PCI strikes back: Benefits of PCI in Chronic Coronary syndrome

Mann Chandavimol MD FRCPC FESC
Ramathibodi Hospital, Mahidol University

January 2024

Goals of treatment of chronic coronary disease

Live longer

- Reduce disease progression
- Reduce ischemic events
  - Anti-thrombotics
  - Lipid-lowering medications
  - ACE-I/ARB/BB
  - Diabetes: GLP-1 RA/SGLT2i

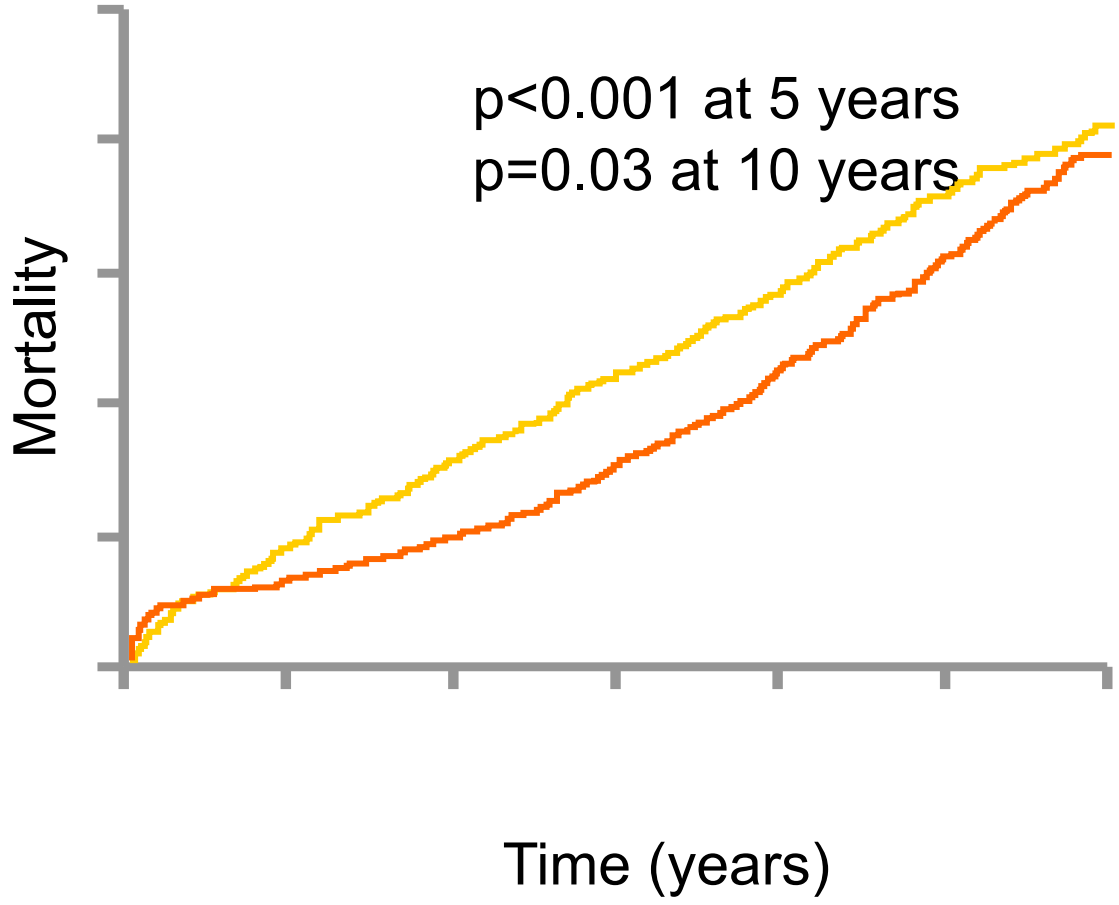
Feel better

- Reduce angina, improve functional status, improve quality of life
  - Anti-anginal medications

? But what does Coronary revascularization fit in ?

Benefit of revascularization in CCD: early trials

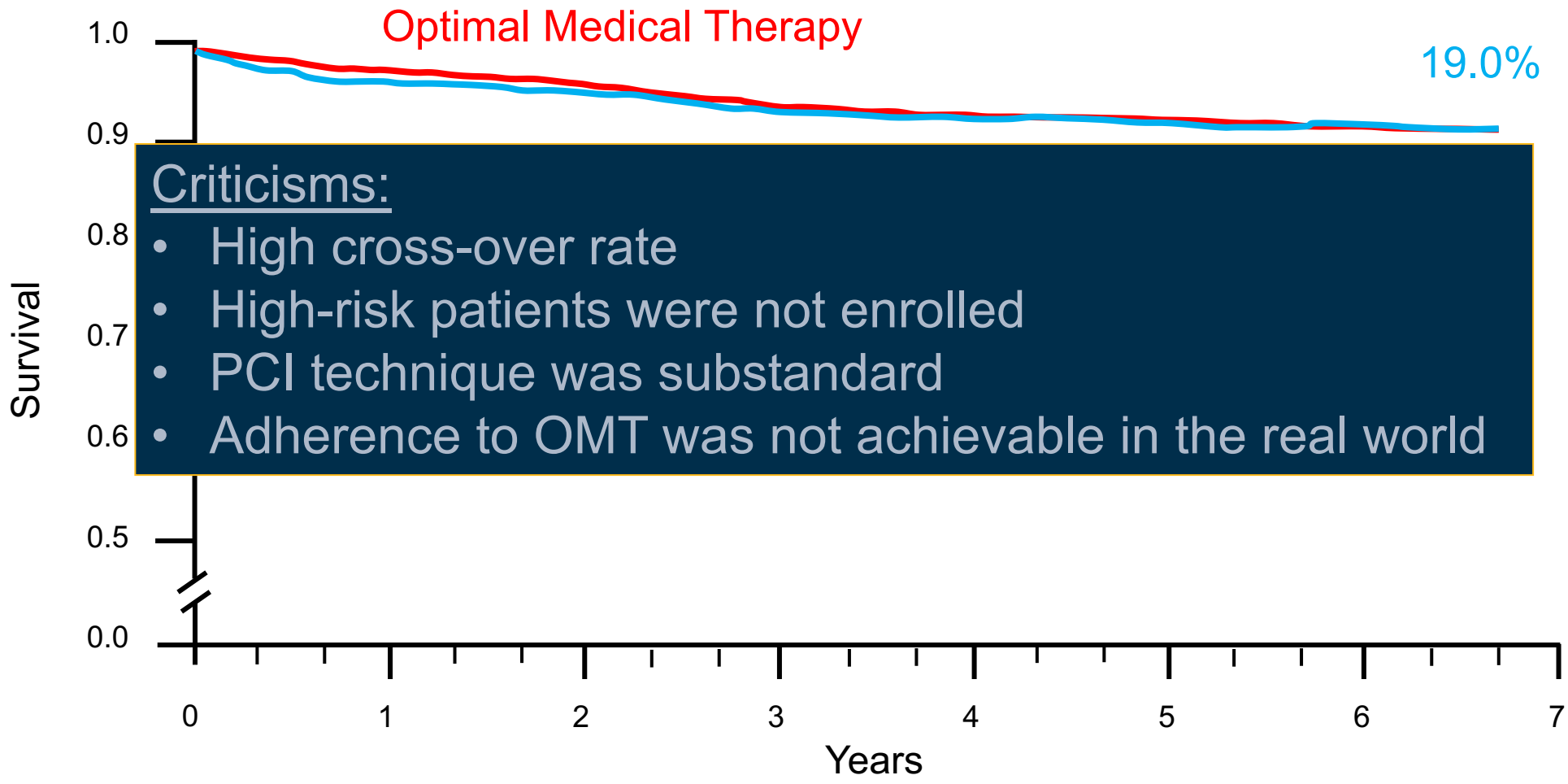
CABG vs. OMT (VA, CASS, European Study)



Studies in 1970-80's with minimal use of medical therapy. Majority of benefit in patients with left main disease.

Yusuf et al. Lancet 1994

COURAGE: PCI vs. OMT in CCD



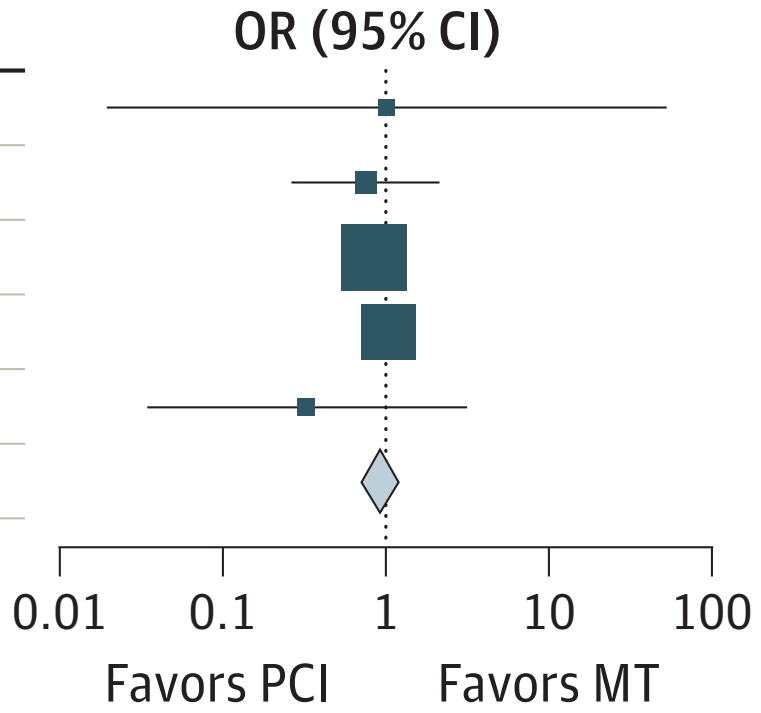
Criticisms:

- High cross-over rate
- High-risk patients were not enrolled
- PCI technique was substandard
- Adherence to OMT was not achievable in the real world

Boden et al. NEJM 2007. Sedlis et al. NEJM 2015

Meta-analyses : No difference in mortality

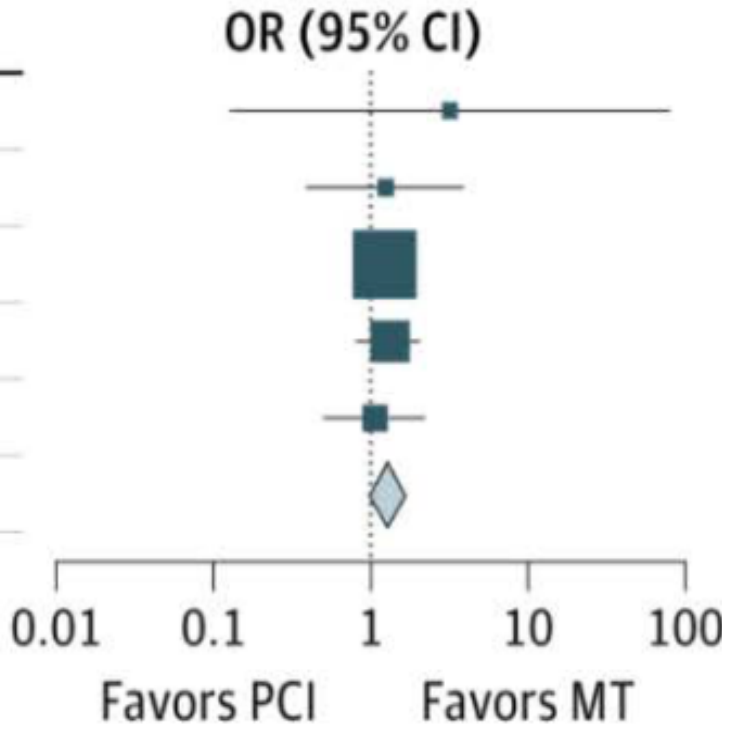
Source	OR (95% CI)	*P* Value
Hambrecht[15]	1.02 (0.02-52.43)	.99
MASS II[13]	0.76 (0.27-2.16)	.60
COURAGE[17]	0.84 (0.61-1.18)	.32
BARI 2D[14]	1.06 (0.71-1.58)	.78
FAME 2[16]	0.33 (0.03-3.16)	.33
Overall	0.90 (0.71-1.16)	.42



