MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Advanced Treatment Choices for Ischemic Heart Disease in 2020

Eric M. Isselbacher, M.D.

Director, MGH Healthcare Transformation Lab
Associate Professor of Medicine, Harvard Medical School

A Teaching Affiliate of Harvard Medical School

Presenter Disclosure Information

- No financial relationships to disclose

Coronary Heart Disease: The Scope of the Problem

- CHD is the leading cause of death in the United States
- 18.2 million people in the U.S. have CHD
  - 9.4 million men (7%) and 8.8 million women (6%)
  - By age 60, 20% of men and 13% of women have CHD
- 1,055,000 people have CHD events / year
  - 720,000 are first events
  - 335,000 are recurrent events
  - 168,000 are silent events
- 363,000 CHD deaths (1 in every 7 deaths)
- 3.4 million people in the U.S. have chronic stable angina.

AHA Heart Disease & Stroke Statistics:2019 Update
https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000659

Goals of Treatments for Chronic CAD

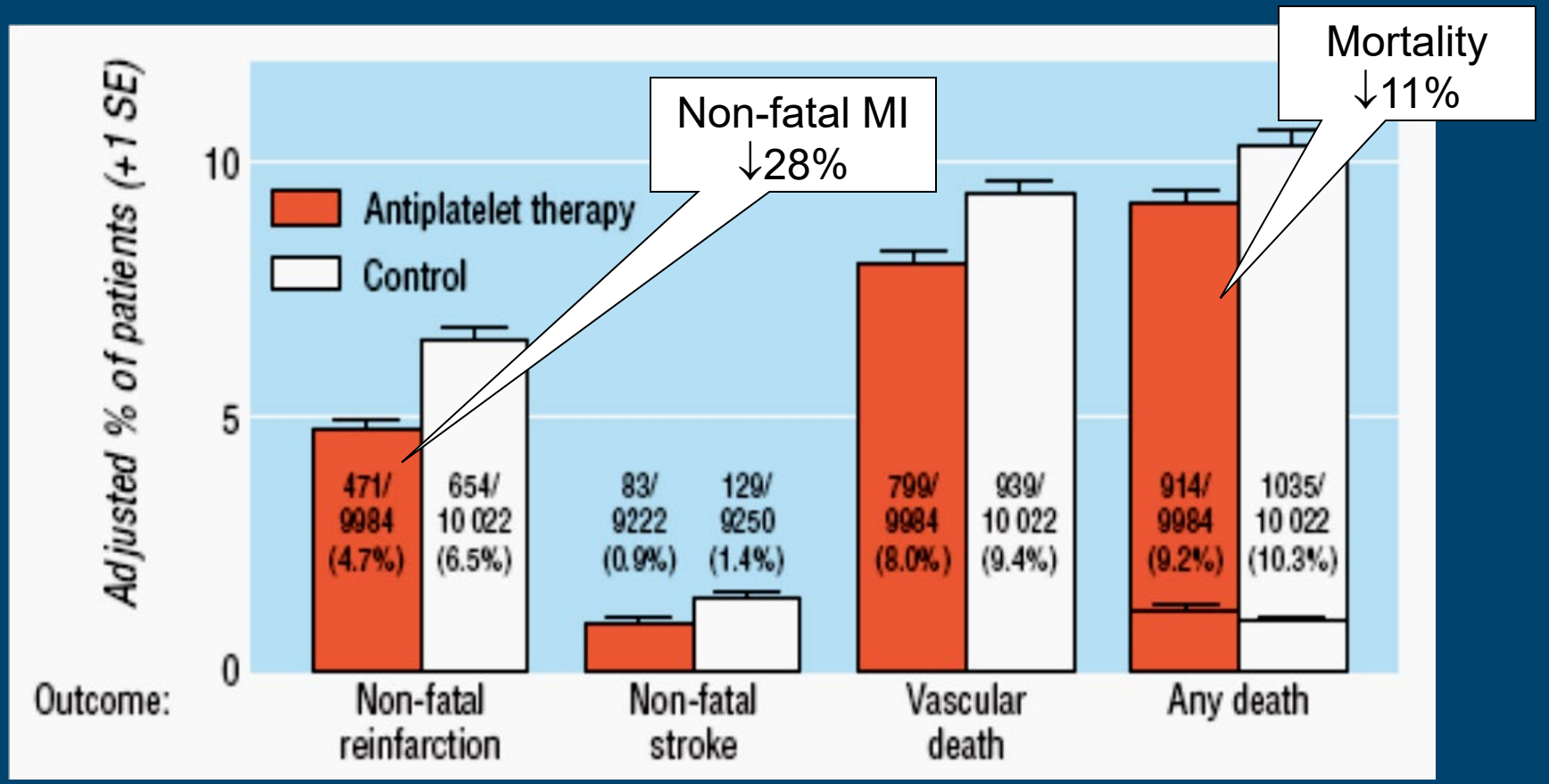
- Reduce acute coronary events (MI, cardiac death)
  - Pacify the platelets
  - Treat the plaques
    - Stabilize the plaques
    - Slow the atherosclerotic process
- Relieve the symptoms of angina

Anti-platelet Therapy

- Aspirin remains the mainstay

Anti-platelet Therapy:
Aspirin for Secondary Prevention

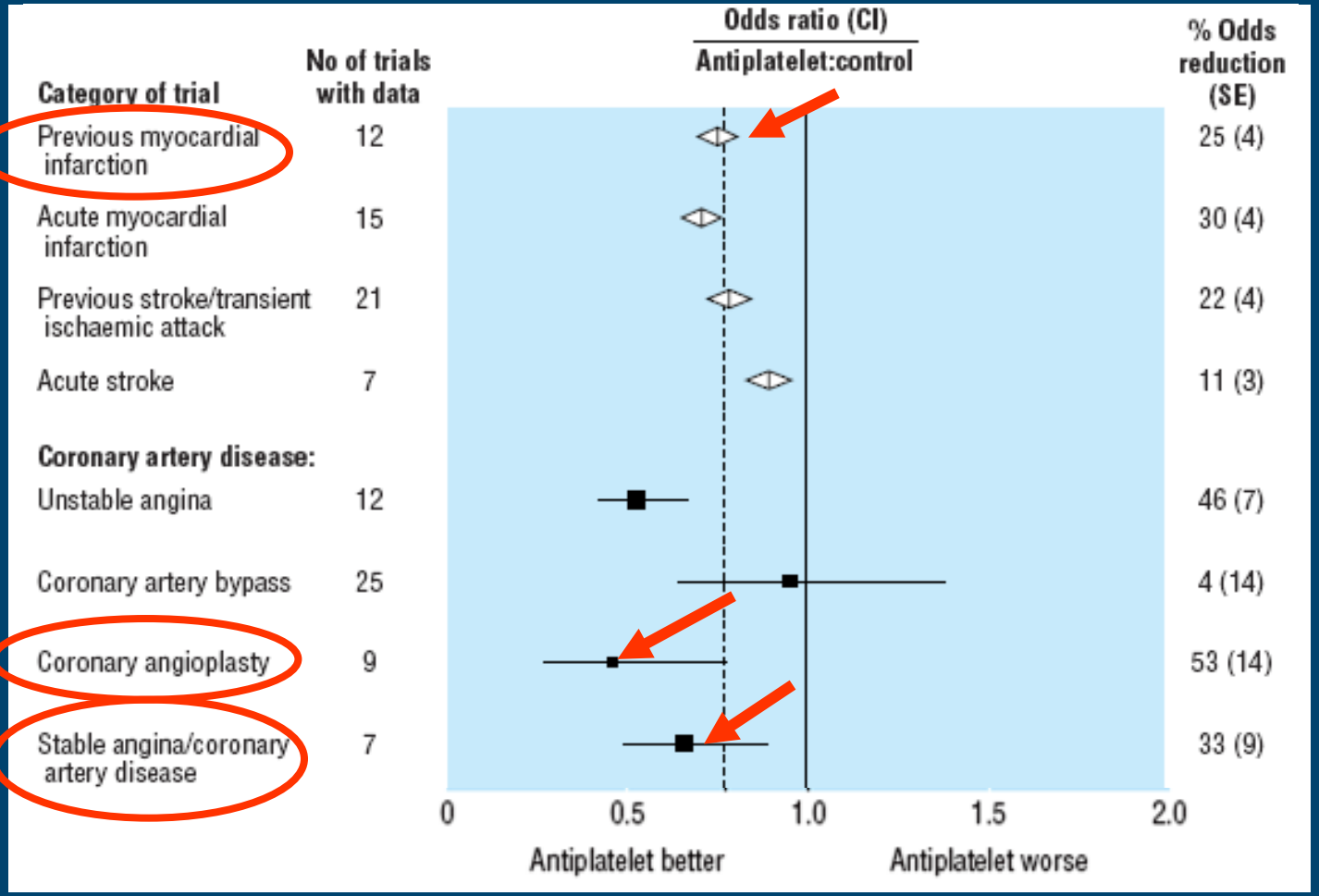
Meta-analysis from the Antithrombotic Trialists' Collaboration



AT Collaboration. BMJ 2002;324:71-86

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

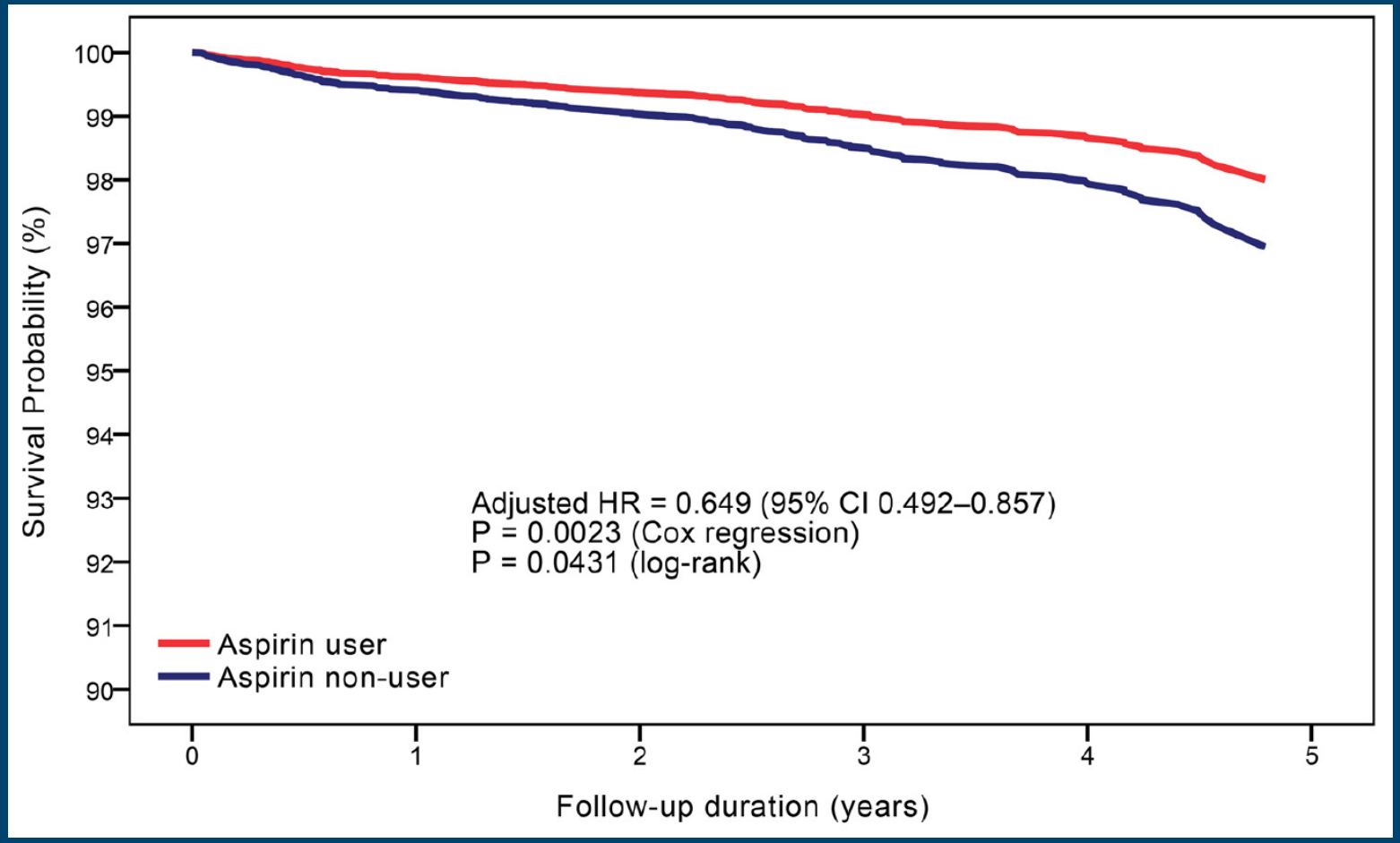
Anti-platelet Therapy:
Aspirin for “Primary and a half” Prevention



AT Collaboration. BMJ 2002;324:71-86

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Aspirin Therapy and Clinical Outcomes in Non-Obstructive CAD (<50%) by Cardiac CTA

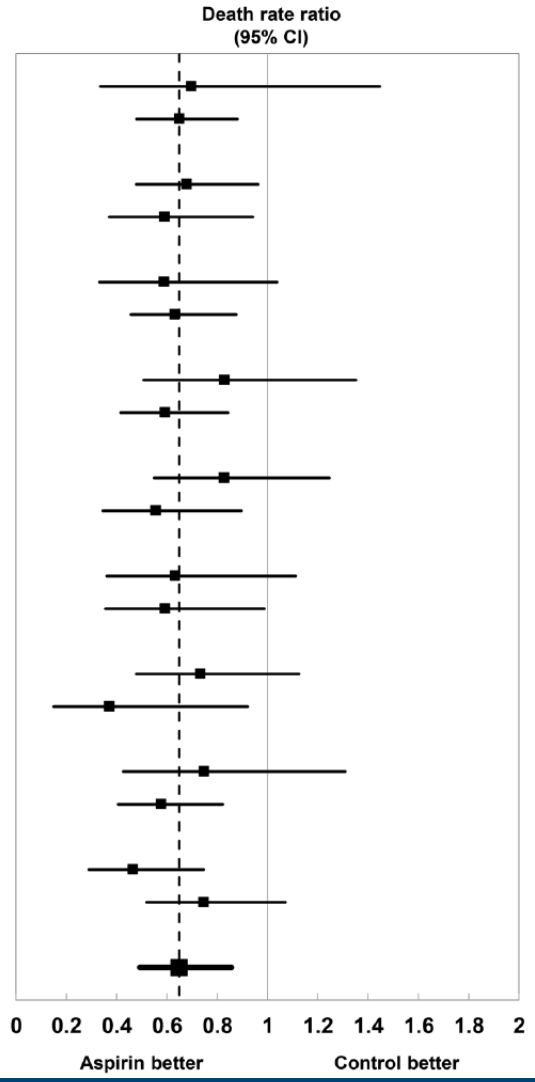


Hwang I-C, et al. PLoS ONE; 2015:10: e0129584.
doi:10.1371/journal.pone.0129584

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Aspirin Therapy and Clinical Outcomes in Non-Obstructive CAD (<50%) by Cardiac CTA

Subgroups	Adjusted HR	95% CI	P value
Age			
< 65 years (n = 5,108)	**0.697**	0.336 – 1.446	0.3326
≥ 65 years (n = 3,264)	**0.650**	0.480 – 0.880	0.0053
Sex			
Male (n = 5,886)	**0.678**	0.478 – 0.962	0.0293
Female (n = 2,486)	**0.591**	0.372 – 0.941	0.0266
Diabetes mellitus			
No (n = 7,100)	**0.588**	0.332 – 1.039	0.0673
Yes (n = 1,272)	**0.632**	0.457 – 0.874	0.0055
Hypertension			
No (n = 5,779)	**0.829**	0.508 – 1.352	0.4522
Yes (n = 2,593)	**0.593**	0.417 – 0.842	0.0035
CACS			
<100 (n = 5,755)	**0.828**	0.549 – 1.247	0.3661
≥ 100 (n = 1,733)	**0.556**	0.345 – 0.896	0.0159
LDL-C (100 mg/dL)			
< 100 mg/dL (n = 2,007)	**0.633**	0.361 – 1.112	0.1117
≥ 100 mg/dL (n = 5,008)	**0.593**	0.356 – 0.988	0.0450
LDL-C (130 mg/dL)			
< 130 mg/dL (n = 4,793)	**0.733**	0.478 – 1.125	0.1556
≥ 130 mg/dL (n = 2,222)	**0.371**	0.150 – 0.922	0.0328
hsCRP			
< 2mg/L (n = 4,458)	**0.747**	0.426 – 1.309	0.3082
≥ 2mg/L (n = 2,400)	**0.577**	0.406 – 0.821	0.0022
GFR			
< 60 mL/min/1.73m^2 (n = 943)	**0.465**	0.290 – 0.746	0.0015
≥ 60 mL/min/1.73m^2 (n = 6,890)	**0.746**	0.520 – 1.071	0.1118
Total (n = 8,372)	**0.649**	0.492 – 0.857	0.0023



MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Anti-platelet Therapy: Clopidogrel (Plavix)

- Currently used most often in combination with aspirin following stent implantation
  - 1 month for bare metal stents
  - ≥ 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.

Aspirin + Clopidogrel vs Aspirin Alone for Preventing Cardiovascular Events Among Patients at High Risk

JAMA Clinical Evidence Synopsis in 2018 summarizing a Cochrane review of 15 clinical trials

Table. Aspirin Plus Clopidogrel Compared With Asp… vascular… Among Patients at High Risk of Cardiovascular E…

Event	No. of RCTs	No. of Partic…	…olute Risk …icipants …one[b]	Relative Risk (95% CI)	P Value
Cardiovascular mortality	7	31 90…		0.98 (0.88-1.10)	.77
All-cause mortality	9	32 9…		1.05 (0.87-1.25)	.62
Myocardial infarction[c]	6	16 17…		0.78 (0.69-0.90)	<.01
Ischemic stroke[c]	5	400…	86	0.73 (0.59-0.91)	<.01
Major bleeding	10	33 300	30 (26-… 21	1.44 (1.25-1.64)	<.01

Abbreviation: RCT, randomized clinical trial.

[a] The risk of having a cardiovascular event in the aspirin plus clopidogr… based on the assumed risk of having a cardiovascular event in the a… e group and the relative risk of having a cardiovascular event in the a… s clopidogrel group.

