Expanding the Armamentarium in the Management of Angina

Stents for all?

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Presenter Disclosures

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Aims/ Objectives

- Discuss management options in CAD
  - Whether to undertake and how to achieve
  - The Placebo effect of PCI
- New(ish) Developments
  - Drug coated balloons
  - Resorbable scaffolds
- Discuss additional medical management in angina

CASE 1:

70 yr male, hypertension, diabetes
Meds: ramipril 10mg OD, metformin 500mg BID

Reproducible chest heaviness with climbing hills x 3 months; no rest pain

ECG NSR; Echo normal LV function, no valvular abnormality

Exercise MIBI: 9 minutes Bruce protocol, 90% APMHR, non-limiting chest heaviness, 1mm horizontal ST depression; reversible anterolateral perfusion abnormality

Management:

1. Proceed to angiography
2. Start ECASA, statin, beta-blocker and proceed to angiography
3. Proceed to CCTA
4. Start ECASA, statin, beta-blocker and proceed to CCTA
5. Start ECASA, statin, beta-blocker and reassess in 4 weeks

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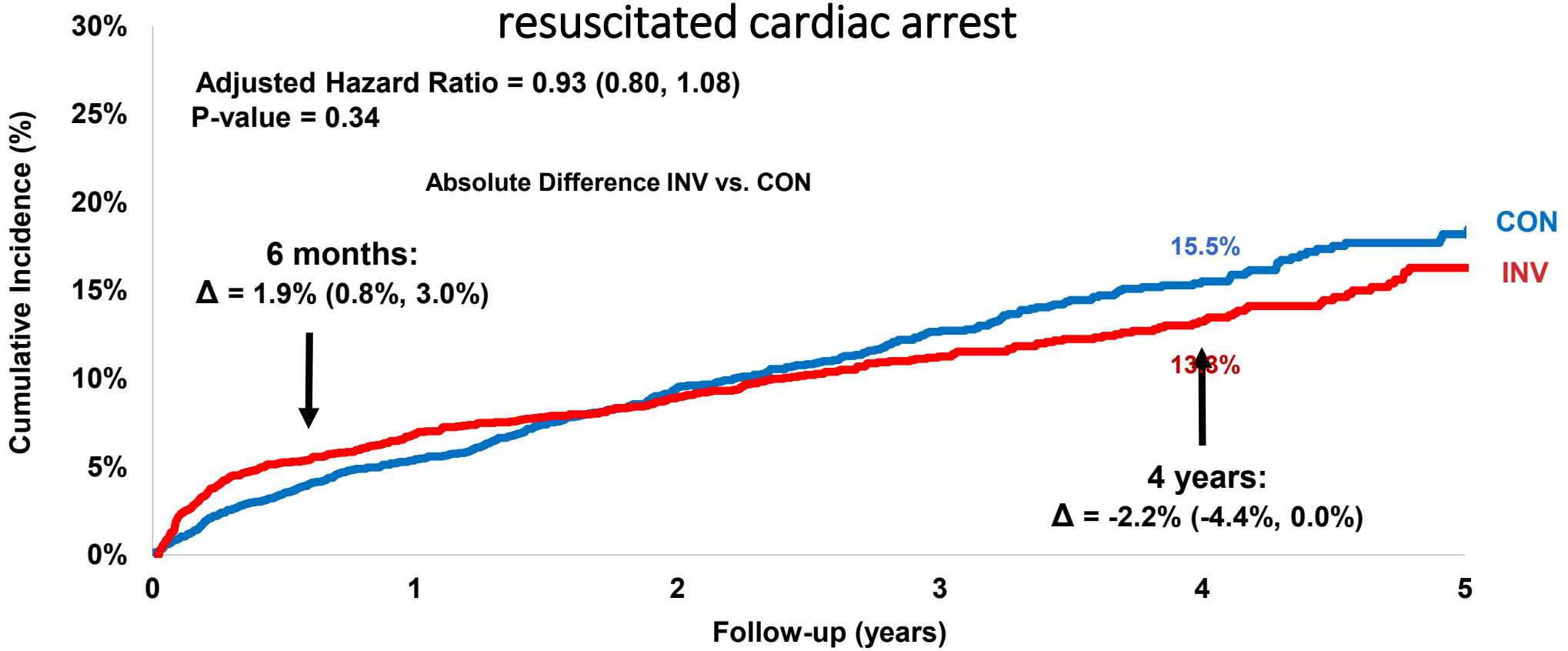
Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest



Subjects at Risk

CON	2591	2431	1907	1300	733	293
INV	2588	2364	1908	1291	730	271

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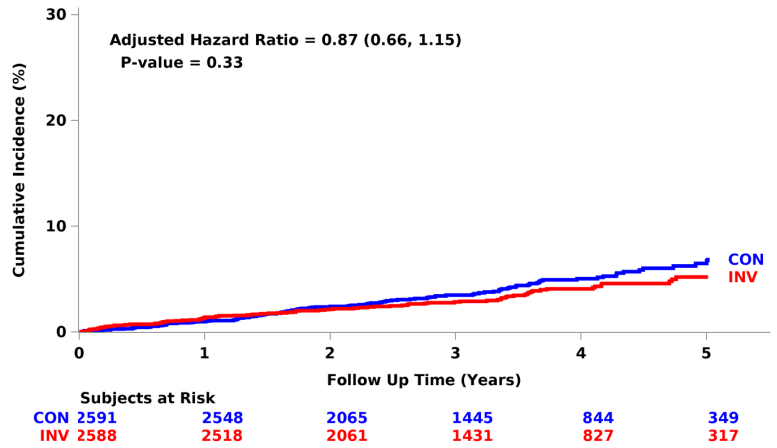
Cardiovascular Death



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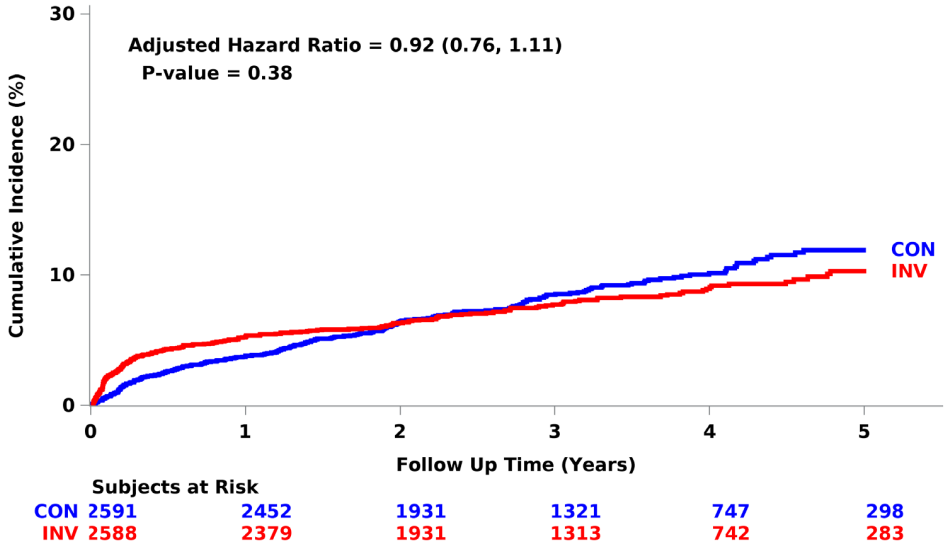
NYU Langone Health Cardiovascular Clinical Research Center

Myocardial Infarction



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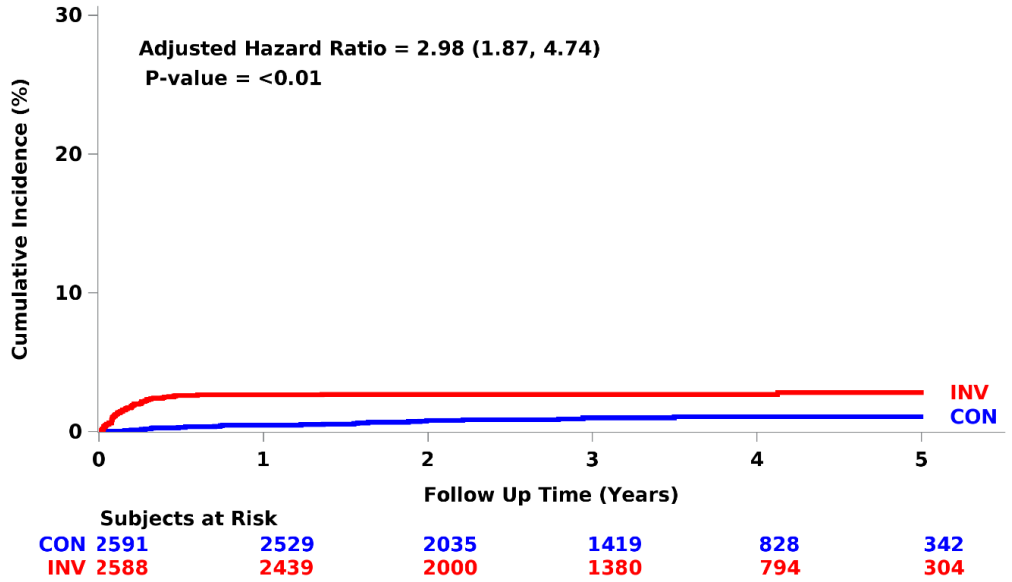
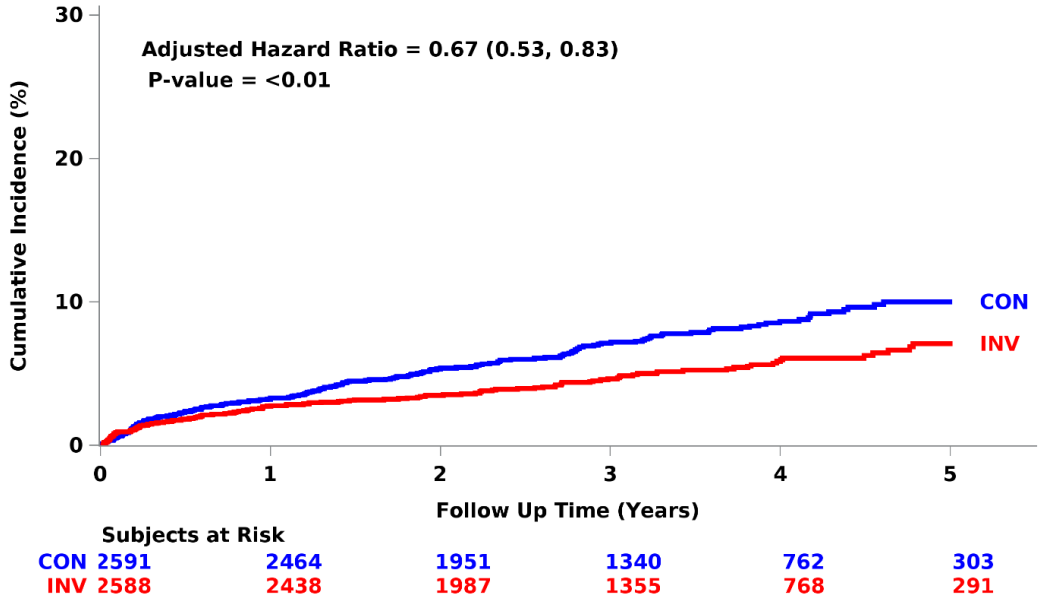
Procedural MI
Type 4a or 5 MI



