CABG & OMT Evolving Again ?

Microcirculation & OMT+Adherence

New York, Dec 9, 2016

No Disclosures

Revascularization for CAD
OMT vs CABG+OMT vs PCI+OMT

1980's. LMD, The Rule of 2 / 3 – CABG

-Moderate <LVEF

-Severe Ischemia

-3 Vessel Disease

or 2vd + pLAD

[1]Severe - Yes, STICH

Moderate – COURAGE OMT

ISCHEMIA

[1]2vd in DM

1990's. The Rule of 2 / 3 – PCI ?

2000's[1]. PCI <, CABG > (DM), Microc., OMT

2020,s. Anatomical, Isch.Score, Microc.: Ninv. - OMT+

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Revascularization for CAD

OMT vs CABG+OMT vs PCI+OMT

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2vd + pLAD

[1]Severe - Yes, STICH

Moderate – COURAGE OMT

ISCHEMIA

[1]2vd in DM

1990's. The Rule of 2 / 3 – PCI ?

2000's[1]. PCI <, CABG > (DM), Microc., OMT

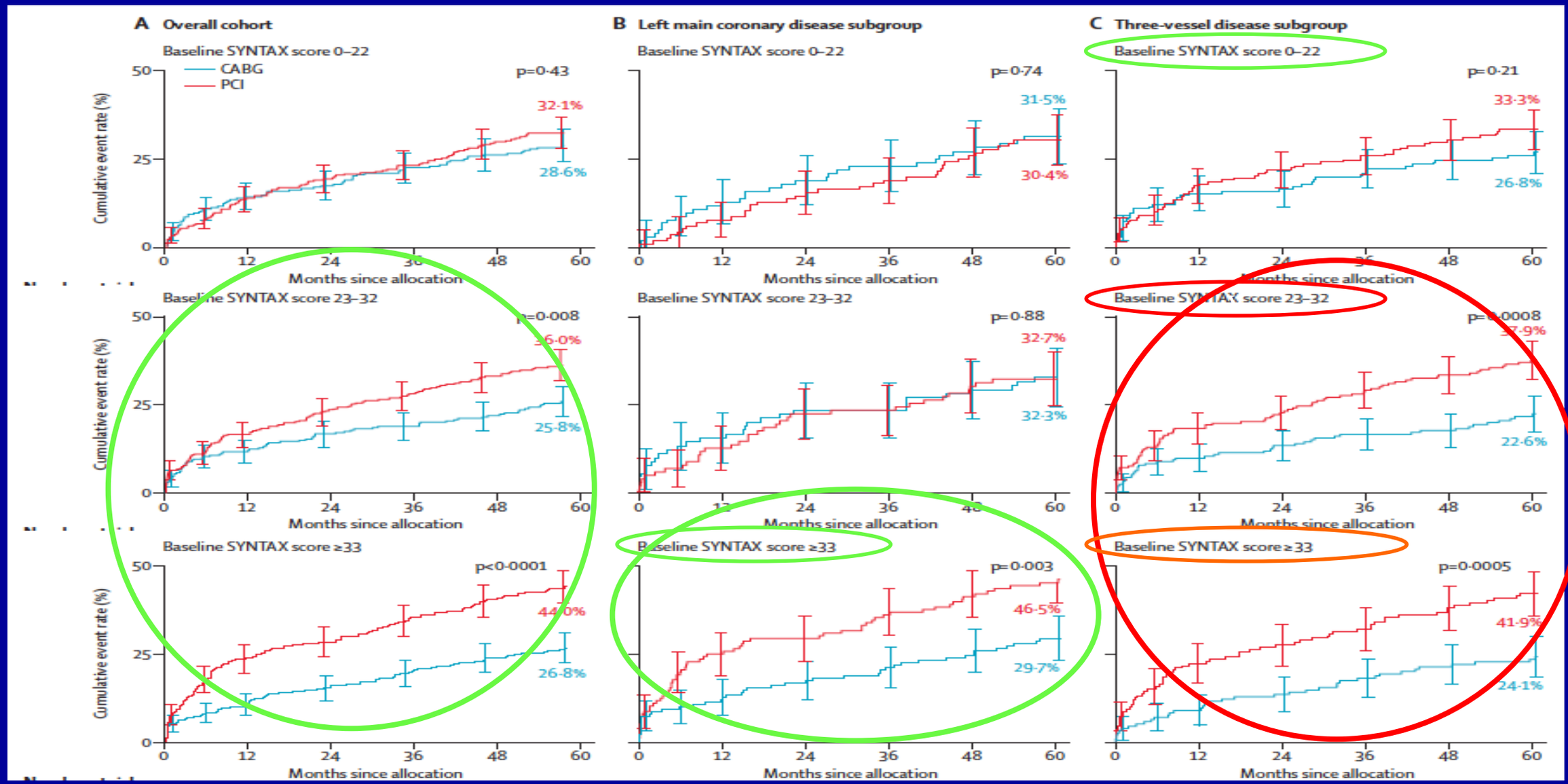
2020,s. Anatomical, Isch.Score, Microc.: Ninv. - OMT+

COMPLEX, STABLE CORONARY DISEASE

TRIAL	MVD	DM	INTERV.	MT.	EP.-R	Data
SYNTAX	+	-	++	-	++	CABG > PCI SYNTAX Score
FAME	-	-	+	-	+	PCI "ISCHEMIA" Score
BARI	-	+	+	+	+	CABG / PCI = MT X.OV.ER 42%
COURAGE	-	-	+	+	+	PCI = MT – X-OVER "ISCHEMIA">10%-Events
FREEDOM	+	+	++	(+)	+	CABG > PCI No Freedom of Choice?

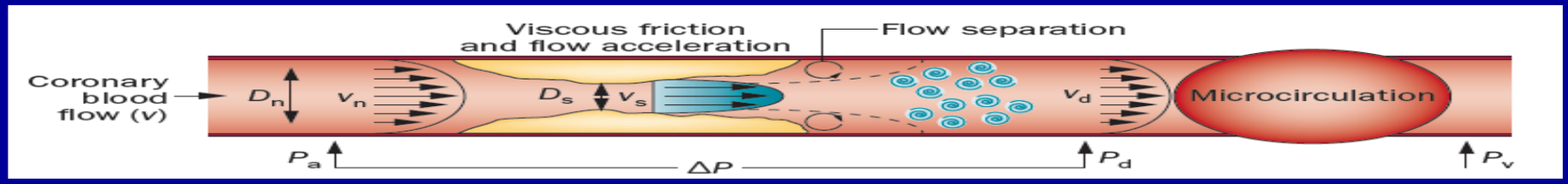
Conditions Methods-Interests Conclusions

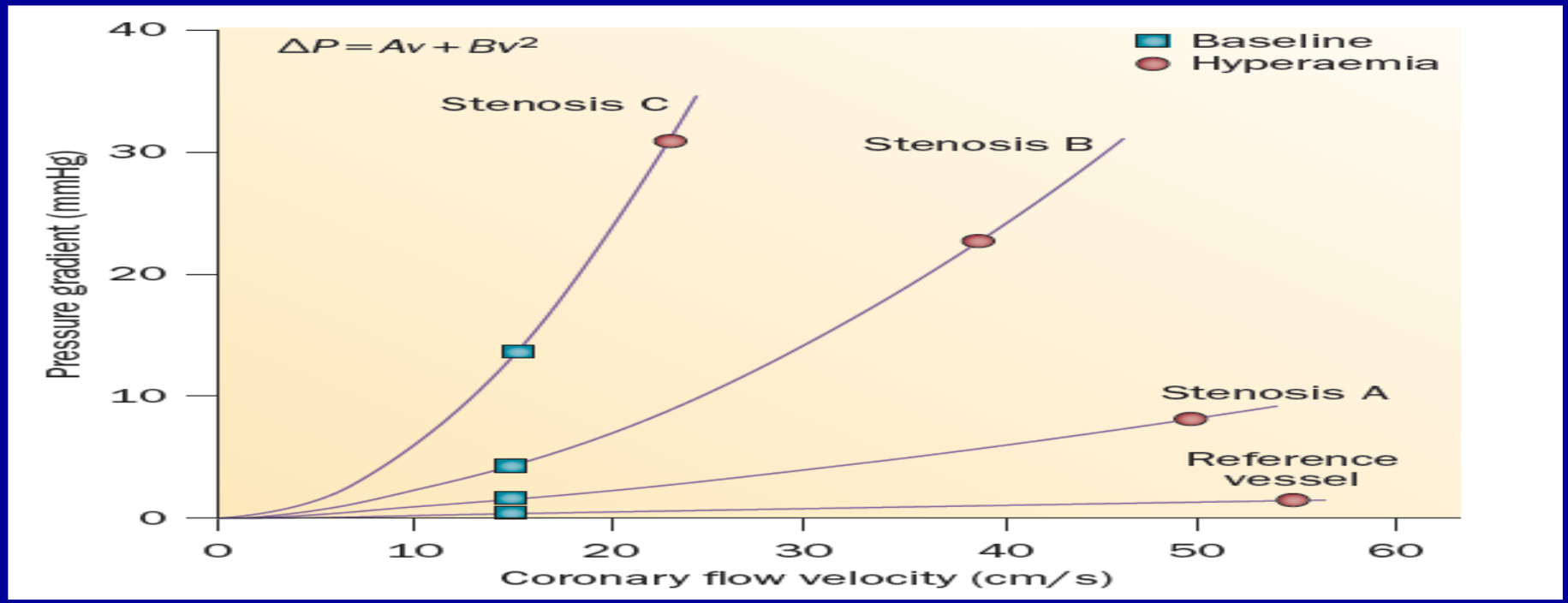
Baseline SYNTAX Score Tercile -CABG
Cumulative Event Curves For MACCE



SYNTAX (FW Mohr, PW Serruys et. al.) Lancet 2013; 381: 629

FFR As A Surrogate For Inducible Myocardial Ischaemia

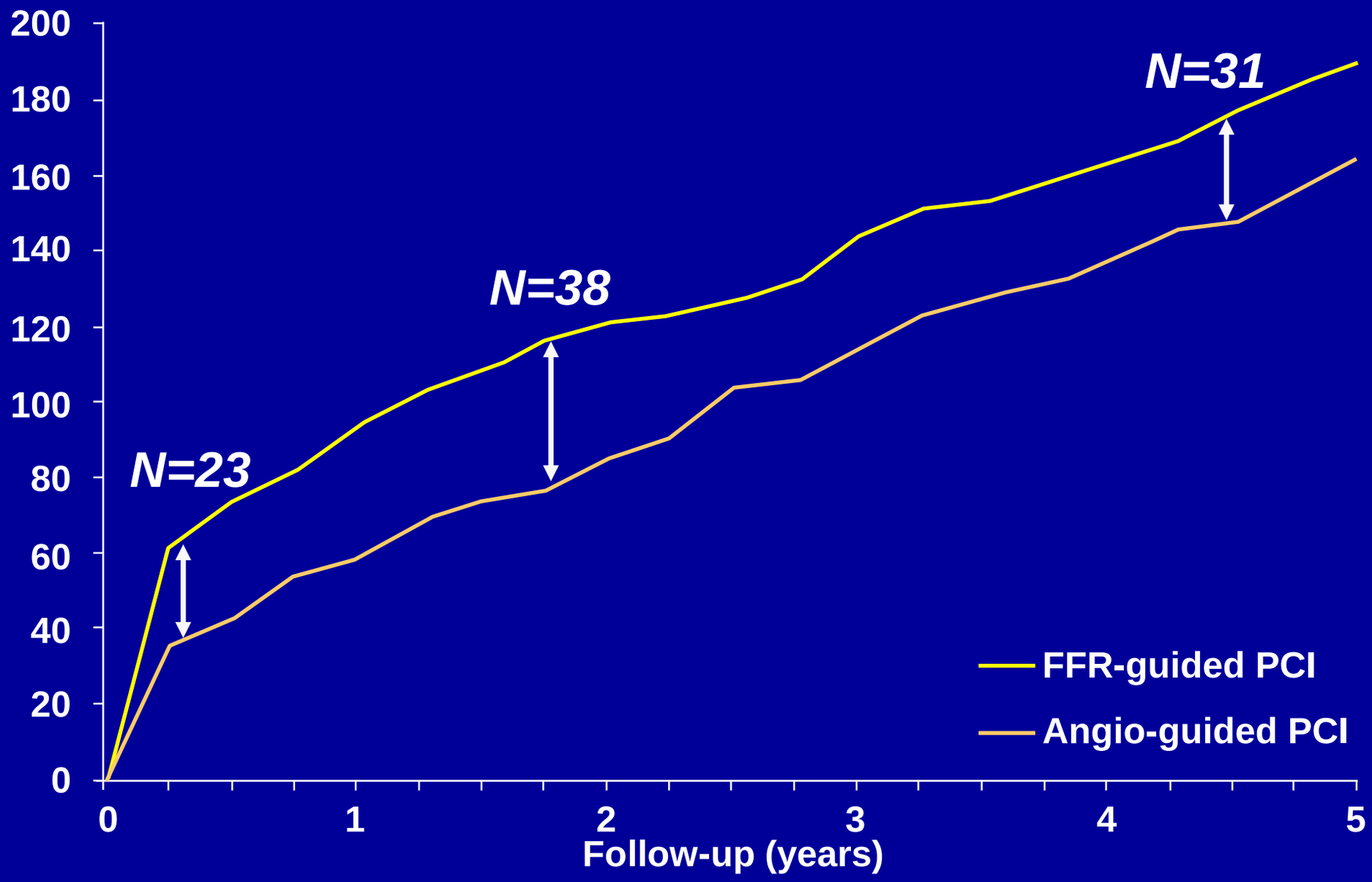




FAME I (FFR>0.8) - OMT of Non-Isch.Les.– Prevent MI/Death
FAME II (FFR<0.8) - PCI Isch. Les. – Prevent MI/Death

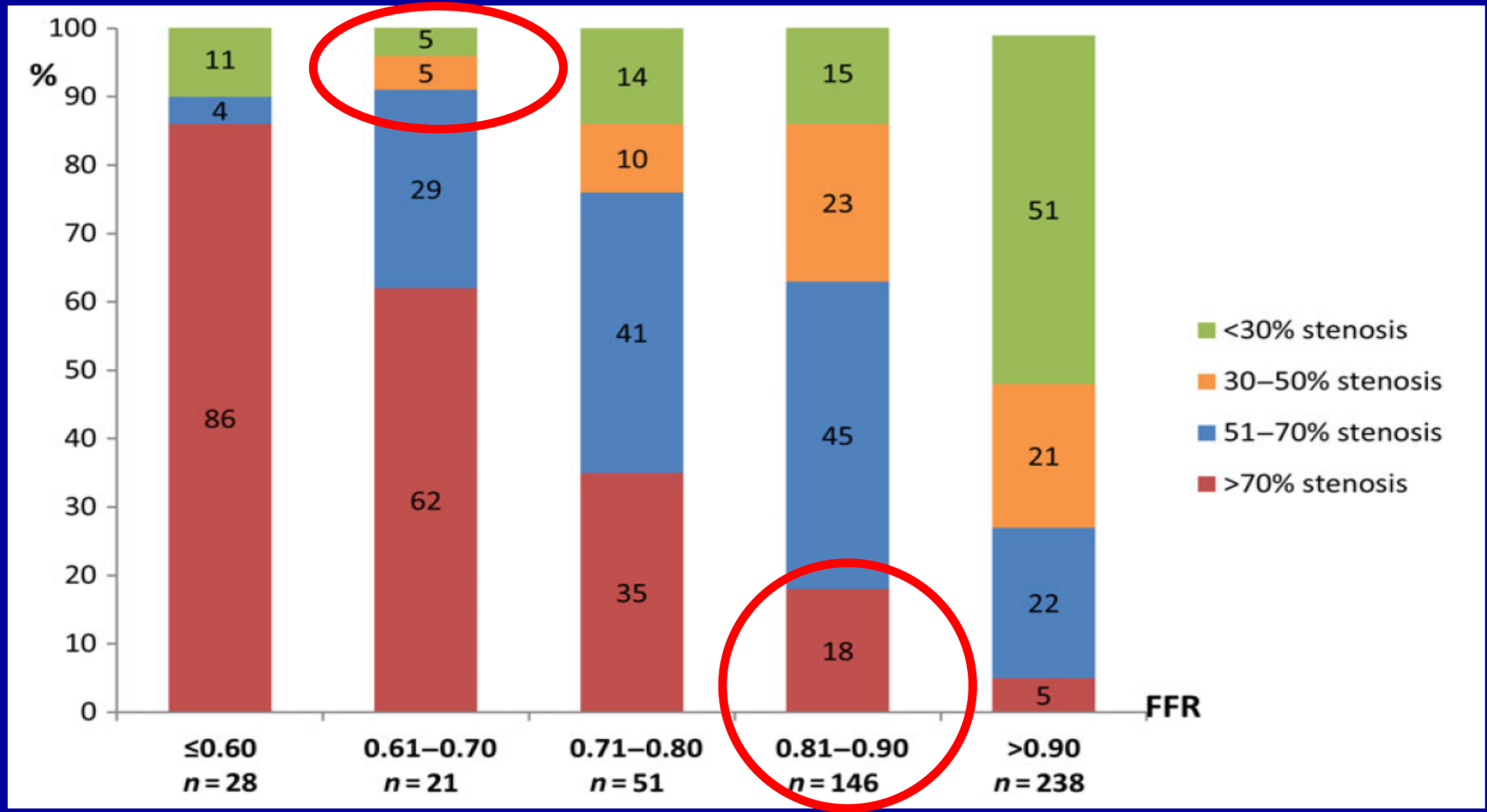
TP van de Hoef Nat. Rev. Cardiol. 2013;10:439 – FAME 2 (B De Bruyne) NEJM 2014; 371:1208

FAME: CUMULATIVE EVENTS DURING 5-YEAR FOLLOW-UP



FAME (LX van Nunen et al., The Lancet 2015; 386:1853

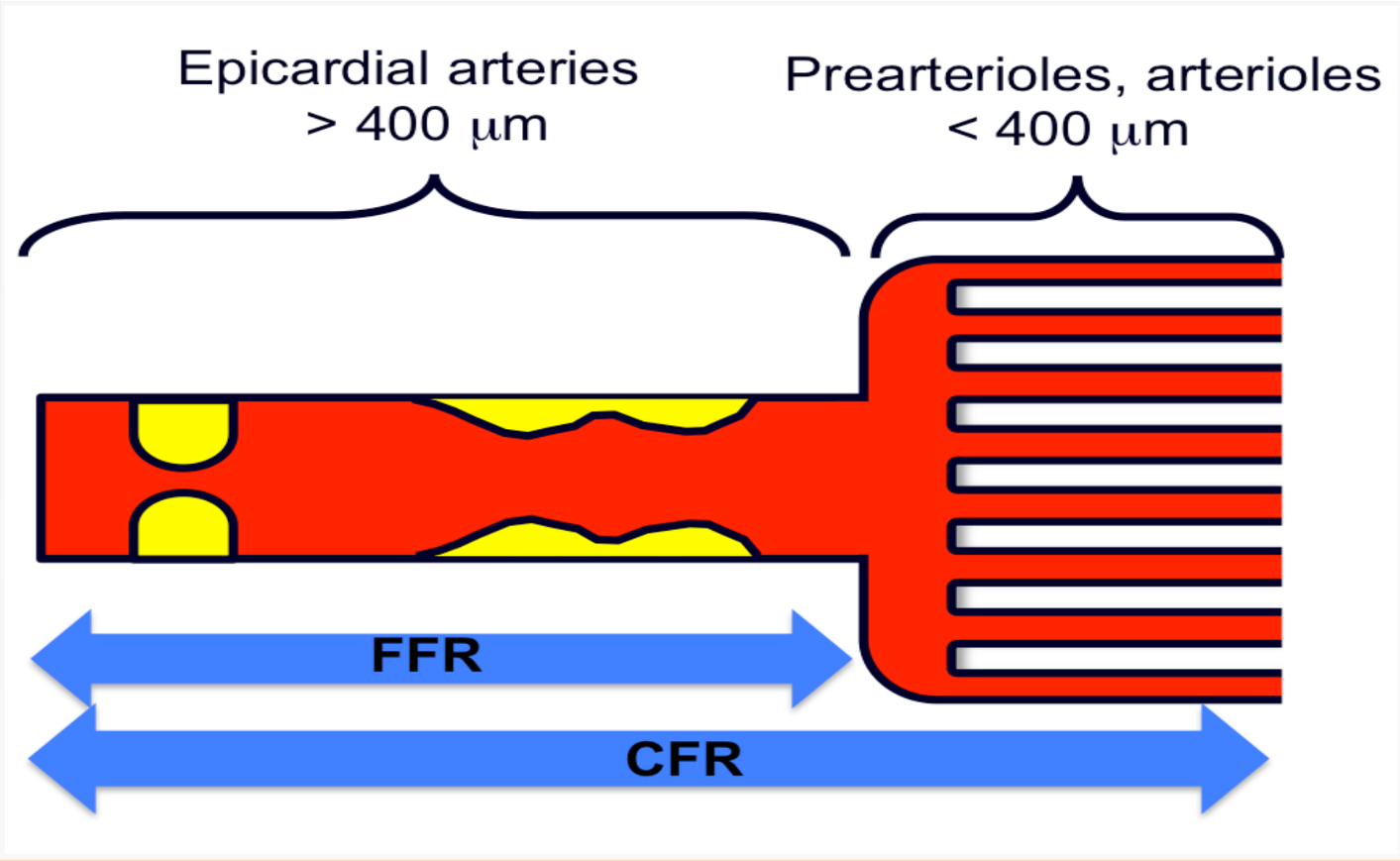
Distribution of Coronary Stenosis Severity Relation To Fractional Flow Reserve



S Gaur et. al. Eur Heart J. 2016;37:1220

Coronary Flow Reserve (CFR)

