for Stable CAD;
Only statin can improve the outcome.

Jang-Whan Bae MD, PhD
Chief, Chungbuk Regional Cardiovascular Center
Associate Professor, Division of Cardiology, Department of Internal Medicine,
Chungbuk National University Hospital, Cheongju, Republic of Korea

CHUNGBUK NATIONAL UNIVERSITY HOSPITAL

20181207-08 JCR2018, Busan

2013 ESC clinical guideline for stable CAD

- **Class I indication: Is this life-saving drug?**

Indication	Class[a]	Level[b]
General considerations		
Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.	I	C
It is recommended to educate patients about the disease, risk factors and treatment strategy.	I	C
It is indicated to review the patient's response soon after starting therapy.	I	C
Angina/ischaemia[d] relief		
Short-acting nitrates are recommended.	I	B
First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.	I	A
For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.	IIa	B
For second-line treatment, trimetazidine may be considered.	IIb	B
According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients.	I	C
In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered.	IIa	C
In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B

Eur Heart J 2013;34:2949-3003.

2013 ESC clinical guideline

- **Class 1 indication: Is this life-saving drug?**

Event prevention		
Low-dose aspirin daily is recommended in all SCAD patients.	I	A
Clopidogrel is indicated as an alternative in case of aspirin intolerance.	I	B
Statins are recommended in all SCAD patients.	I	A
It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes).	I	A

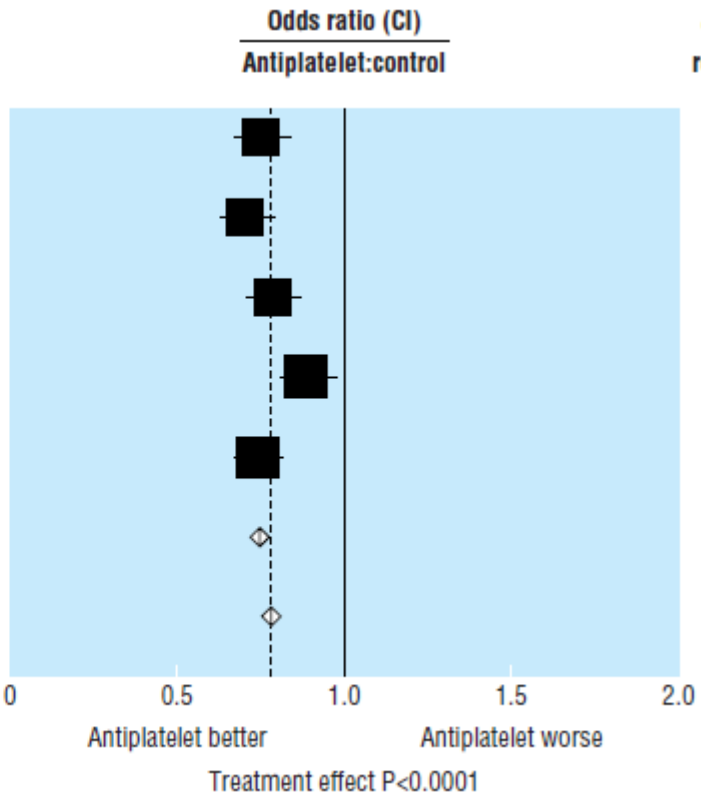
Eur Heart J 2013;34:2949-3003.

Is aspirin in stable angina verified well?

- **collaborative meta-analysis by ATT**
  - secondary prevention trials: 287 studies and 135,000 patients

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6	25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2	30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8	22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3	11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6	25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**	**22 (2)**

Heterogeneity of odds reductions between:
5 categories of trial: χ^2=21.4, df=4; P=0.0003
Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002



ATT collaboration. BMJ 2002;324:71-86.

Is aspirin in stable angina verified well?

- **collaborative meta-analysis by ATT**
  - secondary prevention trials: 287 studies and 135,000 patients

Table 1 Major changes in availability of data between previous and current meta-analyses

	No of patients		No of vascular events	
	Previous	Current	Previous	Current
Antiplatelet therapy *v* control:				
Previous stroke/transient ischaemic attack	10 255	18 270	2062	3530
Acute stroke	29	40 821	5	3528
Stable angina	551	2 920	69	352
Atrial fibrillation	1 792	2 770	195	466
Peripheral arterial disease	4 939	9 214	486	605
Diabetes	1 200	4 961	55	820
Particular regimens:				
Aspirin <75 mg *v* control	357	3 655	45	670
Aspirin <75 mg *v* aspirin ⩾75 mg	56	3 570	7	488
Clopidogrel *v* aspirin	0	19 185	0	2033
Aspirin + dipyridamole *v* aspirin	5 317	10 404	628	1262
Aspirin + glycoprotein IIb/IIIa antagonist *v* aspirin	0	24 802	0	2733

ATT collaboration. BMJ 2002;324:71-86.

Swedish Angina Pectoris Aspirin Trial (SAPAT)

- **Aspirin 75 mg vs Placebo in 2,035 stable angina**
  - 50 months follow-up
  - Primary event: MI and sudden death
    - HR: 0.66 (81 vs 124, 95% CI 24-49%, p=0.003)
    - mainly came from MI reduction, not by sudden death
- **ATTC meta-analysis for primary and secondary prevention**

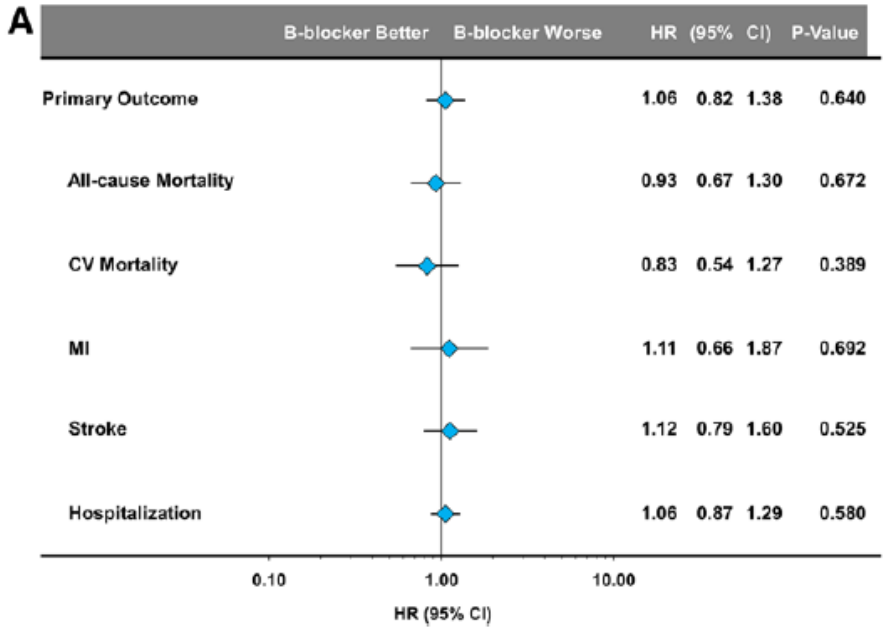
	Number of events (aspirin vs control)		Rate ratio (95% CI) (aspirin vs control)			Yearly absolute difference (% per year)	
	Primary prevention (660 000 person-years)	Secondary prevention (43 000 person-years)	Primary prevention	Secondary prevention	p value for heterogeneity	Primary prevention	Secondary prevention
Major coronary event	934 vs 1115	995 vs 1214	0·82 (0·75–0·90)	0·80 (0·73–0·88)	0·7	−0·06	−1·00*
Non-fatal MI	596 vs 756	357 vs 505	0·77 (0·69–0·86)	0·69 (0·60–0·80)	0·5	−0·05	−0·66
CHD mortality	372 vs 393	614 vs 696	0·95 (0·82–1·10)	0·87 (0·78–0·98)	0·4	−0·01	−0·34
Stroke	655 vs 682	480 vs 580	0·95 (0·85–1·06)	0·81 (0·71–0·92)	0·1	−0·01	−0·46*
Haemorrhagic	116 vs 89	36 vs 19	1·32 (1·00–1·75)	1·67 (0·97–2·90)	0·4	0·01	..†
Ischaemic	317 vs 367	140 vs 176	0·86 (0·74–1·00)	0·78 (0·61–0·99)	0·5	−0·02	..†
Unknown cause	222 vs 226	304 vs 385	0·97 (0·80–1·18)	0·77 (0·66–0·91)	0·1	−0·001	..†
Vascular death	619 vs 637	825 vs 896	0·97 (0·87–1·09)	0·91 (0·82–1·00)	0·4	−0·01	−0·29
Any serious vascular event	1671 vs 1883 (0·51% vs 0·57% per year)	1505 vs 1801 (6·69% vs 8·19% per year)	0·88 (0·82–0·94)	0·81 (0·75–0·87)	0·1	−0·07	−1·49*
Major extracranial bleed	335 vs 219	23 vs 6	1·54 (1·30–1·82)	2·69 (1·25–5·76)	0·2	0·03	..†

