MASSACHUSETTS GENERAL HOSPITAL

HEART CENTER

Treatment of Ischemic Heart Disease in 2015

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Coronary Heart Disease: The Scope of the Problem

- CHD is the leading cause of death in the United States
- 15.4 million people in the U.S. have CHD
  - 8.8 million men, 6.6 million women
  - By age 60, 20% of men and 6% of women have CHD
- 1.2 million people have CHD events / year
  - 620,000 are first events
  - 295,000 are recurrent events
  - 150,000 are silent events
- 380,000 CHD deaths (1 in every 6 deaths)
- 7.8 million people in the U.S. have chronic stable angina.

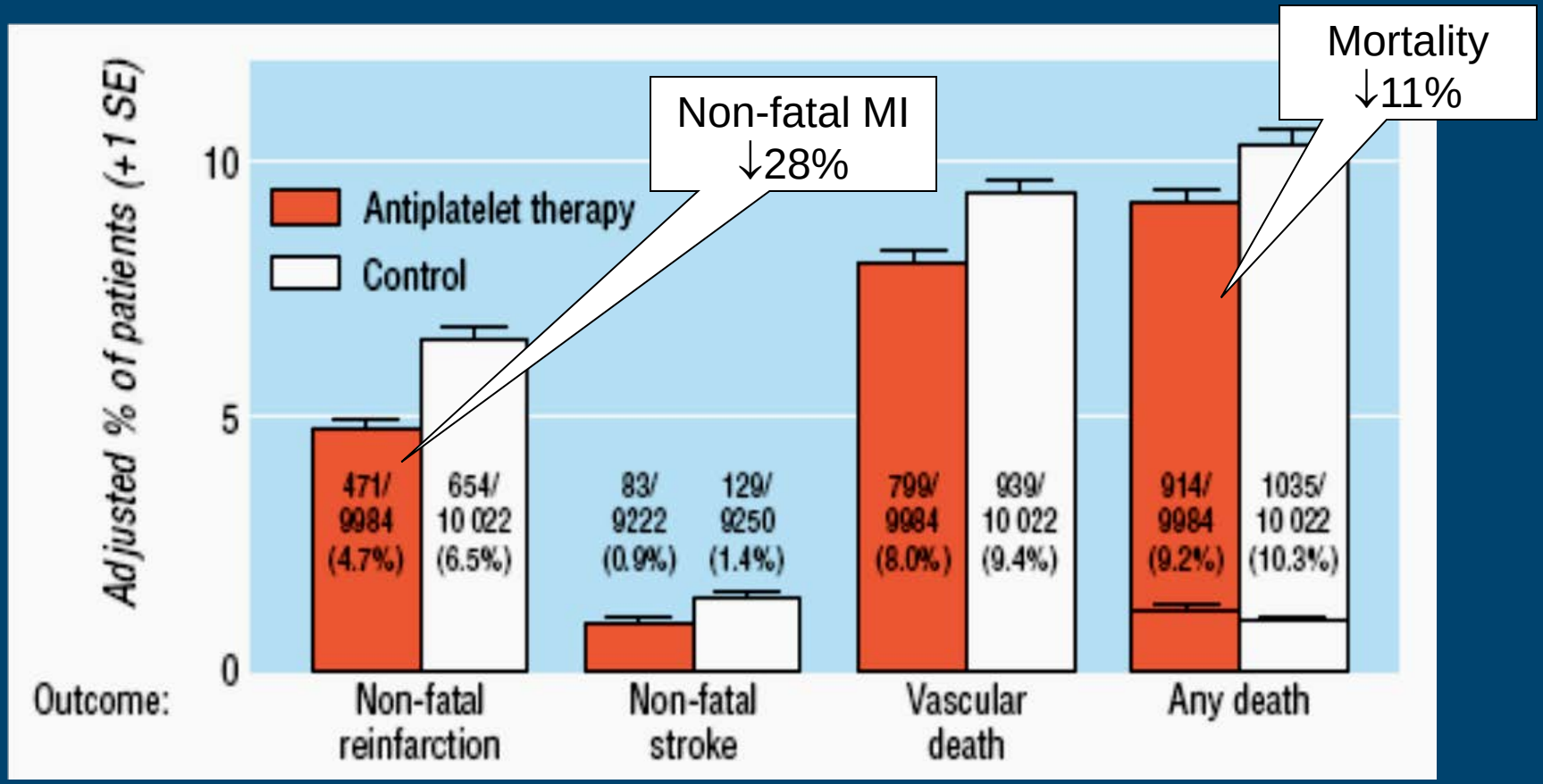
AHA Heart Disease & Stroke Statistics:2014 Update
http://circ.ahajournals.org/content/early/2013/12/18/01.cir.0000441139.02102.80.full.pdf+html

Goals of Treatments for Chronic CAD

- Reduce acute coronary events (MI, cardiac death)
  - Pacify the platelet
  - Treat the plaque
    - Atherosclerotic process
  - Normalize arterial wall physiology
- Relieve the symptoms of angina

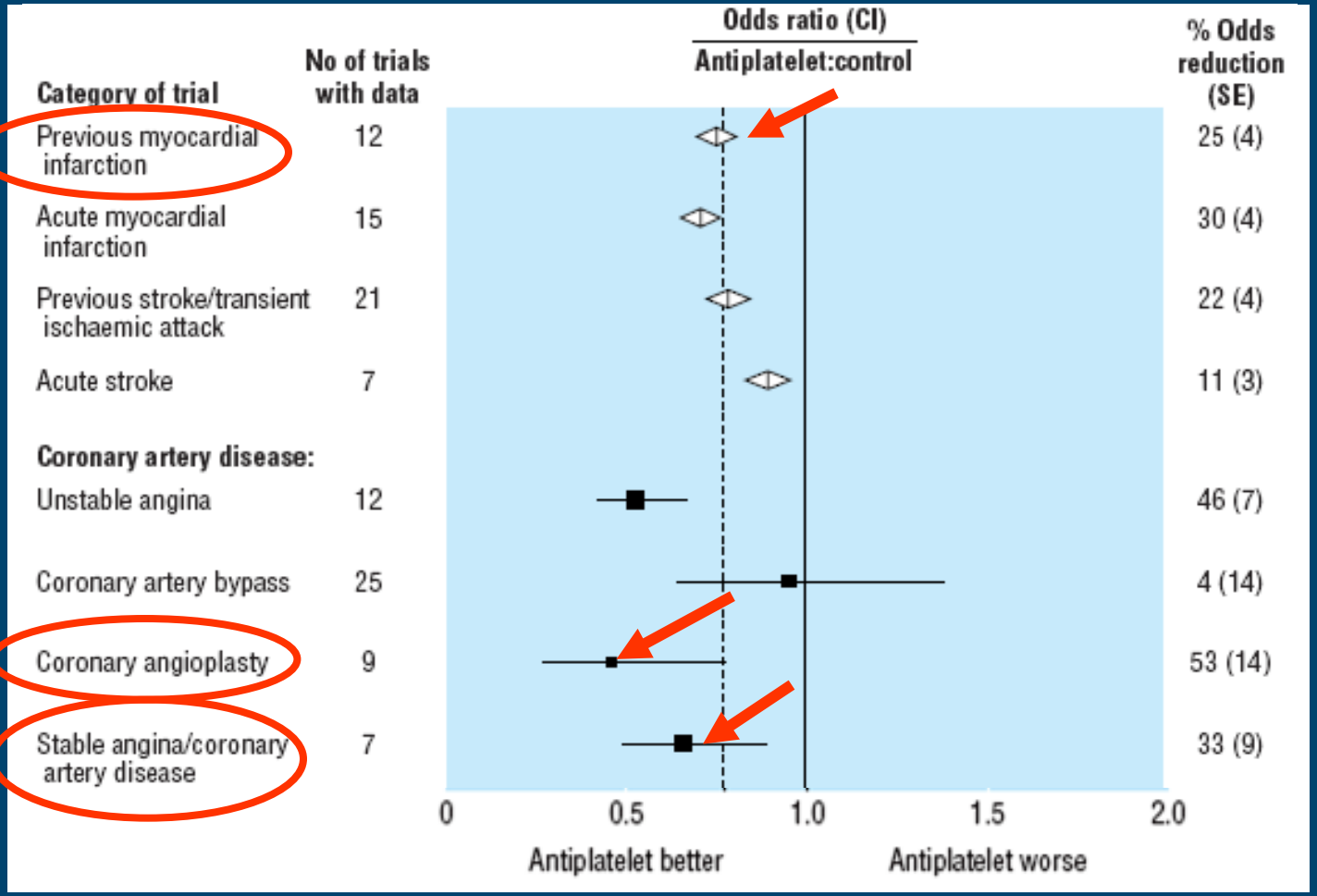
Anti-platelet Therapy: Aspirin for Secondary Prevention

Meta-analysis from the Antithrombotic Trialists' Collaboration



AT Collaboration. BMJ 2002;324:71-86

Anti-platelet Therapy:
Aspirin for "Primary and a half" Prevention



AT Collaboration. BMJ 2002;324:71-86

Anti-platelet Therapy: Aspirin Dosing

- Meta-analysis showed similar benefits for doses from 75 – 325 mg
- However, data suggest that enteric coating may reduce bioavailability and antiplatelet activity compared with plain aspirin
- Recent trial suggests that most aspirin “resistance” is pseudoresistance due effects of enteric coating
- One should consider using plain aspirin at 81 mg dose and reserving enteric coating for 162 mg or 325 mg doses.

AT Collaboration. BMJ 2002;324:71-86
Cox D, et al. Stroke 2006;37:2153-2158
Grosser T, et al. Circulation Dec 4, 2012 published ahead of print

Anti-platelet Therapy: Clopidogrel (Plavix)

- Currently used most often in combination with aspirin following stent implantation
  - 1 month for bare metal stents
  - At least 12 months for drug-eluting stents
- Used with aspirin for 3-9 months following acute coronary syndromes:
  - CURE trial showed a 23% ↓ in MI (6.7% to 5.3%)
  - Event curves continue to separate even at 12 months, so the benefits might continue
  - Some have therefore prescribed combination therapy indefinitely for high-risk patients

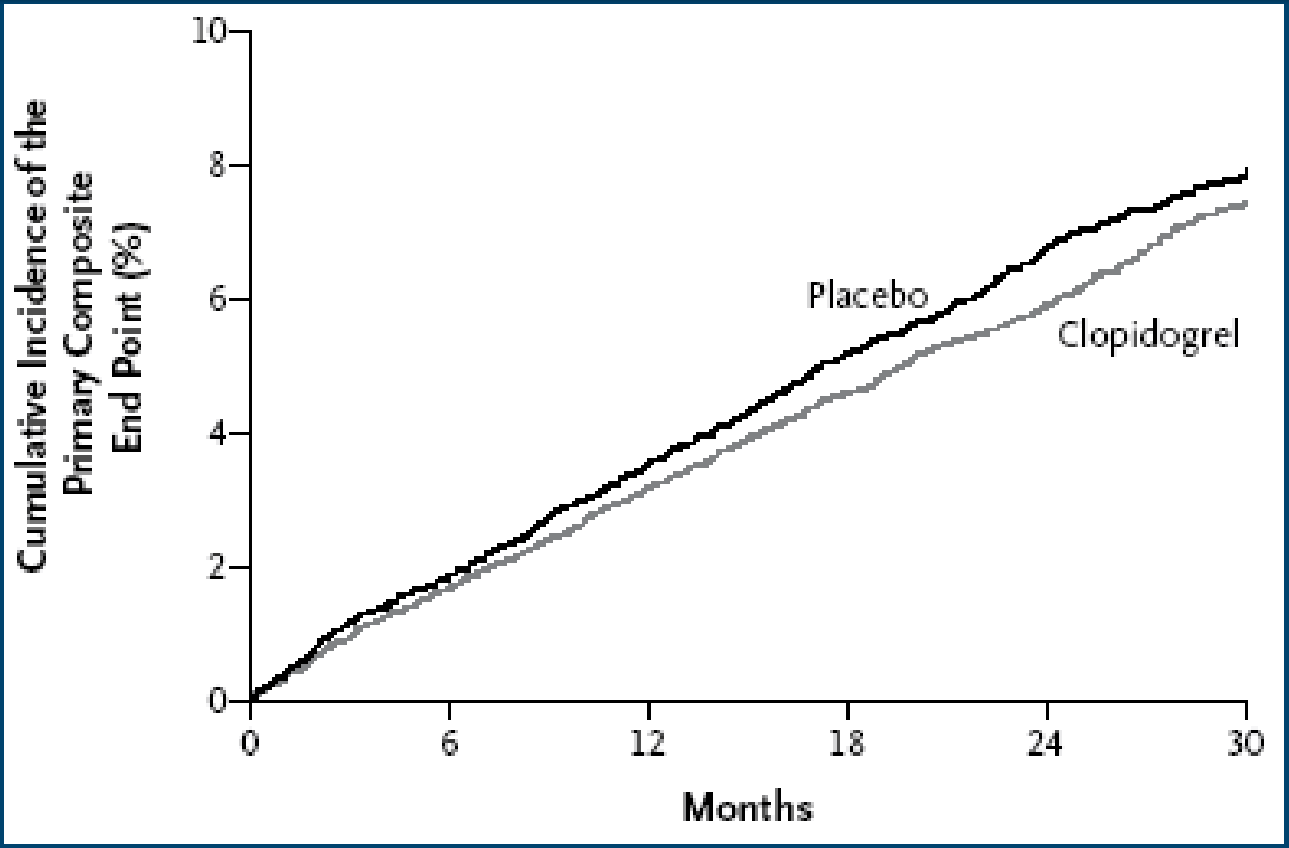
The CURE Investigators. N Engl J Med 2001;345:494–502.

CHARISMA: Clopidogrel and Aspirin vs. Aspirin Alone for Prevention of Atherothrombotic Events

- Hypothesis:
  - Long-term treatment with clopidogrel + aspirin may provide greater protection against CV events than aspirin alone in a broad population of high-risk patients (without ACS or PCI)
- 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors
  - Randomly assigned to clopidogrel 75 mg + low-dose aspirin (75-162 mg) vs. placebo plus low-dose aspirin
  - Median follow up 2.5 years
- Primary end point = composite of MI, stroke, or CV death.

Behatt DL, et al. N Engl J Med 2006;354.

CHARISMA: Clopidogrel and Aspirin vs. Aspirin Alone for Prevention of Atherothrombotic Events



No significant difference in rate of primary end point
(6.8% vs. 7.3%;RR, 0.93; 95% CI, 0.83 to 1.05; P=0.22)

Behatt DL, et al. N Engl J Med 2006;354

CHARISMA:
Some additional reasons for caution…

- In a subgroup analysis, the rate of death from CV causes was actually higher with clopidogrel group vs. placebo, at 3.9% vs. 2.2% (P = 0.01)
- The rate of moderate bleeding was higher with clopidogrel at 2.1% vs. 1.3% (P<0.001).
  - Rates of severe bleeding and intracranial hemorrhage were not different in the two groups.

Behatt DL, et al. N Engl J Med 2006;354

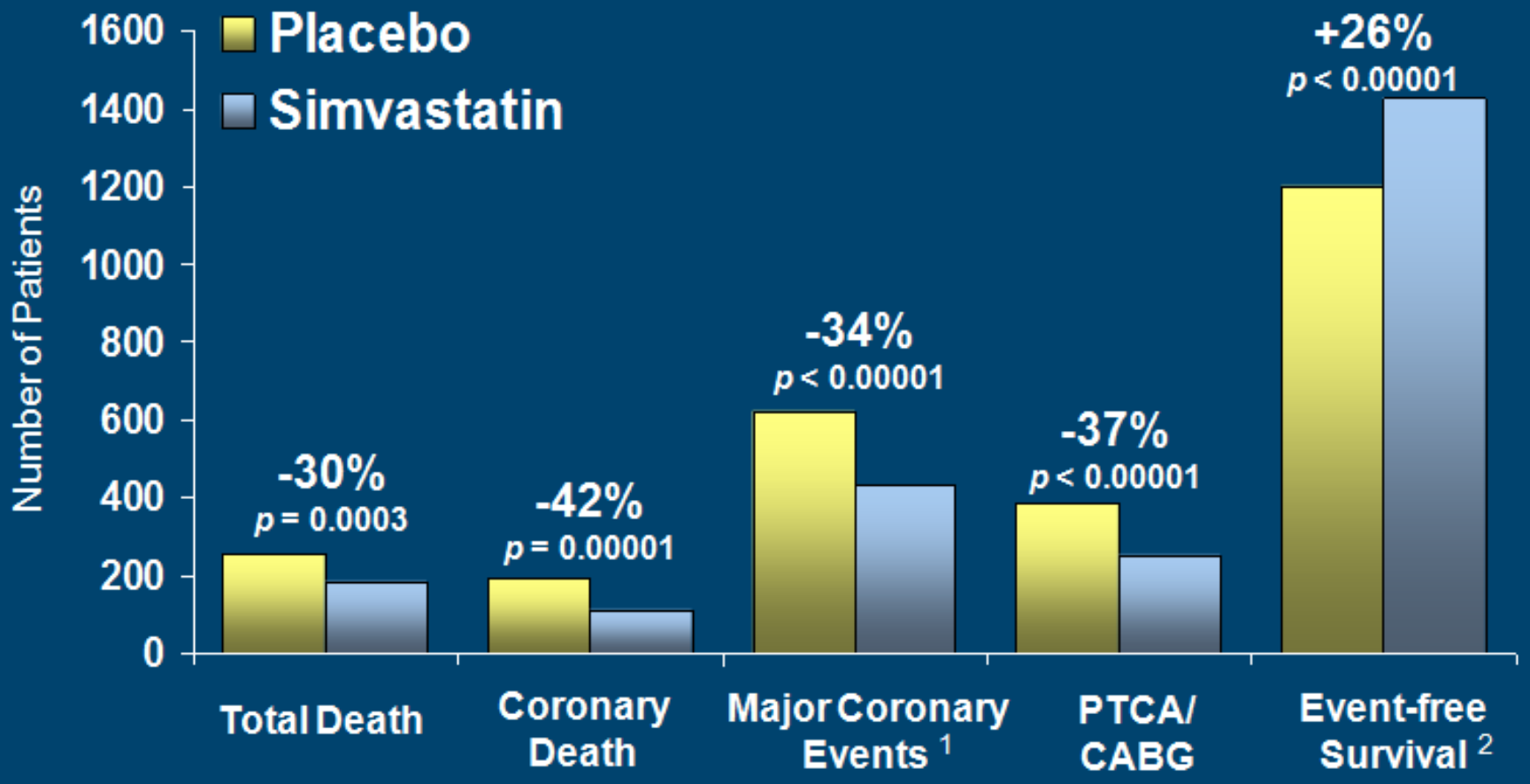
Lipid Lowering Therapy

- Originally intended to halt atherosclerosis and cause plaque regression
- Plaque regression does occur, but only to a small degree, with average stenosis decreasing by 2-4%
  - vs. controls increasing by 2-3%
- However, the clinical benefits of statin therapy far outweigh the angiographic improvements.

