ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

Coronary Artery Disease, Current controversies in mgmt. of SIHD;

ORBITA & ISCHEMIA

Anwar Jelani, MD

King Abdulaziiz Hospital, Alhasa
AJ.ngha.med.sa@gmail.com


ACC Middle East
Conference 2018
In partnership with:
Saudi Heart Association

- No financial disclosure.
- Not smart enough to be one of the interventional cardiologists.

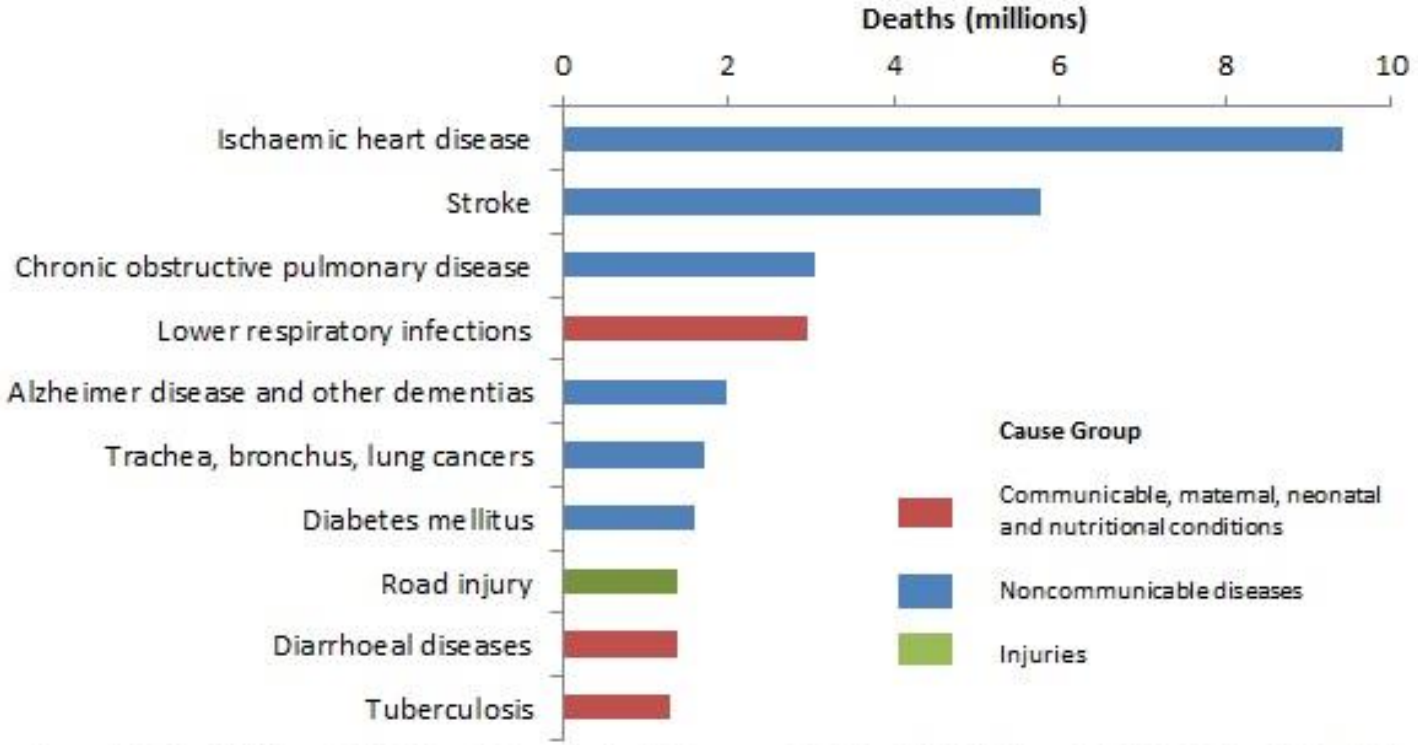
The 10 Leading Causes of Death, Global, 2000 and 2012

No	Causes of death, 2000	Deaths (million)	% of deaths		No	Causes of death, 2012	Deaths (million)	% of deaths
1	Ischaemic heart disease	6.0	11.3	→	1	Ischaemic heart disease	7.4	13.2
2	Stroke	5.7	10.7	→	2	Stroke	6.7	11.9
3	Lower respiratory infections	3.5	6.6	↘	3	COPD	3.1	5.6
4	COPD	3.1	5.8	↗	4	Lower respiratory infections	3.1	5.5
5	Diarrhoeal diseases	2.2	4.1	↘	5	Trachea, bronchus, lung cancers	1.6	2.9
6	HIV/AIDS	1.7	3.2	→	6	HIV/AIDS	1.5	2.8
7	Tuberculosis	1.3	2.5	↘	7	Diarrhoeal diseases	1.5	2.7
8	Prematurity	1.3	2.5	↗	8	Diabetes mellitus	1.5	2.7
9	Trachea, bronchus, lung cancers	1.2	2.2	↗	9	Road injury	1.3	2.3
10	Diabetes mellitus	1.0	2.0	↘	10	Hypertensive heart disease	1.1	2.0
					11	*Prematurity*	*1.1*	*2.0*
12	*Road injury*	*1.0*	*1.9*	↗				
				↘	*13*	*Tuberculosis*	*0.9*	*1.7*
16	*Hypertensive heart disease*	*0.8*	*1.6*					

World Health Organization

ACC Middle East Conference 2018
In partnership with: Saudi Heart Association

Top 10 global causes of deaths, 2016



Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.

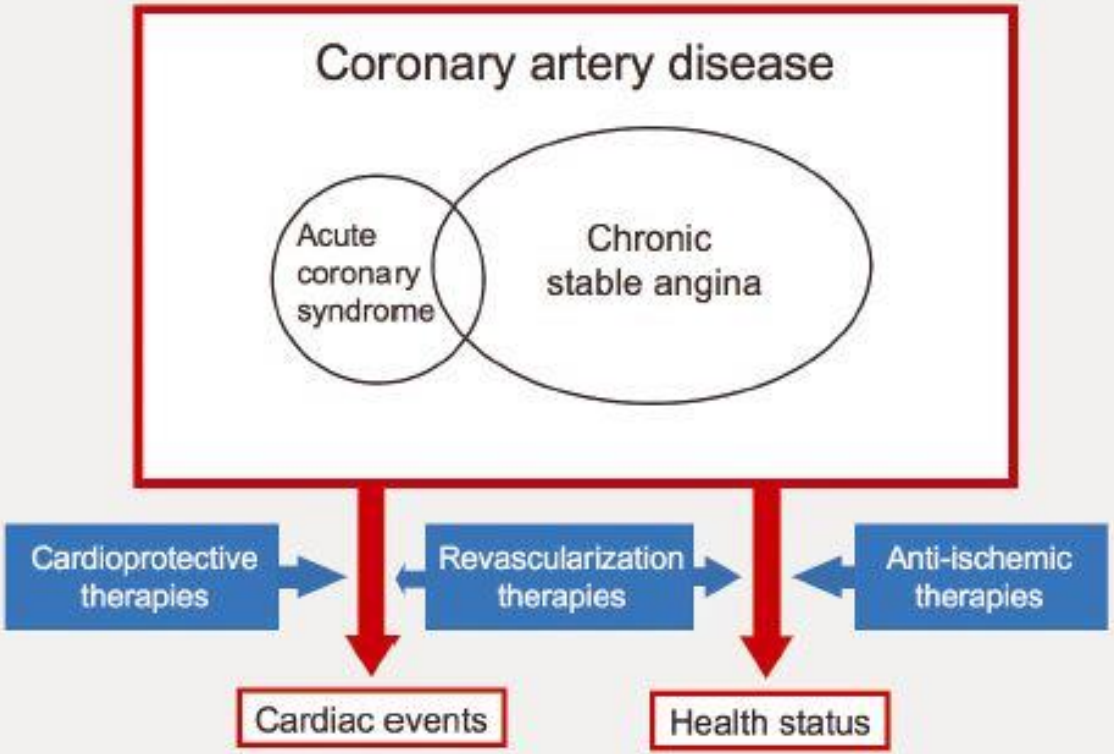
SIHD

- the syndrome of recurrent, transient episodes of chest pain reflecting demand-supply mismatch, that is, angina pectoris.