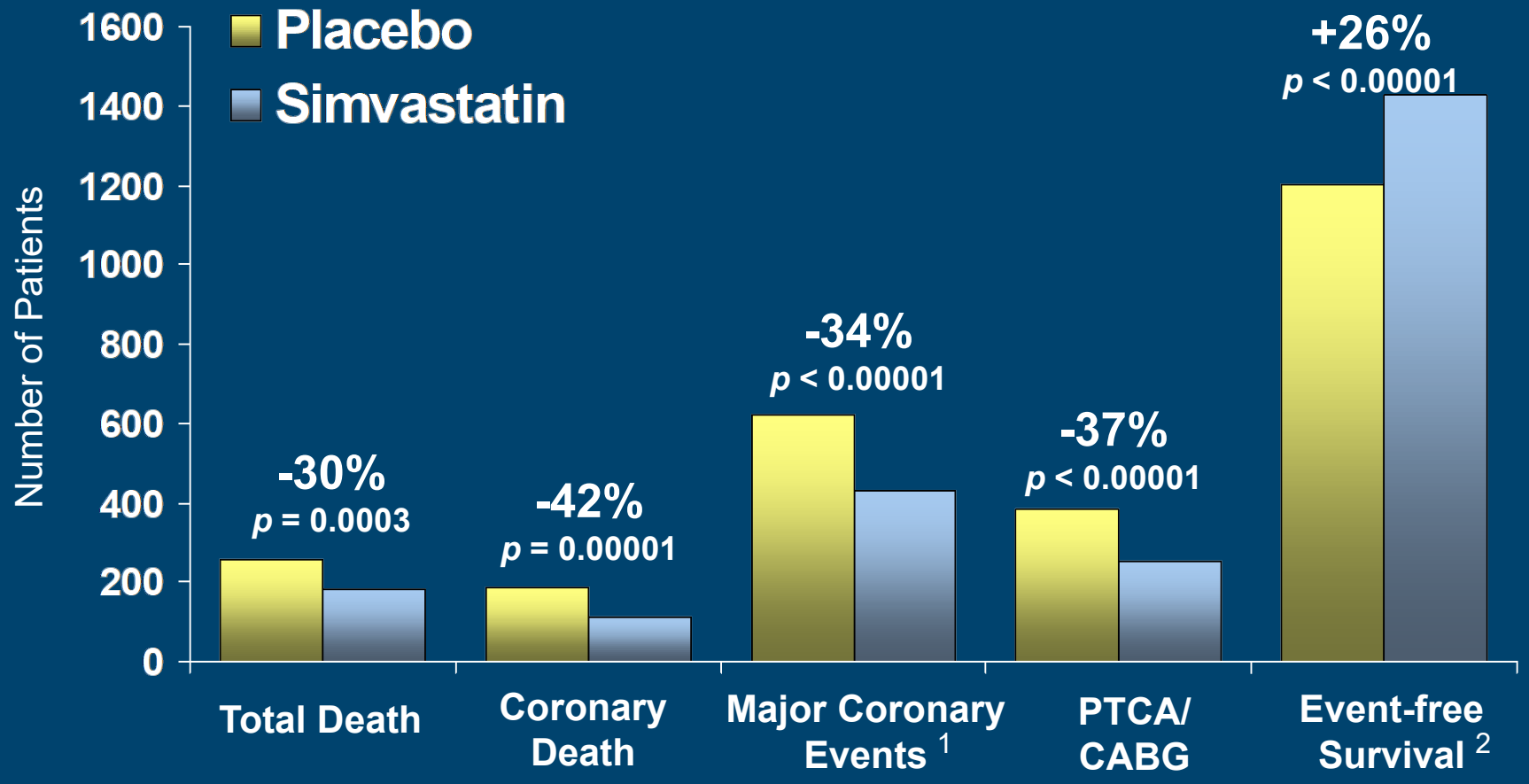
The 95% CIs are not included because this column contains the reference values.

[c] Fatal or nonfatal.

JAMA. Published online July 26, 2018.
doi:10.1001/jama.2018.9641
https://jamanetwork.com/journals/jama/fullarticle/2695067

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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

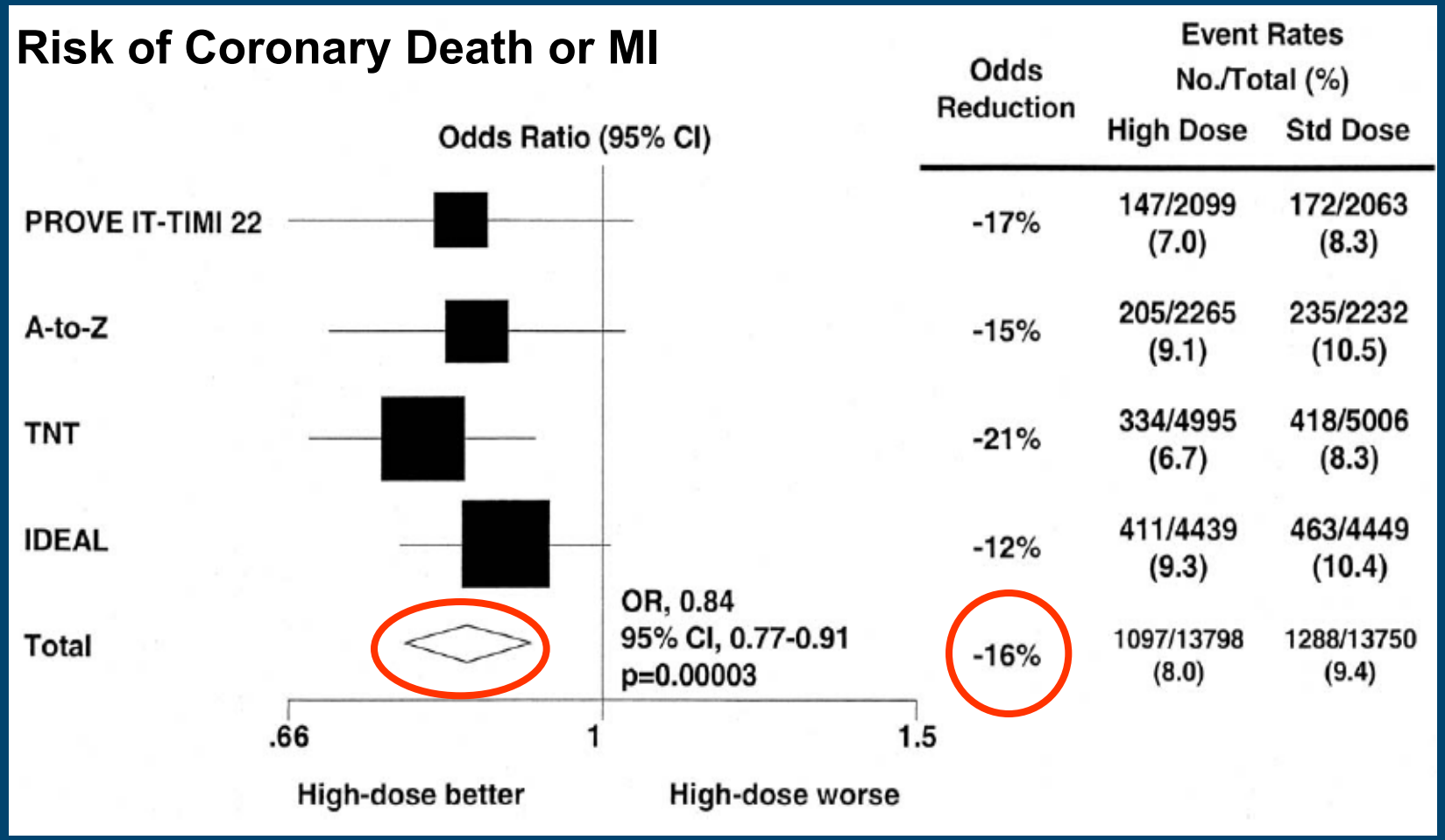


1 Death from coronary disease and non-fatal heart attacks.
2 Finished the study without suffering any coronary events or other atherosclerotic events such as stroke.

Lancet 1994; 344:1383-89

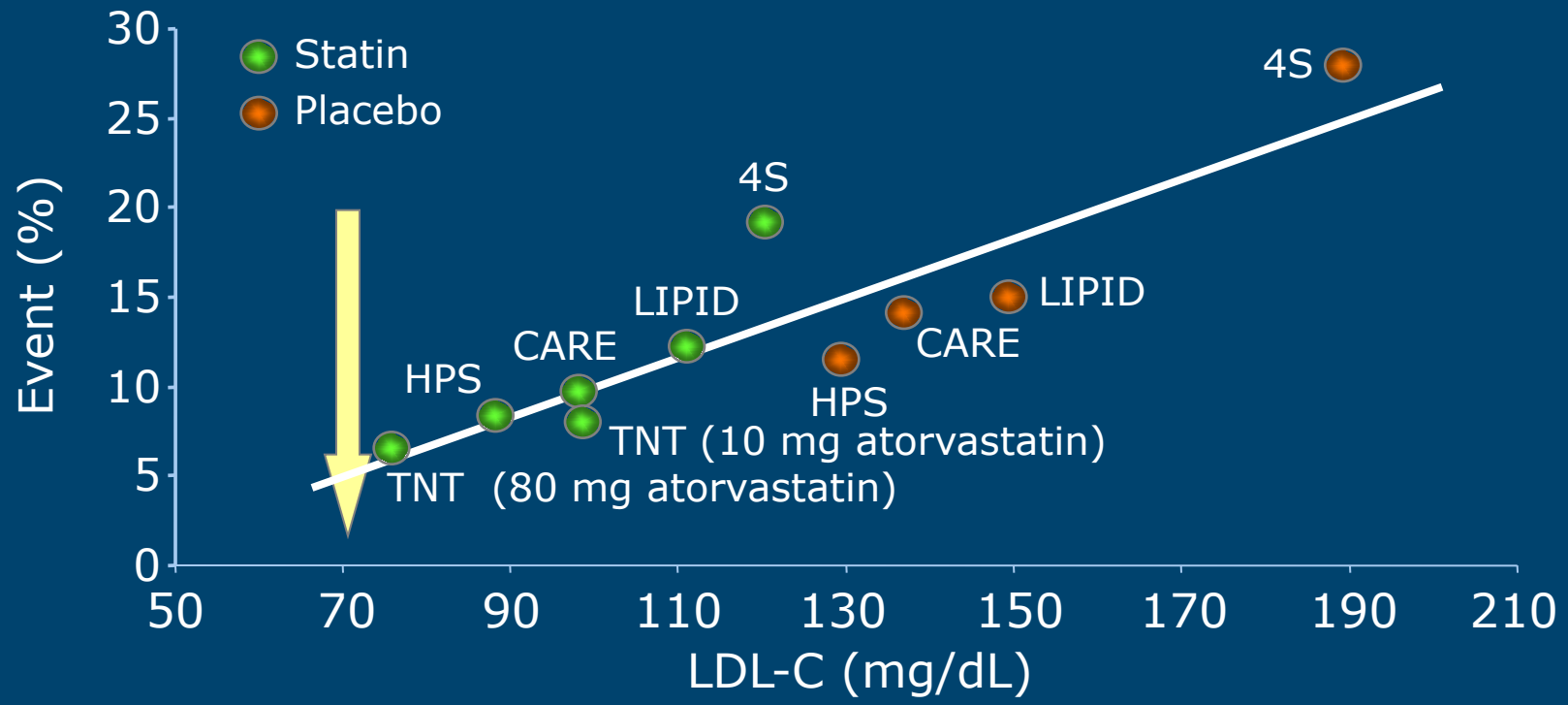
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Meta-analysis of high-dose vs. standard-dose statin therapy: Achieved LDL of 70 vs. 100



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

LDL Goals Over the Prior 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.

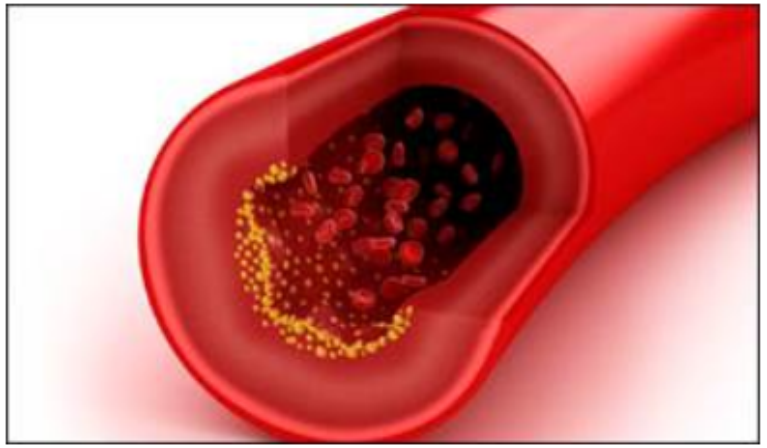
LaRosa et al. N Engl J Med 2005;352:1425–1435.

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.

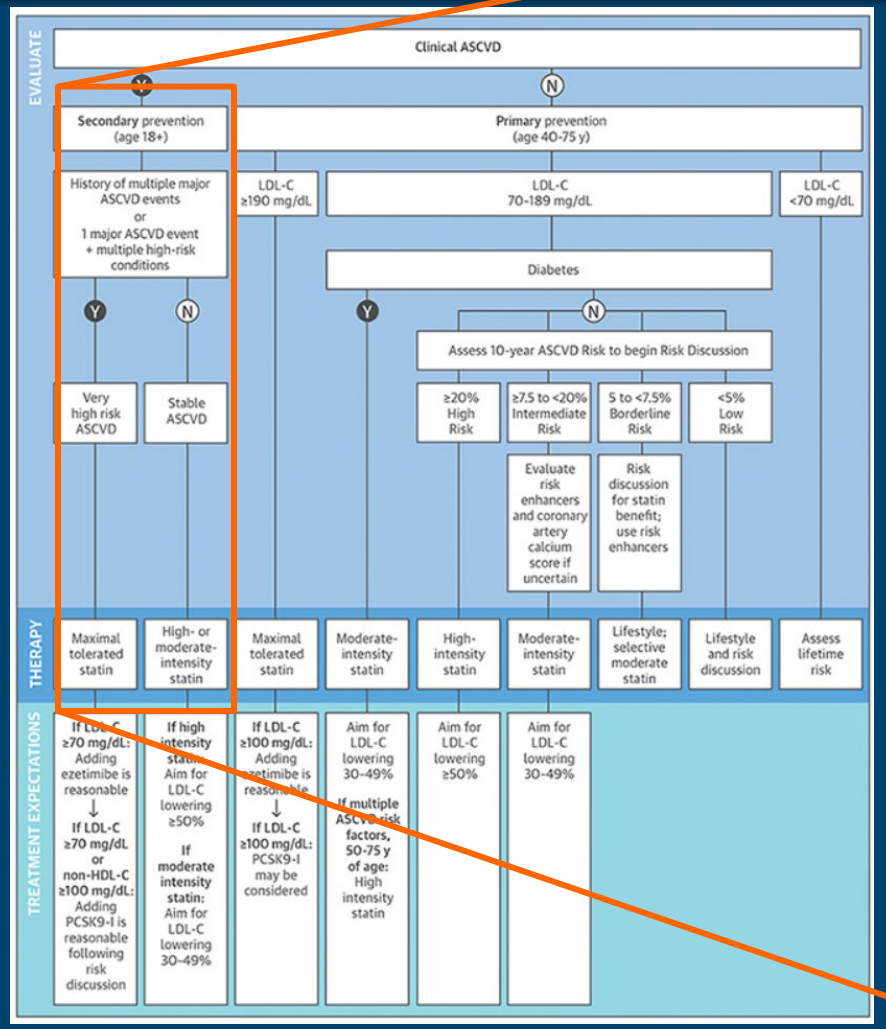
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

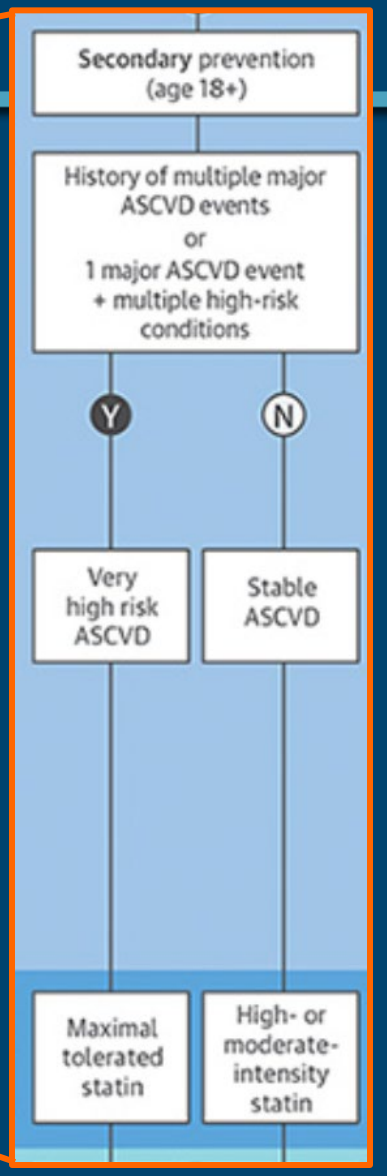
2013 ACC/AHA Cholesterol Guidelines

- 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

2018 ACC/AHA Cholesterol Guidelines

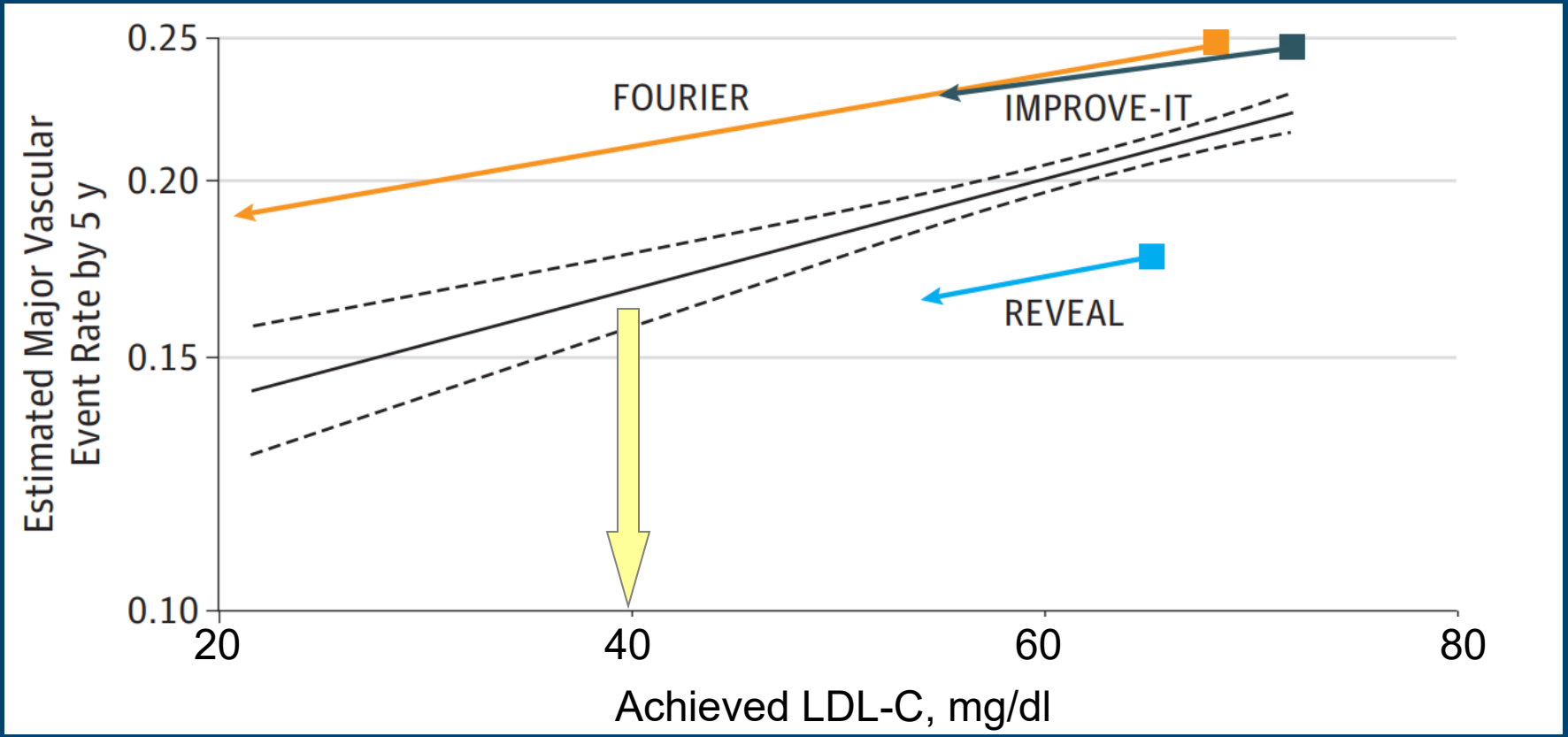




Grundy SM, et al. J AM Coll Cardiol. DOI: 10.1016/j.jacc.2018.11.003

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

2018: Meta-regression of achieved LDL-C and rate of major vascular events



Sabatine MS, et al. JAMA Cardiol. doi:10.1001/jamacardio.2018.2258

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Safety Outcomes in Trials of Therapy to Achieve Very Low LDL-C Levels

Safety Outcome	Patients With Event, No.		Meta-analysis Data	
	Experimental Arm	Control Arm	Risk Ratio (95% CI)	*P* Value
Any serious adverse event	12 809	12 836	1.00 (0.98-1.02)	.89
Myalgias or myopathy	116	135	0.85 (0.66-1.08)	.19
Aminotransferase elevation	488	510	0.96 (0.85-1.08)	.48
New-onset diabetes	1272	1320	0.97 (0.90-1.05)	.46
Hemorrhagic stroke	132	118	1.11 (0.87-1.43)	.40
Cancer	1747	1715	1.02 (0.96-1.09)	.55

Sabatine MS, et al. JAMA Cardiol. doi:10.1001/jamacardio.2018.2258

ACE Inhibitors for Risk Reduction

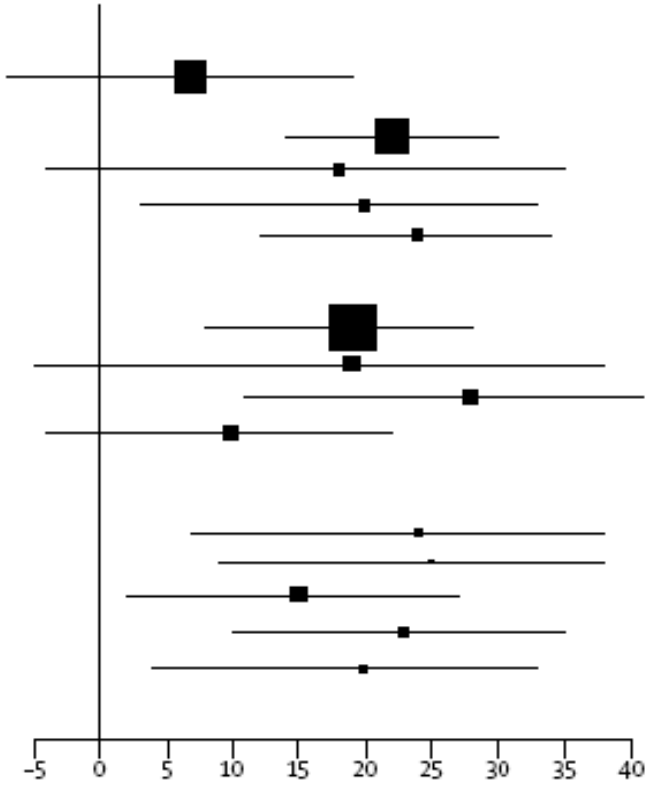
- HOPE (Heart Outcomes Prevention Evaluation) Study in 2000
  - 9300 high-risk patients (vascular disease or DM + one other CV risk factor and no LV dysfunction or CHF)
  - Randomized to ramipril 10 mg qd vs. placebo for 5 years
  - Ramipril group had lower rates of
    - MI ↓ 20%
    - CV mortality ↓ 26%, All-cause mortality ↓ 16%

Yusuf S. N Engl J Med 2000;342:145-53.

