PCI of Culprit Lesion vs. FFR Guided Complete Revasc: Effects on Hard End Points, MACE, and Cost Effectiveness

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Disclosures for Dr. Bhatt

Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; **Board of Directors**: Boston VA Research Institute, Society of Cardiovascular Patient Care; **Chair**: American Heart Association Quality Oversight Committee; **Data Monitoring Committees**: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; **Honoraria**: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); **Other**: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee, VA CART Research and Publications Committee (Chair); **Research Funding**: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); **Site Co-Investigator**: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; **Unfunded Research**: FlowCo, Merck, PLx Pharma, Takeda.

This presentation discusses off-label and/or investigational uses of various drugs and devices.

The NEW ENGLAND JOURNAL of MEDICINE

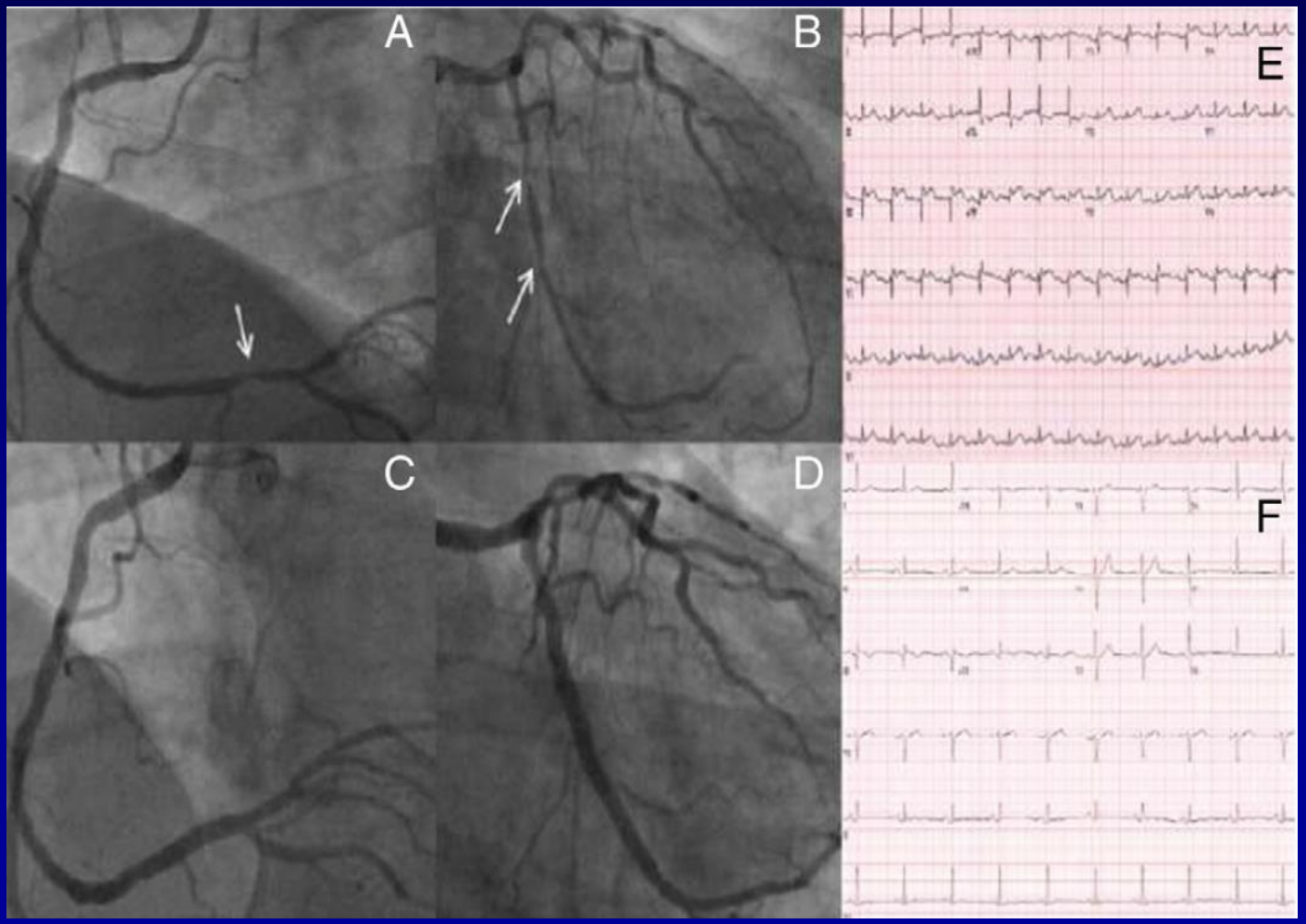
EDITORIALS

Timely PCI for STEMI — Still the Treatment of Choice

Deepak L. Bhatt, M.D., M.P.H.

Bhatt DL. NEJM. 2013.

STEMI: Culprit Only or Complete?



Qamar A, Bhatt DL. Progress in Cardiovascular Disease 2015; 58: 260-266.

PRAMI Trial

Variable	Preventive PCI (N=234)	Medical Rx (N=231)	HR (95% CI)	P value
Cardiac Death, MI, RFA	21	53	0.35 (0.21-0.58)	<0.001
Cardiac death or MI	11	27	0.36 (0.18-0.73)	0.004
All Death	12	16		NS
Cardiac Death	4	11	0.34 (0.11-1.08)	0.07
RFA	12	30	0.35 (0.18-0.69)	0.002

Wald NEJM 2013.

CvLPRIT Trial

Variable	Medical Rx (N=146)	PCI (N=150)	HR (95% CI)	P value
MACE N= (%)	31 (**21.2**)	15 (**10.0**)	0.45 (0.24, 0.84)	<0.001
All-cause mortality	6 (4.1)	2 (1.3)	0.32 (0.06, 1.60)	0.14
Recurrent MI	4 (2.7)	2 (1.3)	0.48 (0.09, 2.62)	0.39
Heart failure	9 (6.2)	4 (2.7)	0.43 (0.13, 1.39)	0.14
Repeat Revascularisation	12 (8.2)	7 (4.7)	0.55 (0.22, 1.39)	0.2