SIHD

- the syndrome of recurrent, transient episodes of chest pain reflecting demand-supply mismatch, that is, angina pectoris.

- the syndrome of recurrent, transient episodes of chest pain reflecting demand-supply mismatch, that is, angina pectoris.

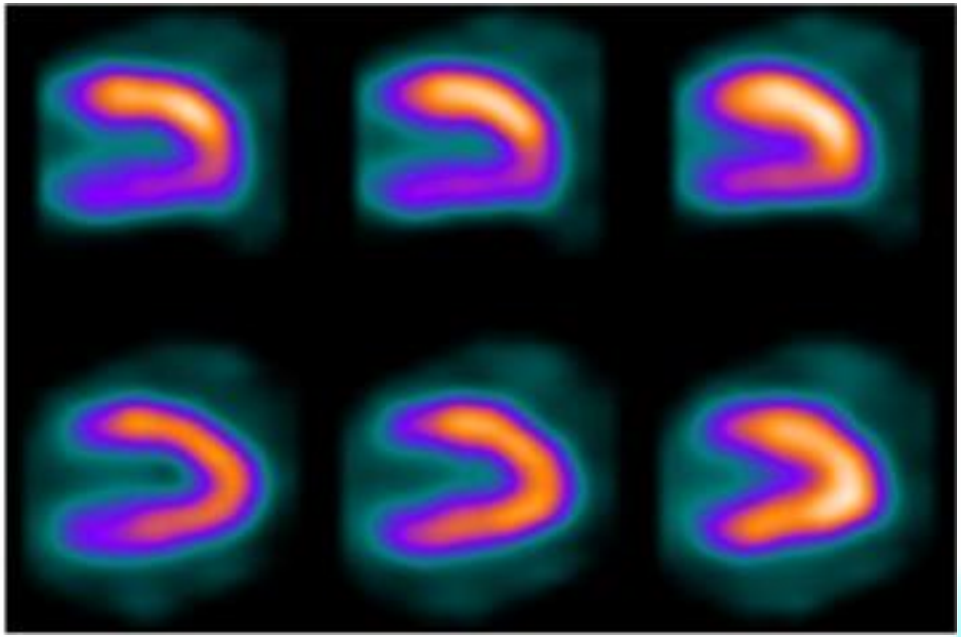

Coronary artery disease
Acute coronary syndrome
Chronic stable angina
Cardioprotective therapies
Revascularization therapies
Anti-ischemic therapies
Cardiac events
Health status

Case in your clinic

- 57 year M
- Not DM
- ?HTN
- DLP/ smoker
- BMI ~32

- Chest pain for 4-5 months.
- Especially on going upstairs.
- Associated with dyspnea
- Normal LV Fx.
- 8 min on Bruce.