Stergiopoulos et al JAMA Int Med 2014;174(2):232-240

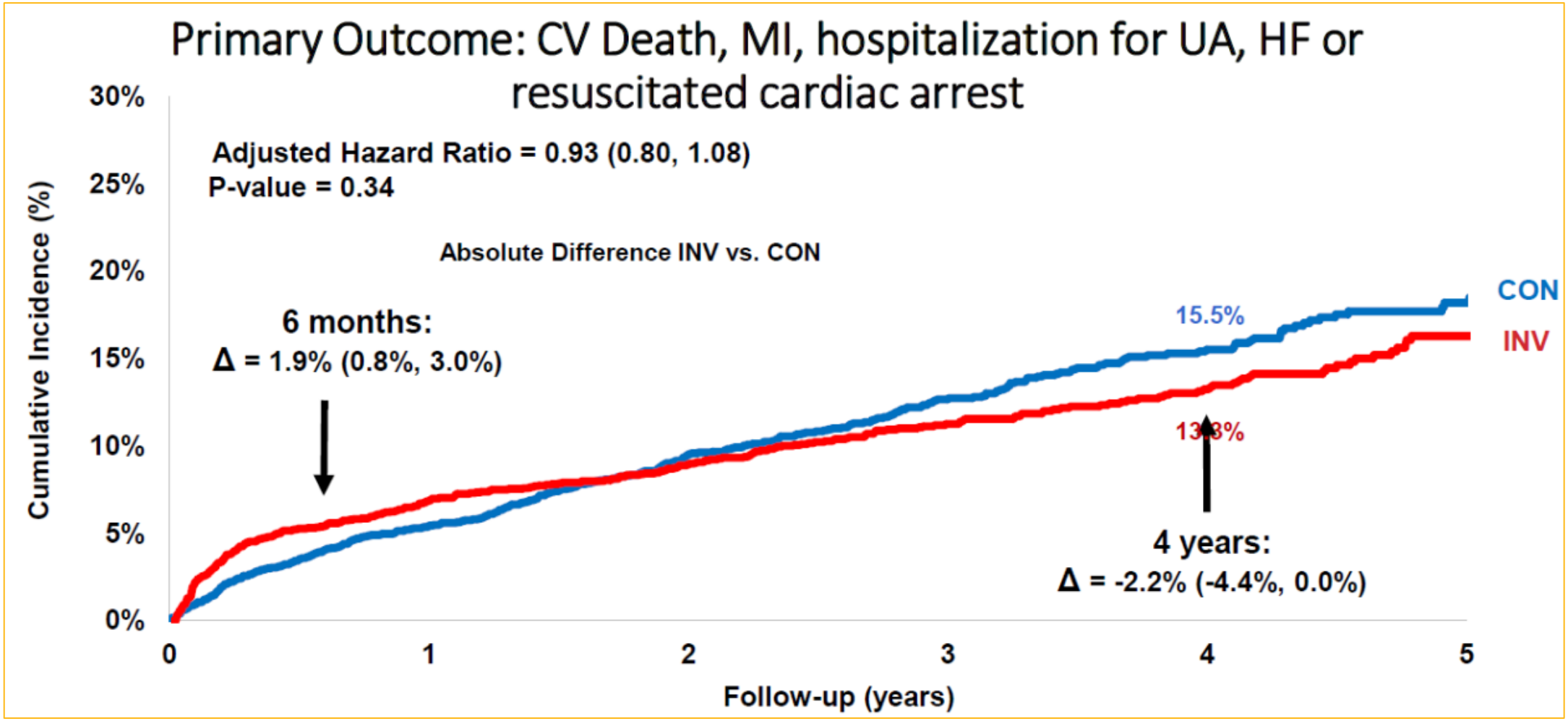
Meta-analyses :
No difference in MI

Source	OR (95% CI)	*P* Value
Hambrecht[15]	3.12 (0.12-78.45)	.49
MASS II[13]	1.24 (0.40-3.88)	.71
COURAGE[17]	1.24 (0.94-1.65)	.13
BARI 2D[14]	1.29 (0.82-2.04)	.27
FAME 2[16]	1.06 (0.51-2.22)	.88
Overall	1.24 (0.99-1.55)	.06



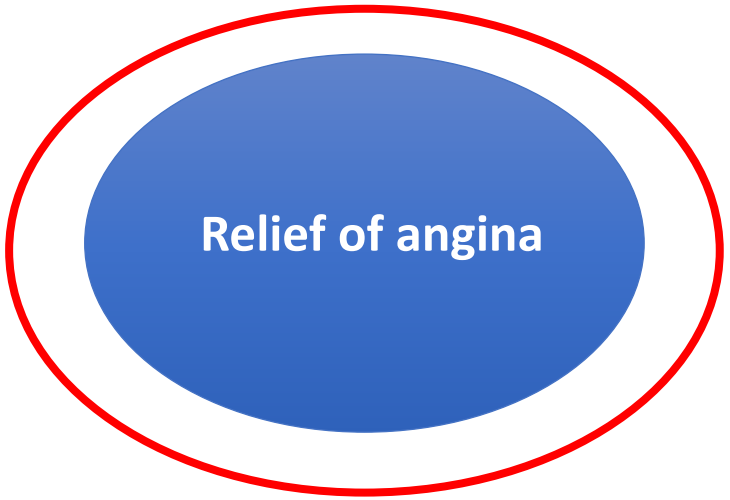
Stergiopoulos et al. JAMA IM 2014.

ISCHEMIA Trial: invasive vs. conservative strategy



5179 patients from 38 countries with CCD and moderate- or high-risk ischemia

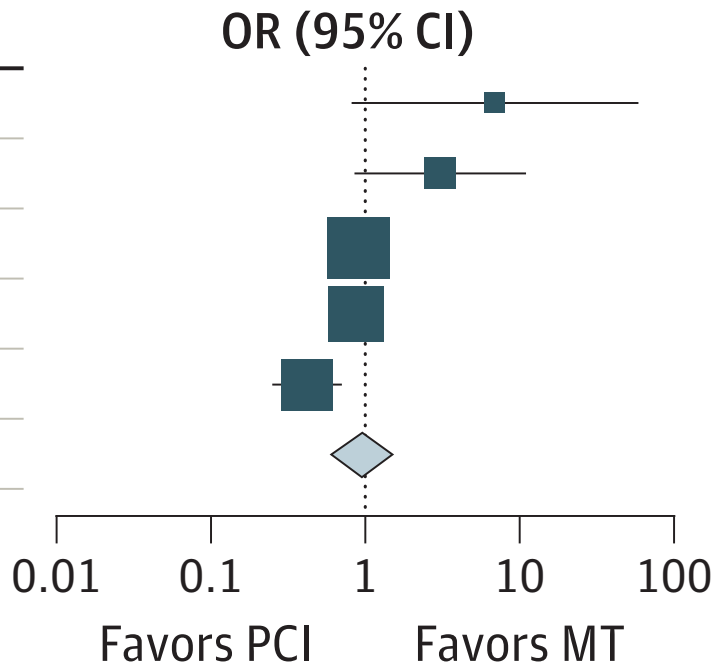
Maron et al. NEJM 2020



DO WE KNOW THAT PCI IMPROVES SYMPTOMS?

No definitive data on anginal relief

Source	OR (95% CI)	*P* Value
Hambrecht[15]	6.82 (0.79-58.85)	.08
MASS II[13]	3.06 (0.83-11.29)	.09
COURAGE[17]	0.91 (0.74-1.10)	.33
BARI 2D[14]	0.87 (0.59-1.28)	.47
FAME 2[16]	0.42 (0.25-0.72)	<.001
Overall	0.90 (0.57-1.44)	.67



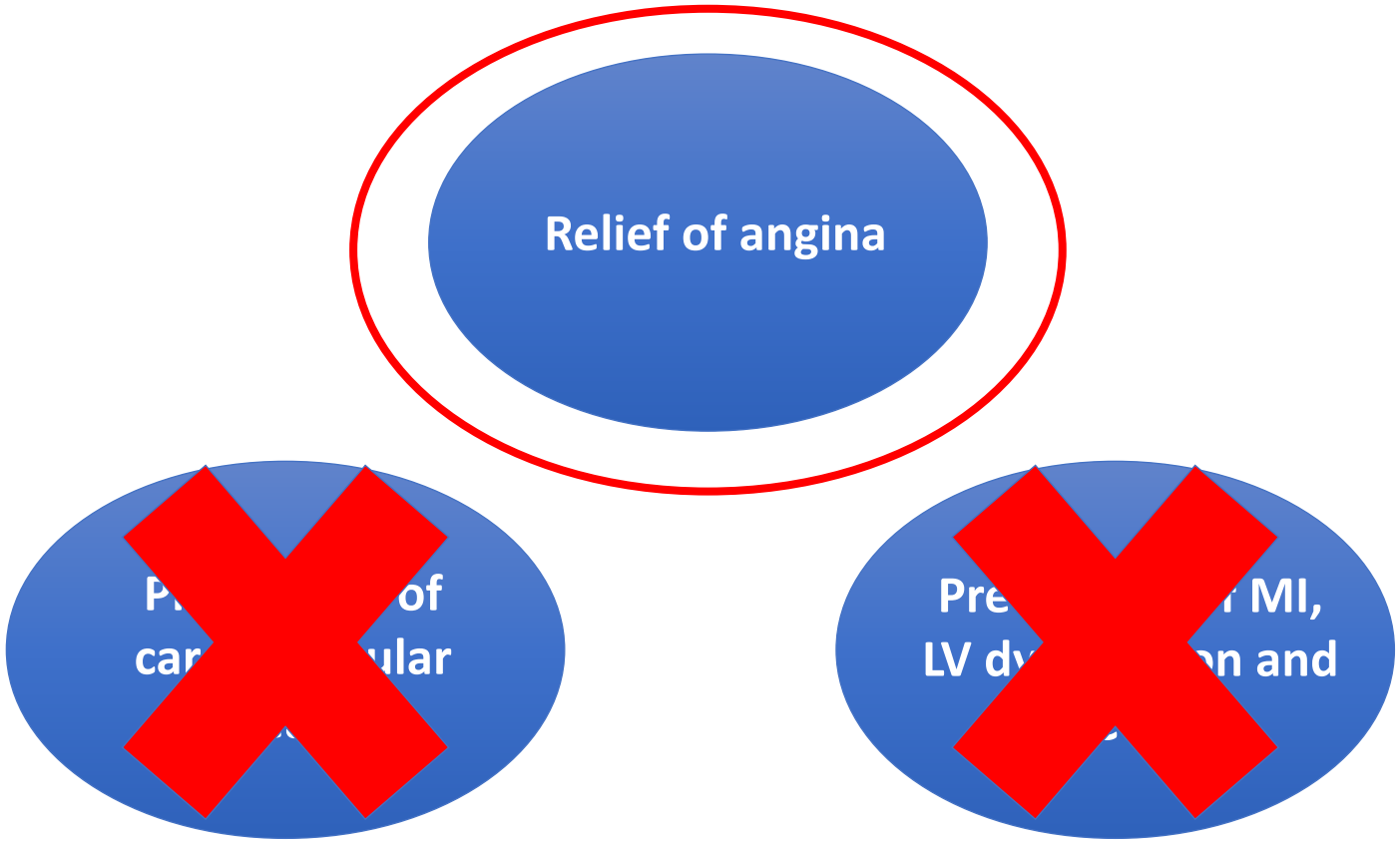
Stergiopoulos et al JAMA Int Med 2014;174(2):232-240

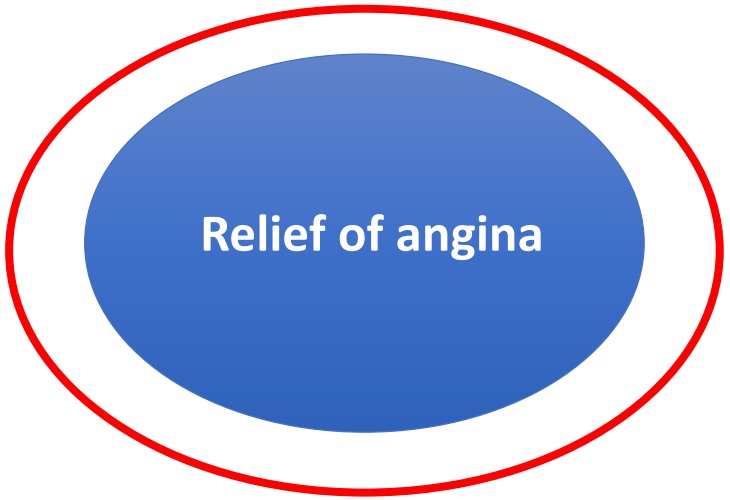
Use of revascularization for CCD

- Due to the early CABG trials, revascularization expanded down the spectrum of risk
- PCI for asymptomatic or minimally symptomatic CCD was common practice—nearly half of all elective PCIs in 2010
- COURAGE and ISCHEMIA challenged this practice, demonstrating that revascularization for CCD did not reduce ischemic events but did reduce angina better than OMT

Chan et al. JAMA 2011

Treatment goals in CCD



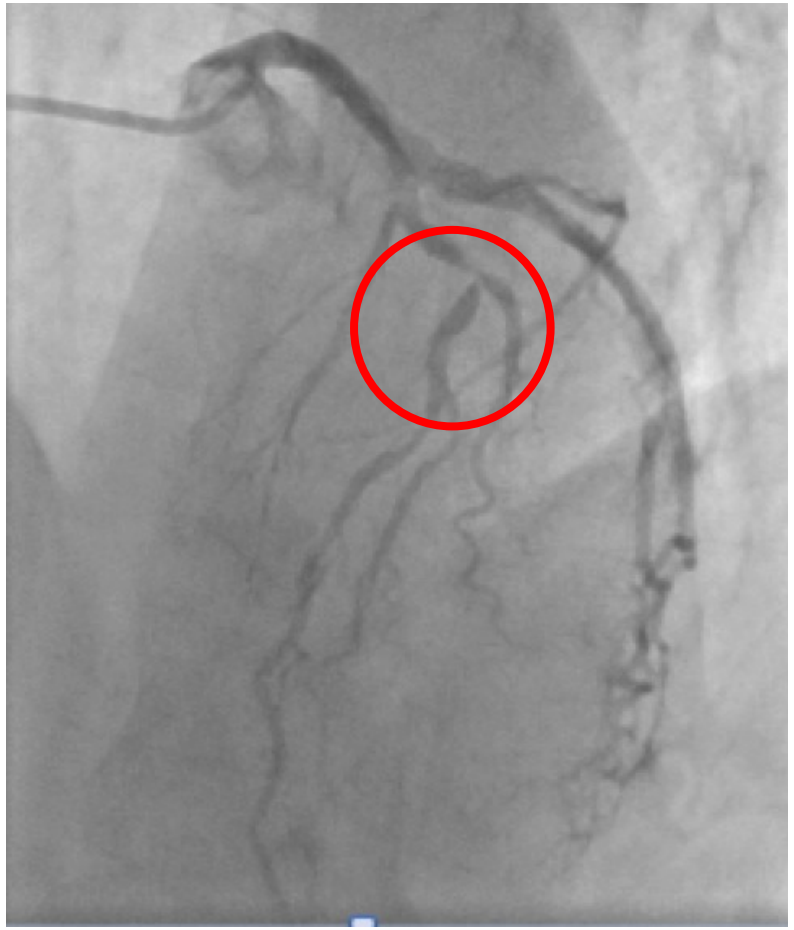


CAN WE PREDICT WHO WILL BENEFIT MOST FROM PCI?

Does ischemic assessment help us?