Gerschlick A. JACC 2014

Early Trials

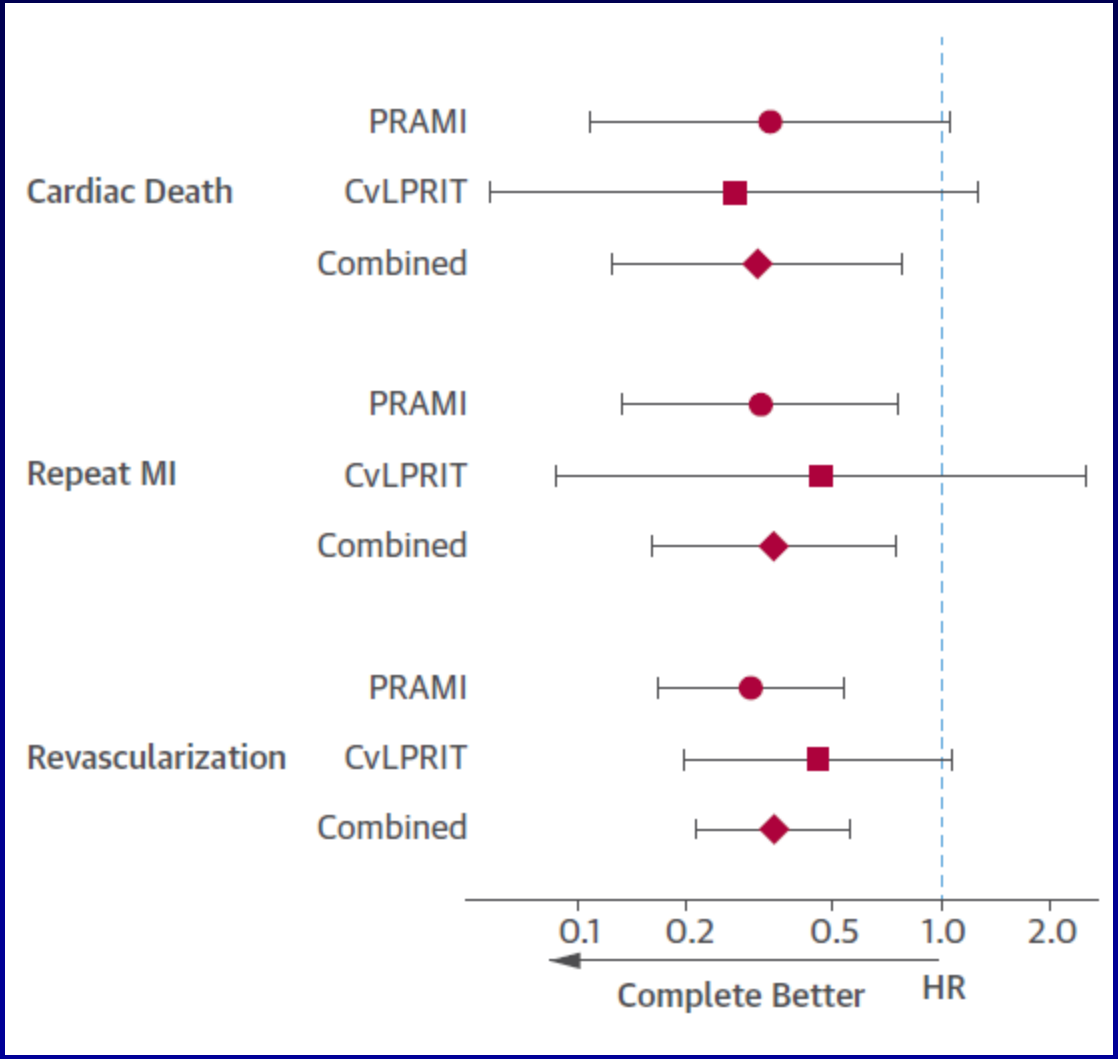
EDITORIAL COMMENT

Do We Really Know the CvLPRIT in Myocardial Infarction? Or Just Stent All Lesions?*

Deepak L. Bhatt, MD, MPH

Bhatt DL. JACC 2015.

Culprit vs Complete Revasc in STEMI



Bhatt DL. JACC 2015.

DANAMI 3 – PRIMULTI Trial: FFR-Guided PCI reduced revasc with no difference in death or MI

	IRA only (n = 313)	Complete revascularisation (n = 314)	HR [95% CI]	p
Primary endpoint	68 (22%)	40 (13%)	0.56 [0.38 – 0.83]	0.004
All-cause death	11 (4%)	15 (5%)	1.4 [0.63 – 3.0]	0.43
Nonfatal MI	16 (5%)	15 (5%)	0.94 [0.47 – 1.9]	0.87
Ischemia-driven revascularization*	52 (17%)	17 (5%)	0.31 [0.18 – 0.53]	<0.001

Engstrøm, Lancet 2015.

Prague Primary Composite Endpoint

	PCI (n=106)	Conservative (n=108)	Hazard ratio (95% CI)	p-value
All-cause mortality / nonfatal MI / stroke	17 (16.0%)	15 (13.9%)	1.35 (0.66 - 2.74)	0.407
All-cause mortality	6 (5.7%)	7 (6.5%)	0.91 (0.30 - 2.70)	0.859
Nonfatal MI	11 (10.4%)	8 (7.4%)	1.71 (0.66 - 4.41)	0.269
Stroke	0	3 (2.8%)		

4 (3.8%) periprocedural infarctions in PCI group with good prognosis.

Hlinomaz et al 2015

EXPLORE Trial Design

- **Patients**

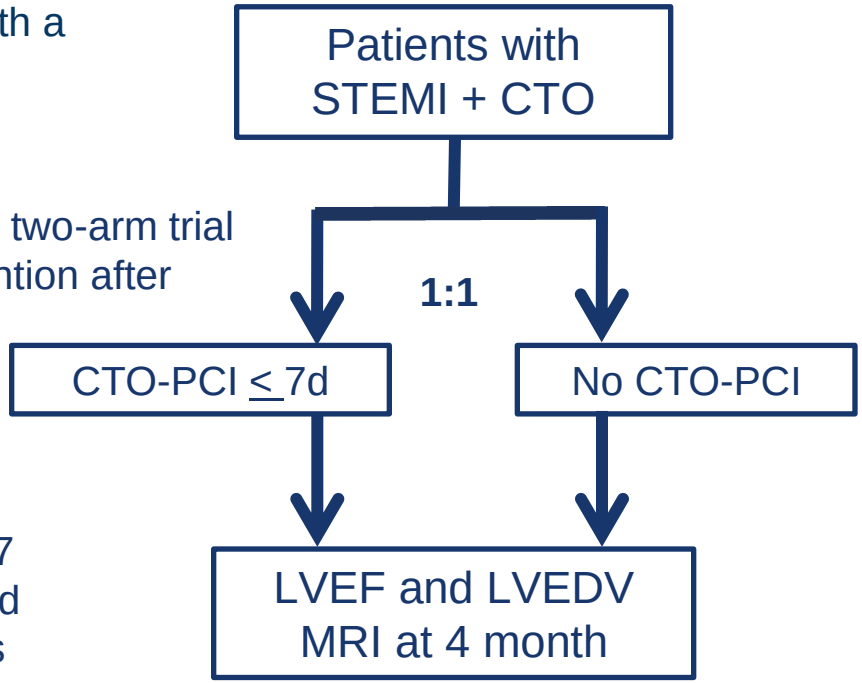
  Patients with STEMI treated with pPCI and with a non-infarct related CTO.

- **Design**

  Global, multi-center, randomized, prospective two-arm trial with either PCI of the CTO or no CTO intervention after STEMI.
  Blinded evaluation of endpoints.

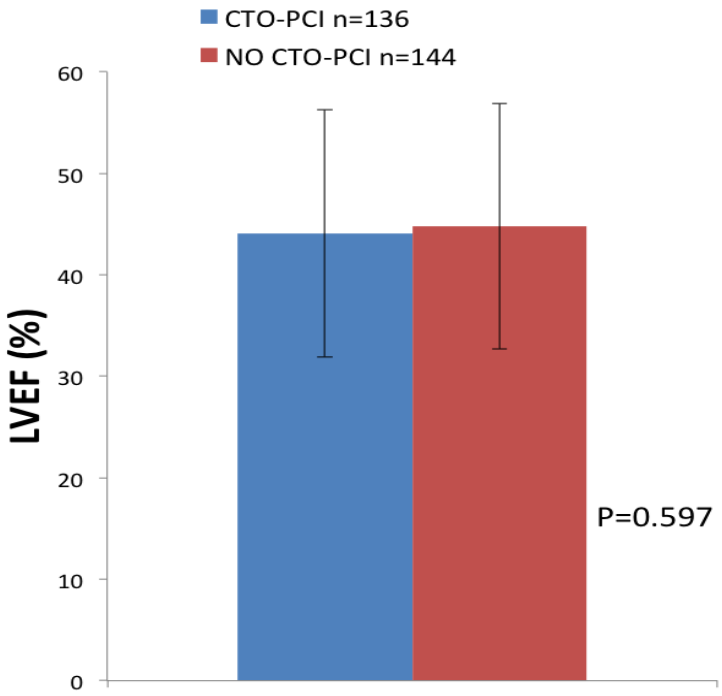
- **Objective**

  To determine whether PCI of the CTO within 7 days after STEMI results in a higher LVEF and a lower LVEDV assessed by MRI at 4 months



Henriques JACC 2016

Primary Endpoint #1 (LVEF @ 4 months)



	CTO-PCI (n=136)		No CTO-PCI (n=144)		Difference (95%CI)		p
LVEF (%)	44·1	(12·2)	44·8	(11·9)	-0·8	(-3·6 to 2·1)	0·597

Henriques JACC 2016

MACE @ 4 months

Major Adverse Cardiac Events (MACE)	CTO-PCI		No CTO-PCI		p
Cardiac death	4	(2·7%)	0	(0%)	0·056
Myocardial infarction (Third Universal definition)	5	(3·4%)	3	(1·9%)	0·494
Periprocedural	4	(2·7%)	1	(0·6%)	0·207
Spontaneous/Recurrent	2	(1·4%)	2	(1·3%)	1·000
CABG surgery	0	-	1	(0·6%)	1·000
MACE	8	(5·4%)	4	(2·6%)	0·212