Stress



Rest

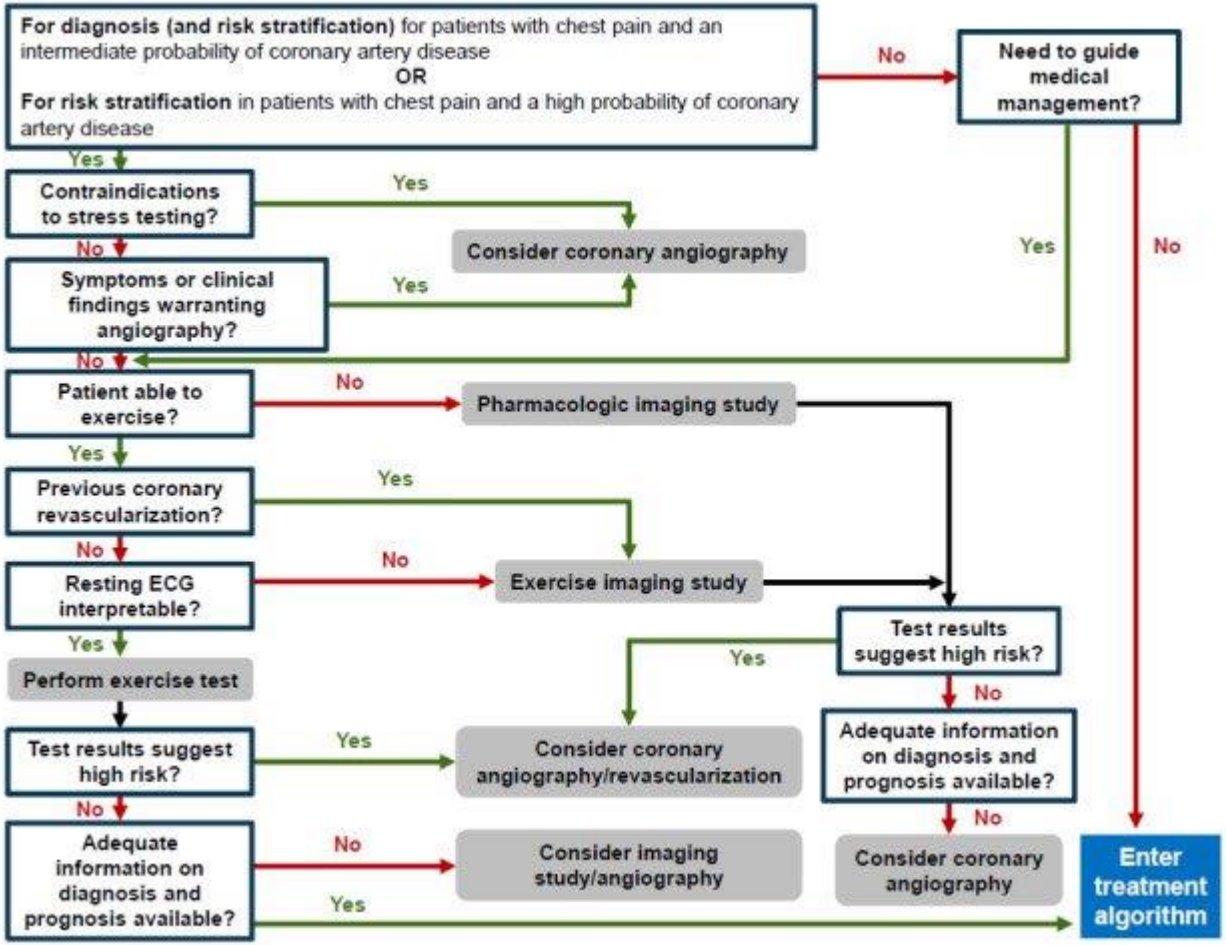
Choices

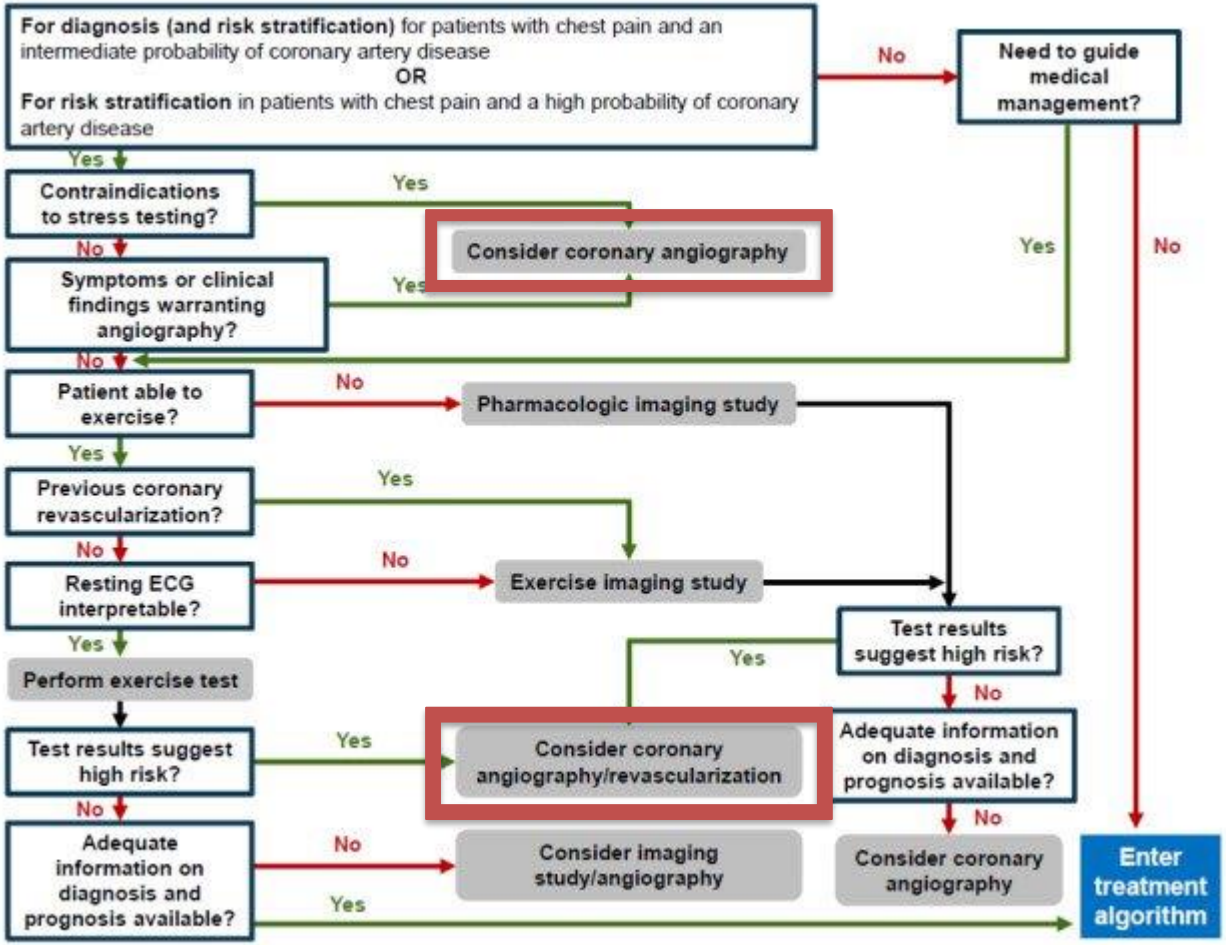
- What would you do?
- GDMT?
- +/- CA?
- Is this evidence based?
- Will you control Sx?
- Prevent MI?
- Improve Mortality?
- Is it cost effective?

Choice 1	Choice 2	Choice 3
• No Chest pain. • WMA • 8 min	• Chest pain. • No WMA • 8 min	• Chest pain. • WMA • >8 min

Choice 1	Choice 2	Choice 3	Choice 4
• No Chest pain. • WMA • 8 min	• Chest pain. • No WMA • 8 min	• Chest pain. • WMA • >8 min	• No Chest pain. • No WMA • >8 min

- Is INV strategy better than GDMT alone?
- Do you believe in “Placebo” Rx?


For diagnosis (and risk stratification) for patients with chest pain and an intermediate probability of coronary artery disease
OR
For risk stratification in patients with chest pain and a high probability of coronary artery disease
No
Need to guide medical management?
Yes
Contraindications to stress testing?
Yes
Consider coronary angiography
No
Symptoms or clinical findings warranting angiography?
Yes
Yes
No
No
Patient able to exercise?
No
Pharmacologic imaging study
Yes
Previous coronary revascularization?
Yes
No
Resting ECG interpretable?
No
Exercise imaging study
Yes
Perform exercise test
Test results suggest high risk?
Yes
Test results suggest high risk?
Yes
No
Consider coronary angiography/revascularization
Adequate information on diagnosis and prognosis available?
No
Adequate information on diagnosis and prognosis available?
No
Consider imaging study/angiography
Consider coronary angiography
Enter treatment algorithm
Yes


For diagnosis (and risk stratification) for patients with chest pain and an intermediate probability of coronary artery disease
OR
For risk stratification in patients with chest pain and a high probability of coronary artery disease
No
Need to guide medical management?
Yes
Contraindications to stress testing?
Yes
Consider coronary angiography
No
Symptoms or clinical findings warranting angiography?
Yes
Yes
No
No
Patient able to exercise?
No
Pharmacologic imaging study
Yes
Previous coronary revascularization?
Yes
No
Resting ECG interpretable?
No
Exercise imaging study
Yes
Perform exercise test
Test results suggest high risk?
Yes
Yes
Test results suggest high risk?
No
Consider coronary angiography/revascularization
Adequate information on diagnosis and prognosis available?
No
Adequate information on diagnosis and prognosis available?
No
Consider imaging study/angiography
Consider coronary angiography
Enter treatment algorithm
Yes

CAD Prognostic Index

Extent of CAD	Prognostic Weight (0-100)	5-Year Survival Rate (%)*
1-vessel disease, 75%	23	93
1-vessel disease, 50% to 74%	23	93
1-vessel disease, ≥95%	32	91
2-vessel disease	37	88
2-vessel disease, both ≥95%	42	86
1-vessel disease, ≥95% proximal LAD artery	48	83
2-vessel disease, ≥95% LAD artery	48	83
2-vessel disease, ≥95% proximal LAD artery	56	79
3-vessel disease	56	79
3-vessel disease, ≥95% in ≥1 vessel	63	73
3-vessel disease, 75% proximal LAD artery	67	67
3-vessel disease, ≥95% proximal LAD artery	74	59

*Assuming medical treatment only.