Spontaneous MI
Types 1, 2, 4b, or 4c MI



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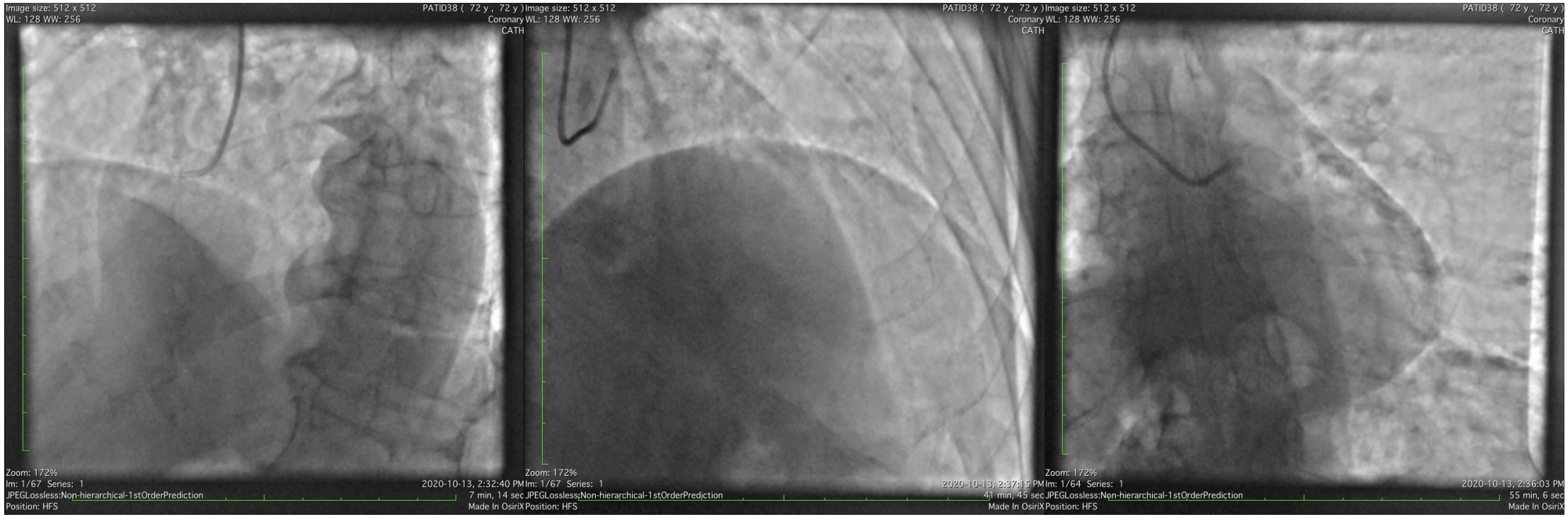
Revascularization for CAD



- Opted to undergo angiography
  - Single vessel disease with severe proximal LAD stenosis
  - Normal LV function

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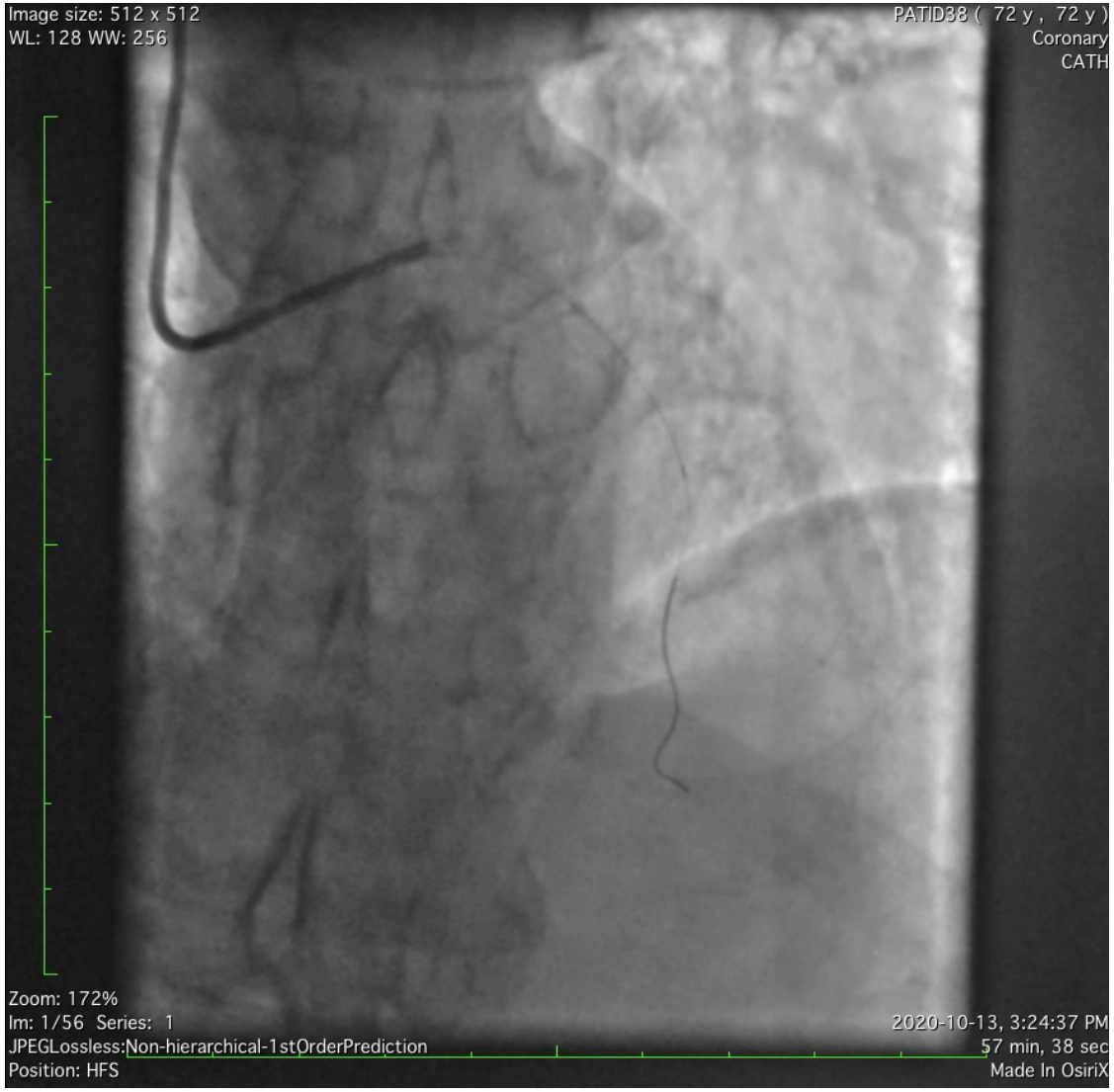
Final Result

- LAD treated with single drug eluting stent with resolution of anginal symptoms

- Treated with:
  - DAPT
  - Statin
  - ACE-I



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Is There A Placebo Effect of PCI?