Henriques JACC 2016

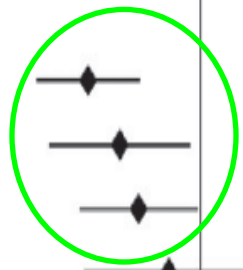
Trials of PCI versus Med Rx in Patients with STEMI and Multivessel Disease

Trial	Same-sitting or Staged	Sample Size
Di Mario 2004	Index	69
Politi 2009	Index or staged	149
Ghani 2012	Staged (FFR guided)	119
PRAMI 2013	Index	465
Cvlprit 2014	Index or staged	296
DANAMI-3 2015	Staged	627
PRAGUE 13	Staged	214
EXPLORE	Staged (CTO)	300

Total 2239

Network Meta-Analysis: MACE

Outcome	RR (95% CI)	P-value
MACE		
Complete-index vs. culprit	0.37 (0.24, 0.59)	<0.01
Staged-hospital vs. culprit	0.49 (0.27, 0.91)	0.02
Staged-after vs culprit	0.58 (0.35, 0.97)	0.04
Complete-index vs Staged-hospital	0.76 (0.36, 1.59)	0.46
Complete-index vs. Staged-after	0.64 (0.36, 1.15)	0.13
Staged-hospital vs. Staged-after	0.85 (0.38, 1.87)	0.68



Elgendy I, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AB. J Am Coll Cardiol Intv 2017;10:315–24.

COMPARE-ACUTE Trial Design

885 STEMI pts + Multi VD (non IRA ≥ 50%)

Estimated MACCE 8% versus 14.5%
Power 80%

Inclusion criteria:
- Pts. 18-85 year old
- Prim. PCI < 12 hours
- Non-IRA lesions ≥ 50% by visual assesment and amendable for PCI

After successful Primary PCI of IRA Randomised

Exclusion criteria:
- LM ≥ 50% stenosis
- Kilip class > 2
- Stent thrombosis
- Non-IRA TIMI flow < 3

R

1:2 randomization

FFR of all lesions ≥ 50% stenosis in >2mm non-IRA

Acute FFR guided complete PCI of non-IRA lesions

FFR of all lesions ≥ 50% stenosis in >2mm non-IRA

Conservative strategy (Treating cardiologist blinded to FFR value)

Primary endpoint: all-cause death, MI, any revasc*, stroke (MACCE) @ 12 mths
*** After 45 days in the conservative arm, unless urgent indication**

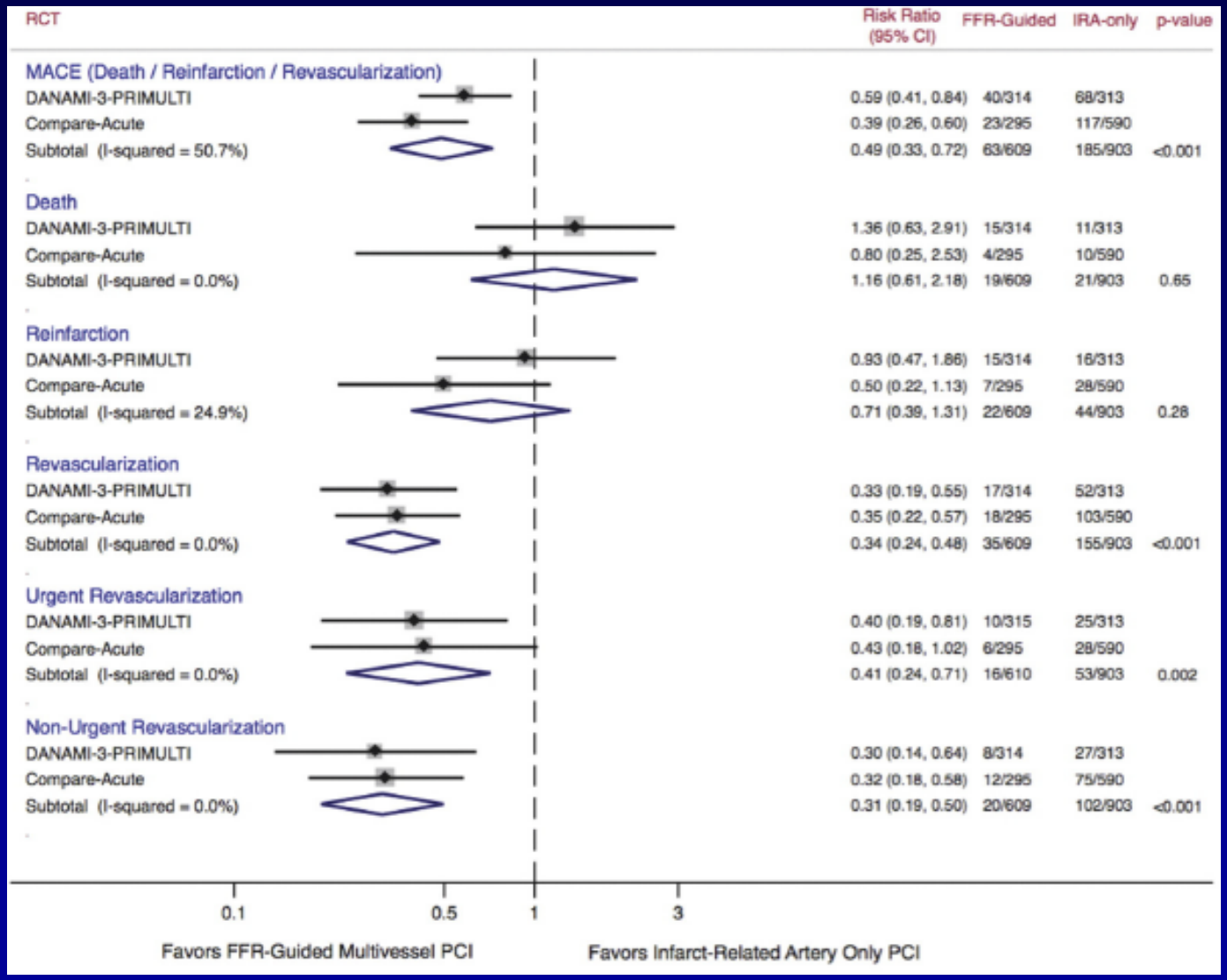
Primary outcome and its components

	FFR guided Complete Revascularization (n=295)	Infarct Artery Only treatment (n=590)	HR	95% CI	P value
Primary endpoint	Number of events (%)				
MACCE* (any first event)	23 (7.8%)	121 (20.5%)	0.35	0.22 – 0.55	**<0.001**
Death, all cause	4 (1.3%)	10 (1.7%)	0.80	0.25 – 2.56	0.70
Cardiac	3 (1.0%)	6 (1.0%)			
Myocardial infarction (MI)	7 (2.4%)	28 (4.7%)	0.50	0.22 - 1.13	0.10
Spontaneous	5 (1.6%)	17 (2.9%)	0.59	0.22 – 1.59	0.29
Peri-procedural	2 (0.6%)	11 (1.9%)	0.36	0.08 – 1.64	0.19
Revascularization	18 (6.1%)	103 (17.5%)	0.32	0.20 – 0.54	**<0.001**
PCI	15 (5.1%)	98 (16.6%)	0.37	0.24 – 0.57	**<0.001**
CABG	3 (1.0%)	5 (0.8%)	1.20	0.29 – 5.02	0.80
Cerebrovascular event	0 (0.0%)	4 (0.7%)	NA	NA	NA

* MACCE = the composite of all-cause mortality, non-fatal myocardial infarction, any revascularization and cerebrovascular events.

Smits PC, et al. N Engl J Med 2017;

Pooled FFR Data



Gupta A, Bajaj NS, Arora P, Arora G, Qamar A, Bhatt DL. IJC 2017.