Statin Therapy: Mechanisms of Benefit

- Lower cholesterol
  - Reduce progression of disease
  - Reduce lipid content in plaque core:
    Vulnerable plaque $\rightarrow$ stable plaque
- Pleiotropic benefits
  - Reduce inflammation
  - Improve endothelial dysfunction.

The Benefits of Statin Therapy Are Clear: 4S (Simvastatin Survival) Study



1 Death from coronary disease and non-fatal heart attacks.
2 Finished the study without suffering any coronary events or other atherosclerotic events such as stroke.

Lancet 1994; 344:1383-89

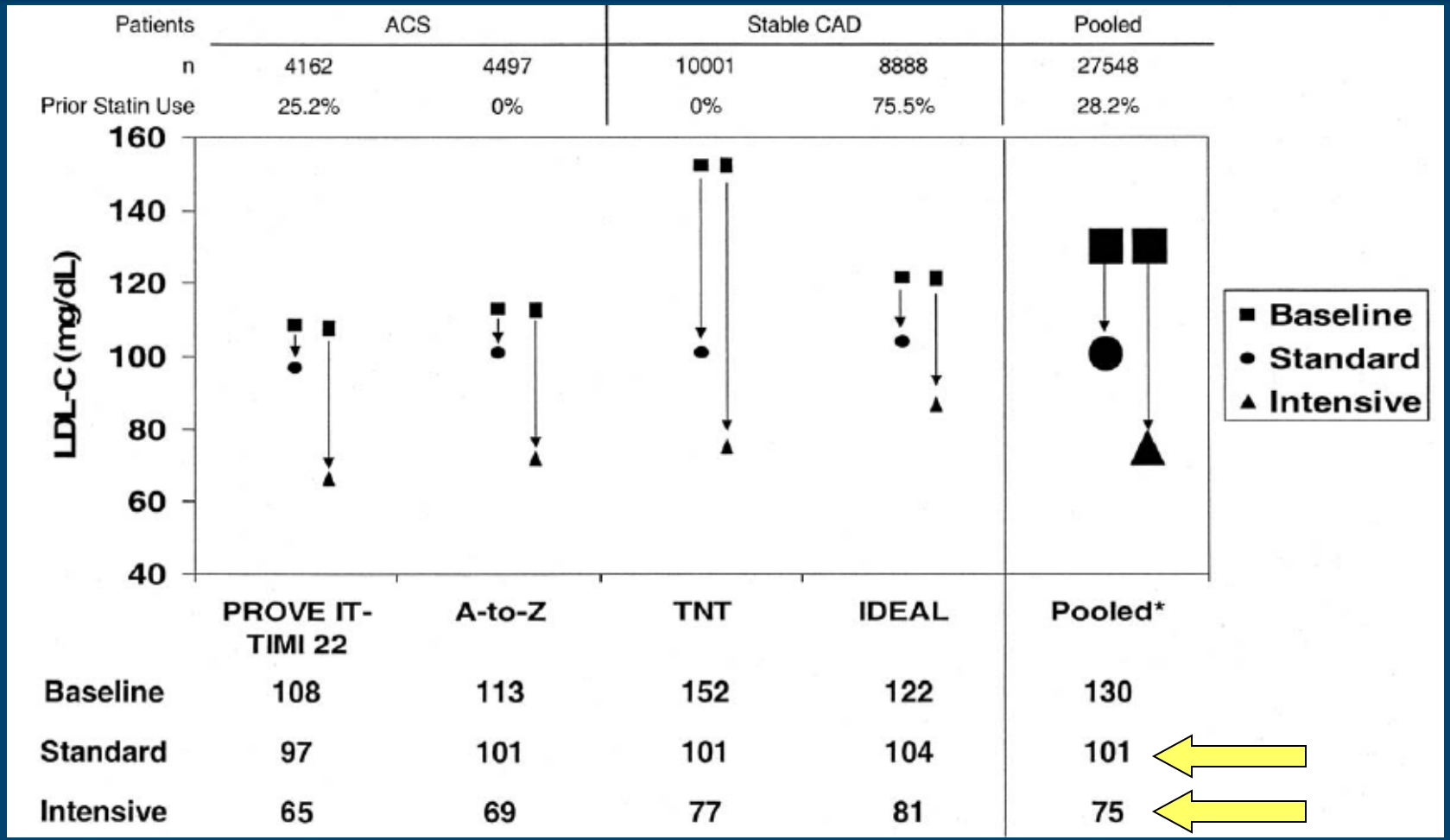
Statin Therapy: What Should Be the Target LDL?

- ATP III Guidelines in 2001:
  - Treat to a target LDL < 100 in all patients with known CAD or at high risk
- But more recent trial data of intensive lipid lowering therapy show that even lower LDL is better

Current LDL Goals: Randomized Trials of Intensive Statin Therapy

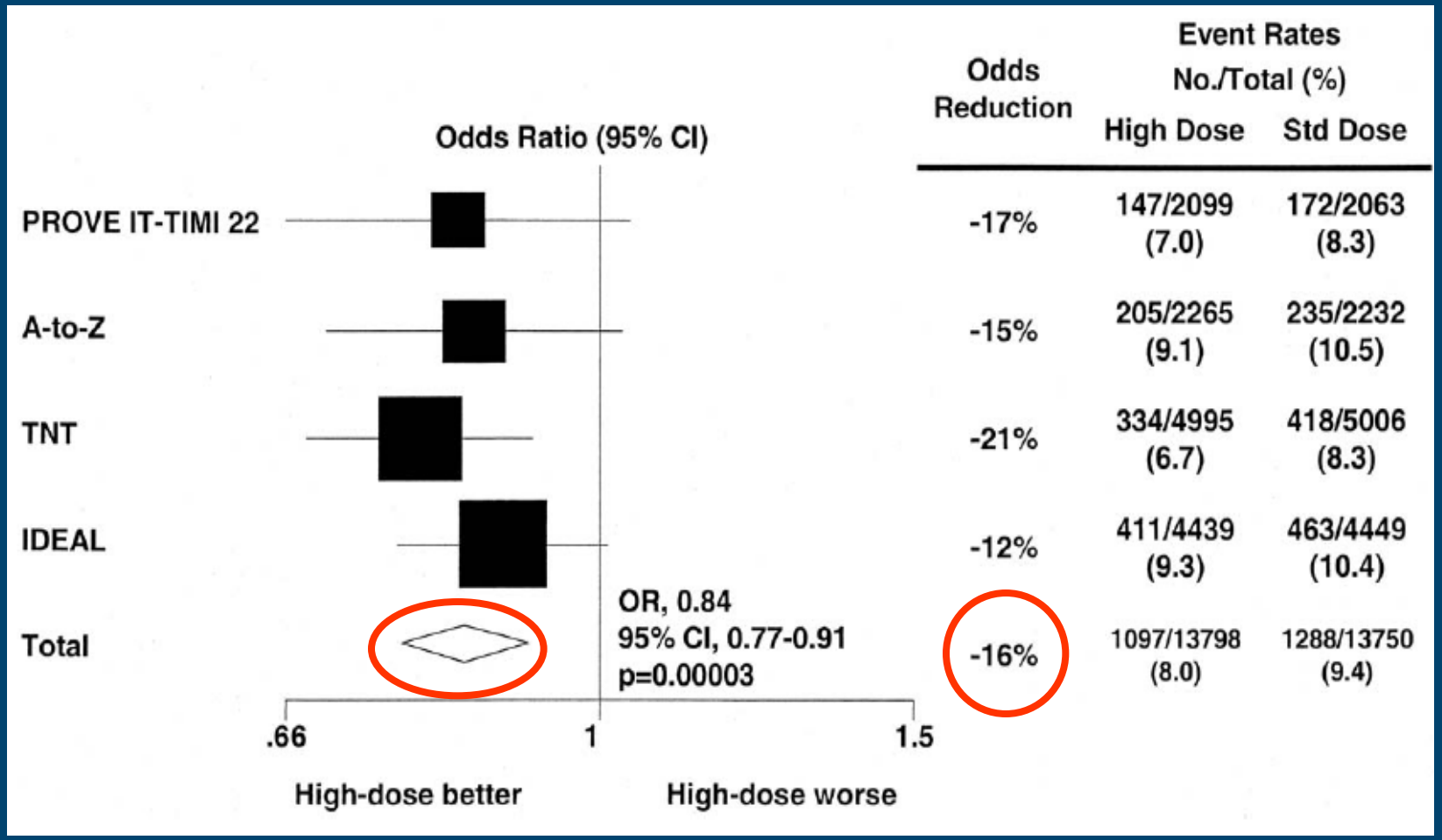
- Acute Coronary Syndromes:
  - PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy)
  - A-to-Z (Aggrastat to Zocor Trial)
- Stable CAD
  - IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering)
  - TNT (Treating to New Targets Study)

Meta-analysis of Intensive Statin Therapy: LDL Levels for High-dose vs. Standard-dose



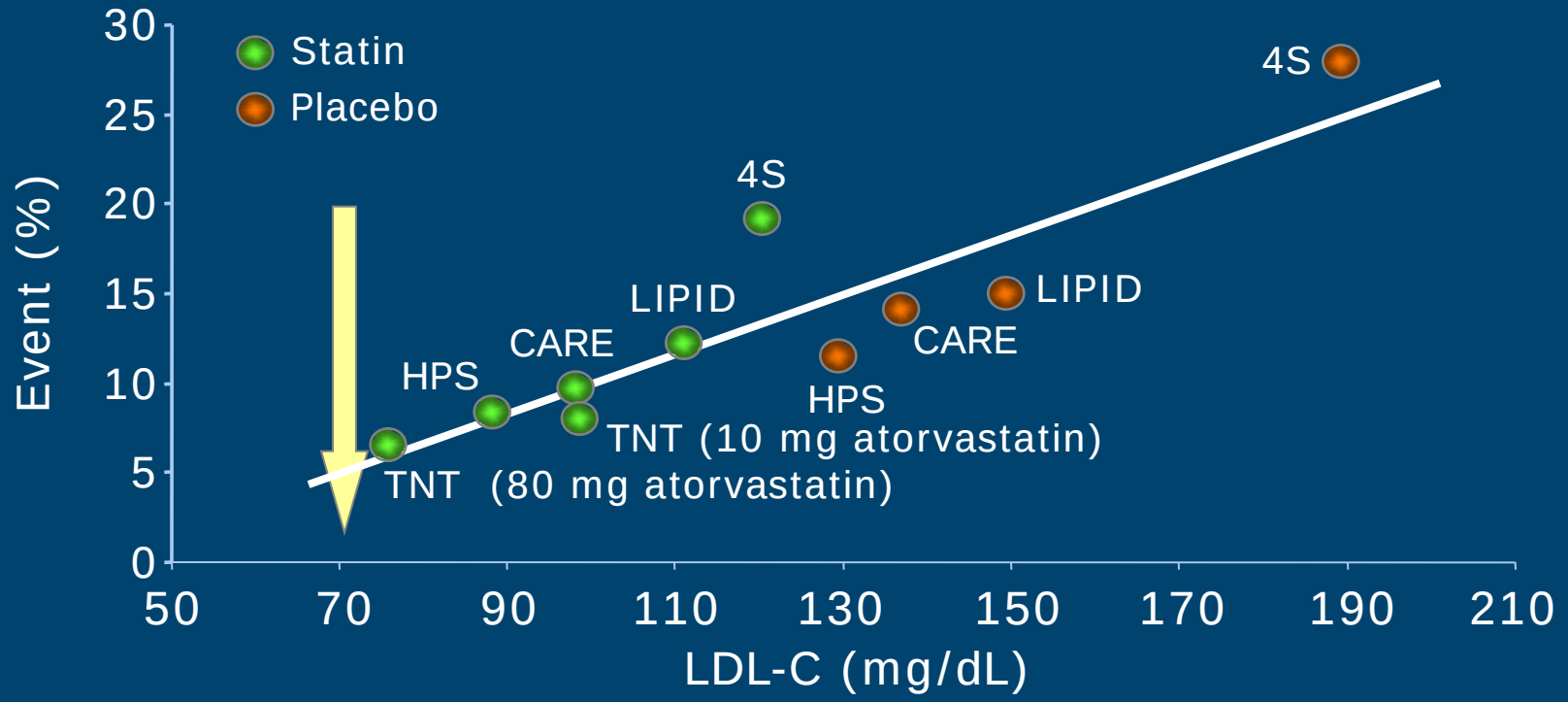
Cannon CP, et al. JACC 2006;48:438-45.

Meta-analysis of Intensive Statin Therapy: Risk of Coronary Death or MI



Cannon CP, et al. JACC 2006;48:438-45.

LDL Goals Over the Past Decade: Lower is Better



ATP III Updated Guidelines in 2004 (ATP III-R): Target LDL ≤ 70 (Grundy SM, et al. Circulation 2004;110:227-39.)

HPS = Heart Protection Study; CARE = Cholesterol and Recurrent Events Trial; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; 4S = Scandinavian Simvastatin Survival Study.

LaRosa et al. N Engl J Med 2005;352:1425–1435.

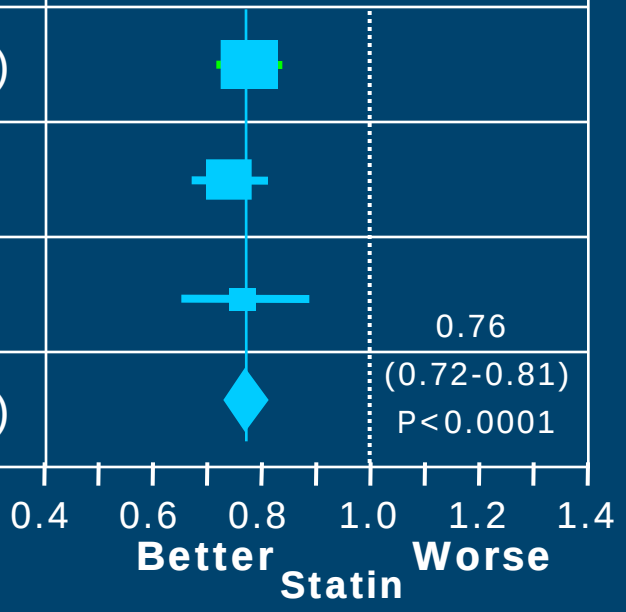
Should We Treat CHD Patients with Baseline LDL Levels <100?