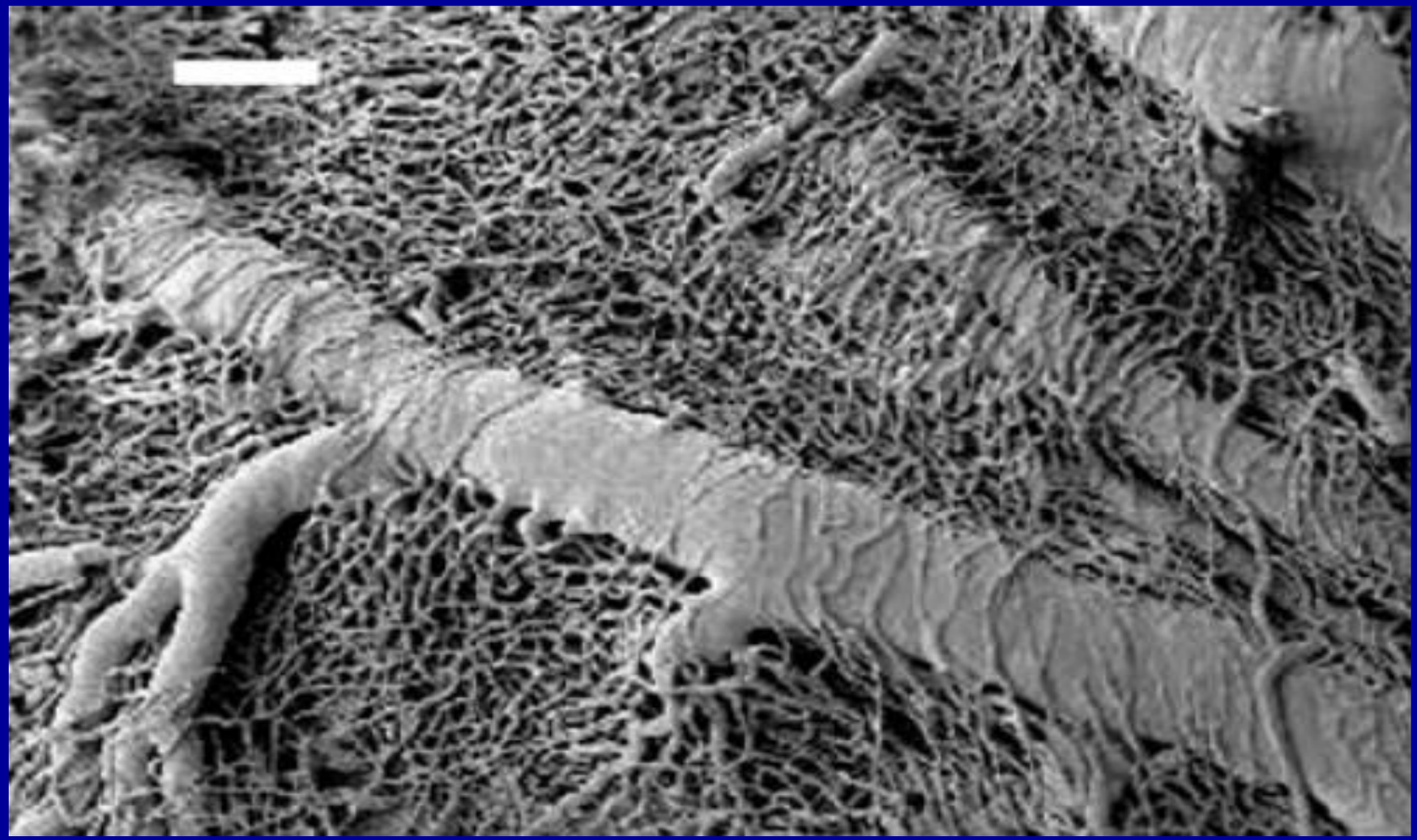
➔ Measures *integrated* hemodynamic effects of epicardial CAD, diffuse atherosclerosis, vessel remodeling and microvascular dysfunction on myocardial tissue perfusion



$$CFR = \frac{MBF_{\text{peak hyperemia}}}{MBF_{\text{rest}}}$$

VR Taqueti and MF Di Carli 2014

Coronary Vascular Regulation, Remodelling, And Collateralization



AR Pries et. al. Eur Heart J. 2015;36:3134

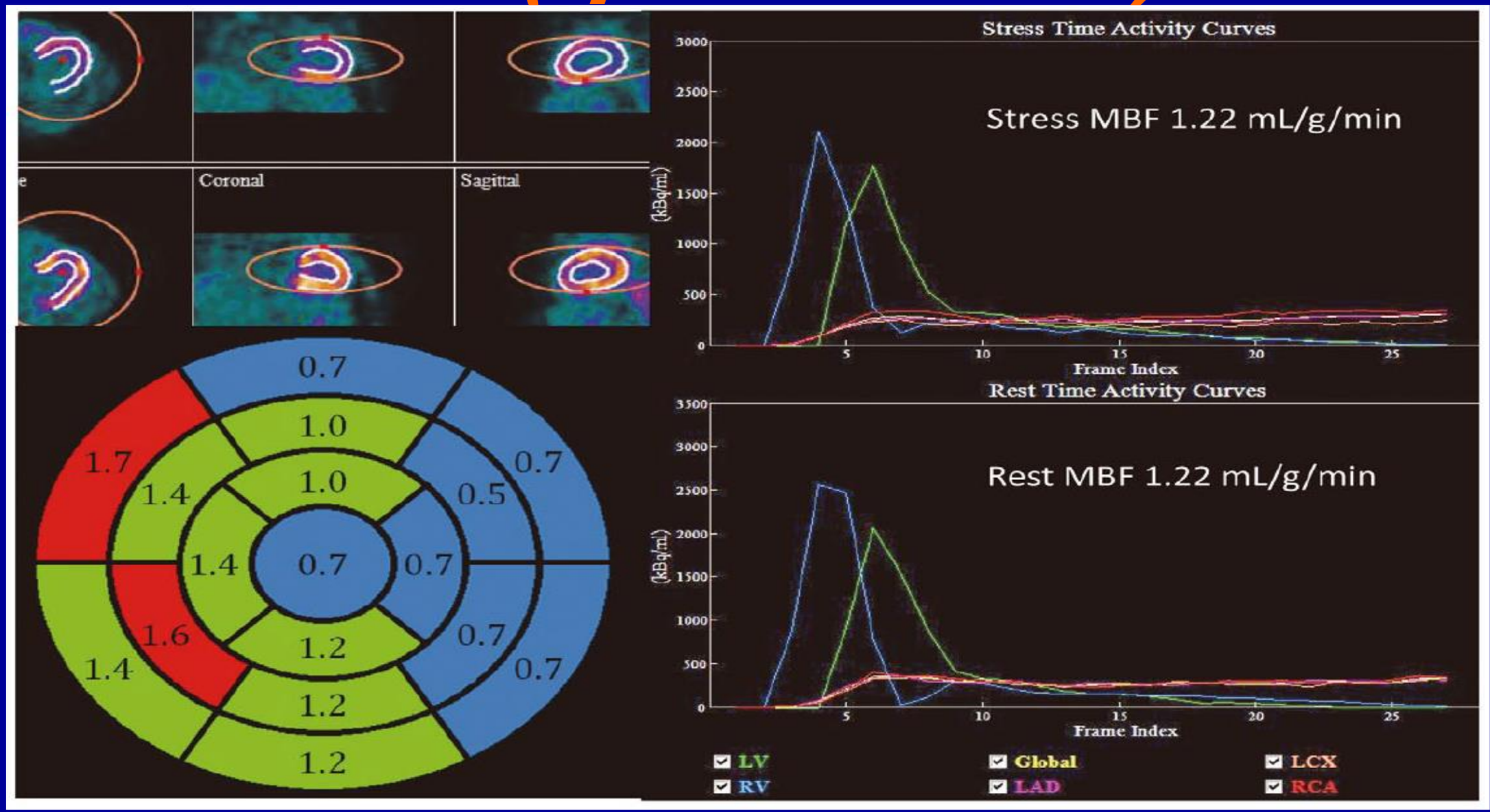
Working Group On Coronary Pathophysiology And Microcirculation

The Human Microcirculation

The microcirculation is responsible for orchestrating adjustments in vascular tone to match local tissue perfusion with oxygen demand. The concept is put forth that vasculoparenchymal communication is multinodal, with vascular release of nitric oxide eliciting dilation and preserving normal parenchymal function by inhibiting inflammation and proliferation. Likewise, in disease or stress, endothelial release of reactive oxygen species mediates both dilation and parenchymal inflammation leading to cellular dysfunction, thrombosis, and fibrosis. This paradigm may help explain why microvascular dysfunction is such a powerful predictor of cardiovascular events and help identify new approaches to treatment and prevention.

DD Gutterman et al., Circ Res 2016; 118:157

A1. 17-segment Coronary Flow Reserve PET (Epic. vs Microv.?)



B Tu et. al. Ann Intern Med. 2014;161:724

A2. MRI / CFR (Epic. vs Microv?)

Cardiac Imaging

Multiparametric Cardiovascular Magnetic Resonance Assessment of Cardiac Allograft Vasculopathy

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Josephine H. Naish, PhD,† Nizar Yonan, MD,*‡ Simon G. Williams, MD,*‡ Steven M. Shaw, PhD,*‡
David Clark, BSc,§ Keith Pearce, BSc,* Martin Stout, PhD,* Rahul Potluri, MBChB,*†
Alex Borg, MD,* Glyn Coutts, PhD,|| Saqib Chowdhary, PhD,*‡ Gerry P. McCann, MD,¶
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Manchester and Leicester, United Kingdom

JACC: CARDIOVASCULAR IMAGING
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Diagnostic Accuracy of Myocardial Magnetic Resonance Perfusion to Diagnose Ischemic Stenosis With Fractional Flow Reserve as Reference

Systematic Review and Meta-Analysis

Min Li, MD, Tao Zhou, MD, Lin-feng Yang, MD, Zhao-hui Peng, MD, Juan Ding, MD, Gang Sun, MD, PhD

JACC 2014;63:799 - JACC Imag. 2014;7: 1936

A3. Diagnostic Evaluation of Chest Pain

Clinical Implications From SCOT-HEART and PROMISE

SCOT-HEART and PROMISE represent the 2 largest and most comprehensive CV imaging outcome trials in patients with stable chest pain and provide significant insights into patient diagnosis, management, and outcomes. The overall goal was to better inform the practicing clinician in the selection of noninvasive testing for stable chest pain. Similarities and differences between SCOT-HEART and PROMISE are highlighted, and clinical and practical implications are discussed. Both trials show that CT angiogr. should have a greater role in the diagnostic pathway of patients with stable chest pain.

CB Fordyce et al., JACC 2016; 67:843

CT Angiography Derived FFR Feasibility Further Information (Both, Epic. & Microc.)

In symptomatic patients with suspected CAD, CTA improves patient selection for invasive CA compared with functional testing. The impact of measuring by CTA (FFR_{CT}) is unknown. At 11 sites, 584 patients with new onset chest pain were prospectively assigned to receive either usual testing (n=287) or CTA/FFR_{CT}(n=297). Test interpretation and care decisions were made by the clinical care team. **CTA/FFR was a feasible and safe alternative to ICA and was associated with a significantly lower rate of invasive angiography showing no obstructive CAD.**

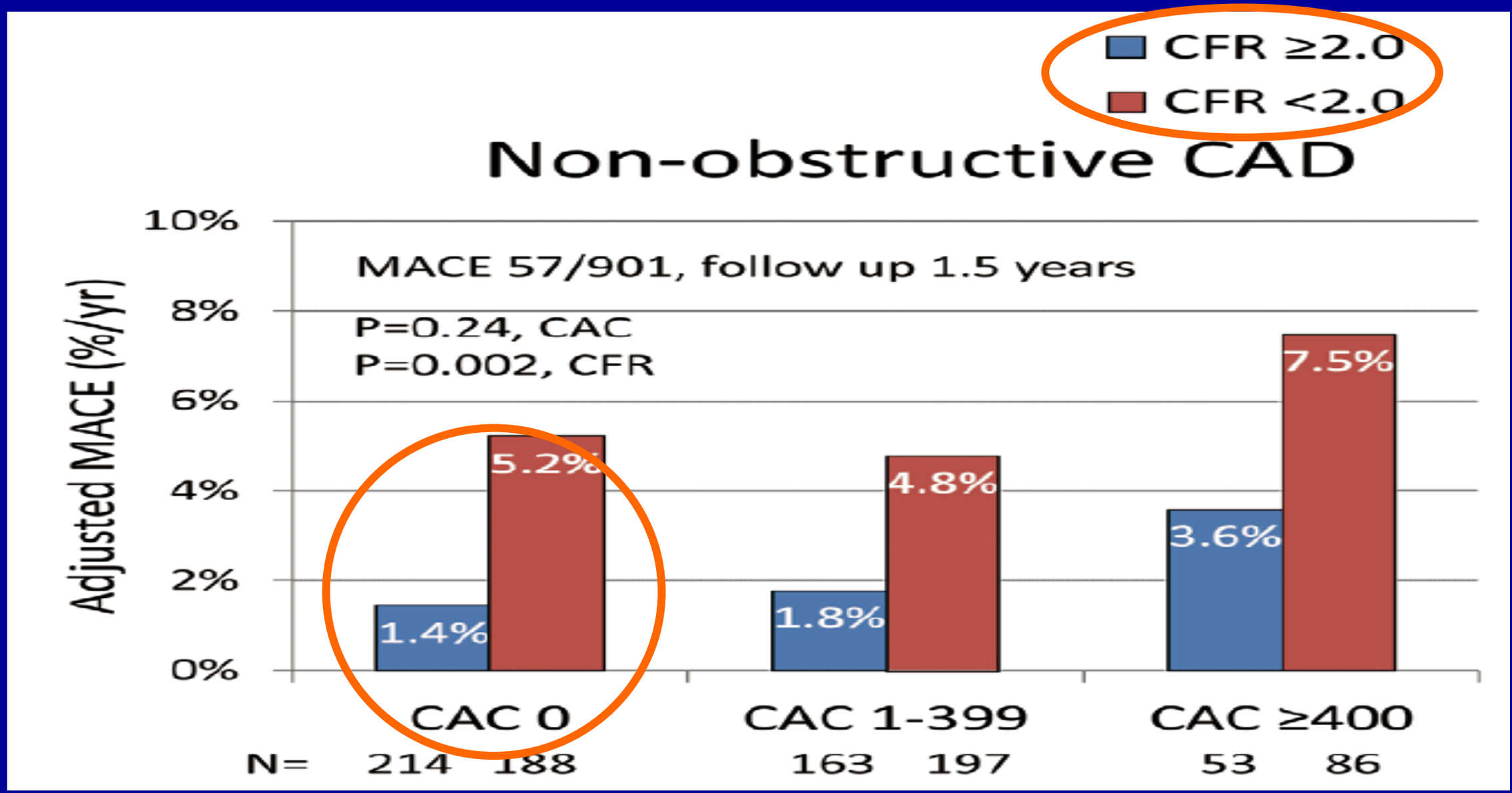
PLATFORM *(PS Douglas et al.) Eur Heart J 2015; 36:3359*

CT Angiography Derived FFR Feasibility (Both, Epic. & Microc.)

In symptomatic patients with suspected CAD, CTA improves Coronary calcification was assessed by using the Agatston score (AS) in 214 patients suspected of having CAD who underwent coronary CTA, FFR_{CT}, and FFR. The diagnostic performance of FFR_{CT} (≤0.80) in identifying vessel-specific ischemia (FFR ≤0.80) was investigated across AS quartiles. FFR_{CT} provided high and superior diagnostic performance compared with coronary CTA interpretation alone

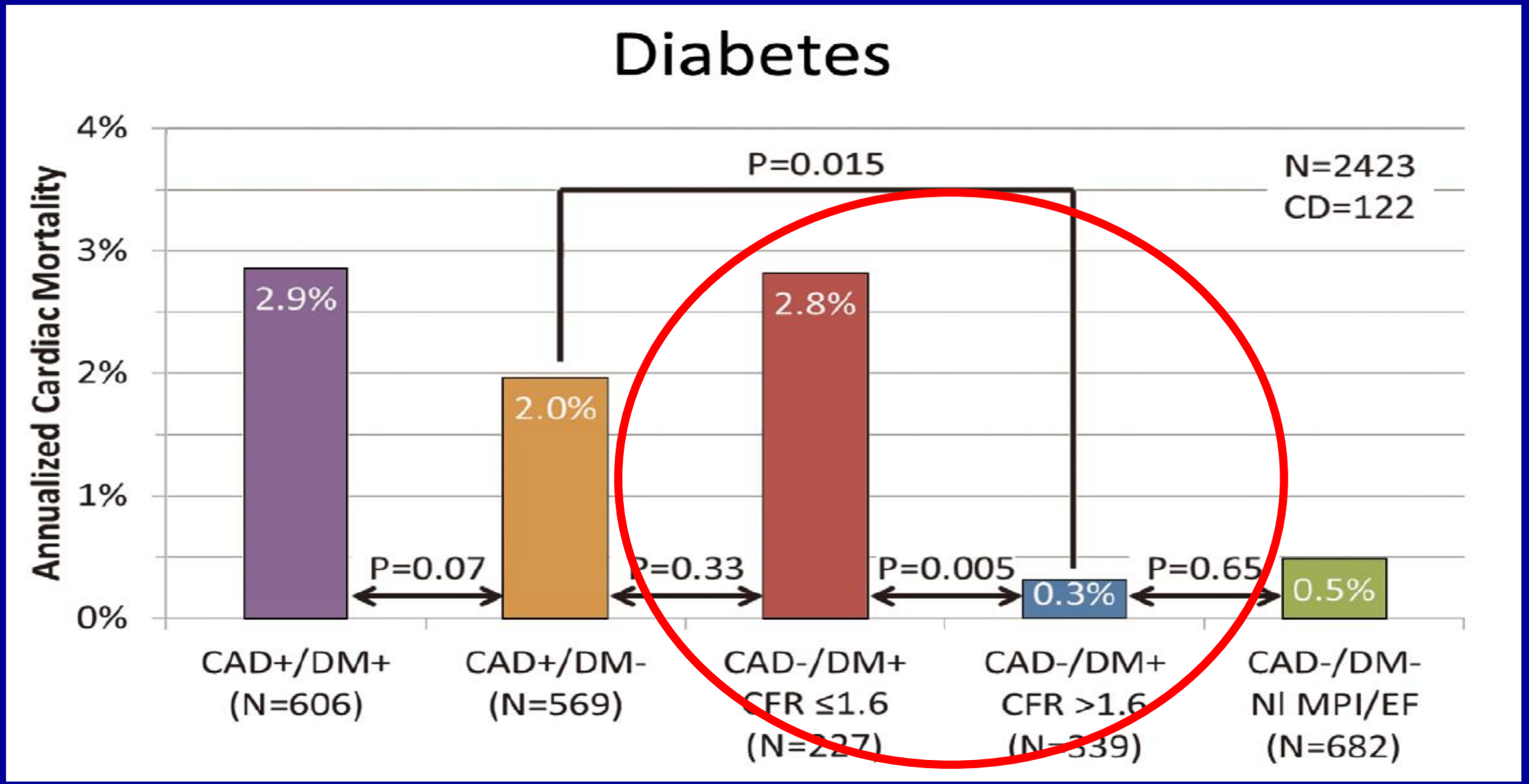
***NXT Trial** (BL Nørgaard et al.), J Am Coll Cardiol Img 2015; 8:1045*

B1. Impaired CFR & Zero CAC - MACE



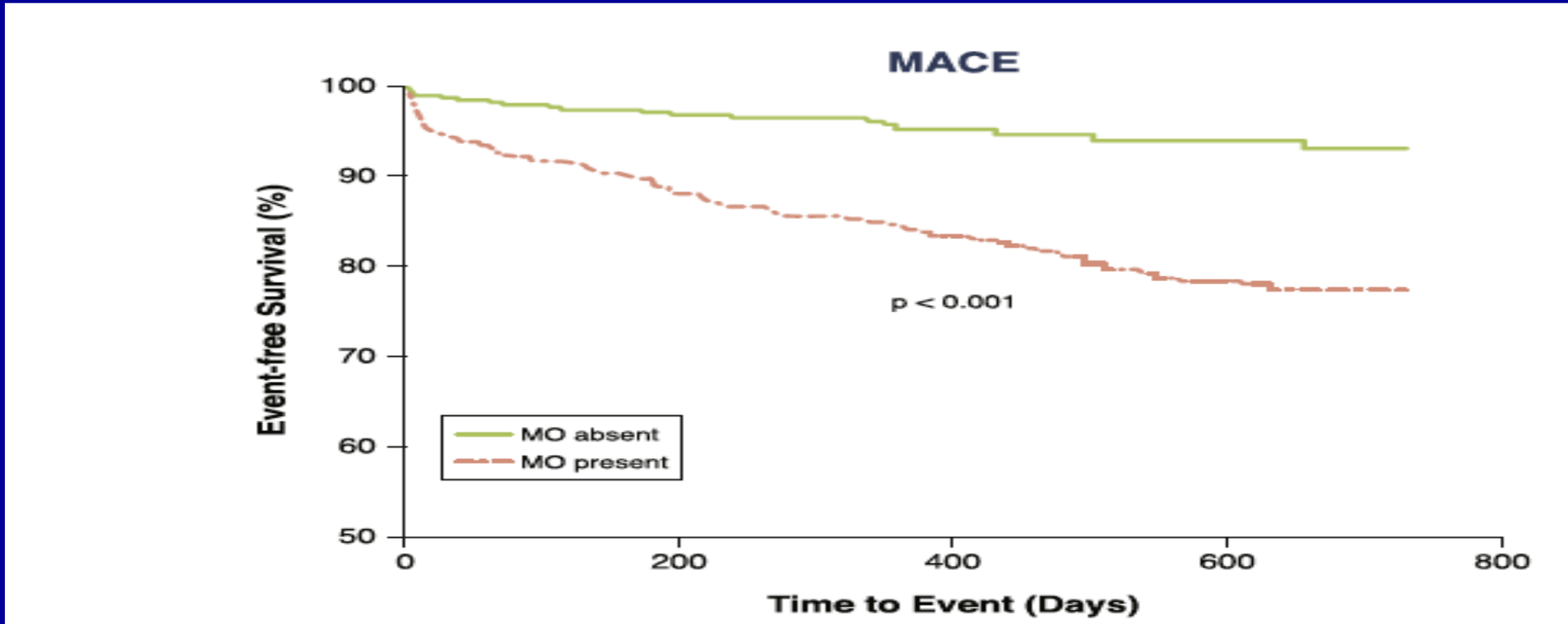
M Naya et. al. JACC 2013;61:2098 - M Naya et. al. Circ J 2015; 79: 15

B2. Diabetes - CFR w/wo Epicardial CAD, Relation To Cardiac Death



VL Murthy et. al. Circulation 2012;126:1858 - M Naya et. al. Circ J 2015; 79: 15

B3. Prognostic Value of Microvascular Obstruction and Infarct Size, as by CMR in STEMI Patients