COMPLETE Trial: Design

STEMI with successful culprit lesion PCI (primary, rescue, or pharmacoinvasive) + ≥ 70% stenosis or ≥ 50% with FFR < 0.80

RANDOMIZED
Within 72 h of index Primary PCI

Staged Non-culprit lesion PCI+OMT
Staged PCI of all suitable non-culprit lesions
N=1950

Optimal Medical Therapy Alone
No further revsac of non-culprit lesions (OMT Alone)
N=1950

ALL patients receive OMT (ASA, Ticagrelor, Statin, Beta Blocker, RF Modification)

Follow-up: Discharge, 30 Days, 6 Months, then Annually

Primary Outcome: CV Death / MI
Key Secondary Outcome: CV Death/MI/Ischemia driven revascularization

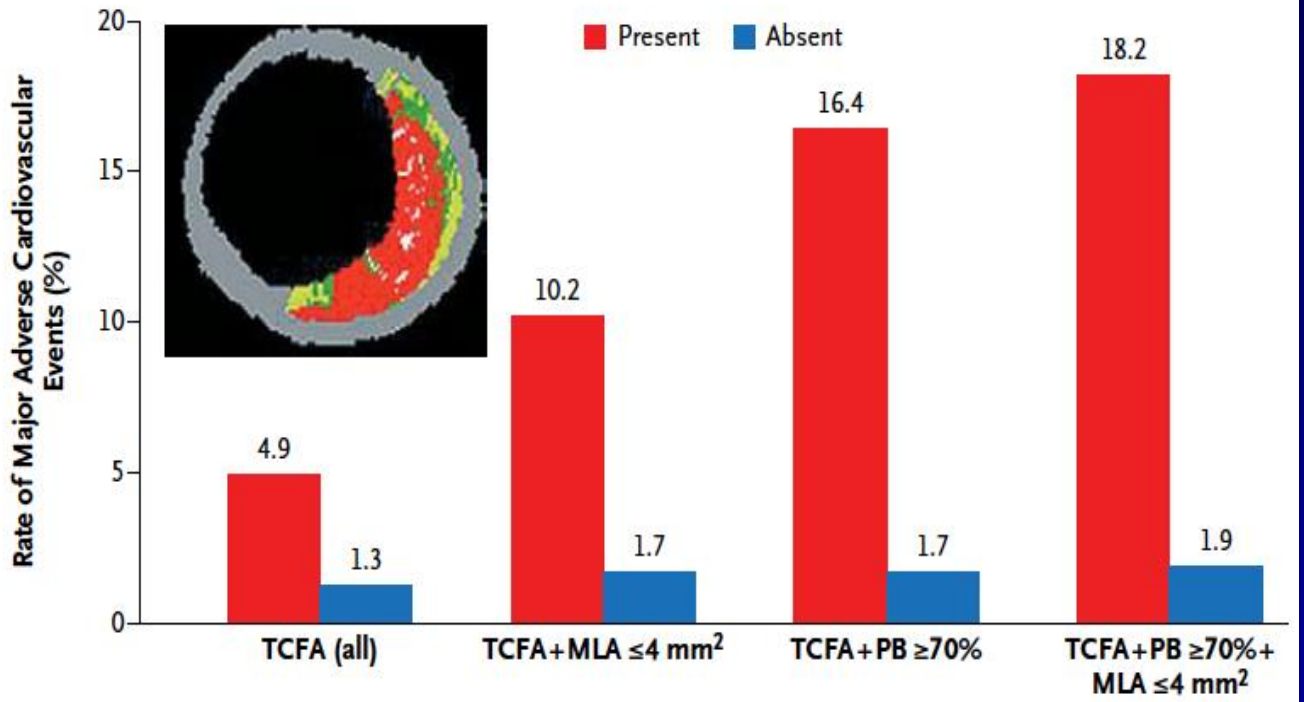
Clinicaltrials.gov NCT0174049

Funded by CIHR, AstraZeneca and Boston Scientific

COMPLETE: Unique Features

- Global trial involving >130 high volume STEMI centers
- Powered to detect reductions in CV death or MI
- High proportion of DAPT with ASA and ticagrelor
- Very high proportion of DES use
- Angiographic Core Lab (100% of all angiograms)
- OCT Non-culprit Lesion Substudy
- CABG Surgery Registry

IVUS Findings that Predict Future Events: PROSPECT



Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Stone et al NEJM 2011;364:226-35