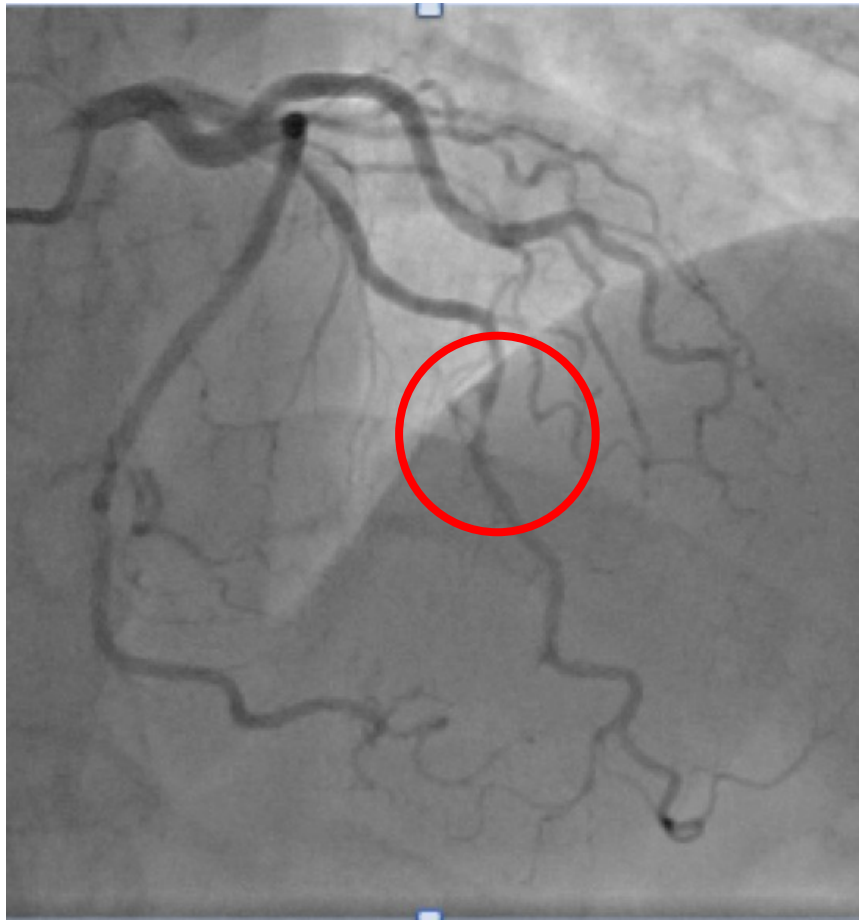
1

iFR 0.43
FFR 0.51

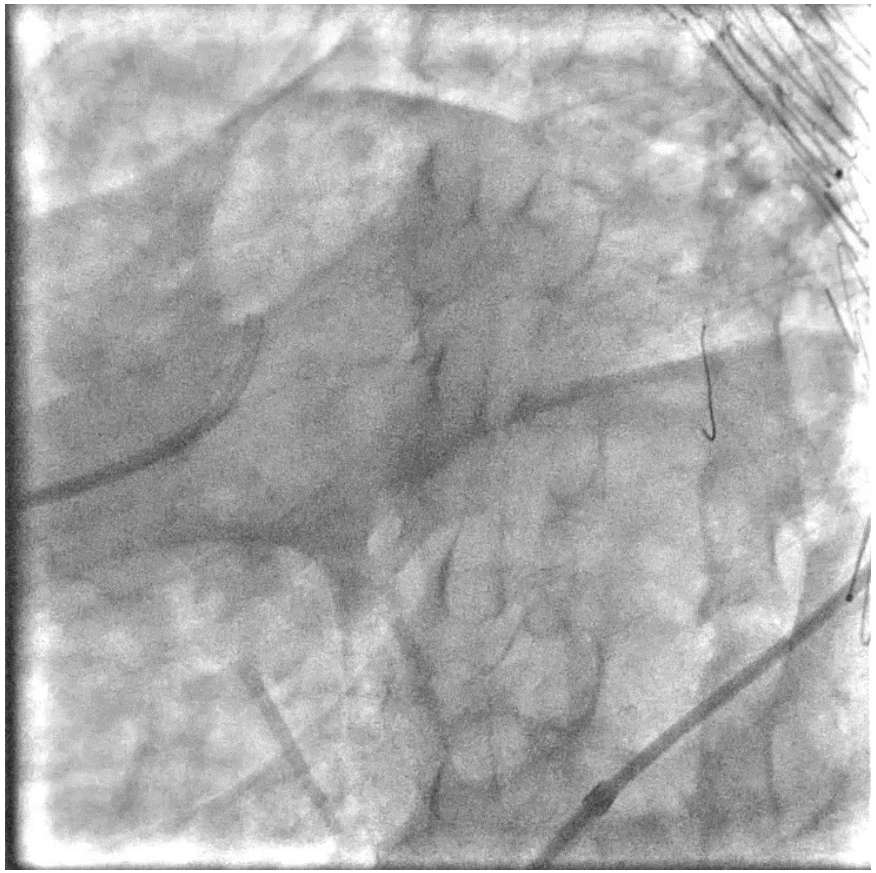


2

iFR 0.92
FFR 0.76

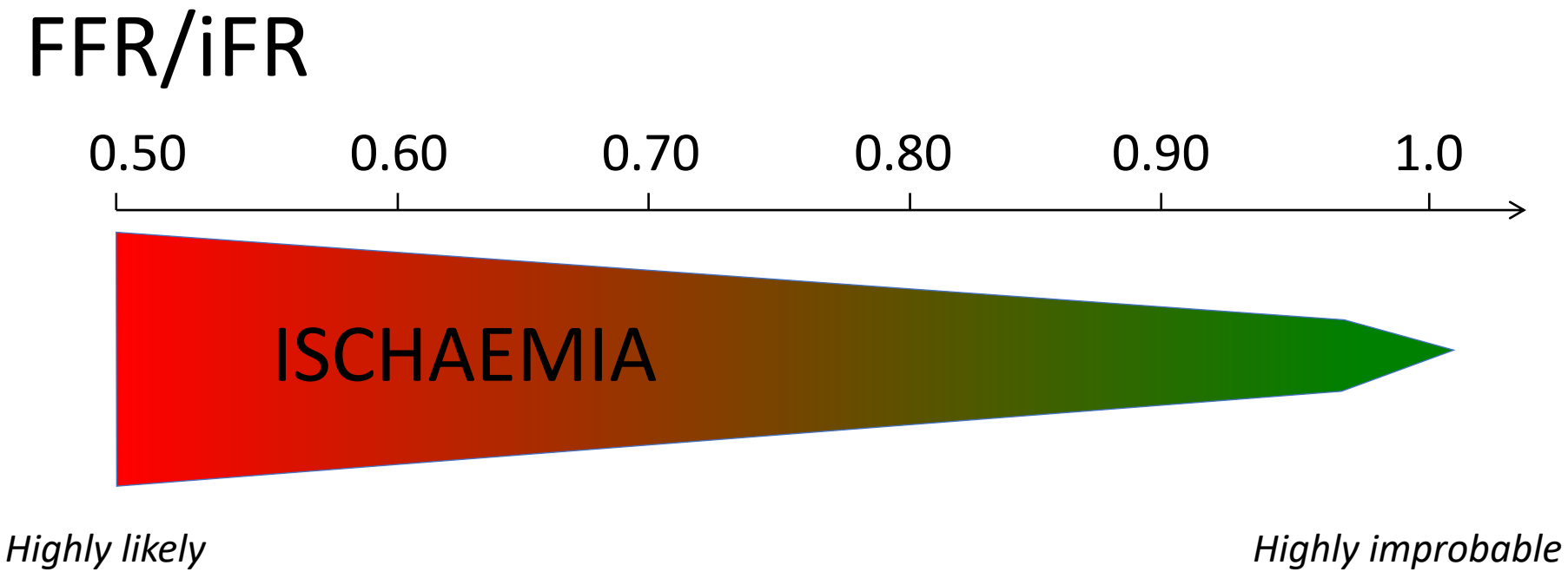


FFR: LCx



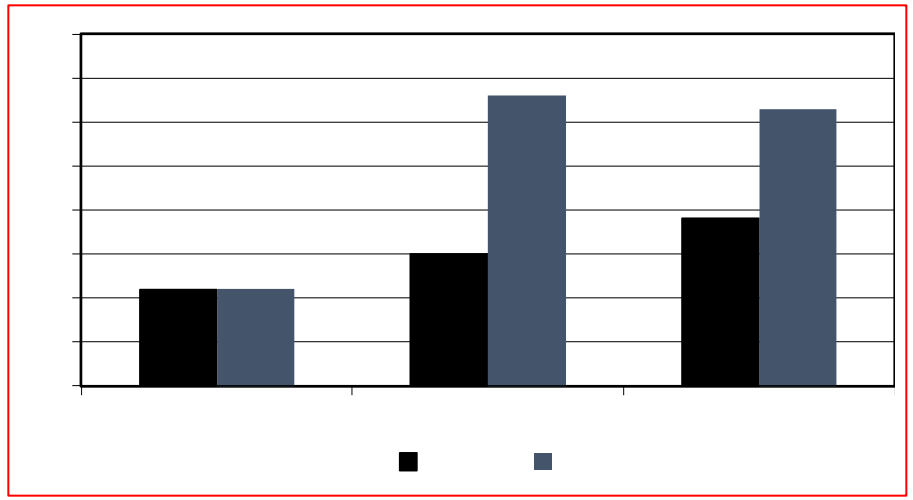
Resting Pd/Pa = 0.88
Adenosine 200 mcg IC
FFR = 0.87