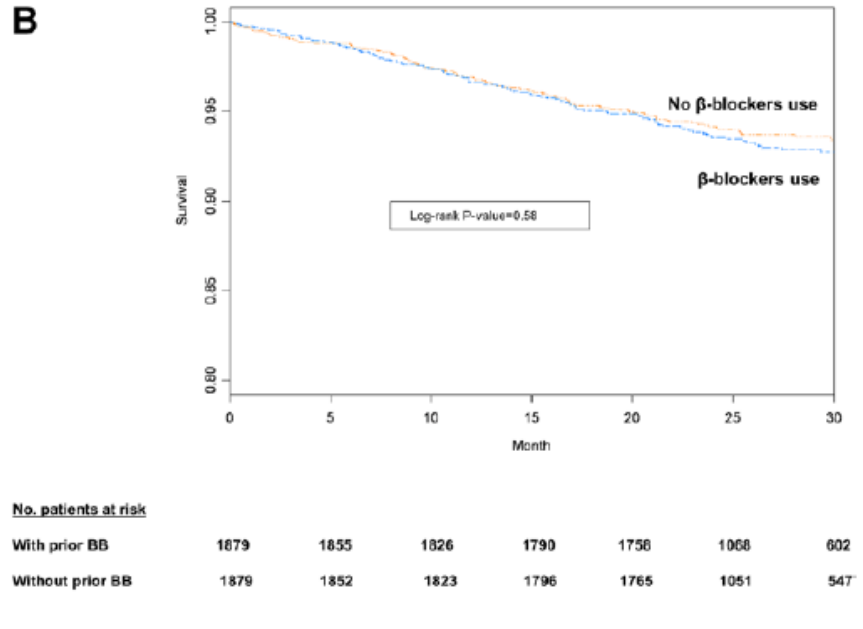
Juul-Moller S. Lancet 1992;340:1421-5. ATT Collaboration Lancet 2009;373:1849-60.

Is beta blocker effective in CAD cohort?

- **post hoc analysis with CHARISMA trial (n=7,804)**
  - Beta blocker did not reduce MACE, but ischemic episodes.
  - analysis in 3 groups: prior MI, established CAD, risk population

Aspirin effect in established CAD population from the CHARISMA

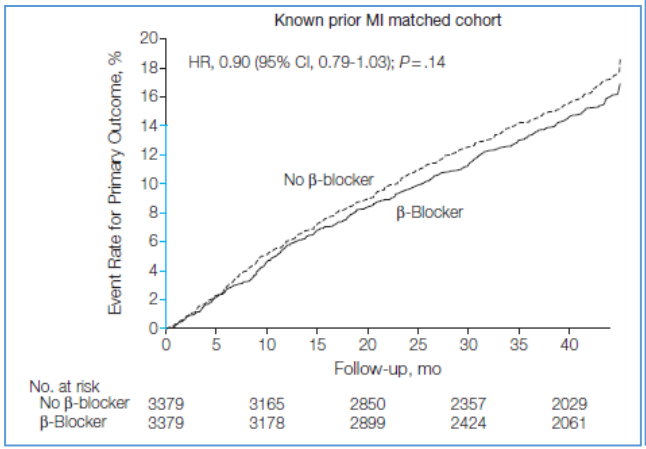


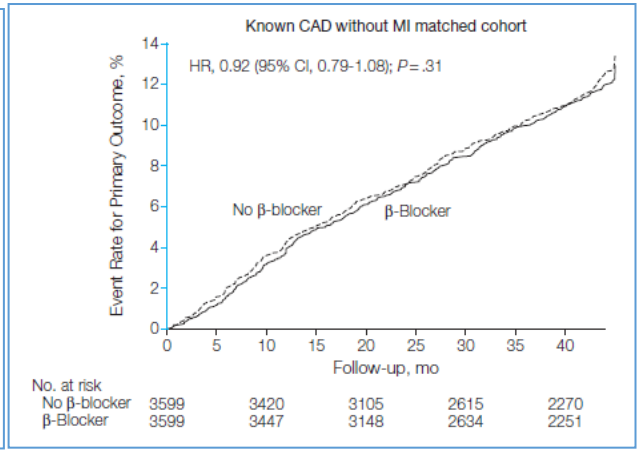


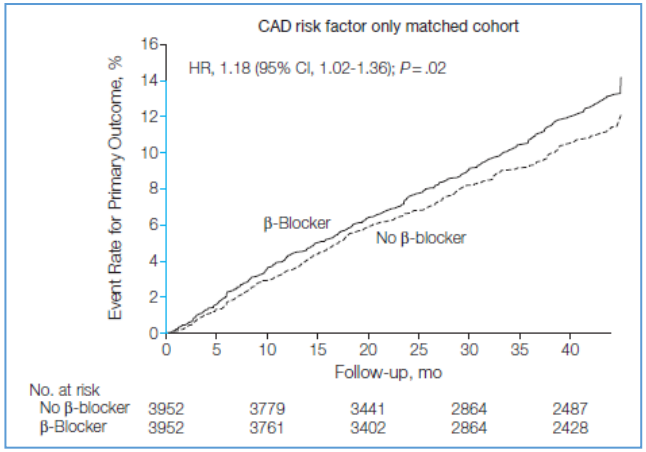
Bangalore S. Circ Cardiovasc Qual Outcomes 2014;7:872-81.

Impact of beta blocker use for CAD

- **REACH registry**
  - 3 groups: CAD with prior MI, CAD without prior MI, risk factor only
    - Primary outcome: CV death, MI, stroke
    - Secondary outcome: PO, atherothrombotic admission, revascularization



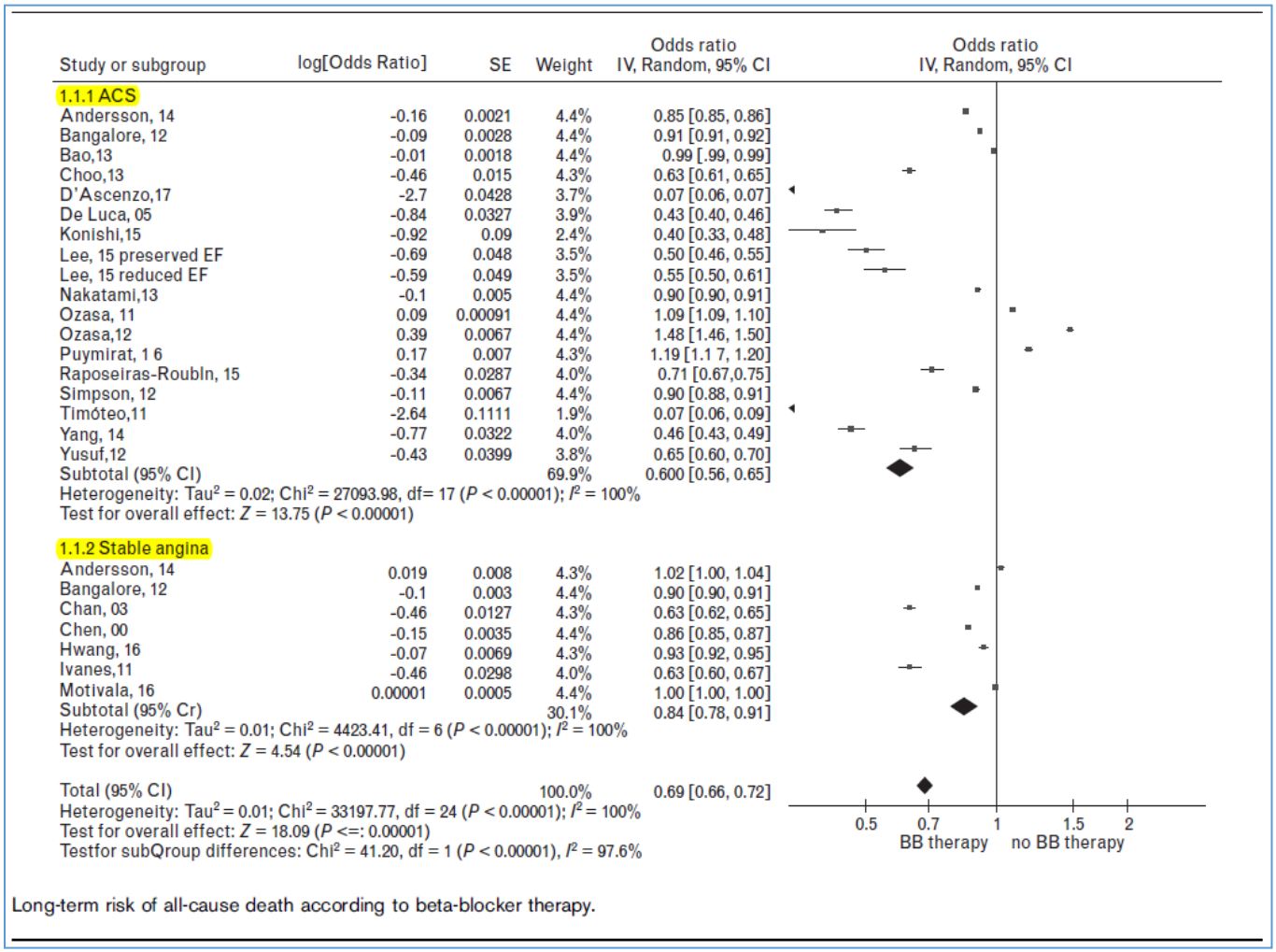




Bangalore S. JAMA 2012;308:1340-9.