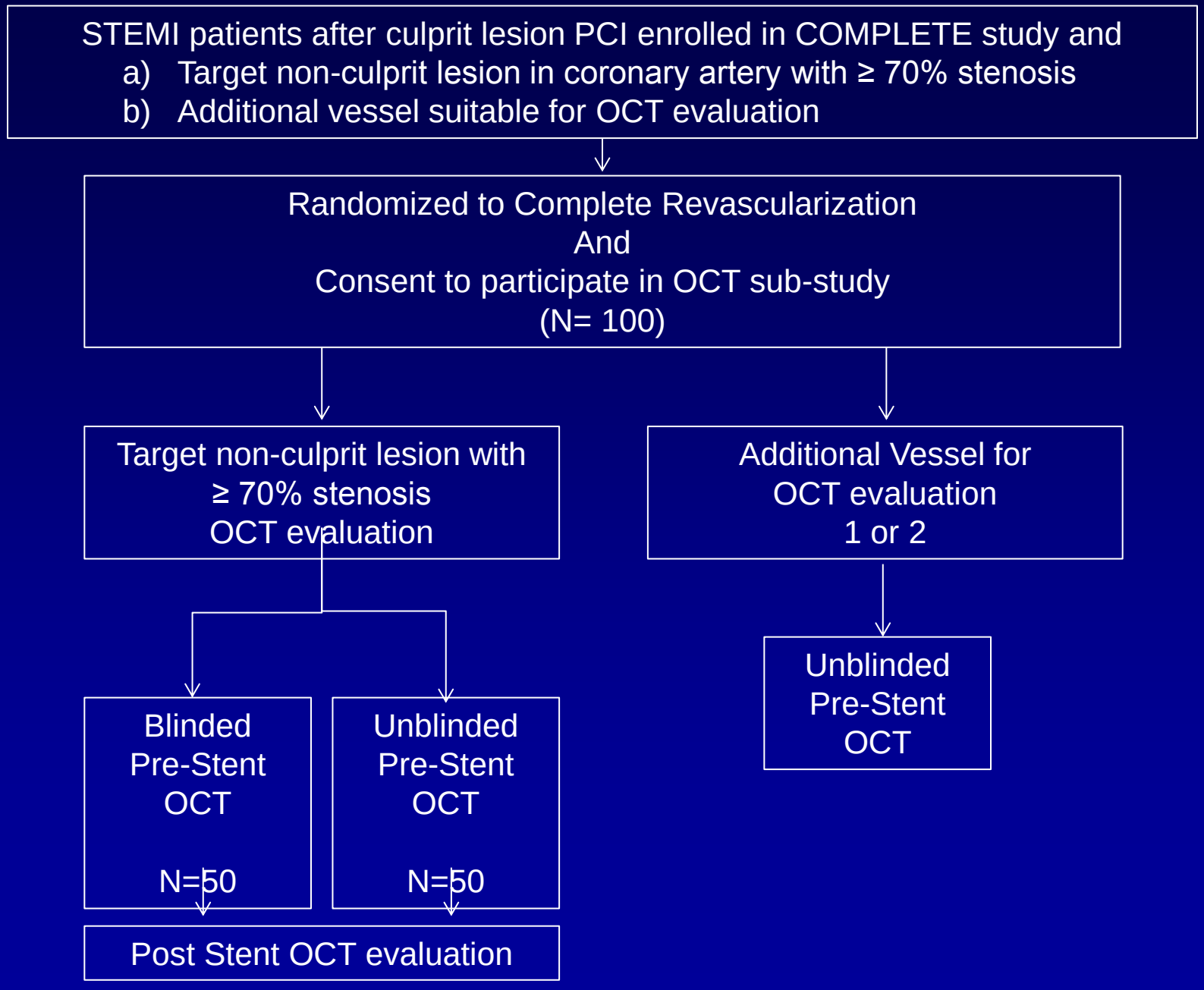
The PROSPECT Trial: MACE

3-year follow-up, hierarchical

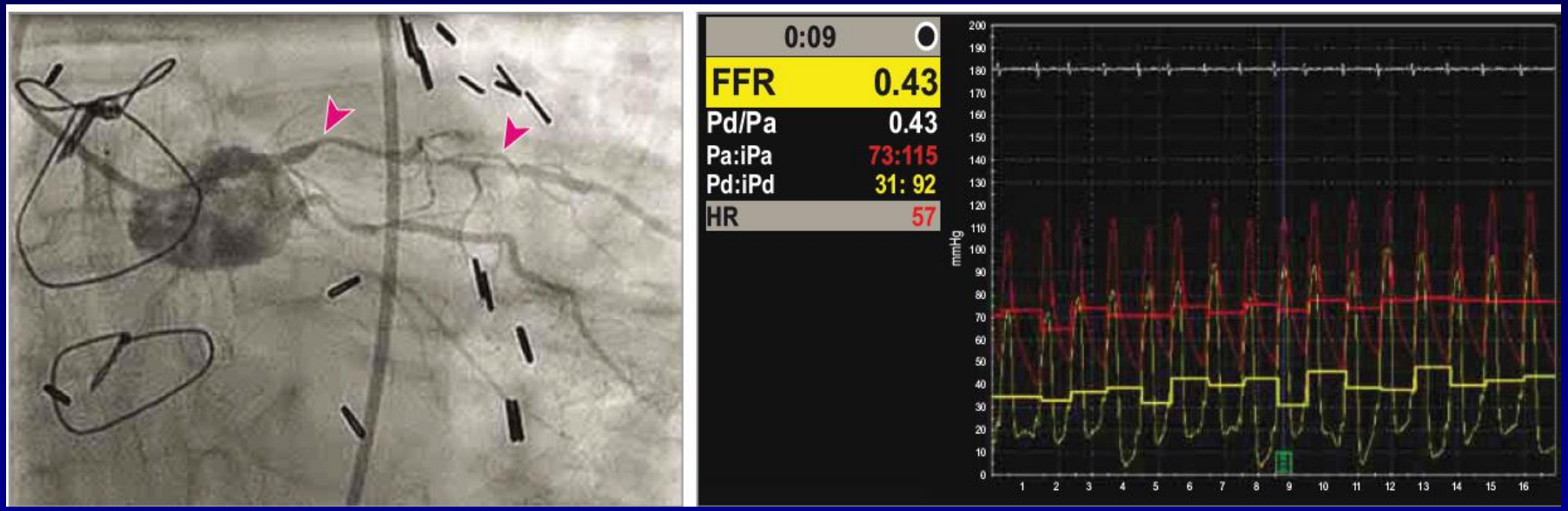
	All	Culprit lesion related	Non culprit lesion related	Indeter-minate
Cardiac death	1.9% (12)	0.2% (1)	0% (0)	1.7% (11)
Cardiac arrest	0.3% (2)	0.3% (2)	0% (0)	0% (0)
MI (STEMI or NSTEMI)	2.7% (17)	1.7% (11)	1.0% (6)	0.2% (1)
Rehospitalization for unstable or progressive angina	15.4% (101)	10.4% (69)	10.7% (68)	0.8% (5)
Composite MACE	20.4% (132)	12.9% (83)	11.6% (74)	2.7% (17)
Cardiac death, arrest or MI	4.9% (31)	2.2% (14)	1.0% (6)	1.9% (12)

Rates are 3-yr Kaplan-Meier estimates (n of events)

COMPLETE OCT Substudy



FFR - Serial Stenoses



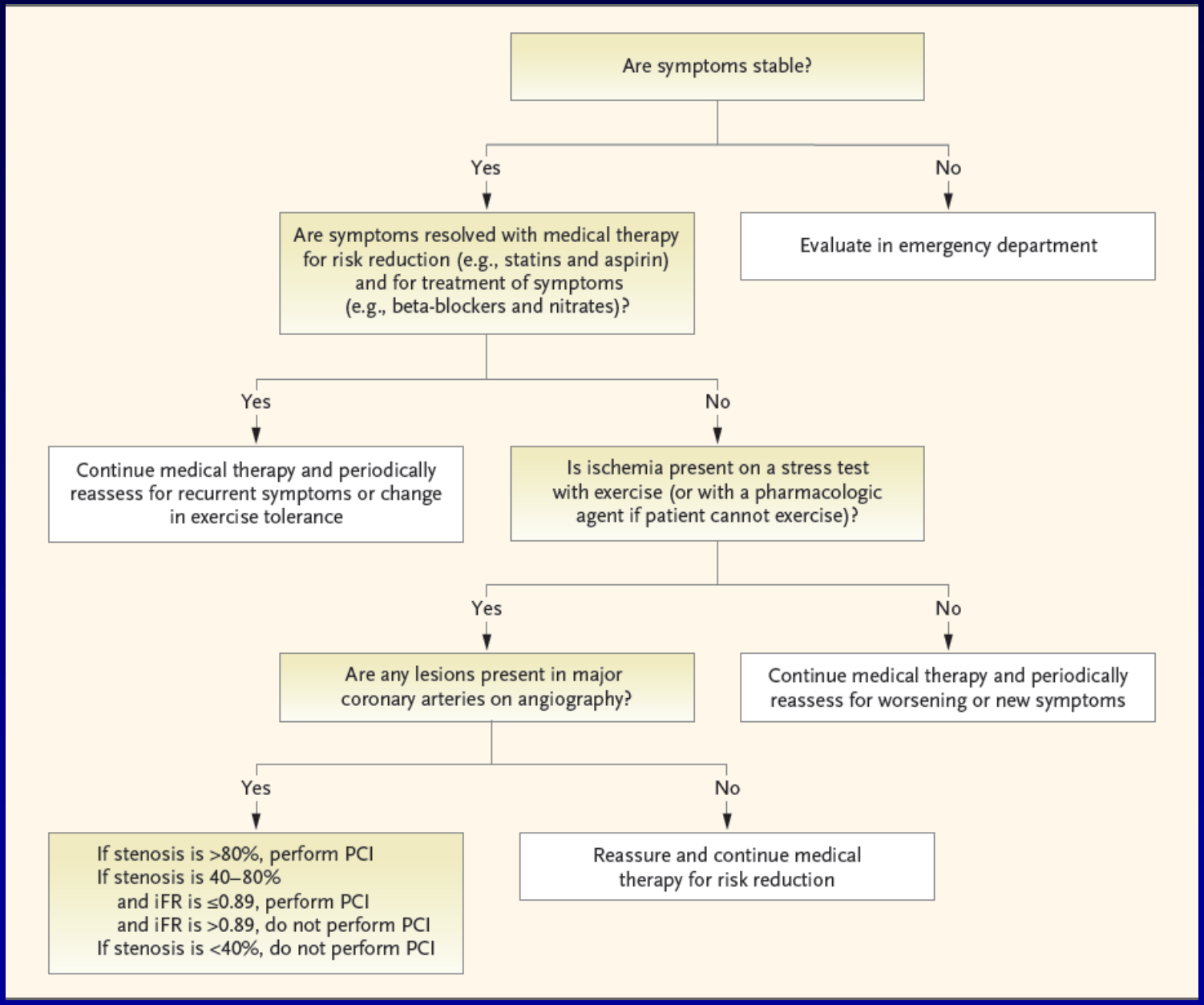
Flow through one lesion can affect FFR in the other!

Kumbhani and Bhatt. JAMA Cardiology 2016.