Probability of Ischaemia

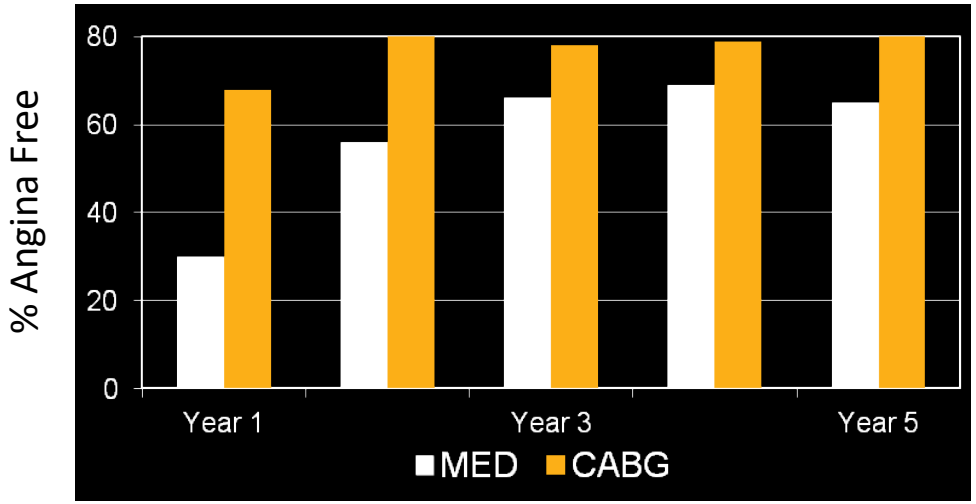


Angina relief with revascularization

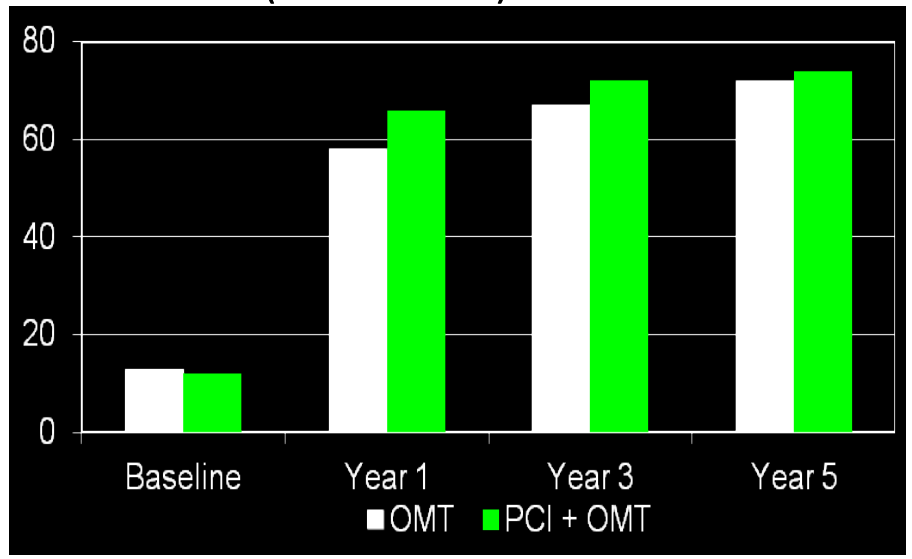
CASS (1975-79): CABG vs. no CABG



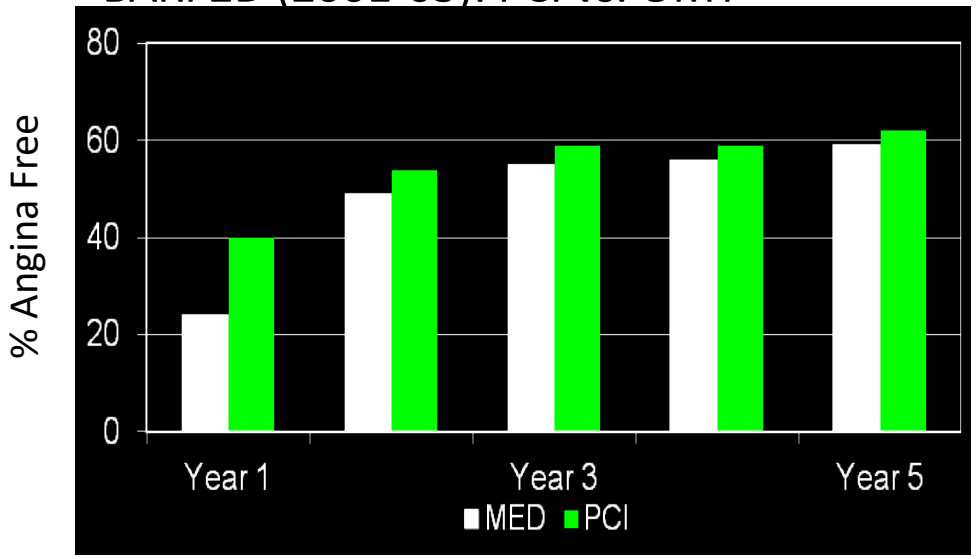
BARI 2D (2001-05): CABG vs. OMT



COURAGE (1999-2004): PCI vs. OMT



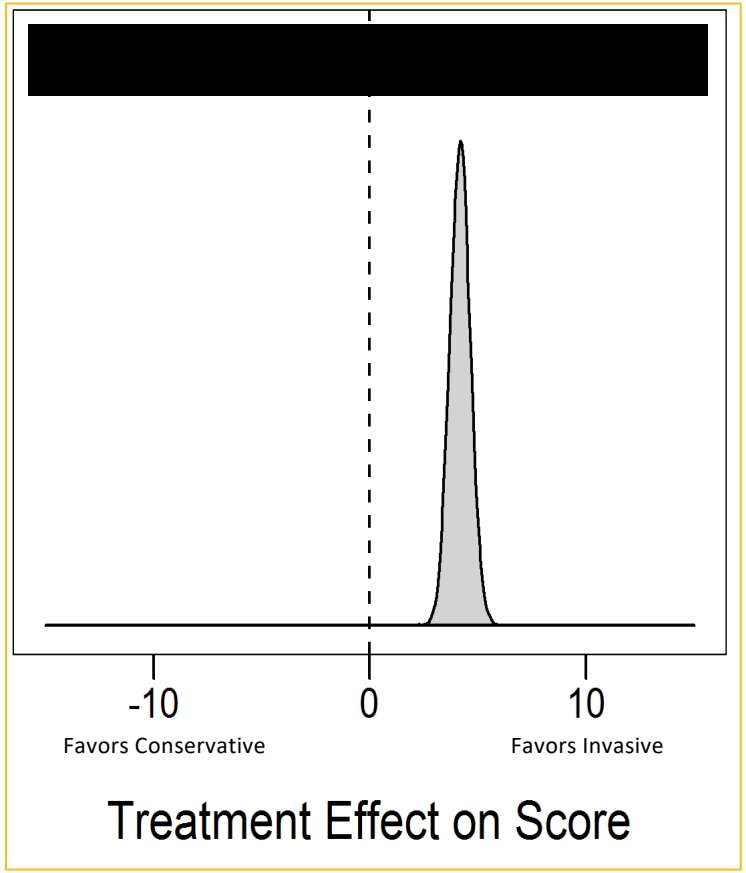
BARI 2D (2001-05): PCI vs. OMT



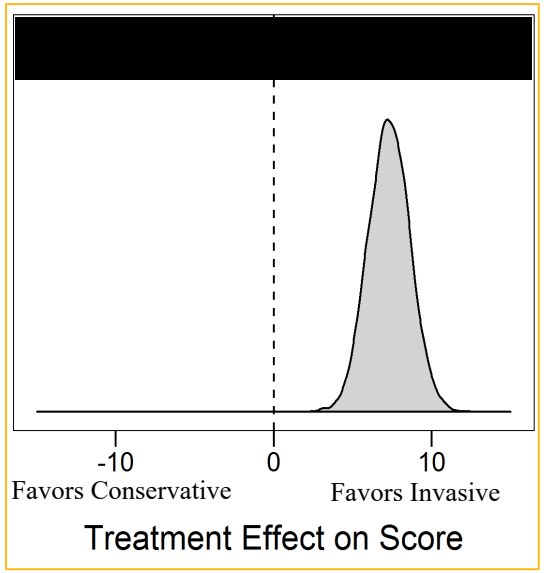
Rogers et al. Circ 1990; Boden WE et al. NEJM 2007; Dagenais et al. Circ 2011

Angina relief with revascularization: ISCHEMIA

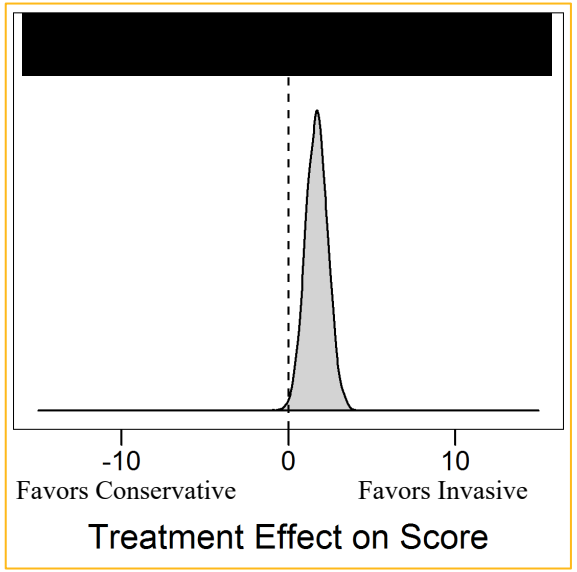
All patients



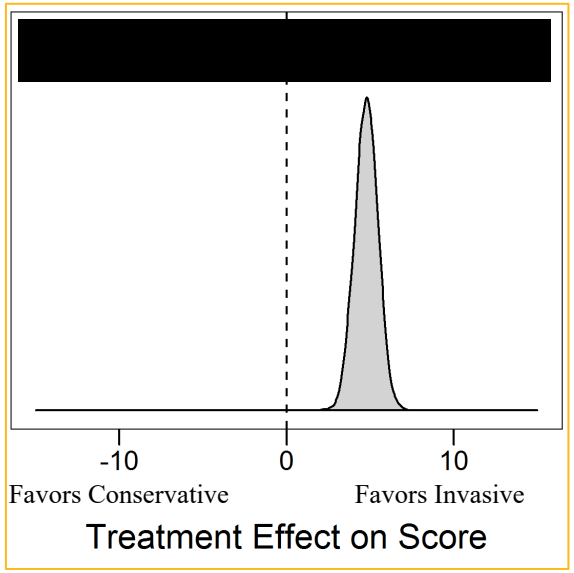
Daily/weekly angina (n=936)



Monthly angina (n=2043)



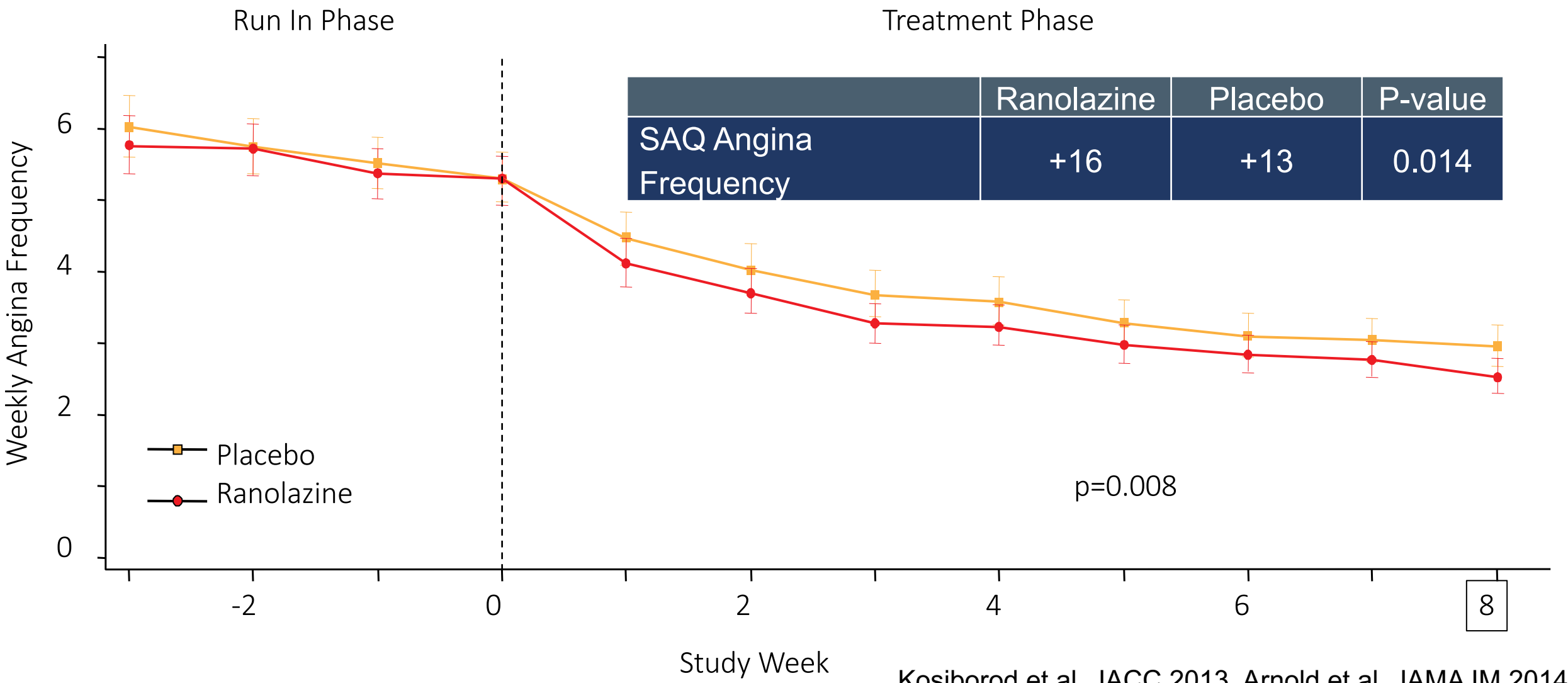
No angina (n=1635)



Spertus et al. NEJM 2020

927 patients with CCD and diabetes randomized to ranolazine vs. placebo

Angina relief with medications: TERISA



	Ranolazine	Placebo	P-value
SAQ Angina Frequency	+16	+13	0.014

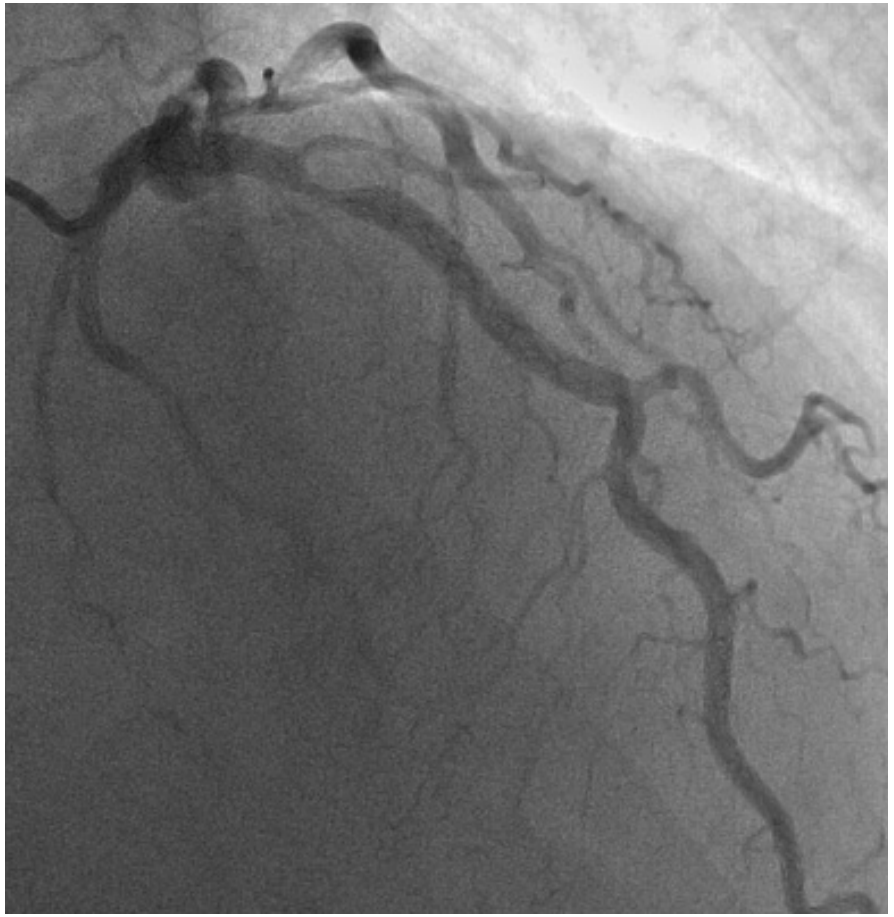
Kosiborod et al. JACC 2013. Arnold et al. JAMA IM 2014

Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA)