Results of the Heart Protection Study

Vascular Events by Baseline LDL

Baseline LDL-C (mg/dL)	Simvastatin 40 mg (n=10,269)	Placebo (n=10,267)
≥130	1083 (21.6%)	1356 (26.9%)
100 - 129	668 (18.9%)	871 (24.7%)
<100	282 (16.4%)	358 (21.0%)
All patients	2033 (19.8%)	2585 (25.2%)

Risk ratio and 95% CI



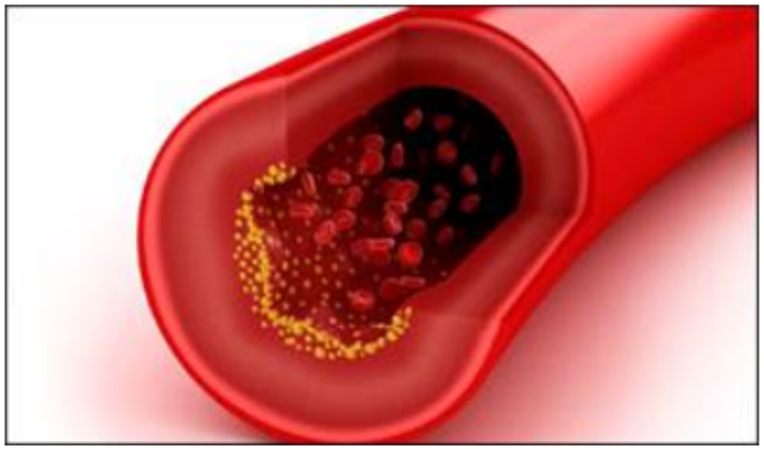
Heart Protection Study Collaborative Group. Lancet 2002;360:7-22

2013 ACC/AHA Cholesterol Guidelines

December 16, 2013

New ACC/AHA Guidelines -- Part 3: Panel Member Addresses Controversies Surrounding New Cholesterol Guideline

On Nov. 12, 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) released four new sets of clinical practice guidelines to assist primary care clinicians in identifying adults who may be at high risk for developing atherosclerotic cardiovascular disease (ASCVD) and who may benefit from lifestyle changes or drug therapy for prevention.[1]



New ACC/AHA Guidelines -- Part Three: Controversies Surrounding New Cholesterol Guidelines

MPR offers a four-part series summarizing the new guidelines and discussing how they differ from earlier recommendations.

2013 ACC/AHA Cholesterol Guidelines

- High-intensity statin therapy
  - Goal = lowering LDL–C by ≥ 50%
  - Atorvastatin 40-80 mg, rosuvastatin 20-40 mg daily
- Moderate-intensity statin therapy
  - In those ≥ 75 years of age, or those who don't tolerate or are at risk from high-dose statins
  - Goal = lowering LDL–C by 30-50%
  - Atorvastatin 10-20 mg, rosuvastatin 5-10 mg daily

http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.full.pdf+html

ACE Inhibitors for Risk Reduction

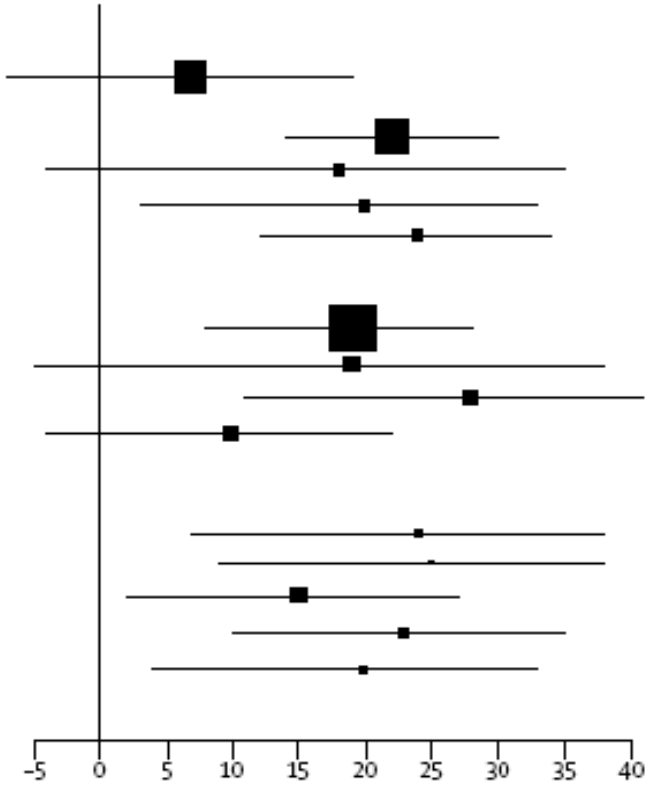
- HOPE (Heart Outcomes Prevention Evaluation) Study in 2000
  - 9300 high-risk patients (vascular disease or DM + one other CV risk factor and no LV dysfunction or CHF)
  - Randomized to ramipril 10 mg qd vs. placebo for 5 years
  - Ramipril group had lower rates of
    - MI ↓ 20%, CV mortality ↓ 26%, All-cause mortality ↓ 16%
- EUROPA study in 2003
  - Showed a similar 20% reduction in primary cardiac endpoints from high dose perindopril
- PEACE (Prevention of Events with ACE Inhibition) trial in 2004
  - Failed to show an overall benefit from trandolapril

Yusuf S. N Engl J Med 2000;342:145-53.
Fox KM, et al. Lancet. 2003;362:782–788.
The PEACE Trial Investigators. N Engl J Med 2004; 351:2058.

ACE Inhibitors for Risk Reduction: A Combined Analysis of Multiple Trials

Percent reduction in odds of CV death, non-fatal MI, or stroke

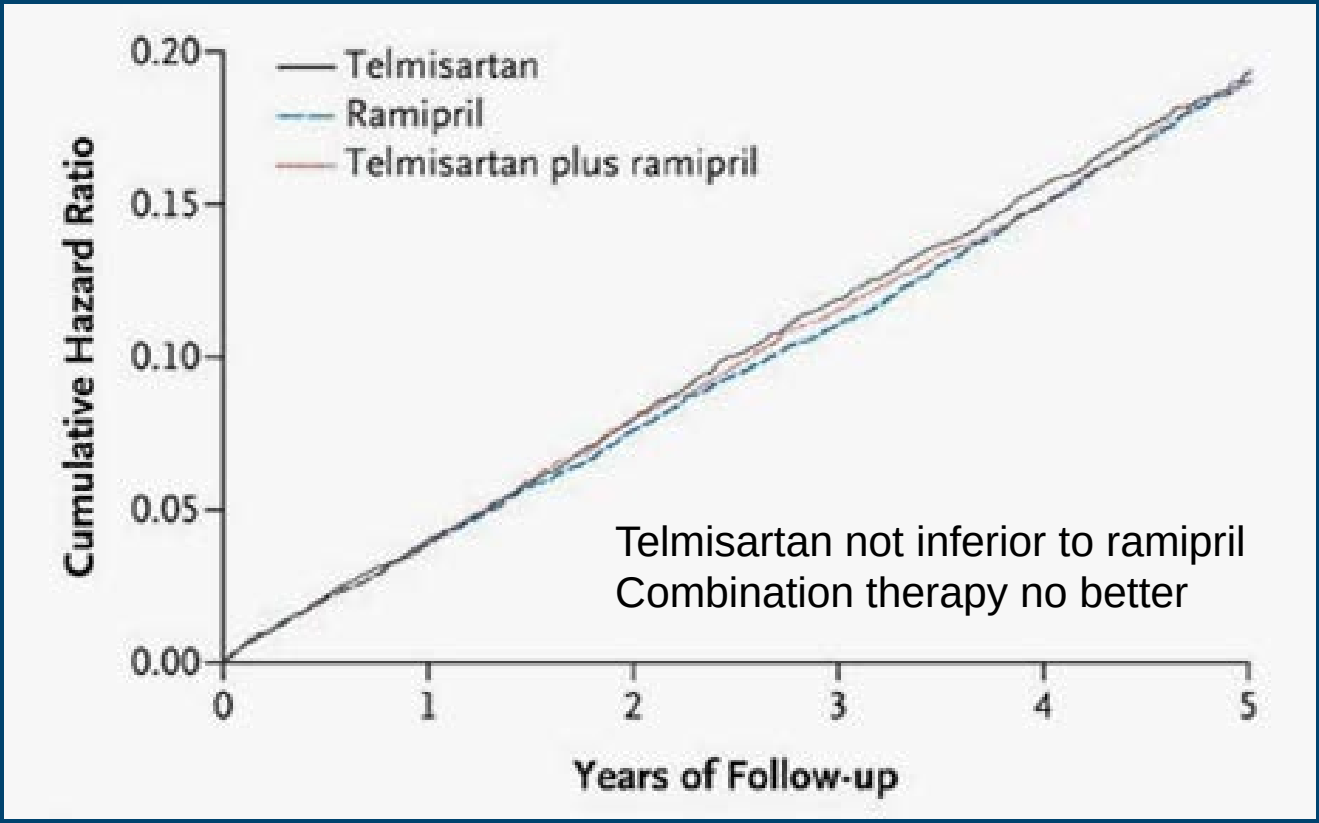
Trials	Number of patients	Annual rates in placebo groups	OR (95% CI)	p
PEACE	8290	2·13	7 (–8 to 19)	0·328
HOPE total	9297	3·95	25 (16 to32)	0·0001
HOPE lower risk	3083	2·17	18 (–4 to 35)	
HOPE medium risk	3100	3·58	20 (3 to 33)	
HOPE high risk	3114	5·98	24 (12 to 34)	
EUROPA total	12218	2·60	19 (8 to 28)	0·0007
EUROPA lower risk	3976	1·40	19 (–5 to 38)	
EUROPA medium risk	3975	2·41	28 (11 to 41)	
EUROPA high risk	3975	4·00	10 (–4 to 22)	
AIRE	1986	22·6	24 (7 to 38)	0·0068
TRACE	1749	17·0	25 (9 to 33)	0·0028
SOLVD-P	4228	7·4	15 (2 to 27)	0·0252
SOLVD-T	2569	13·1	23 (10 to 33)	0·0009
SAVE	2231	9·8	20 (4 to 33)	0·0168



Dagenais GR, et al. Lancet 2006; 368:581-588

Do ARBs Confer Similar Benefit?: ONTARGET Study

Kaplan–Meier curves for the primary outcome = CV death, MI, stroke, or hospitalization for CHF



The ONTARGET Investigators. N Engl J Med 2008;385:1547-59

Other Therapeutic Strategies: Treating Elevated Homocysteine

- Vitamin treatments can lower homocysteine
  - Folic acid, vitamin B12, vitamin B6
- We had been treating for years, presumptively, while awaiting evidence of improved CV outcomes
- 3 large randomized trials in 2006 and 2010 showed no reduction in MI or stroke
  - HOPE 2 Study
  - The Norwegian Vitamin Trial (NORVIT)
  - SEARCH trial

HOPE 2 Investigators. N Engl J Med 2006;354:1567.
Bønaa KA, et al. N Engl J Med 2006;354.
Armitage JM et al. JAMA 2010; 303:2486-2494.

Other Potential Therapeutic Strategies: Antioxidant Vitamins

- There is no evidence of improved outcomes
  - Simvastatin and niacin trial: 800 IU vitamin E, 1000 mg vitamin C, 25 mg beta carotene, 100 mcg selenium; No benefit from vitamins alone, but when given with statin therapy there was a blunting of the outcomes improvement of statin therapy
  - Heart Protection Study : 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily: Neutral effect on mortality and vascular events in 5 years
  - SECURE trial: Vitamin E had no effect on progression of atherosclerosis in carotid arteries by ultrasound

Brown, BG et al. N Engl J Med 2001;1583-92.
Heart Protection Study. Lancet 2002;360:23-33.
Lonn E, et al. Circulation, 2001;103:919-25.

Other Potential Therapeutic Strategies: Multivitamins

- TACT Trial
- 1700 patients aged ≥ 50 years s/p MI
- Double-blind, placebo-controlled trial of high-dose MVI vs. placebo
- Median follow-up 31 months
- Primary end point = total death, recurrent MI, stroke, coronary revascularization, or hospitalization for angina
- No significant reduction in cardiovascular events

Lamas GA, et al. Ann Intern Med. 2013;159:797-804.

Omega-3 Fatty Acids: Early Recommendations

- 2000: AHA recommended 2 servings of fish per week or 1g supplement daily
- 2004: NIH Working Group Report on Future Clinical Research Directions on Omega-3 Fatty Acids and Cardiovascular Disease:
  - *"The body of evidence is consistent with the hypothesis that intake of omega-3 FA reduces CVD but a definitive trial is needed."*
- Several randomized controlled trials ongoing
  - One has been completed

Harris WS, et al. Circulation 2009;119:902-7.
http://www.nhlbi.nih.gov/meetings/workshops/omega-3/omega-3-rpt.htm

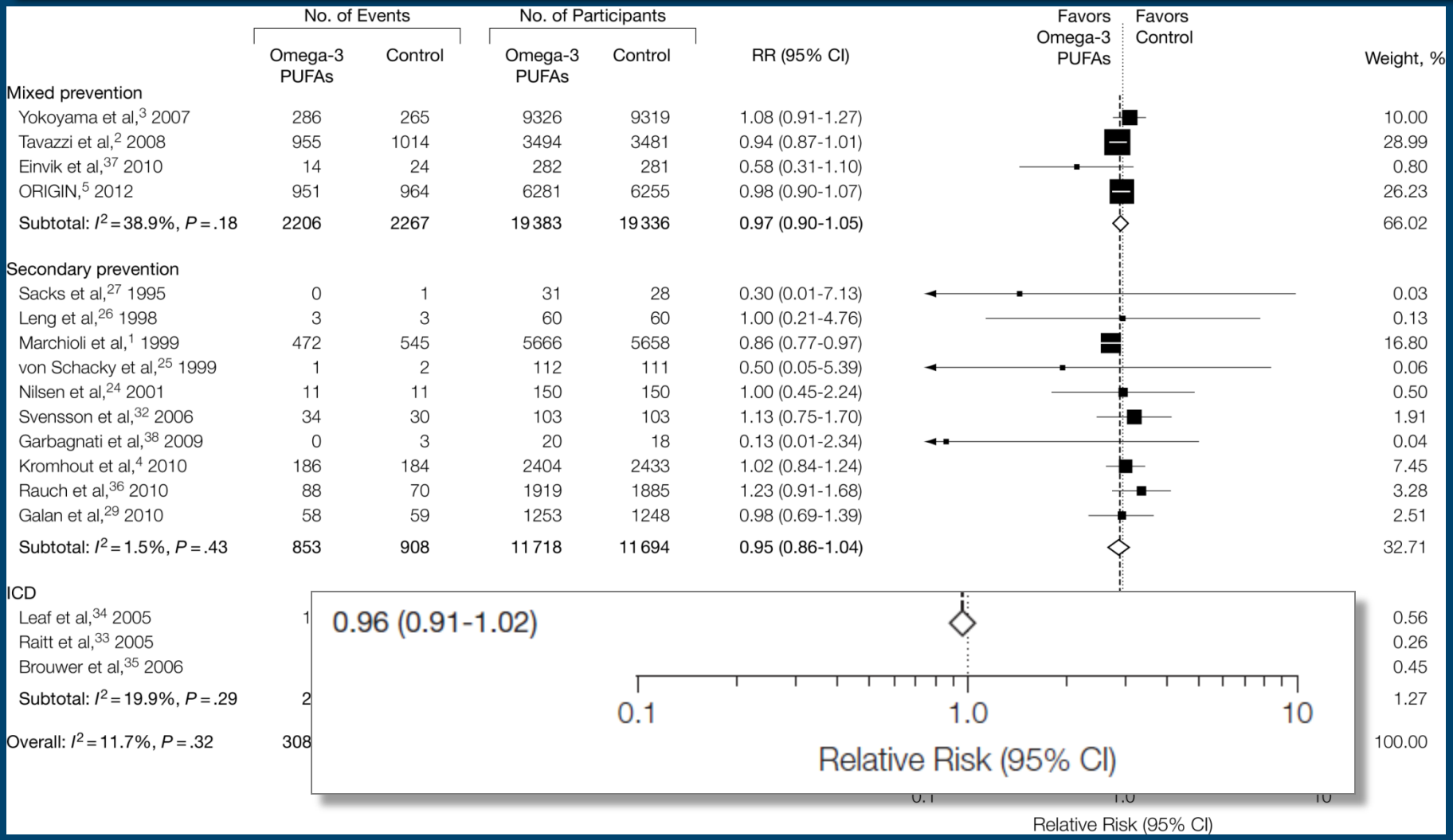
Alpha Omega Trial: Primary and secondary outcomes in EPA-DHA alone vs. placebo/ALA

Outcome	EPA-DHA (n=2404), %	Placebo or ALA-only (n=2433), %	Hazard ratio (95% CI)
Major CV events*	14.0	13.8	1.01 (0.87–1.17)
Incident CV disease	7.0	7.6	0.92 (0.75–1.13)
Death from CV disease	3.3	3.4	0.98 (0.72–1.33)
Death from CHD	2.8	2.9	0.95 (0.68–1.32)
Ventricular arrhythmia-related events	2.8	3.0	0.90 (0.65–1.26)
Any death	7.7	7.6	1.01 (0.82–1.24)

*Primary end point; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; ALA=alpha-linolenic acid

Kromhout D et al. N Engl J Med 2010; 363:2015-26

Meta-analysis of Omega-3 Supplements for All-Cause Mortality



Rizos EC, et al. JAMA. 2012;308:1024-33

Control Other Risk Factors

- Smoking cessation
- Control hypertension
- Control of hyperglycemia in diabetics
  - United Kingdom Prospective Diabetes Study: For each 1% reduction in mean HbA1c there was a 14% RR for nonfatal MI ($p < 0.0001$)
- Avoid saturated fats:
  - Avoid saturated fat, cholesterol, and trans-fats
  - Increase intake of polyunsaturates
- Weight loss