Impact of beta blocker use for CAD

- **beta blocker reduced mortality in PCI performed patients**



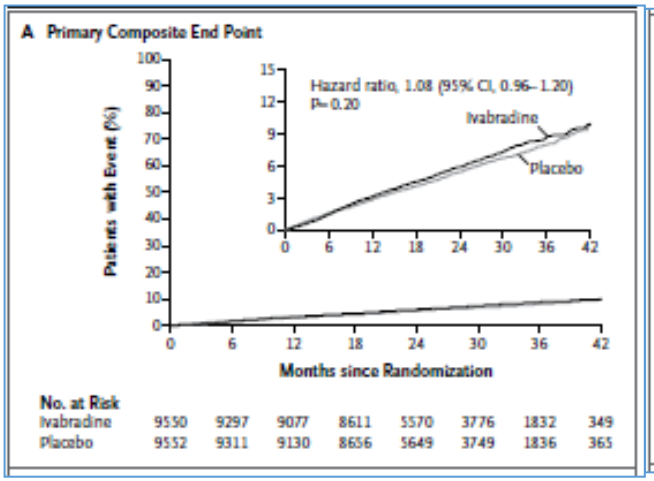
Study or subgroup	log[Odds Ratio]	SE	Weight	Odds ratio IV, Random, 95% CI
1.1.1 ACS				
Andersson, 14	-0.16	0.0021	4.4%	0.85 [0.85, 0.86]
Bangalore, 12	-0.09	0.0028	4.4%	0.91 [0.91, 0.92]
Bao,13	-0.01	0.0018	4.4%	0.99 [.99, 0.99]
Choo,13	-0.46	0.015	4.3%	0.63 [0.61, 0.65]
D'Ascenzo,17	-2.7	0.0428	3.7%	0.07 [0.06, 0.07]
De Luca, 05	-0.84	0.0327	3.9%	0.43 [0.40, 0.46]
Konishi,15	-0.92	0.09	2.4%	0.40 [0.33, 0.48]
Lee, 15 preserved EF	-0.69	0.048	3.5%	0.50 [0.46, 0.55]
Lee, 15 reduced EF	-0.59	0.049	3.5%	0.55 [0.50, 0.61]
Nakatami,13	-0.1	0.005	4.4%	0.90 [0.90, 0.91]
Ozasa, 11	0.09	0.00091	4.4%	1.09 [1.09, 1.10]
Ozasa,12	0.39	0.0067	4.4%	1.48 [1.46, 1.50]
Puymirat, 1 6	0.17	0.007	4.3%	1.19 [1.1 7, 1.20]
Raposeiras-Roubln, 15	-0.34	0.0287	4.0%	0.71 [0.67,0.75]
Simpson, 12	-0.11	0.0067	4.4%	0.90 [0.88, 0.91]
Timóteo,11	-2.64	0.1111	1.9%	0.07 [0.06, 0.09]
Yang, 14	-0.77	0.0322	4.0%	0.46 [0.43, 0.49]
Yusuf,12	-0.43	0.0399	3.8%	0.65 [0.60, 0.70]
Subtotal (95% CI)			69.9%	0.600 [0.56, 0.65]
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 27093.98$, df= 17 ($P < 0.00001$); $I^2 = 100\%$				
Test for overall effect: $Z = 13.75$ ($P < 0.00001$)				
1.1.2 Stable angina				
Andersson, 14	0.019	0.008	4.3%	1.02 [1.00, 1.04]
Bangalore, 12	-0.1	0.003	4.4%	0.90 [0.90, 0.91]
Chan, 03	-0.46	0.0127	4.3%	0.63 [0.62, 0.65]
Chen, 00	-0.15	0.0035	4.4%	0.86 [0.85, 0.87]
Hwang, 16	-0.07	0.0069	4.3%	0.93 [0.92, 0.95]
Ivanes,11	-0.46	0.0298	4.0%	0.63 [0.60, 0.67]
Motivala, 16	0.00001	0.0005	4.4%	1.00 [1.00, 1.00]
Subtotal (95% Cr)			30.1%	0.84 [0.78, 0.91]
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4423.41$, df = 6 ($P < 0.00001$); $I^2 = 100\%$				
Test for overall effect: $Z = 4.54$ ($P < 0.00001$)				
Total (95% CI)			100.0%	0.69 [0.66, 0.72]
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 33197.77$, df = 24 ($P < 0.00001$); $I^2 = 100\%$				
Test for overall effect: $Z = 18.09$ (P <=: 0.00001)				
Testfor subQroup differences: $Chi^2 = 41.20$, df = 1 ($P < 0.00001$), $I^2 = 97.6\%$				

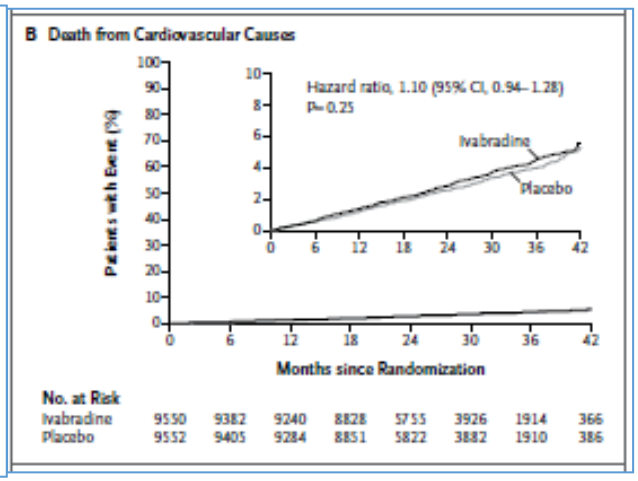
Long-term risk of all-cause death according to beta-blocker therapy.

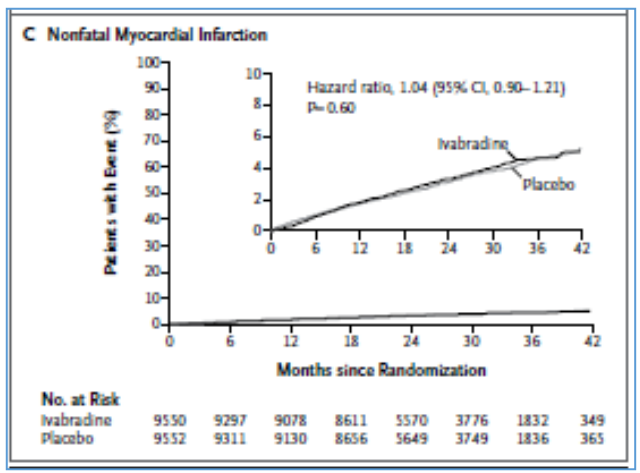
Peyracchia M. J Cardiovasc Med 2018;19:337-43.

SIGNIFY

- **Did Ivabradine reduce MACE in sCAD patients without HF?**
  - CCS 1-4 sCAD patient with > 70 BPM (n=19,012)







Fox Kim. N Engl J Med 2014;371:1091-9.

Historic trials for ischemic heart disease

- **50 years of CABG, 40 years of PCI, and 11 years of OMT**
  - Rene Favaloro, Andreas Gruentzig, William Boden

Table Major Trials of Revascularization for Stable Ischemic Heart Disease

Trial Type	Name	N	References	Year First Reported
CABG vs Medical Therapy	VA Cooperative	596	15,16,20	1977
	CASS	780	17,19,22	1983
	European Coronary Surgery	768	18	1982
	STICH	1212	23, 24	2011
CABG vs PTCA	EAST	392	25	1994
	BARI	1829	26, 32	1996
	GABI	359	27	1994
	RITA I	1011	28	1993
	CABRI	1054	29	1995
	ERACI	127	30	1996
PTCA vs Medical Therapy	ACME	107	33	1 992
	RITA II	1018	34	1997
CABG vs PCI, BMS	ARTS	1205	36	2001
	SoS	988	37	2002
PCI vs Medical Therapy	COURAGE	2287	3, 38, 39	2007
	BARI 2D	2368	40, 41	2009
	FAME-2	888	42, 43	2012
	ORBITA	200	45	2017
CABG vs PCI, DES	SYNTAX	1800	48, 49, 50	2009
	FREEDOM	1900	51	2012
	EXCEL	1905	52	2016
	NOBLE	1201	53	2016

Weintraub WS. Am J Med 2018;131:1285-92.