Contemporary Trials of OMT with or without Revascularization

- COURAGE (2007)
- BARI 2D (2009)
- FAME 2 (2012)
- Few Meta-analyses

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 12, 2007 VOL. 356 NO. 15

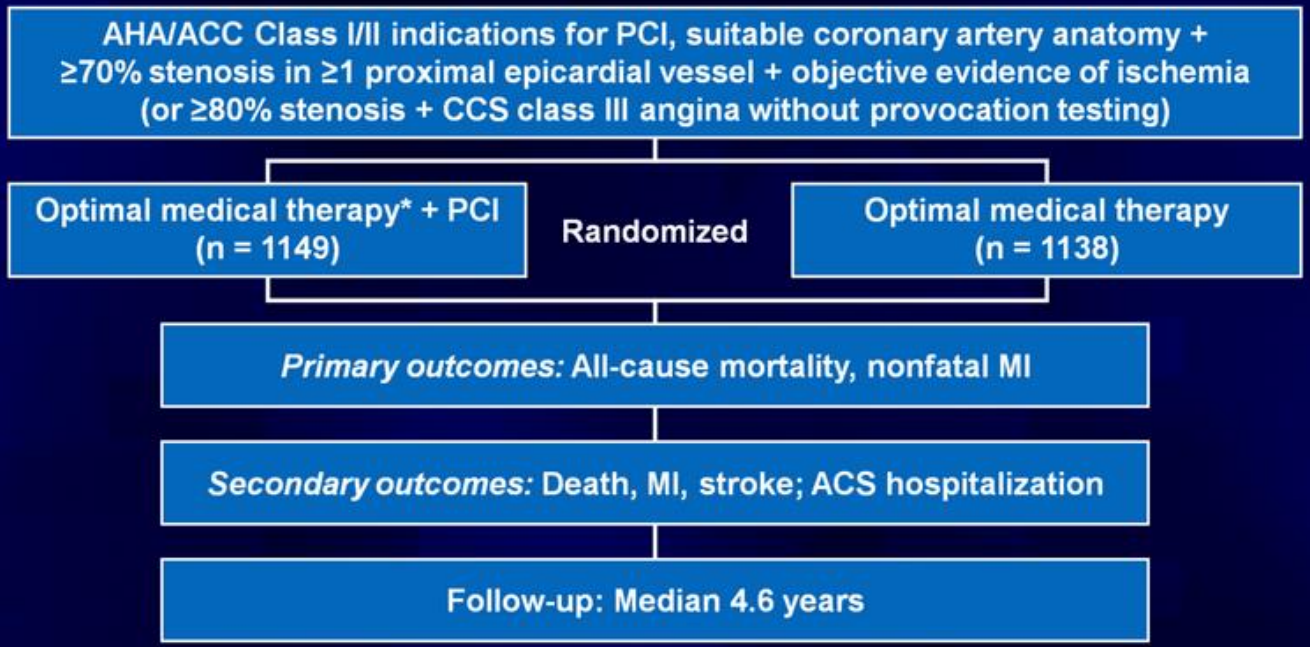
Optimal Medical Therapy with or without PCI for Stable Coronary Disease

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merril Knudtson, M.D., Marcin Dada, M.D., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., and William S. Weintraub, M.D., for the COURAGE Trial Research Group*

ACC Middle East Conference 2018

In partnership with:

COURAGE: Study design



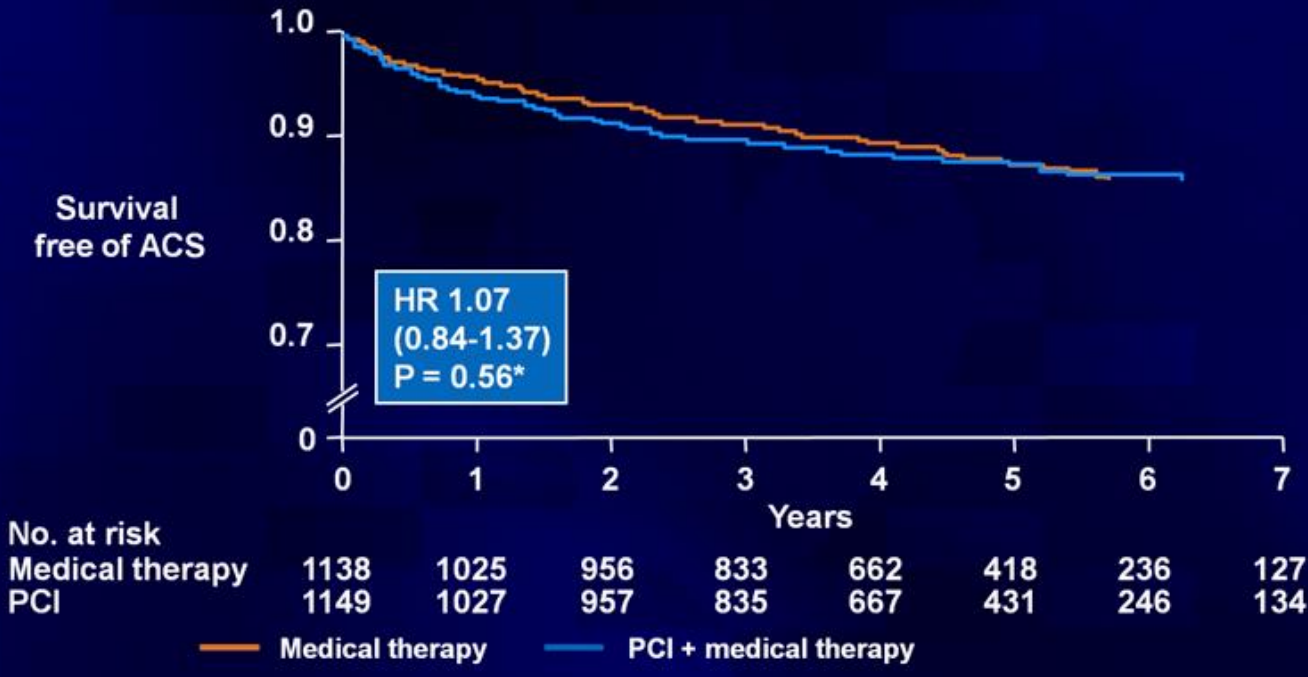
*Intensive pharmacologic therapy + lifestyle intervention
CCS = Canadian Cardiovascular Society

Boden WE et al. *Am Heart J.* 2006;151:1173-9.
Boden WE et al. *N Engl J Med.* 2007;356:1503-16.

In partnership with:
جمعية القلب السعودية
Saudi Heart Association

VBWG

COURAGE: Treatment effect on hospitalization for ACS

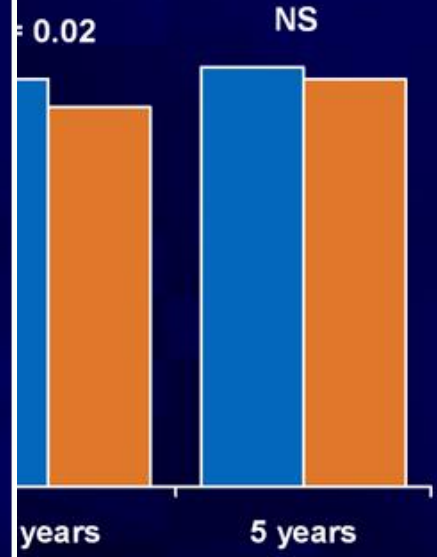


*Unadjusted

Boden WE et al. *N Engl J Med.* 2007;356:1503-16.

VBWG

ngina



py

et al. *N Engl J Med.* 2007;356:1503-16.