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

*Rasha Al-Lamee, David Thompson, Hakim-Moulay Dehbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Darrel P Francis, on behalf of the ORBITA investigators**

- Historic data showing benefit of PCI
  - Symptom relief/ improved exercise time
- Potential of placebo effect
- RCT comparing PCI versus ‘Sham Control’ PCI
- 200 patients with stable ‘de novo’ CAD

Al-Lamee R, et al. The Lancet. 2018, 391 (10115): 31-40

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Trial Schema

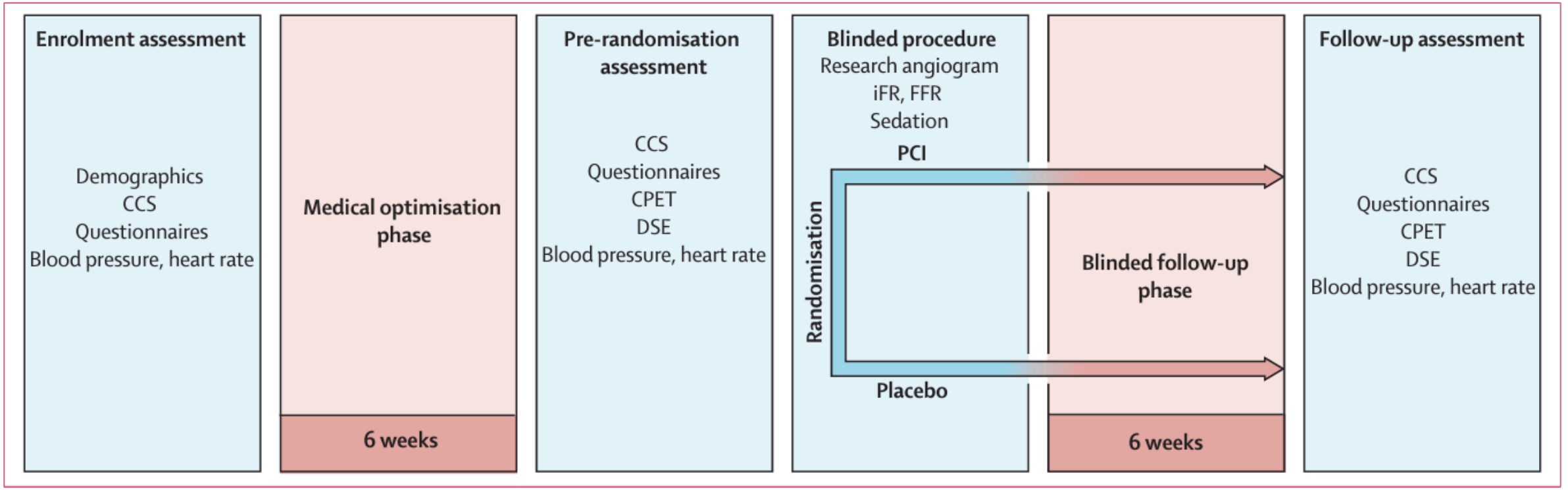

Figure 1: **ORBITA study design**

CCS=Canadian Cardiovascular Society angina severity grading. CPET=cardiopulmonary exercise testing. DSE=dobutamine stress echocardiography. iFR=instantaneous wave-free ratio. FFR=fractional flow reserve. PCI=percutaneous coronary intervention.

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RESULTS

	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	..
SAQ-physical limitation		
Patients assessed	100	88
Pre-randomisation	71·3 (22·5)	69·1 (24·7)
Follow-up	78·6 (24·0)	74·1 (24·7)
Increment (pre-randomisation to follow-up)	7·4 (19·7; 95% CI 3·5 to 11·3)	5·0 (21·2; 95% CI 0·5 to 9·5)
Difference in increment between groups	2·4 (95% CI −3·5 to 8·3)	..
p value	0·420	..

	PCI	Placebo
SAQ-angina frequency		
Patients assessed	103	90
Pre-randomisation	63·2 (20·4)	60·0 (25·1)
Follow-up	74·4 (21·4)	67·7 (22·1)
Increment (prerandomisation to follow-up)	11·2 (20·3; 95% CI 7·2 to 15·1)	7·7 (22·7; 95% CI 2·9 to 12·4)
Difference in increment between groups	3·5 (95% CI −2·6 to 9·6)	..
p value	0·260	..
SAQ-angina stability		
Patients assessed	102	89
Pre-randomisation	64·7 (25·5)	68·5 (24·3)
Follow-up	60·5 (23·7)	63·5 (25·6)
Increment (Pre-randomisation to follow-up)	−4·2 (33·4; 95% CI −10·7 to 2·4)	−5·1 (31·6; 95% CI −11·7 to 1·6)
Difference in increment between groups	0·9 (95% CI −8·4 to 10·2)	..
p value	0·851	..

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PCI as an Anti-Anginal Therapy – ORBITA-2 Trial

ORIGINAL ARTICLE

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

Christopher A. Rajkumar, M.B., B.S., Michael J. Foley, M.B., B.S., Fiyyaz Ahmed-Jushuf, M.B., B.S., Alexandra N. Nowbar, Ph.D., Florentina A. Simader, M.D., John R. Davies, Ph.D., Peter D. O'Kane, M.D., Peter Haworth, M.B., B.S., Helen Routledge, M.D., Tushar Kotecha, Ph.D., Reto Gamma, M.D., Gerald Clesham, Ph.D., et al., for the ORBITA-2 Investigators*

- Sham-controlled PCI Procedure
- On enrolment, anti-anginal medications stopped
  - DAPT, statins commenced
  - Switch of medicines allowed for alternate reasons
- Run in period of 2 weeks
  - Daily assessment of symptoms/ medication usage via smartphone app
- Patients with no symptoms excluded

N Engl J Med 2023; 389:2319-2330

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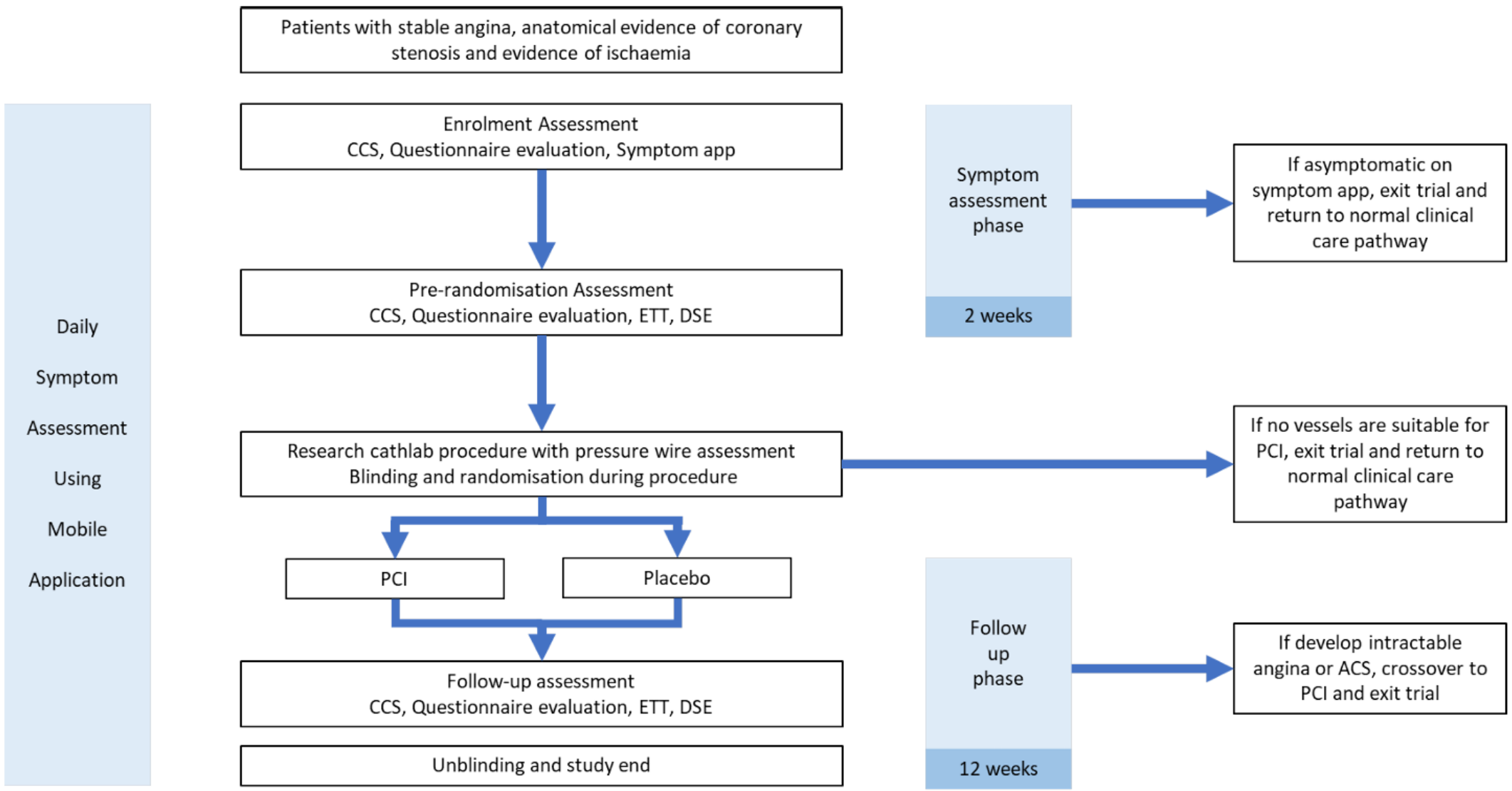
ORBITA-2 Schedule



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Results

Table 3. Primary and Secondary End Points.*

End Point	PCI (N=151)		Placebo (N=150)		Odds Ratio or Difference (95% CI)†
	value	*no. of patients with data*	*value*	*no. of patients with data*	
Primary end point: angina symptom score — mean score‡	2.9	151	5.6	150	2.21 (1.41 to 3.47)§
Mean daily angina episodes — no.	0.3	151	0.7	150	3.44 (2.00 to 5.91)
Mean daily antianginal medication use — units¶	0.2	151	0.3	150	1.21 (0.70 to 2.10)
Secondary end points					
Mean treadmill exercise time — sec	700.9	123	641.4	112	59.5 (16.0 to 103.0)
CCS class — mean	0.9	147	1.7	146	3.76 (2.43 to 5.82)
End points assessed with the use of the SAQ‖					
Frequency of angina	80.6	146	66.2	145	14.4 (9.5 to 19.4)
Physical limitation	82.7	139	73.9	144	8.8 (4.7 to 12.9)
Angina stability	61.8	145	55.3	145	6.5 (0.5 to 12.5)
Quality of life	62.8	145	51.6	145	11.2 (6.2 to 16.1)
Freedom from angina	40	146	15	145	3.69 (2.10 to 6.46)
EQ-5D-5L descriptive system — mean score**	0.82	145	0.73	144	0.09 (0.05 to 0.13)
EQ-VAS — mean score**	73.1	146	66.9	143	6.2 (2.4 to 10.0)
Stress echocardiography score — mean score††	0.79	119	1.95	111	−1.17 (−1.56 to −0.78)