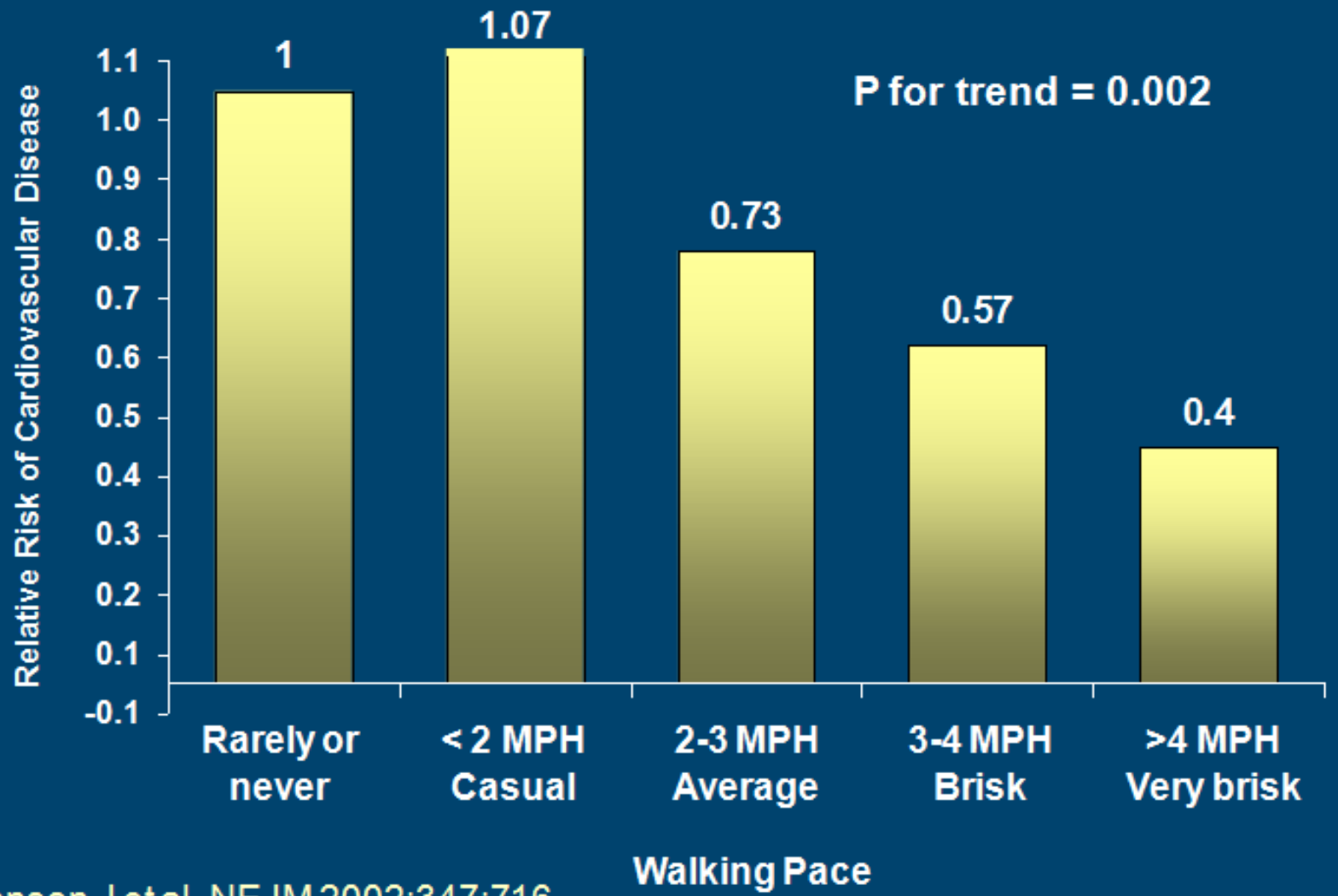
Stratton IM, et al. BMJ. 2000;321:405-412.

Benefits of Exercise ≈ Other "Interventions"

- Reduces atherosclerosis
  - Patients with angiographically proven CAD randomized to regular exercise or usual care
  - After 1 year, underwent repeat coronary angiography
  - Least exercise: atherosclerosis progressed
  - Most exercise: atherosclerosis modestly regressed ($p < 0.005$)
- Reduces CV events and mortality
  - ↓ mortality post-MI by 20-25%
  - Even with only moderate levels of exercise

Hambrecht R, et al. J Am Coll Cardiol. 1993;22:468-477;

Relative Risk of Cardiovascular Disease vs. Pace (Adjusted for Age and Walking Time)



Manson J et al. NEJM 2002;347:716

“Prescribe” Exercise

- Moderate intensity aerobic exercise for a total of ≥ 30 min at least 5 days per week
  - Episodes of exercise should be at least 10 min long
- Moderate resistance (strength) training at least twice per week

American Heart Association and
American College of Sports Medicine 2007 guidelines

Anti-ischemic Medications: Mechanism of Action

- Decrease myocardial oxygen demand in the face of limited blood flow
  - Reduce heart rate
  - Reduce contractility
  - Reduce wall tension: afterload (SBP), preload
- Increase oxygen delivery
  - Vasodilation in the setting of increased vasomotor tone or vasospasm
  - Increase duration of diastole.

Anti-ischemic Medications: Beta Blockers

- Mainstay of therapy of angina in CAD
- ↓ heart rate, ↓ BP, and ↓ contractility
- Reduce late mortality and non-fatal recurrent infarction post-MI by 25%
- Note: Despite a widely held belief, there is NO reduction in MI or mortality among those with CAD but without a prior MI

Bangalore S, et al. Circ Cardiovasc Qual Outcomes 2014;7:872-881.

Anti-ischemic Medications: Nitrates

- ↓ Preload by venodilation, ↓ BP, ↑ collateral circulation
- Minimize any component of increased vasomotor tone or spasm
- Relieve symptoms of exertional angina
- Particularly useful in patients with LV dysfunction
- Sublingual: PRN or prophylactically

Anti-ischemic Medications: Calcium Channel Blockers

- Nifedipine or amlodipine
  - For those with hypertension, vasospasm
  - Long-acting preparations are safest
- Diltiazem or verapamil
  - For those with higher heart rates or who cannot tolerate beta blockers

Anti-ischemic Medications: Combination Therapy

- When one alone does not provide symptomatic relief two or three agents are more efficacious
- Nitrates and beta-blockers are especially complementary

Persistent Angina

- Of the 7.8 million Americans with chronic stable angina, 5-15% may have symptoms refractory to triple therapy
- Revascularization is an option
  - But some patients are poor candidates for revascularization
  - Some have persistent angina despite revascularization
- Is there any other pharmacologic option for anti-anginal therapy?

An Additional Pharmacologic Option: Ranolazine (Ranexa)

- Newer antianginal agent
  - Approved by the FDA in 1/06
- Mechanism of action is uncertain:
  - Orally active piperazine derivative
  - Does not decrease heart rate or blood pressure
  - Theory: Inhibits late Na^{+} current → reduces influx of Ca^{++} → reduces Ca^{++} overload → reduces myocyte dysfunction → reduces diastolic stiffness → reduces extravascular compression of intramural vessels → preserves myocardial blood flow → improves myocardial oxygen delivery

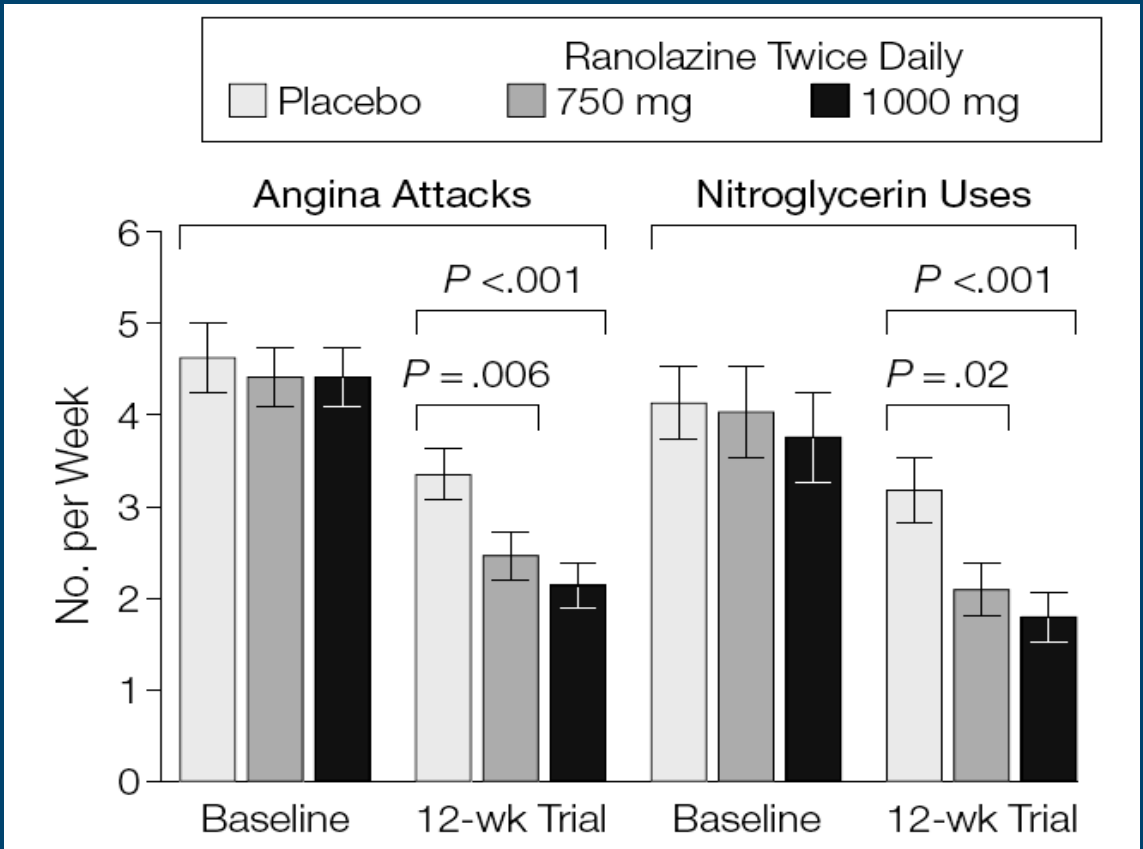
Boden J, et al. J Am Coll Cardiol.2010; 56: 943-945

Ranolazine

- Dosage = 500 mg or 1000 mg twice daily
- Has anti-ischemic efficacy when used alone
  - Efficacy similar to atenolol
- Effective in combination with other anti-anginal medications
  - Because it does not decrease HR or BP it can be added even when HR or BP limits standard therapy.

Combination Assessment of Ranolazine in Stable Angina (CARISA) Trial

Double blind trial of 823 patients with CSA symptoms on standard doses of BBs and CCBs randomized to placebo vs. ranolazine and followed for 12 weeks



Chaitman BR, et al. JAMA 2004;291:309 –16.

Ranolazine: Precautions

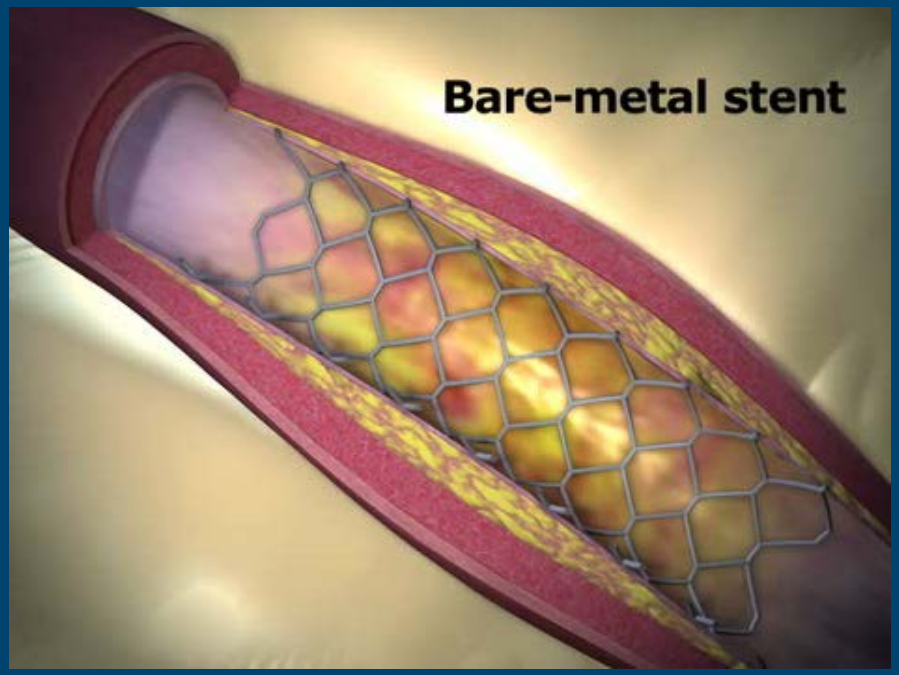
- Side effects:
  - Dizziness, nausea, constipation, vasovagal syncope
- May slightly prolong QTc (avg. 2-5 ms)
  - But trial data showed no evidence of proarrhythmia or sudden death
- Metabolized by liver (cytochrome P3A), excreted in urine
  - Avoid use in sig. liver dysfunction, reduce dose in renal failure
  - Limit dose to 500 mg for those on digoxin, diltiazem, verapamil, erythromycin, fluconazole, TCAs, grapefruit
  - Do not use with strong CYP3A inhibitors: ketoconazole, clarithromycin, etc.
  - Long list of drug interactions, so read prescribing info each time

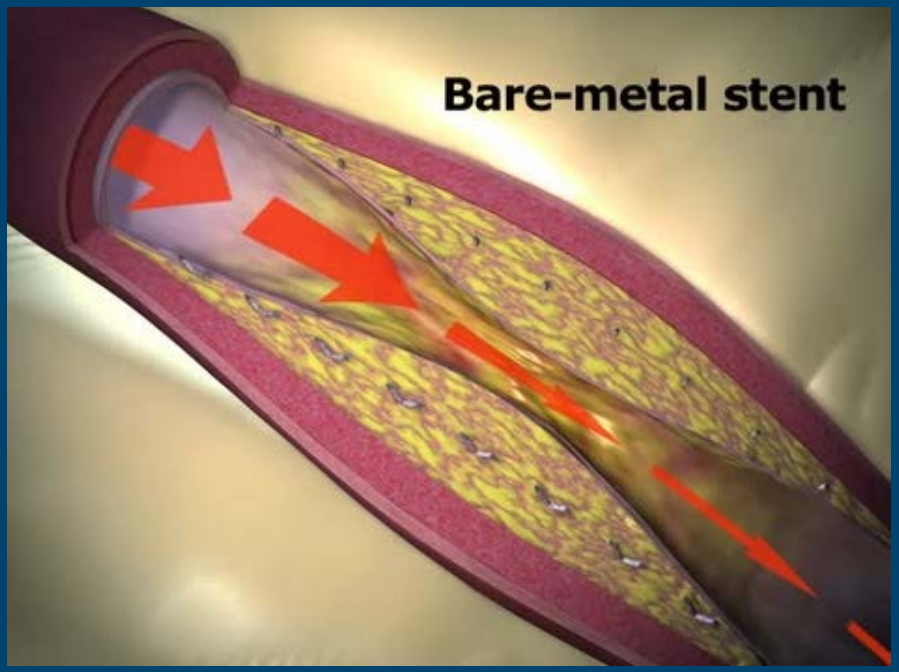
CV Therapeutics package insert

Percutaneous Coronary Intervention (PCI)

- Balloon angioplasty (PTCA → POBA)
  - Initial success rate = 90-95%
  - Restenosis rate = 30-35%
- Intracoronary stents
  - Clinical restenosis rate decreased to 17%
  - Made angioplasty safer for high risk lesions (e.g. proximal LAD)
  - Not useful in small vessels