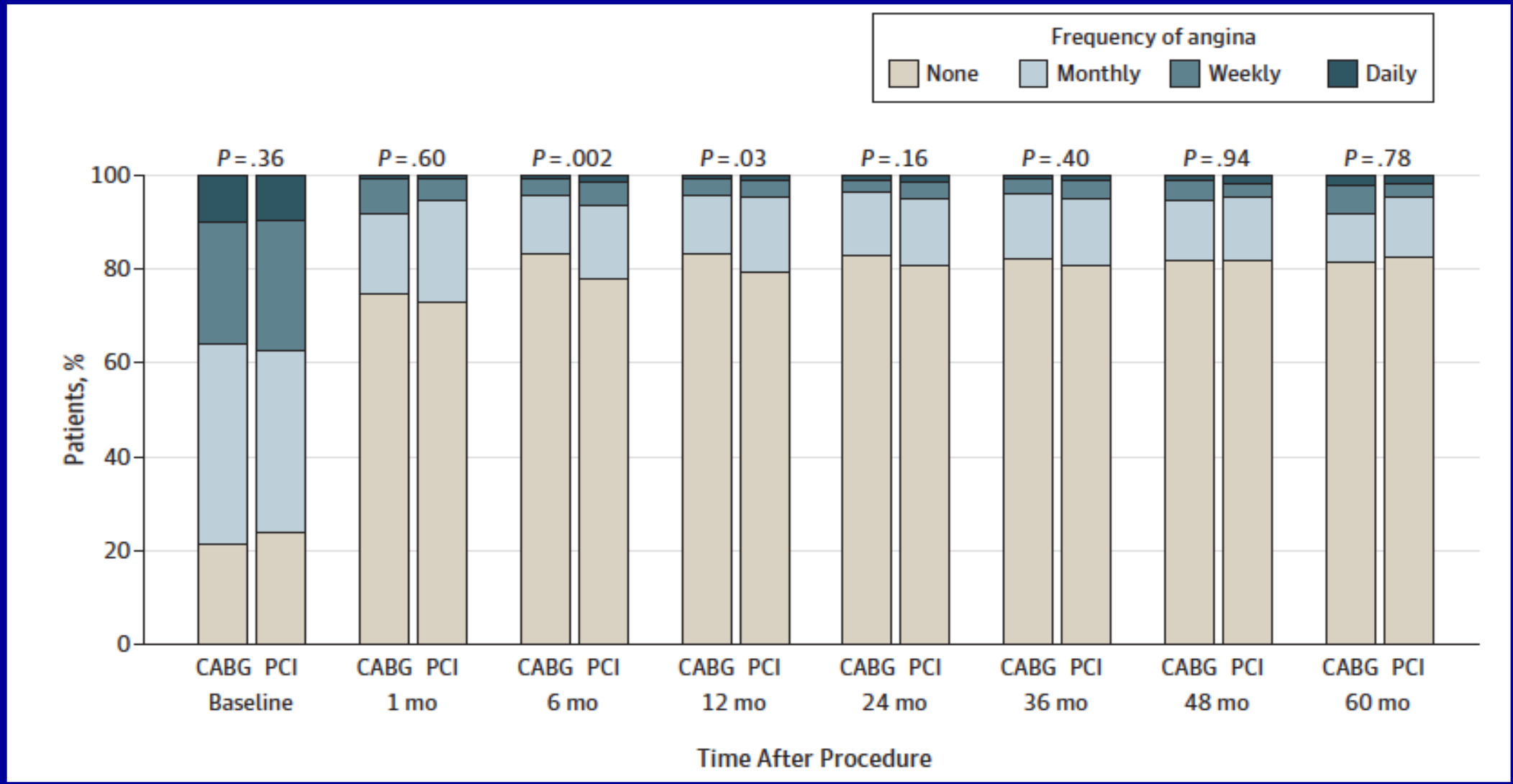


Number at Risk					
MO absent	447	293	161	119	93
MO present	566	379	256	168	114

MO - Visualized With Late Gadolinium Enhancement, Defined As Any Region Of Hypoenhancement Within The Hyperenhanced Area

M van Kranenberg et. al. J Am Coll Cardiol Img 2014;7:930

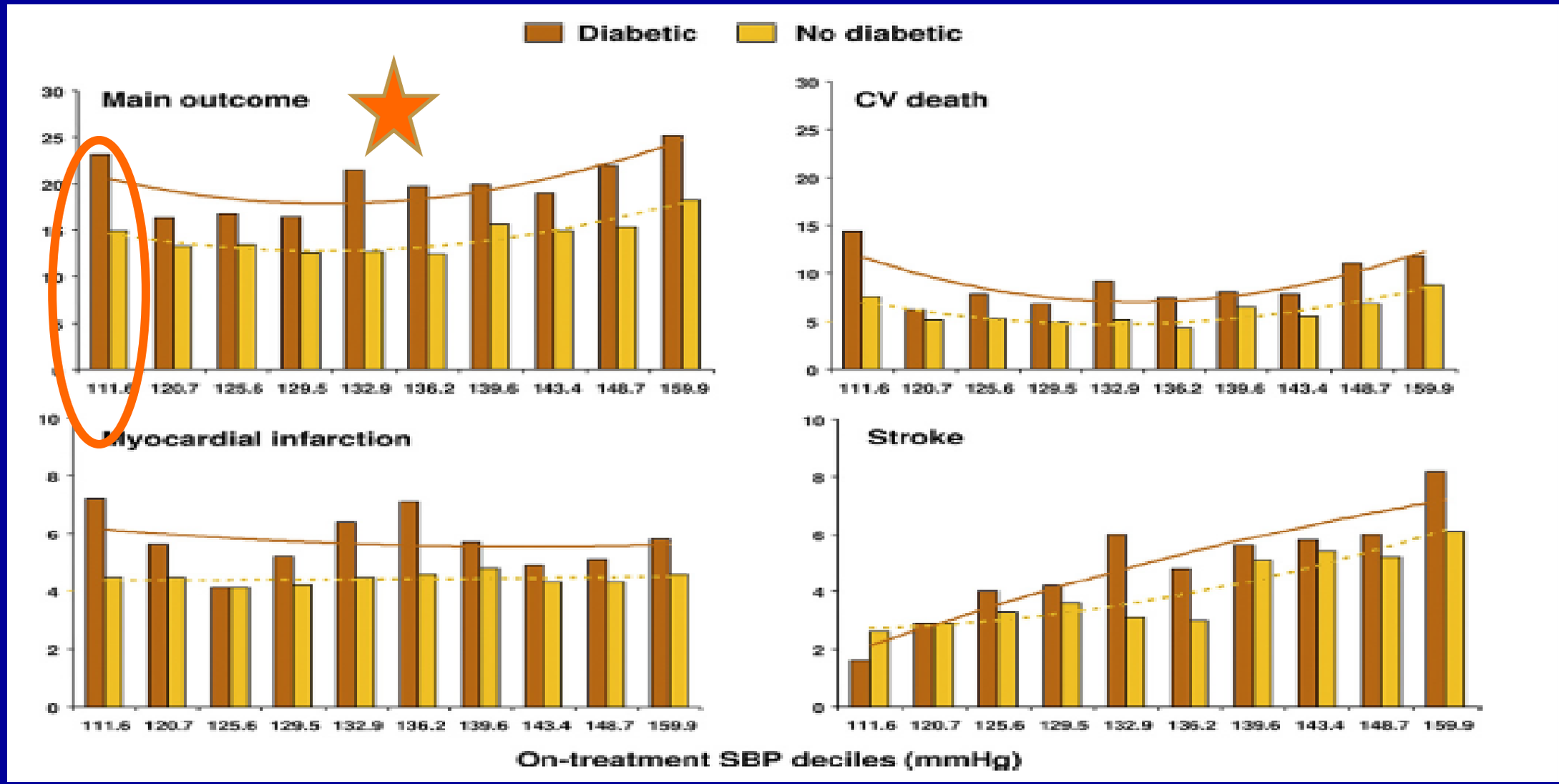
B4. Angina During Follow-up



FREEDOM *(MS Abdallah, V Fuster et. al.) JAMA. 2013;310(15):1581*

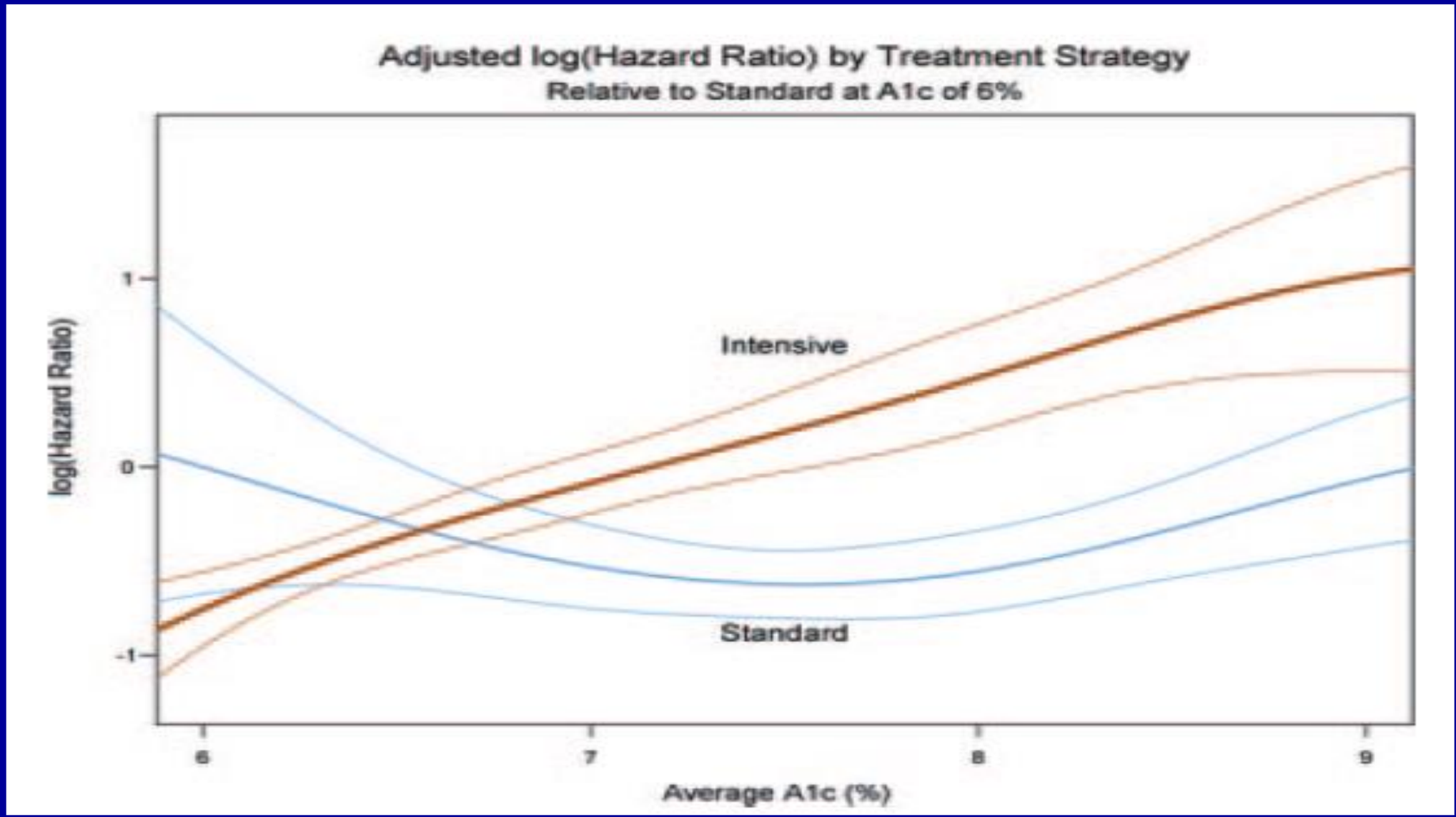
SJ Head et. al. EHJ. 2014;35:2821 – ***Usually, Angina in PCI > CABG***

B5. Proportion of Outcome Event by Achieved SBP - ONTARGET Trial



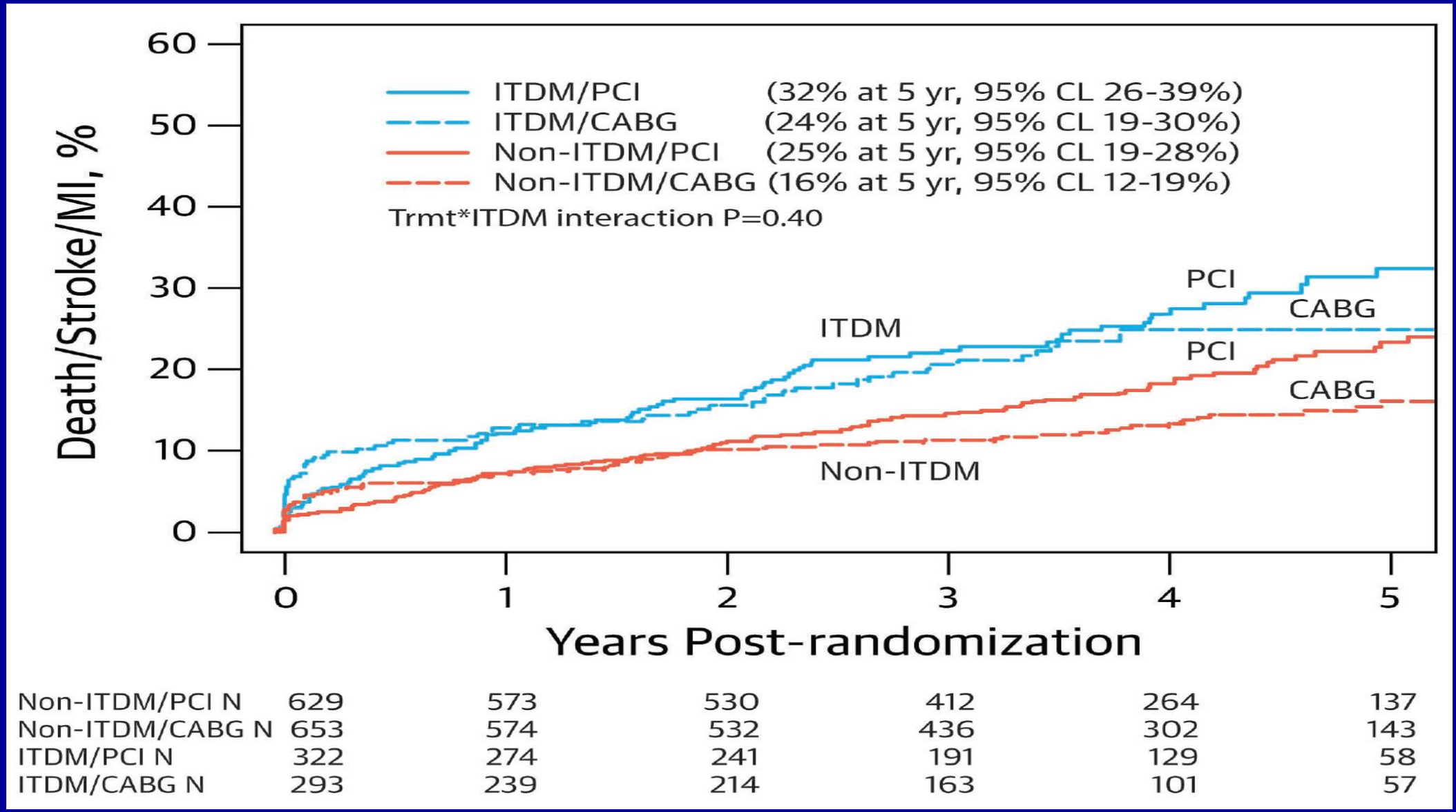
ONTARGET (J Redon et. al.)J ACC2012;59:74 – Microvasculature, Underperfusion ?
FREEDOM (M Farkouh, V Fuster) 2016 (In Press)

B6. Mortality in the ACCORD Population Over a Range of On-treatment HbA1c Values



ACCORD (MC Riddle et al) Circ 2010;122:844 - *Microvascular / Catecholamines*

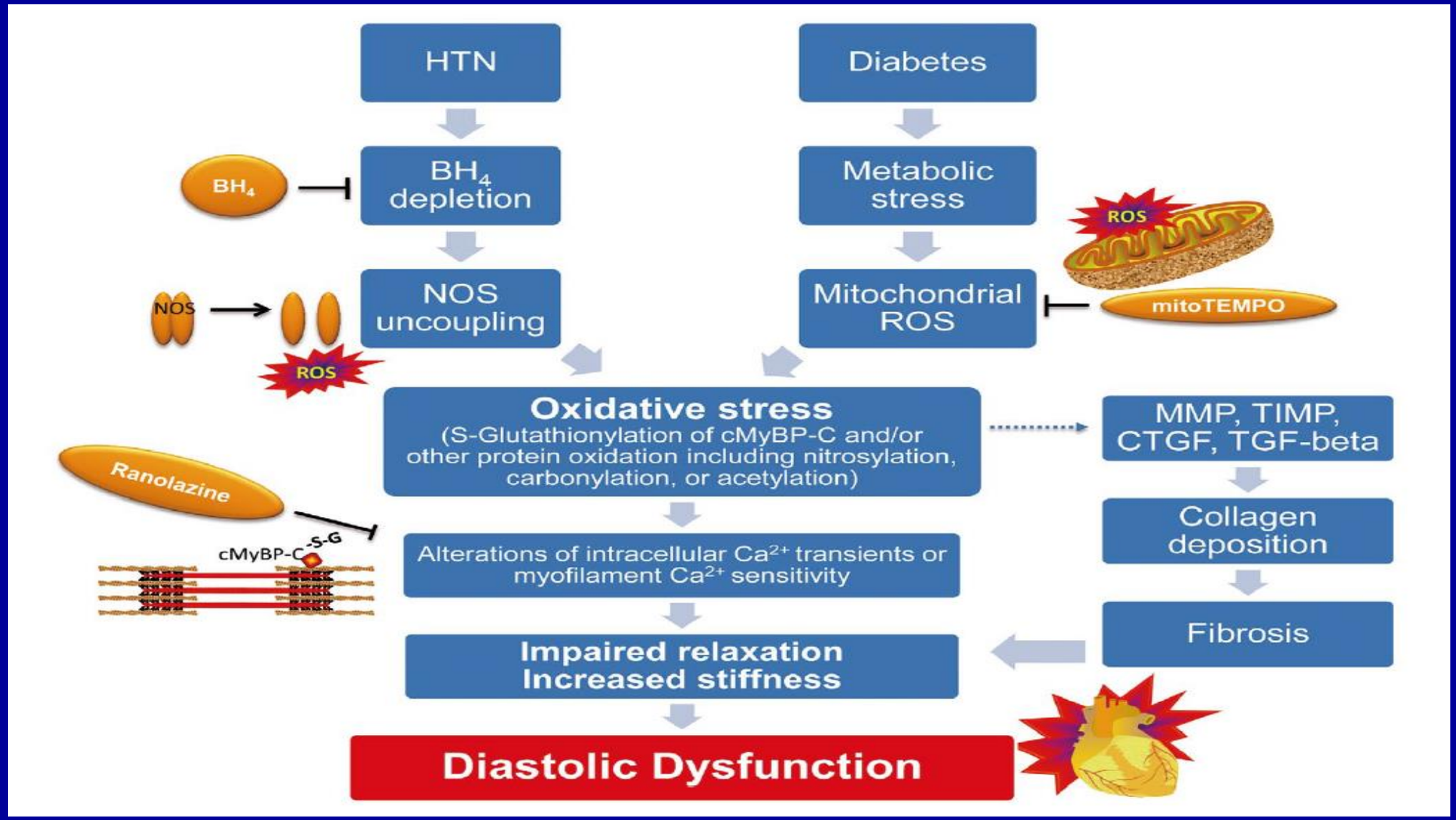
B7. PCI versus CABG in Insulin and Non-Insulin Treated Diabetic Patients: Results from FREEDOM



Non-ITDM/PCI N	629	573	530	412	264	137
Non-ITDM/CABG N	653	574	532	436	302	143
ITDM/PCI N	322	274	241	191	129	58
ITDM/CABG N	293	239	214	163	101	57

FREEDOM (GD Dangas, V Fuster et. al.) JACC 2014; 64: 1189

B8. Diastolic Dysfunction & Microcirculation



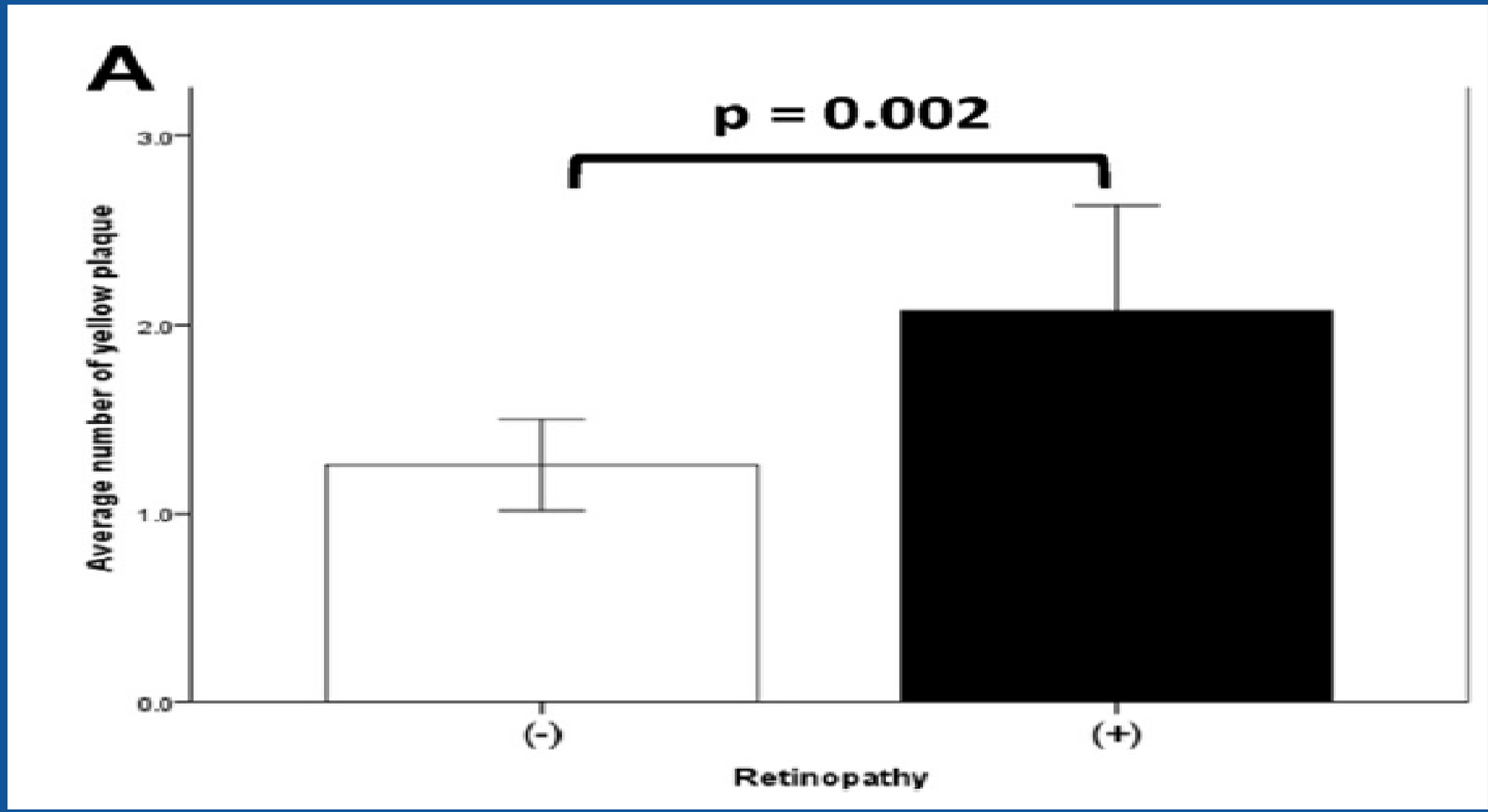
EM Jeong et. al. Circ J 2015; 79: 470

B9. Impact of Diabetic Retinopathy on Vulnerability of Atherosclerotic Coronary Plaque & Incidence of ACS

Fifty-seven diabetic patients with CAD, classified as non-DR (n=42) or DR (n=15), underwent angioscopic observation of at least 1 entire coronary artery. The number of yellow plaques (NYP) through the observed coronary artery was counted and their color grades, defined as 1 (light yellow), 2 (yellow), or 3 (intense yellow), were evaluated. The association between the presence of DR and incidences of acute coronary syndrome (ACS) was analyzed during the follow-up period (mean 7.1 ± 3.3 years). Our findings indicate that coronary atherosclerosis and plaque vulnerability are more severe in patients with DR. DR as a microvascular complication may be directly linked with macrovascular plaque vulnerability & fatal events such as ACS.