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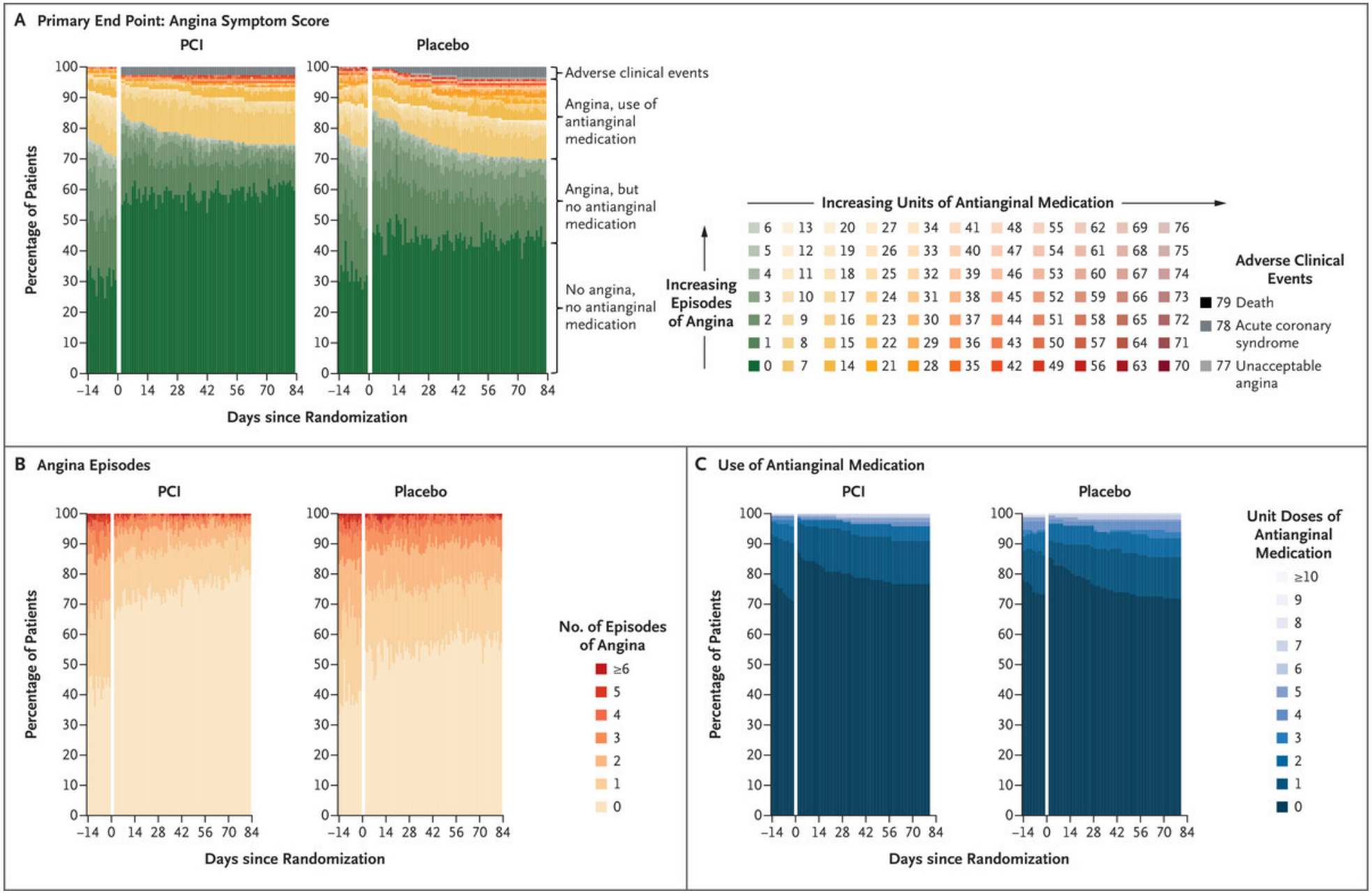
Results



Take Home Message – ISCHEMIA/ ORBITA/ ORBITA--2

- Patient involvement crucial in all aspects of care
  - Decision to perform angio
  - Revascularisation
    - Yes or no
    - PCI vs CABG
- Revascularisation only one aspect of their care
  - Disease modifying drugs at least as important
- Perfectly reasonable to manage medically with no revascularisation

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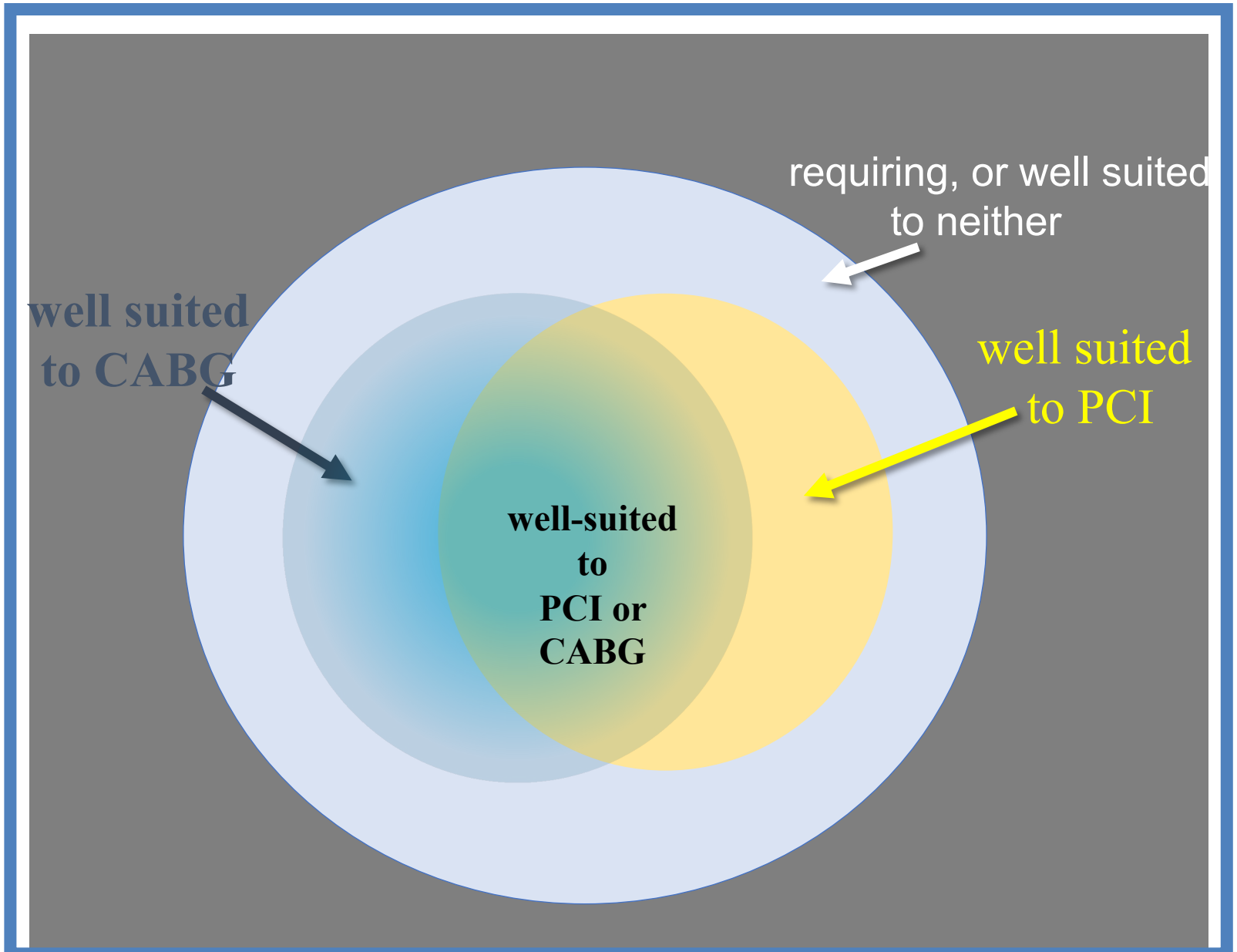
Thoughts on Multi-Vessel CAD



Diffuse Coronary Artery Disease

- Long been the ‘heartsink’ condition of the cath lab
- No ‘ideal’ revascularization method
  - CABG – difficult to implant graft onto diffusely diseased vessel
  - PCI – extensive stenting (the Full Metal Jacket)
- Revascularization itself prone to issues
  - CABG – diseased implant spot requires endarterectomy
    - Higher rates early and late graft failure
  - PCI – higher rates of restenosis
    - Metal stent has permanent presence

Drug Coated Balloons (DCB) for PCI

- Drug eluting stents useful but not a panacea
  - Permanent scaffold in artery
  - Require DAPT until stent endothelialised
- DCBs rely on previous lessons gained from balloon angioplasty era
- Balloon has anti-proliferative drug (typically paclitaxel) on its surface
  - Lipophilic
  - Excipient vehicle
  - Facilitate rapid drug transfer to vessel smooth muscle during single balloon inflation