CABG

- **robust extension of CABG, but we need data …**
  - Eugene Braunwald

The New England Journal of Medicine

Official Organ of
The Massachusetts Medical Society

CORONARY-ARTERY SURGERY AT THE CROSSROADS

THE surgical treatment of coronary-artery disease began early in this century when surgical sympathectomy was reported as a successful treatment for angina pectoris. Since then a variety of procedures have been tried, all of which were greeted with initial enthusiasm, which then rapidly waned. However, aortocoronary-artery bypass graft (CABG) is qualitatively superior to the earlier operations because it is associated with marked and sustained relief of angina pectoris in most patients. Since the delivery of substantial quantities of blood to previously ischemic myocardium can be accomplished with relatively low mortality by a skilled, experienced surgical team, the indications for this procedure are now being extended from patients with incapacitating angina pectoris, in whom it was first applied, to those with unstable angina pectoris, healed myocardial infarction with and without angina pectoris, and to some patients with coronary-artery disease without a history of infarction who have minimal or even no angina.

Braunwald E. N Engl J Med 1977;297:661-3.

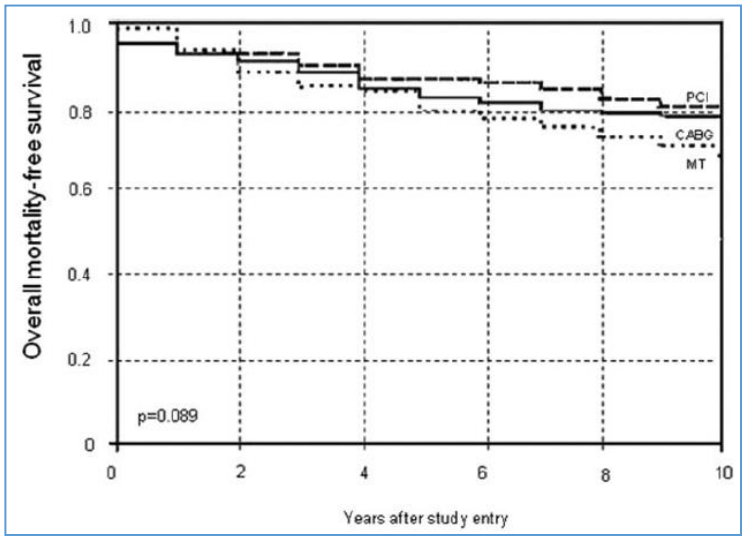
MASS II

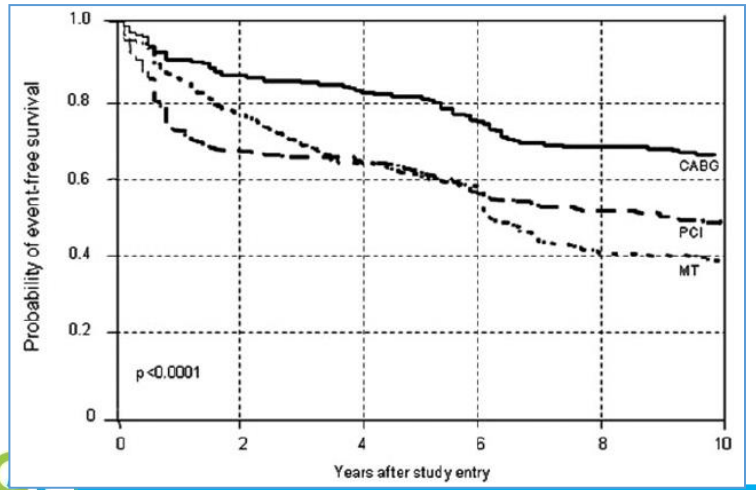
- **Medicine, angioplasty, or surgery study**
  - MVD, sCAD, and preserved LV systolic function, 10 years follow-up
  - POBA era

Table 2. Major Adverse Cardiac Events at 10-Year Follow-Up

	PCI	MT	CABG	*P* (Log-Rank)
Primary end points	42.4	59.1	33.0	<0.001
Overall mortality	24.1	31.0	25.1	0.089
Cardiac death	14.3	20.7	10.8	0.019
Additional intervention	41.9	39.4	7.4	0.001
AMI	13.3	20.7	10.3	0.010
CVA	5.4	6.9	8.4	0.550

AMI indicates acute MI; CVA, cerebrovascular accident.
Values are percentages.





Hueb W. Circulation 2010;122:949-57.

MASS II

- **Medicine, angioplasty, or surgery study**
  - MVD, sCAD, and preserved LV systolic function, 10 years follow-up

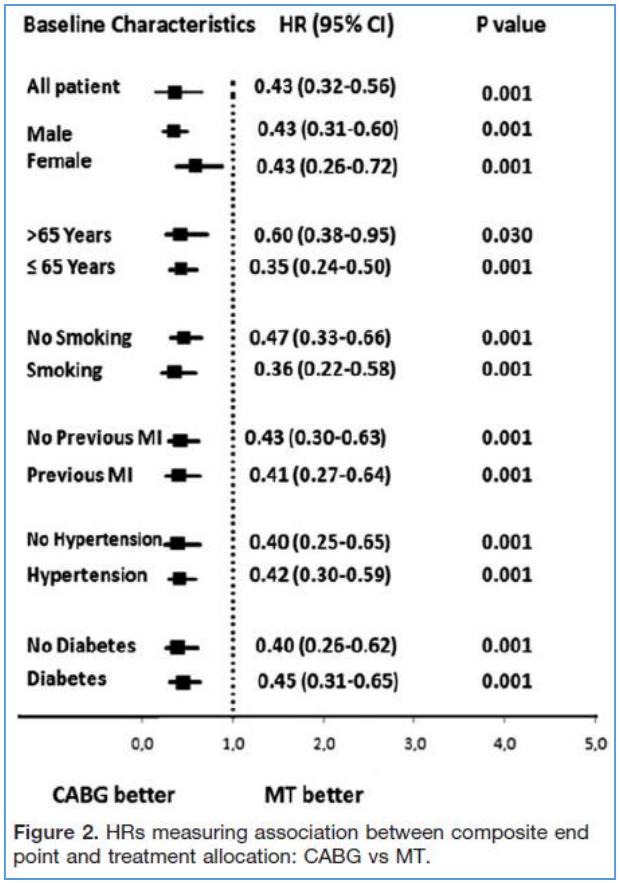


Figure 2. HRs measuring association between composite end point and treatment allocation: CABG vs MT.

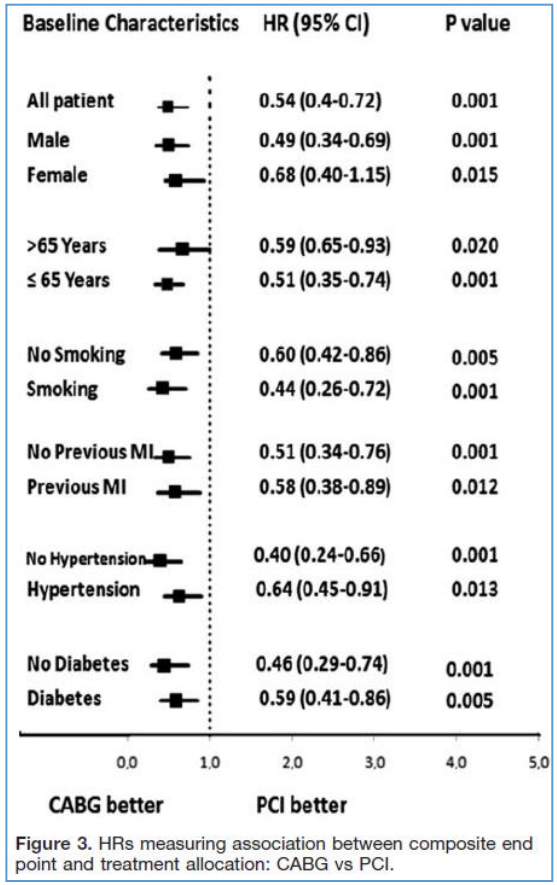


Figure 3. HRs measuring association between composite end point and treatment allocation: CABG vs PCI.