Rasha Al-Lamee, MA (Oxon) MB BS MRCP
Imperial College London

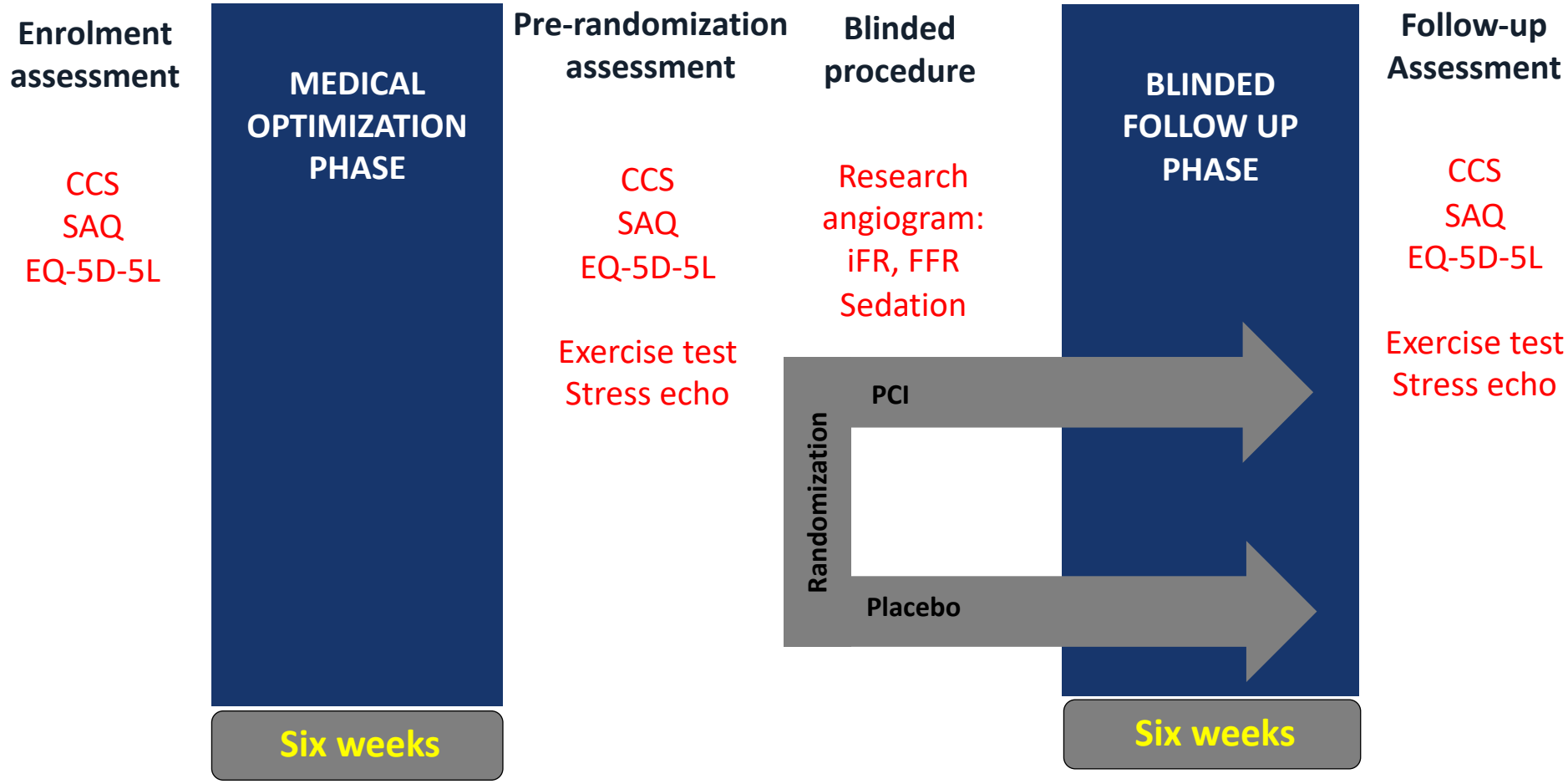
Al-Lamee et al. Lancet 2018. Al-Lamee et al. Circ 2018

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

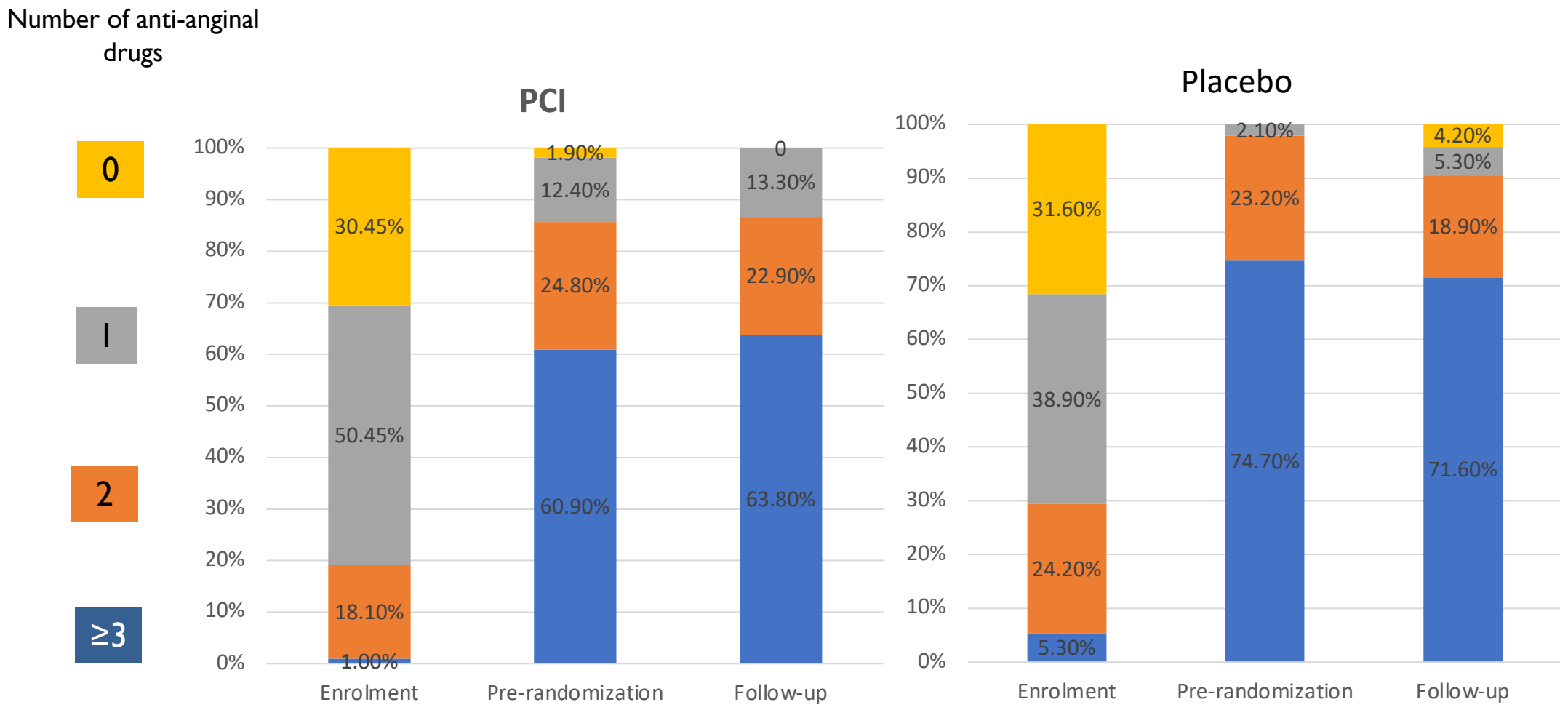
Baseline demographics

	PCI n = 105	Placebo n = 95
Age (yrs)	65.9 (SD 9.5)	66.1 (SD 8.4)
Male	74 (70%)	72 (76%)
Type II diabetes	15 (14%)	21 (22%)
Hypertension	72 (69%)	66 (69%)
Hyperlipidaemia	81 (77%)	62 (65%)
Current smoker	11 (10%)	15 (16%)
Previous MI	5 (5%)	7 (7%)
Previous PCI	10 (10%)	15 (16%)

Baseline demographics

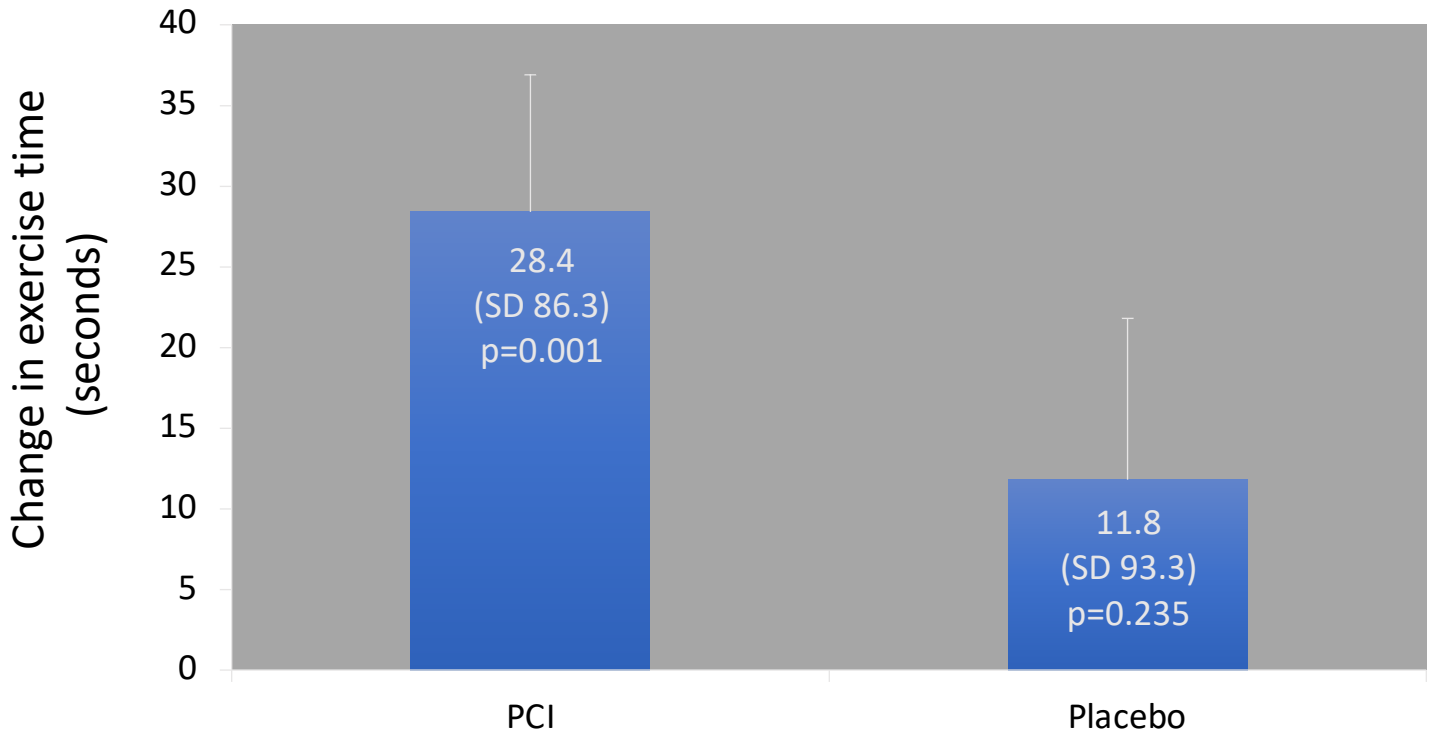
	PCI n = 105	Placebo n = 95
LV systolic function		
Normal	98 (93%)	85 (89%)
Mild	3 (3%)	7 (7%)
Moderate	4 (4%)	3 (3%)
CCS Class		
I	2 (2%)	3 (3%)
II	64 (61%)	54 (57%)
III	39 (37%)	38 (40%)
Angina duration (mo)	9.5 (SD 15.7)	8.4 (SD 7.5)