Drug Coated Balloons (DCB) for PCI

- Expanding evidence for their use in various scenarios
  - Restenosis
  - Small vessel disease
  - Long LAD lesions
- Found to be non-inferior to conventional DES

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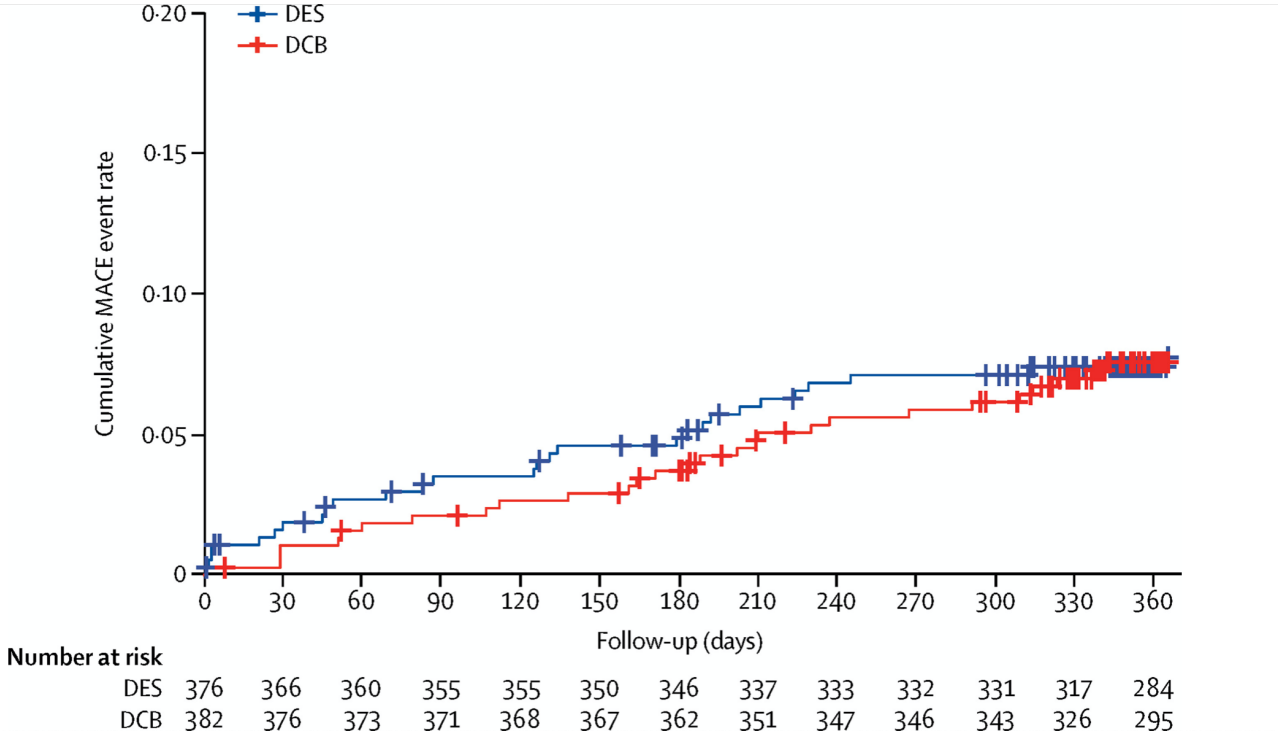
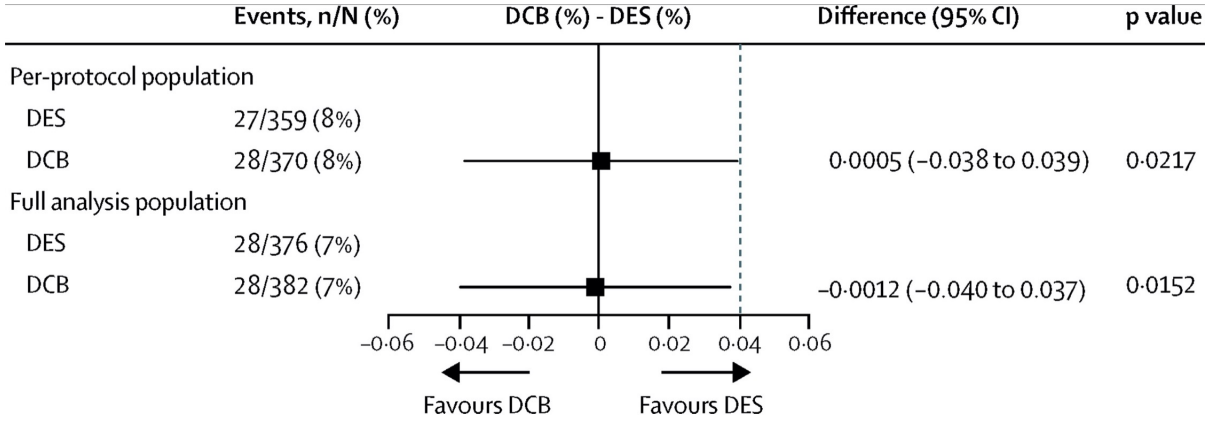
DCB In Small Vessels –BASKET SMALL-2 Trial





BASKET SMALL2 – The Lancet. 2018. 392; 10150: 849-856

DCB Typical Case

- 60 yo male
- Multiple CV risk factors
  - DM2, HTN, dyslipidemia
- Known CAD – S/P PCI to proximal and distal LAD a decade previous for ACS
- Recurrent angina with abnormal Sestamibi
  - Exertional chest pain
  - Anterior/inferior ischemia

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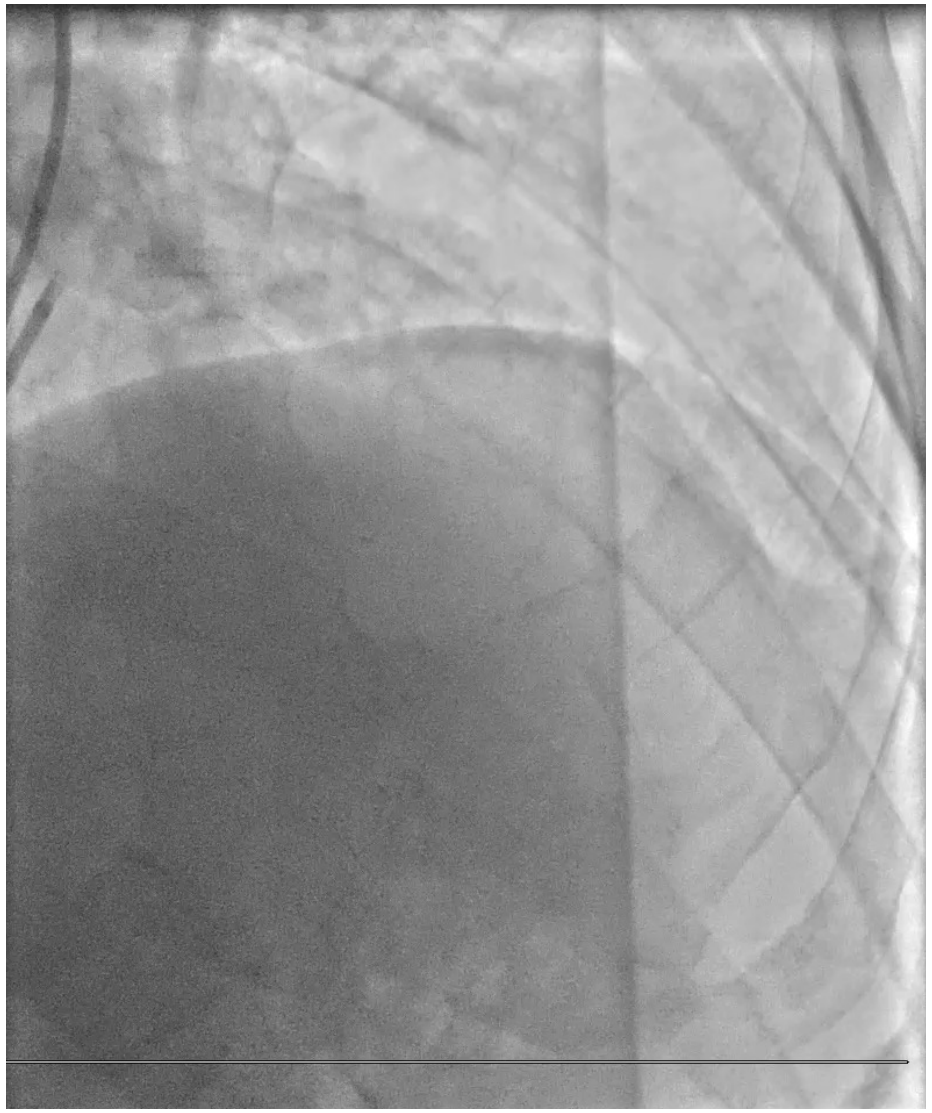
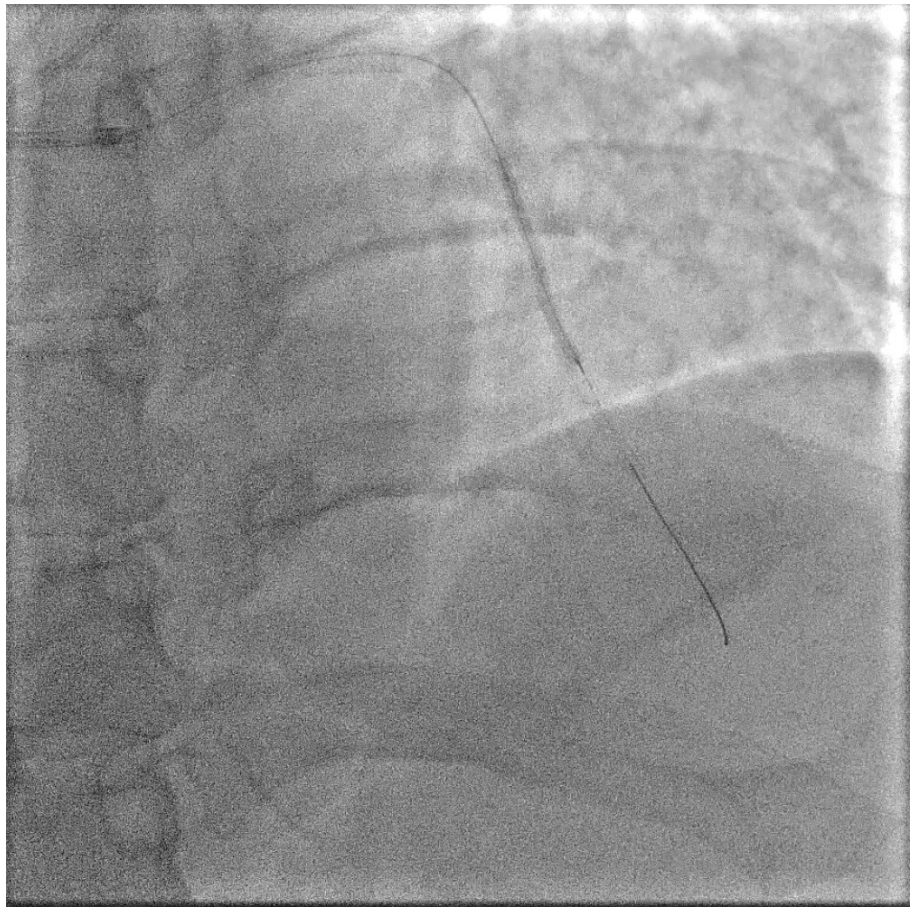
DCB Typical Case