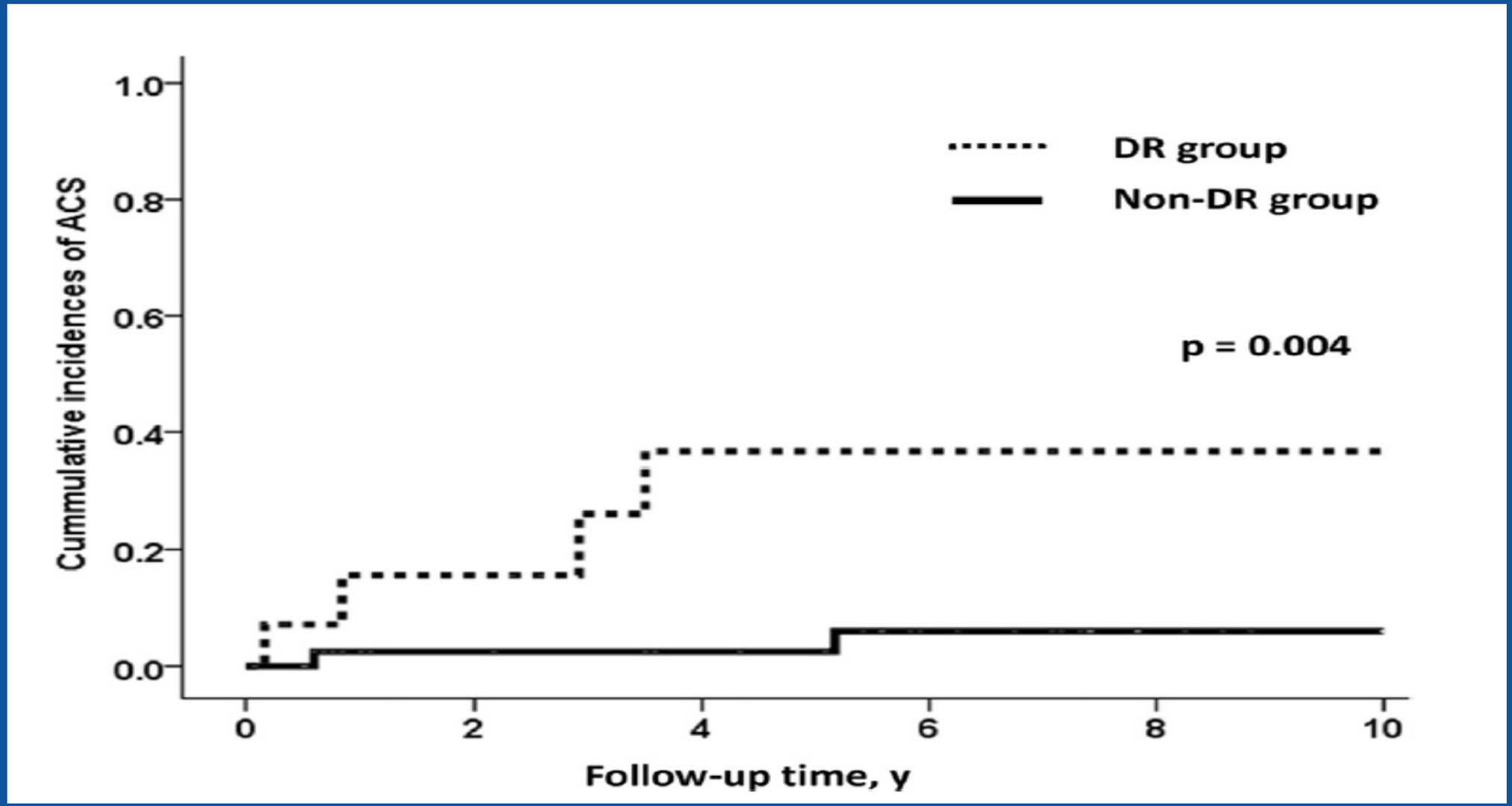
O Kurihara et al., Am J Cardiol 2016; 118:944

Comparisons Of Coronary Atherosclerosis On Angioscopy



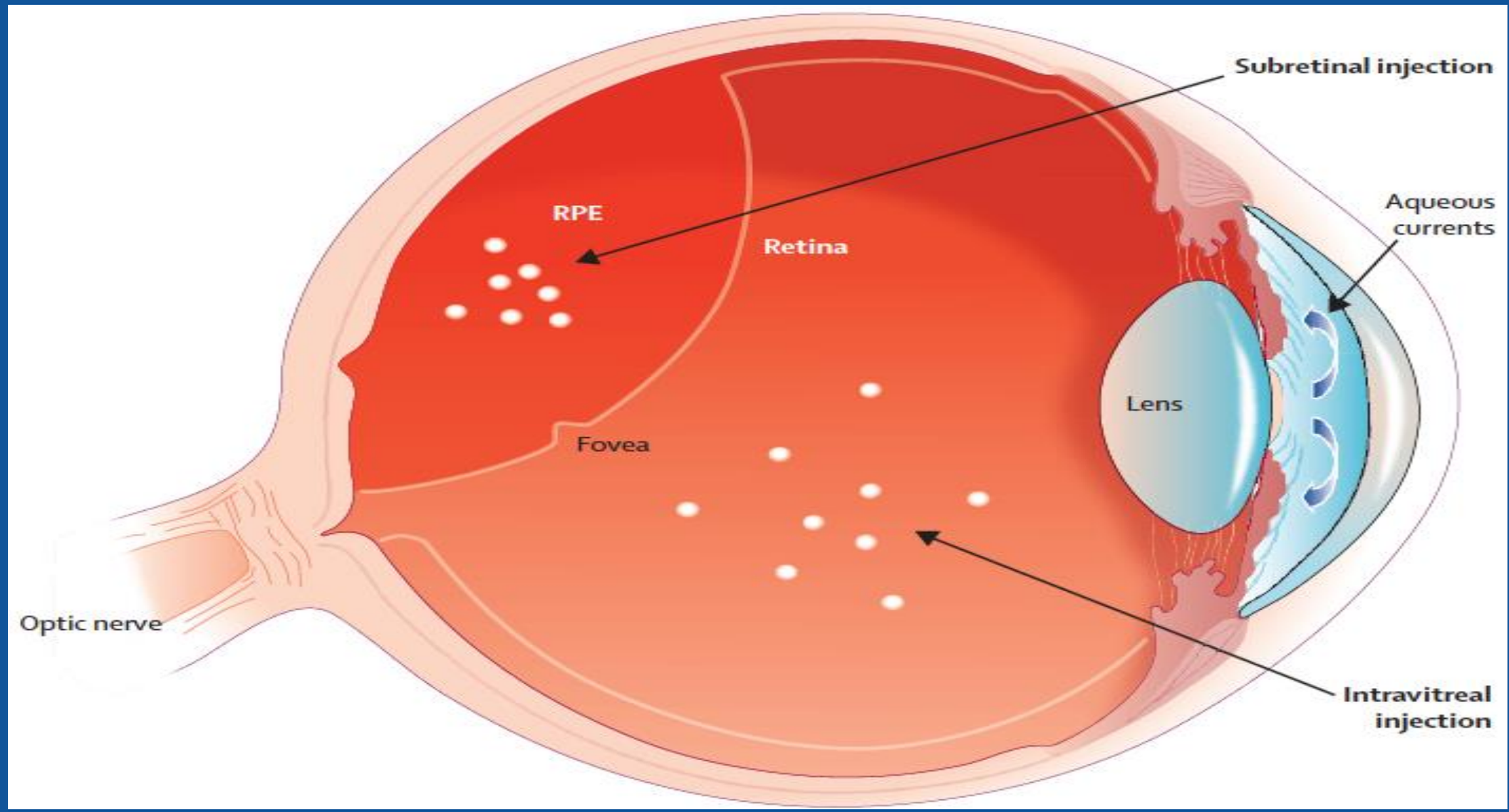
O Kurihara et. al. Am J Cardiol 2016;118:944

Impact of Diabetic Retinopathy on Vulnerability of Atherosclerotic Coronary Plaque & Incidence of ACS



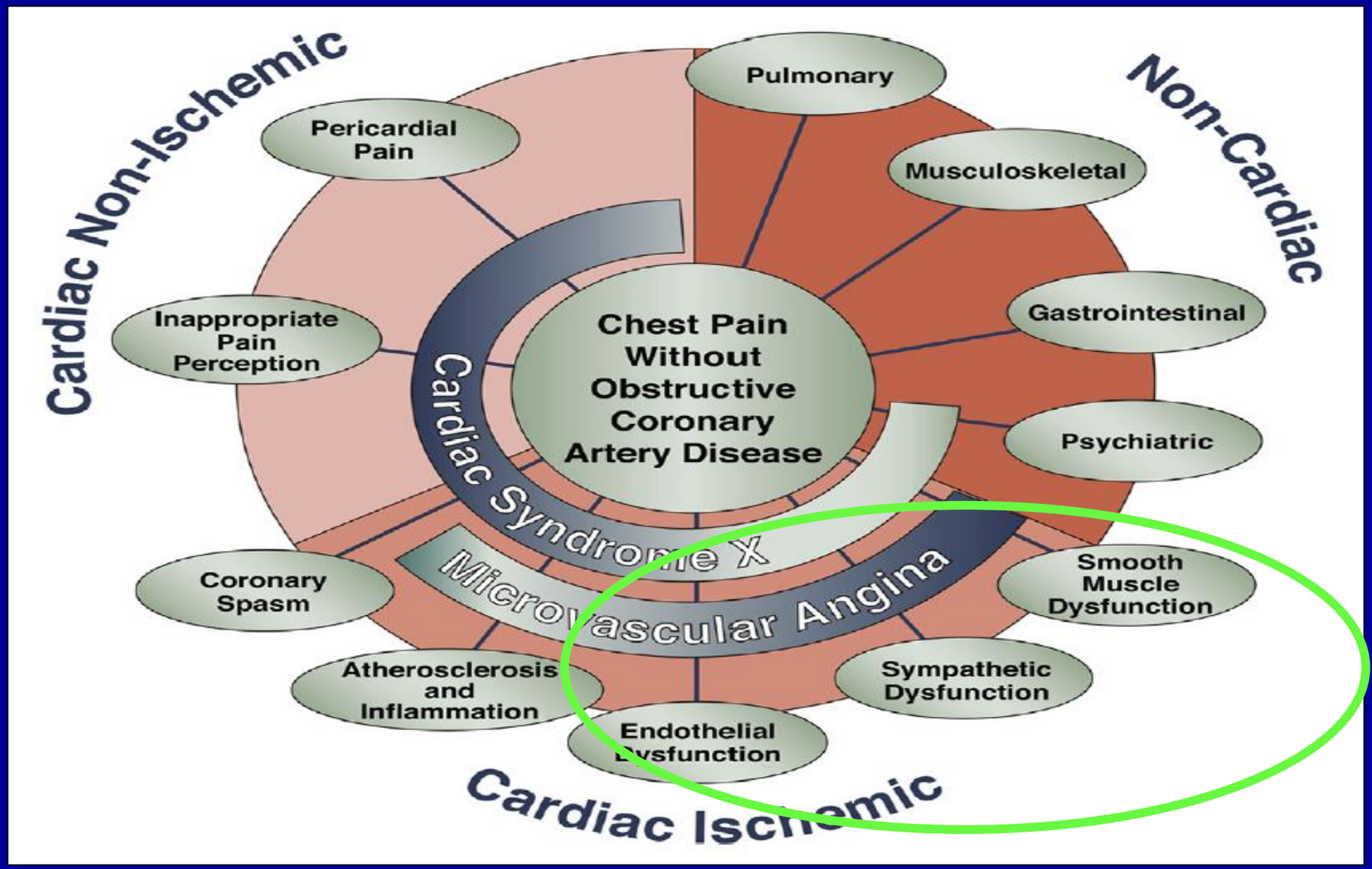
O Kurihara et. al. Am J Cardiol 2016;118:944

Routes Of Gene Therapy To The Retina



RE MacLaren. Lancet. 2016; 388: 635.

B10. Chest Pain Without Obstructive CAD



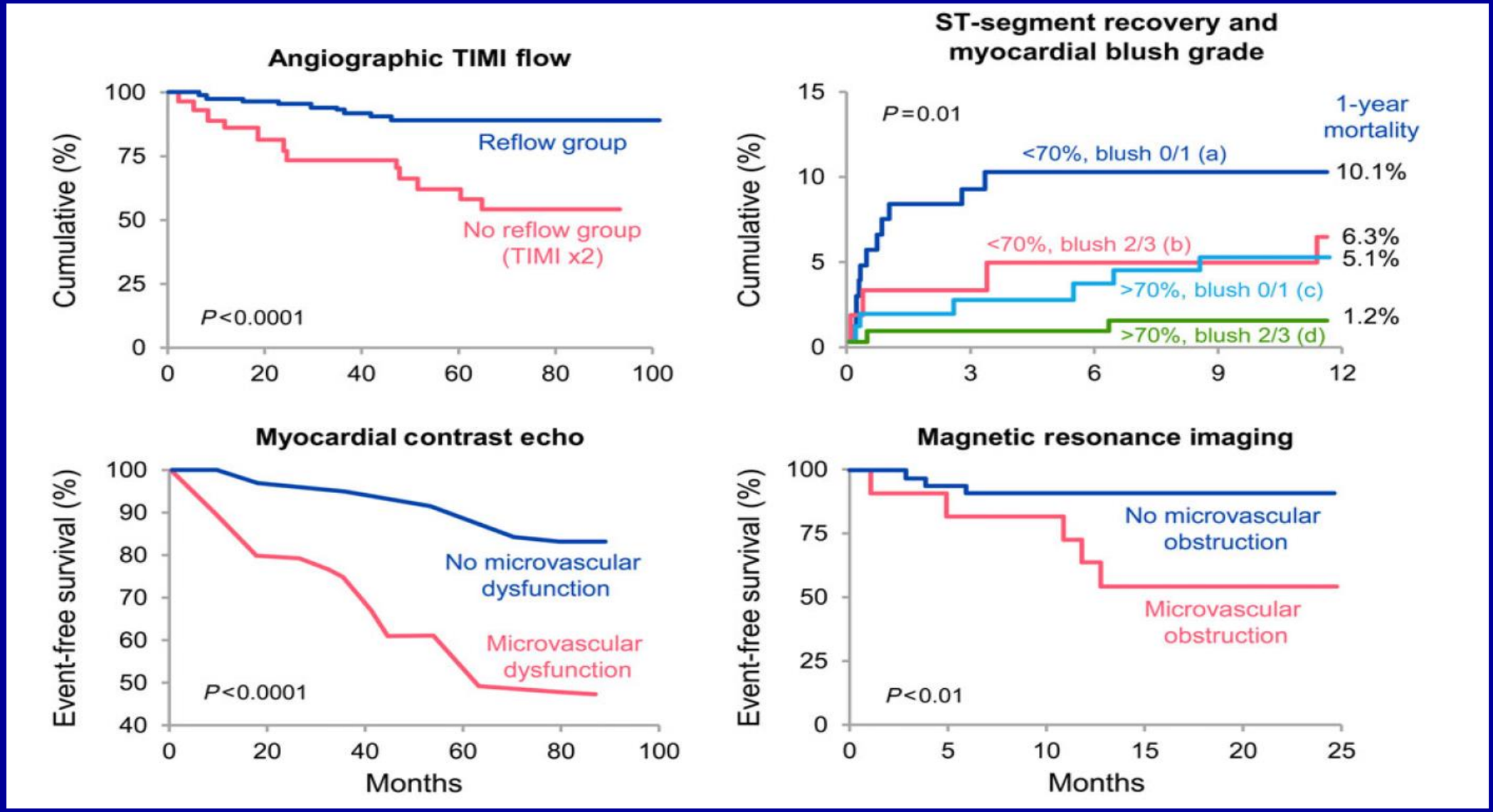
MA Marinescu et. al. J Am Coll Cardiol Img 2015;8:210

Conditions Linked to Microvascular Dysfunction

Ischemic cardiomyopathy	Stress-related cardiomyopathy
Diabetes mellitus	Systemic lupus erythematosis
Obstructive sleep apnea	Cerebral vasospasm
HFpEF	Tumor angiogenesis
HFrEF	No-reflow phenomenon
Aging	Inflammatory bowel disease
Schizophrenia	Tobacco abuse
Dementia	Hypertrophic obstructive cardiomyopathy
Peripheral neuropathy	Obesity
Chagas disease	Systemic sclerosis
Amyloidosis	Hypertension
Chronic thromboembolic pulmonary	Idiopathic cardiomyopathy

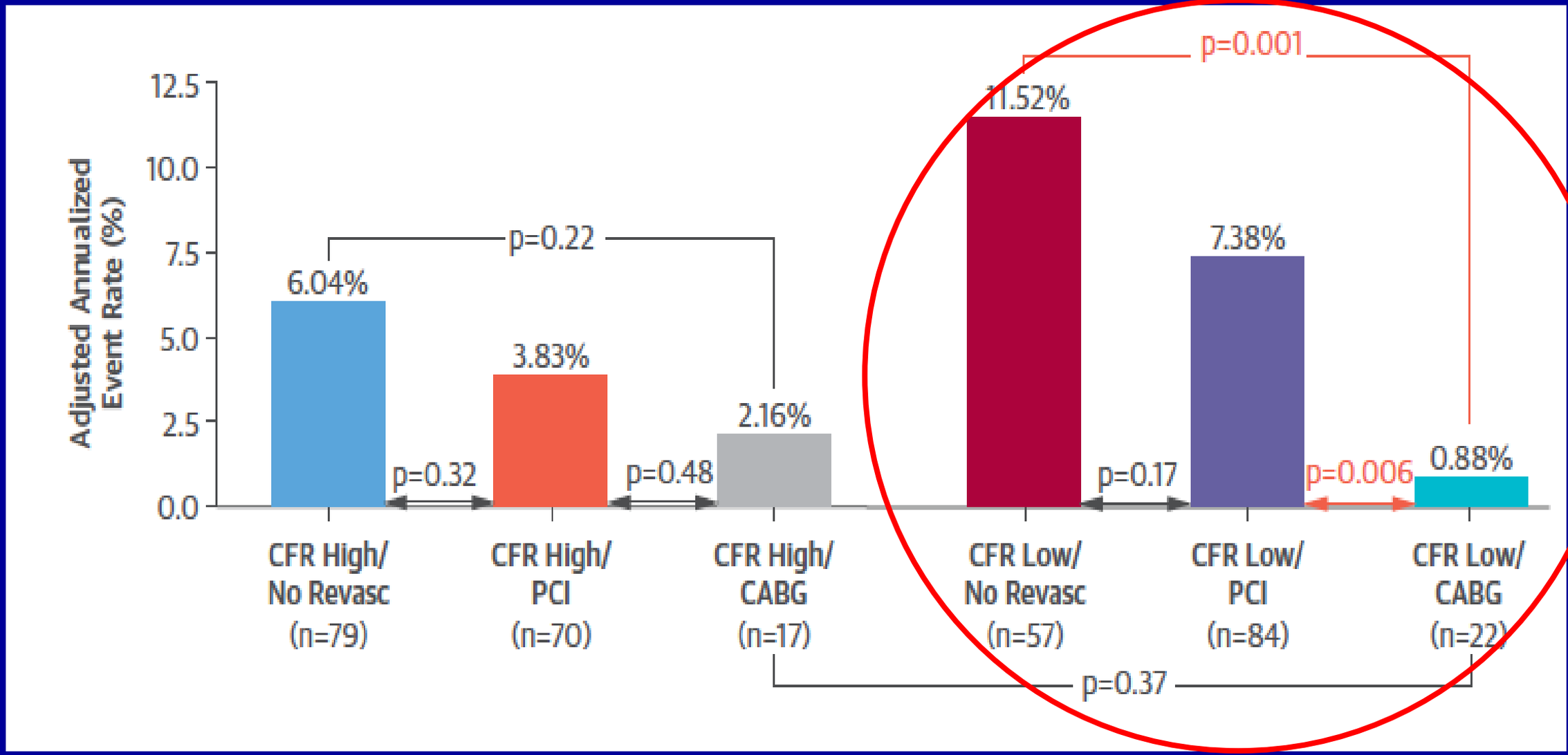
DD Gutterman et. al. Circ Res. 2016;118:157