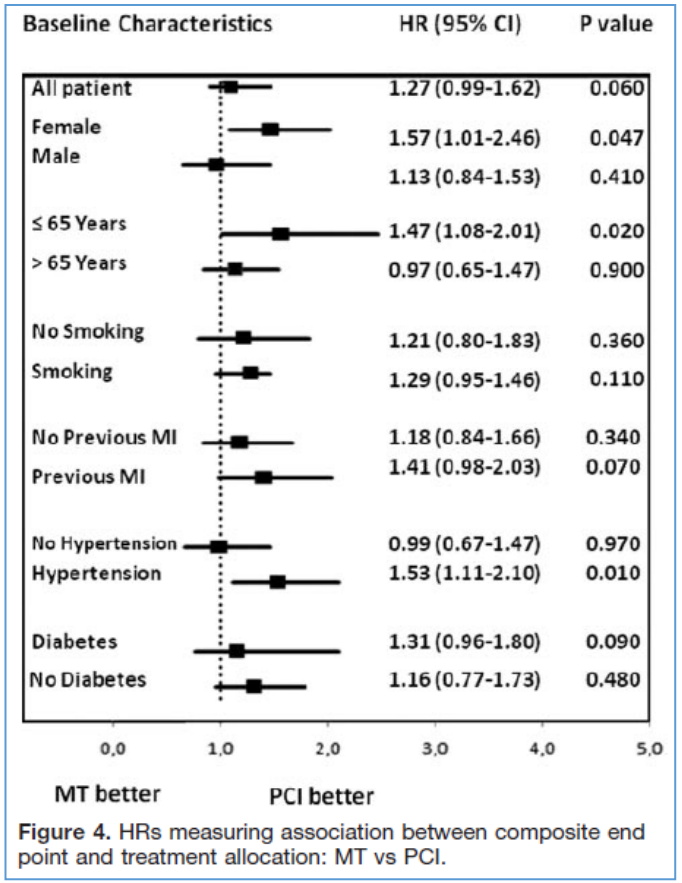
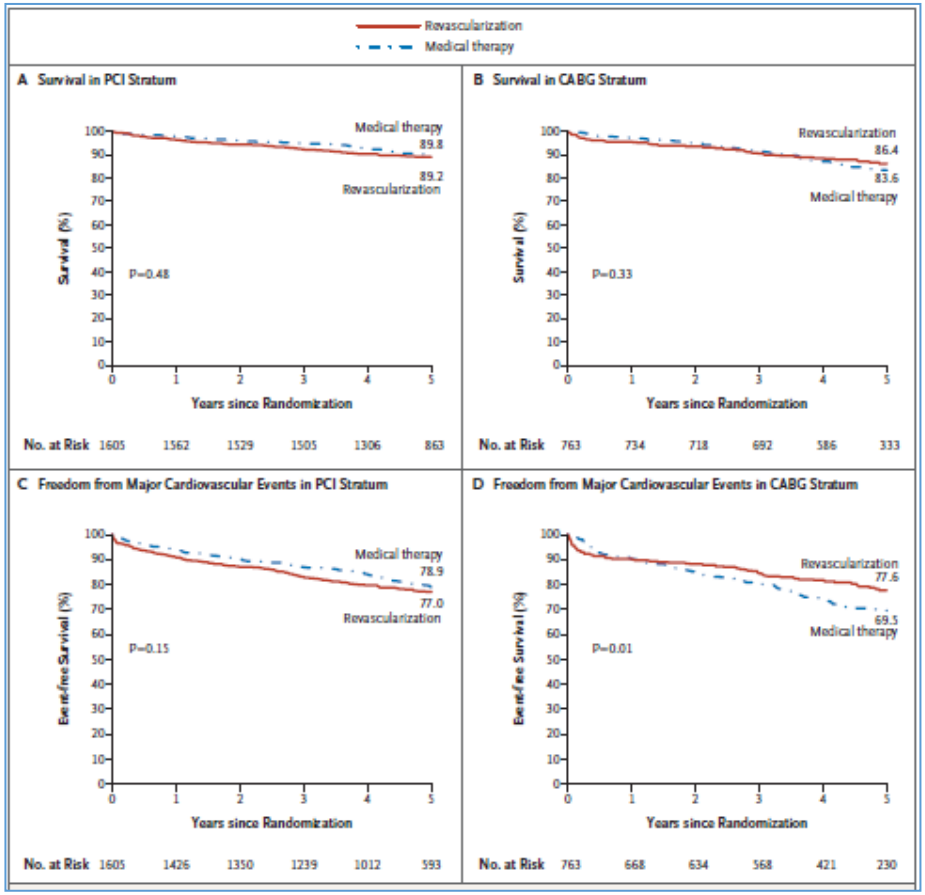


Figure 4. HRs measuring association between composite end point and treatment allocation: MT vs PCI.

Hueb W. Circulation 2010;122:949-57.

BARI 2D

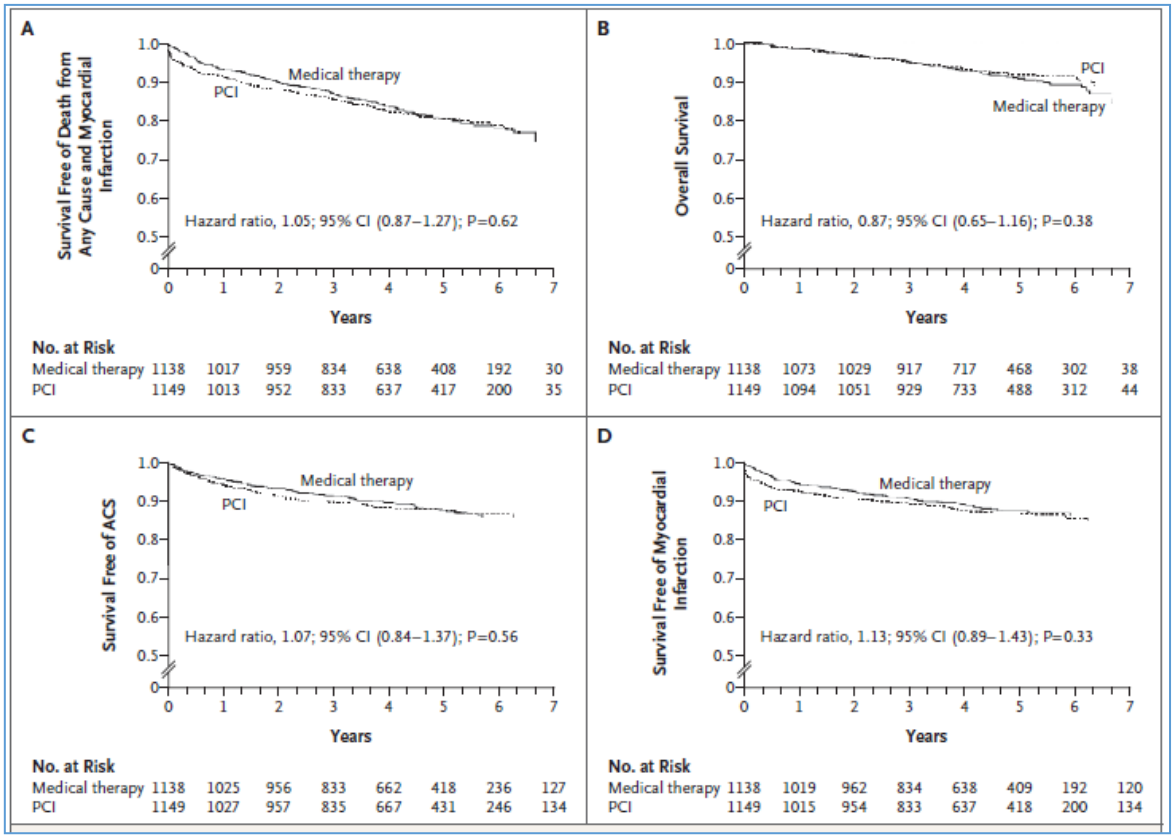
- **Medical therapy vs Revascularization with PCI or CABG**
  - 2368 T2DM and sCAD
  - CABG stratum (n=763), PCI stratum (n=1605)



BARI 2D Study Group. N Engl J Med 2009;360:2503-15.

COURAGE

- **Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation**
  - 2287 sCAD patients, PCI plus OMT vs OMT
  - Primary outcome: any cause of death, MFMI for 4.6 years



Weintraub WS. N Engl J Med 2007;356:1503-16.

