ORBITA trial

"Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina"

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tct2017

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- This trial suggest that in patients with stable angina and significant single vessel disease (PCI) may not increase exercise time, compared to placebo.
- However, PCI significantly reduced ischemia as assessed by FFR, iFR and stress echo.
- This is the first placebo-controlled randomized trial of PCI in this patient population.

Introduction

- Percutaneous coronary intervention (PCI) is commonly utilized for stable angina, with the aim of reducing events (such as myocardial infarction and death) and reducing symptoms.

- The previous COURAGE trial (2007) randomized patients with stable angina to either PCI or medical therapy and found no difference with regard to myocardial infarction and death.

- There was a suggestion that patients who received (unblinded) PCI were more likely to be free of angina with a higher quality of life at 6 months, although this benefit was no longer statistically significant 36 months.

- Meta-analyses including COURAGE and other similar trials have also failed to demonstrate a clear benefit to PCI in patients with stable angina.

- As a result of these findings, current consensus *guidelines* recommend medical therapy as first-line for treatment of stable angina, but continue to support the use of PCI in patients with obstructive coronary disease who remain symptomatic despite medical therapy.

2014 ESC/EACTS Guidelines on myocardial revascularization

Indications for revascularization in patients with stable angina or silent ischaemia

Extent of CAD (anatomical and/or functional)		Class[a]	Level[b]
For prognosis	Left main disease with stenosis >50%[c]	I	A
	Any proximal LAD stenosis >50%[c]	I	A
	Two-vessel or three-vessel disease with stenosis >50%[c] with impaired LV function (LVEF<40%)[d]	I	A
	Large area of ischaemia (>10% LV)	I	B
	Single remaining patent coronary artery with stenosis >50%[e]	I	C
For symptoms	Any coronary stenosis >50%[c] in the presence of limiting angina or angina equivalent, unresponsive to medical therapy	I	A

ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/ STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease

TABLE A Revascularization to Improve Survival Compared With Medical Therapy

3-vessel disease with or without proximal LAD artery disease*		
CABG	I	B
	IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score >22) who are good candidates for CABG.	B
PCI	IIb—Of uncertain benefit	B
2-vessel disease with proximal LAD artery disease*		
CABG	I	B
PCI	IIb—Of uncertain benefit	B
2-vessel disease without proximal LAD artery disease*		
CABG	IIa—With extensive ischemia	B
	IIb—Of uncertain benefit without extensive ischemia	C
PCI	IIb—Of uncertain benefit	B
1-vessel proximal LAD artery disease		
CABG	IIa—With LIMA for long-term benefit	B
PCI	IIb—Of uncertain benefit	B
1-vessel disease without proximal LAD artery involvement		
CABG	III: Harm	B
PCI	III: Harm	B

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TABLE 1.1 One-Vessel Disease

Appropriate Use Score (1-9)

One-Vessel Disease

	Asymptomatic				Ischemic Symptoms			
	Not on AA Therapy or With AA Therapy		Not on AA Therapy		On 1 AA Drug (BB Preferred)		On ≥2 AA Drugs	
Indication	**PCI**	**CABG**	**PCI**	**CABG**	**PCI**	**CABG**	**PCI**	**CABG**
No Proximal LAD or Proximal Left Dominant LCX Involvement								
1. ▪ Low-risk findings on noninvasive testing	R (3)	R (1)	R (3)	R (3)	M (4)	R (3)	A (7)	M (5)
2. ▪ Intermediate- or high-risk findings on noninvasive testing	M (4)	R (3)	M (5)	M (4)	M (6)	M (4)	A (8)	M (6)
3. ▪ No stress test performed or, if performed, results are indeterminate ▪ FFR >0.80*	M (4)	R (3)	M (5)	R (3)	M (6)	M (4)	A (8)	M (6)
Proximal LAD or Proximal Left Dominant LCX Involvement Present								
4. ▪ Low-risk findings on noninvasive testing	M (4)	R (3)	M (4)	M (4)	M (5)	M (5)	A (7)	A (7)
5. ▪ Intermediate- or high-risk findings on noninvasive testing	M (5)	M (5)	M (6)	M (6)	A (7)	A (7)	A (8)	A (8)
6. ▪ No stress test performed or, if performed, results are indeterminate ▪ FFR >0.80	M (5)	M (5)	M (6)	M (6)	M (6)	M (6)	A (8)	A (7)

- The previous trials have not blinded patients to treatment allocation, raising the question of whether symptomatic improvement is mediated by the placebo effect.
- A placebo-controlled randomized trial of PCI in stable angina was needed to test for an effect beyond any placebo element.

Clinical Question

- In patients with stable angina despite medical therapy and single-vessel disease, does PCI improve angina as measured by treadmill exercise time compared to placebo procedure?

Design

- Multicenter
- Double-blinded(neither patients nor their physicians knew which group they were assigned)
- Randomized trial
- N=200
  - Angiography-guided PCI (n=105)
  - Sham PCI (n=95)

  (coronary angiography and iFR/FFR measurement but no stent placement)
- Enrollment: 2013-2017
- Duration of follow-up: 6 weeks
- Primary Outcome: Difference in treadmill exercise time increment (s)

Population
Inclusion Criteria

- Aged 18-85
- Both of:
  - Angina or equivalent symptoms
  - At least one angiographically significant (≥70%) lesion in a single vessel that is appropriate for PCI

Exclusion Criteria

- Angiographic stenosis ≥50% in a non-target vessel
- Acute coronary syndrome
- Previous CABG
- Left main disease
- Contraindication to drug eluting stent
- Chronic total occlusion
- Severe valvular disease
- Severe left ventricular systolic dysfunction
- Moderate or greater pulmonary hypertension
- Life expectancy <2 years
- Inability to provide informed consent

Baseline Characteristics

From all groups.