DEFINE-FLAIR
iFR-SWEDEHEART

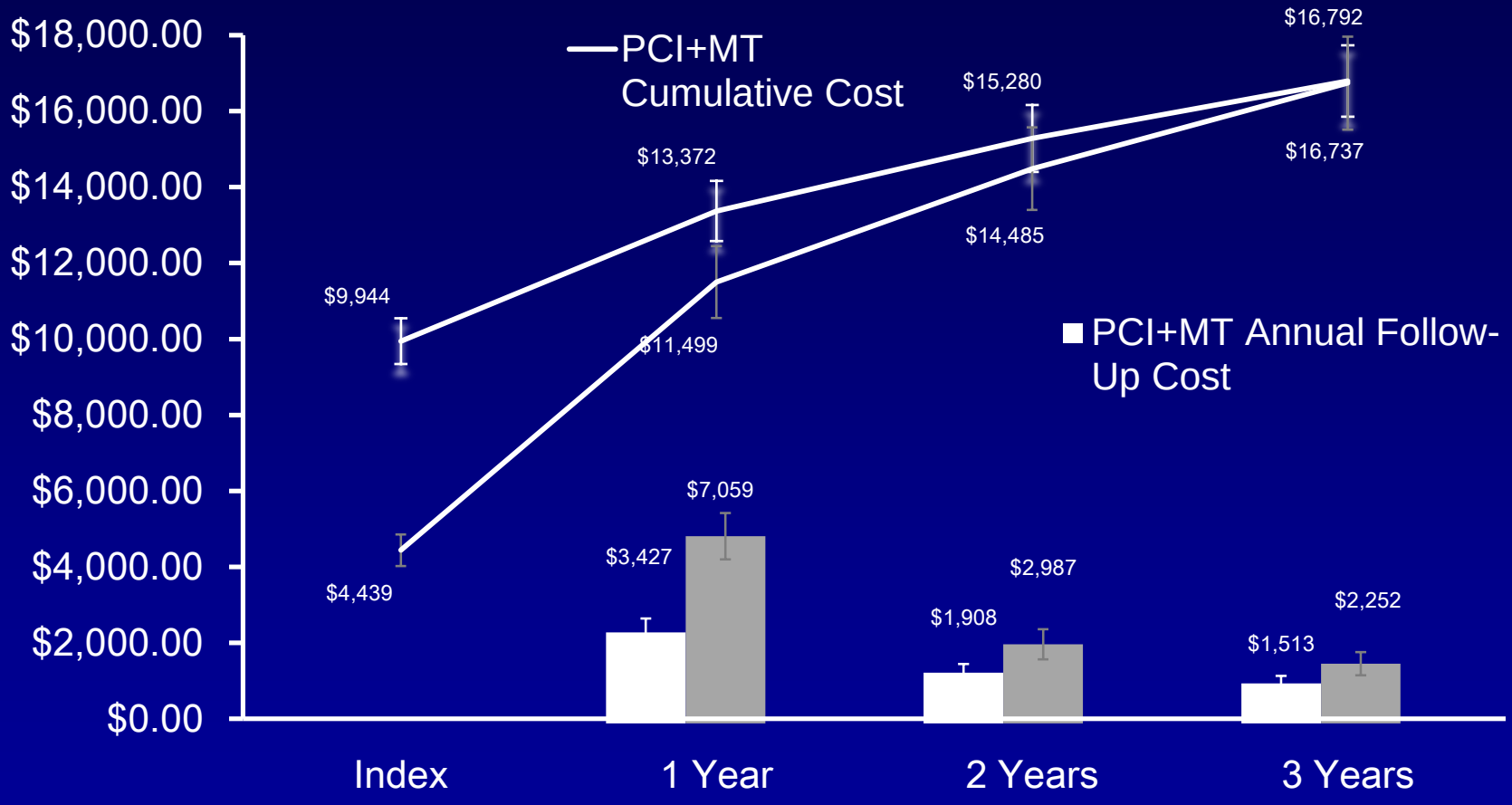
- iFR non-inferior to FFR
- RR 1.03; 95%CI 0.82 to 1.28
- no need for vasodilator for iFR, simplifies MVD
- easier, quicker procedure

Davies et al. NEJM. 2017.
Gotberg et al. NEJM 2017.
Bhatt et al. NEJM 2017.



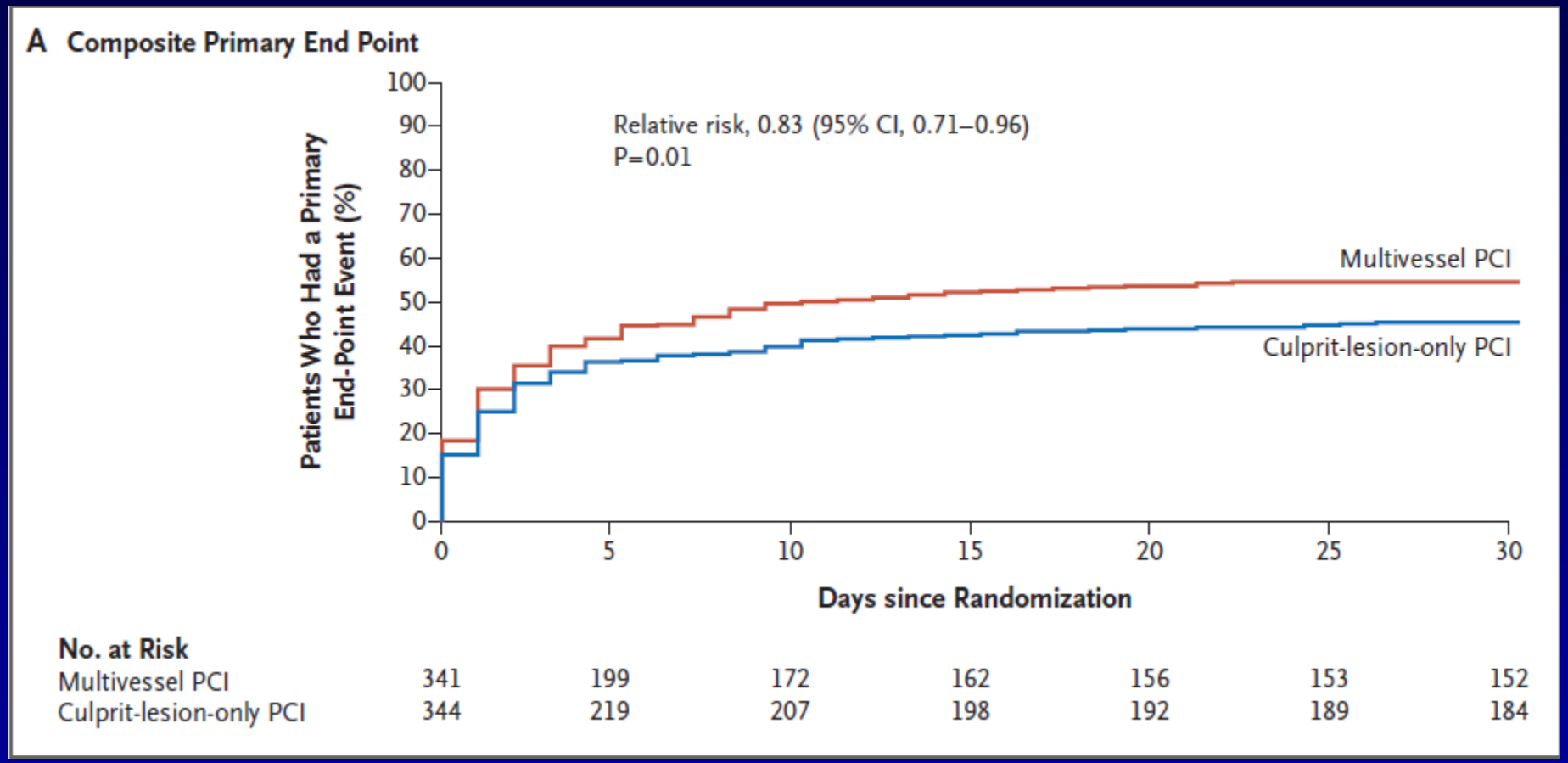
Bhatt DL. NEJM. 2017.