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

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

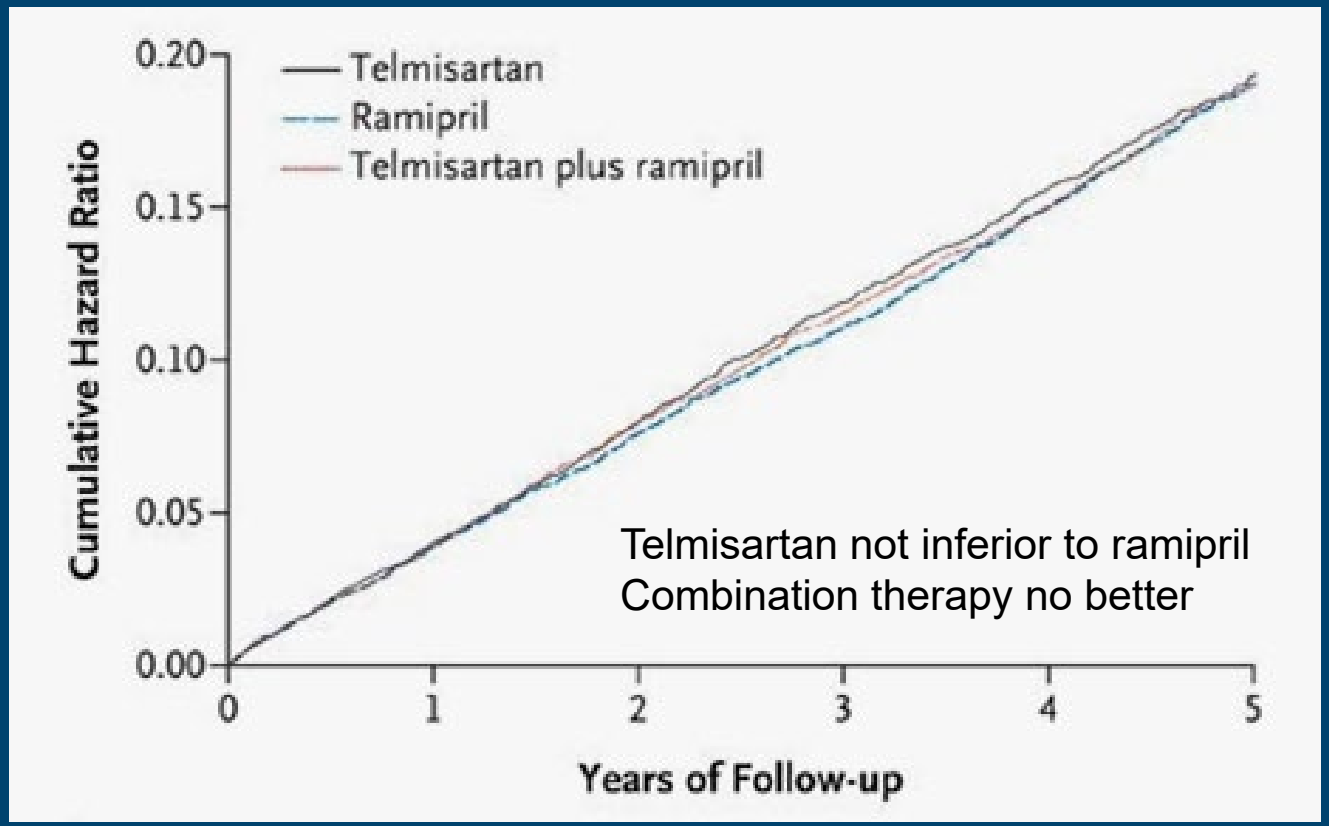
Trials	Number of patients	Annual rates in placebo groups	OR (95% CI)	p
PEACE	8290	2·13	7 (–8 to 19)	0·328
HOPE total	9297	3·95	25 (16 to 32)	0·0001
HOPE lower risk	3083	2·17	18 (–4 to 35)	
HOPE medium risk	3100	3·58	20 (3 to 33)	
HOPE high risk	3114	5·98	24 (12 to 34)	
EUROPA total	12218	2·60	19 (8 to 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 Potential 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

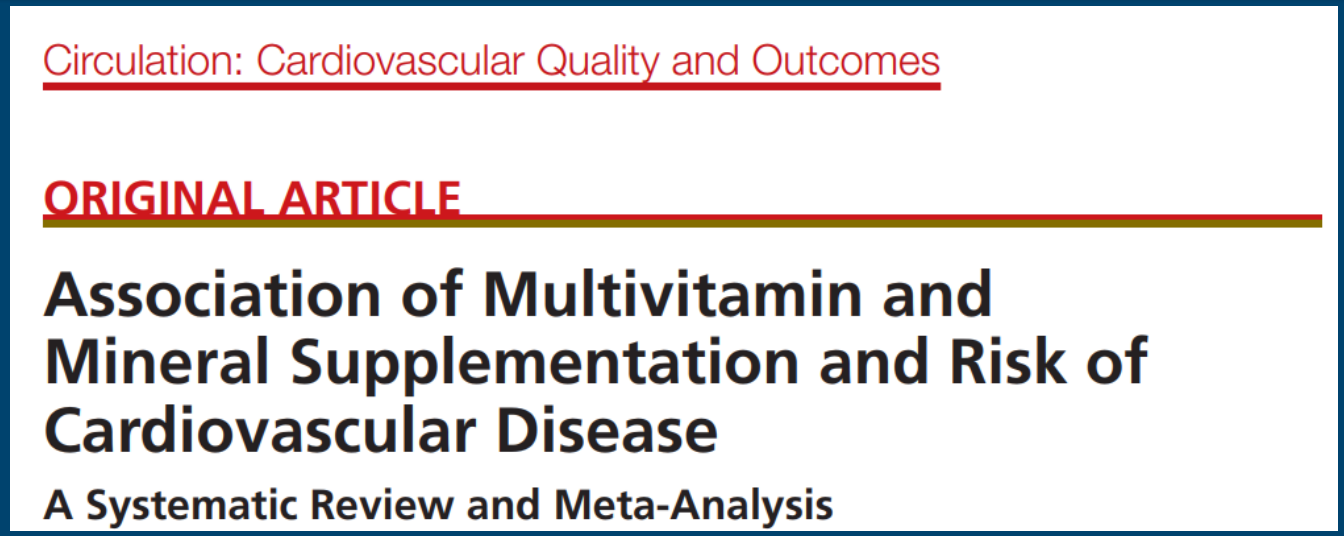
HOPE 2 Investigators. N Engl J Med 2006;354:1567.
Bønaa KA, et al. N Engl J Med 2006;354.
Armitage JM et al. JAMA 2010; 303:2486-2494.

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

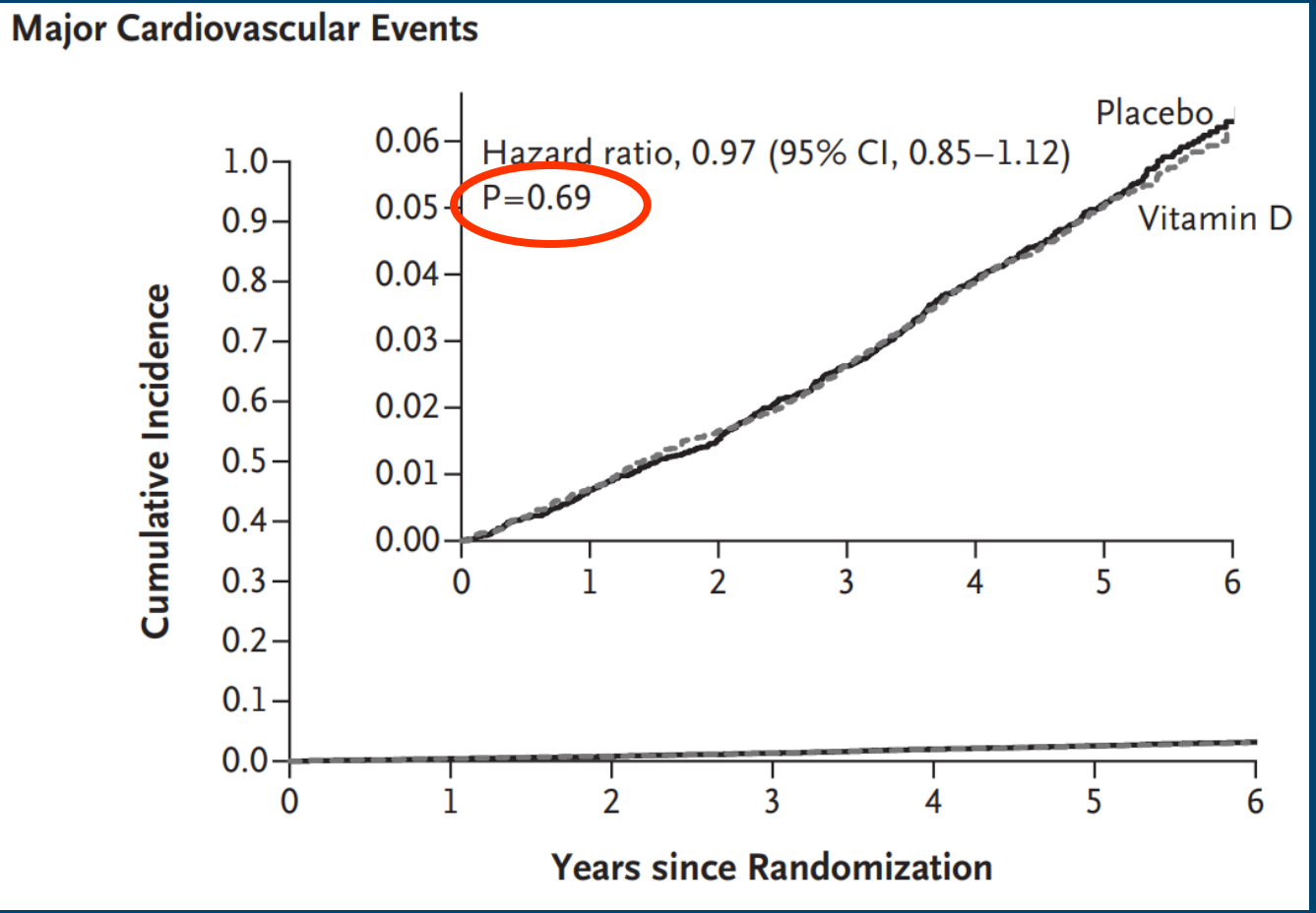


- 18 trials, 2 million subjects
- No benefit in incidence of CHD, CHD mortality, or overall cardiovascular mortality

Kim J, et al. Circ Cardiovasc Qual Outcomes 2018;11:e004224.

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Vitamin D: Results from the VITAL Trial (Vitamin D and Omega-3 Trial)



Manson JE, et al. N Engl J Med 2019; 380:33-44

Other Potential Therapeutic Strategies: Omega-3 Fatty Acids

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

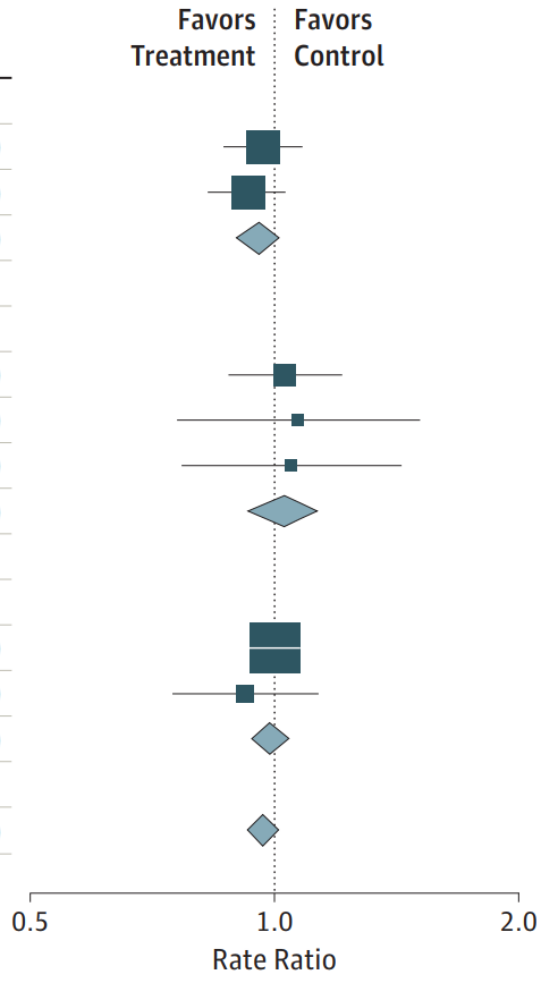
Outcome	EPA-DHA (n=2404), %	Placebo or ALA-only (n=2433), %	Hazard ratio (95% CI)
Major CV events*	14.0	13.8	1.01 (0.87–1.17)
Incident CV disease	7.0	7.6	0.92 (0.75–1.13)
Death from CV disease	3.3	3.4	0.98 (0.72–1.33)
Death from CHD	2.8	2.9	0.95 (0.68–1.32)
Ventricular arrhythmia-related events	2.8	3.0	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 in 2018: Association of Omega-3 Fatty Acids With Major Vascular Events

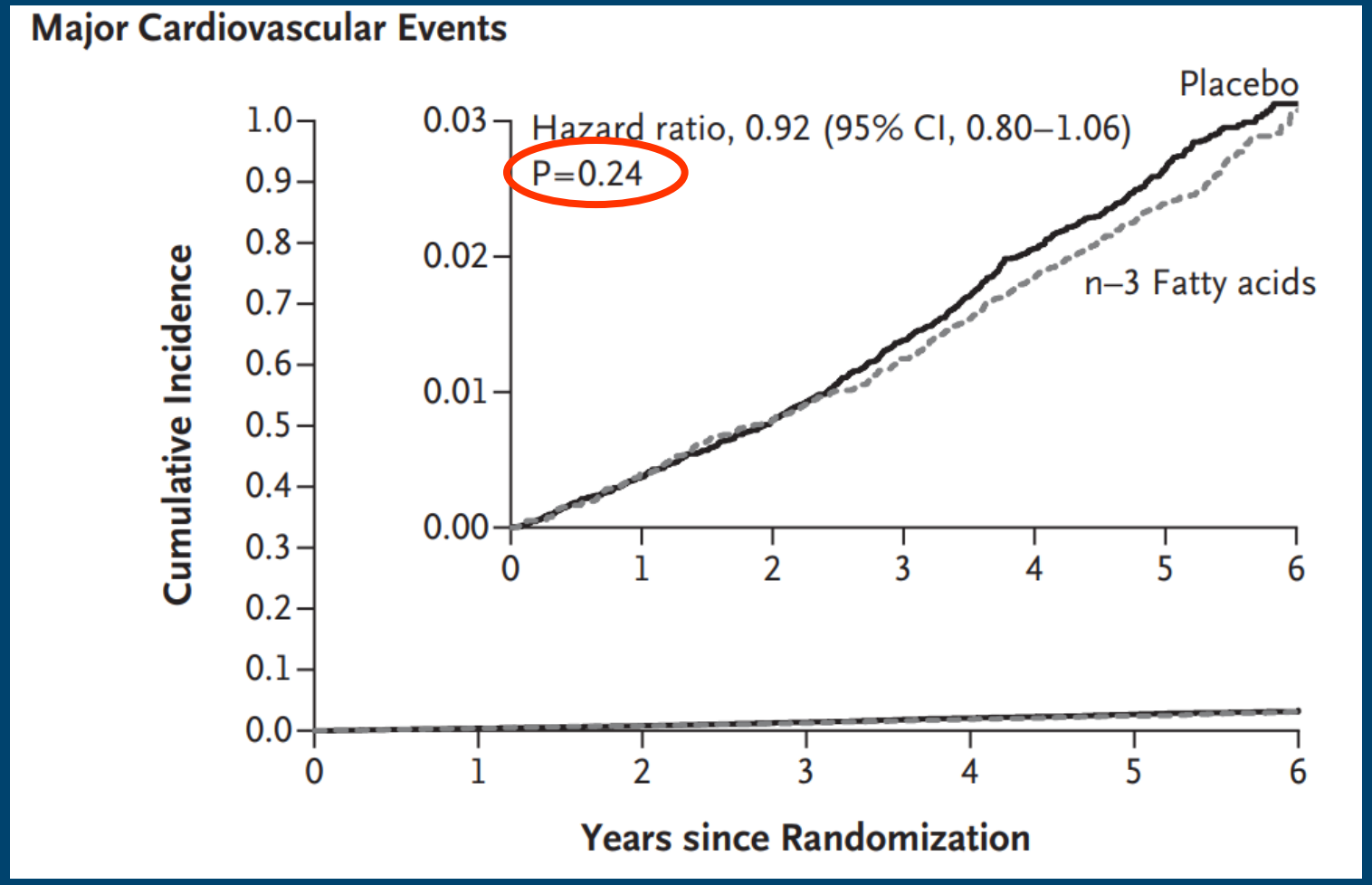
Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary Heart Disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87-1.08)
Coronary heart disease death	1301 (3.3)	1394 (3.6)	0.93 (0.83-1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88-1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76-1.51)
Unclassified/Other	142 (0.4)	135 (0.3)	1.05 (0.77-1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93-1.13)
			P = .60
Revascularization			
Coronary	3044 (9.3)	3044 (9.3)	1.00 (0.93-1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75-1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94-1.04)
			P = .60
Any major vascular event	3230 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P = .10



10 randomized clinical trials, 77 917 participants

Aung T, et al. JAMA Cardiol 2018;3:225-234

Omega-3: Results from the VITAL Trial (Vitamin D and Omega-3 Trial)