B11. The Prognostic Role of Coronary Microvascular Obstruction



G Niccoli et. al. Eur Heart J. 2016; 37:1024

B12. Potential Benefit of Revascularization for Low CFR



NP Johnson et. al. JACC. 2016;67:2772

B13. Angiographic Classification of CAD

CHD Stages	Description	Risk of MI or CV Death/Year (%)
Stage 0	No coronary atherosclerotic disease by coronary angiography	<0.1
Stage 1	Mild coronary atherosclerotic disease: <30% lumen stenosis affecting 1 or 2 vessels	0.1-0.9
Stage 2	Moderate coronary atherosclerotic disease: 30-49% lumen stenosis affecting 1 or 2 vessels; or mild disease in 3 vessels	1-1.9
Stage 3	Severe coronary atherosclerotic disease: ≥50% lumen stenosis affecting 1 or 2 vessels; or moderate disease in 3 vessels	2-4
Stage 4	Very severe coronary atherosclerotic disease: ≥50% lumen stenosis affecting 3 vessels, or 2 vessels including pLAD, or LM disease	>4

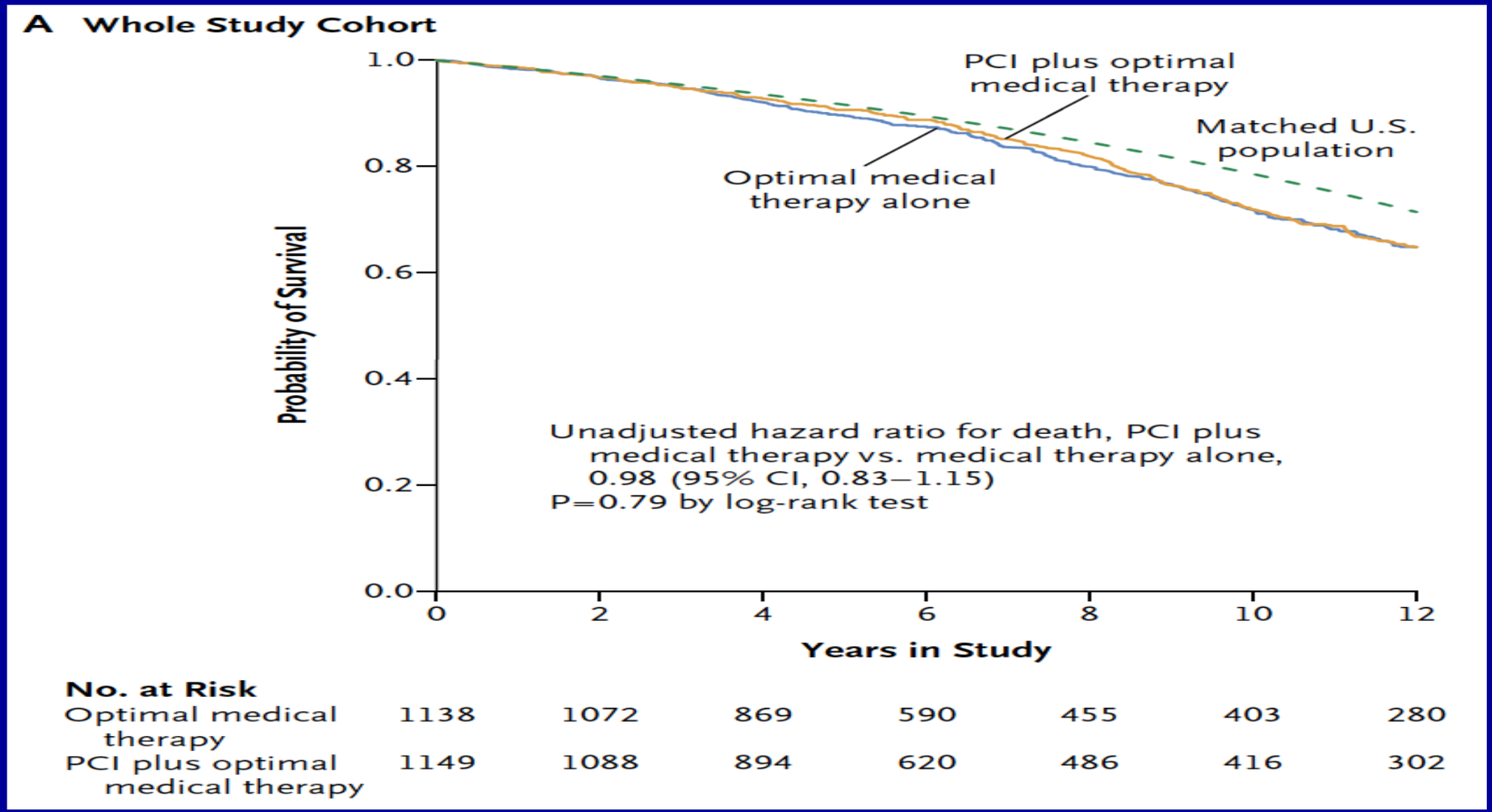
A Arbab-Zadeh, V Fuster. 2016 (In Press)

COMPLEX, STABLE CORONARY DISEASE

TRIAL	MVD	DM	INTERV.	MT.	EP.-R	Data
SYNTAX	+	-	++	-	++	CABG > PCI SYNTAX Score
FAME	-	-	+	-	+	PCI "ISCHEMIA" Score
BARI	-	+	+	+	+	CABG / PCI = MT X.OV.ER 42%
COURAGE	-	-	+	+	+	PCI = MT - X.OVER "ISCHEMIA">10%-Events
FREEDOM	+	+	++	(+)	+	CABG > PCI No Freedom of Choice?

Conditions Methods-Interests Conclusions

PCI and Long-Term Survival in Patients with Stable Ischemic Heart Disease



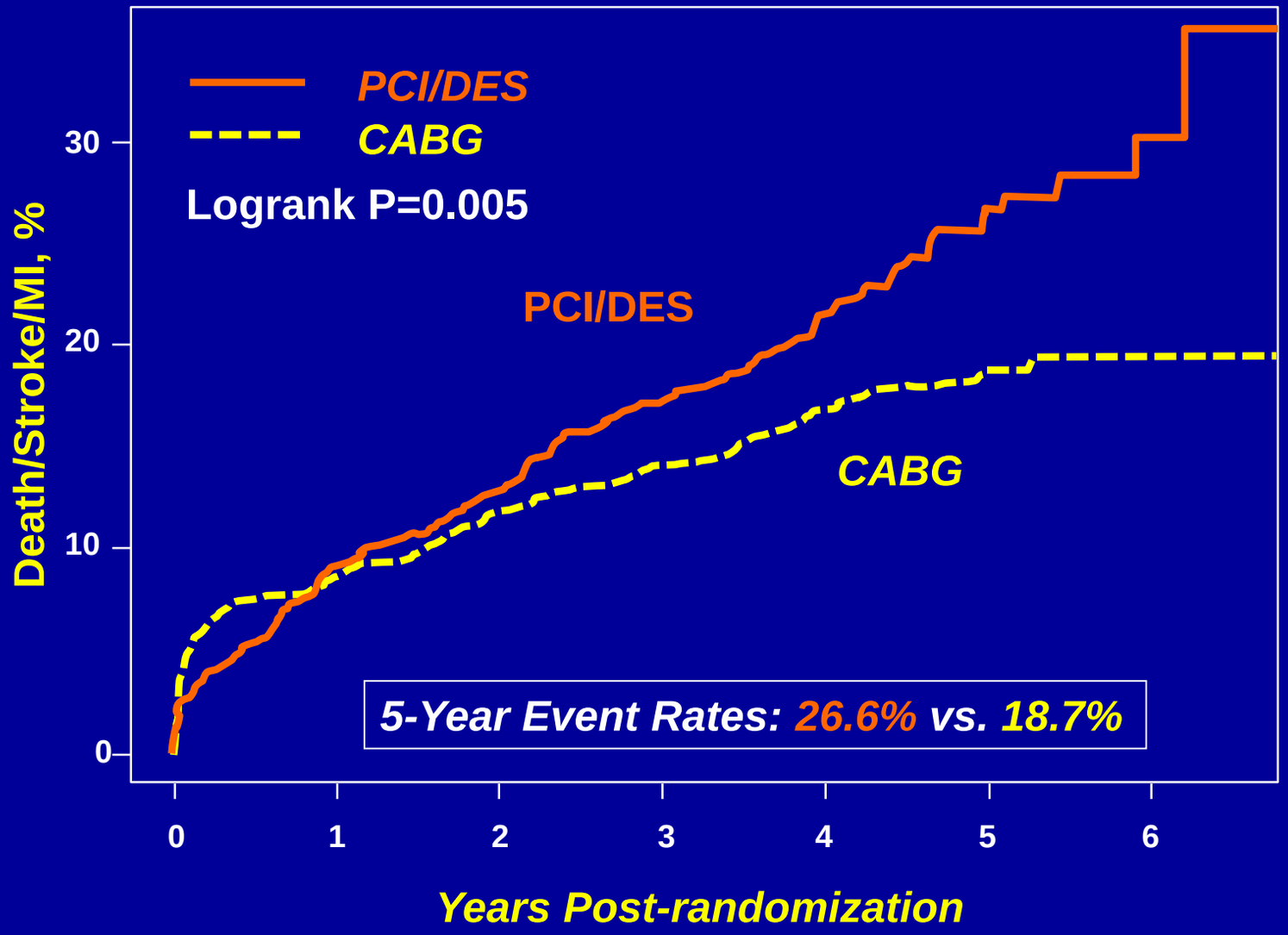
COURAGE (SP Sedlis et. al.) NEJM 2015;373:1937- 53% of the original

COMPLEX, STABLE CORONARY DISEASE

TRIAL	MVD	DM	INTERV.	MT.	EP.-R	Data
SYNTAX	+	-	++	-	++	CABG > PCI SYNTAX Score
FAME	-	-	+	-	+	PCI "ISCHEMIA" Score
BARI	-	+	+	+	+	CABG / PCI = MT X.OV.ER 42%
COURAGE	-	-	+	+	+	PCI = MT "ISCHEMIA">10%-Events
FREEDOM	+	+	++	(+)	+	CABG > PCI No Freedom of Choice?

Conditions Methods-Interests Conclusions

FREEDOM TRIAL – MI / DEATH / STROKE



New Engl. J. Med . 2012; 367: 2375 – All Subgroups (Syntax etc)
(Circ Cardiovasc Interv. 2014;7:518 – Newer Generation DES, Still Gap)

1. ACC/AHA - Recommendations for CAD Revascularization In Patients with Diabetes

2012 Recommendation	2014 Focused Update Recommendations	Comments
Class IIa	Class I	
1. CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery.[58–65] *(Level of Evidence: B)*	1. A Heart Team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD.[66] *(Level of Evidence: C)*	New recommendation
	2. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD), particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery.[58–69] *(Level of Evidence: B)*	Modified recommendation (Class of Recommendation changed from IIa to I, wording modified, additional RCT added).

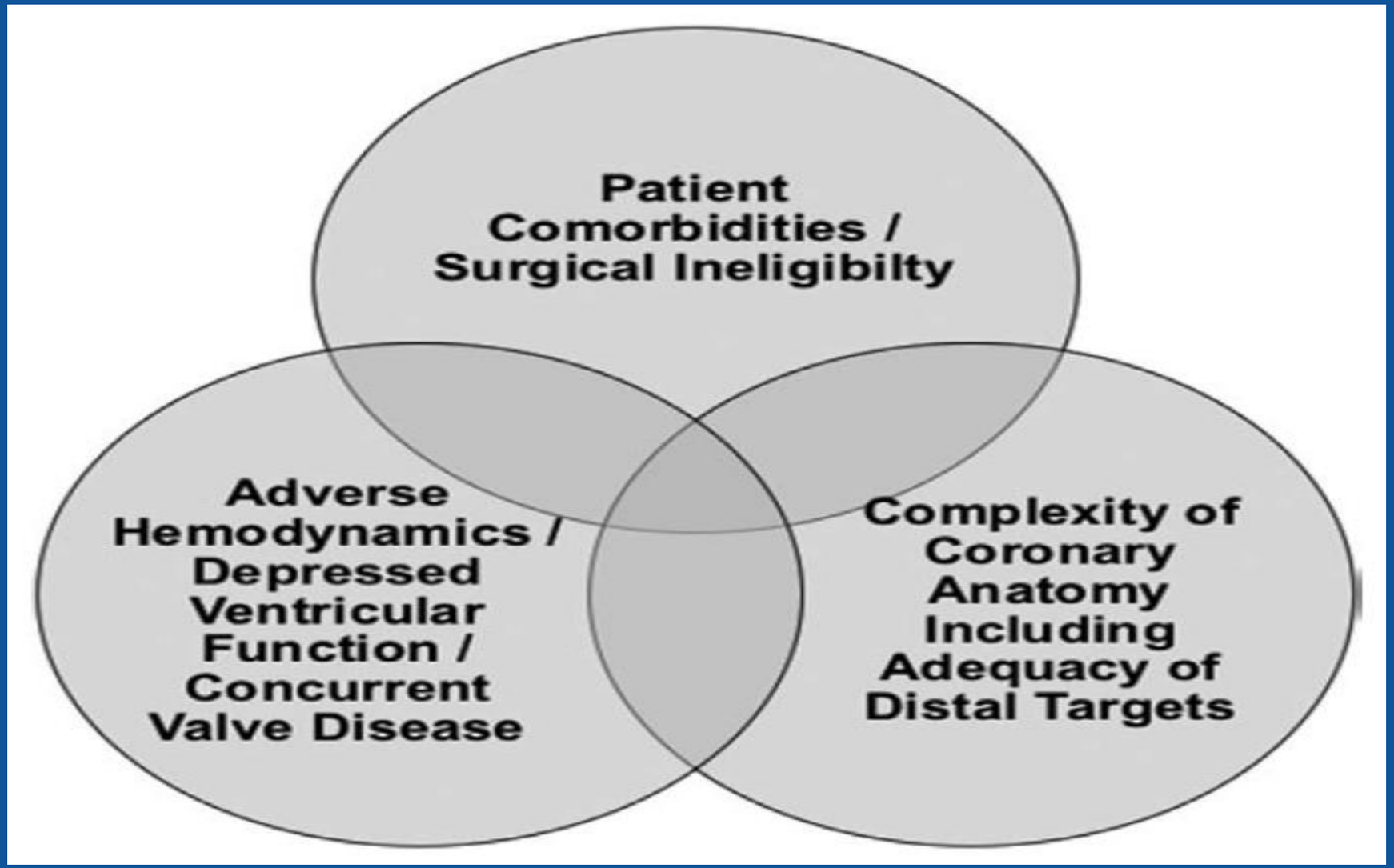
Circulation. 2014;130:1749

Recommendations	Class[a]	Level[b]	Ref[c]
In patients presenting with STEMI, primary PCI is recommended over fibrinolysis if it can be performed within recommended time limits.	I	A	363
In patients with NSTE-ACS, an early invasive strategy is recommended over non-invasive management.	I	A	180,338, 364–366
In stable patients with multivessel CAD and/or evidence of ischaemia, revascularization is indicated in order to reduce cardiac adverse events.	I	B	93,367
In patients with stable multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI.	I	A	106,175,349
In patients with stable multivessel CAD and SYNTAX score ≤22, PCI should be considered as alternative to CABG.	IIa	B	346,350
New-generation DES are recommended over BMS.	I	A	351,352
Bilateral mammary artery grafting should be considered.	IIa	B	368
In patients on metformin, renal function should be carefully monitored for 2 to 3 days after coronary angiography/PCI.	I	C	

Specific Recommendations For Revascularization In Patients With Diabetes

*The Task Force on Myocardial Revascularization of the **ESC and the EACTS** (S Windecker et. al.) Eur Heart J. 2014;35:2541*

The High-risk Patient Population With Indications For Revascularization Who May Be Considered For PCI



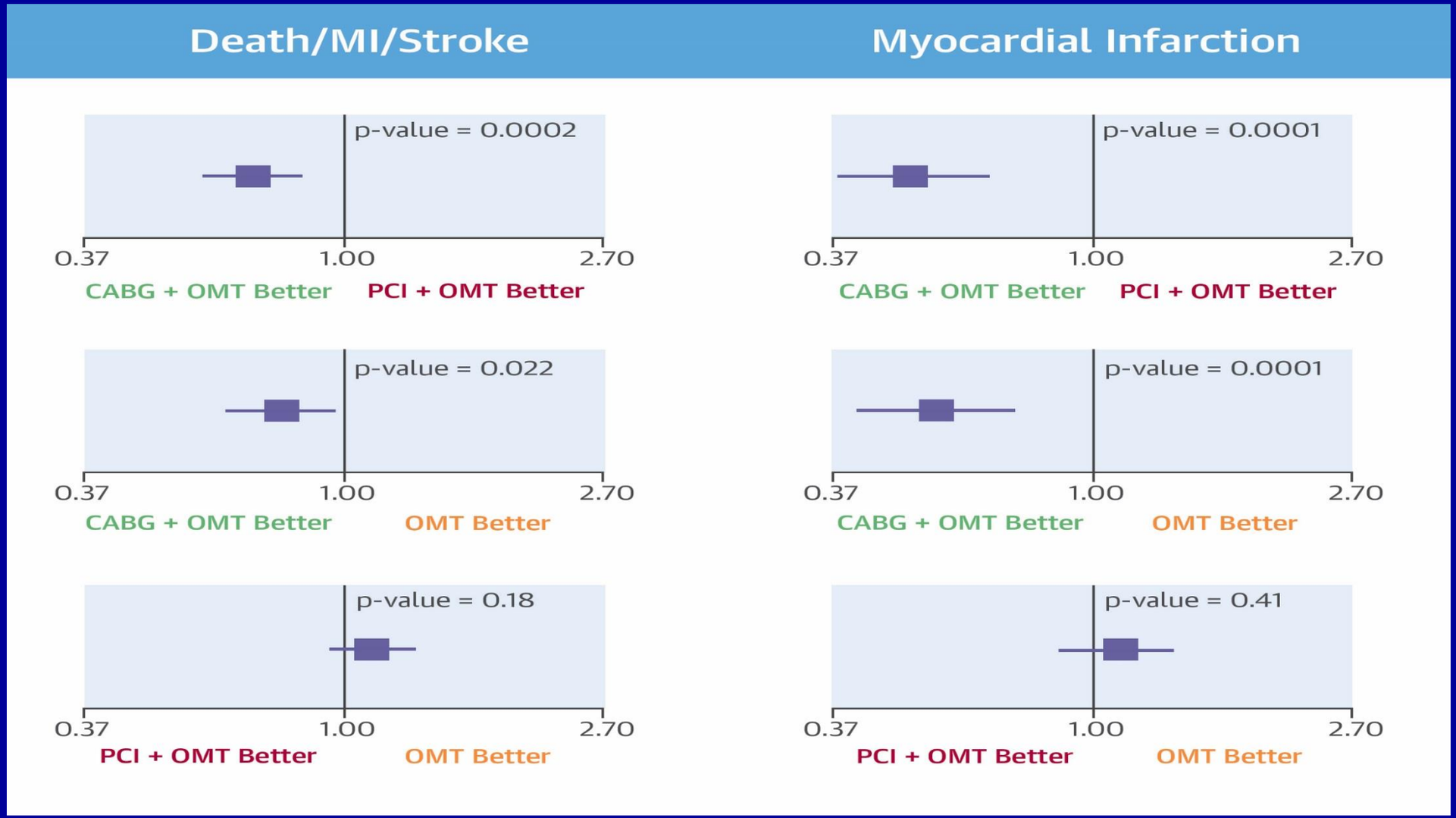
AJ Kirtane et. al. Circulation 2016;134:422.

2a. Medical Treatment & Revascularization Options in Patients With Type 2 Diabetes and Coronary Disease

A patient-level pooled analysis was undertaken in 3 federally-funded trials. The primary endpoint was the composite of death, MI, or stroke, adjusted for trial and randomization strategy. Among 5,034 subjects, 15% had LVEF <50%, 77% had multivessel CAD, and 28% had proximal left anterior descending artery involvement. During a median 4.5-year follow-up, CABG + OMT was superior to PCI + OMT for the primary endpoint, death but not stroke. CABG + OMT reduced the primary endpoint during long-term follow-up in patients with type 2 diabetes and stable CAD, supporting this as the preferred management strategy.