Medical therapy optimization



Primary endpoint result

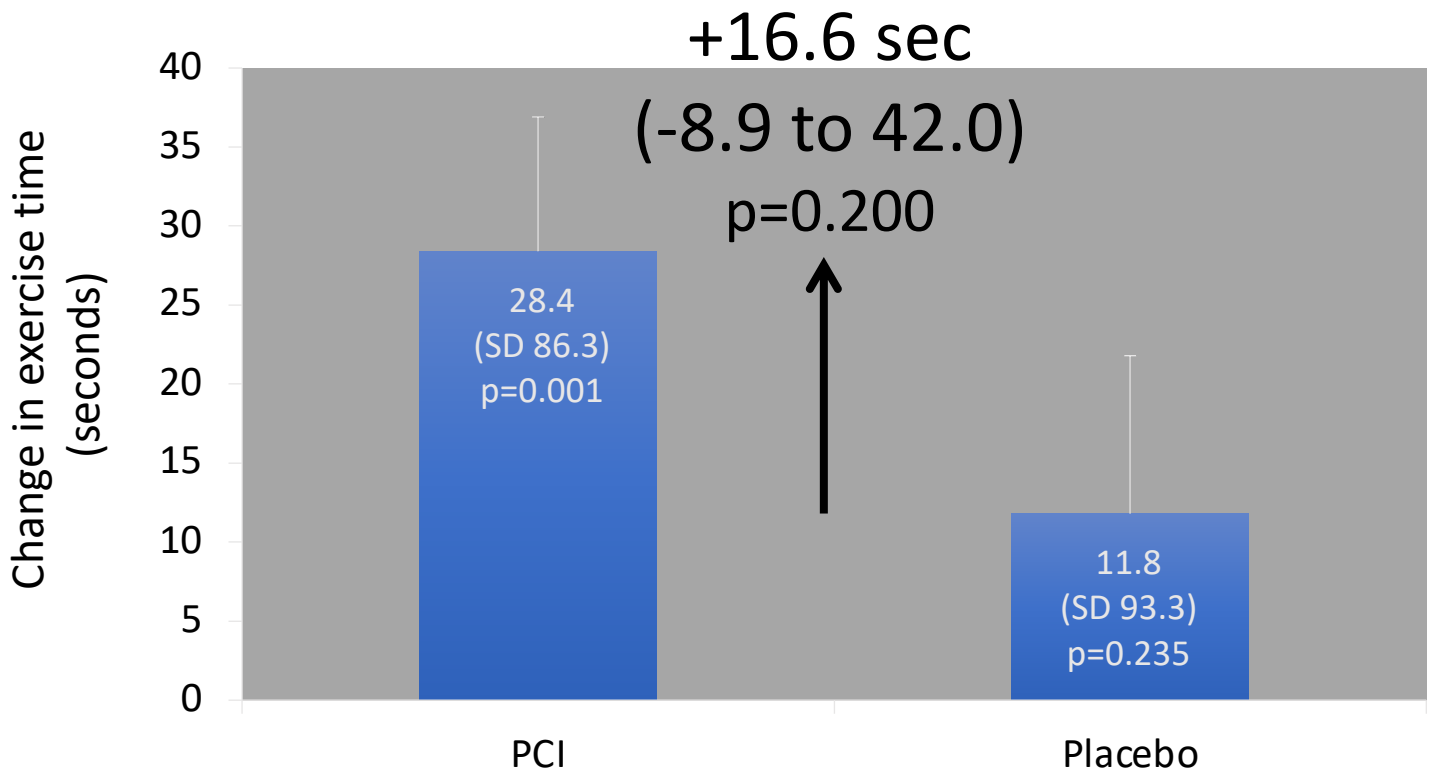
Change in total exercise time



Error bars are standard errors of the mean

Primary endpoint result

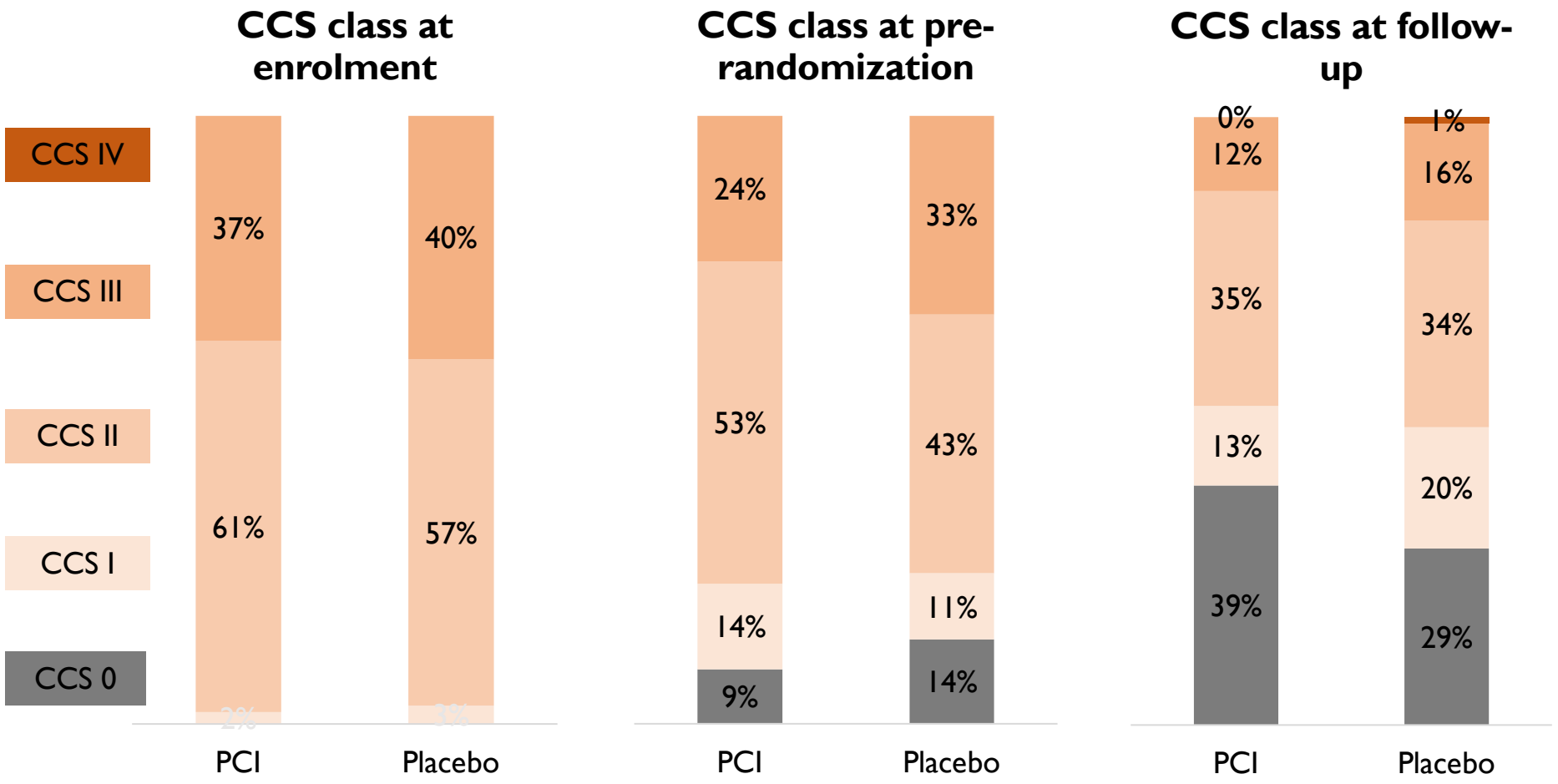
Change in total exercise time



Error bars are standard errors of the mean

Secondary endpoint results

CCS class improved in both groups



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

Differences are Δ PCI minus Δ placebo

Adverse clinical events

Adverse clinical event	PCI n = 105	Placebo n = 95
All cause death	0	0
Myocardial infarction	0	0
Cerebrovascular event	0	0
Unplanned revascularization	0	5

Angina relief with revascularization: ORBITA

200 UK patients with 1-vessel CCD randomized to PCI vs. sham procedure

6-week Follow-up	PCI	Sham	P-value
Exercise time	+28 seconds	+12 seconds	0.20
SAQ angina frequency	+14 points	+10 points	0.26
Freedom from angina	50%	32%	0.006

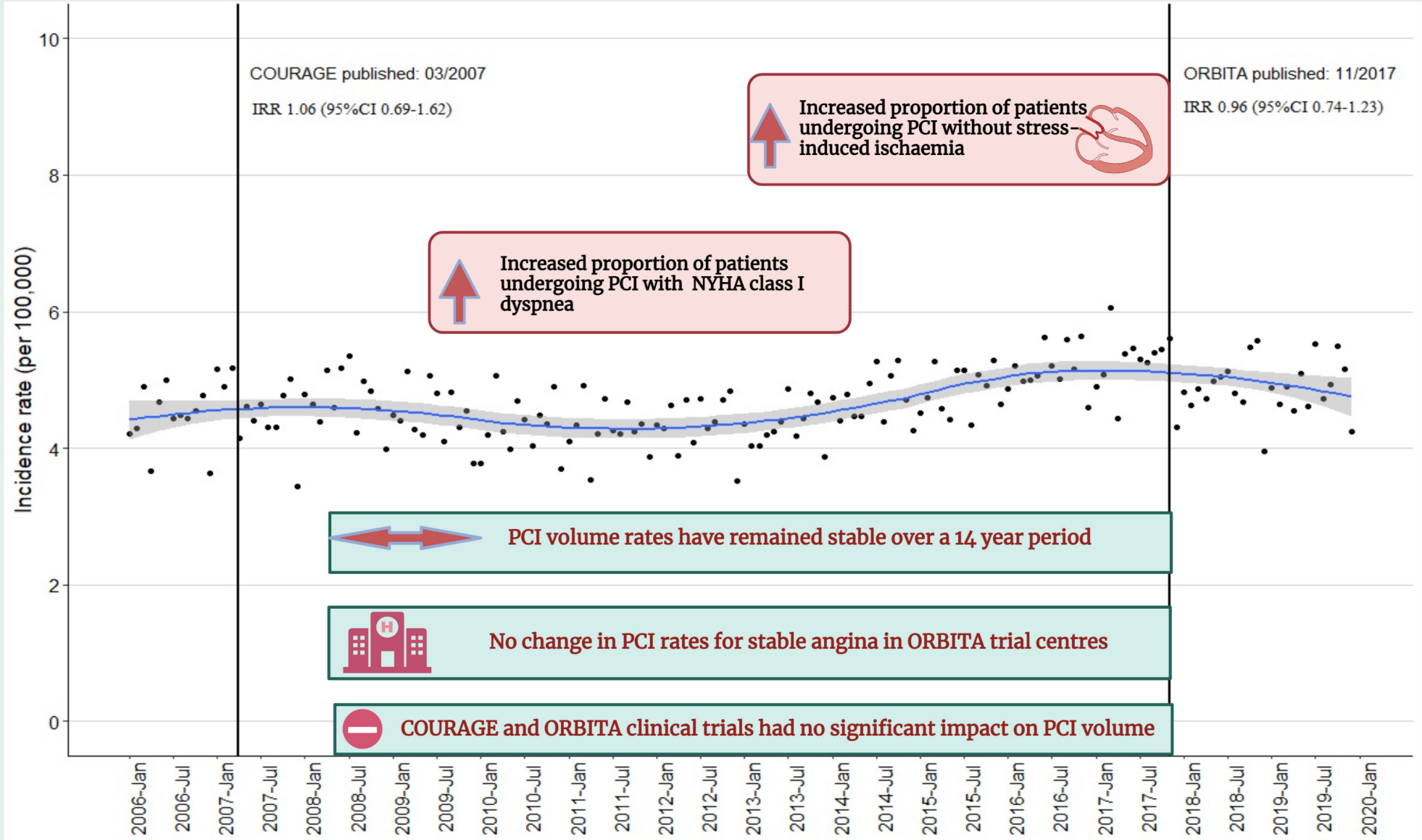
Al-Lamee et al. Lancet 2018. Al-Lamee et al. Circ 2018

Conclusions: ORBITA

- 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
- In this single vessel, angiographically guided trial there was no difference in exercise time increment between PCI and placebo

Trends in Elective PCI volume across England and Wales

430,248 PCI procedures were undertaken for stable angina between 2006 to 2019



The NEW ENGLAND JOURNAL of MEDICINE

A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina

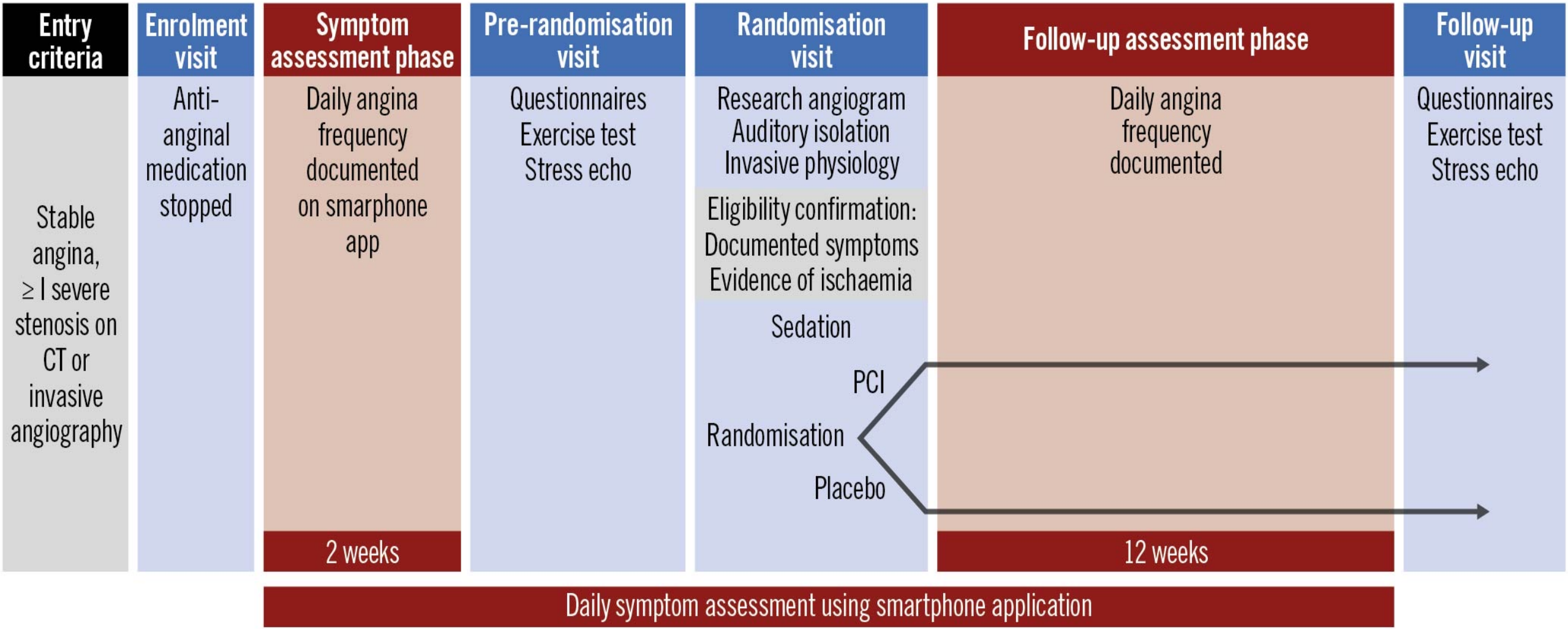
C.A. Rajkumar, M.J. Foley, F. Ahmed-Jushuf, A.N. Nowbar, F.A. Simader, J.R. Davies, P.D. O'Kane, P. Haworth, H. Routledge, T. Kotecha, R. Gamma, G. Clesham, R. Williams, J. Din, S.S. Nijjer, N. Curzen, N. Ruparelia, M. Sinha, J.N. Dungu, S. Ganesananthan, R. Khamis, L. Mughal, T. Kinnaird, R. Petraco, J.C. Spratt, S. Sen, J. Sehmi, D.J. Collier, A. Sohaib, T.R. Keeble, G.D. Cole, J.P. Howard, D.P. Francis, M.J. Shun-Shin, and R.K. Al-Lamee, for the **ORBITA-2** Investigators*

November 11, 2023

Feature	ORBITA	ORBITA-2	Rationale
Coronary disease	Single-vessel	Single- and multivessel	More representative of patients referred for clinical PCI, only half of whom have single-vessel disease[22]
Enrolment	Only after invasive angiography	After either CT or invasive angiography	Representative of modern patient pathways
Requirement for symptoms	Originally referred for angina. Antianginals then given to optimise microvascular state without affecting coronary lesion. Not required to have ongoing symptoms in the days before randomisation.	Inclusion of a symptom assessment phase. Participants must have one or more documented angina episodes in 2-week symptom assessment phase	Maximise chance of detecting relief of angina by requiring documented angina in a prespecified narrow window of time after enrolment
Requirement for ischaemia evidence	As per clinical guidelines and FAME 2[12], only required for lesions of moderate anatomical severity.	Regardless of anatomical severity, required to have one or more tests suggestive of ischaemia, including FFR, iFR or any non-research, non-invasive tests	In ORBITA, 94% or 96%[10] had one or more positive pre-randomisation ischaemia tests. In ORBITA-2 this will be 100%
Primary outcome	Exercise treadmill time[9]	Angina symptom score using an ordinal clinical outcome scale	Relevant to all patients who present with angina; covers the entire 12-week follow-up period rather than a single time-point
Pre-randomisation phase	Established on ~3 antianginals	Stop antianginals. Only eligible for randomisation if one or more episodes of angina documented in 2 weeks	PCI being tested as monotherapy rather than as an add-on to antianginals
Duration of follow-up	6 weeks	12 weeks	Even more certain to be long enough to demonstrate effect