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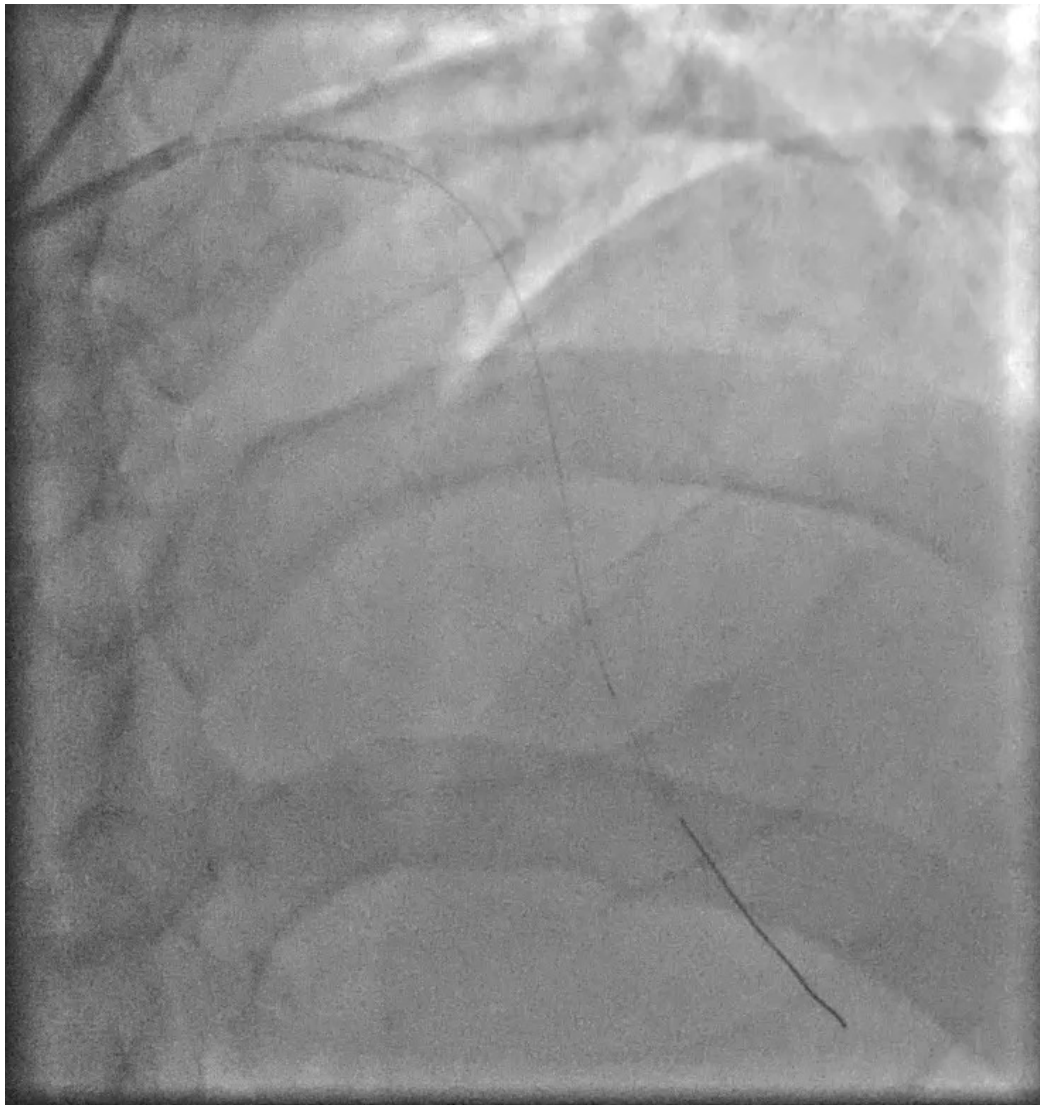
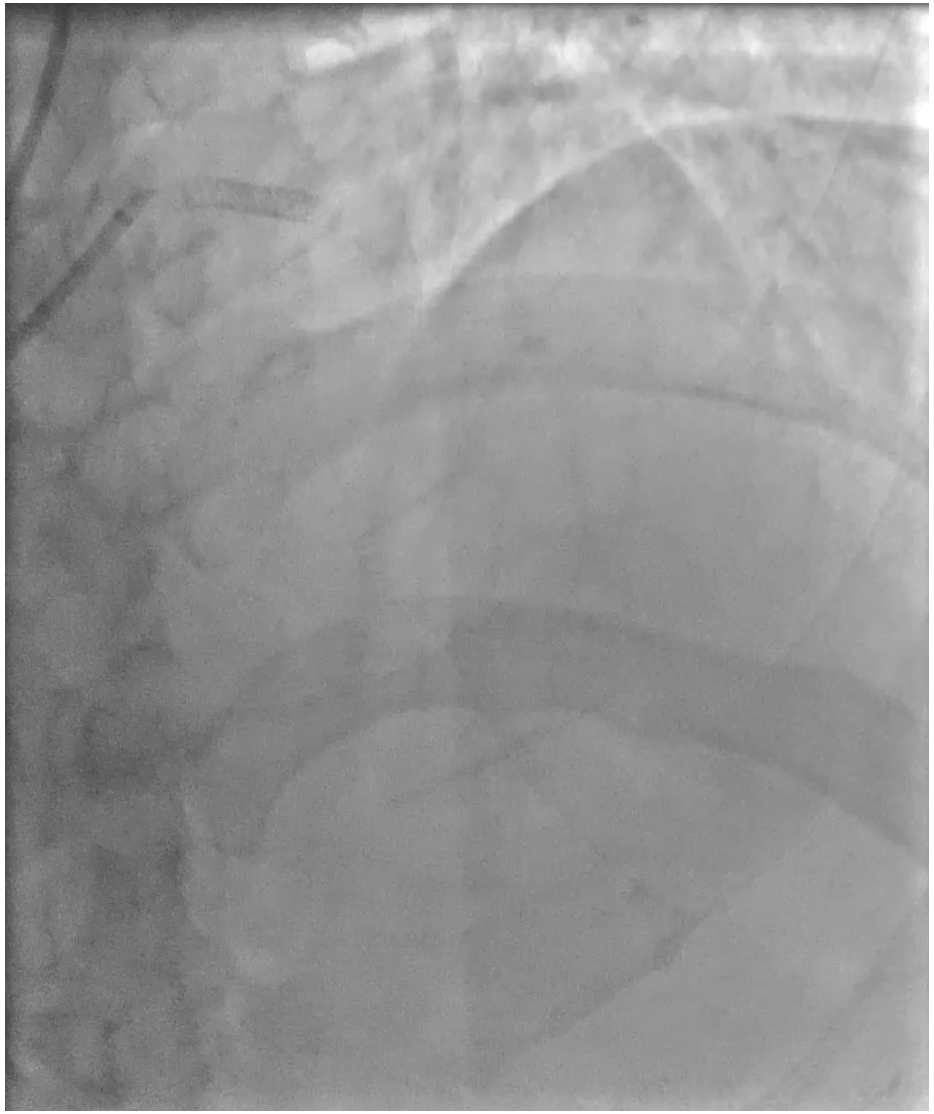
DCB Typical Case

