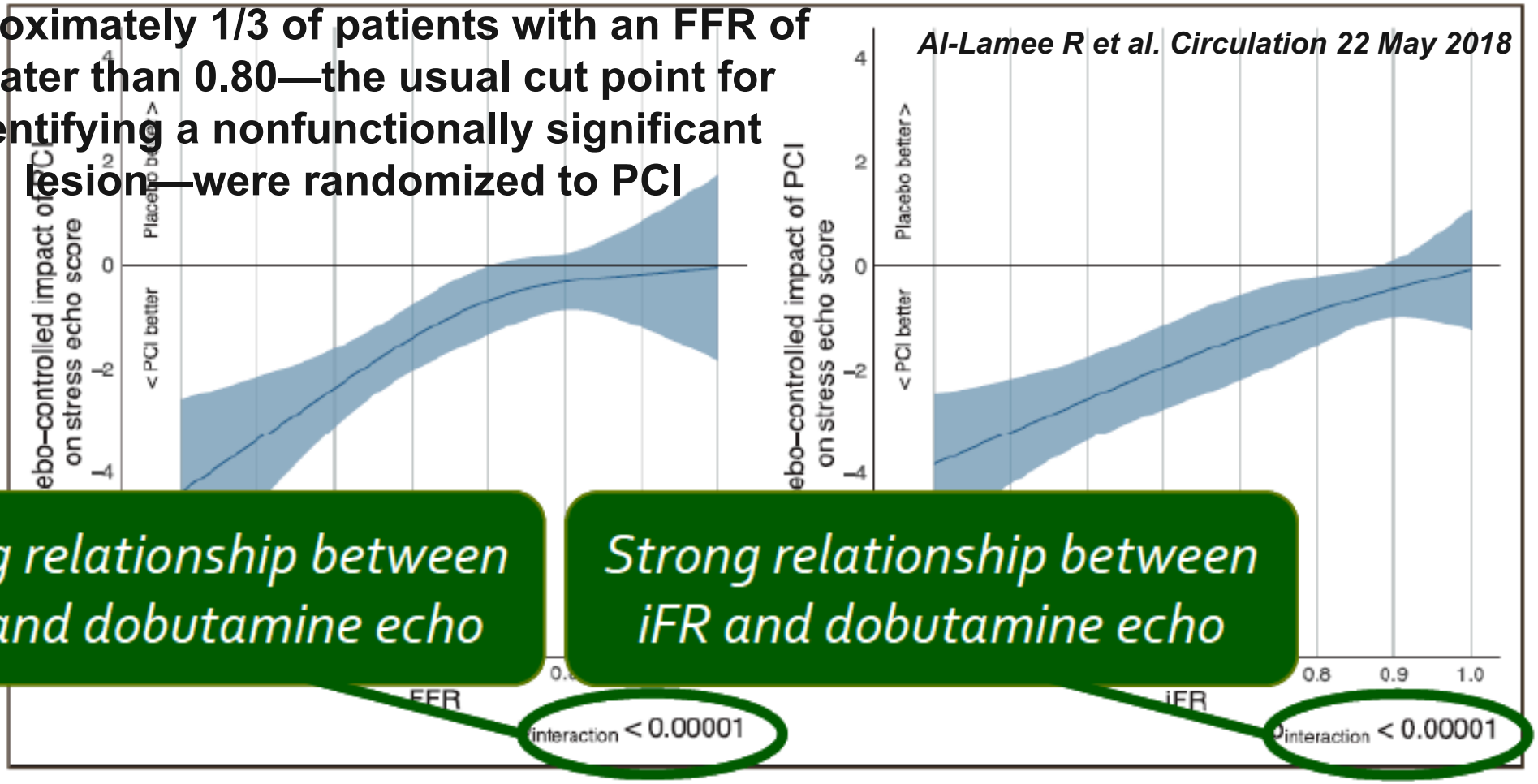
ORBITA: Relationship between Baseline FFR Improvement in Stress Echo Wall Motion Score with PCI Relative to Placebo

Approximately 1/3 of patients with an FFR of greater than 0.80—the usual cut point for identifying a nonfunctionally significant lesion—were randomized to PCI

Al-Lamee R et al. Circulation 22 May 2018



Strong relationship between FFR and dobutamine echo

Strong relationship between iFR and dobutamine echo

"The…stress echo score was very clearly improved by PCI versus placebo; and the more severe the FFR and iFR, the larger the PCI effect on the stress echo score."

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Impact of Percutaneous Revascularization on Exercise Hemodynamics in Patients With Stable Coronary Disease

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ABSTRACT

BACKGROUND Recently, the therapeutic benefits of percutaneous coronary intervention (PCI) have been challenged in patients with stable coronary artery disease (SCD).