GBJ Mancini, ME Farkouh, V Fuster et al., J Am Coll Cardiol 2016 68:985

CABG vs Stents For Diabetic Multivessel Disease FU 5 yrs



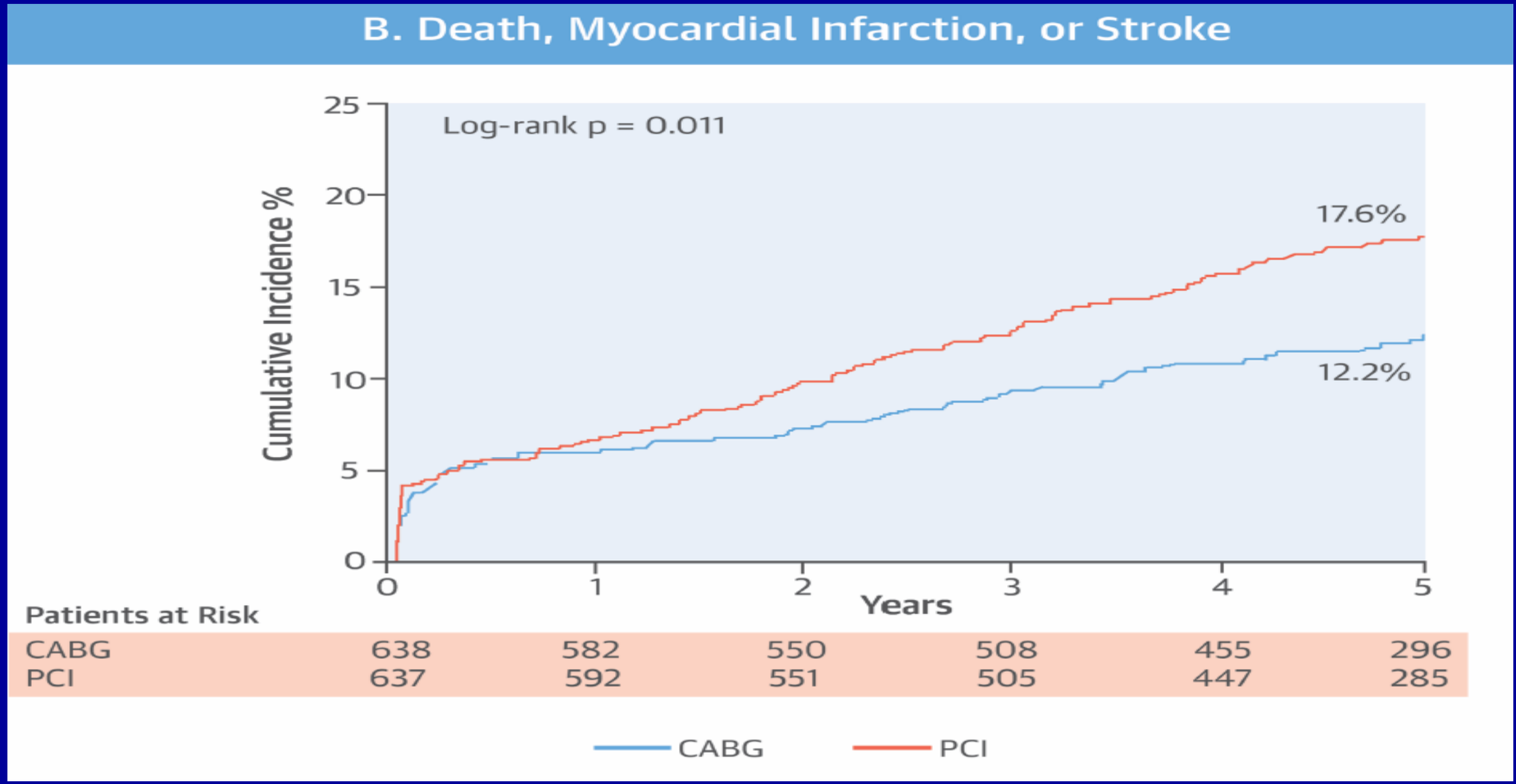
J Mancini, V Fuster et al. J Am Coll Cardiol 2016; 68:985

2b. Long-Term Mortality After Coronary Revasc. in Nondiabetic Patients With Multivessel Disease

Patient-level meta-analysis to compare the effect of CABG versus PCI with DES on long-term mortality in 1,275 nondiabetic patients with multivessel CAD. Individual patient data from the SYNTAX and the BEST trials were pooled. The primary outcome was death from any cause. The median follow-up time was 61 months. The risk of death from any cause was significantly lower in the CABG group than in the PCI group. A similar finding was observed for the risk of death from cardiac causes. The superiority of CABG over PCI was consistent across the major clinical subgroups. Likewise, the rate of MI was remarkably lower after CABG than after PCI. However, the rate of stroke was not different between the 2 groups. Repeat revasc. was significantly lower in the CABG group than in the PCI group

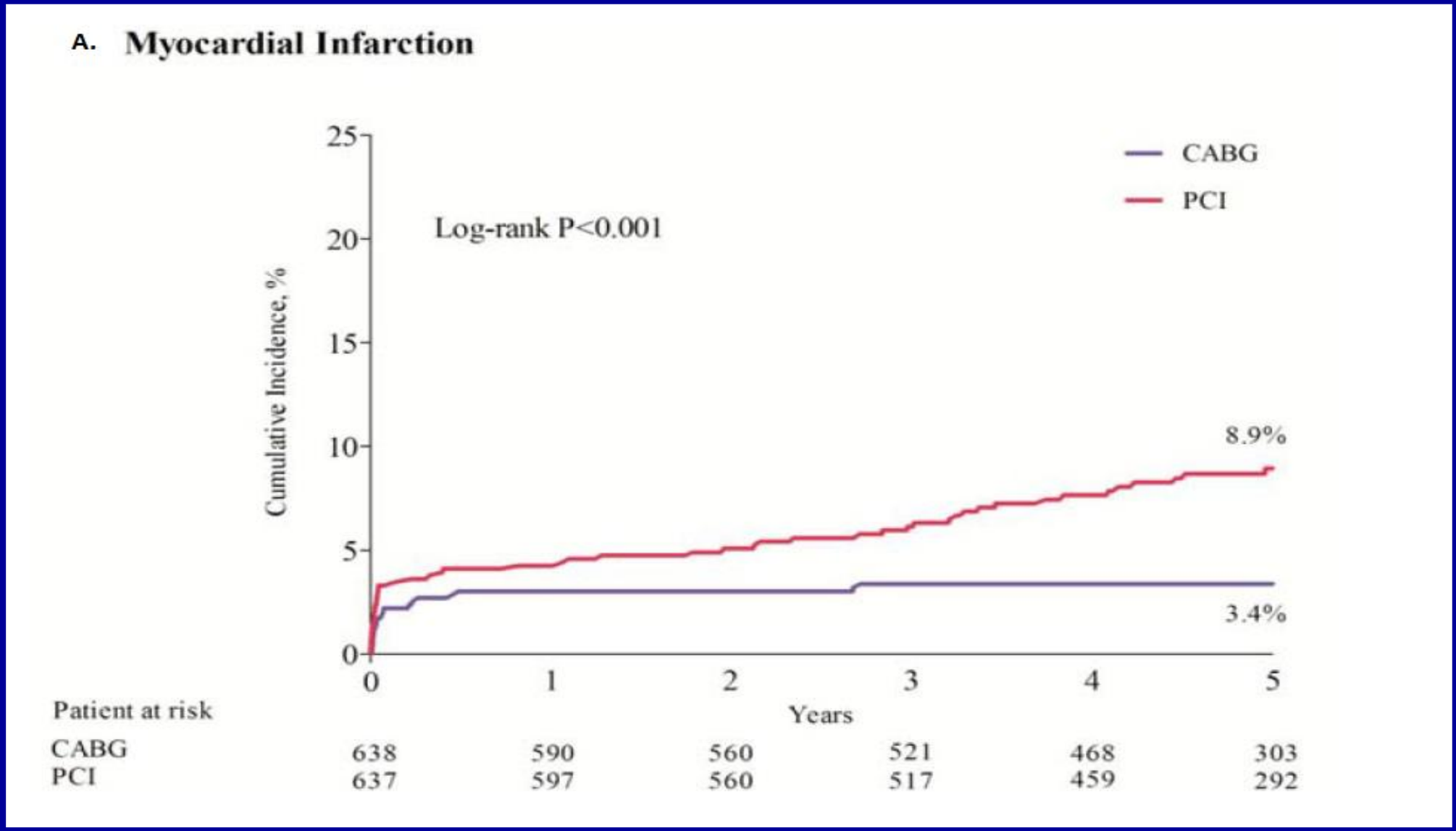
M Chang, S-J Park et al., J Am Coll Cardiol 2016; 68:29

CABG vs Stents For Non-diabetic Multivessel Disease



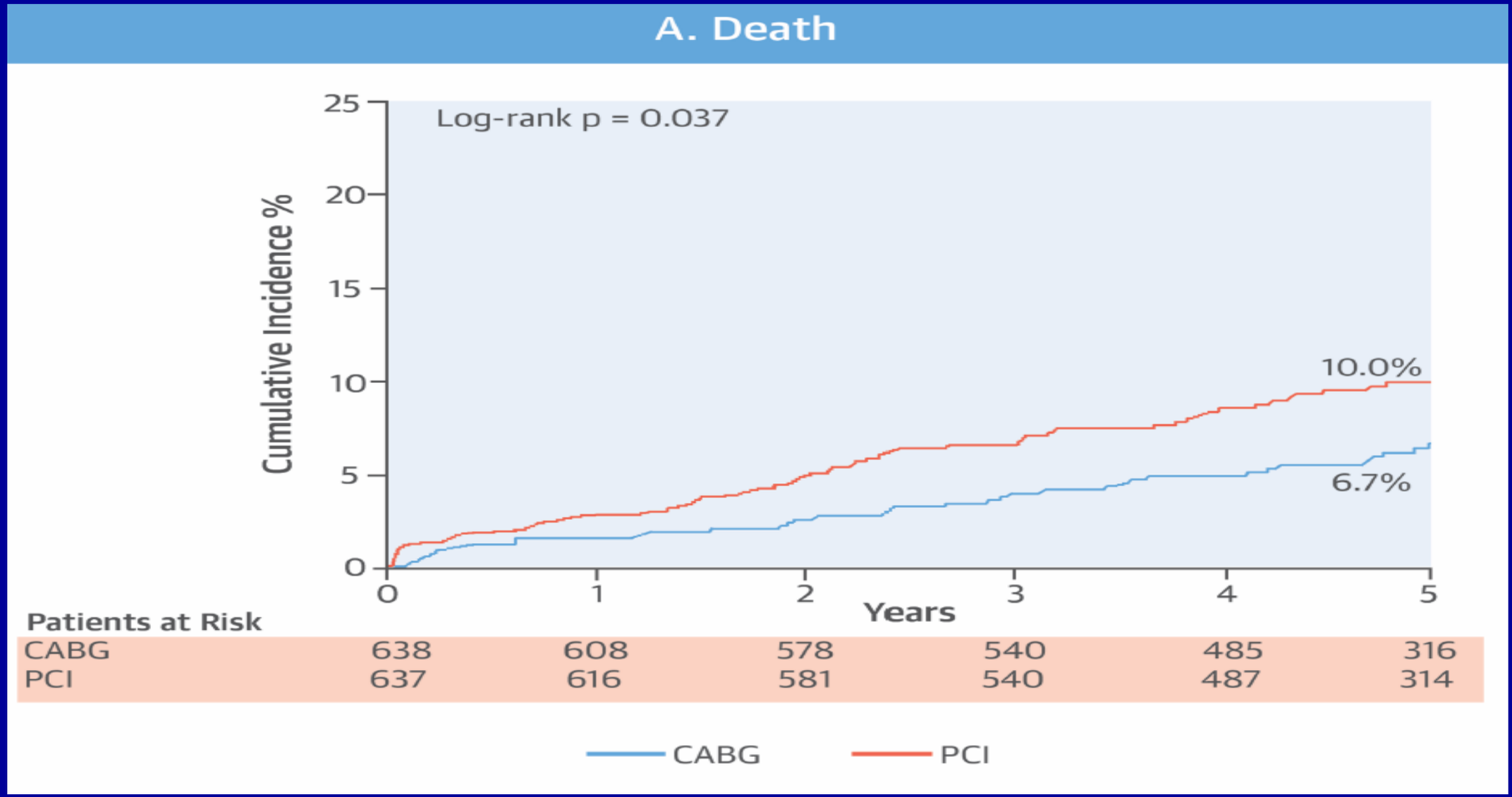
M Chang et. al. J Am Coll Cardiol 2016;68 (In Press)

CABG vs Stents For Non-diabetic Multivessel Disease



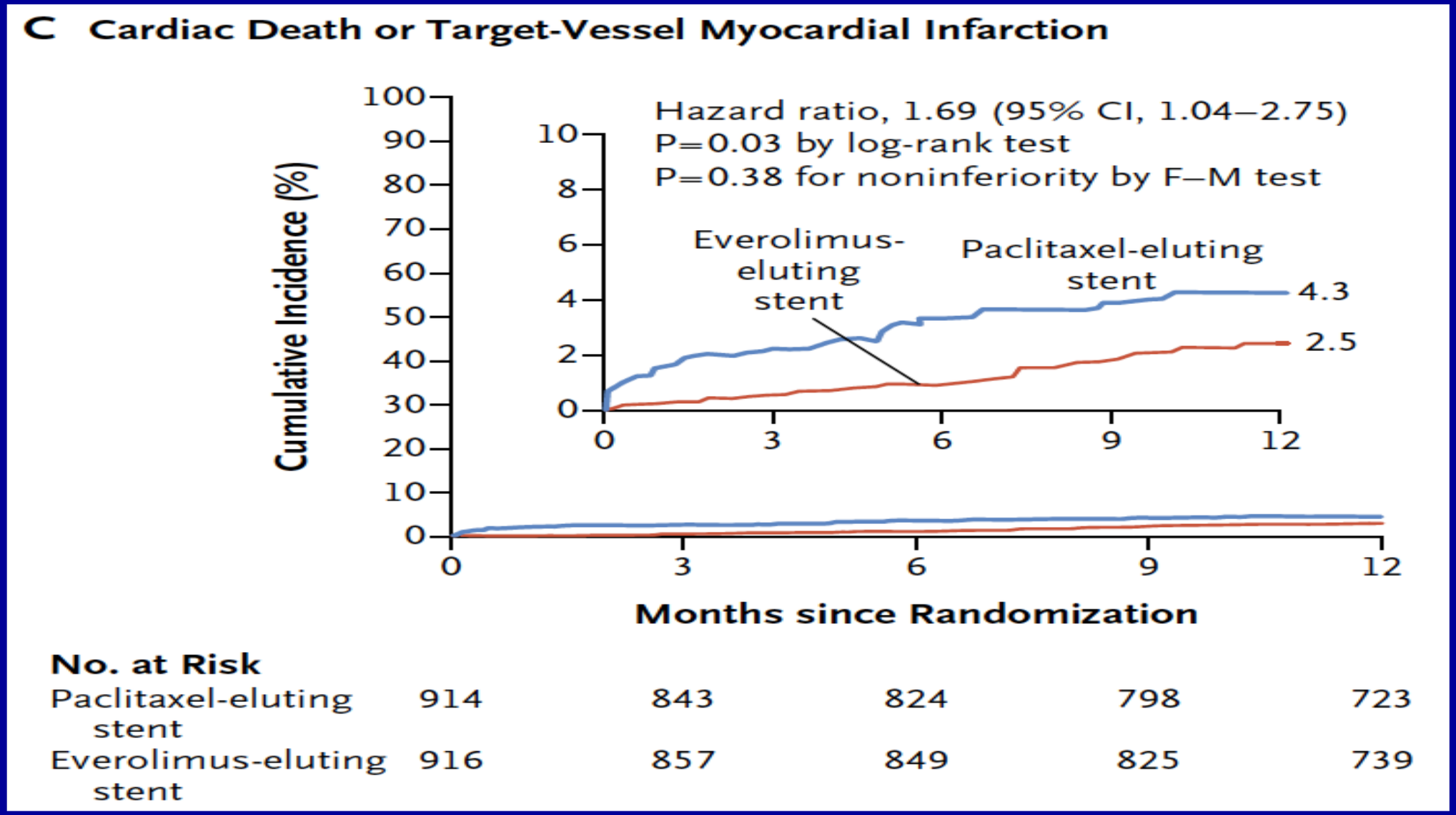
M Chang et. al. J Am Coll Cardiol 2016;68 (In Press)

CABG vs Stents For Non-diabetic Multivessel Disease



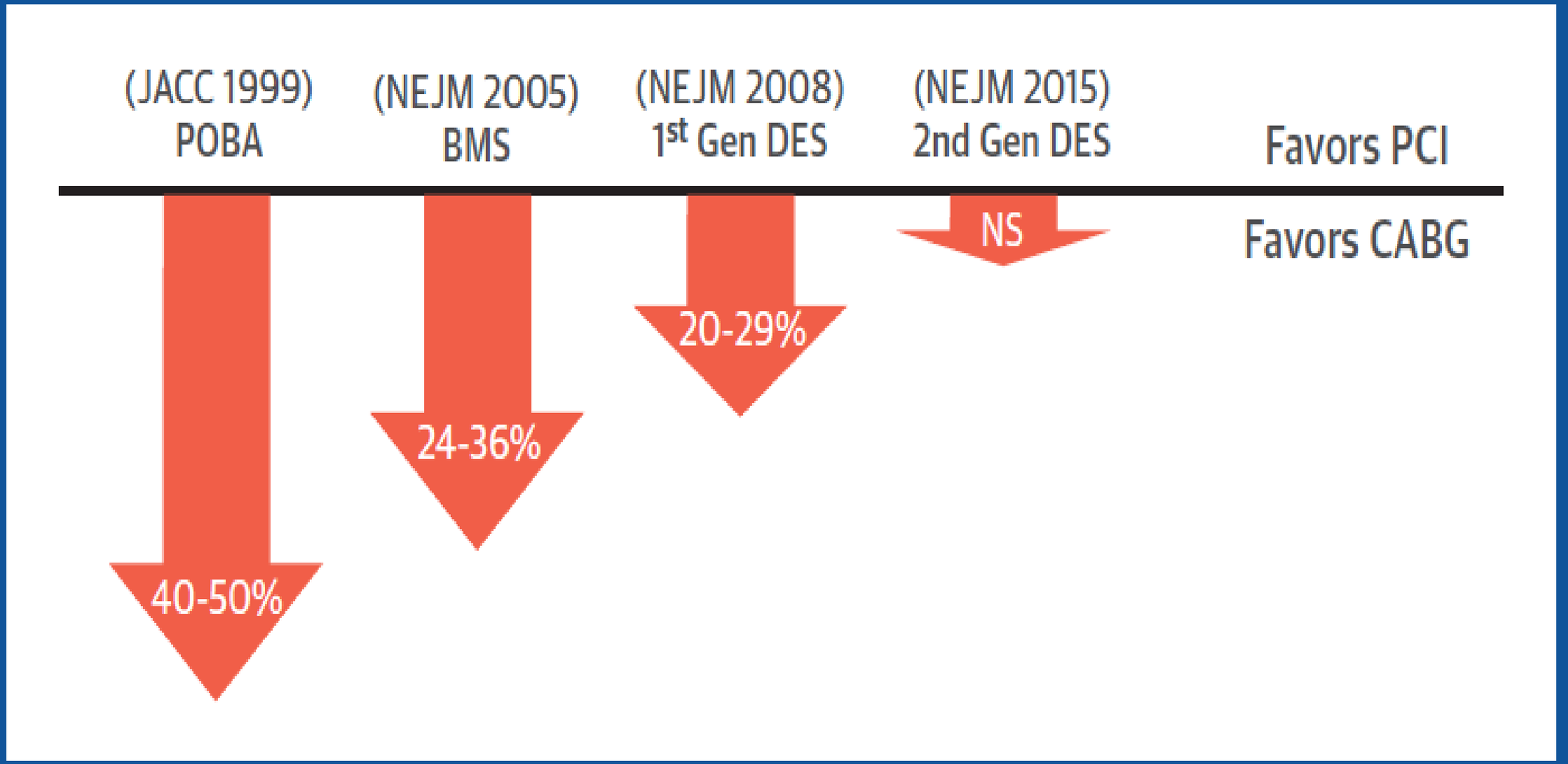
M Chang et. al. J Am Coll Cardiol 2016;68 (In Press)

Paclitaxel-Eluting vs Everolimus-Eluting Coronary Stents in Diabetes



TUXEDO-India (U Kaul et. al.) NEJM 2015;373:1709

Diminishing Mortality Gap Between PCI and CABG For Multivessel Disease From the NY State Registries



S Bangalore. J Am Coll Cardiol 2016;68:996

3. ADHERENCE FOR RISK FACTOR CONTROL?

Risk Factors - Proportion of Participants at Goal % – 1 year

Trials	LDL	SBP	DBP	Hb A1C	Meet Goals Base	Meet Goals FU
BARI-2D	75	56	70	52	14	20
COURAGE	51	55	55	59	12	19
FREEDOM	55	63	53	55	12	20

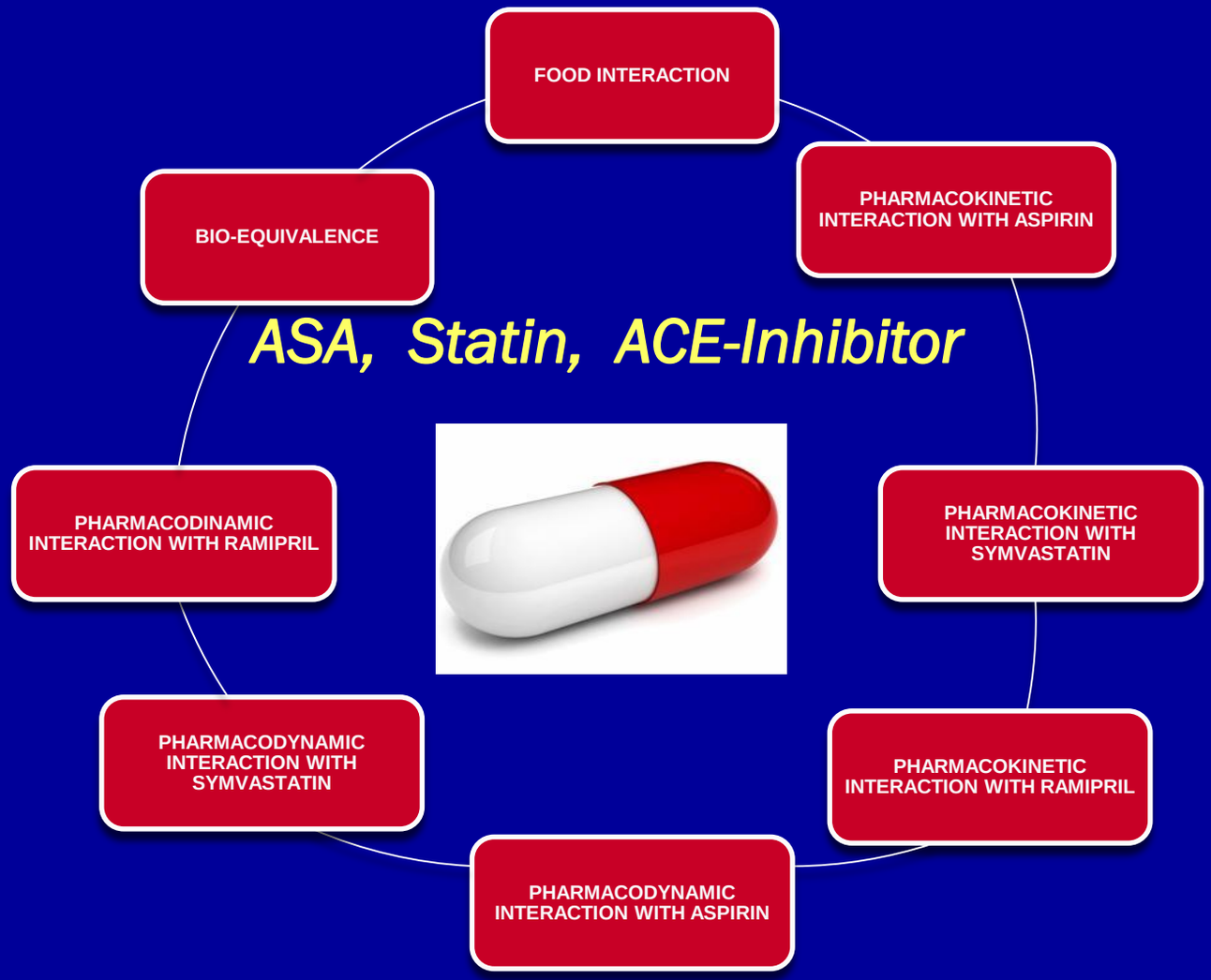
Freedom, Bari-2D, Courage Investigators, JACC 2013;61:1607
PURE (S Yusuf et al.) Lancet 2011; Aug 28 - Poor Countries,7% !!!
NHANES, AHA, NHLBI-JNC-7, NHLBI-NCEP – Significant < Adherence
P Muntner, V Fuster et al., AHJ 2011; 161: 719 – 49 seconds !!!!