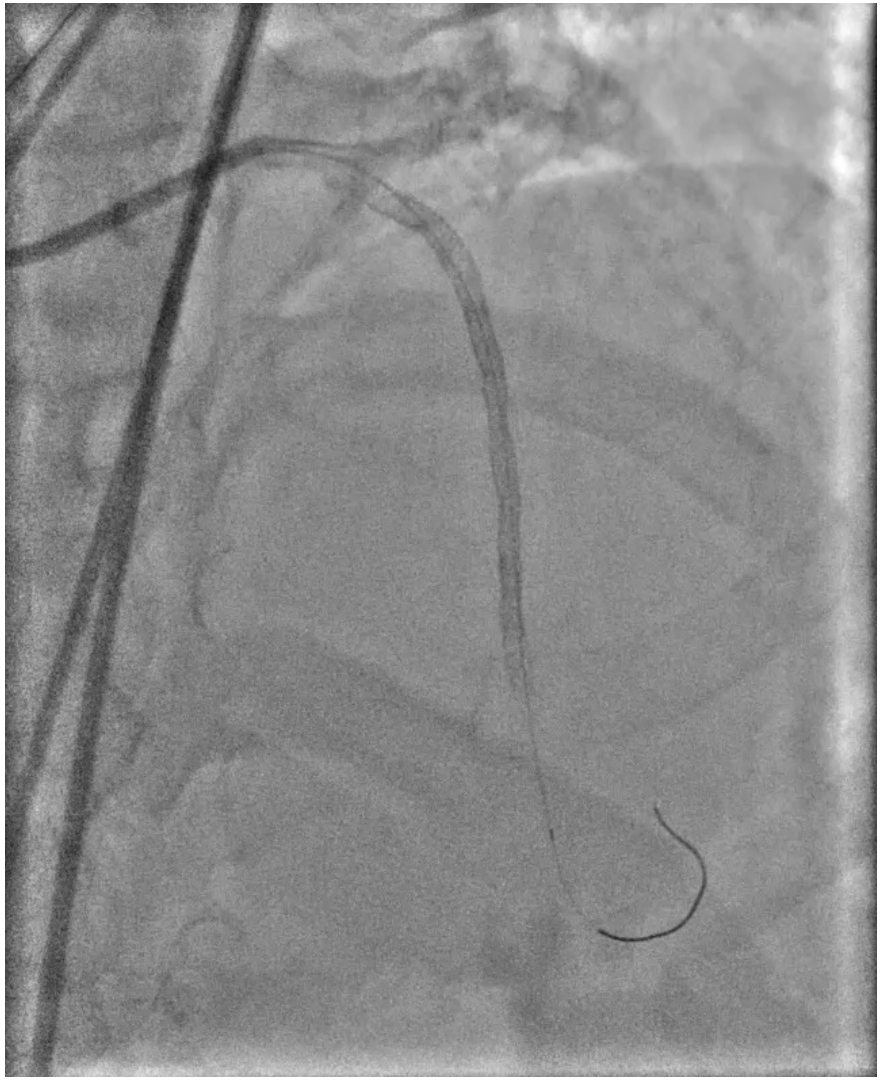




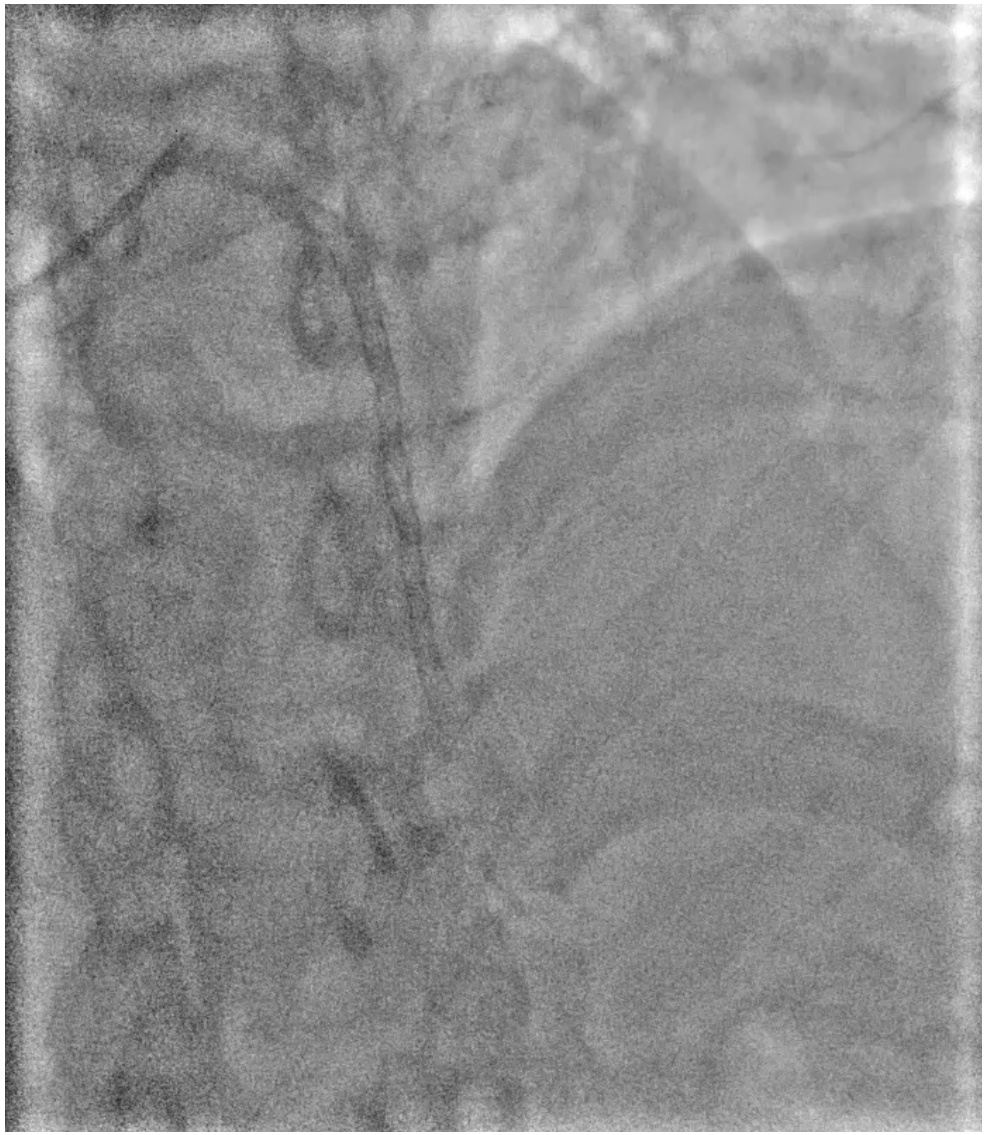
The Issue with a Full Metal Jacket

- 53 y.o. female with multiple CV RFs
  - DM2, +ve FHx, dyslipidemia
- CAD first manifest 2017 with stable angina at age 46
  - Angiography – PCI to LAD and LCx
- Multiple repeat presentations due to ISR of LAD stent, in variably treated with further DES inside DES. Now has seven (7) stents in LAD
- Referred with further intractable angina

The Issue with a Full Metal Jacket



The Issue with a Full Metal Jacket



- CV Surgery felt distal LAD not big enough to graft
- Intensified medical therapy
  - Beta-blocker
  - LA nitrate
  - Ca++ channel blocker
- Dosing hampered by symptomatic hypotension

New (Old) Anti-Ischemic Medications

- Ranolazine
- Developed as anti-anginal and patented in 1986
- Unclear mechanism of action
  - ?inhibition fatty acid oxidation
  - ?improvement post-ischemic function
  - ? Reduced calcium overload in ischemic myocytes
- License purchased in early 2020’s
- Health Canada approval 2021

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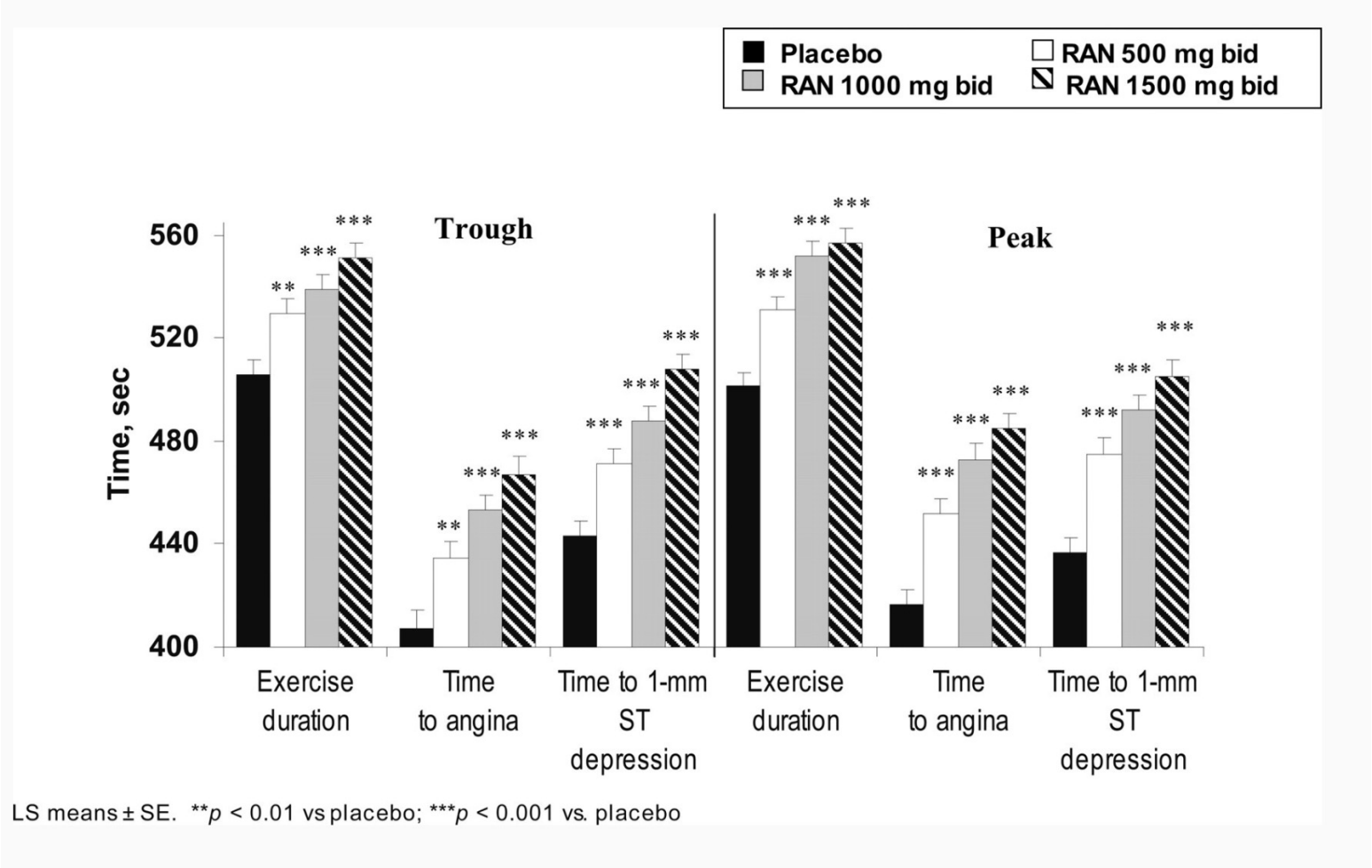
MARISA Trial – Ranolazine vs Placebo in Stable Angina



Chaitman, BR, **J Am Coll Cardiol**. 2004; *43*: 1375–1382.