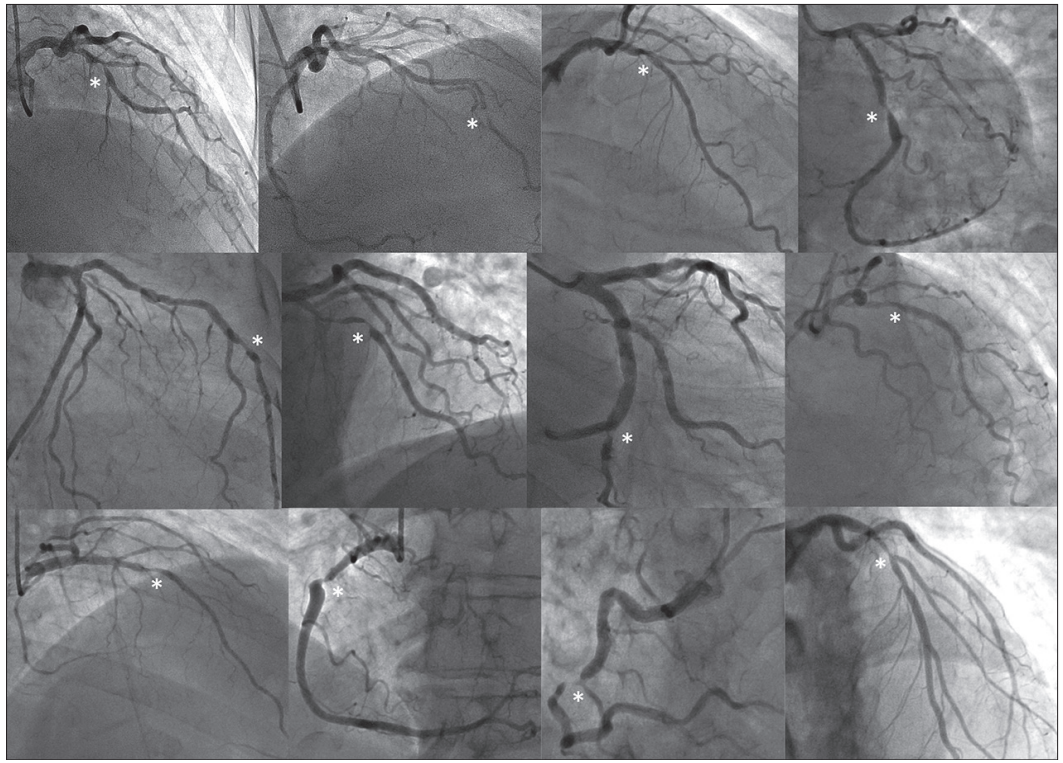
CT: computed tomography; FAME 2: Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; ORBITA: Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; PCI: percutaneous coronary intervention

ORBITA - 2


Entry criteria
Stable angina, ≥ I severe stenosis on CT or invasive angiography
Enrolment visit
Anti-anginal medication stopped
Symptom assessment phase
Daily angina frequency documented on smarphone app
2 weeks
Pre-randomisation visit
Questionnaires
Exercise test
Stress echo
Randomisation visit
Research angiogram
Auditory isolation
Invasive physiology
Eligibility confirmation:
Documented symptoms
Evidence of ischaemia
Sedation
PCI
Randomisation
Placebo
Follow-up assessment phase
Daily angina frequency documented
12 weeks
Follow-up visit
Questionnaires
Exercise test
Stress echo
Daily symptom assessment using smartphone application

ORBITA - 2

1. Angina or angina-equivalent symptoms
2. Anatomical evidence of a severe coronary stenosis in at least 1 vessel, either:
   - Invasive diagnostic coronary angiography indicating ≥70% stenosis
   - Computerised tomography coronary angiography (CTCA) indicating severe stenosis
3. Evidence of ischaemia, on any of the following tests:
   - Dobutamine stress echocardiography
   - Stress perfusion cardiac magnetic resonance imaging (MRI)
   - Nuclear medicine myocardial perfusion scan
   - Invasive pressure wire assessment suggestive of ischaemia, as judged by the interventional cardiologist, at the time of clinical or research coronary angiography



ORBITA - 2

Control arms and Primary Endpoints

- Patients in the placebo arm underwent angiogram and pressure wire studies when auditory isolated, and then were sedated and left on the table.

- Both the post-procedure management team and patients were blinded.

- ORBITA-2 used a unique endpoint of a daily symptom score. Patients had a smartphone app in which they recorded whether and how many episodes of angina they had each day.

  (The ordinal score accounted for the presence of antianginal medications. For instance, one episode of daily angina on no meds scored a 2; but one episode of angina while taking two antianginals scored a 16.)

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	PCI (N=151)	Placebo (N=150)	Overall (N=301)
Age — yr	65±9	64±9	64±9
Male sex — no. (%)	120 (79)	118 (79)	238 (79)
Hypertension — no. (%)	97 (64)	92 (61)	189 (63)
Diabetes — no. (%)			
Non–insulin-dependent	40 (26)	24 (16)	64 (21)
Insulin-dependent	9 (6)	11 (7)	20 (7)
Hyperlipidemia — no. (%)	113 (75)	104 (69)	217 (72)
Smoking status — no. (%)			
Never smoked	65 (43)	50 (33)	115 (38)
Previous smoker	67 (44)	84 (56)	151 (50)
Current smoker	19 (13)	16 (11)	35 (12)
Left ventricular systolic function — no. (%)†			
Normal	144 (95)	146 (97)	290 (96)
Mild impairment	6 (4)	3 (2)	9 (3)
Moderate impairment	1 (1)	1 (1)	2 (1)
CCS class — no. (%)‡			
I	10 (7)	1 (1)	11 (4)
II	87 (58)	87 (58)	174 (58)
III	54 (36)	62 (41)	116 (39)
Median time since diagnosis of angina (IQR) — mo	8 (4–14)	8 (5–14)	8 (5–14)

Table 2. Procedural Characteristics.

Characteristic	PCI (N=151)	Placebo (N=150)	Overall (N=301)
No. of vessels with disease — no. (%)*			
1 vessel	122 (81)	120 (80)	242 (80)
2 vessels	25 (17)	27 (18)	52 (17)
3 vessels	4 (3)	3 (2)	7 (2)
Vessels leading to patient randomization†			
No. of vessels	193	190	383
Left anterior descending coronary artery — no. (%)	108 (56)	103 (54)	211 (55)
Circumflex coronary artery — no. (%)	16 (8)	17 (9)	33 (9)
Right coronary artery — no. (%)	42 (22)	43 (23)	85 (22)
Branch vessels — no. (%)	27 (14)	27 (14)	54 (14)
Serial stenoses — no. (%)	29 (19)	20 (13)	49 (16)
Percent diameter stenosis‡			
Mean	61±18	62±17	61±18
Median (IQR)	60 (48–74)	63 (50–74)	61 (49–74)
Area of stenosis‡			
Percentage	80±15	82±15	81±15
Median (IQR) — %	83 (73–92)	85 (75–93)	84 (74–92)
Fractional flow reserve			
Mean	0.60±0.16	0.62±0.16	0.61±0.16
Median (IQR)	0.61 (0.47–0.74)	0.65 (0.51–0.75)	0.63 (0.49–0.75)
No. of vessels assessed — no./total no. of target vessels	178/193	171/190	349/383
Instantaneous free-wave ratio§			
Mean	0.68±0.22	0.71±0.23	0.70±0.22
Median (IQR)	0.76 (0.50–0.86)	0.81 (0.58–0.89)	0.78 (0.55–0.87)
No. of vessels assessed — no./total no. of target vessels	178/193	174/190	352/383
Interventions			
Median no. of stents implanted (IQR)	2 (1–2)	—	—
Median total length of stent implanted (IQR) — mm	42 (23–64)	—	—
Median diameter of stent implanted (IQR) — mm	3.0 (2.5–3.5)	—	—
No. of stents in which postdilation was performed — no./total no. (%)	242/284 (85)	—	—
Intravascular imaging performed — no. (%)	104 (69)	—	—
Type of drug-eluting stent¶			
Everolimus-eluting — no. (%)	171 (60)	—	—
Zotarolimus-eluting — no. (%)	83 (29)	—	—
Other drug-eluting stent — no. (%)	29 (10)	—	—

ORBITA - 2

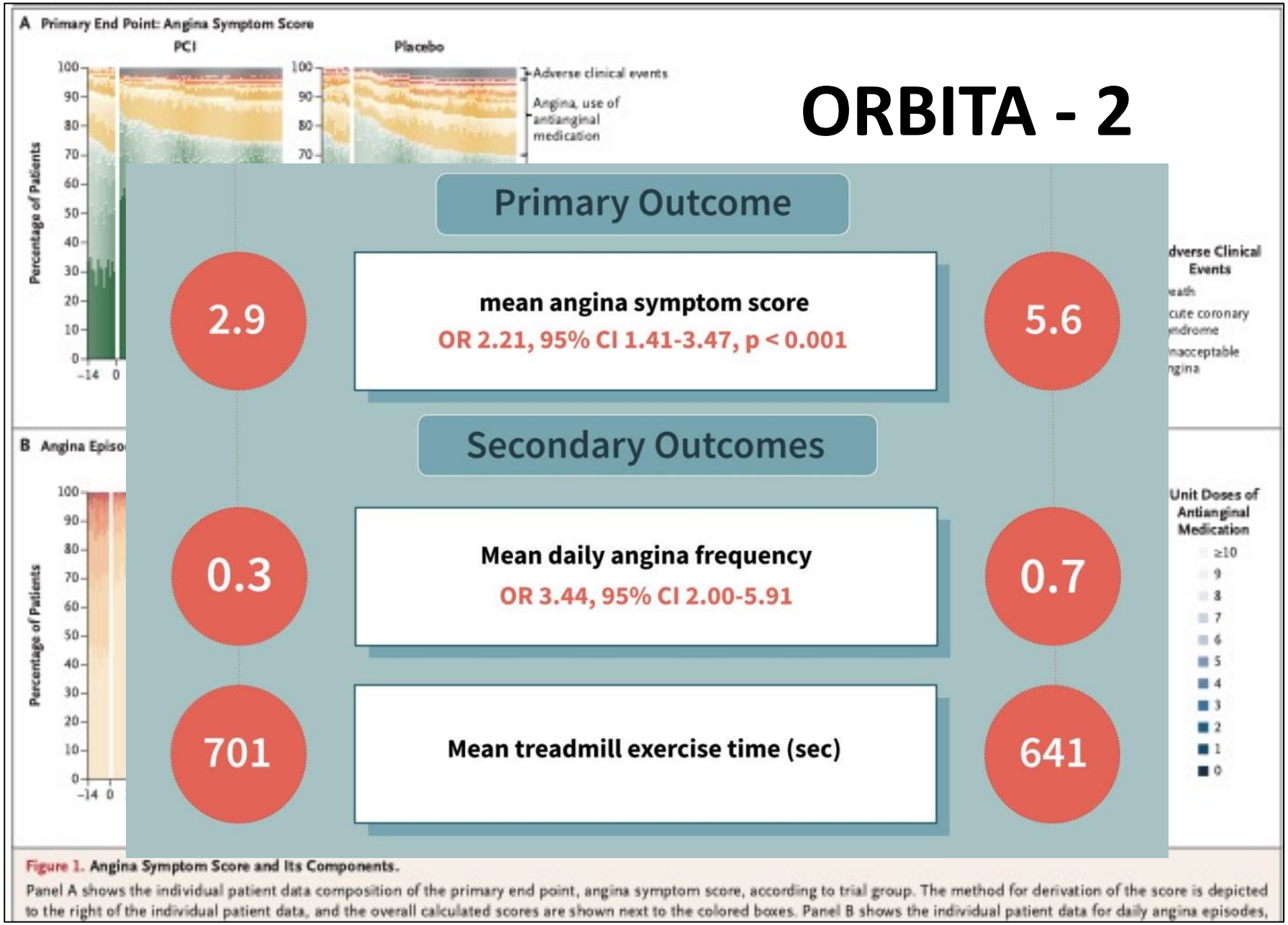
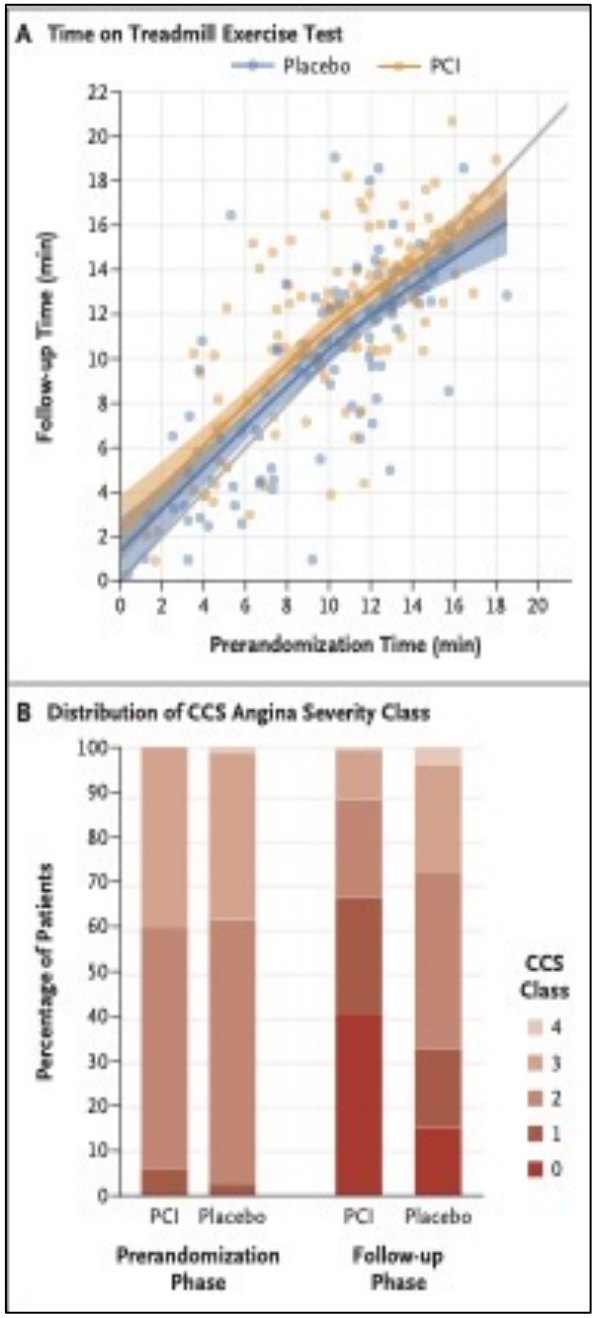