FAME-2 Cost Effectiveness



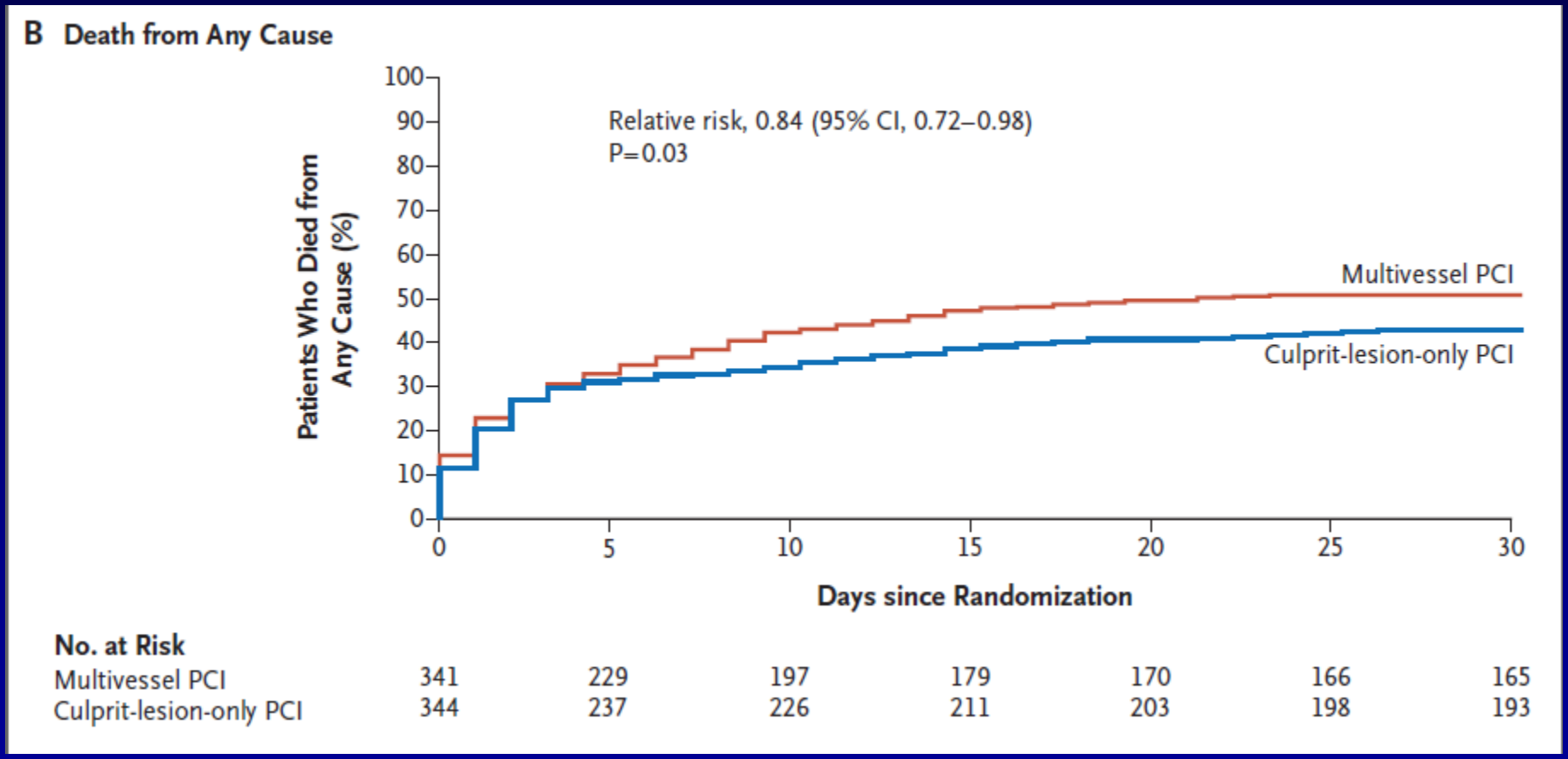
Fearon W et al. Circulation 2017.

CULPRIT-SHOCK (N=706)



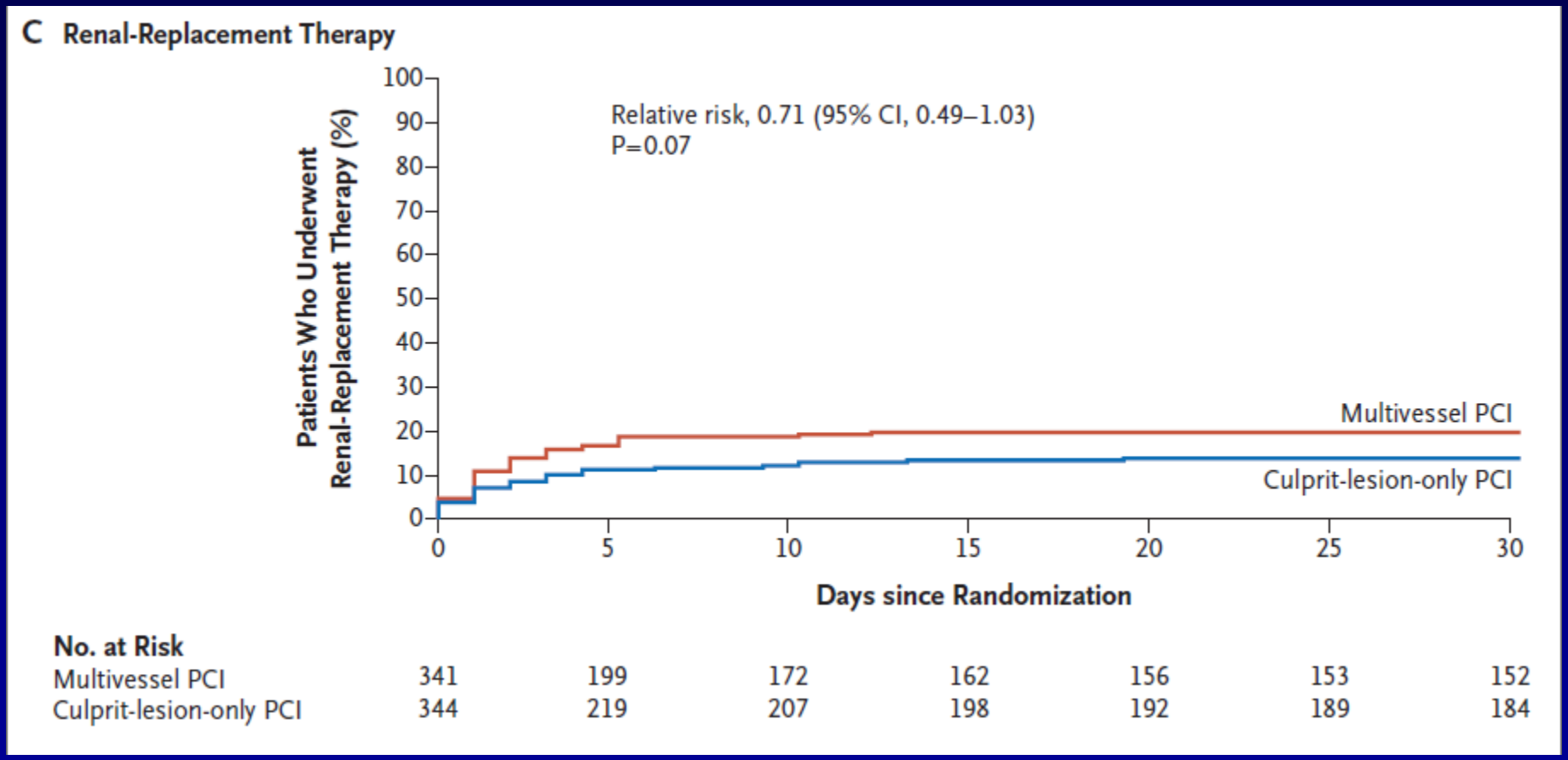
Thiele H et al. NEJM 2017.

CULPRIT-SHOCK (N=706)



Thiele H et al. NEJM 2017.

CULPRIT-SHOCK (N=706)



Thiele H et al. NEJM 2017.