NORSTENT

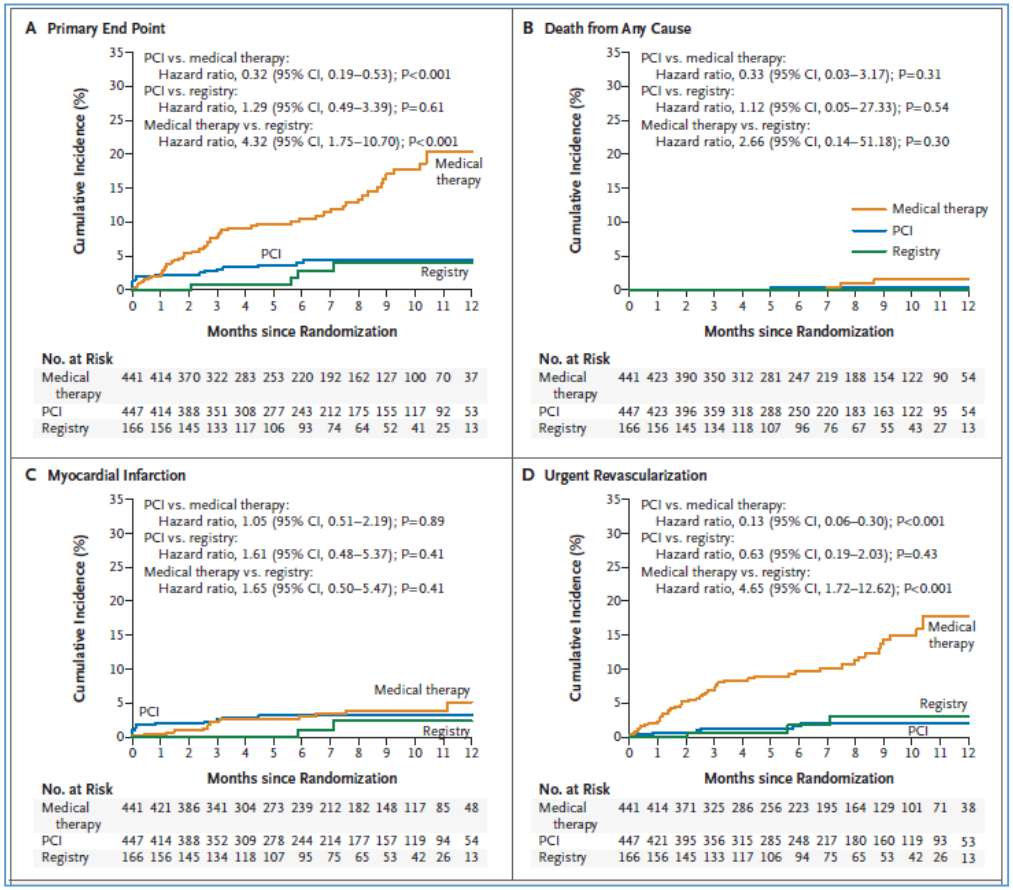
- **contemporary DES vs BMS in ACS and sCAD**
  - 9013 patients (SA:UA:NSTEMI:STEMI = 29:13:31:26%), 6 years follow-up
  - Everolimus, Zotarolimus stent – major DES

	DES (n=4504)	BMS (n=4509)	HR (95% CI)	P Value
Primary outcome	643 (16.6)	656 (17.1)	0.98 (0.88-1.09)	0.66
any cause of death	356 (9.8)	399 (10.5)	0.89 (0.77-1.02)	0.10
NFMI	287 (7.5)	257 (7.4)	1.11 (0.94-1.32)	0.21
Any revascularization	630 (16.5)	799 (19.8)	0.76 (0.69-0.85)	<0.001
Target lesion	205 (5.3)	421 (10.3)	0.47 (0.40-0.56)	<0.001
with PCI	178 (4.6)	360 (8.9)	0.48 (0.40-0.58)	<0.001
with CABG	77 (2.0)	116 (2.8)	0.66 (0.50-0.88)	0.005
Any PCI	567 (14.9)	709 (17.7)	0.78 (0.70-0.87)	<0.001
Definite ST	32 (0.8)	50 (1.2)	0.64 (0.41-1.00)	0.0498

Weintraub WS. N Engl J Med 2008;359:677-87.

FAME 2 trial for all comer

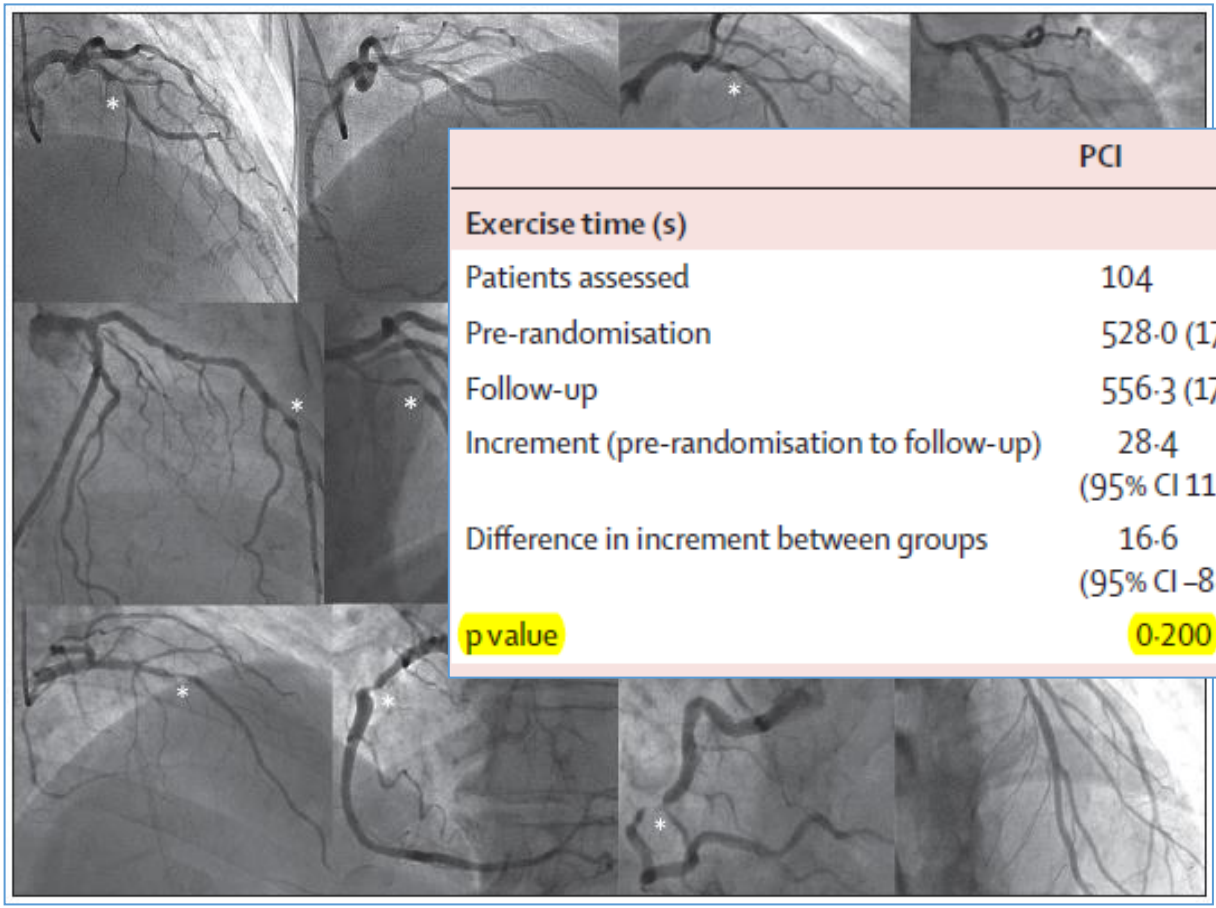
- **PCI with FFR vs OMT for sCAD**
  - 1200 sCAD patients with FFR < 0.8
  - EP: death from any cause, MI, urgent revascularization



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

ORBITA

- **PCI vs no-PCI on OMT in 1 VD and stable angina**
  - PEP: increment of exercise time
  - > 70% DS (86%), < 0.7 FFR



	PCI	Placebo
Exercise time (s)		
Patients assessed	104	90
Pre-randomisation	528·0 (178·7)	490·0 (195·0)
Follow-up	556·3 (178·7)	501·8 (190·9)
Increment (pre-randomisation to follow-up)	28·4 (95% CI 11·6 to 45·1)	11·8 (95% CI −7·8 to 31·3)
Difference in increment between groups	16·6 (95% CI −8·9 to 42·0)	..
p value	0·200	..

Al-Lamee R. Lancet 2018;391:31-40.

Critical meta-analysis with OMT vs PCI for sCAD

- **Meta-analysis with 5 trials**

Table 2. Characteristics of Patients With Documented Ischemia[a]

	MASS II[13]		Hambrecht[15]		COURAGE[17]		BARI 2D[14]		FAME 2[16]	
Characteristic	MT+PCI	MT	MT+PCI	MT	MT+PCI	MT	MT+PCI	MT	MT+PCI	MT
Participants, No.	68	97	50	51	968	970	483	489	447	441
Age, mean, y	59	59	61	62	62	62	62	62	64	64
Male	62	79	100	100	86	85	73	73	80	77
Diabetes	22	31	22	24	33	35	100	100	28	27
Prior MI	38	33	40	51	35	40	26	25	37	37
Ejection fraction, mean	69	68	62	64	61	61	57	57	NR	NR
Vessels with stenosis >50%, mean No.	2.35	3.37	1.52	1.6	1.98	2.0	1.55	1.63	1.87	1.73
Stent placed	66	NA	100	NA	94	NA	90	NA	97	NA
Drug-eluting stent	0	NA	0	NA	3	NA	37	NA	95	NA
Medications										
Aspirin	100	97	98	98	93	93	97	95	87	90
β-Blocker	85	85	86	88	83	83	92	91	76	78
ACEI or ARB	28	28	88	75	74	73	94	94	69	70
Statin	74	59	80	71	89	90	96	96	83	82

			Heterogeneity	
Outcome	Odds Ratio (95% CI)	*P* Value	*Q* (I^2)	*P* Value
Death	0.90 (0.71-1.16)	.42	1.6 (0)	.80
Nonfatal MI	1.24 (0.99-1.56)	.06	0.52 (0)	.97
Unplanned revascularization	0.64 (0.35-1.17)	.14	39.2 (90)	<.001
Angina	0.91 (0.57-1.44)	.67	14.2 (72)	.007

Stergiopoulos K. JAMA Intern Med. 2014;174:232-40.