Manson JE, et al. N Engl J Med 2019; 380:23-32

Omega-3 Fatty Acids:
…The Picture Remains Murky

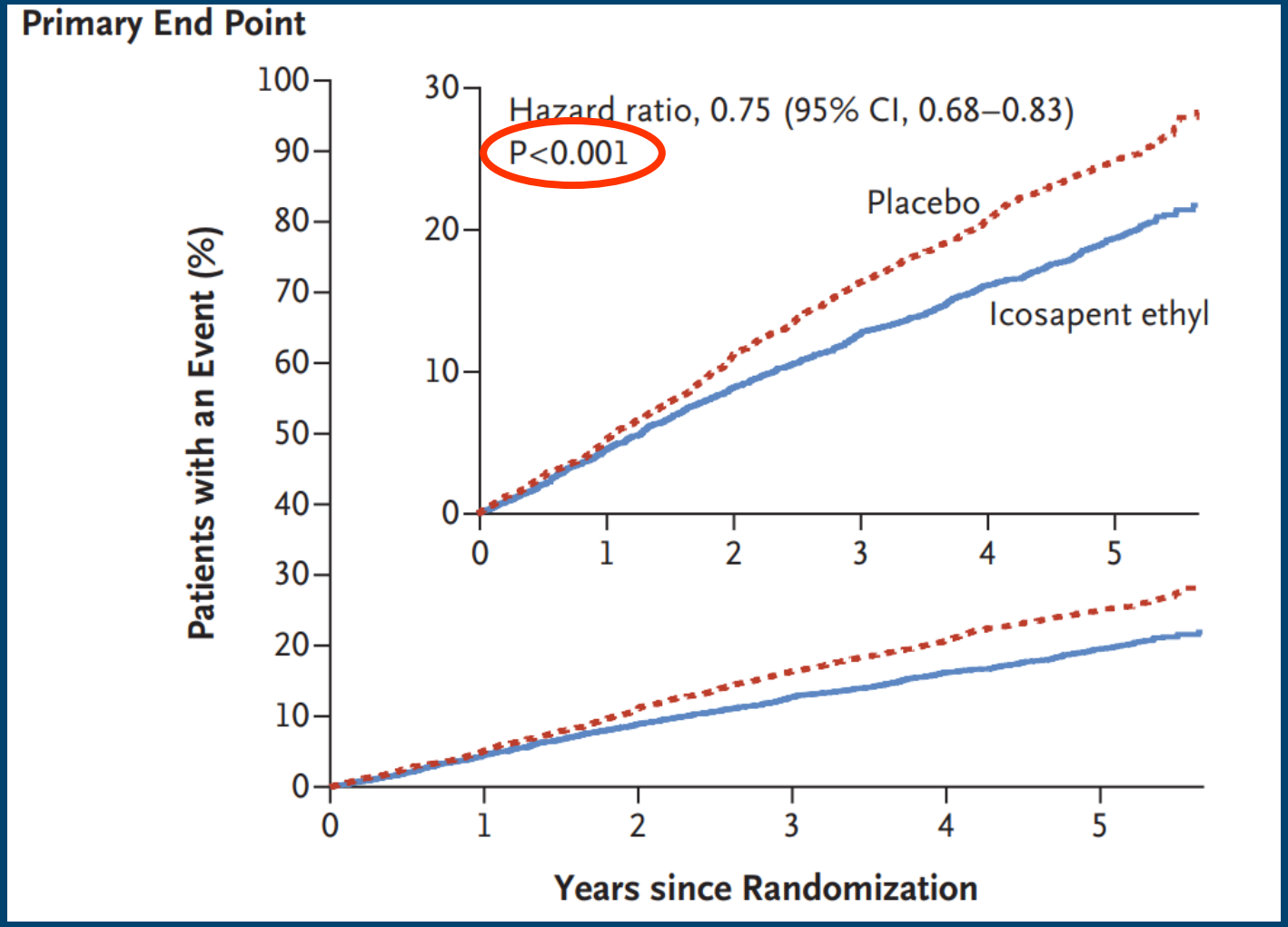
REDUCE-IT: Vascepa

- Vascepa (Amarin Pharma) = pure EPA (vs. combination of EPA+DHA in other fish oils)
  - Currently FDA approved for hypertriglyceridemia
- Multicenter, randomized, double-blind, placebo-controlled trial
  - 2 g EPA twice daily (4 g total) vs. placebo
  - Patients had established CVR disease or DM + other risk factors, on statin therapy with an LDL 41-100, and fasting trig 135-499
  - Primary end point = composite of CVR death, nonfatal MI, nonfatal CVA, coronary revascularization, or unstable angina

EPA = eicosapentaenoic acid
DHA = docosahexaenoic acid

Bhatt DL, et al. N Engl J Med 2019; 380:11-22

REDUCE-IT: Vascepa



Bhatt DL, et al. N Engl J Med 2019; 380:11-22

BREAKINGNEWS

REDUCE-IT: Downside?

- $2400 / year

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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 ($p < 0.0001$)
- Limit saturated fats
  - Avoid trans-fats
  - Increase intake of polyunsaturates
- Weight loss.

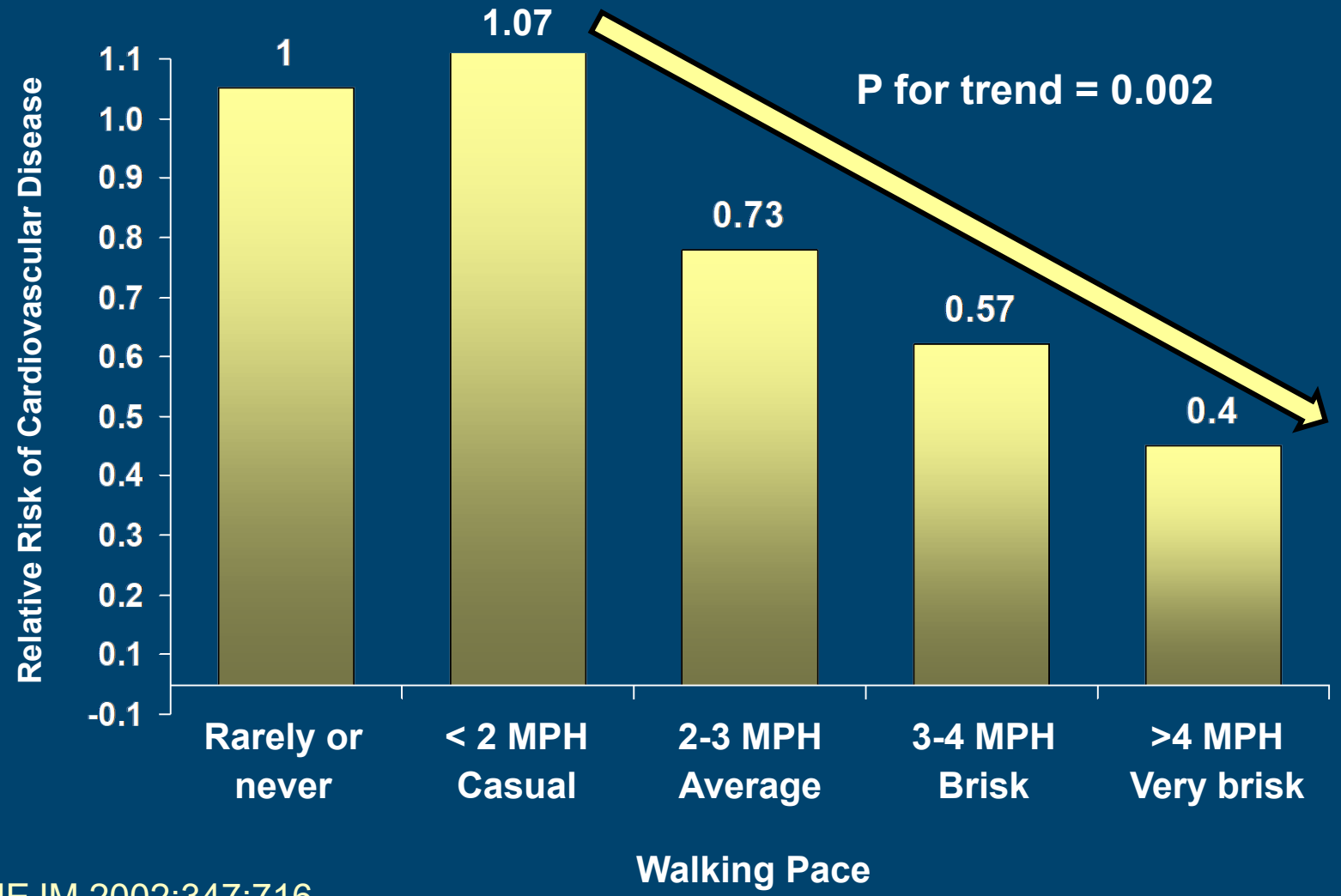
Stratton IM, et al. BMJ. 2000;321:405-412.

Benefits of Exercise ≈ Other "Interventions"

- Reduces atherosclerosis
  - Pts 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

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

“Prescribe” Exercise

- Get at least 150 minutes per week of moderate-intensity aerobic activity or
- 75 minutes per week of vigorous aerobic activity, or a combination of both
- Preferably spread throughout the week
- Episodes of exercise should be at least 10 min long
- Ideally, add in moderate resistance (strength) training at least twice per week

American Heart Association Recommendations 2019

Treating the Symptoms of Angina

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%
- Please 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 3.4 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 FDA in 2006
- Mechanism of action is uncertain:
  - Does not decrease heart rate or blood pressure
- 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
- Dosage = 500 mg or 1000 mg twice daily.

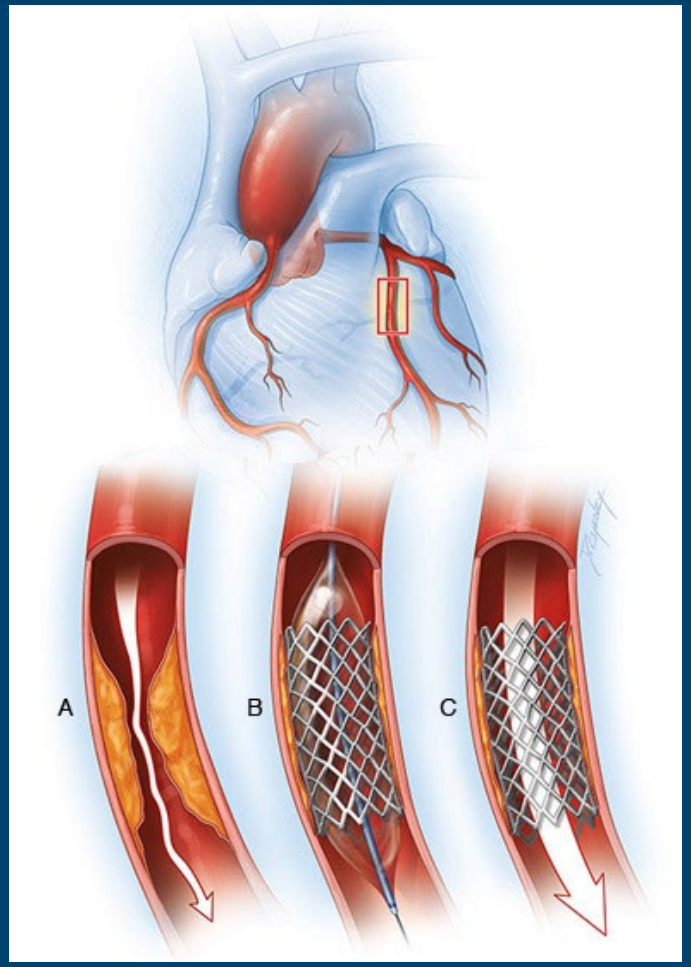
Boden J, et al. J Am Coll Cardiol.2010; 56: 943-945

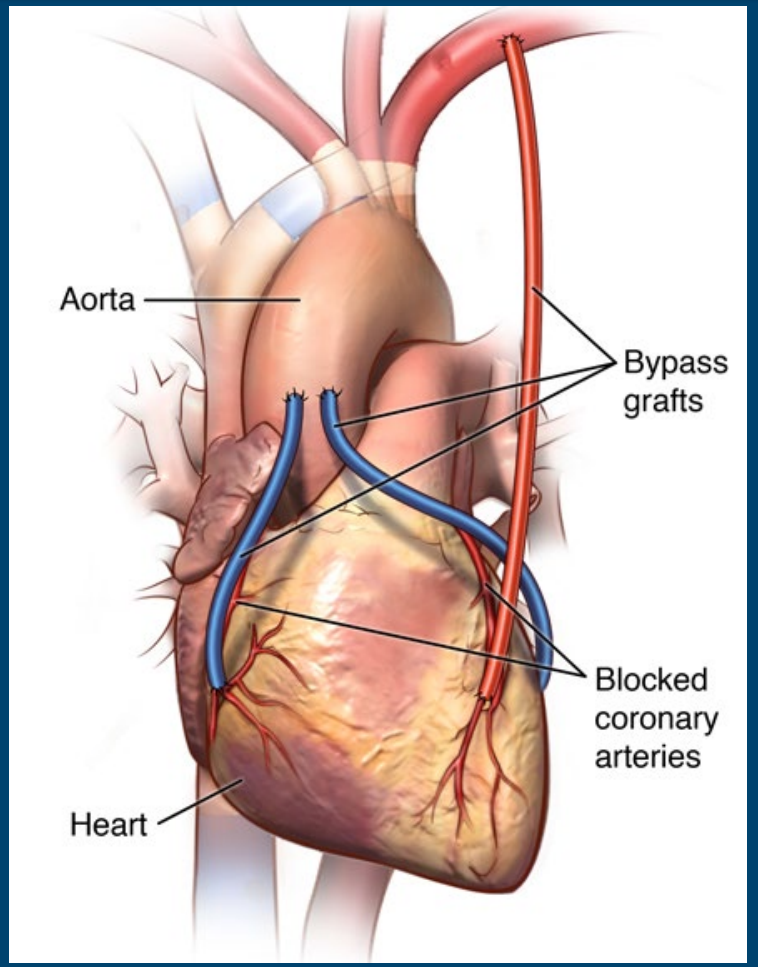
Ranolazine: Precautions

- 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

Coronary Artery Revascularization

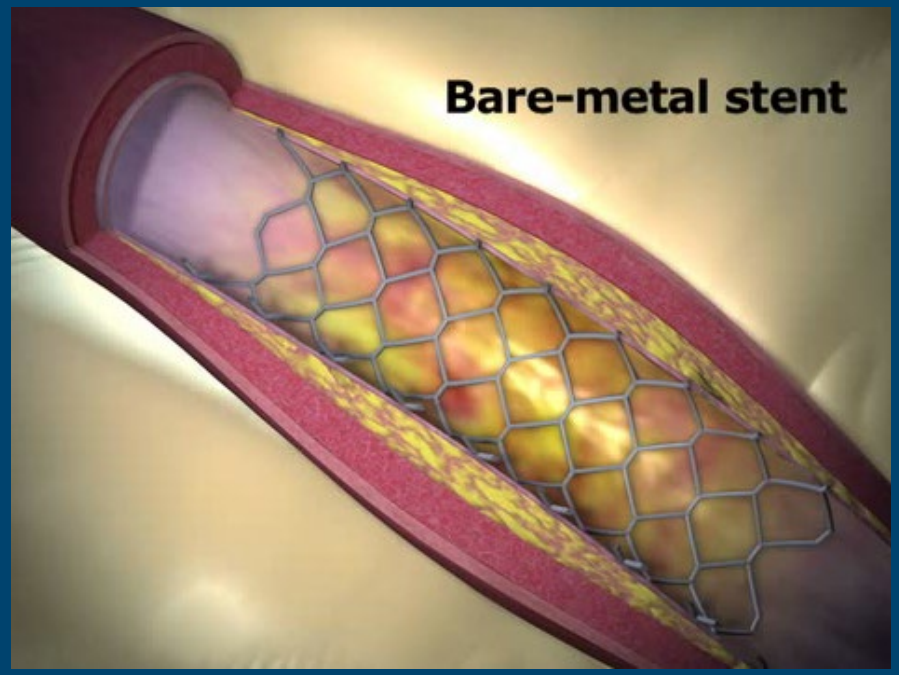


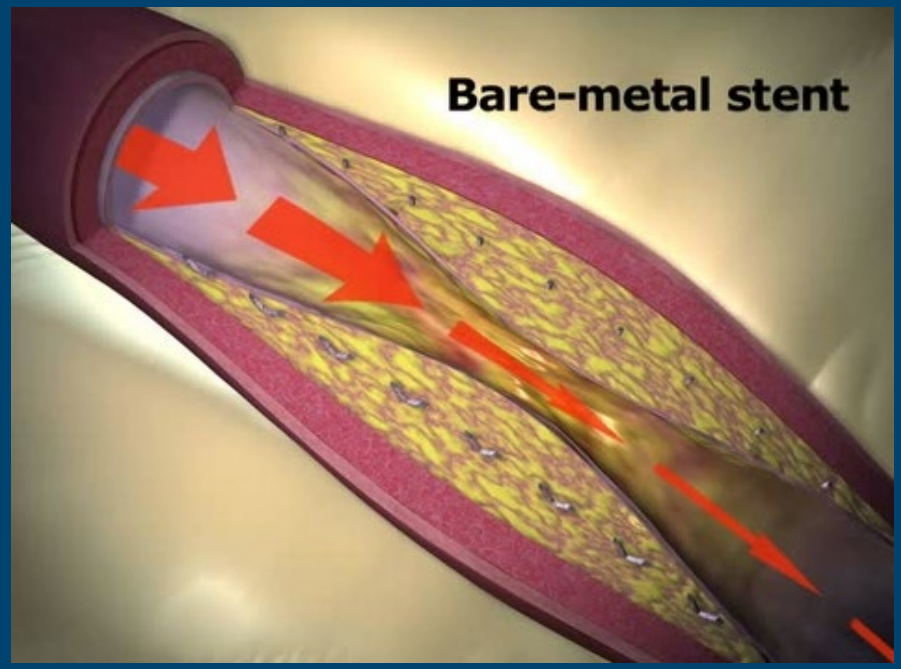


Percutaneous Coronary Intervention (PCI)

- 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).