CV Drugs Underuse - Polypill, 2ary Prevention.

FOCUS 1 & 2

Argentina
Brazil
Paraguay
Italy
Spain

FREEDOM
AETNA-DIABETES
SECURE-EC 2015



Am. H J 2011;162:811
Semin.Thor.Cardiov.Surg 2011;23:24
JACC, 2014; 64:2071

Approved in 27 Countries

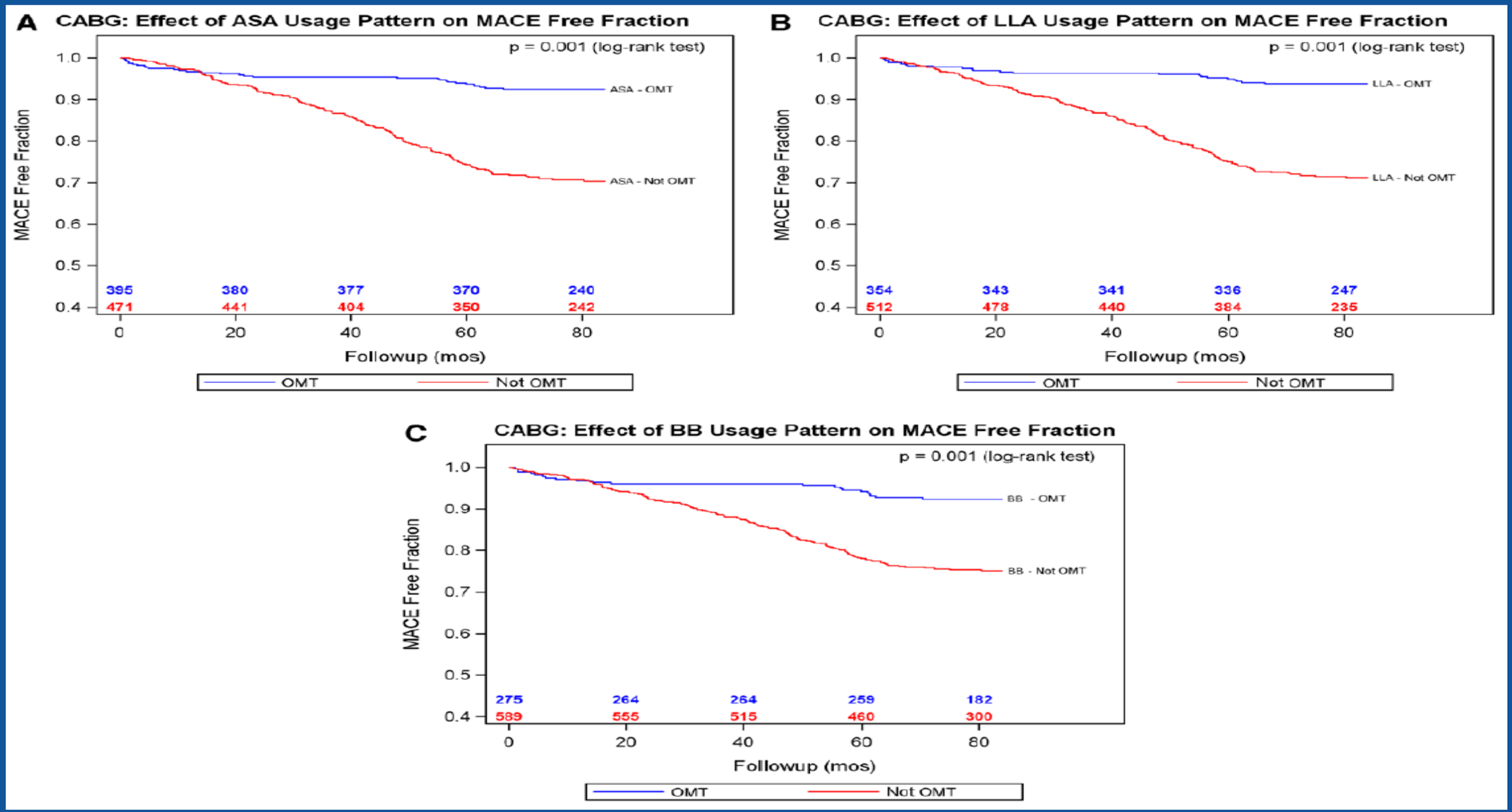
HOPE-3-NEJM 2016;374:2032 – Polypill for 1ary Prevention ?

CABG Versus PCI -Impact of Adherence to Medical Therapy on Comparative Outcomes

All non-STEMI patients undergoing revascularization in an 8-hospital network were followed for up to 8 years. Among the 973 CABG and 2255 PCI patients. There was a significant benefit for antiplatelet, lipid-lowering, and β-blocker therapy in both the CABG and PCI groups. Compliance with optimal medical therapy as a more powerful predictor of major adverse cardiac event-free survival than choice of therapy. Among comparable patients who adhere to optimal medical therapy, outcomes of PCI and CABG may not differ; however, among nonadherent patients, CABG affords better major adverse cardiac event-free survival.

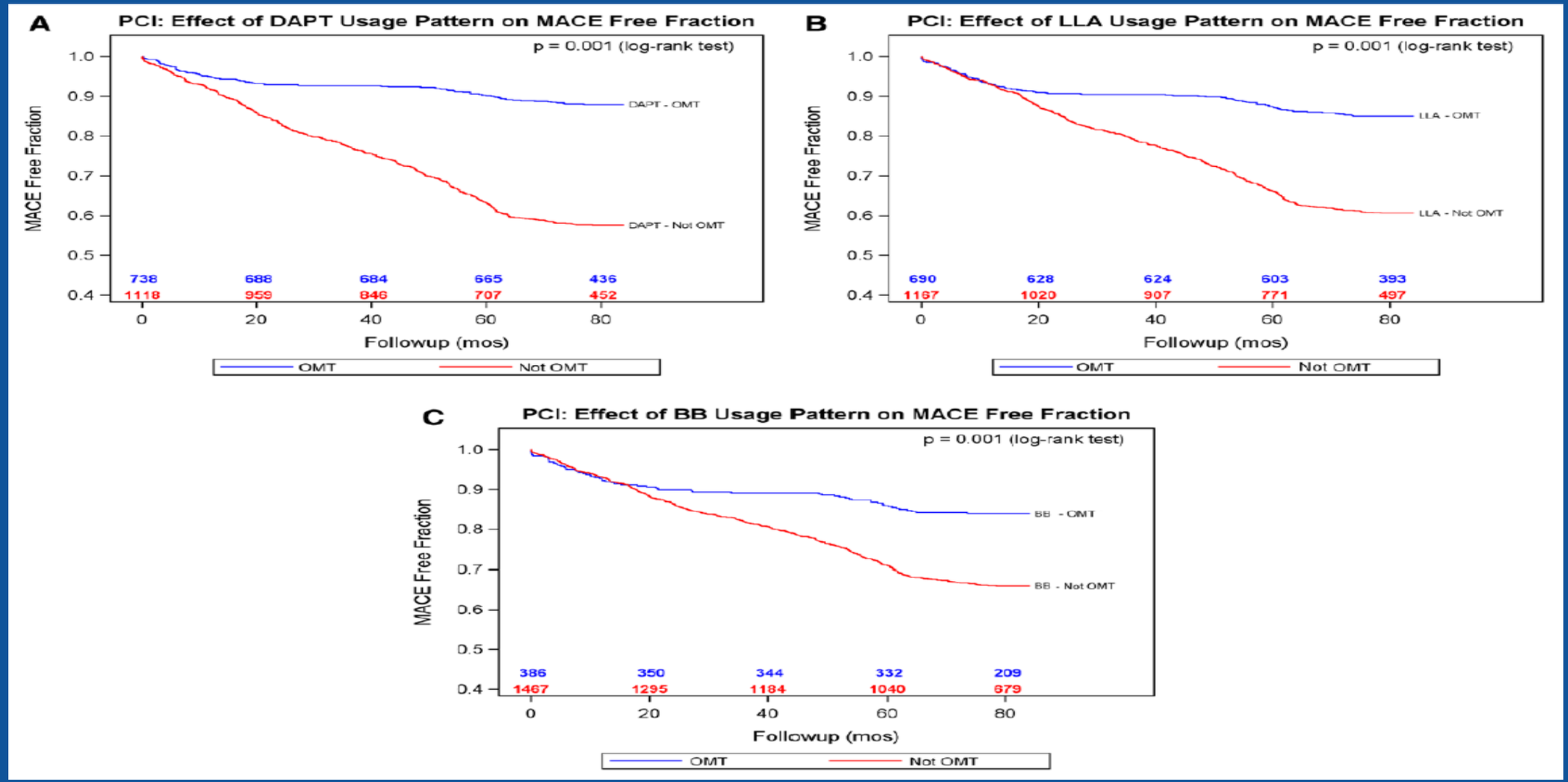
P Kurlansky, M Mack et al., Circulation 2016; 134:1238

Effect of Adherence In Patients Who Underwent CABG



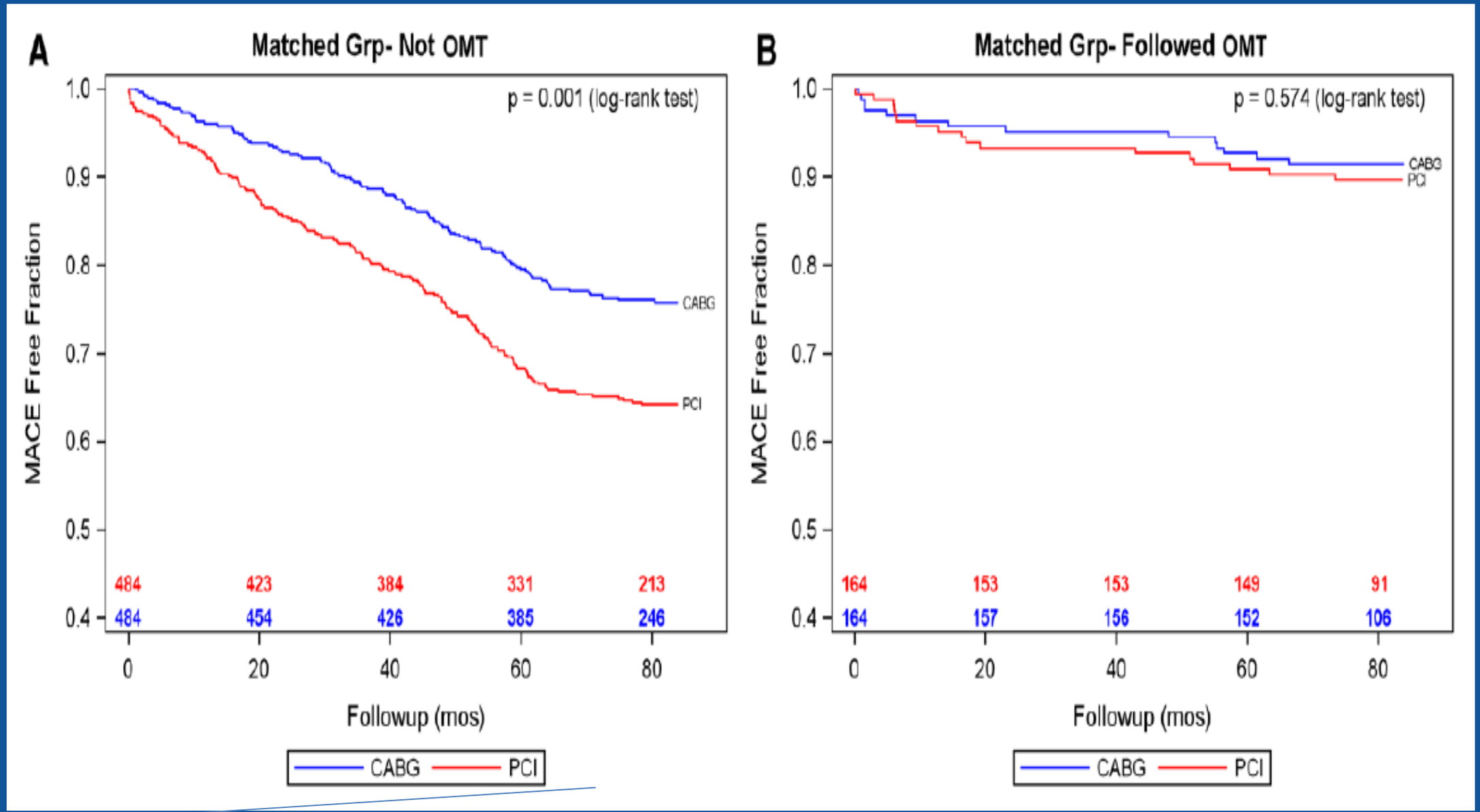
P Kurlansky, M Mack et. al. Circulation. 2016;134:1238

Effects Of DAPT, Lipid-lowering Agent (LLA) Therapy, And B-blockers In Patients Who Underwent PCI



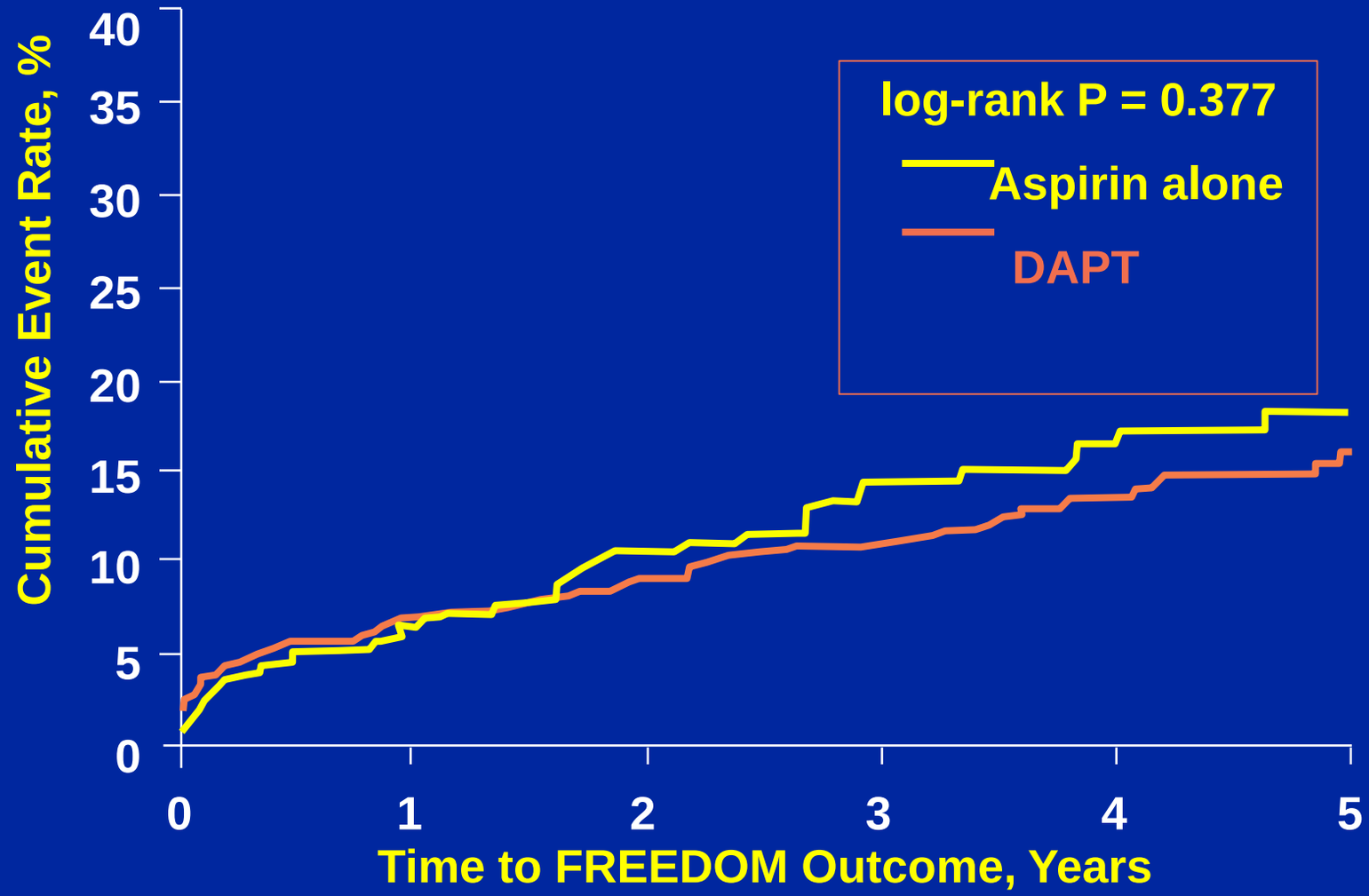
P Kurlansky, M Mack et. al. Circulation. 2016;134:1238

Survival Free From MACE In Matched Patients And Optimal Antiplatelet And Lipid-lowering Regimen



P Kurlansky, M Mack et. al. Circulation. 2016;134:1238

4. DAPVs. Aspirin Alone After CABG In Diabetics With MVD: FREEDOM Trial Insights



DAPT (Yes/No) / Number of patients at risk

Yes	540	492	449	349	233	111
No	251	231	207	166	107	43

S van Diepen, V Fuster, ME Farkouh et al., JACC 2016 (In Press)

Revascularization for Coronary Artery Disease

OMT vs PCI vs CABG

1980's. LMD, The Rule of 2 / 3 – CABG

-Moderate <LVEF

-Severe Ischemia

-3 Vessel Disease

2vd + pLAD

[1]Severe - Yes, STICH

Moderate – COURAGE OMT

ISCHEMIA

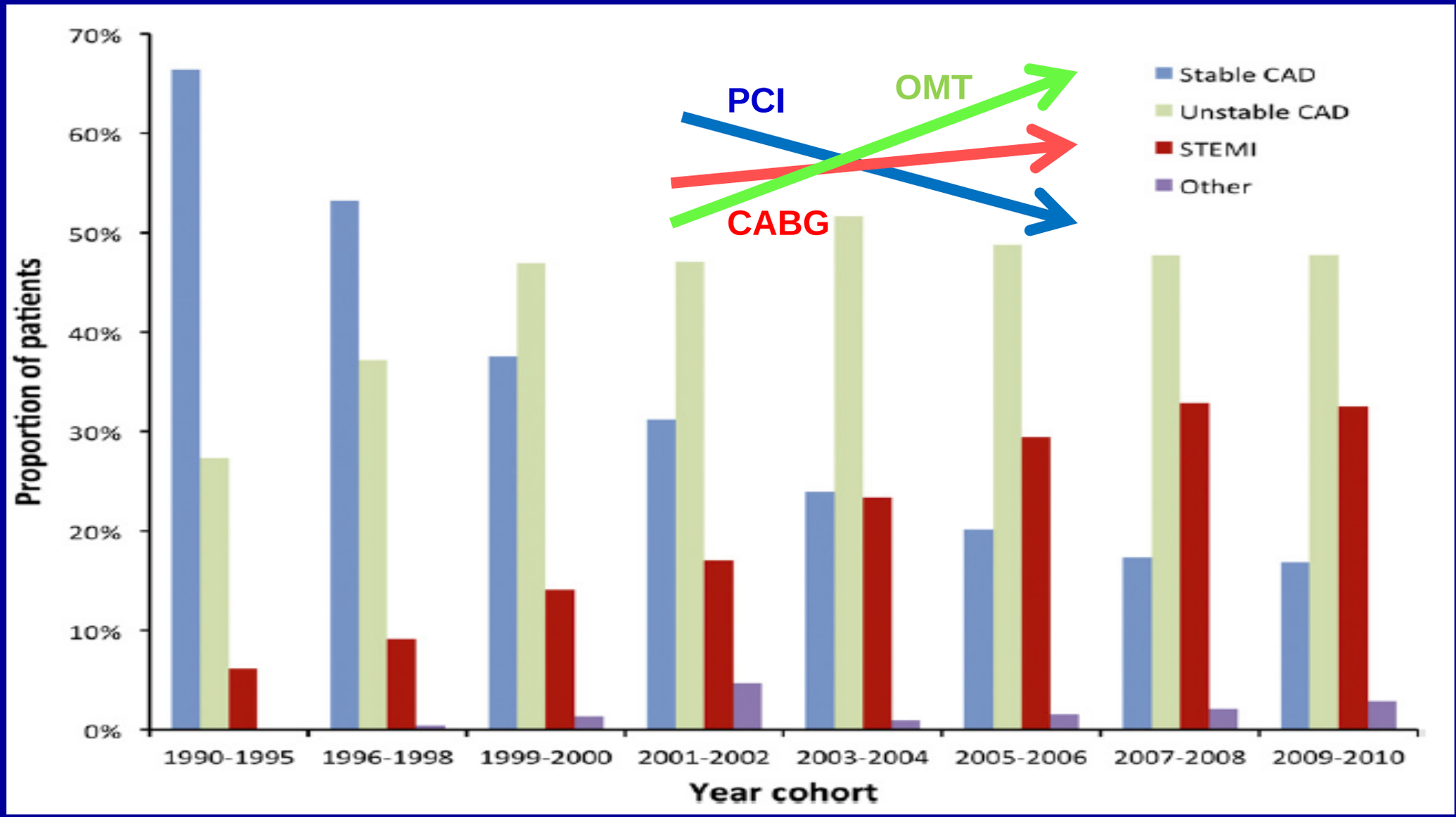
[1]2vd in DM

1990's. The Rule of 2 / 3 – PCI ?