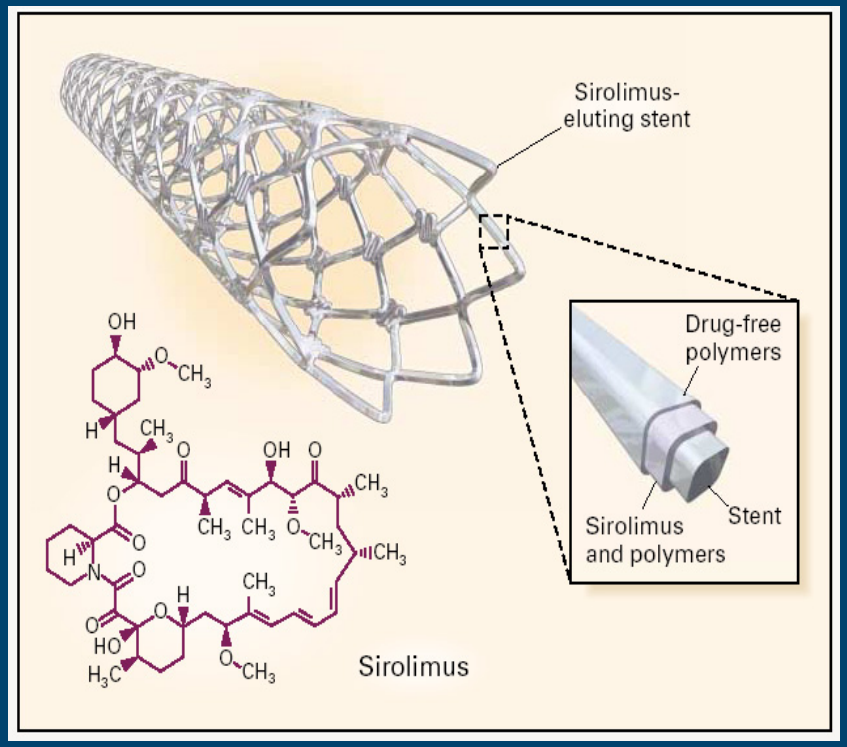
Bare-metal Stents: The Risk of Restenosis



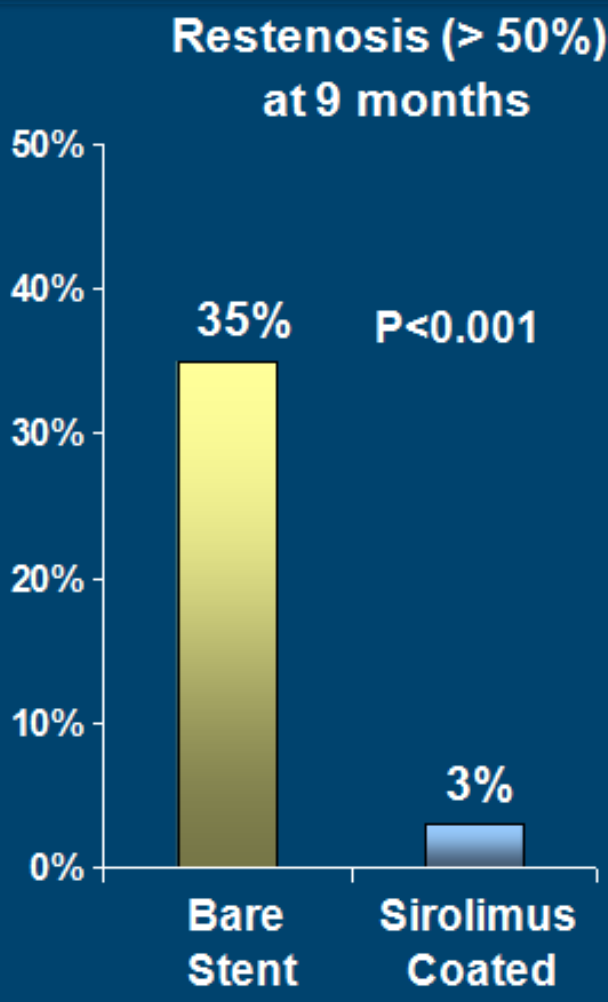


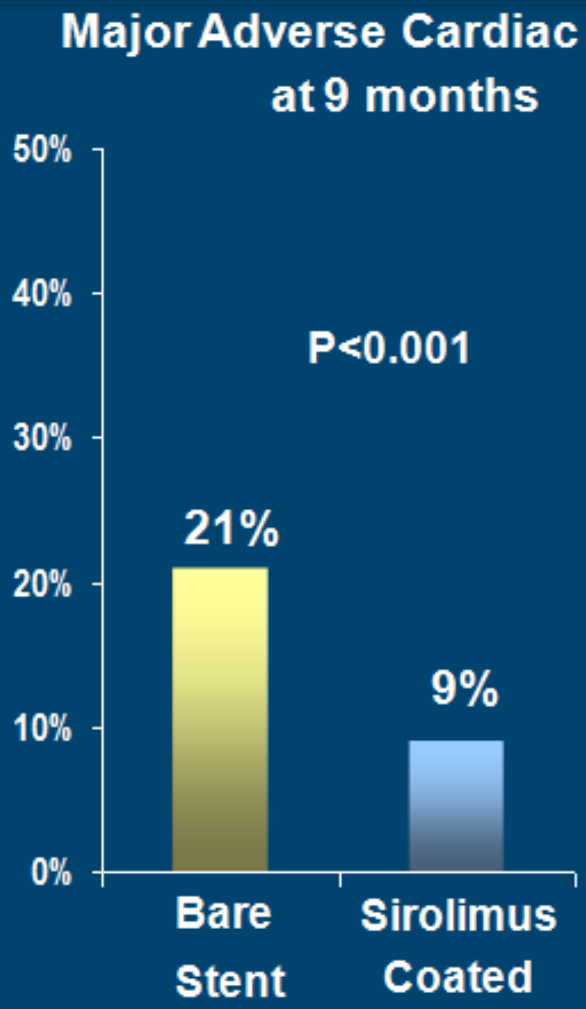
Drug-Eluting Stents

- Stents are coated with polymers impregnated with drugs to arrest the cell cycle and thus prevent neointimal proliferation after stent placement



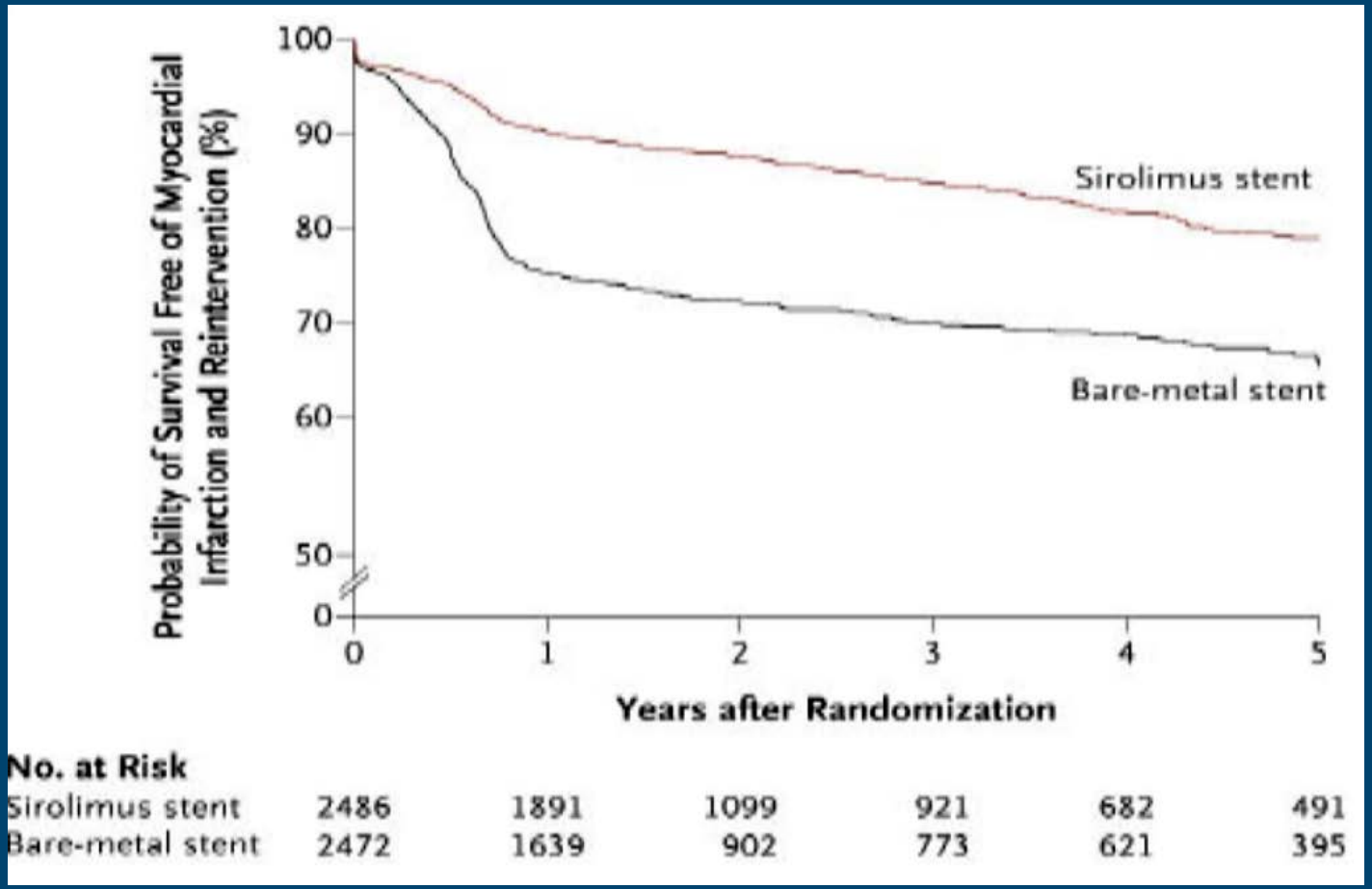
Drug-Eluting Stents: Intermediate Outcomes





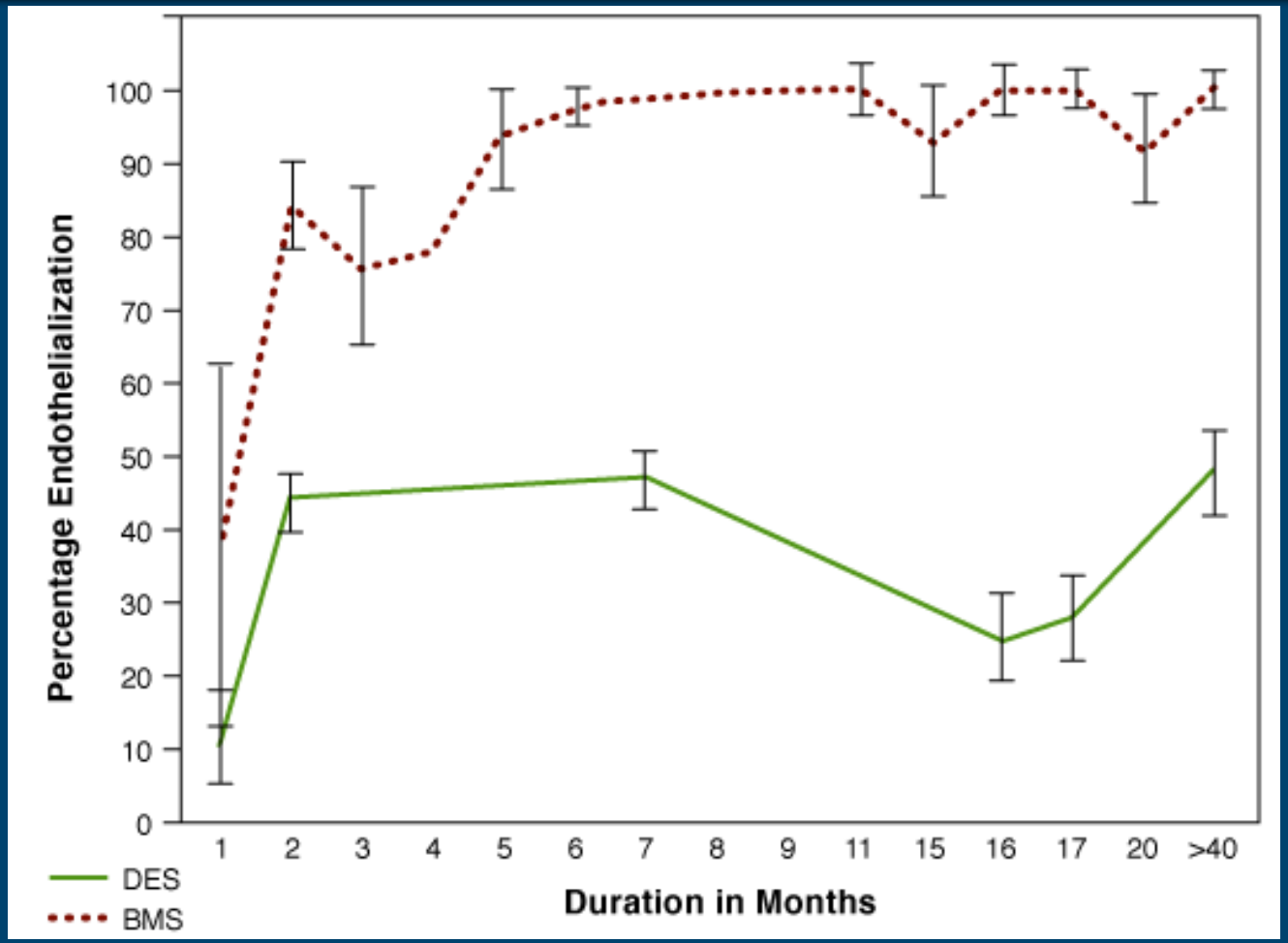
The SIRIUS Study: 1058 patients at 53 US centers
Moses JW, et al. N Engl J Med 2003;349:1315-23

Large Trial Data of DES vs. BMS: Survival Free of MI and Reintervention



Kastrati A et al. N Engl J Med 2007;356:1030-1039

Endothelialization in Drug-Eluting Stents vs. Bare Metal Stents



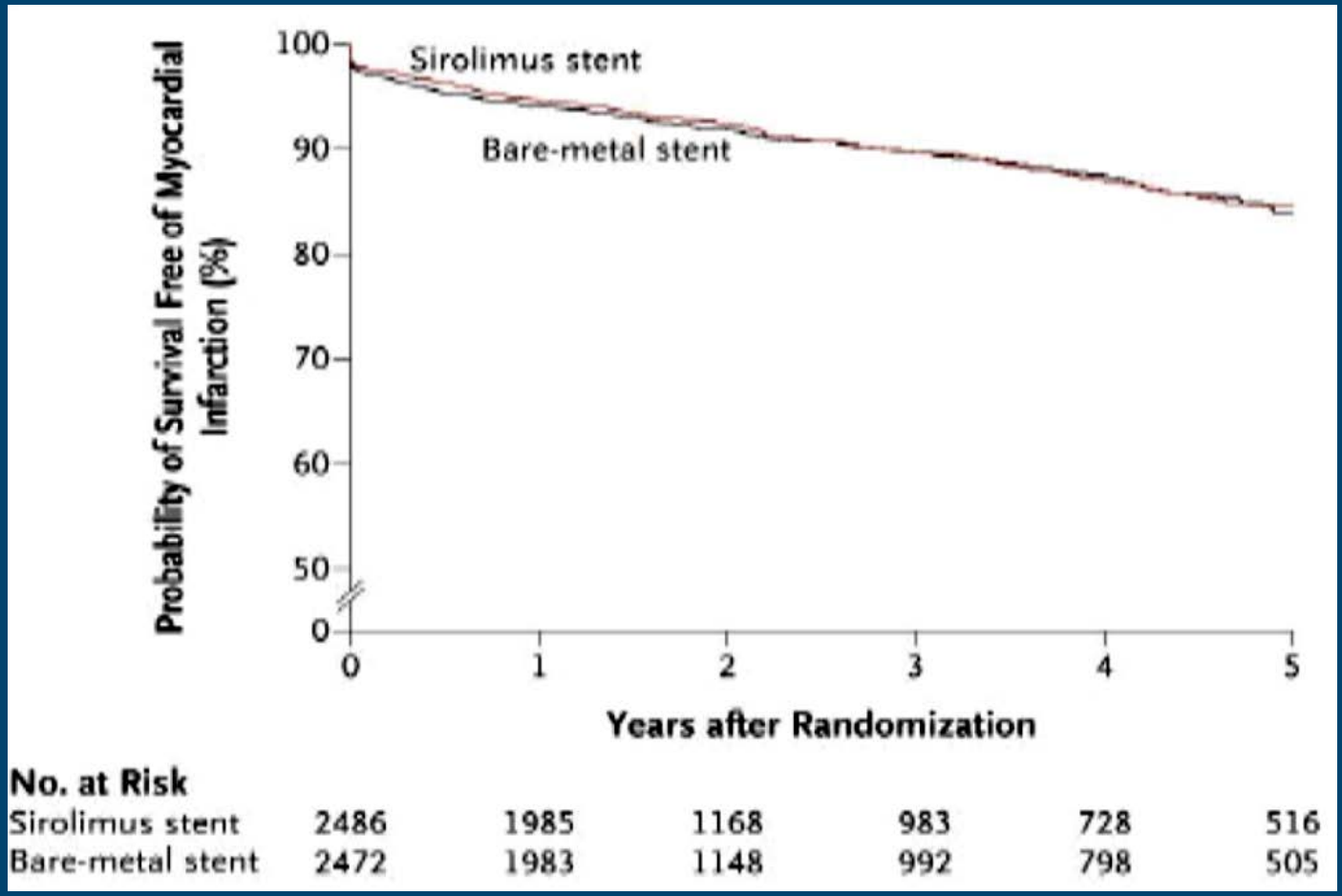
Joner M, et al. J Am Coll Cardiol 2006;48:193-202.