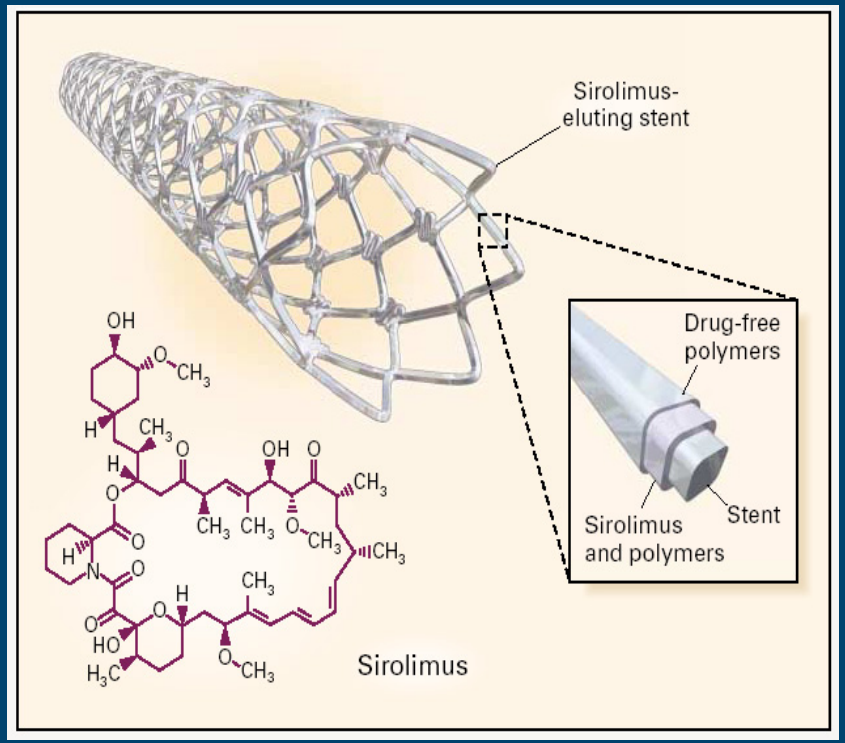
Bare-metal Stents:
The Risk of Restenosis



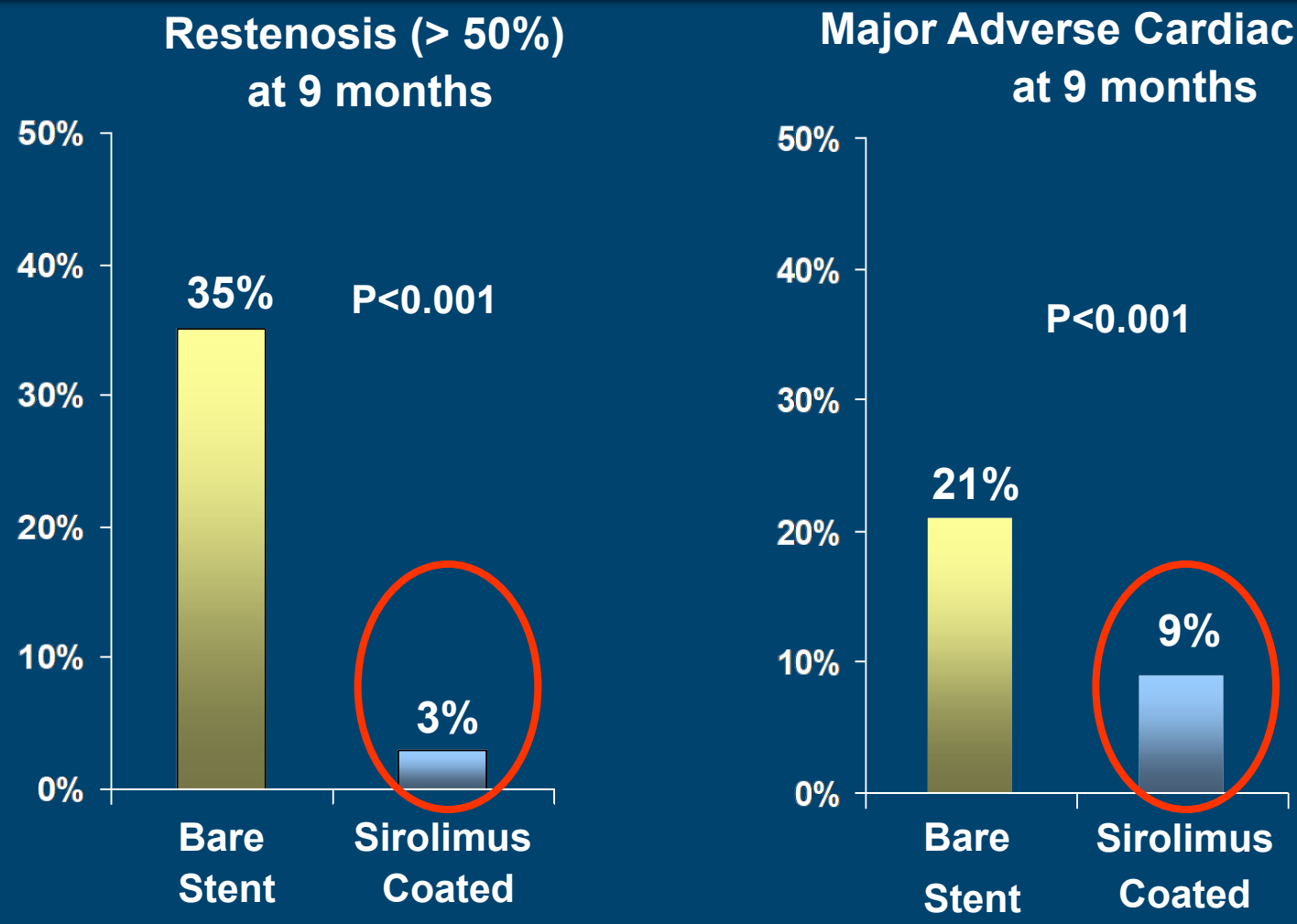


Drug-Eluting Stents (DES)

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

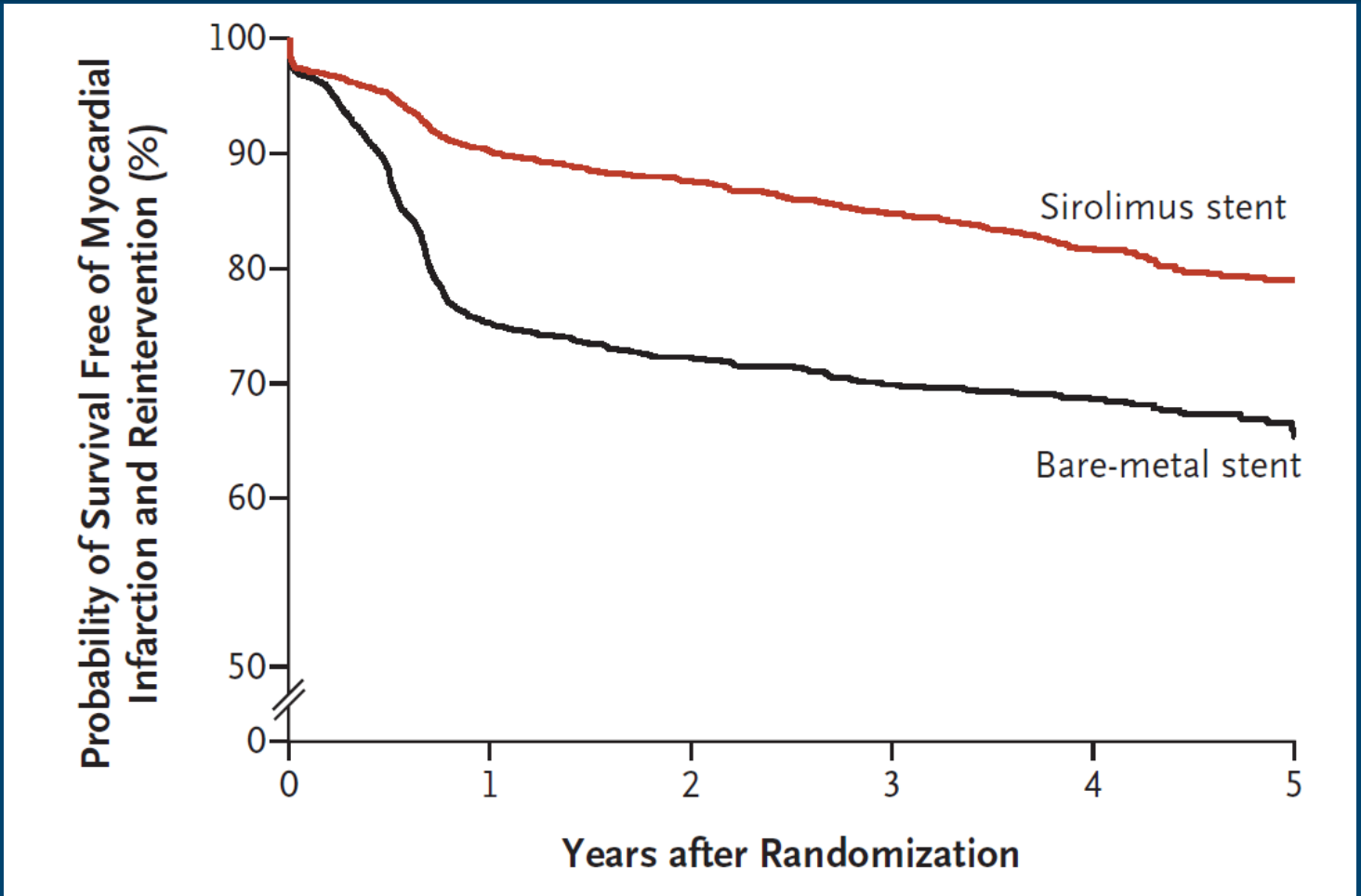


Drug-Eluting Stents: Intermediate Outcomes



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

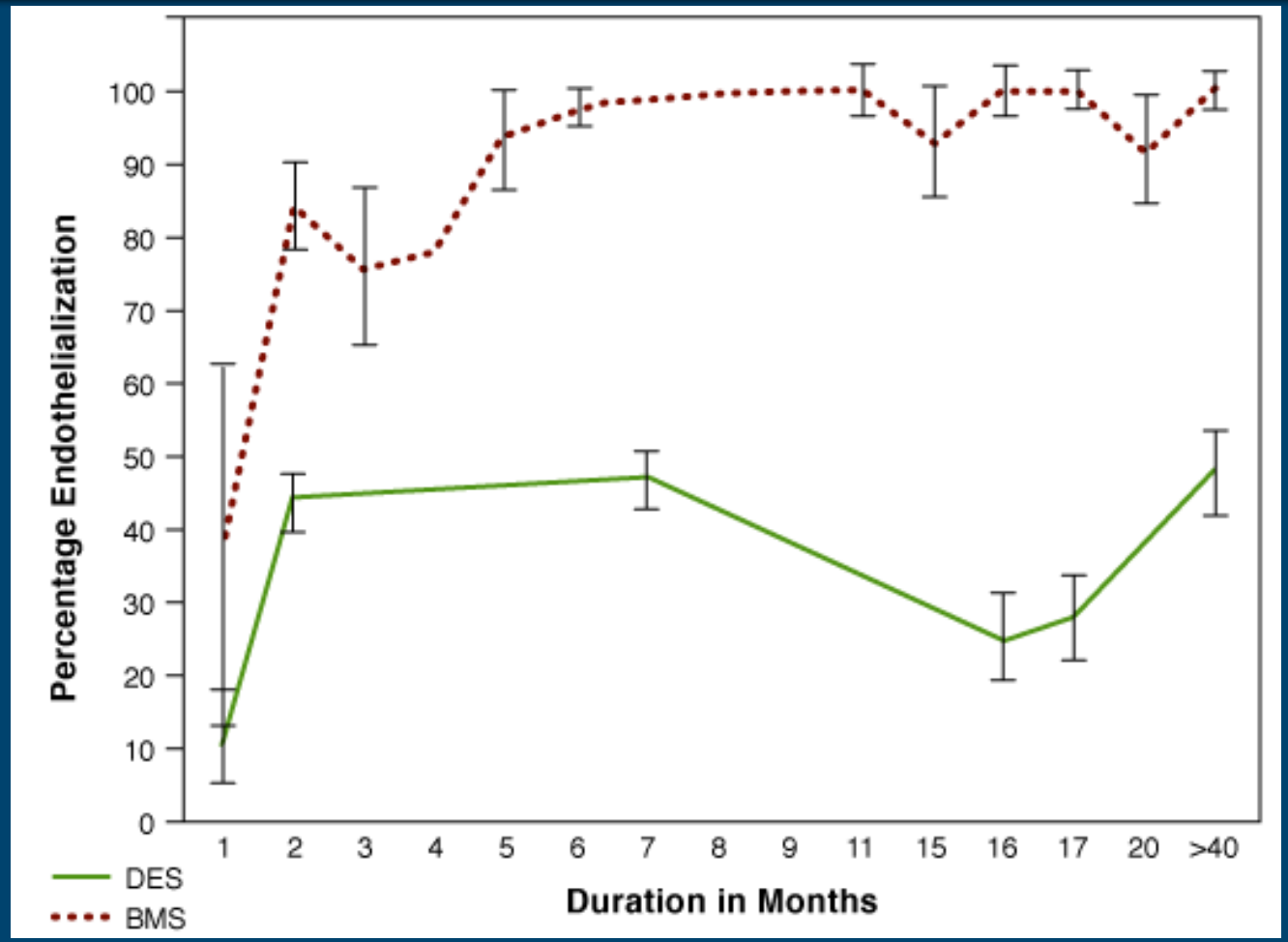


Kastrati A et al. N Engl J Med 2007;356:1030-1039

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

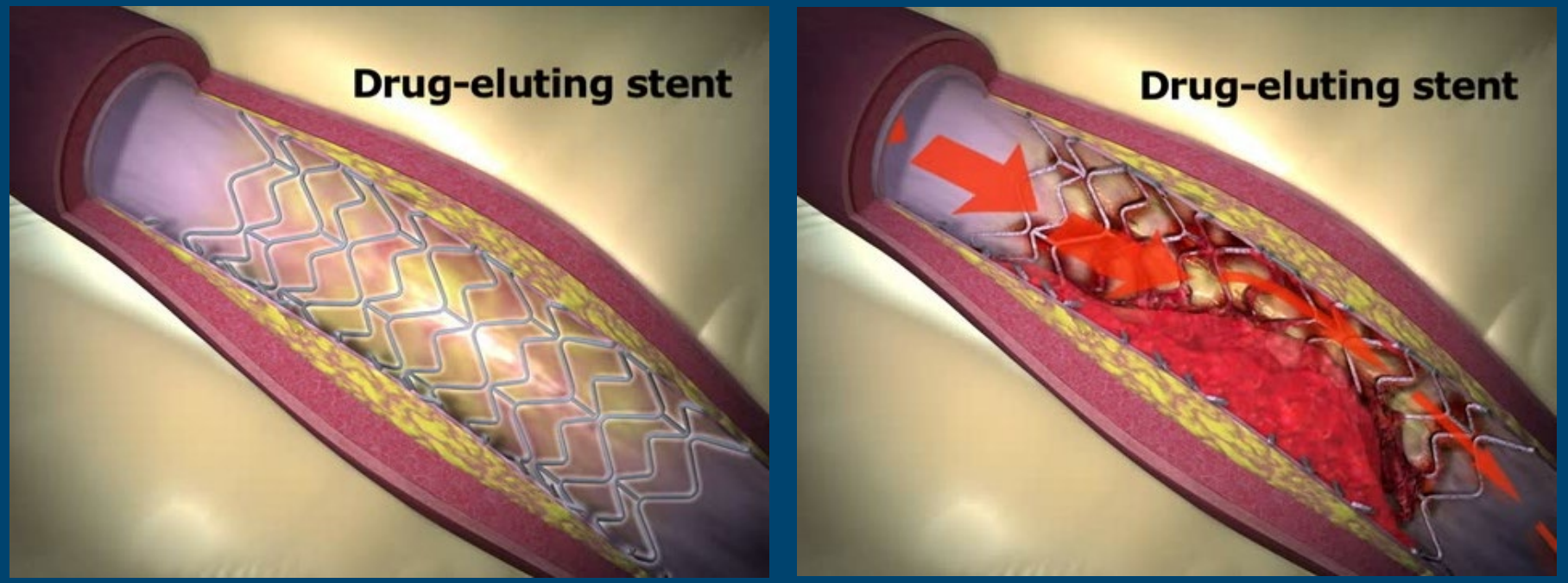
Drug-Eluting Stents:
Is there is a downside to arresting cell growth?

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



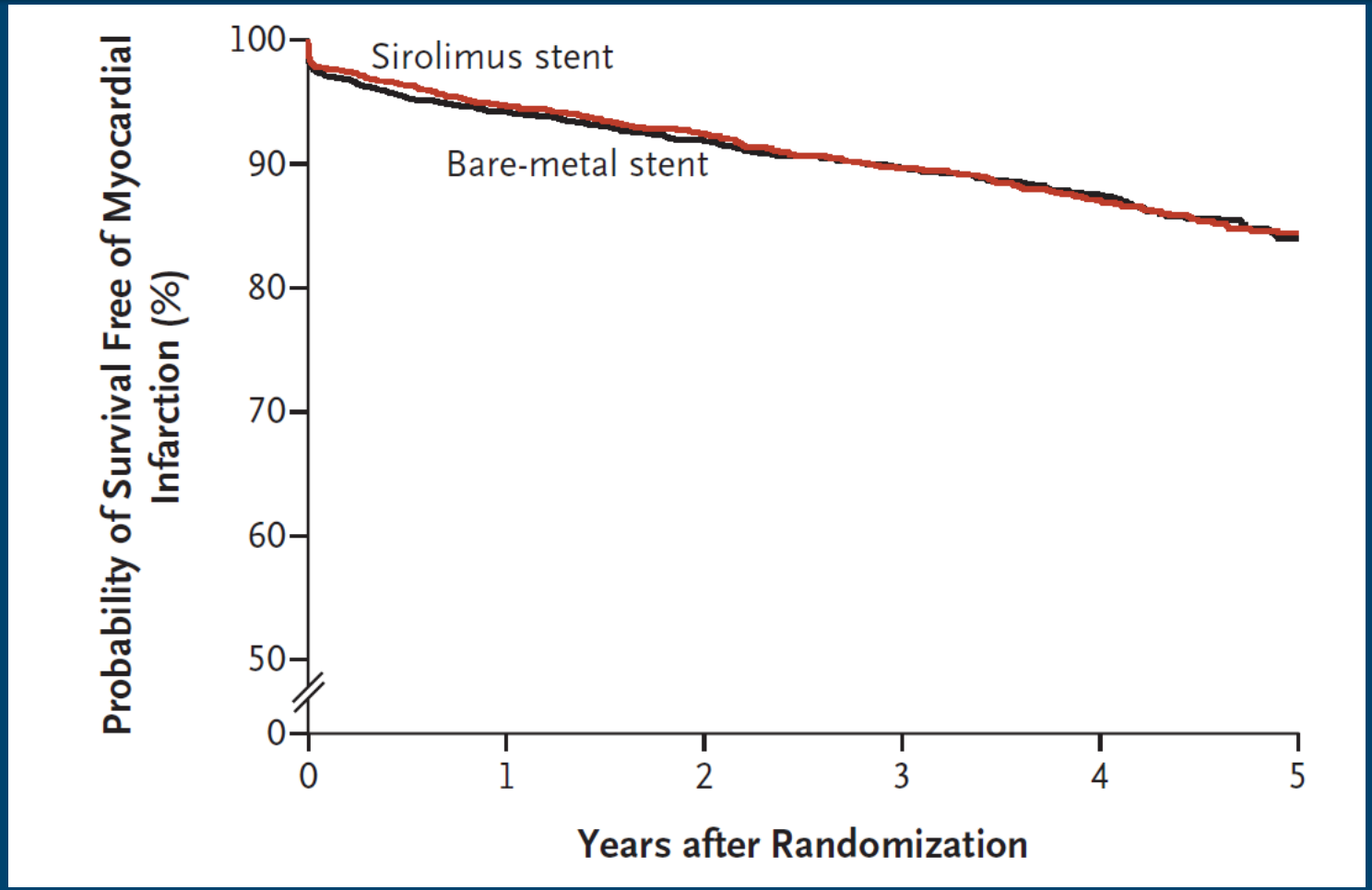
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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

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

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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