OBJECTIVES The authors examined the impact of PCI on exercise responses in the coronary circulation, the microcirculation, and systemic hemodynamics in patients with SCD.

METHODS A total of 21 patients (mean age 60.3 ± 8.4 years) with SCD and single-vessel coronary stenosis underwent cardiac catheterization. Pre-PCI, patients exercised on a supine ergometer until rate-limiting angina or exhaustion. Simultaneous trans-stenotic coronary pressure-flow measurements were made throughout exercise. Post-PCI, this process was repeated. Physiological parameters, rate-limiting symptoms, and exercise performance were compared between pre-PCI and post-PCI exercise cycles.

Rasha Al-Lamee

Darrel Francis

Justin Davies

Cook CM et al. J Am Coll Cardiol 2018; 72:970–83

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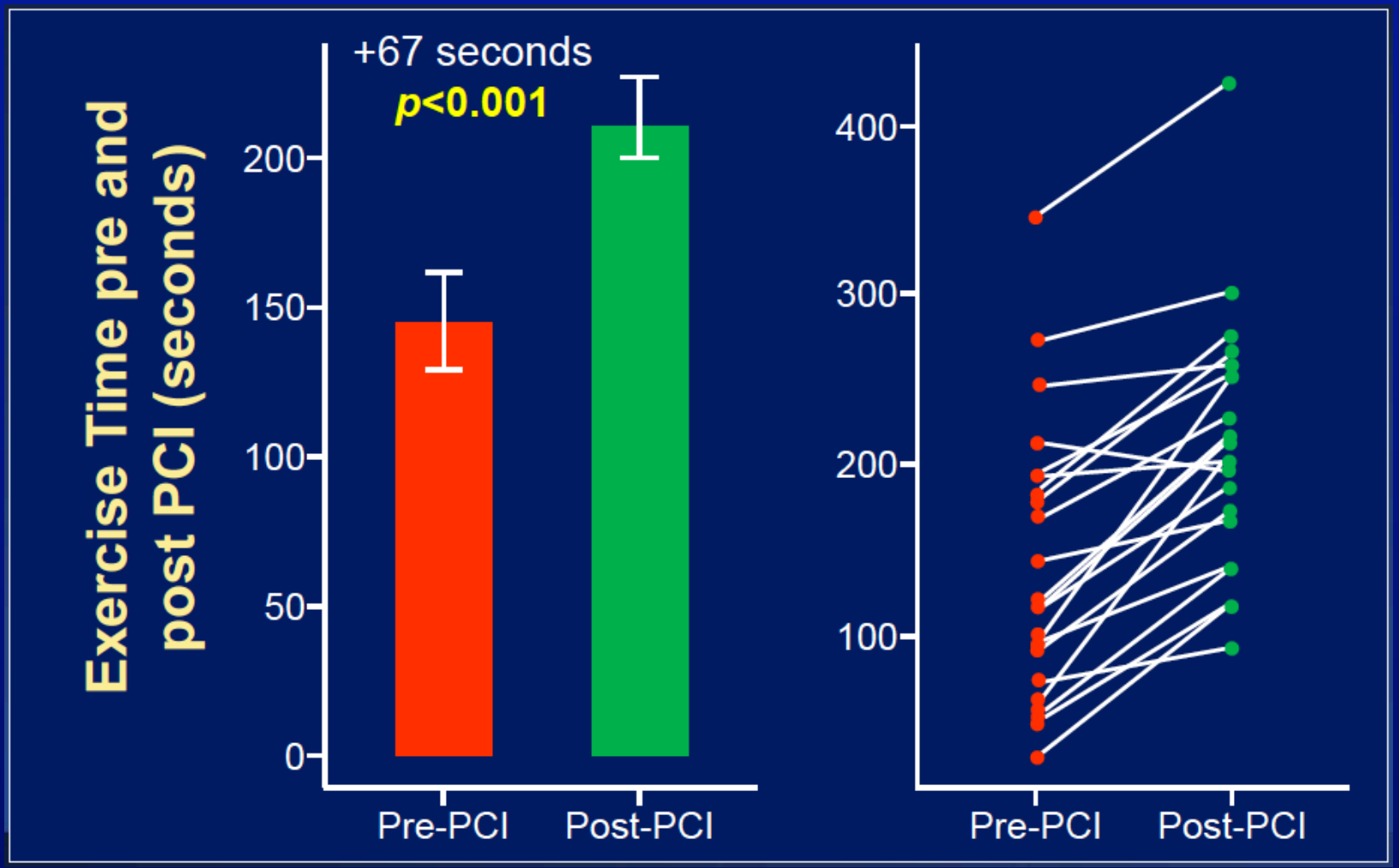
Newsflash, PCI Works