COURAGE

Clinical Outcomes Utilizing Revascularization and Aggressive Guideline-Driven Drug Evaluation

Trial tested whether PCI and optimal medical therapy or optimal medical therapy alone was superior in preventing death and nonfatal MI.

- **Design:** randomized
- **Patients:** 2,287
- **Centers:** 50
- **Countries:** United States and Canada

Results: No significant differences were found between the PCI and optimal medical therapy group (n=1,149) and optimal medical therapy alone group (n=1,138) in MI, death and stroke (20% vs. 19.5%, respectively; HR 1.05; 95% CI 0.87-1.27). There was no difference in hospitalization for ACS between the groups (12.4% PCI group vs. 11.8% medical therapy, HR 1.07; 95% CI 0.84-1.37) or MI (13.2% PCI vs. 12.3% medical therapy alone; HR 1.13; 95% CI 0.89-1.43). *Presented at ACC 2007.*

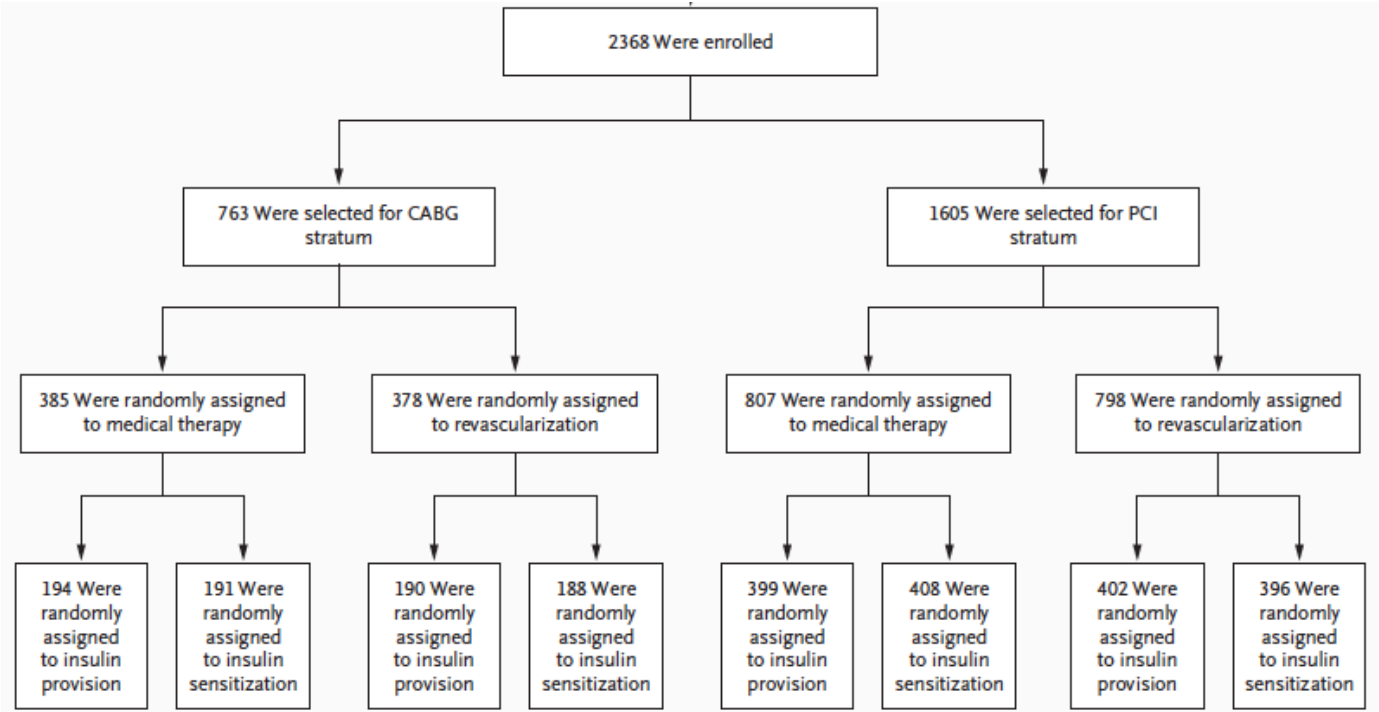
today in CARDIOLOGY

Boden WE et al. *N Engl J Med.* 2007;356:1503-16.

In partnership with:
جمعية القلب السعودية
Saudi Heart Association

A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

The BARI 2D Study Group

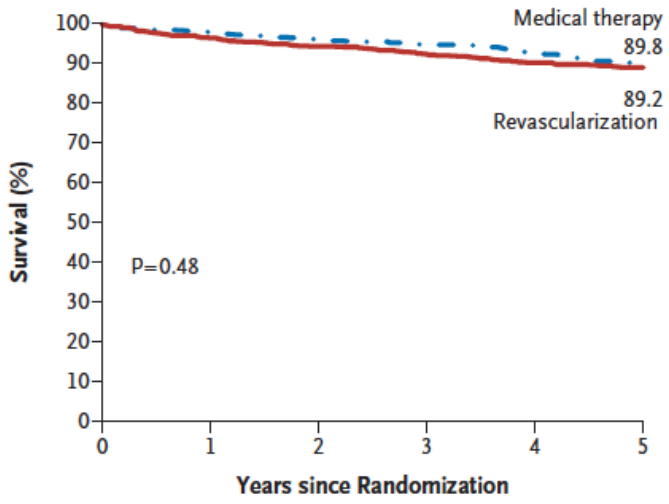


N Engl J Med 2009;360:2503-15.

A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

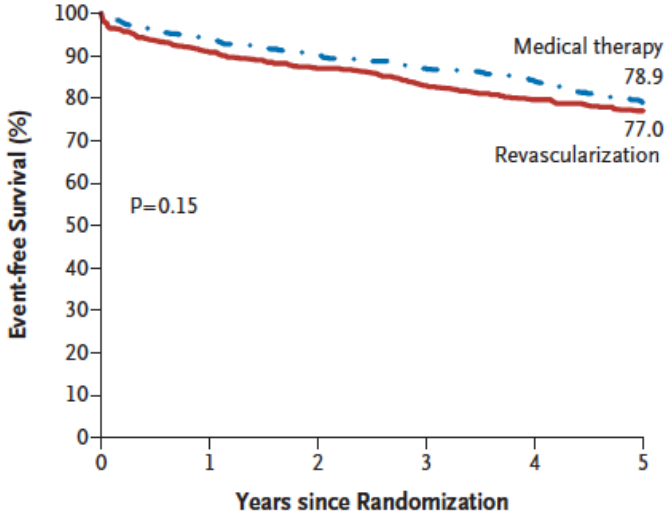
The BARI 2D Study Group

A Survival in PCI Stratum



No. at Risk	1605	1562	1529	1505	1306	863

C Freedom from Major Cardiovascular Events in PCI Stratum



No. at Risk	1605	1426	1350	1239	1012	593

N Engl J Med 2009;360:2503-15.