Anyway, what is sCAD?

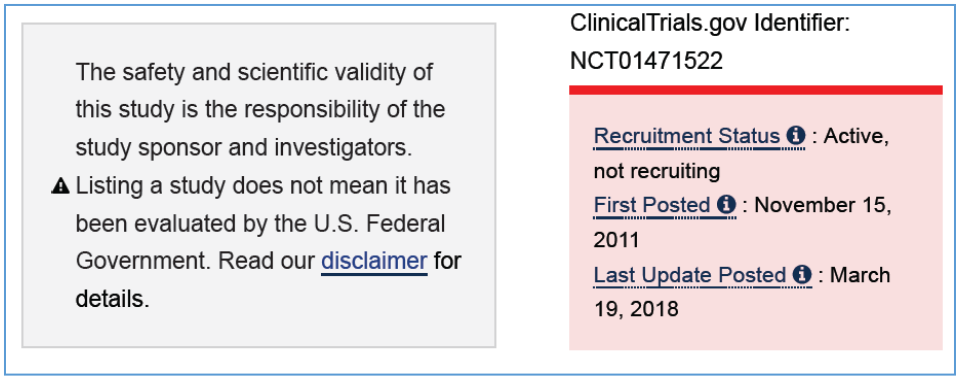
- **Each trial has its own definition for sCAD.**

	TIME[475]	MASS II[479]	SWISSI II[431]	COURAGE[23]	BARI–2D[25]	JSAP[477]	FAME–2[400]
Recruitment (years)	1996–2000	1995–2000	1991–97	1999–2004	2001–2005	2002–2004	2010–2012
Study size (n)	301	611	201	2287	2368	384	888
Mean age (years)	80	60	55	61	62	64	64
Angina CCS	II–IV	II–III	0	0–III	0–II	0–II	I–IV
Stress ischaemia (% of patients)	69	NA	100	NA	NA	NA	100
Prior MI (% of patients)	47	44	100	39	38	15	37
Mean LVEF (%)	52	67	57	62	NA	65	16% with EF<0.50
Angiographic selection	No	Yes	Yes	Yes	Yes	Yes	Yes
Mandatory documented ischaemia	No	No	Yes	No	No	No	Yes
Revascularization	PCI *or* CABG	PCI *or* CABG	PCI	PCI	PCI *or* CABG	PCI	PCI
Primary Endpoint (PEP)	Angina	Death/MI/ refractory angina	Death/MI/ revascularization	Death/MI	Death	Death/ACS	Death/MI/ Urgent revascularization
Revascularization better on PEP	Yes	No at 1 year Yes at 5 yrs (CABG)	Yes	No	No	Yes	Yes

Montalescot G. Eur Heart J 2013;34:2949-3003.

ISCHEMIA

- **International Study of Comparative Health Effectiveness With Medical and Invasive Approaches**
  - 5179 patients
    - At least moderate ischemia on an ischemia test
    - Participant willing to comply with all aspects of protocol
    - Informed consent and at least 20 years old
  - Exclusion
    - EF < 35%
    - History of unprotected LM
    - < 50% stenosis of lesion
    - ACS < 2 months, PCI < 12 months, stroke < 6 months
    - NYHA Fc III-IV of HF
    - ESRD



https://clinicaltrials.gov/ct2/show/NCT01471522. Maron DJ. Am Heart J 2018;201:124-35.

ISCHEMIA

Table 3
Inclusion and exclusion criteria*

Inclusion Criteria (at enrollment)

1. At least moderate ischemia on a qualifying stress test
2. Participant is willing to give informed consent
3. Age ≥ 21 years

Exclusion Criteria

1. LVEF <35%
2. History of unprotected left main stenosis ≥50% on prior CCTA or prior cardiac catheterization (if available)
3. Finding of "no obstructive coronary artery disease" (<50% stenosis in all major epicardial vessels) on prior CCTA or prior catheterization, performed within 12 months
4. Coronary anatomy unsuitable for either PCI or CABG
5. Unacceptable level of angina despite maximal medical therapy
6. Very dissatisfied with medical management of angina
7. History of noncompliance with medical therapy
8. Acute coronary syndrome within the previous 2 months
9. PCI within the previous 12 months
10. Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time
11. History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause
12. NYHA class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months
13. Non-ischemic dilated cardiomyopathy or hypertrophic cardiomyopathy
14. End stage renal disease on dialysis or estimated glomerular filtration rate <30 mL/min (not an exclusion criterion for CKD ancillary trial, see CKD ancillary trial)
15. Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial
16. Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast
17. Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery)
18. Life expectancy less than the duration of the trial due to non-cardiovascular comorbidity
19. Pregnancy (known to be pregnant; to be confirmed pre-CCTA and/or randomization, if applicable)
20. Patient who, in the judgment of the patient's physician, is likely to have significant unprotected left main stenosis (those who are able to undergo CCTA will have visual assessment of the left main coronary artery by the CCTA core laboratory)
21. Enrolled in a competing trial that involves a non-approved cardiac drug or device
22. Inability to comply with the protocol
23. Exceeds the weight or size limit for CCTA or cardiac catheterization at the site
24. Canadian Cardiovascular Society Class III angina of recent onset, or angina of any class with a rapidly progressive or accelerating pattern
25. Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina
26. High risk of bleeding which would contraindicate the use of dual antiplatelet therapy
27. Cardiac transplant recipient
28. Prior CABG, unless CABG was performed more than 12 months ago and coronary anatomy has been demonstrated to be suitable for PCI or CABG to accomplish complete revascularization of ischemic areas (CCC approval required)

https://clinicaltrials.gov/ct2/show/NCT01471522. Maron DJ. Am Heart J 2018;201:124-35.

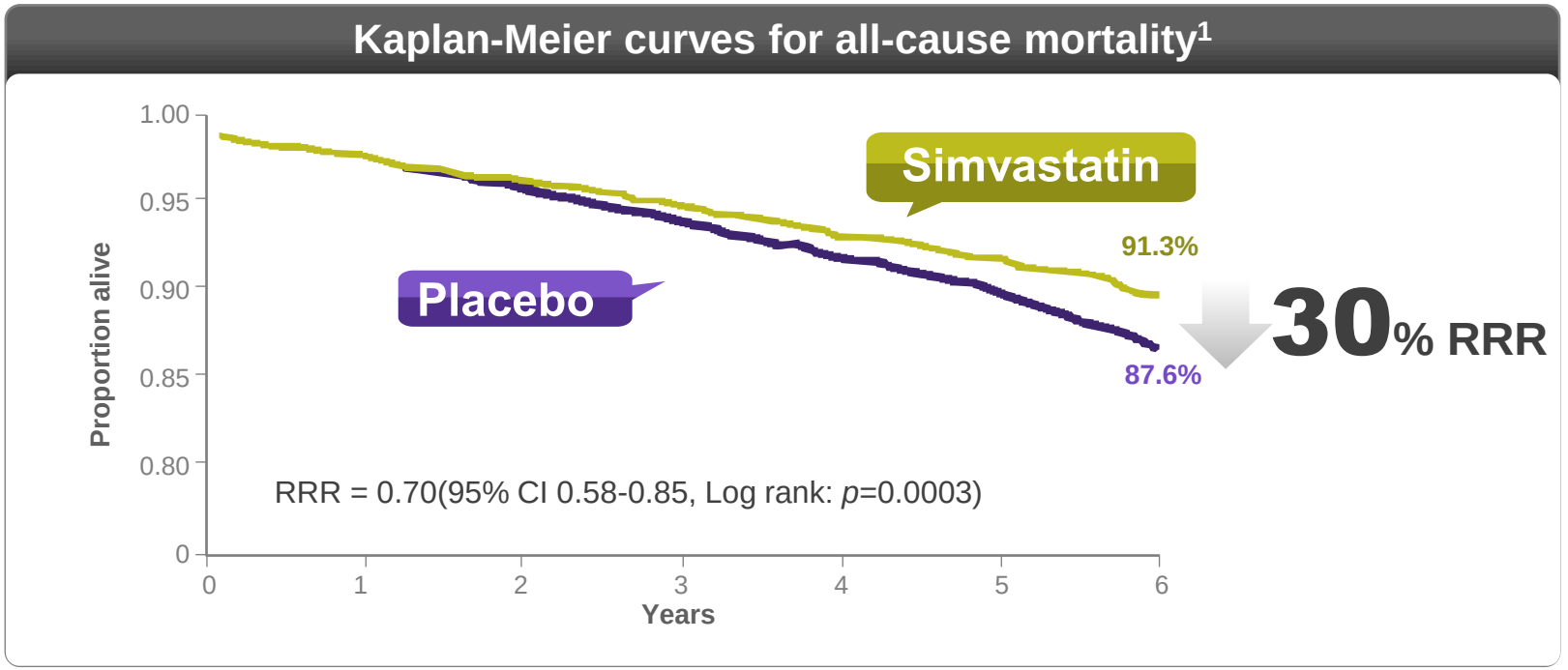
So many great trials with Statin in CVD

- **primary prevention**
  - AFCAPS, TexCAPS
  - WOSCOPS
- **Secondary Prevention**
  - 4S
  - HPS
  - CARE
  - PROVE-IT TIMI 22
- **Plaque regression**
  - REVERSAL
  - ASTEROID