Stenting Stenoses Increases Coronary Blood Flow During Exercise and Reduces Ischemia



Cook CM et al. J Am Coll Cardiol 2018; 72:970–83

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Newsflash, PCI Works

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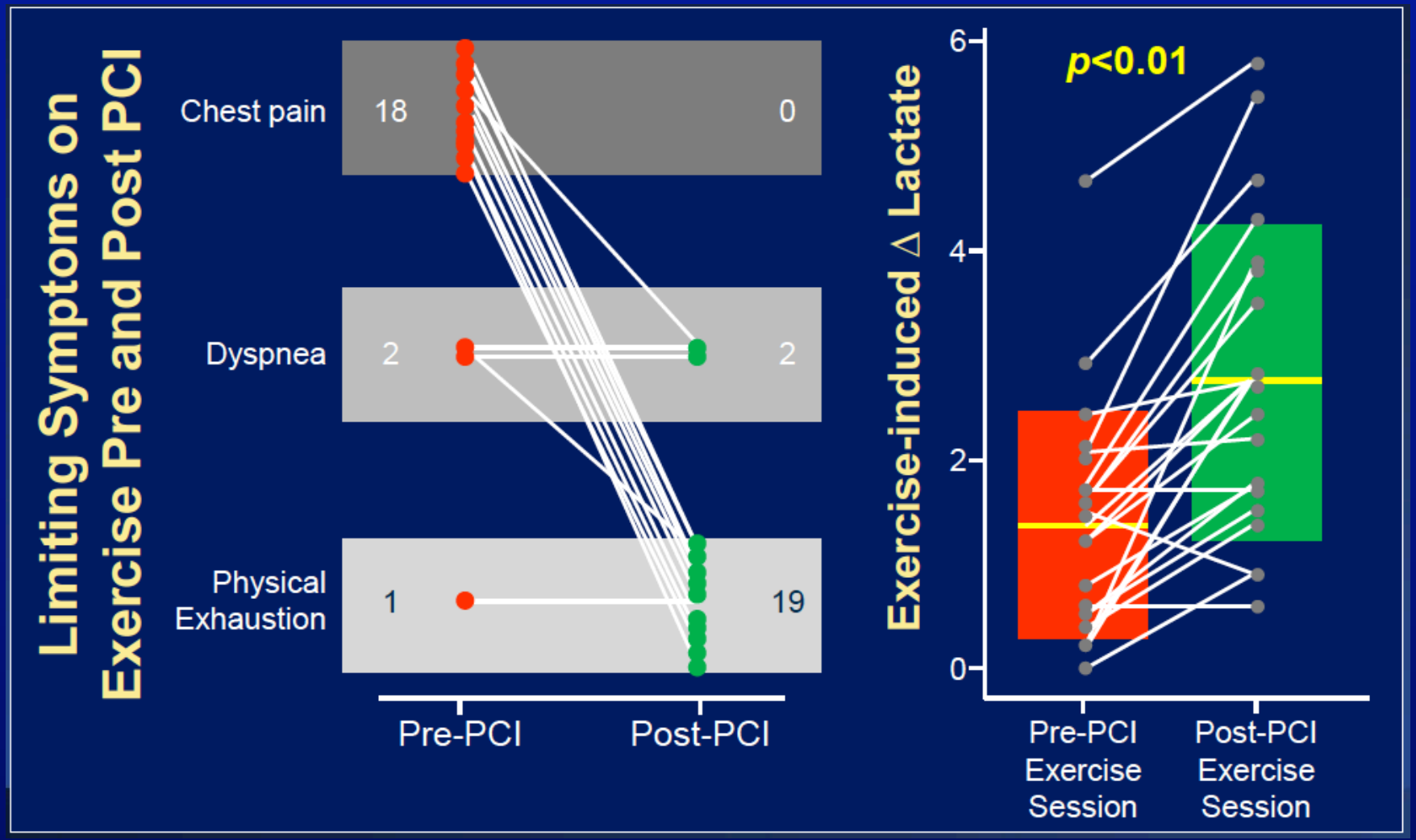