2011 ACCF/AHA/SCAI PCI Guideline

- "The findings from individual studies and systematic reviews of PCI vs medical therapy can be summarized as follows:
  - *PCI reduces the incidence of angina*
  - *PCI has not been demonstrated to improve survival in stable patients*
  - *PCI may increase the short-term risk of MI*
  - *PCI does not lower the long-term risk of MI"*

Coronary Revascularization: Factors to Consider in Evaluating Patients

- Assessment of clinical risk
- Consideration and integration of functional/imaging data
- Burden/extent of CAD
- Symptoms and medical therapy, including side effects and adherence
- Individual values and preferences

Principal hypothesis:
Symptom relief in stable angina

PCI increases exercise time more than placebo procedure

Primary endpoint

Difference in exercise time increment between the arms

For patients to be willing to participate in this first placebo-controlled trial of PCI, duration must long enough for full hemodynamic effect but not so long as to inhibit recruitment

Sample size calculation

To detect 30 sec,

at 80% power,

within-arm SD 75 sec,

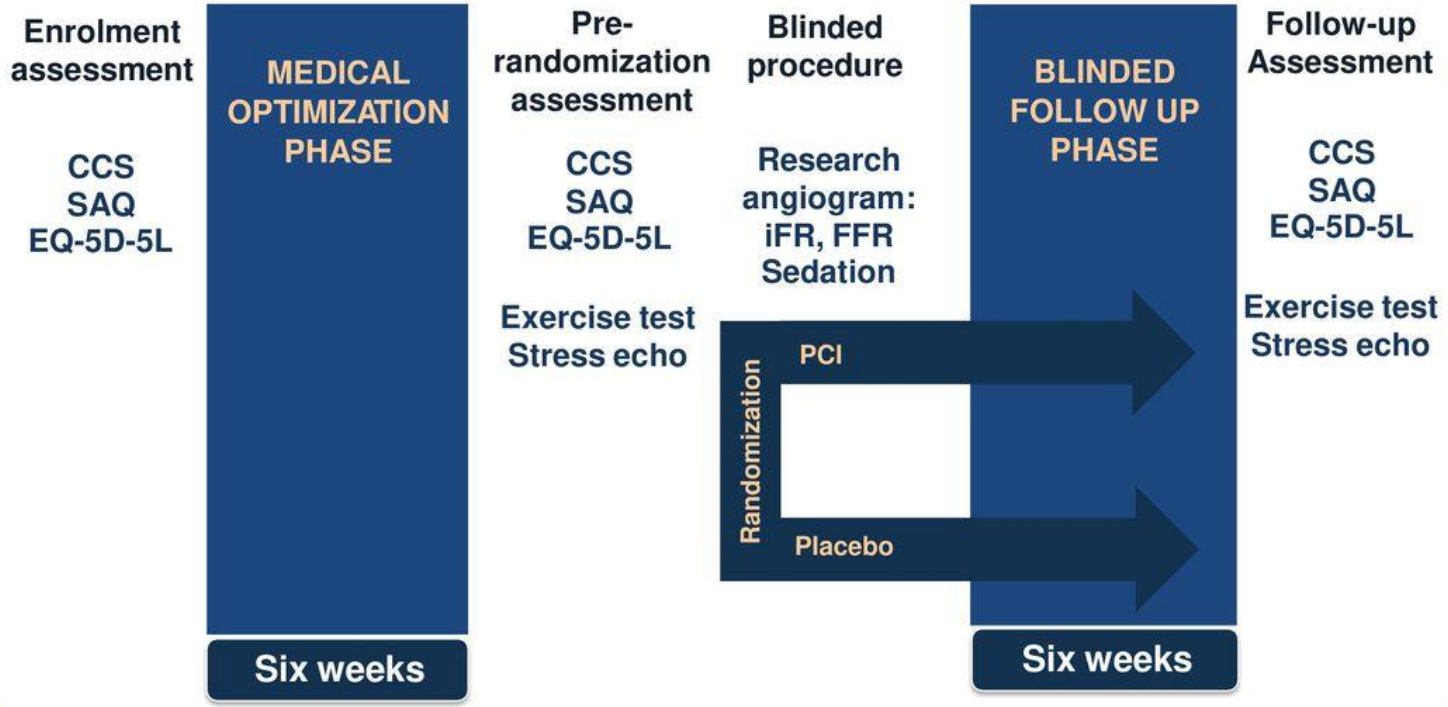
needs 200 randomized patients

This sample size is comparable to other trials assessing *this question.*

Inclusion criteria

- **Stable angina**
- **One or more ≥ 70% stenosis in a single vessel**
- **Suitable for PCI**

Trial design



Blinding techniques

Patient

Headphones and music
Sedation
Minimum 15 min wait

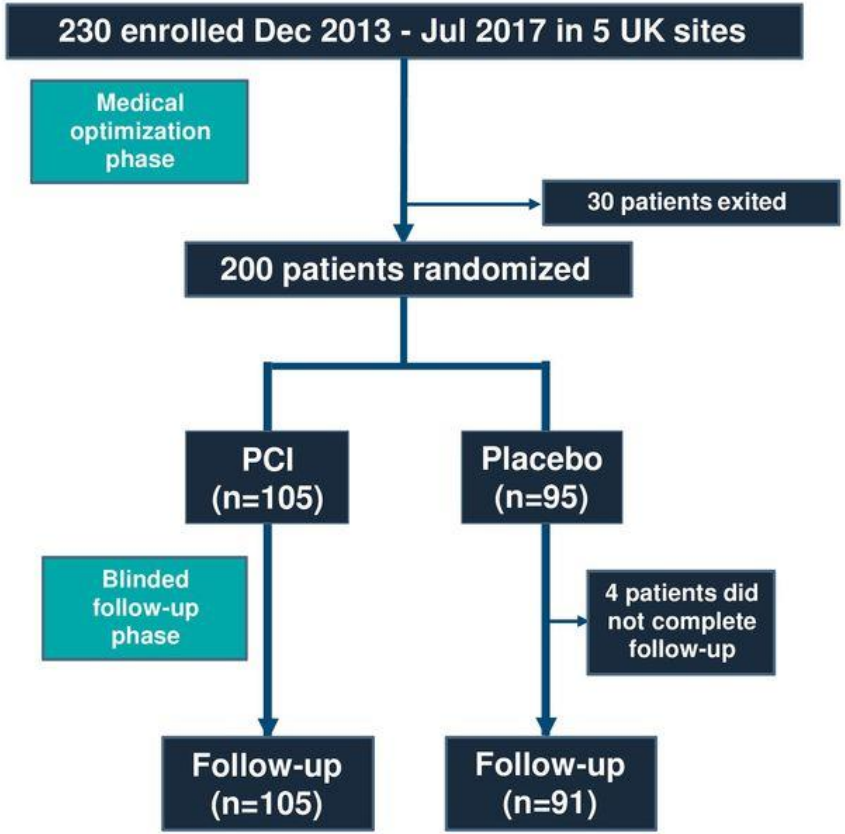
Both arms:
- DAPT
- Same post-procedural instructions
- Same discharge letter

Clinical team

Standardised handover
Ward team blinded

Both arms:
- Treated as if PCI
- No access to cath report
- Same discharge letter