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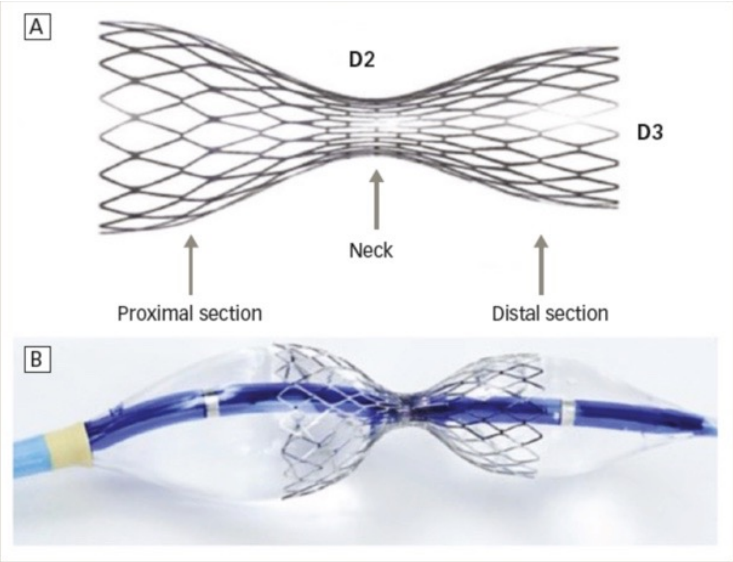
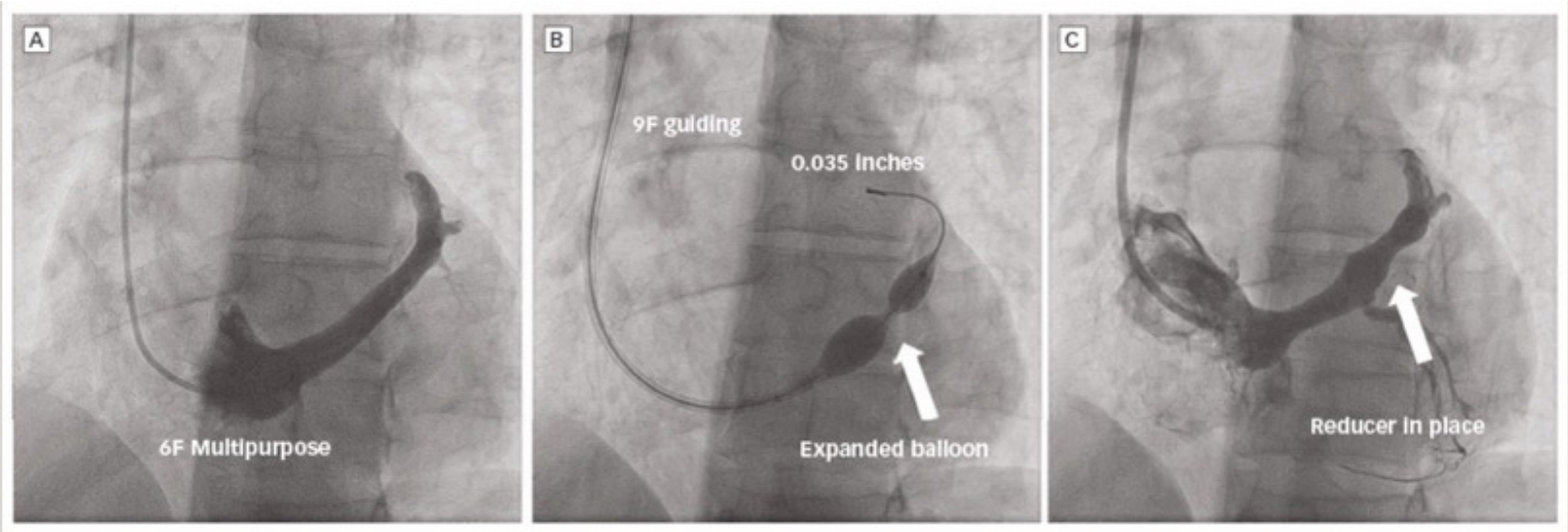
Coronary Sinus Reducer





Proposed Mechanisms of Action

- In obstructive CAD, particularly with LV dysfunction and high filling pressures, there is a substantial coronary flow resistance and ischemia particularly of sub endocardial tissue

- Focal narrowing in CS raises pressure in venous drainage system, including dilatation of arterial capillaries and reduction of flow resistance; this leads to redistribution of blood from less ischemic to more ischemic sub-endocardium

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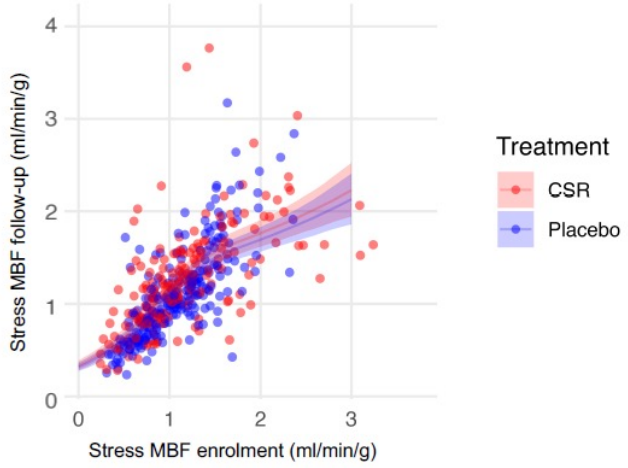
ORBITA-COSMIC: 51 patients randomized to CSR vs. placebo

Primary imaging outcome

Difference
0.06ml/min/g

(95% CrI -0.09 to 0.20)

Pr(Benefit)=78.8%

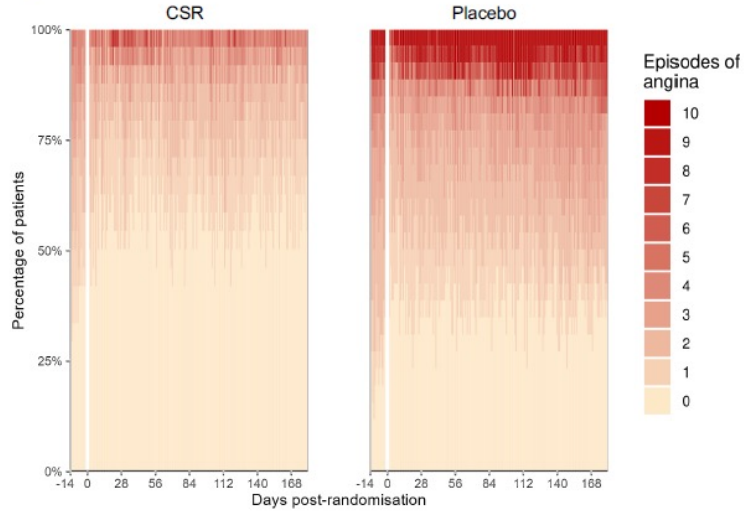


Primary symptom outcome

CSR improved angina episodes

OR 1.40
(95% CrI 1.08 to 1.83)

Pr(Benefit)=99.4%



ORBITA-COSMIC conclusions

The coronary sinus reducer resulted in:

- No improvement in transmural myocardial perfusion
- Improvement in subendocardial perfusion

- Reduced angina frequency
- Improved heart disease related quality of life

Foley MJ, et al. The Lancet. 2024, April 20. **403**: 10436; 1543-1553,

My Take On This

Revascularization vs. Med Rx alone

- OMT for all
- Rule out LM with anatomical test
- No reduction in CV death/MI at 3.3 years
- Reduction in spontaneous MI at cost of increase in peri-procedural MI; symptomatic benefit
- Individualize approach/discussion with patient

My Take On This

Stable Symptomatic Coronary Disease

- Percutaneous Coronary Intervention
  - **MAY** – improve symptoms/exercise capacity more than anti-anginal meds

My Take On This

- Newer technology can increase options for patients (particularly previous ‘untreatable’ due to diffuse disease
  - Drug coated balloons show great promise in increasing areas
  - Magnesium based resorbable scaffolds are on the horizon
- If symptomatic with no revascularization option, don’t forget the ‘older’ therapies

THANK YOU

- John.Graham@unityhealth.to

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