Cook CM et al. J Am Coll Cardiol 2018; 72:970–83

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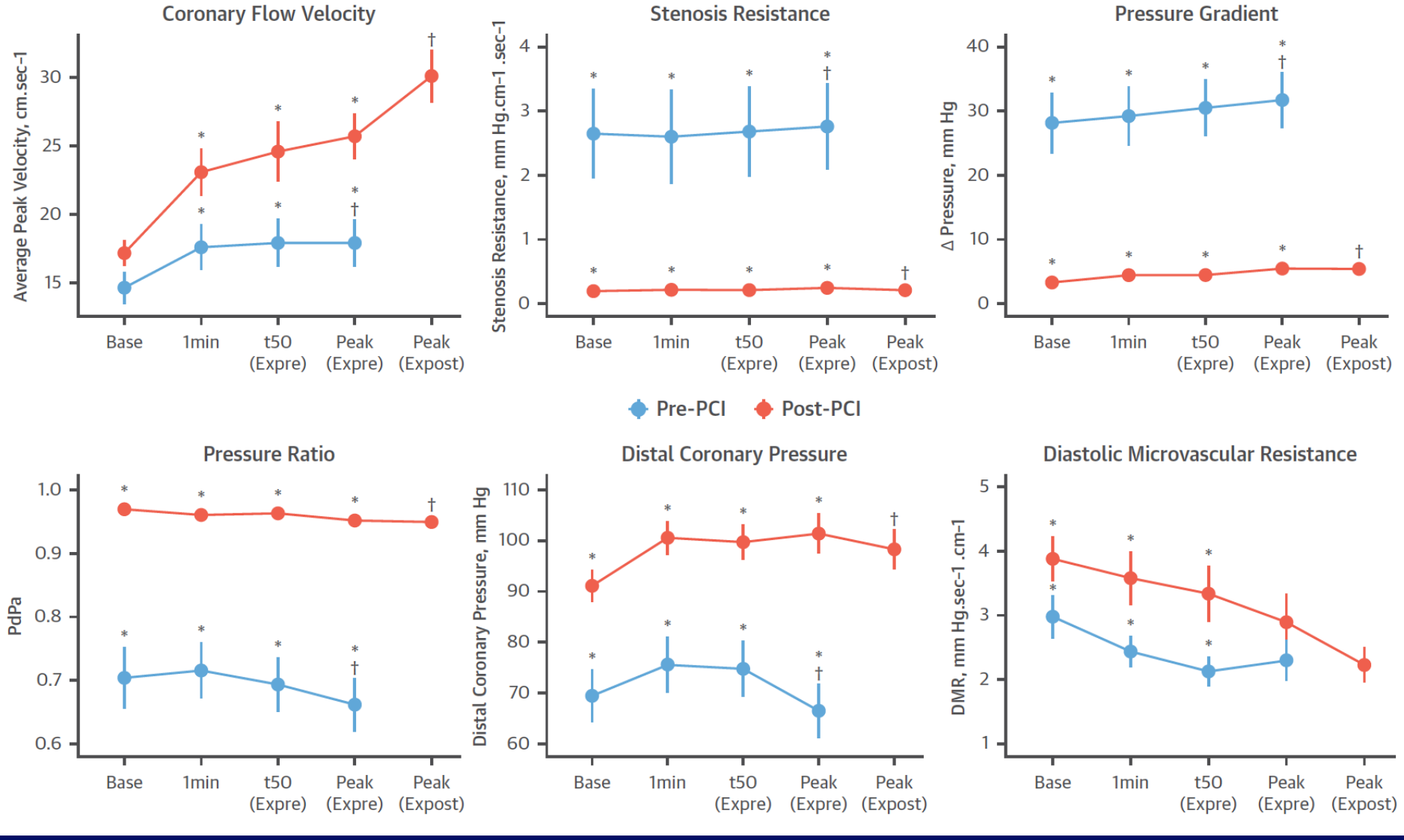
Coronary and Microcirculatory Hemodynamic Responses to Exercise



Cook CM et al. J Am Coll Cardiol 2018; 72:970–83

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Clinical implications of the ORBITA trial

- ORBITA was a small, clever, randomized, sham-controlled trial that at best, was hypothesis generating. It is a wake-up call about potential placebo effects of PCI.
- ORBITA posed important unanswered questions about the relationship between physiology and ischemia, its relationship to angina and the response to PCI
- However, the trial should not presently change existing guidelines for PCI in stable angina

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SIHD Treatment: important tenets

- Aggressive risk-factor control and adherence to GL medical therapy are the cornerstones of treatment
- Revas… …ys be cons… …ategy
- Relie… …ents in card… dem…
- Restricting use of PCI to just those stable patients who have limiting symptoms and ischemia despite medical therapy is appropriate and guideline-compliant

In appropriate candidates with stable angina, PCI is still safely ORBITaING the cardiology universe

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