ORBITA trial

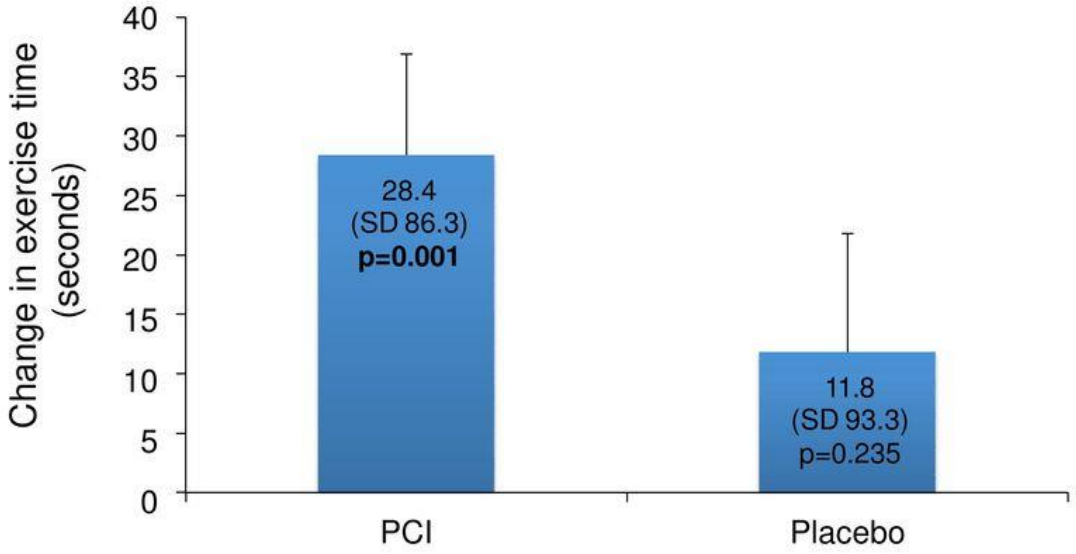


Stenosis severity

	PCI n = 105	Placebo n = 95	P
Area stenosis by QCA (%)	84.6 (SD 10.2)	84.2 (SD 10.3)	0.781
FFR	0.69 (SD 0.16)	0.69 (SD 0.16)	0.778
iFR	0.76 (SD 0.22)	0.76 (SD 0.21)	0.751

Primary endpoint result

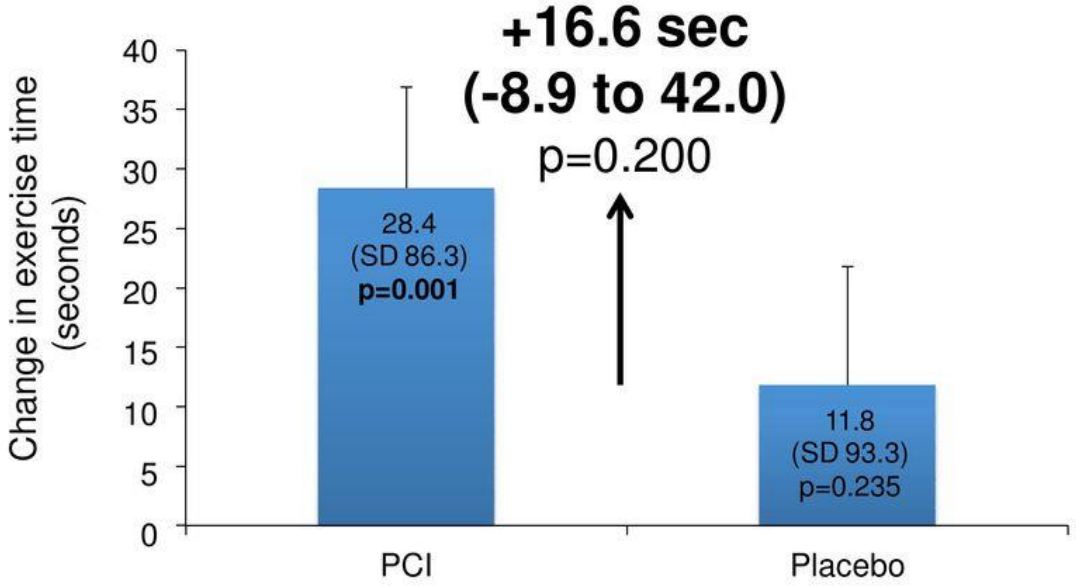
Change in total exercise time



Error bars are standard errors of the mean

Primary endpoint result

Change in total exercise time



Error bars are standard errors of the mean

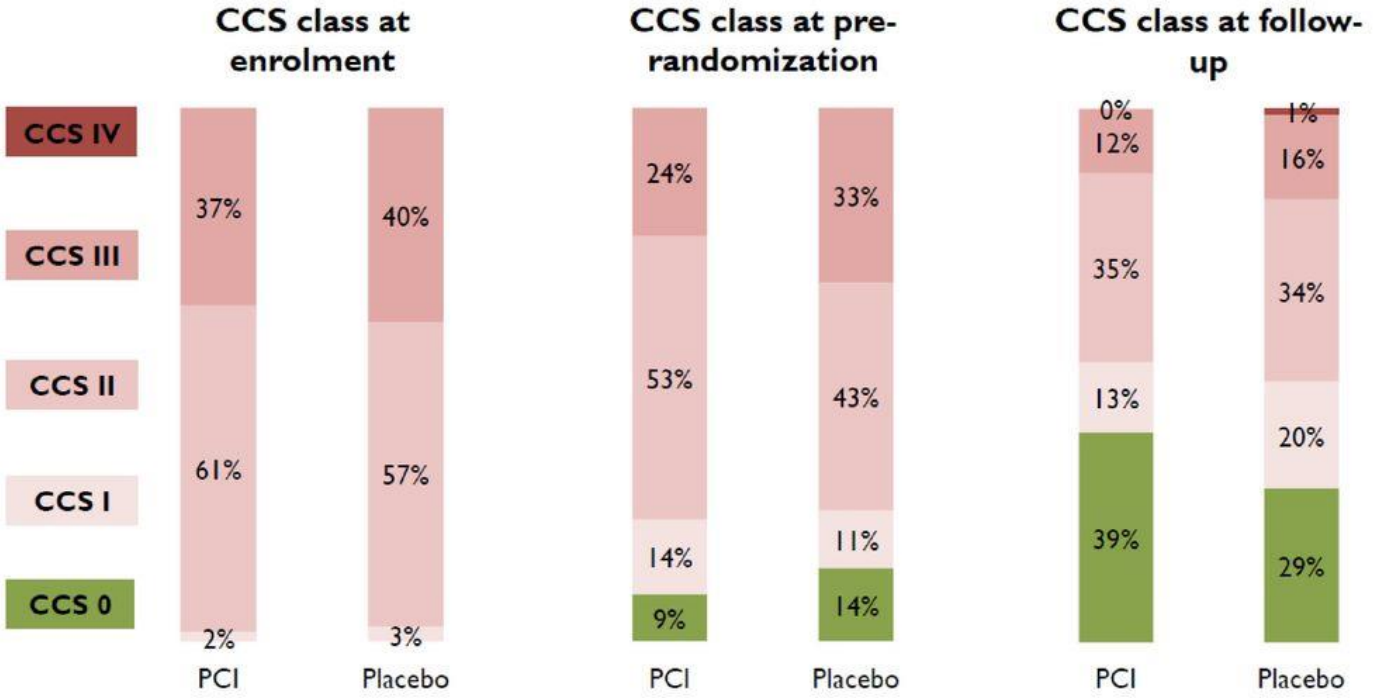
Secondary endpoint results

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**	

Secondary endpoint results

CCS class improved in both groups



In partnership with:
Saudi Heart Association
ORBITA

Conclusions

- ORBITA is the first placebo-controlled randomized trial of PCI in stable angina
- Area stenosis QCA 84.4%, FFR 0.69, iFR 0.76
- PCI was safe and physiologically effective
- PCI significantly reduced ischemic burden as assessed by stress echo
- In this single vessel, angiographically guided trial there was no difference in exercise time increment between PCI and placebo

ORBITA in context

- Single vessel
  - To allow complete revascularization
- PCI guided by angina + angiogram
  - In line with common practice
- Focus is on symptomatic relief
  - Not risk or events
- Intensive medical therapy
  - In line with Guidelines

https://www.medscape.com/viewarticle/888743 120%

blood, sweat, and tears of the actual people who do these trials and take care

> “I think the most important point of this trial overall is that there is a powerful placebo effect to the procedure of PCI.”