Stroke, Renal Failure, Bleeding

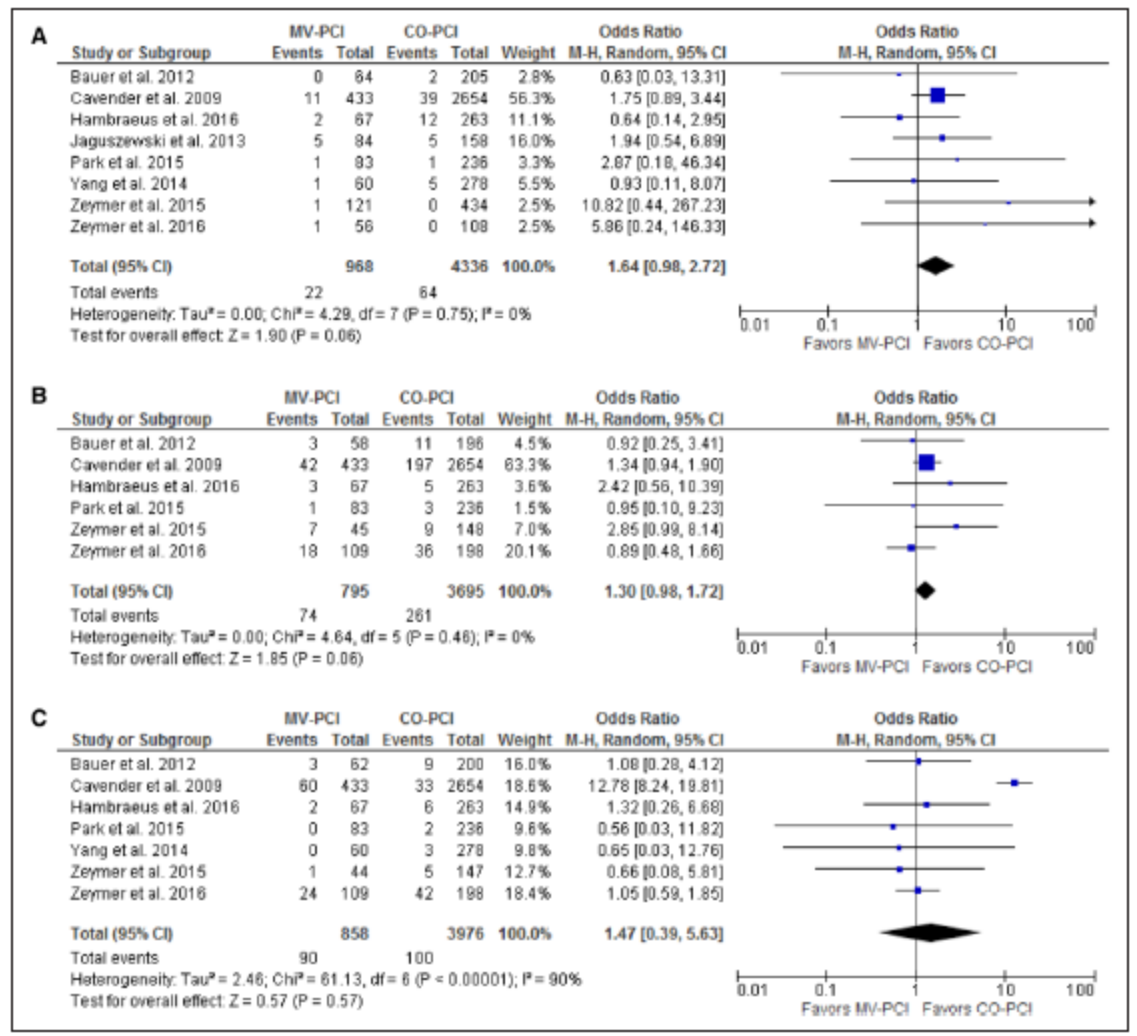


Figure 7. Comparison of in-hospital stroke (**A**), renal failure (**B**), and major bleeding (**C**) after multivessel (MV) versus culprit vessel–only (CO) percutaneous coronary intervention (PCI). Studies included in this analysis are Bauer et al,[6] Cavender et al,[13] Hambraeus et al,[15] Jaguszewski et al,[16] Park et al,[19] Yang et al,[21] Zeymer et al,[1] and Zeymer et al.[22] CI indicates confidence interval.

Kolte D et al. Circulation Intervention 2017.

Conclusions

- Timely primary PCI for STEMI remains the optimal therapy
- Non-culprit PCI in “stable” STEMI reduces future revascularization
- Suggestion that complete revascularization may influence death/MI
- Trials, such as COMPLETE, are ongoing and powered for death/MI
- DEFINE-FLAIR and iFR-SWEDEHEART show value of iFR (~FFR)
- FAME-2 shows cost effectiveness of FFR for stable lesions
- CULPRIT-SHOCK shows harm with complete revasc in shock!
- Since harm in sick STEMI, need to question benefit in stable STEMI

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Thank You!

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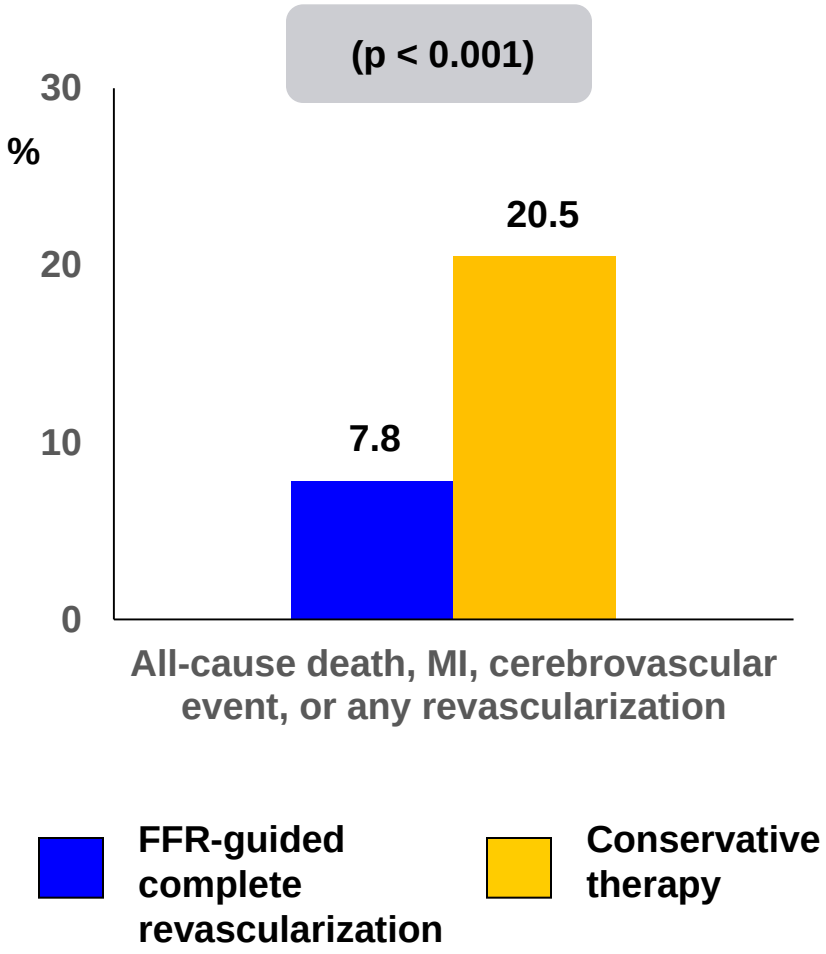
Compare-Acute

Trial design: STEMI patients undergoing primary PCI were randomized to FFR-guided complete revascularization (n = 295) versus infarct artery only revascularization (n = 590).



Results

- All-cause death, MI, cerebrovascular event, or any revascularization at 12 months: 7.8% of the complete group versus 20.5% of the infarct artery only group (p < 0.001)
- MI: 2.4% for complete vs. 4.7% for infarct artery only (p = 0.10)
- Revascularization: 6.1% for complete vs. 17.5% for infarct artery only (p < 0.001)

Conclusions

- Among STEMI patients undergoing primary PCI, FFR-guided complete revascularization was superior to infarct artery only revascularization. In most cases, FFR-guided complete revascularization occurred during the index procedure and was associated with a reduction in adverse cardiovascular events.

Smits PC, et al. N Engl J Med 2017;