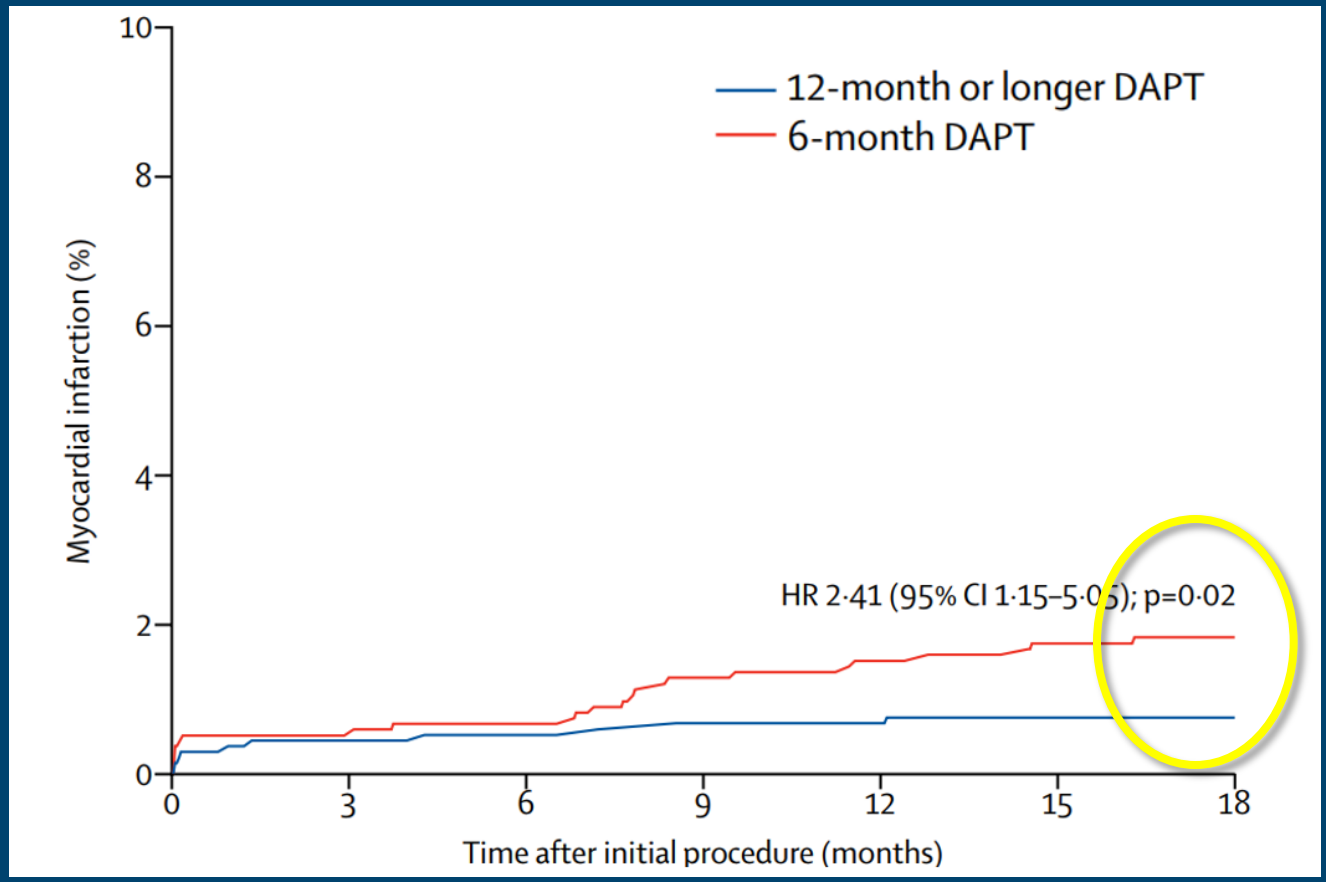


Kastrati A et al. N Engl J Med 2007;356:1030-1039

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

SMART-DATE: Randomized open-labelled trial of 6 vs 12-months of DAPT following PCI

- 2712 patients s/p drug eluting stent for acute coronary syndrome
- Randomized to 6-months vs 12 or more months of DAPT, followed for 18 months

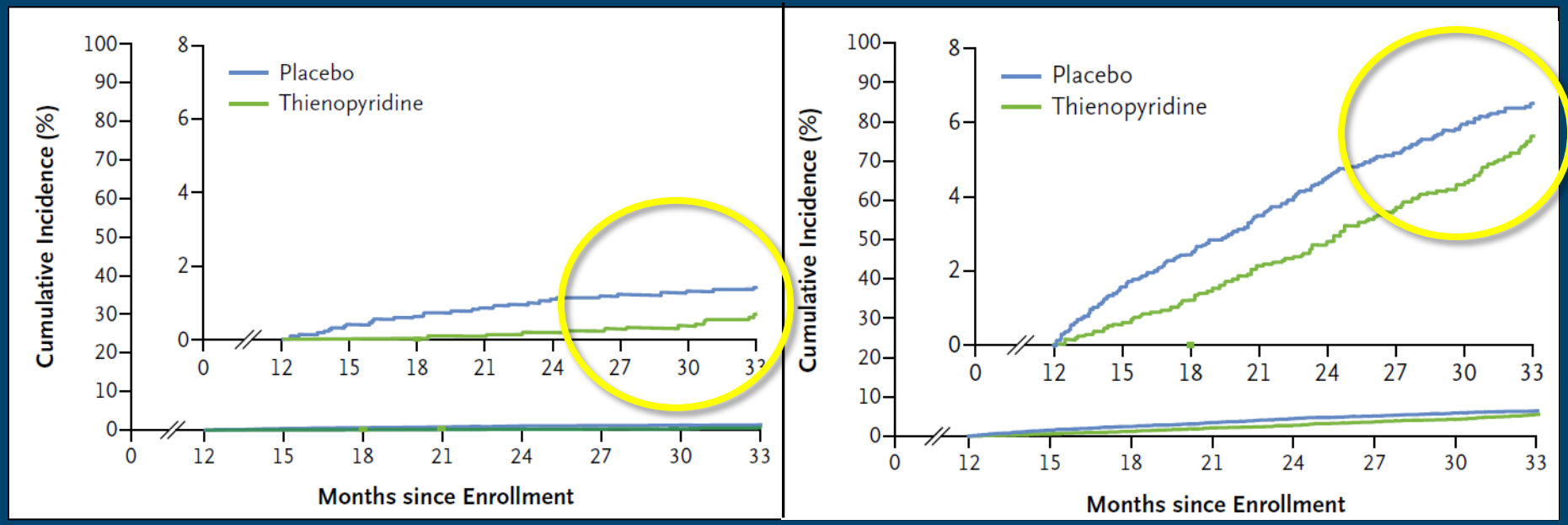


Hahn J-Y, et al. The Lancet 2018. http://dx.doi.org/10.1016/ S0140-6736(18)30493-8

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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 DES
- Randomized to an additional 18 months of DAPT vs. aspirin



Incidence of Stent Thrombosis

Incidence of Major Cardiovascular or Cerebrovascular Events

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

Prediction Rule for Benefit and Harm of DAPT Beyond 1 Year After PCI: The "DAPT Score"

Clinical Prediction Score	
Variable	**Points**
Age, y	
≥75	-2
65-<75	-1
<65	0
Cigarette smoking	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Paclitaxel-eluting stent	1
Stent diameter <3 mm	1
CHF or LVEF <30%	2
Vein graft stent	2
Total score range: -2 to 10	

Low risk < 2
High risk ≥ 2

Yeh RW, et al. JAMA. 2016;315:1735-49.

Conclusions About Drug-eluting Stents

- DES are effective in reducing restenosis
- DAPT should be continued for at least 6 and preferably at least 12 months after DES
- Continuation of DAPT for longer than 12 months after DES may be reasonable for patients who tolerated DAPT without a bleeding complication and are not at high risk of bleeding.

Mauri L, Smith SC, Jr.. JAMA Cardiol 2016;1:733-734

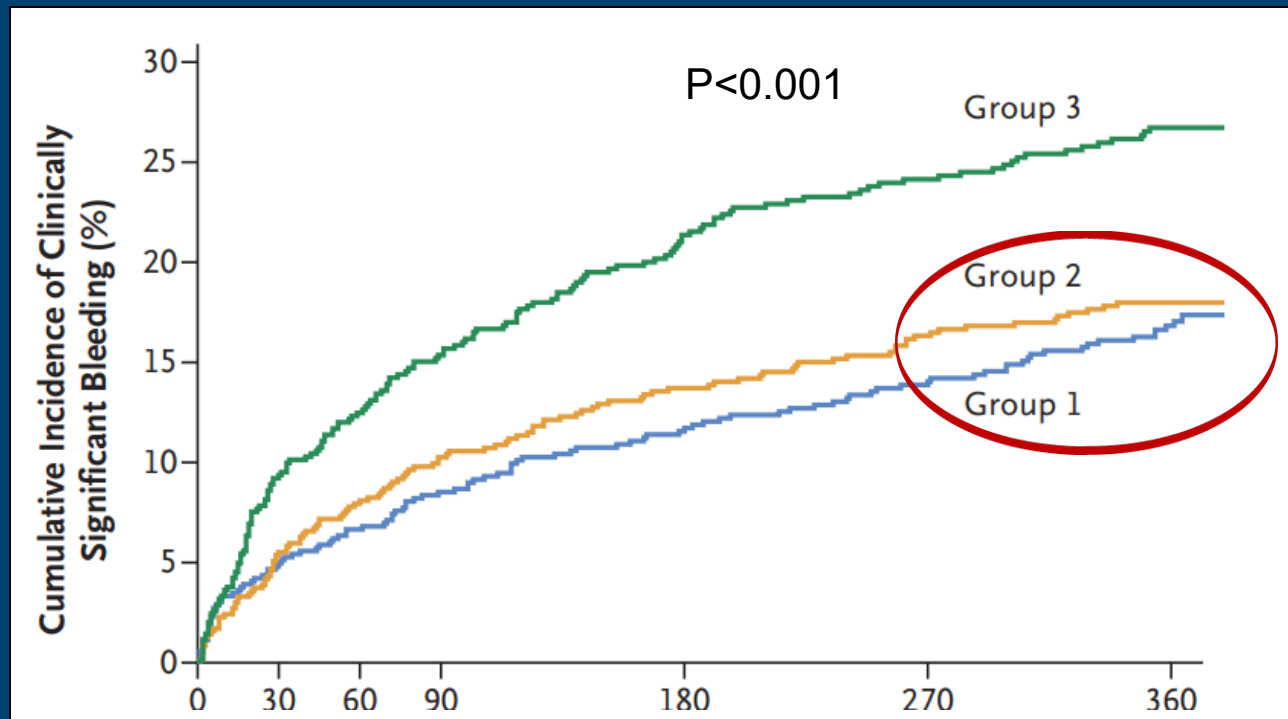
What About Patients With Atrial Fibrillation Who Need DAPT?

PIONEER Trial

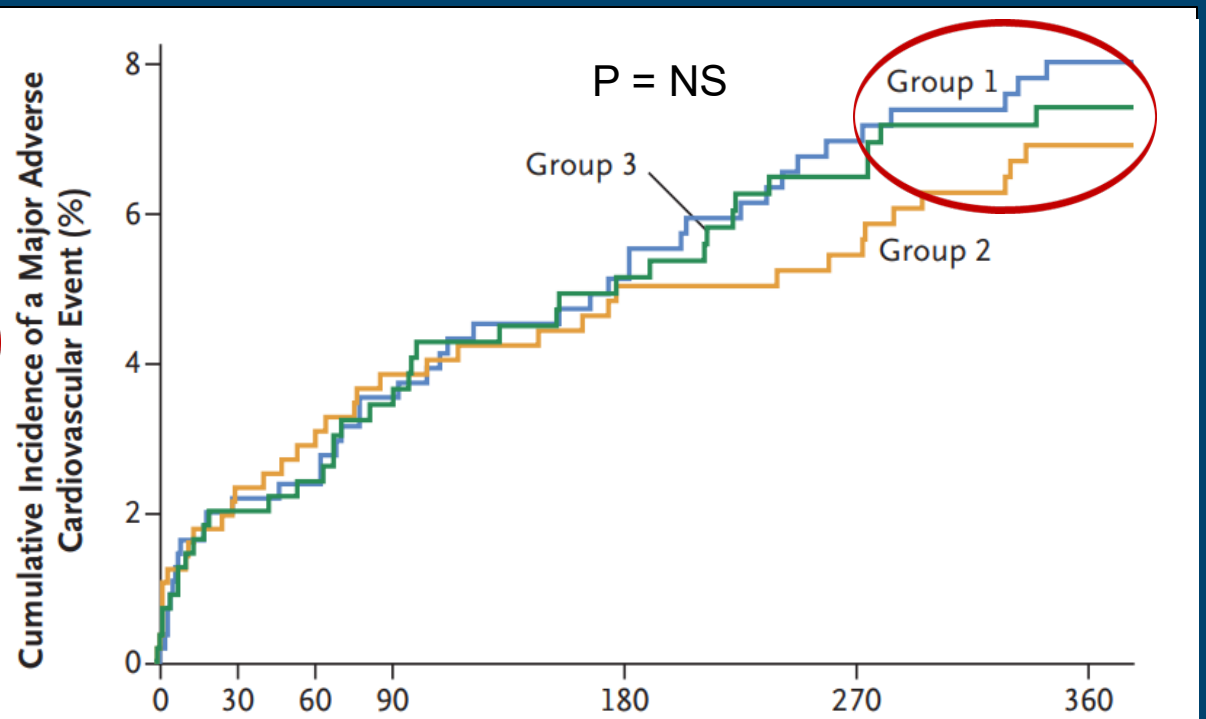
- 2124 pts with nonvalvular AF who had undergone PCI with stenting
- Randomly assigned to receive:
  - Low-dose rivaroxaban (15 mg qd) + P2Y12 inhibitor for 12 months (group 1)
  - Very-low-dose rivaroxaban (2.5 mg bid) + DAPT 12 months (group 2)
  - Standard therapy with warfarin + DAPT for 12 months (group 3)
- Primary safety outcome = clinically significant bleeding (composite of major and minor bleeding)
- Secondary efficacy endpoint = MACE (CVR death, MI, or stroke)

Gibson CM, et al. N Engl J Med 2016;375:2423-34.

PIONEER Trial



Incidence of Significant Bleeding



Major Adverse Cardiac Events

Gibson CM, et al. N Engl J Med 2016;375:2423-34.

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

PIONEER Trial

- 2124 pts with nonvalvular AF who had undergone PCI with stenting
- Randomly assigned to receive:
  - Low-dose rivaroxaban (15 mg qd) + P2Y12 inhibitor for 12 months (group 1)
  - Very-low-dose rivaroxaban (2.5 mg bid) + DAPT 12 months (group 2)
  - Standard therapy with warfarin + DAPT for 12 months (group 3)
- Primary safety outcome = clinically significant bleeding (composite of major and minor bleeding
- Secondary efficacy endpoint = MACE (CVR death, MI, or stroke)

Gibson CM, et al. N Engl J Med 2016;375:2423-34.

Two Other Trials Draw the Same Conclusion: Dual Beats Triple

- WOEST trial
  - Dual therapy of warfarin + clopidogrel vs. triple therapy (with aspirin)

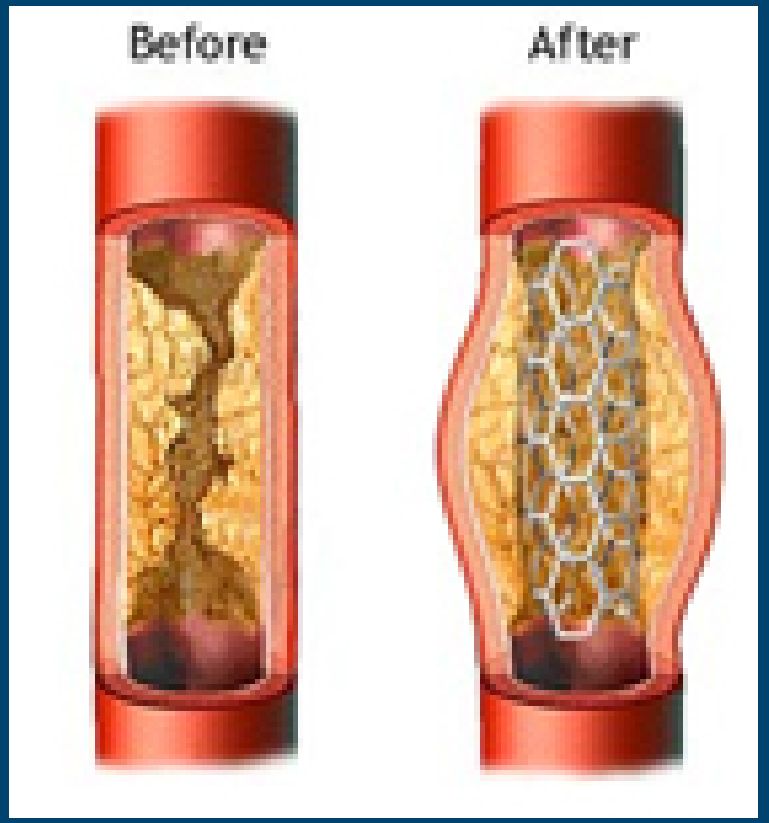
- RE-DUAL PCI trial
  - Dual therapy of dabigatran + P2Y12 inhibitor (clopidogrel or ticagrelor) vs. triple therapy (with aspirin)

The Lancet. 2013; 381(9872):1107-1115.
Cannon CP, et al. N Engl J Med 2017; 377:1513-1524

Is PCI the Holy Grail for Management of CAD?

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.

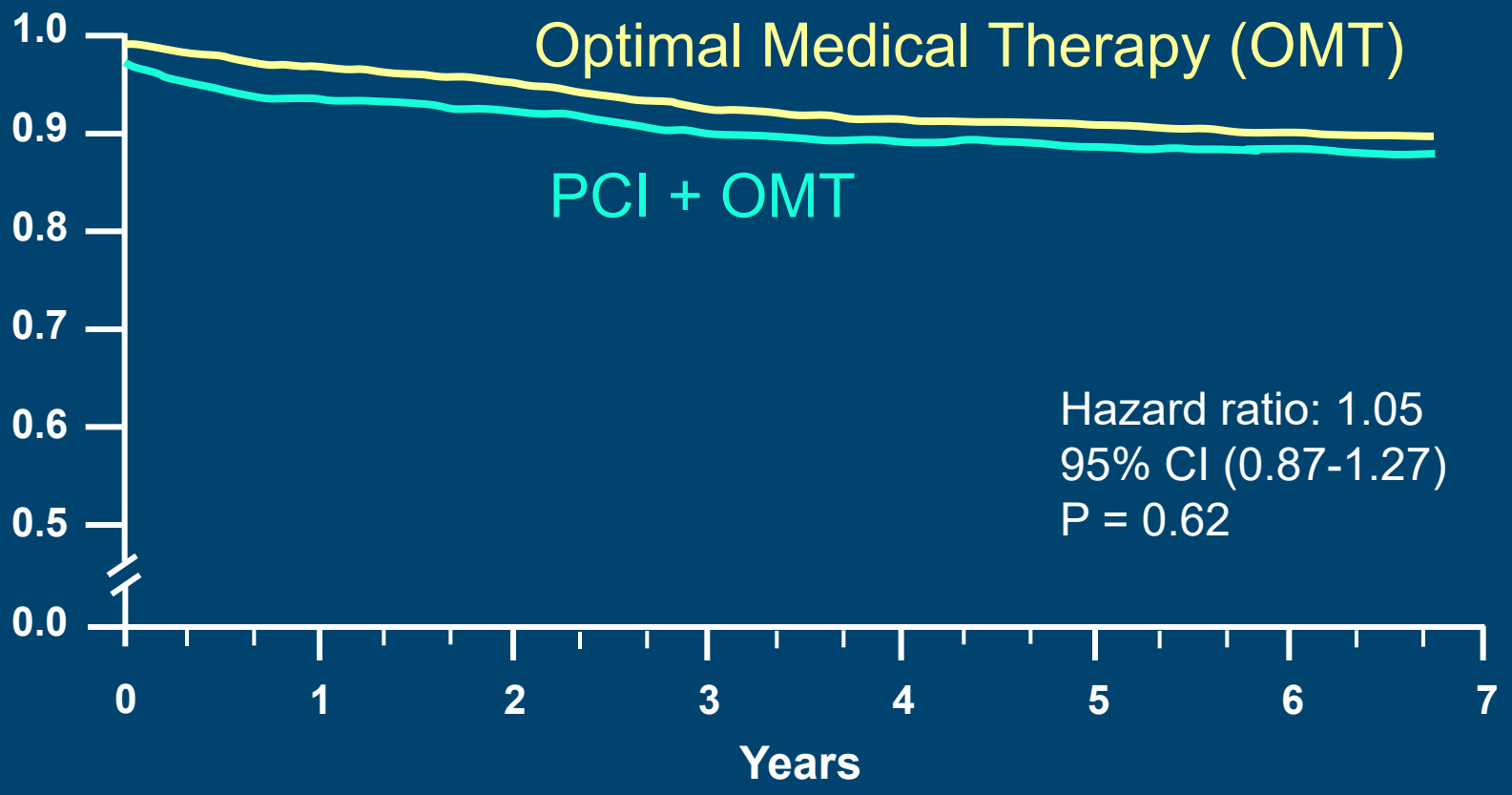


Routine stenting of significant coronary stenoses: The COURAGE Trial

- 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 med. therapy vs. optimal med. 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