Drug-Eluting Stents: The Risk of Thrombosis

Drug-Eluting Stents: Require Dual Antiplatelet Therapy (DAPT) for at Least 12 Months

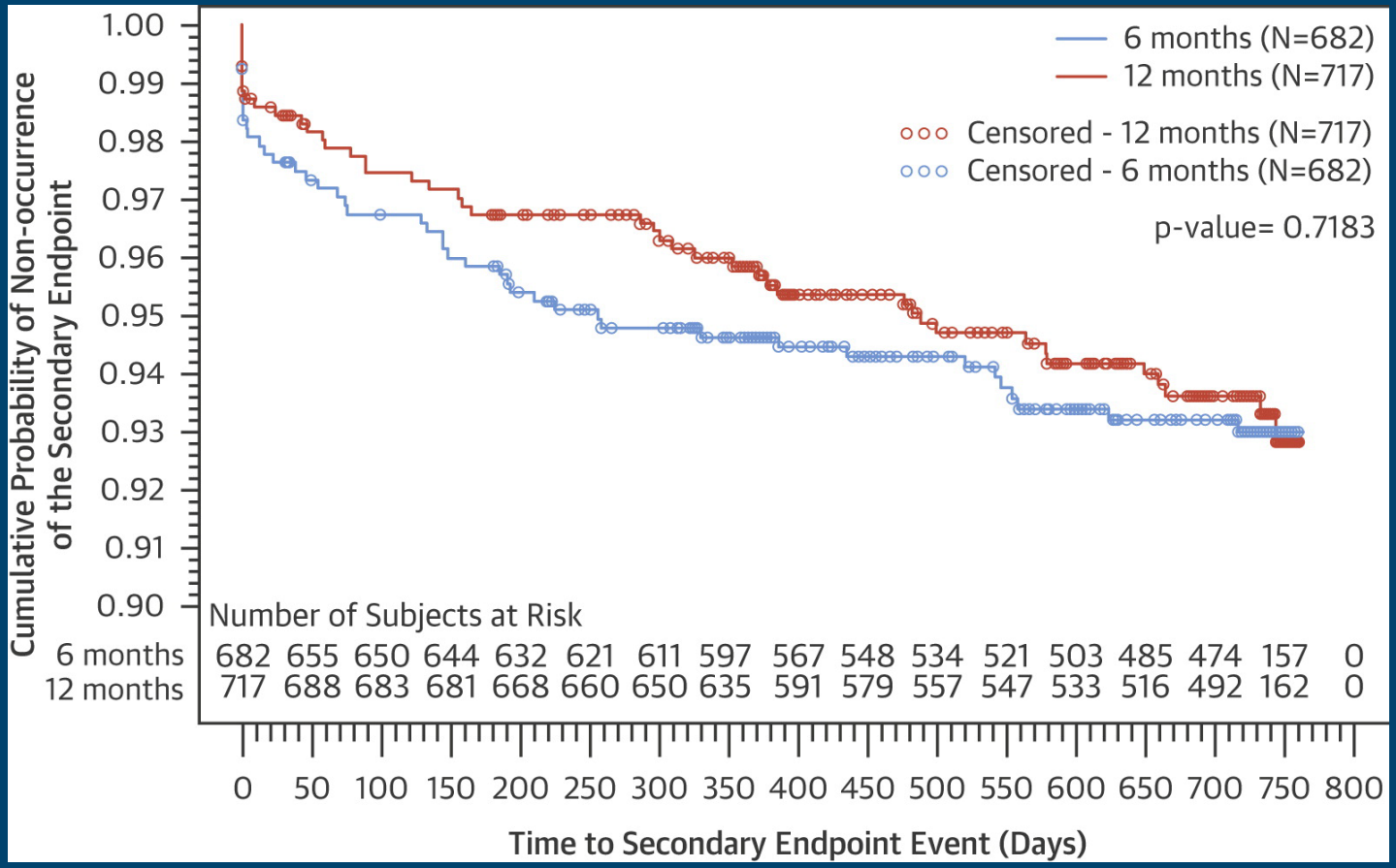
Aspirin plus clopidogrel (or other P2Y12 inhibitor, i.e., ticagrelor or prasugrel)

Large Trial Data of DES vs. BMS: Survival Free of MI



Kastrati A et al. N Engl J Med 2007;356:1030-1039

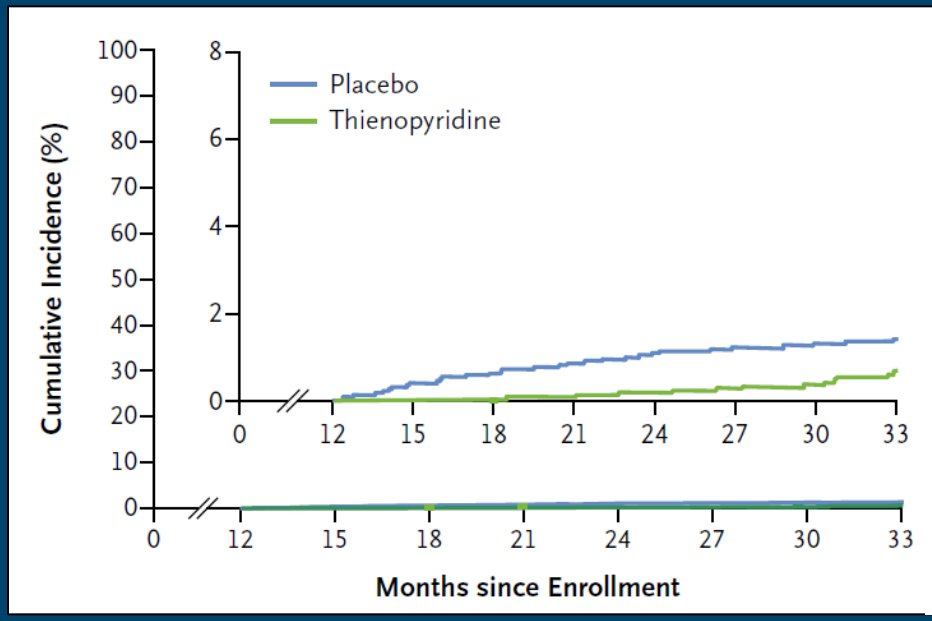
SECURITY: 6 vs.12-months of dual antiplatelet therapy after 2nd-generation drug eluting stents



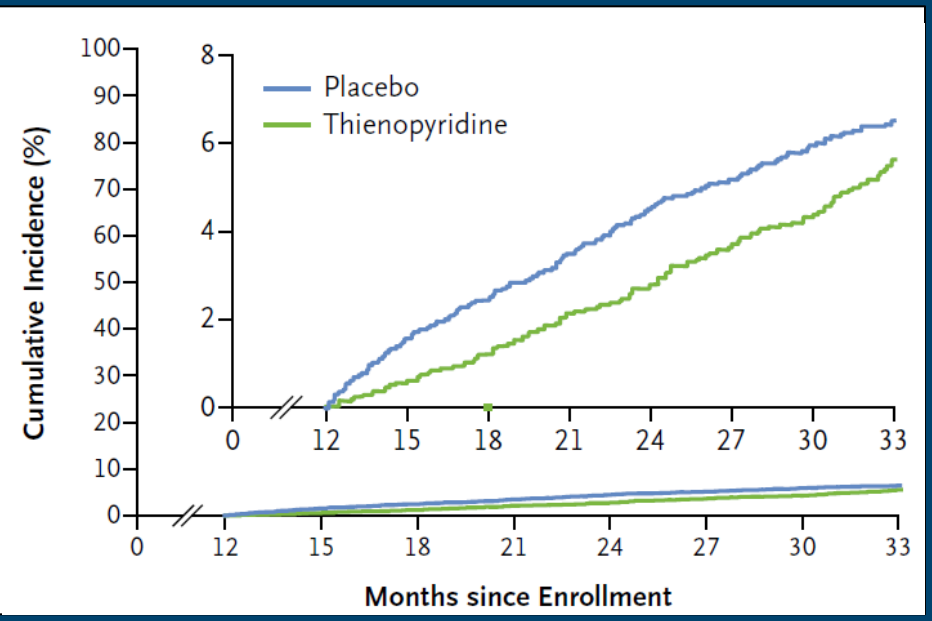
Colombo A, et al. J Am Coll Cardiol 2014;64:2086-2097

DAPT Study: 12 vs. 30 months of dual antiplatelet therapy after drug eluting stents

- 9961 patients who had completed 12 months of DAPT after a drug-eluting stent
- Randomized to an additional 18 months of thienopyridine therapy (clopidogrel or prasugrel) or placebo
- All the patients continued to take aspirin



Incidence of Stent Thrombosis



Incidence of Major Cardiovascular or Cerebrovascular Events

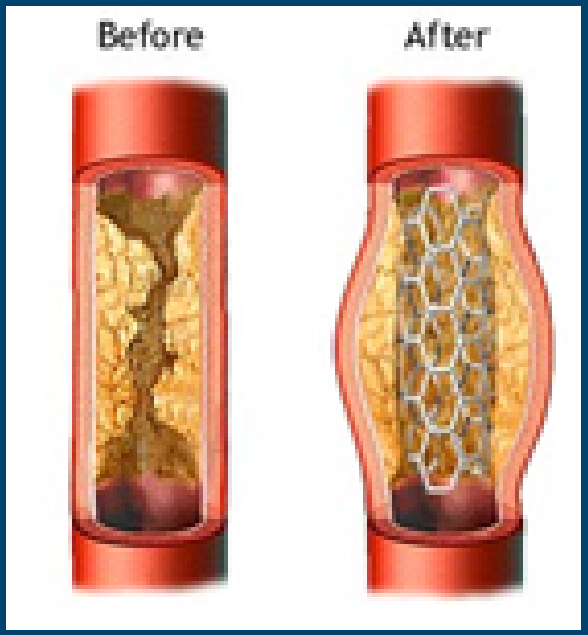
Mauri L, et al. N Engl J Med 2014;371:2155-66

Conclusions About Drug-eluting Stents

- DES are effective in reducing restenosis
- Dual antiplatelet therapy (DAPT) should be continued for at least 12 months post DES, and perhaps indefinitely
- Risk is potentially lower for 2nd generation drug eluting stents, so for select patients DAPT might be discontinued at 6 months
- Impact of DAPT should be considered prior to stent implantation when such therapy may be problematic in the long-term, e.g.:
  - A surgical procedure is anticipated
  - Chronic warfarin therapy is required
  - Peptic ulcer disease / GI bleeding

Traditional Assumptions Regarding Treatment of CAD with Ischemia

- Patients with symptomatic CAD and chronic angina who have significant coronary stenoses “need” revascularization
- PCI will improve prognosis
  - Prevent MI
  - Prevent cardiac death
- PCI will significantly improve symptoms.

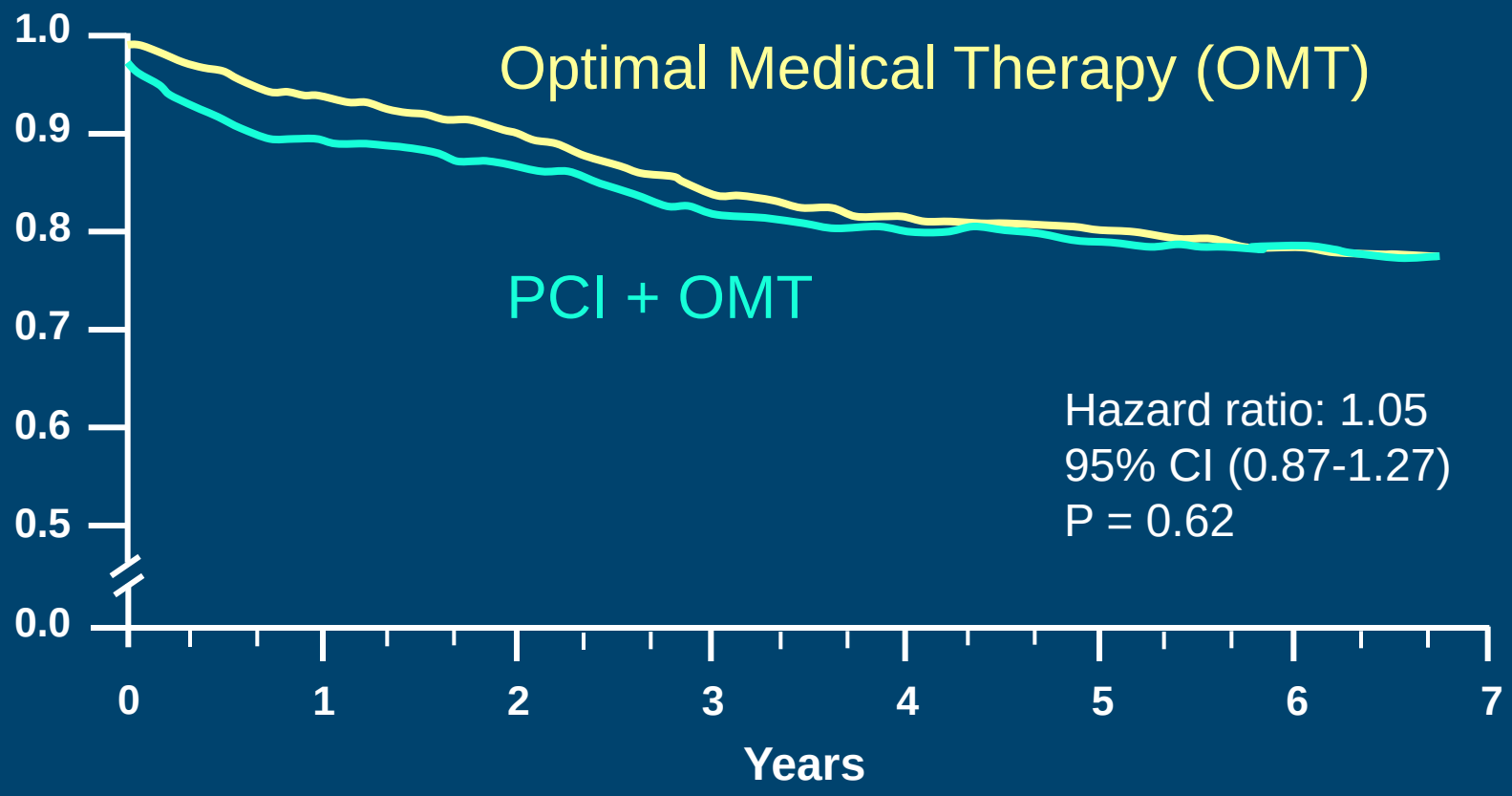


Routine stenting of significant coronary stenoses: The COURAGE Trial

- COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
  - 2278 subjects with stable CAD
  - ≥ 70% stenosis in a proximal epicardial coronary artery and objective evidence of myocardial ischemia
  - Mild to moderate angina
  - Anatomy suitable for PCI
- Randomized to PCI + optimal medical therapy vs. optimal medical therapy alone
- 2.5 to 7 year follow-up (mean 4.6 years)
- Primary outcome: Death or non-fatal MI.