- Demographics: Age 66 years, male 73%
- Comorbidities: BMI 28.7, smoker 13%, HTN 69%, Dyslipidemia 72%, DM 18%, previous MI 6%, previous PCI 13%
- Cardiac: Normal LV function 92%
- Angina: CCS I 3%, CCS II 59%, CCS III 39%,
- Angina duration: 12.5 months
- Angiographic: LAD culprit 69%, RCA culprit 16%, LCx culprit 10%, QCA area stenosis 84.4%, FFR 0.69, iFR 0.76

Interventions

- Patients randomized 1:1 to PCI or sham PCI
- Patients were approached after diagnostic angiography and enrolled after giving informed consent
- Patients allocated to PCI underwent stenting of all lesions deemed angiographically significant

- In the placebo group, patients were kept sedated for at least 15 minutes on the table and the coronary catheters were withdrawn with no intervention performed
- After enrollment, the study consisted of two consecutive phases
  - Phase 1: 6-week medical optimization phase focused on initiation and uptitration of guideline-directed medical therapy
  - Baseline prerandomization assessment
  - Phase 2: 6-week post-randomization blinded period

- Medical optimization was focused on antianginal therapy, with goal of at *least two antianginal medications* per patient
- All patients underwent cardiopulmonary exercise testing, symptom questionnaires, and dobutamine stress echocardiography before and six weeks after the procedure.

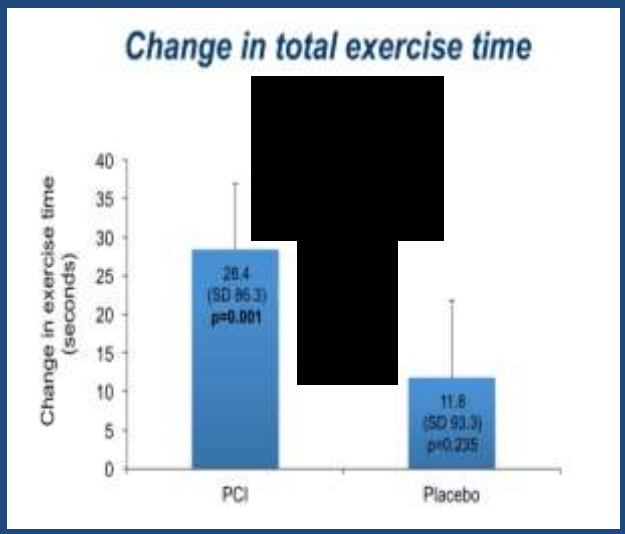
- All patients were pretreated with dual antiplatelet therapy and were continued until the last assessment visit
- Coronary angiography was performed via a radial or femoral arterial approach with auditory isolation achieved using headphones
- After follow-up assessment, patients were unblinded and given the opportunity to undergo PCI after consultation with their physician

Primary Outcome

Comparisons are PCI vs. sham PCI

- **Change in treadmill exercise time (s):**
  28.4 (95% CI 11.6 to 45.1) vs. 11.8 (95% CI -7.8 to 31.3), difference 16.6 (95% CI -8.9 to 42.0), p=0.20

Primary End-point



Secondary Outcomes

- **Peak stress wall motion index score(DSE):**
  Patients randomized to PCI showed significant improvement in peak stress wall motion score versus placebo (difference of differences 0.09, P value 0.001) which indicates that the PCI was technically successful in reducing the ischemic burden.

- **Change in peak oxygen uptake**(mL/min):
  2.0 (95% CI -54.1 to 50.1) vs. 10.9 (95% CI -47.2 to 69.0), difference -12.9 (95% CI -90.2 to 64.3), p=0.74

- **Time to 1mm ST depression** (s):
  472.7 vs. 470.1, p=0.16

- **Change in SAQ - Angina frequency:**
  14.0 (95% CI 9.0 to 18.9) vs. 9.6 (95% CI 3.6 to 15.5), difference 4.4 (95% CI -3.3 to 12.0), p=0.26

- **Change in Duke treadmill score :**
  1.22 (95% CI 0.37 to 2.07) vs. 0.10 (95% CI – 0.99 to 1.19), difference 1.12 (95% CI -0.23 to 2.47), p=0.10

- **≥ 1 CCS angina class improvement:**
  27 (26%) vs. 22 (24%), p=NS

Adverse Events

- No deaths
- Four wire complications in the placebo group requiring PCI
- Five major bleeding events;
  - Two in the PCI group and
  - Three in the placebo group.

Criticisms

1- It was a very small study ,the results can not be generalized

2-Patients in the study has single vessel, normal LV function, no LMT

3-FFR or iFR was not used to select patients for participation:

~30% of patients had FFR values in excess of 0.80. ORBITA is therefore likely to have have underestimated the benefit of PCI in low-FFR patients.

4-The pre-randomization medical optimization phase was very intensive, involving 1-3 telephone consultations per week and regular monitoring of home BP and HR measurements.

In a real-world setting, such speed of uptitration would not be necessary or possible.

5-The 6-week follow up period cannot rule out development of angina relief after 6 weeks.

6-Medical therapy included ranolazine which is often expensive and it is not always covered by insurance companies

Conclusions

- ORBITA is the first placebo controlled randomized trial of PCI in stable angina
- Angiography guided PCI for single vessel disease did not increase exercise time, however decreased ischemic burden compared to placebo procedure
- Health-care providers should focus their attention on treating patients with stable coronary artery disease with optimal medical therapy, and improving the lifestyle choices (heart-healthy diets, regular physical activity)

- These findings need to be validated in a larger randomized controlled trial
- ORBITA highlights the importance of including sham controls and double blinding in order to avoid the powerful placebo effect of procedures such as PCI

Thank You