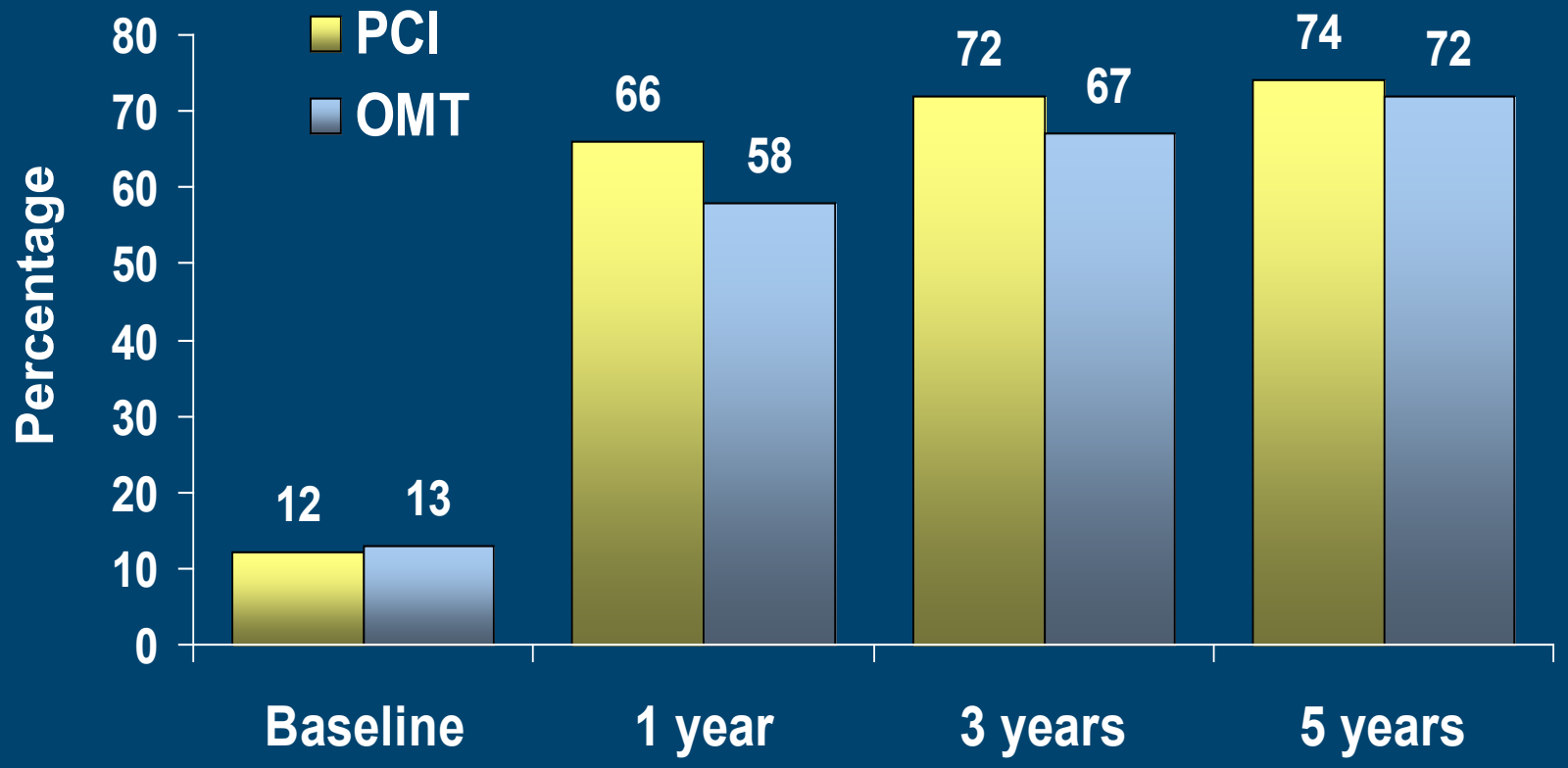
Survival Free from Death or Non-Fatal MI



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

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

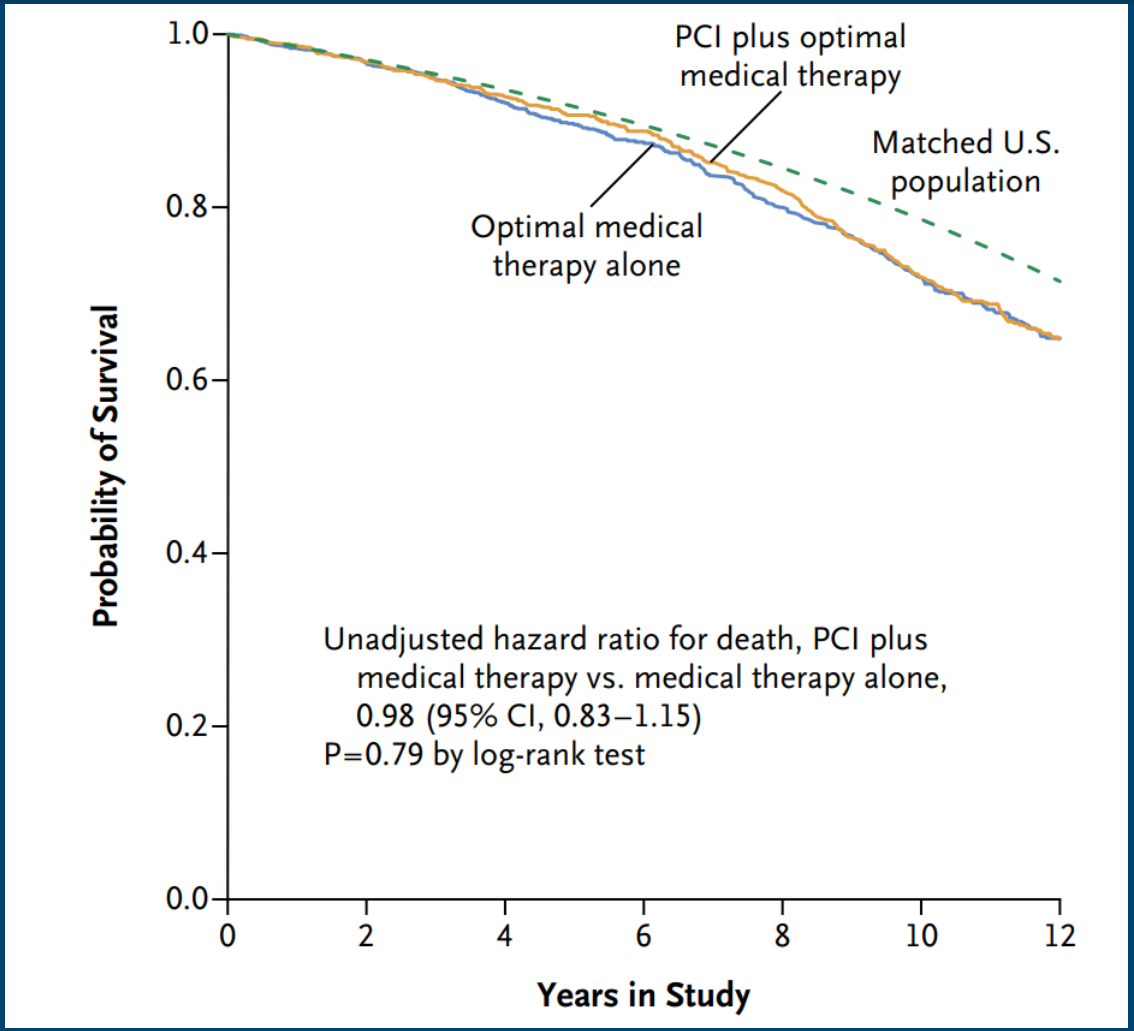
Freedom from Angina During Follow-up



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

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Courage: Extended follow-up to 12 years



Sedlis S, et al. N Eng J Med, 2015;373:1937-1946

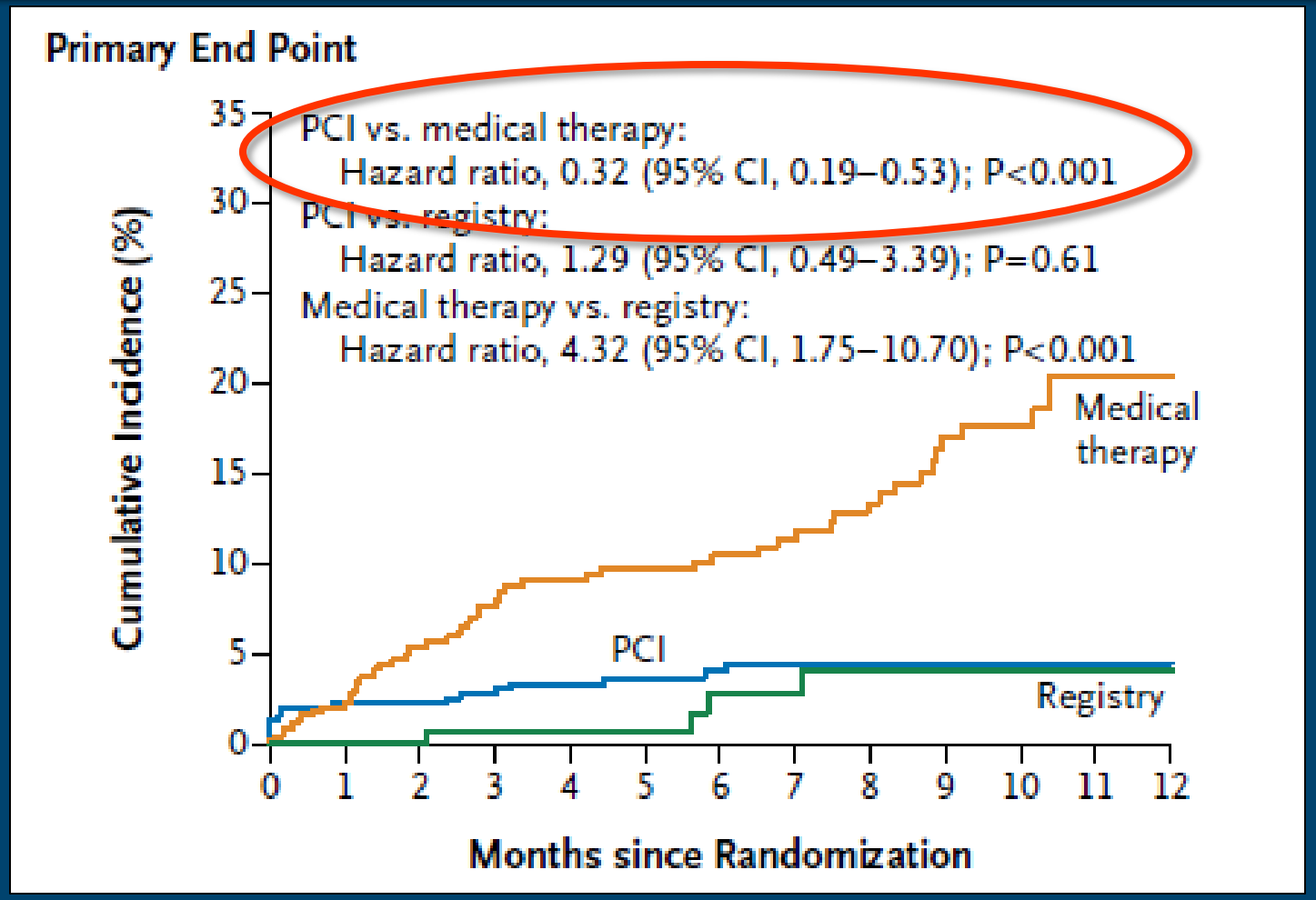
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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 pts with FFR > 0.80 (non stenotic) 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

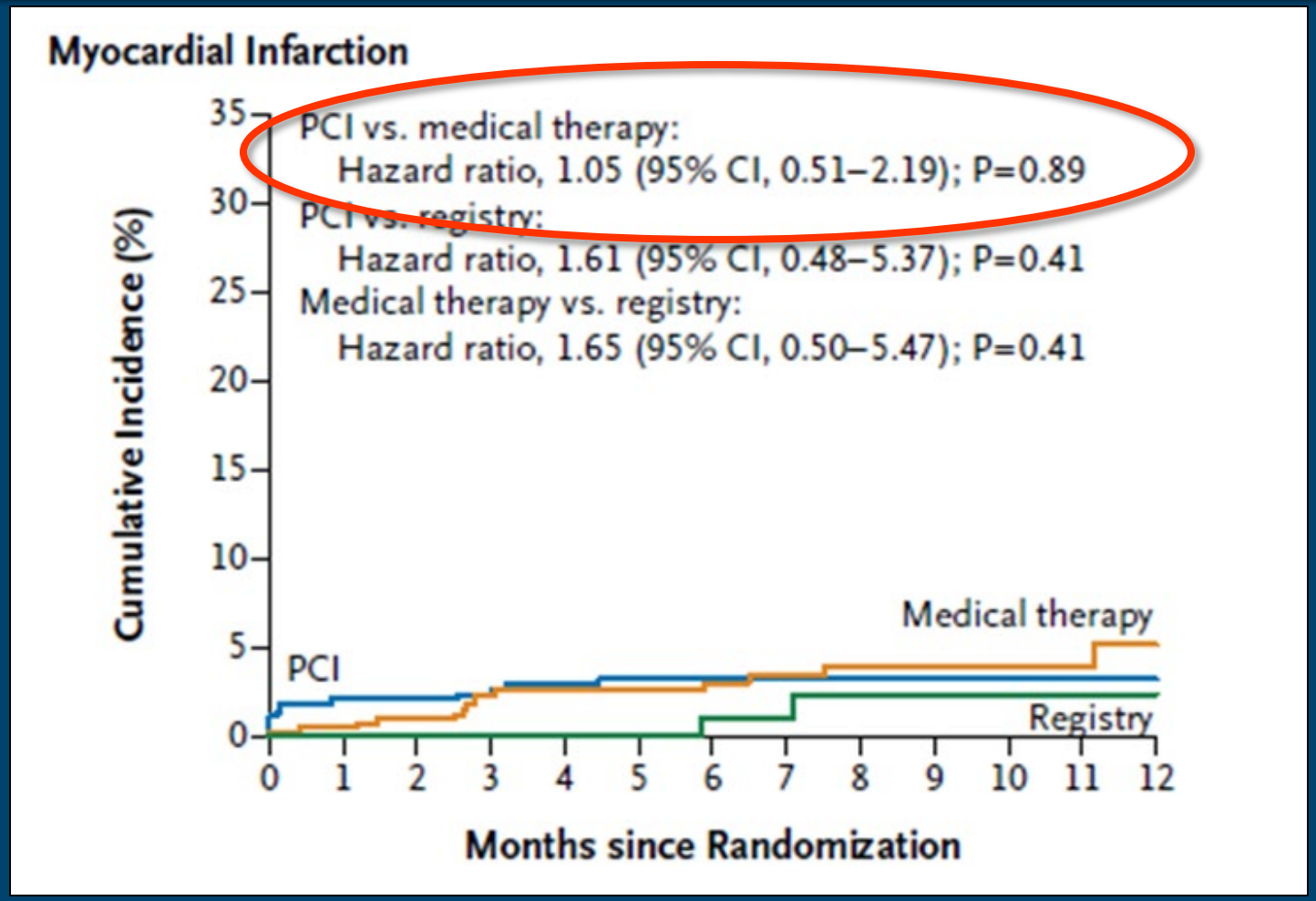
FAME 2: Incidence of Primary End Point of Death, MI, or Urgent Revascularization



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

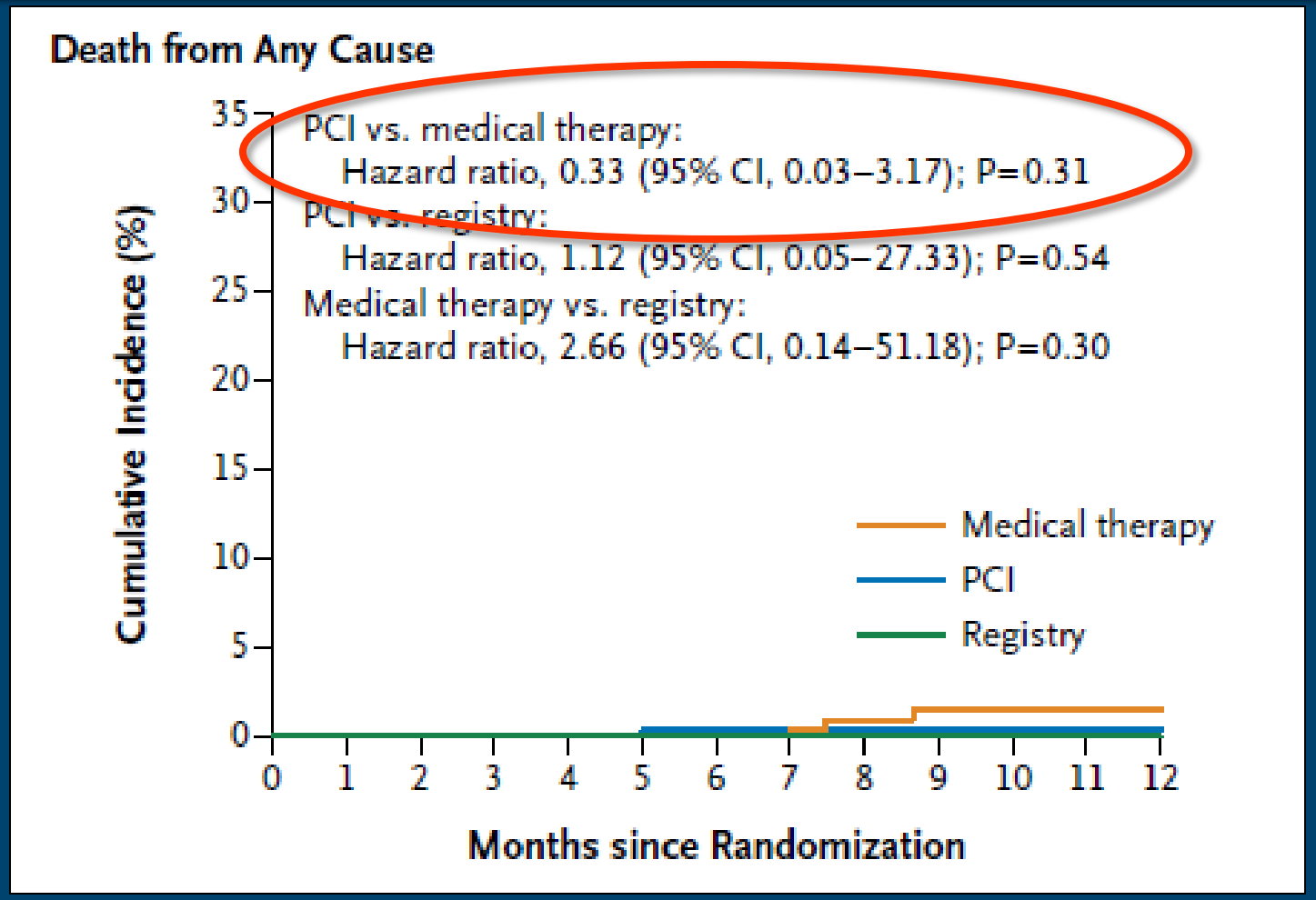
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