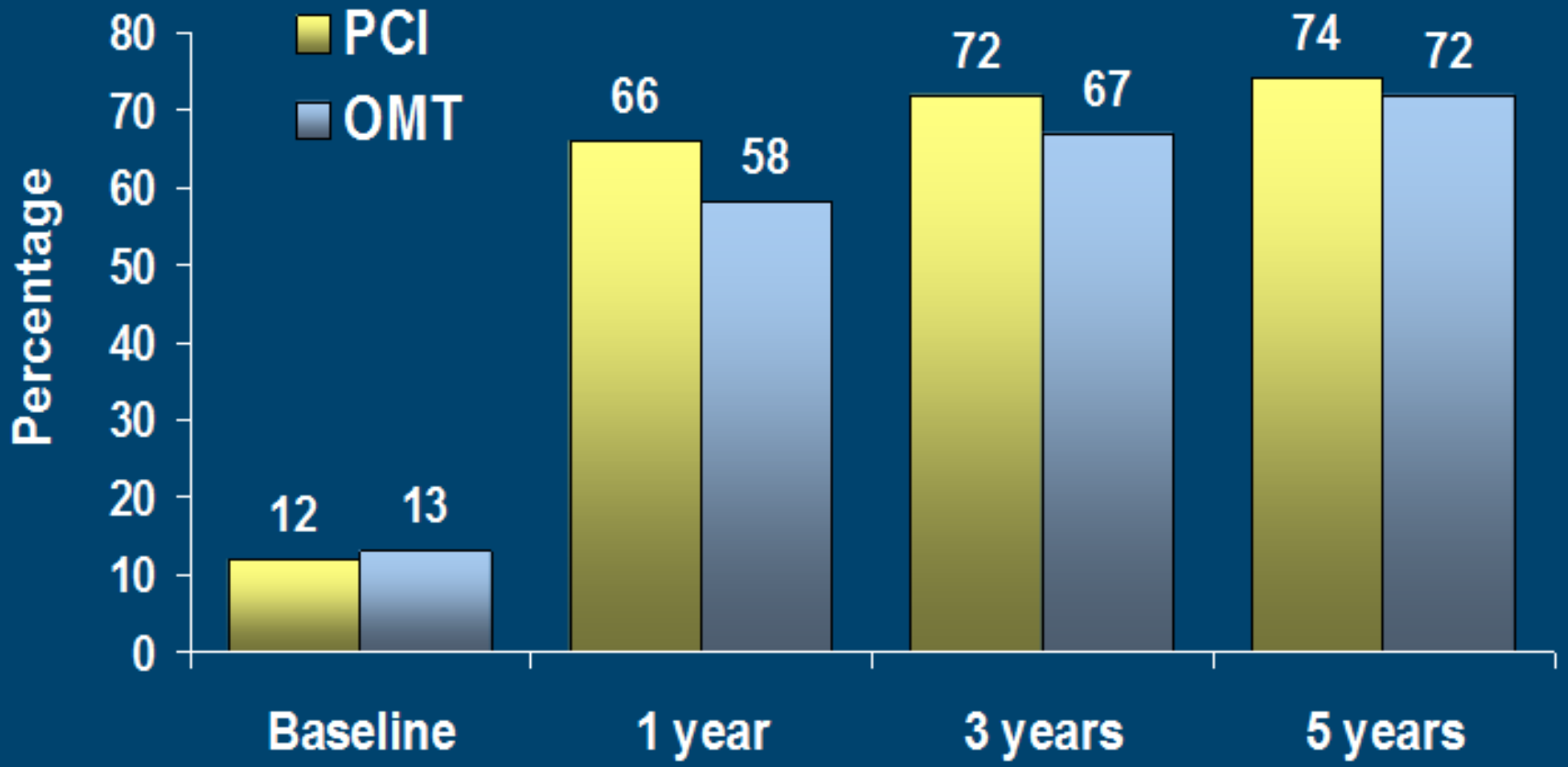
Boden WE, et al. N Engl J Med 2007;365:1503

Survival Free from Death or Non-Fatal MI



Boden WE, et al. N Engl J Med 2007;365:1503

Freedom from Angina During Follow-up

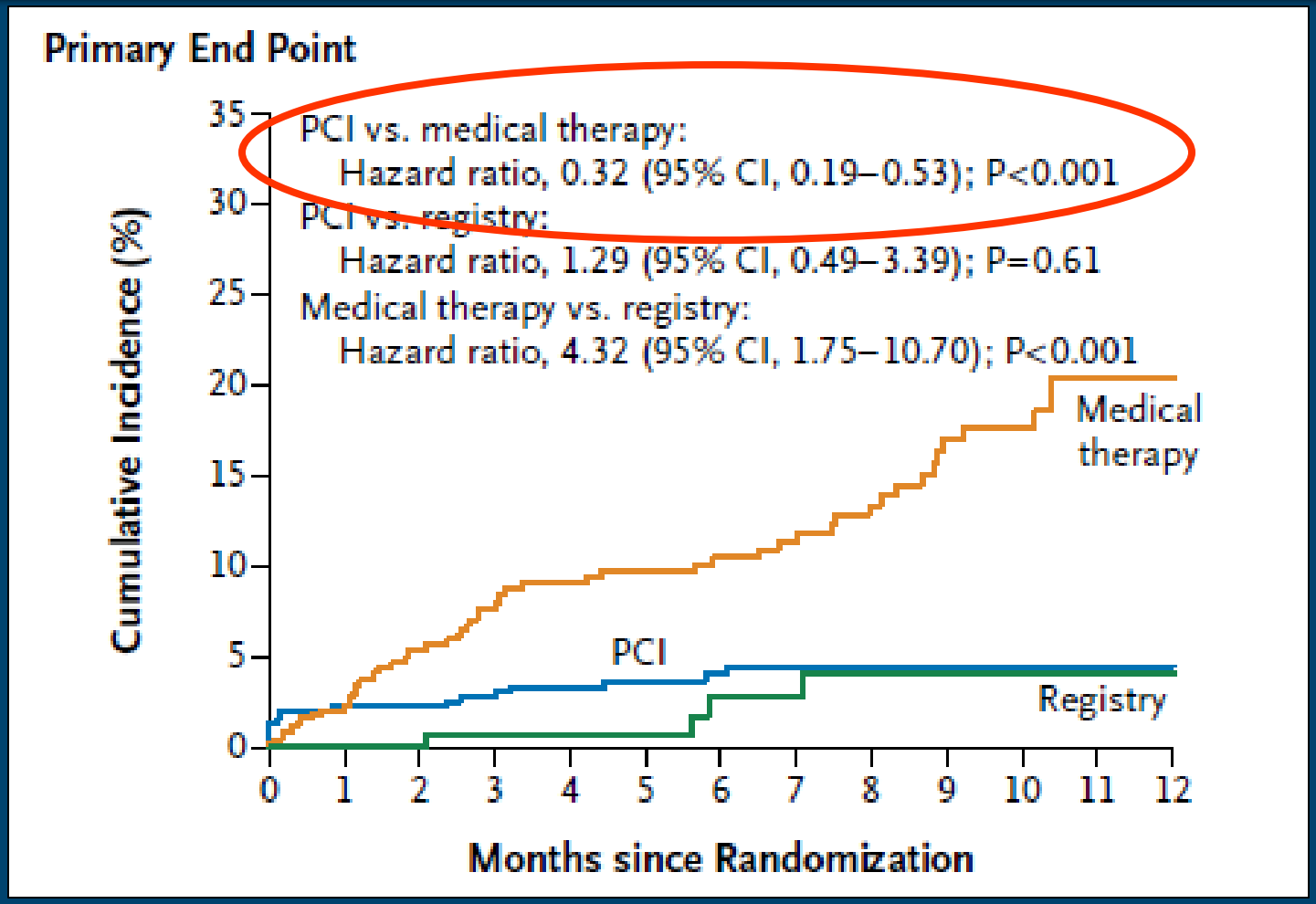


Fractional Flow Reserve vs. Angiography for Multivessel Evaluation 2 (FAME 2) Trial

- Hypothesis: Patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), PCI plus BMT would be superior to BMT alone.
- 888 patients were randomized to PCI vs. BMT alone
  - With stable CAD for whom PCI was being considered
  - Who had a functionally significant stenosis (FFR ≤ 0.80) in at least one visually stenotic (≥50%) coronary were randomly assigned
  - 332 patients with FFR > 0.80 (non stenotic) were entered into a registry and received BMT
- The primary end point was a composite of death, MI, or urgent revascularization.
  - Study terminated early due to sig. differences in primary endpoint

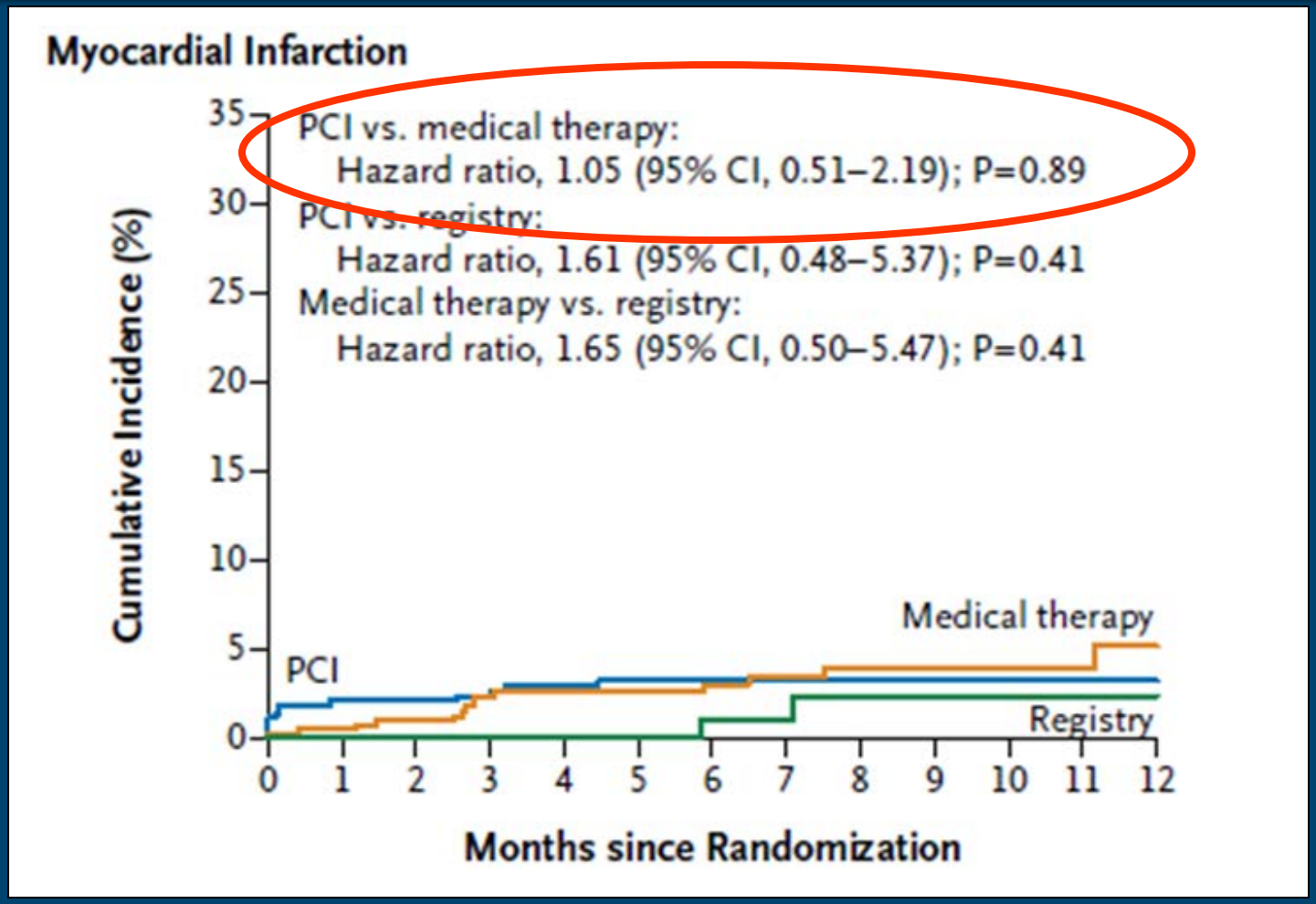
De Bruyne B, et al. N Engl J Med 2012; 367:991-1001

FAME 2: Incidence of Primary End Point of Death, MI, or Urgent Revascularization



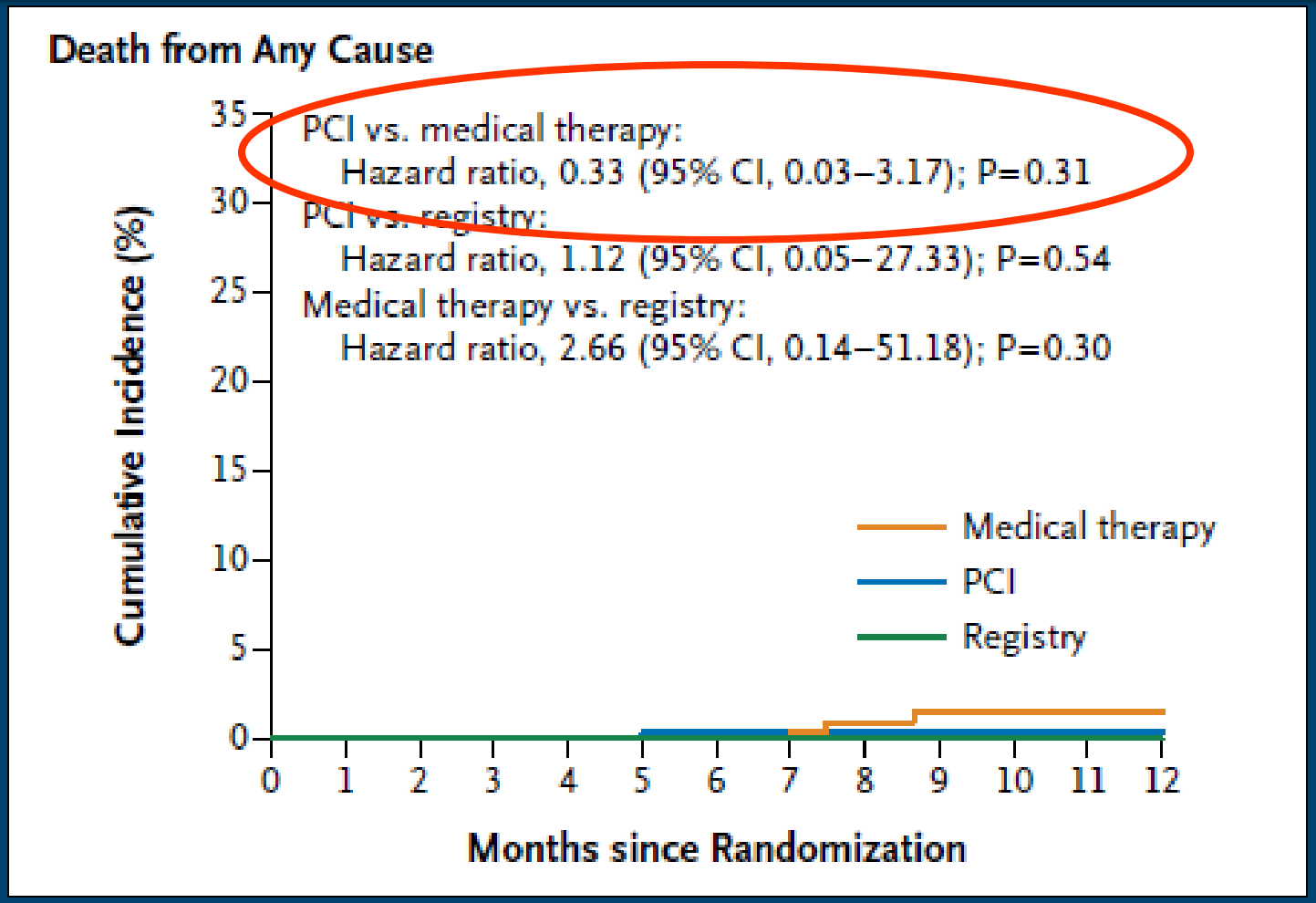
De Bruyne B, et al. N Engl J Med 2012; 367:991-1001

FAME-2: Incidence of MI



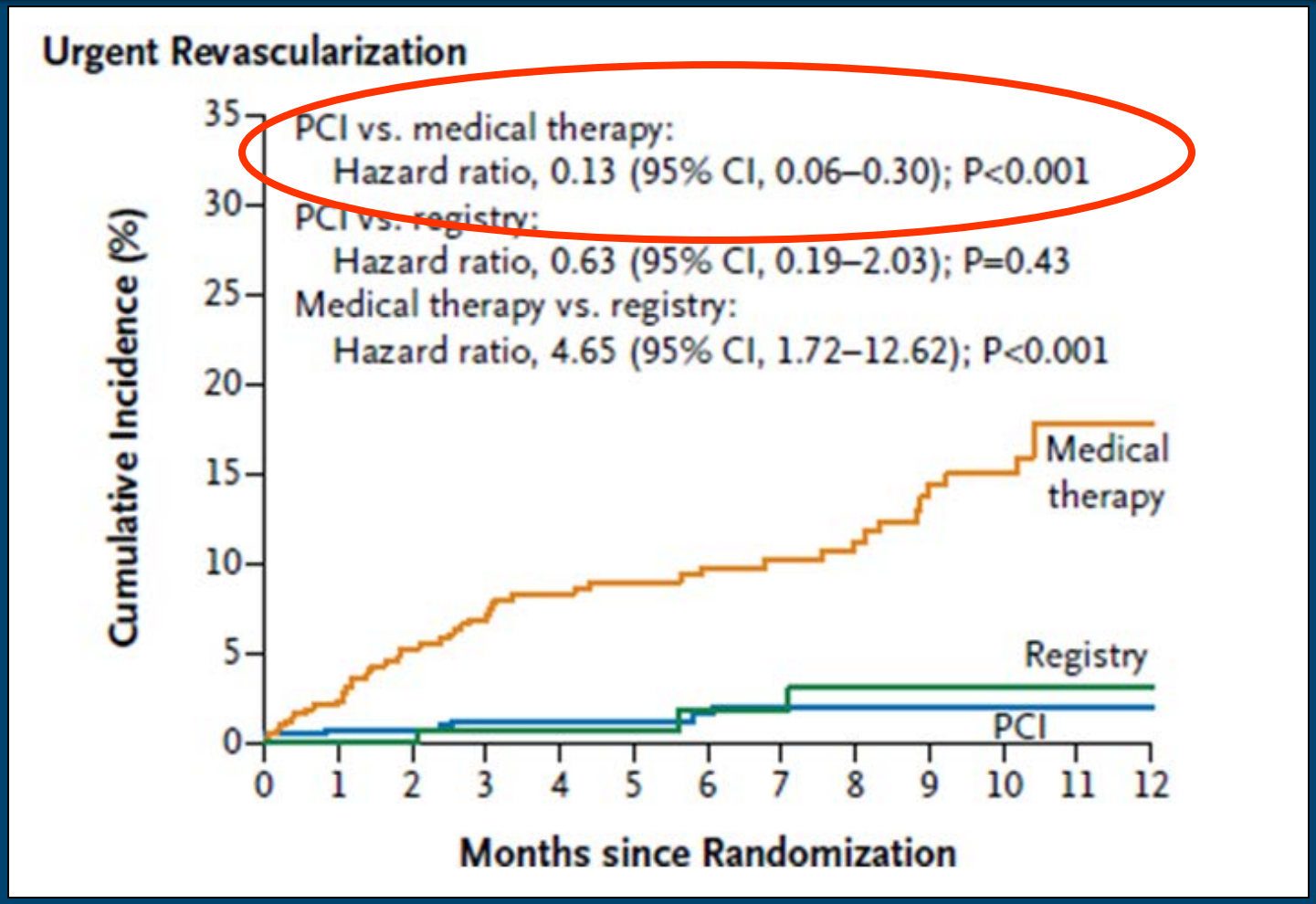
De Bruyne B, et al. N Engl J Med 2012; 367:991-1001