2000's[1]. PCI <, CABG > (DM), Microc., OMT

2020,s. Anatomical, Isch.Score, Microc.: Ninv. - OMT+

Future For PCI / CABG – OMT ADHERENCE



SCAAR (ML Fokkema et.al.) JACC **2013**;61:1222 - **Swedish Registry**

Diab.Trialists' Collab. – 2015 - FREEDOM, BARI 2D, COURAGE

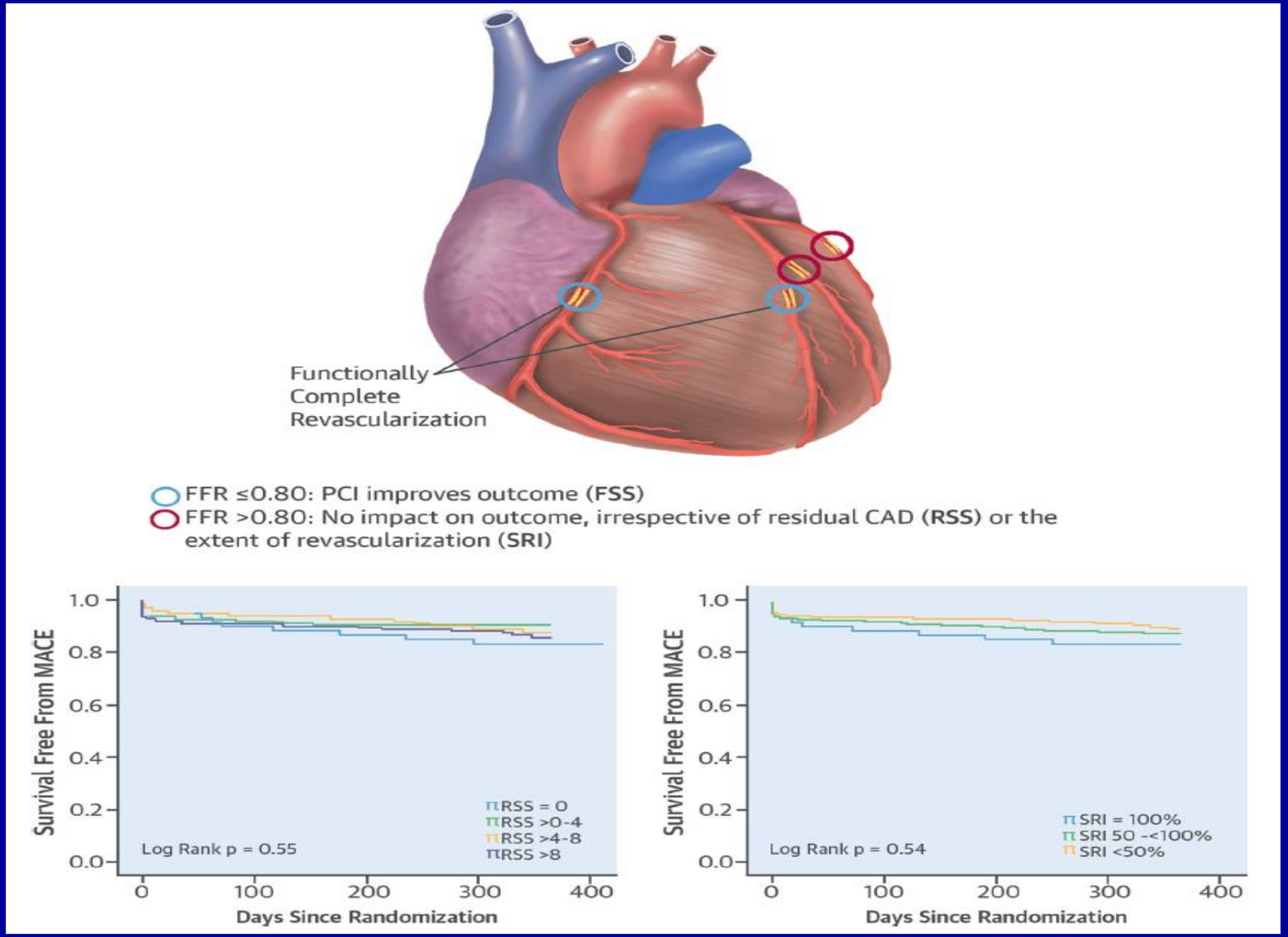
CABG & OMT Evolving Again ?

Microcirculation & OMT+Adherence

New York, Dec 9, 2016

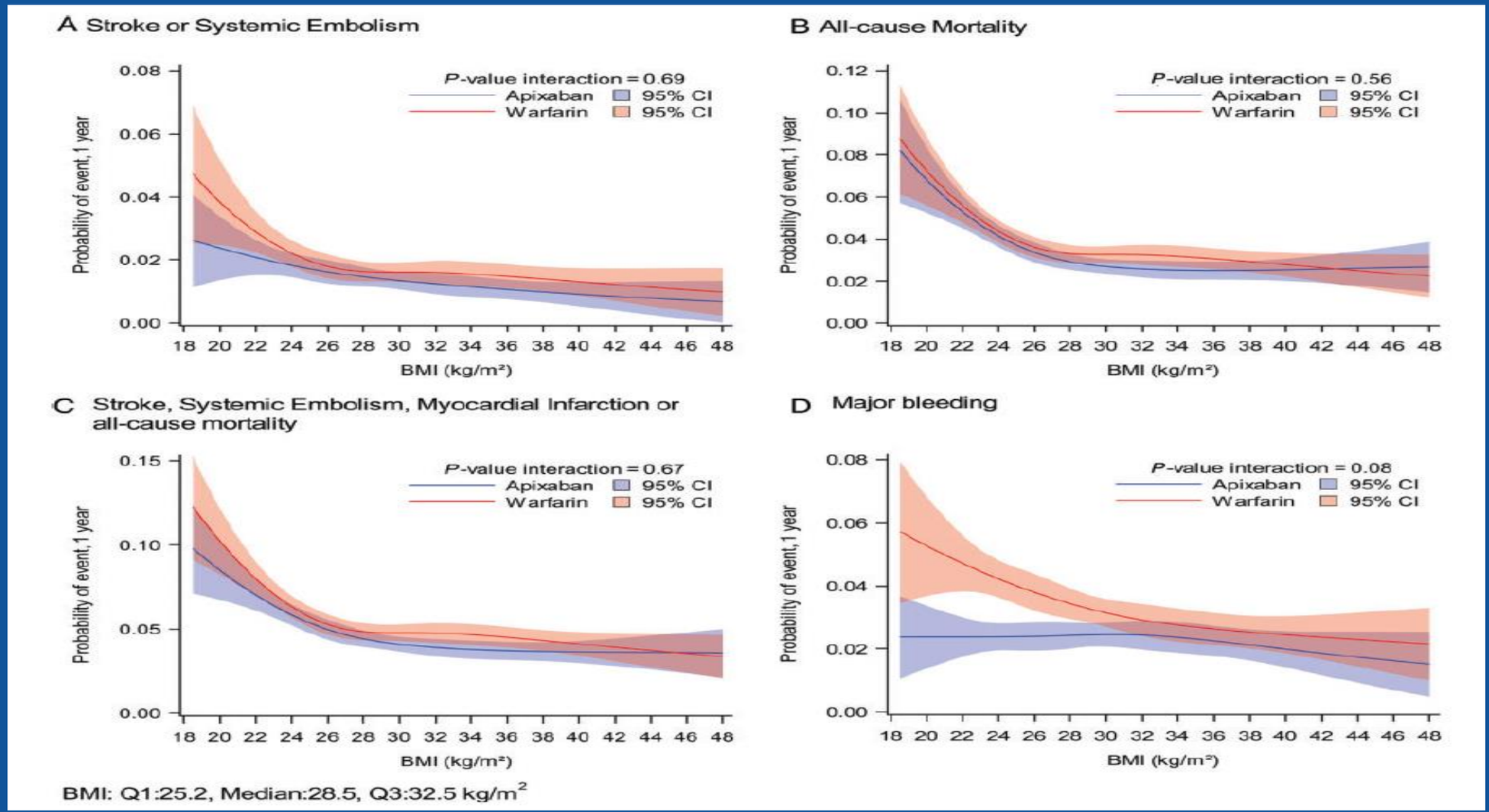
No Disclosures

Untreated Lesions After FFR-Guided PCI: The Concept of CompleteRevascularization



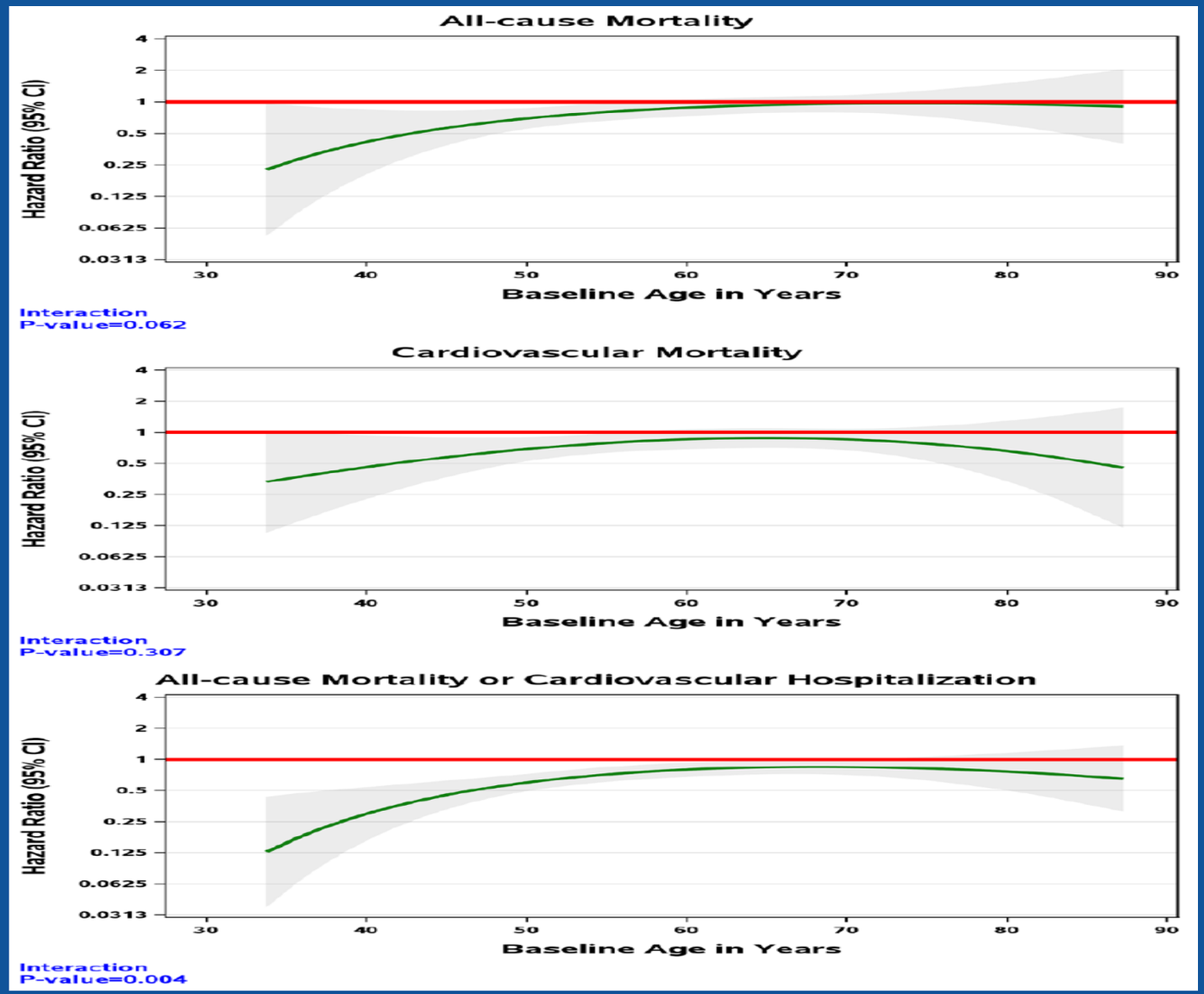
FAME (Y Kobayashi et. al.) JACC 2016;67:1701

One-year Event Rates For Continuous Body Mass Index According To Study Treatment



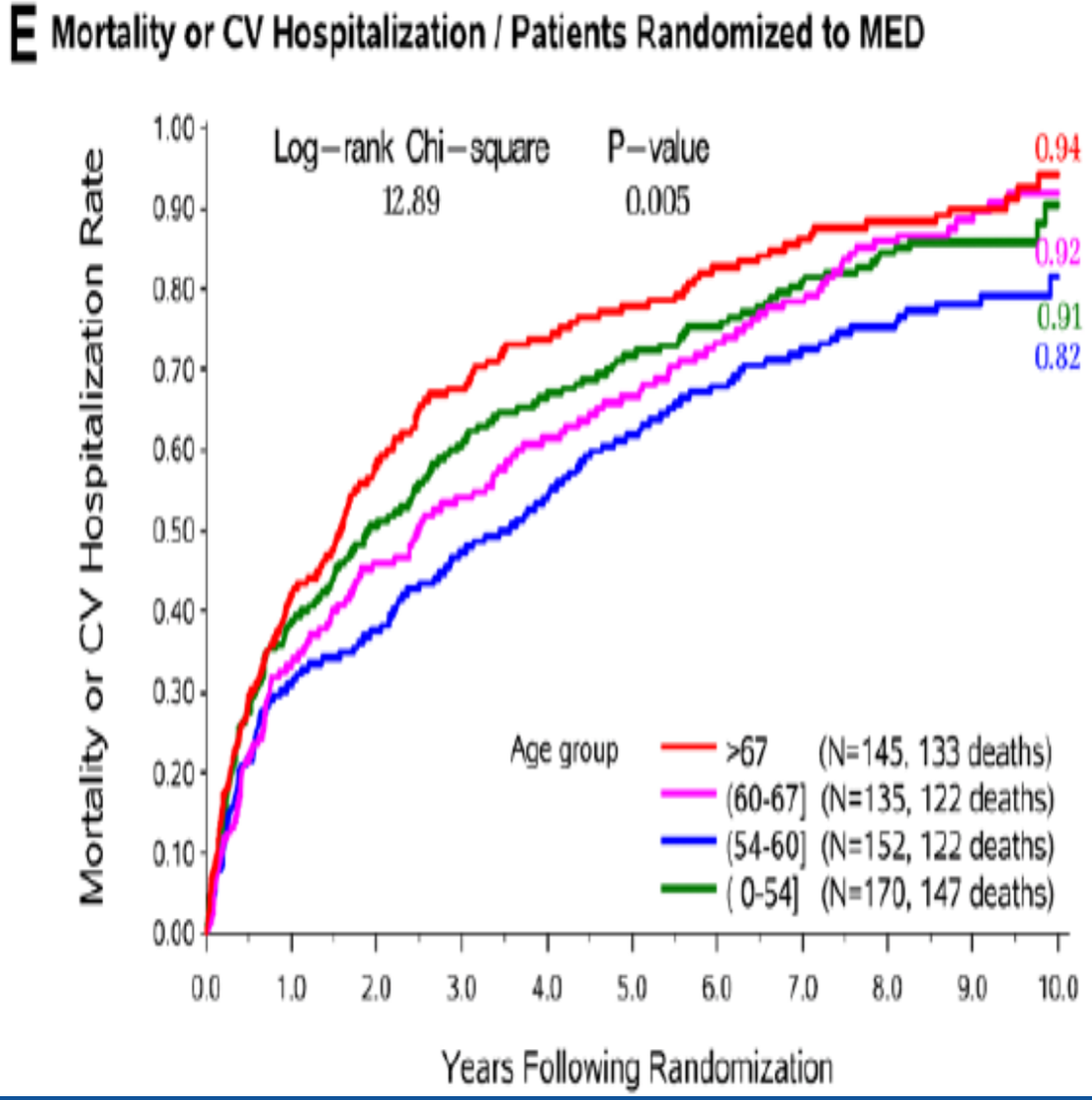
TF Lüscher. Eur Heart J. 2016;37:2847 - RK Sandhu et. al. Eur Heart J. 2016;37:2869

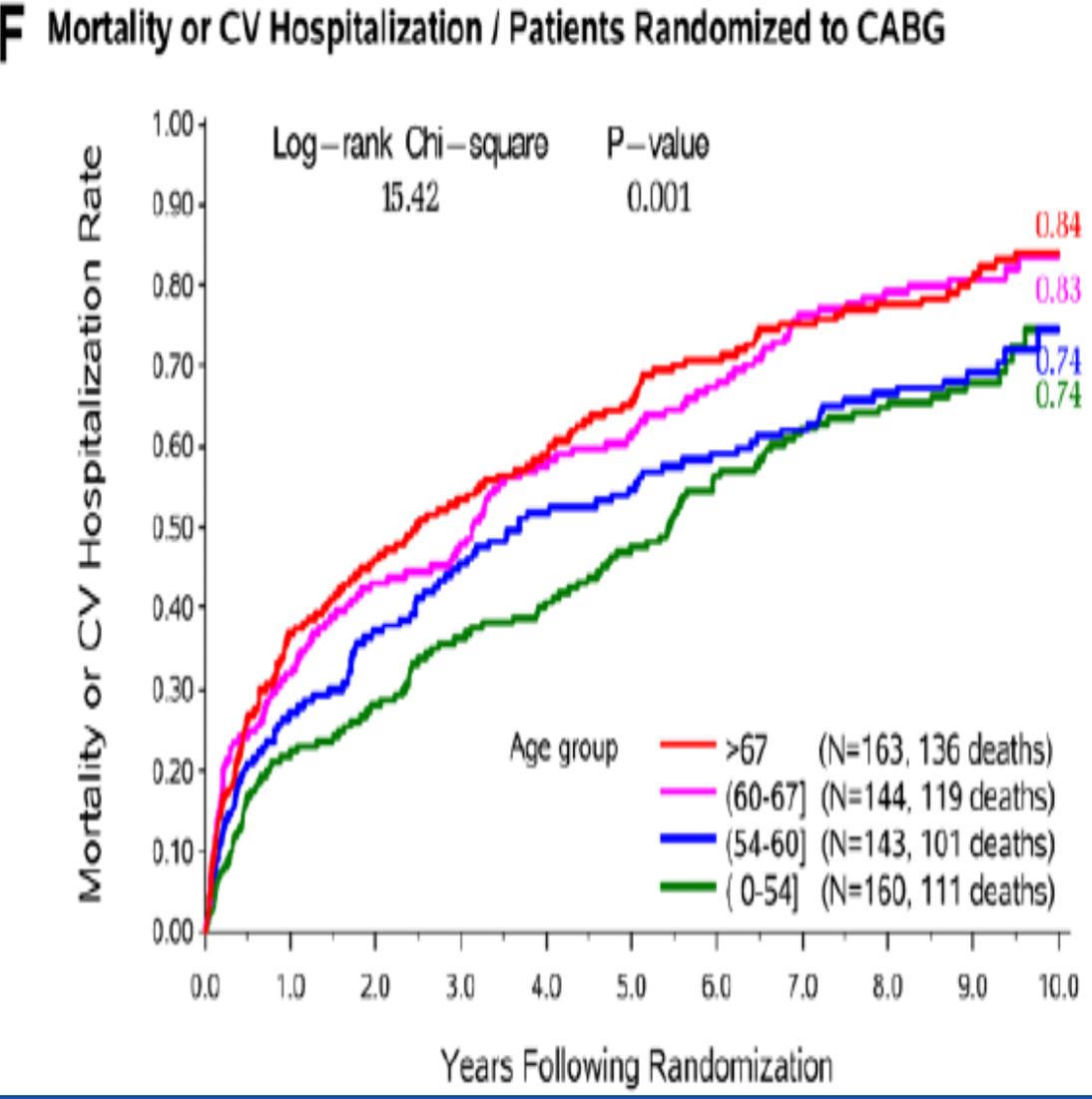
HR (Solid Line) And 95% Confidence Interval (CI; Gray Area) For The Effect Of CABG Vs Medical Rx Across Ages



STICH (MC Petrie et. al.) Circulation. 2016;134:1314

Ten-Year Outcomes After CABG According to Age in Patients With HF and LV Systolic Dysfunction

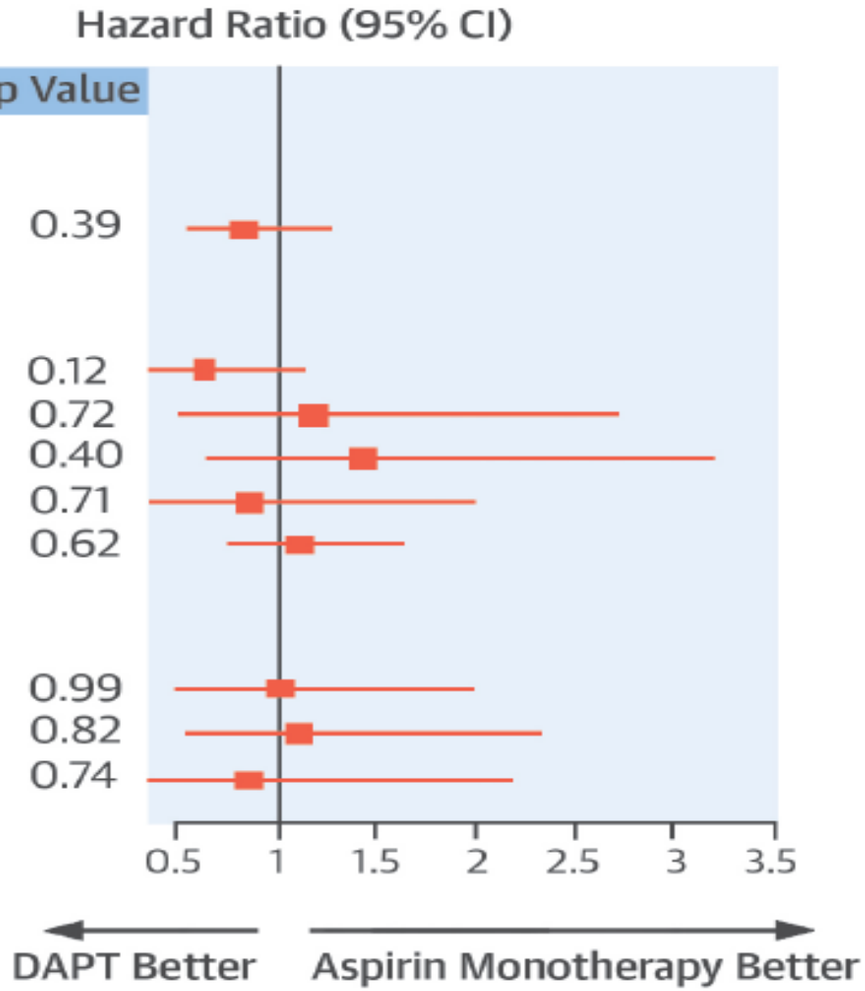




STICH (MC Petrie et. al.) Circulation. 2016;134:1314

Adjusted Hazard Ratio Plot Of Clinical And Safety Outcomes

	DAPT n = 544	SAPT n = 251	p Value
Primary FREEDOM Outcome			
All-cause Mortality, MI, or Stroke	12.5	16.0	0.39
Secondary Outcomes			
All-cause Mortality	5.8	9.4	0.12
Vascular Mortality	3.5	3.3	0.72
Myocardial Infarction	5.2	3.7	0.40
Stroke	3.2	4.1	0.71
Cardiovascular Hospitalizations	19.5	18.1	0.62
Primary Safety Outcomes			
Major Bleeding	5.6	5.7	0.99
Blood Transfusions	4.8	4.5	0.82
Bleeding Hospitalization	2.6	3.3	0.74



S van Diepen, V Fuster, ME Farkouh et. al. J Am Coll Cardiol 2016. (In Press)