When you talk to the investigators, their intent was to prove the benefit of what happens in stable angina because it had not been carried out before. This is in

Does it reflect Real life?

- 6 weeks of intense follow up…
- 1-3 times/week access to Cardiologist…
- Intro/Increase of anti anginal agents to medications….

Stable IHD… What to do?

- Aggressive vs Conservative approach?
- Especially in “Moderate” ischemic burden…
- Do you start with Invasive and then medical strategy or vice versa….

- How about your usual patient in OD?
- Multivessel ….
- Moderate Ischemia…

ISCHEMIA Trial

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

ISCHEMIA Overview

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

Chair- Judith Hochman, PI - David Maron
Co-PI's William Boden, Bruce Ferguson, Robert Harrington, Gregg Stone, David Williams

- Patients: at least moderate ischemia, EF ≥35%
- Hypothesis: an initial invasive strategy of cath and optimal revascularization (PCI or CABG) + OMT is superior to a conservative strategy of OMT alone with cath reserved for OMT failure
- Composite Primary Endpoint: CV death, MI, or hospitalization for UA, resuscitated cardiac arrest, or heart failure (adjudicated)
- Secondary Aim—Major: test hypothesis that invasive strategy improves angina-related QOL compared with OMT alone
- Sample Size: 8,000
- Follow-up: average 4 years

Ischemia Trial Version 04-14-2011

ISCHEMIA Trial

International Study of Comparative Health Effectiveness with Medical &Invasive Approaches

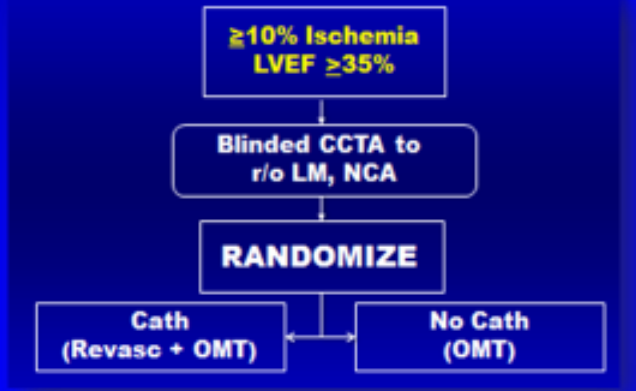
- **Patients**: Stable w/ at Least Moderate Ischemia (Core Lab)

SPECT	Echo / CMR RWMA	CMR Perfusion
≥10% LV	≥3/16 segments New / Worse WMA	>12% LV

OR

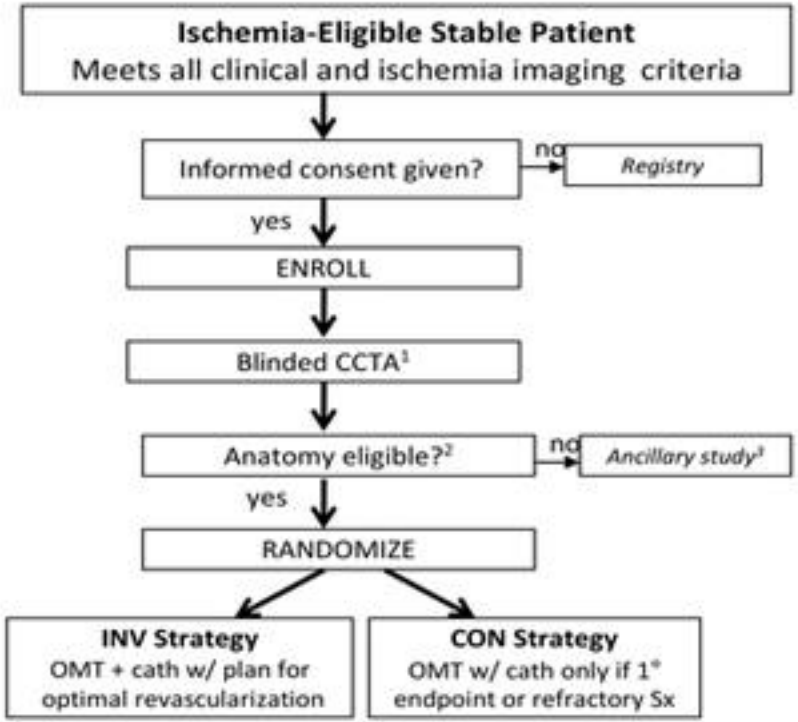
Ex ECG
ST ↓ ≥1.5 mm in 2 leads or
≥2.0 mm in ≥1 lead OR
ST ↑ ≥1.0 mm in non-infarct territory

- **Primary Aim**: To Determine if Initial Invasive Strategy of Cath & PCI / CABG + Medical Therapy Will Reduce Events Compared to a Strategy of Medical Therapy Alone (Cath - Reserved for Failed Medical Therapy)
  - **Sample Size**: 5,000 Followed for ~4 years



Chair – Judith Hochman, MD; Co-Chair / PI: David Maron, MD
Imaging Coordinating Center: Leslee Shaw, PhD

National Heart Lung and Blood Institute



[1] CCTA will not be performed in patients with eGFR<60 ml/min
[2] Exclude and register left main disease patients and <50% stenosis in all major epicardial coronary arteries
[3] Funding for this ancillary study will be sought via a separate application

Ischemia Trial Version 04-14-2011

- Multi center, Intl. 300 centers. 30 countries.
- 2012—2017.
- Follow up 3 years

Address previous limitations:

- Enroll pt BEFORE cath (not excluding high risk pt)..
- Higher risk patient (moderate Ischemia).
- Minimize cross over.
- DES/FFR to resolve ischemia (not only stenosis)
- Adequately powered..

- Things did not go as planned.
- Lower than expected event rate in OMT group…
- 16% event rate DID NOT happen!
- What you do??

13,183 views | Mar 18, 2018, 06:32pm

Cardiology World Erupts Into Controversy Over Change In Major Clinical Trial

Larry Husten Contributor ⓘ

Pharma & Healthcare

I'm a medical journalist covering cardiology news.

News

Stent trial researchers are accused of changing endpoints to suit results

BMJ 2018 ; 360 doi: https://doi.org/10.1136/bmj.k1298 (Published 20 March 2018)
Cite this as: *BMJ* 2018;360:k1298

- 5179 recruited.
- $110 million and counting…….

- ”Might not have an answer”….
- CV death, MI → resust Cardiac Arrest, hosp for Angina, HF;
- Will this affect the credibility of the study?

- So for now,
- ORBITA is what we go with….
- “Placebo effect” is a reality…..
- We will discuss further with our panel

- Thank you……