FAME-2: Incidence of MI



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

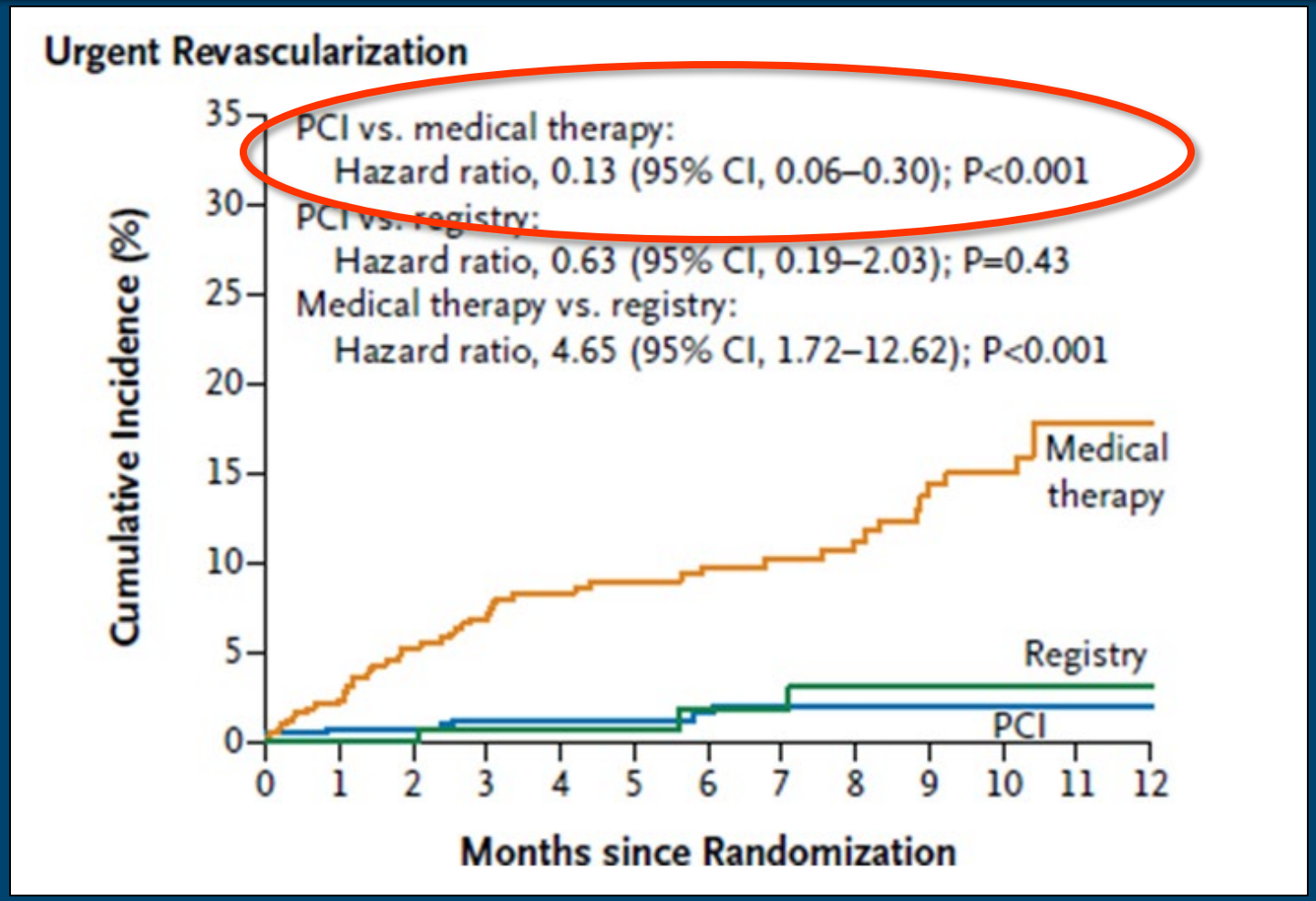
FAME-2: Incidence of All-Cause Mortality



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

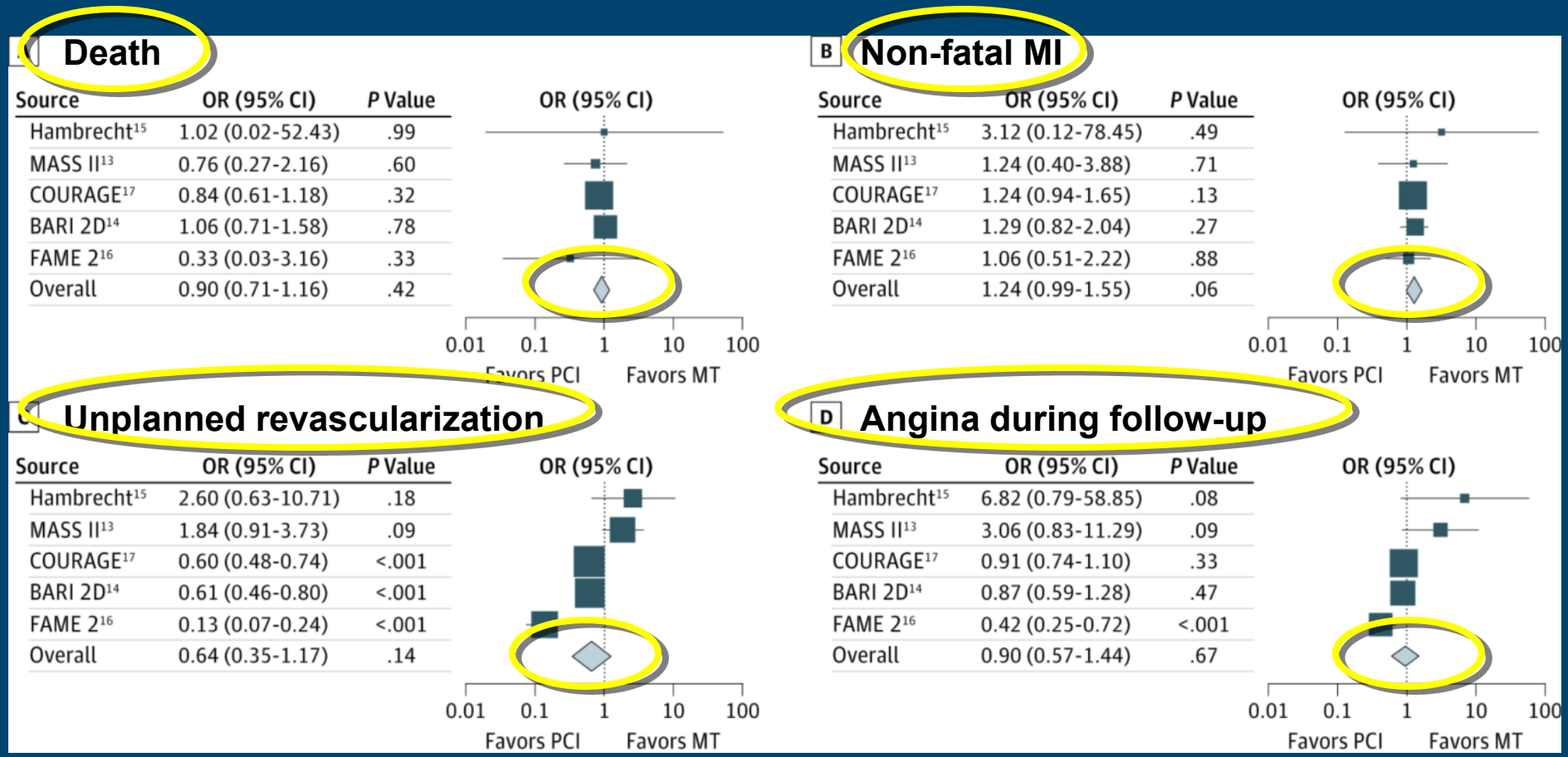
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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. 2014;174:232–240

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

ISCHEMIA Trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches)

- Presented at the AHA Scientific Sessions in 11/2019
- 5200 patients with stable CHD and moderate to severe ischemia
- Randomized to routine invasive therapy vs. OMT
  - In the routine invasive group, pts underwent coronary angiography and PCI or CABG as appropriate
- Mean duration of follow-up = 3.3 years
- ISCHEMIA failed to show that routine invasive therapy was associated with a reduction in major adverse ischemic events compared with OMT
- There was a modest reduction in anginal symptoms and antianginal medication use with PCI or CABG.

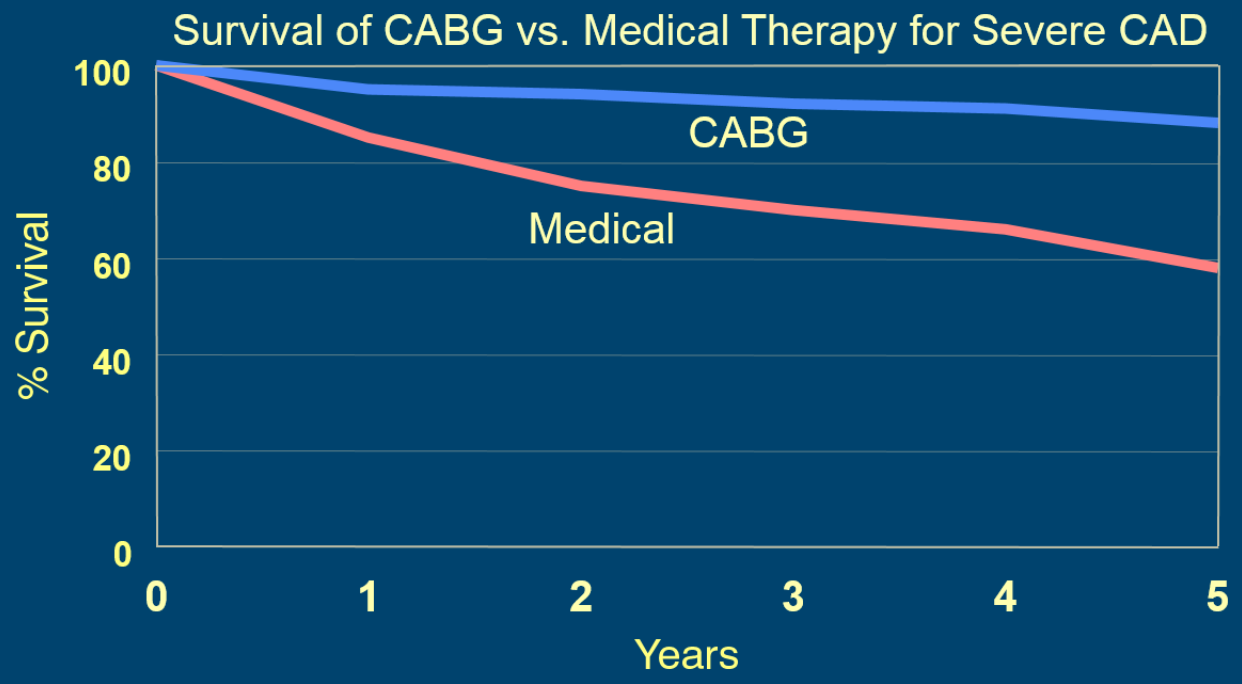
https://www.ischemiatrial.org/ischemia-study-results

Routine Coronary Intervention For Ischemia

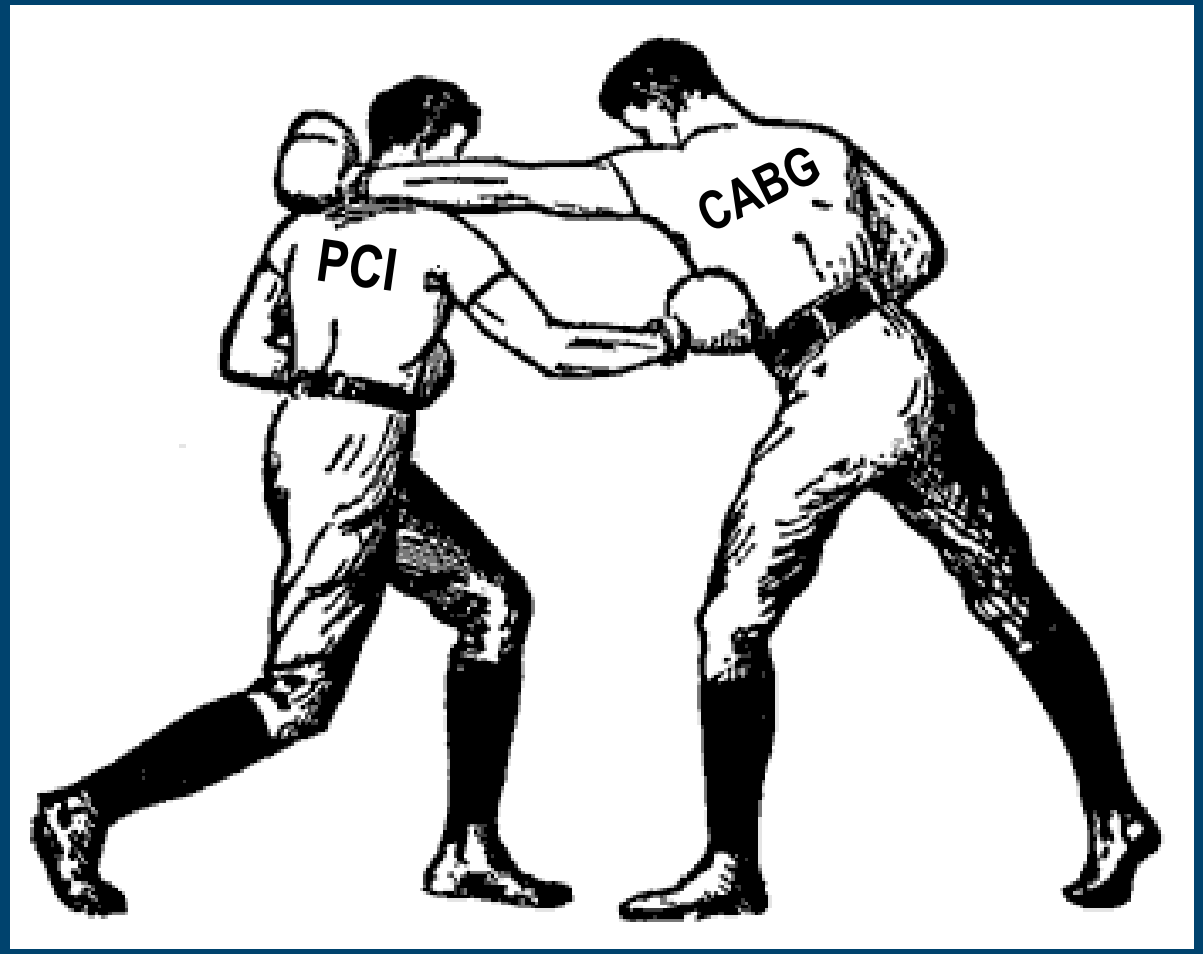
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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)
  - Particularly in those with severe symptoms, early positive exercise tests, and/or impaired LV function



How Does PCI Stack Up vs. CABG?



MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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

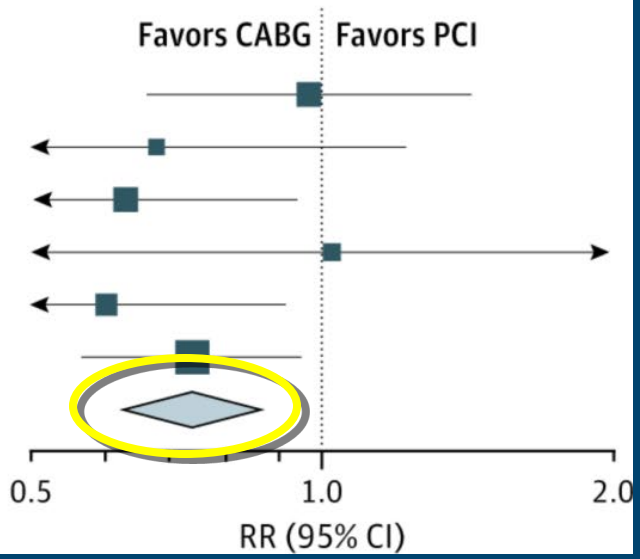
- 6 randomized trials
  - 6055 patients with multi-vessel CAD
  - Median follow-up 4.1 years
- Primary outcomes
  - Death
  - Myocardial infarction
  - Repeat revascularization
  - Stroke

Sipahi I, et al. JAMA Intern Med 2014;174:223-230

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

Mortality

Source	Statistics for Each Study RR (95% CI)	*Z* Value	*P* Value	Death/Total 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**



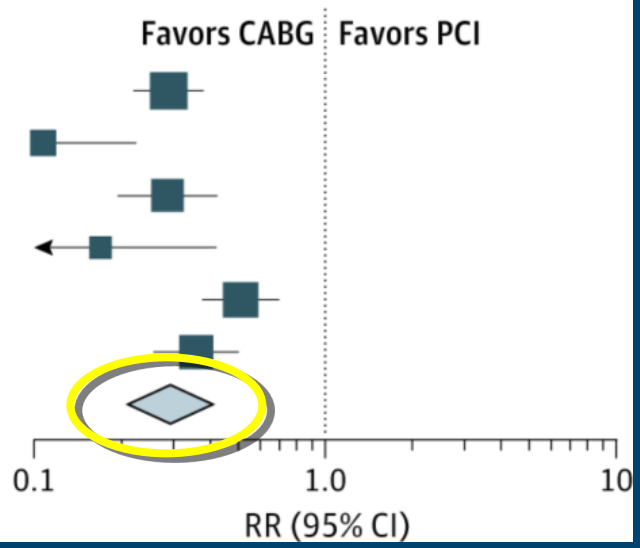
Sipahi I, et al. JAMA Intern Med 2014;174:223-230

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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**



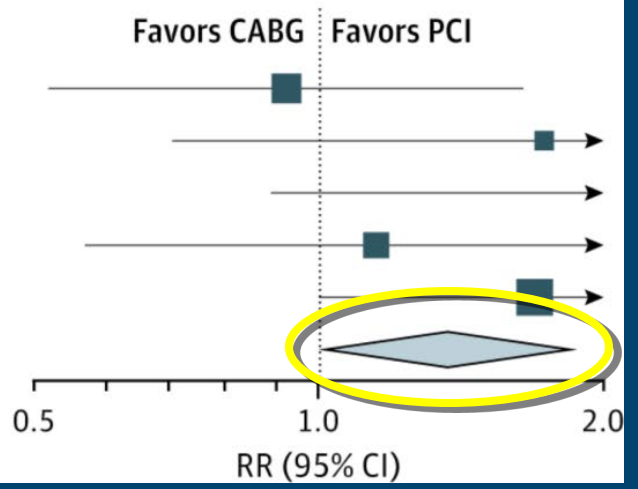
Sipahi I, et al. JAMA Intern Med 2014;174:223-230

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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

Stroke

Source	Statistics for Each Study				Stroke/Total	
	RR (95% CI)		*Z* Value	*P* Value	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**



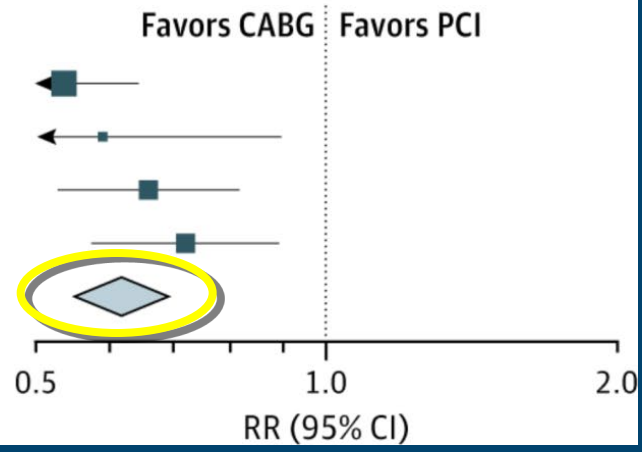
Sipahi I, et al. JAMA Intern Med 2014;174:223-230

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

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)**	**-8.56**	**<.001**	**375/2320**	**615/2339**



Sipahi I, et al. JAMA Intern Med 2014;174:223-230

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

THE GOOD NEWS: Hospital discharges for CHD in the United States from 2000-2014

AHA Heart Disease & Stroke Statistics:2019 Update
https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000659

THE BAD NEWS: Frequency of Use of Statins and Aspirin in Patients with Previous CABG

Curl K, et al. Am J Cardiol 2016;118:40-3

Coronary Heart Disease: Reflective Statement

- Key Points:
  - Aspirin, statins, ACEIs/ARBs, and exercise all reduce risk of MI and/or cardiac death in pts with CAD
  - Routine PCI in pts with stable angina or ischemia does not reduce risk of MI or cardiac death
- Next Best Steps:
  - Make sure your patients with CAD are on OMT, including aspirin + a mod. or high-dose statin
  - Prescribe aerobic exercise
  - Maintain DAPT ≥ 12 months in patients s/p drug-eluting stent.