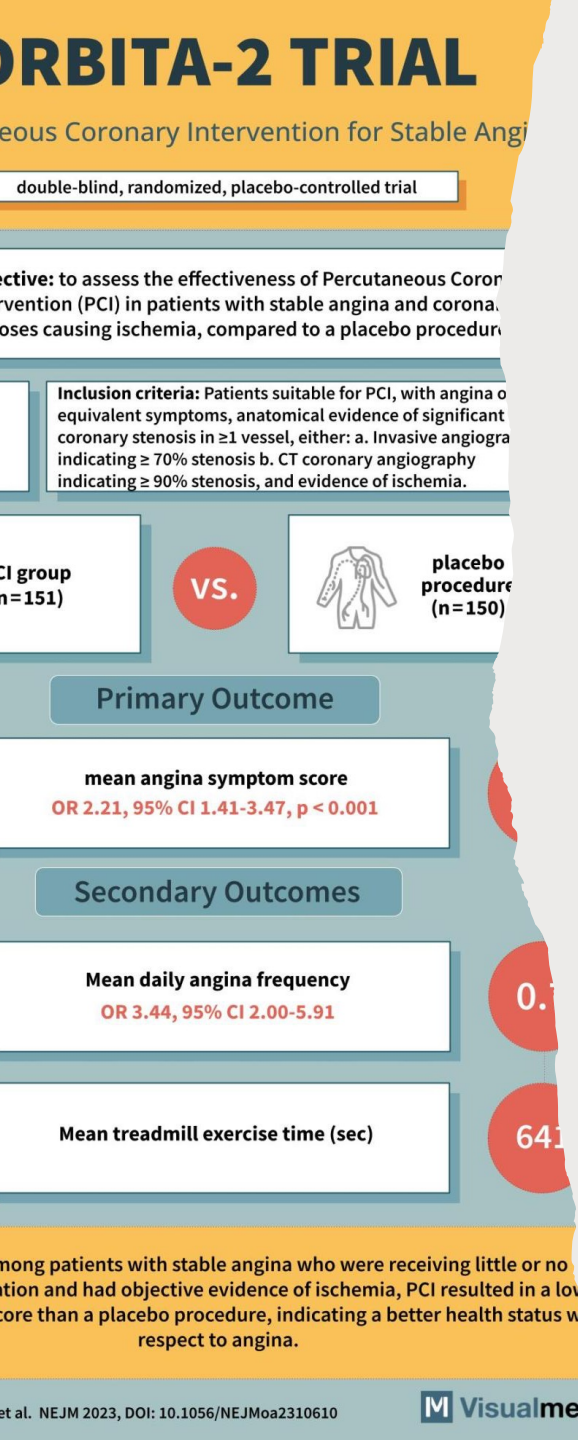
Figure 1. Angina Symptom Score and Its Components.

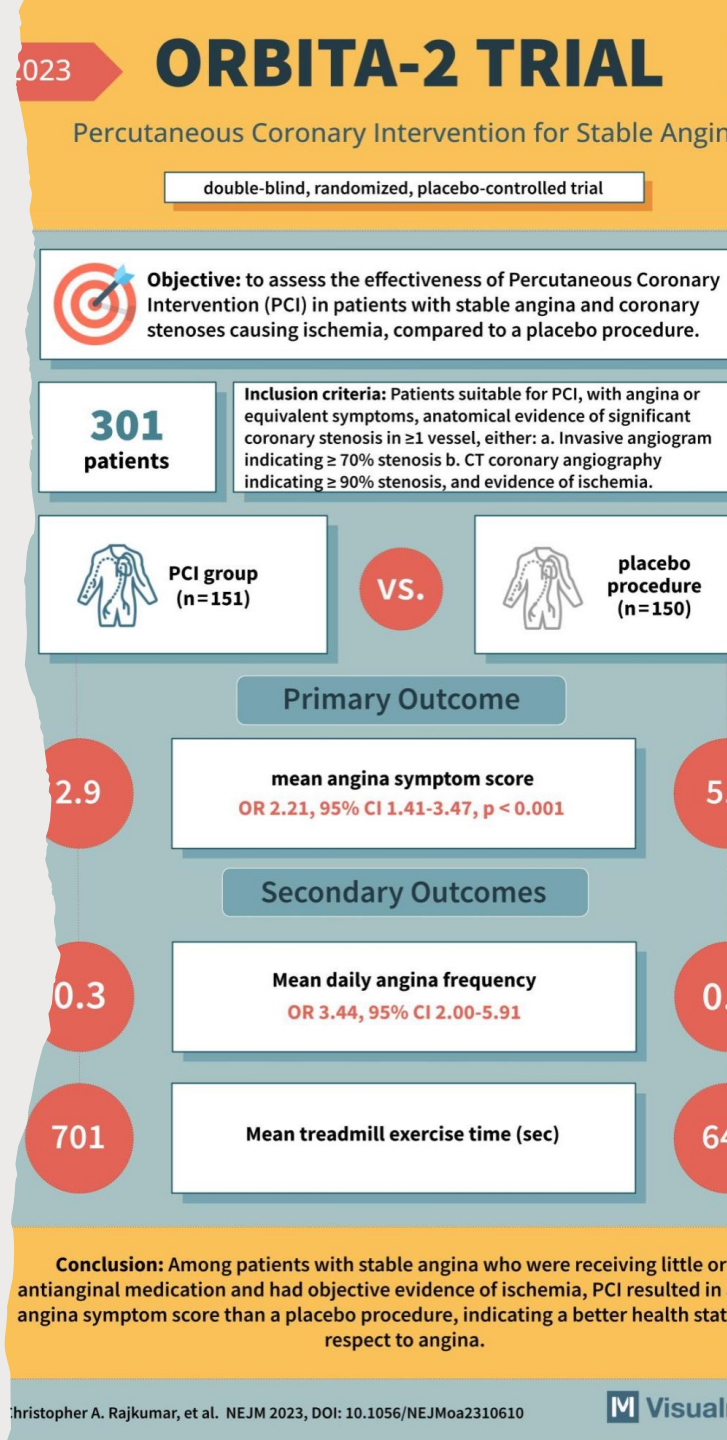
Panel A shows the individual patient data composition of the primary end point, angina symptom score, according to trial group. The method for derivation of the score is depicted to the right of the individual patient data, and the overall calculated scores are shown next to the colored boxes. Panel B shows the individual patient data for daily angina episodes,



Conclusion

- Among **patients with stable angina who were receiving little or no antiangina medication and had objective evidence of ischemia, PCI resulted in a lower angina symptom score** than a placebo procedure, indicating a better health status with respect to angina over 12 weeks





The ORBITA-1 and ORBITA-2 Trials

1. ORBITA allowed only patients with single-vessel disease; ORBITA-2 allowed multivessel disease, but 80% of enrolled patients had single-vessel disease.

2. The first ORBITA trial required maximal medical therapy and then tested PCI as an add-on procedure. ORBITA-2 did the opposite.

3. ORBITA-2 used a unique endpoint of a daily symptom score. Patients had a smartphone app in which they recorded whether and how many episodes of angina they had each day. The ordinal score accounted for the presence of antianginal medications.

The ORBITA-1 and ORBITA-2 Trials

4.The ORBITA-2 results were clearly positive for PCI. Compared with the placebo procedure, PCI improved the angina symptom score.

5.Treadmill exercise time increased by 59 seconds in the PCI arm vs placebo. This was statistically significant and equivalent to the increase seen with a placebo-controlled trial of an anginal medication.

6.There were no differences in clinical outcomes nor safety issues.

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease

Medical Therapy For Angina in patients with CCD

Beta blocker, CCB or long-acting nitrate is recommended for angina relief. (Class 1)

↓

If symptoms continue, add a second antianginal agent from a different class (beta blockers, CCB, long-acting nitrates). (Class 1)

↓

Ranolazine is recommended in patients who remain symptomatic. (Class 1)

Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief. (Class 1)

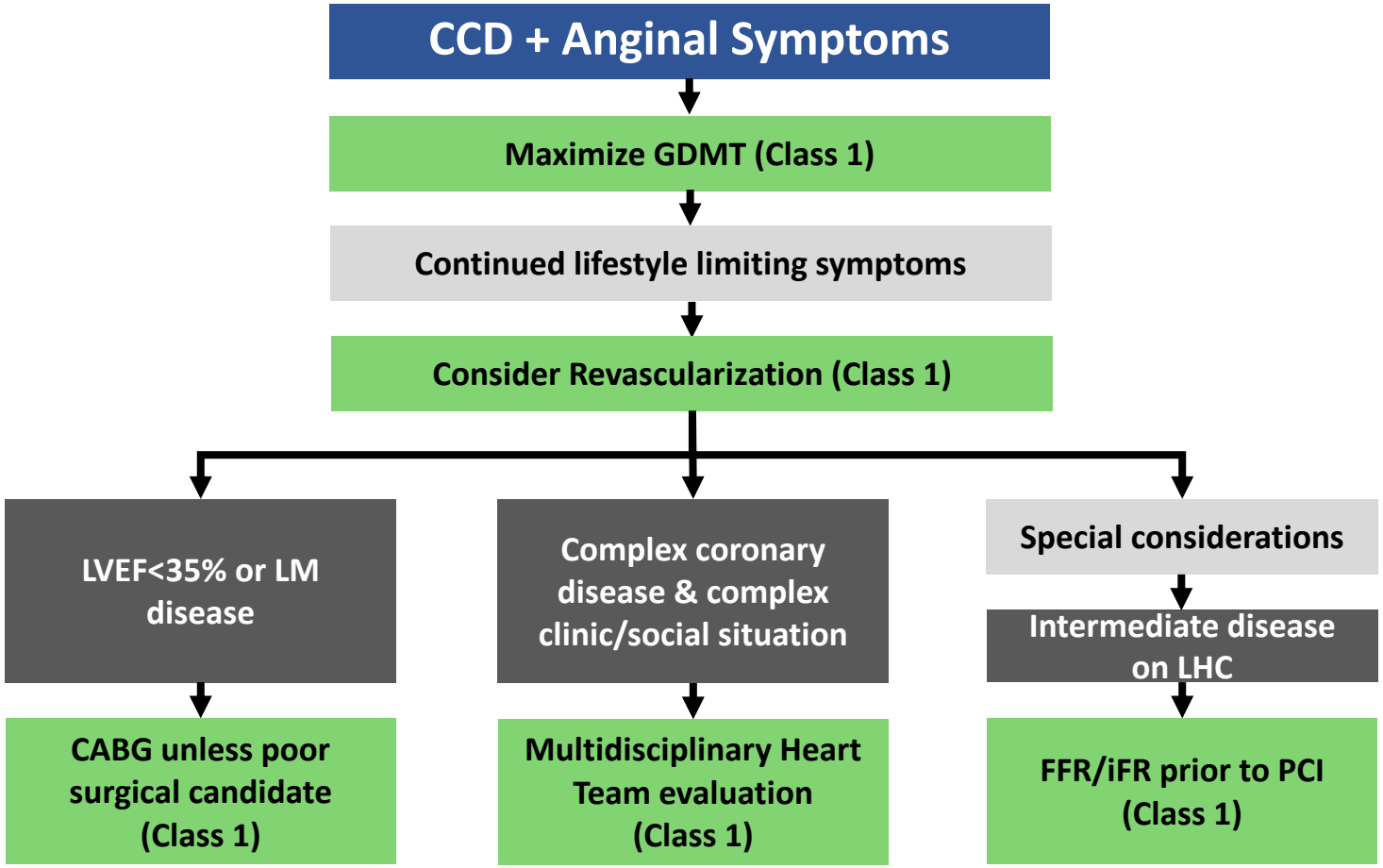
Adding ivabradine to standard anti-anginal therapy is potentially harmful in those with normal LV function. (Class 3: Harm)

Abbreviations: CCB indicates calcium channel blocker; CCD, chronic coronary disease; and LV, left ventricular.

American Heart Association.

Virani, S. S., et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease. *Circulation*.

Revascularization in CCD



Principles of CCD Management in patients with Stable Angina

- Relief of symptoms
- Prevention of non-fatal events
- Improve long-term survival

Abbreviations: CABG indicates coronary artery bypass graft; CCD, chronic coronary disease; FFR, fractional flow reserve; GDMT, guideline direction medical therapy; iFR, instantaneous wave-free ratio; LHC, left heart catheterization; LM, left main; LVEF, left ventricular ejection fraction; and PCI, percutaneous coronary intervention.

Virani, S. S., et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease. *Circulation*.

SCAI
Society for Cardiovascular Angiography & Interventions

NOV 11TH 2023

ORBITA-2 Confirms Benefit of Percutaneous Coronary Intervention in Patients with Chronic Coronary Artery Disease

The ORBITA-2 trial findings underscore the importance of shared medical decision-making between physicians and patients. SCAI encourages the development of individualized treatment plans to ensure the best patient-centered care possible.