FAME-2: Incidence of All-Cause Mortality



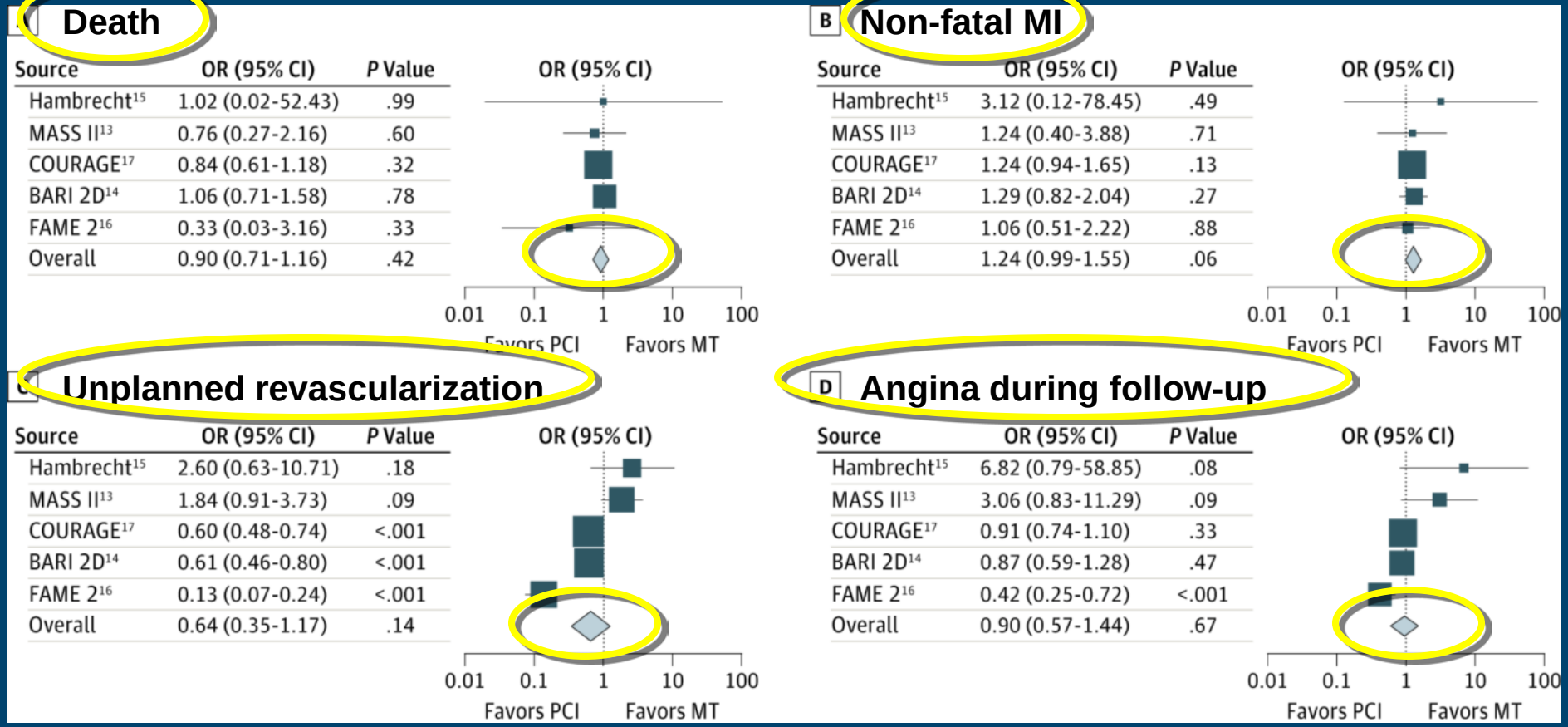
De Bruyne B, et al. N Engl J Med 2012; 367:991-1001

FAME-2: Incidence of "Urgent" Revascularization



De Bruyne B, et al. N Engl J Med 2012; 367:991-1001

Meta-analysis of Initial Stenting vs. Medical Management for Stable Coronary Stenoses



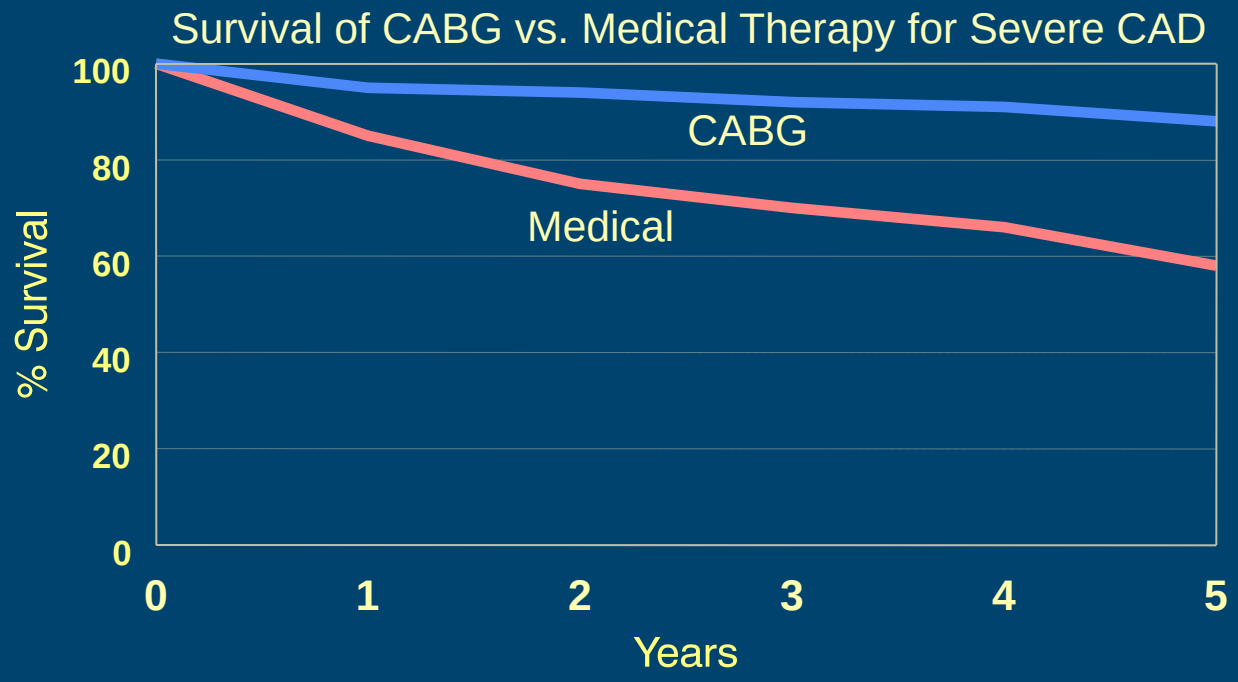
Stergiopoulos K, et al. JAMA Intern Med. 2013;():-. doi:10.1001/jamainternmed.2013.12855

Waiting for the final word…

- The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)
- NIH granted $84 million
- Designed and powered to evaluate the long-term superiority of revascularization plus OMT vs. OMT alone
- Patients with stable CAD and moderate-to-severe myocardial ischemia documented noninvasively
- Outcomes = cardiovascular death or MI
- Currently enrolling

Coronary Artery Bypass Surgery (CABG): Long-term Outcomes

- Effectively relieves symptoms of angina
- Reduces mortality in selected groups
  - 3 vessel-disease
  - Left main stenosis (or left-main equivalent)



Meta-analysis of Randomized Trials of CABC vs. PCI in the Modern Era

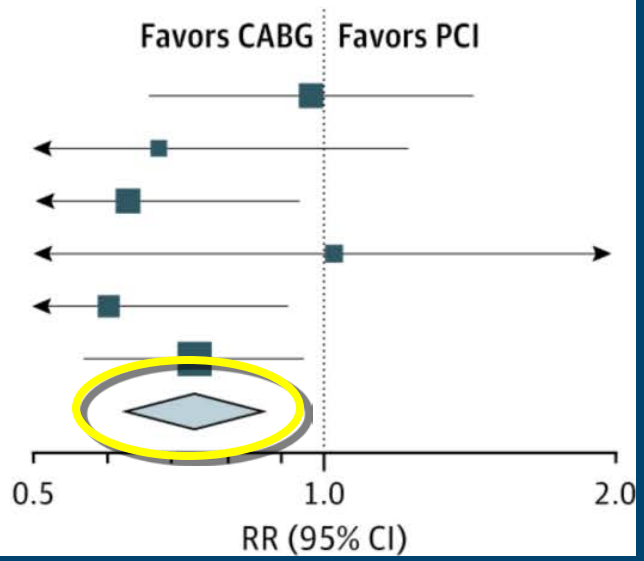
- 6 randomized trials
  - 6055 patients with multi-vessel CAD
  - Median follow-up 4.1 years
- Primary outcomes
  - Death
  - Myocardial infarction
  - Repeat revascularization
  - Stroke

Sipahi I, et al. JAMA Intern Med. 2013;():-. doi:10.1001/jamainternmed.2013.12844

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

Mortality

Source	Statistics for Each Study				Death/Total	
	RR (95% CI)		*Z* Value	*P* Value	CABG	PCI
ARTS[10,11]	0.97	(0.66-1.43)	-0.16	.87	46/584	48/590
MASS II[6]	0.67	(0.37-1.23)	-1.29	.20	16/203	24/205
SoS[2,15]	0.63	(0.41-0.95)	-2.23	.03	34/500	53/488
CARDia[7]	1.02	(0.39-2.69)	0.05	.96	8/242	8/248
SYNTAX multivessel[9,12]	0.60	(0.39-0.92)	-2.36	.02	31/547	52/548
FREEDOM[16]	0.73	(0.56-0.95)	-2.31	.02	86/947	118/953
Meta-analysis	**0.73**	**(0.62-0.86)**	**-3.69**	**<.001**	**221/3023**	**303/3032**

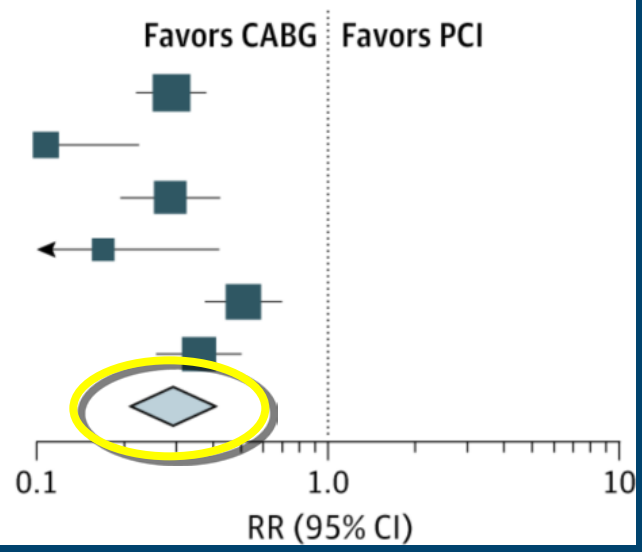


Sipahi I, et al. JAMA Intern Med. 2013;():-. doi:10.1001/jamainternmed.2013.12844

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

Repeat Revascularization

Source	Statistics for Each Study				Repeat Revascularization/ Total	
	RR (95% CI)		*Z* Value	*P* Value	CABG	PCI
ARTS[10,11]	0.29	(0.22-0.39)	-8.45	<.001	53/584	182/590
MASS II[6]	0.11	(0.05-0.23)	-5.80	<.001	7/203	66/205
SoS[2,15]	0.29	(0.20-0.43)	-6.26	<.001	30/500	101/488
CARDia[7]	0.17	(0.07-0.43)	-3.72	<.001	5/242	30/248
SYNTAX multivessel[9,12]	0.52	(0.38-0.70)	-4.23	<.001	55/547	106/548
FREEDOM[16]	0.37	(0.26-0.51)	-5.83	<.001	43/947	118/953
Meta-analysis	**0.29**	**(0.21-0.41)**	**-7.00**	**<.001**	**193/3023**	**603/3032**

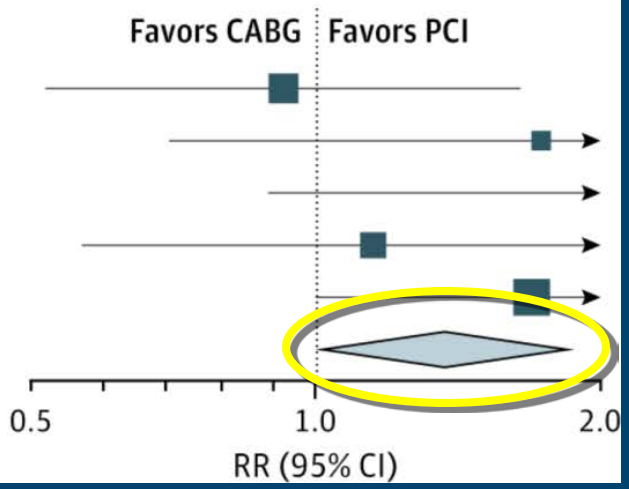


Sipahi I, et al. JAMA Intern Med. 2013;():-. doi:10.1001/jamainternmed.2013.12844

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

Stroke

Source	Statistics for Each Study RR (95% CI)	*Z* Value	*P* Value	Stroke/Total CABG	PCI
ARTS[10,11]	0.92 (0.52-1.65)	-0.27	0.79	21/584	23/590
MASS II[6]	1.73 (0.70-4.31)	1.18	0.24	12/203	7/205
CARDia[7]	7.17 (0.89-57.87)	1.85	0.06	7/242	1/248
SYNTAX multivessel[9,12]	1.14 (0.56-2.32)	0.38	0.71	16/547	14/548
FREEDOM[16]	1.69 (1.01-2.85)	1.98	0.05	37/947	22/953
Meta-analysis	**1.36 (0.99-1.86)**	**1.91**	**0.06**	**93/2523**	**67/2544**

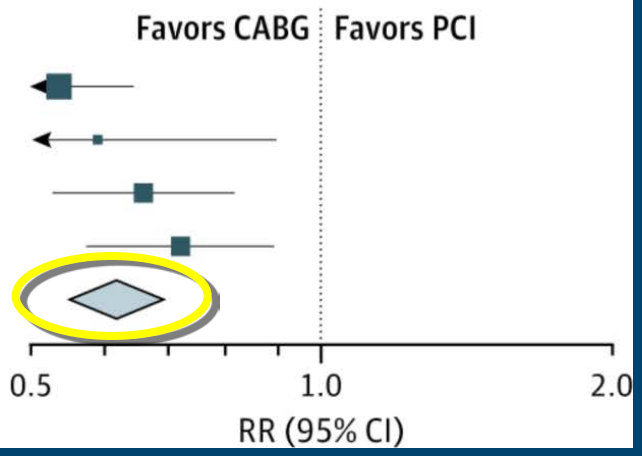


Sipahi I, et al. JAMA Intern Med. 2013;():-. doi:10.1001/jamainternmed.2013.12844

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)

Source	Statistics for Each Study RR (95% CI)	Z Value	P Value	MACCE/Total CABG	MACCE/Total PCI
ARTS[10,11]	0.53 (0.45-0.64)	-6.95	<.001	132/584	250/590
CARDia[7]	0.59 (0.38-0.90)	-2.44	.01	28/242	49/248
SYNTAX multivessel[9,12]	0.65 (0.53-0.81)	-3.83	<.001	103/547	158/548
FREEDOM[16]	0.71 (0.57-0.89)	-2.95	<.001	112/947	158/953
Meta-analysis	**0.61 (0.54-0.68)**	**-8.55**	**<.001**	**375/2320**	**615/2339**



Sipahi I, et al. JAMA Intern Med. 2013;():-. doi:10.1001/jamainternmed.2013.12844

Intermediate Results of Revascularization: Outcomes at 5 years

- BARI trial (Bypass Angioplasty Revascularization Investigation),1990s:
  - Revascularization failure comparable (20% vs 22%)
  - Recurrence of angina was predominantly due to progression of native CAD and less often the failure of the original revascularization procedure
- Therefore we need to diligently treat the underlying atherosclerosis even among those who have been revascularized

Alderman EL, et al. JACC 2004;44:766–74