Peyracchia M. J Cardiovasc Med 2018;19:337-43.

Scandinavian Simvastatin Survival Study

- **Simvastatin vs Placebo in 4444 with AP or prior MI**
  - 5.4 years follow-up, > 6 mo of ACS
  - Entry LDL-C 188 mg/dL, 35% reduction of LDL-C



Adapted from Scandinavian Simvastatin Survival Study Group[1]

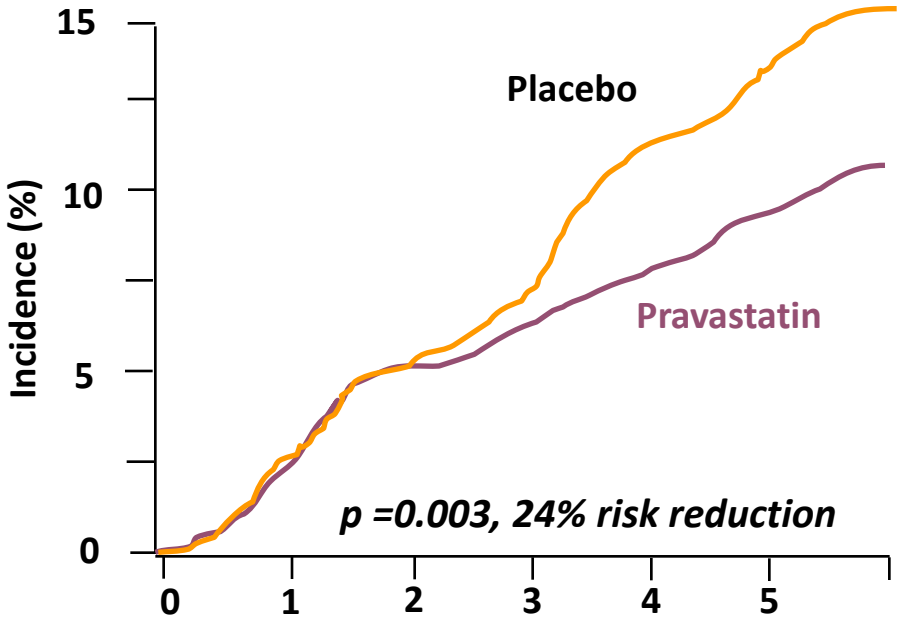
[simvastatin group the mean changes from baseline in LDL-C] :188 → 122 mg/dL[1]

4S Study group. Lancet 1994;344:1383-9.

The Cholesterol and Recurrent Events (CARE)

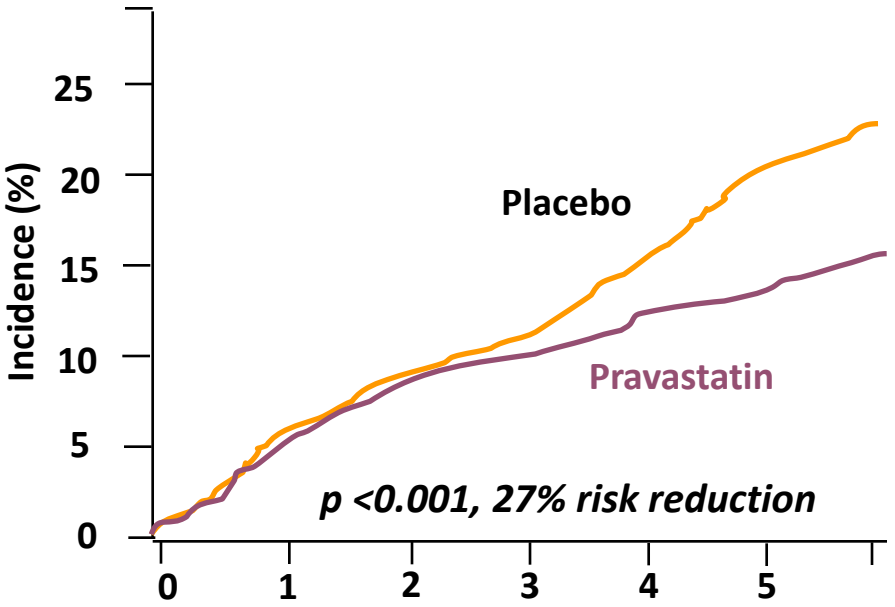
- **Pravastatin vs Placebo in 4,519 prior MI (3~26 months earlier)**
  - Entry LDL-C 139±15 mg/dL

Fatal CHD, nonfatal MI



No. at risk						
Placebo	2078	2009	1956	1881	1810	854
Pravastatin	2081	2015	1963	1915	1856	900

CABG or angioplasty



Placebo	2078	1956	1857	1739	1634	754
Pravastatin	2081	1969	1877	1800	1716	819

Sacks FM N Engle J Med 1996;335:1002

Statin vs PCI in low risk sCAD

- **effect of atorvastatin 80 mg in sCAD (n=341) for 18 months**

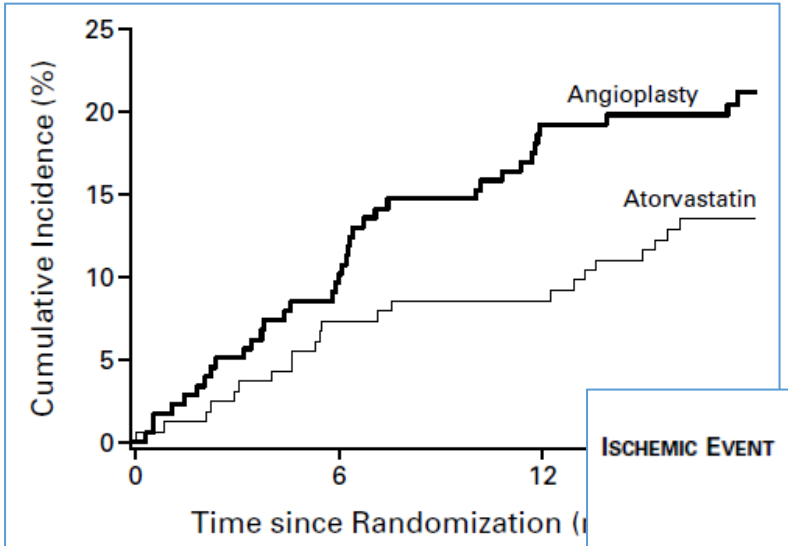


Figure 2. Cumulative Incidence of First Ischemi
The time to an ischemic event was significantl
atorvastatin group (P=0.03), and the risk reduct
cent (95 percent confidence interval, 5 to 67 per

Ischemic Event	Atorvastatin Group (N=164)		Angioplasty Group (N=177)	
	No. of patients for whom the event was the first	No. of patients (%) with the event	No. of patients for whom the event was the first	No. of patients (%) with the event*
Death from cardiac causes	1	1 (0.6)	1	1 (0.6)
Resuscitation after cardiac arrest	0	0	0	0
Nonfatal myocardial infarction	2	4 (2.4)	4	5 (2.8)
Cerebrovascular accident	0	0	0	0
Coronary-artery bypass grafting	0	2 (1.2)	3	9 (5.1)
Angioplasty as an event	9	18 (11.0)	5	21 (11.9)
Worsening angina with objective evidence of myocardial ischemia resulting in hospitalization	10	11 (6.7)	24	25 (14.1)
Any ischemic event		22 (13.4)		37 (20.9)

Pit B. N Engl J Med 1999;341:70-6.

TNT trial

- **80 mg vs 10 mg of atorvastatin in sCAD**
  - 4.9 years follow-up with 10001 patients
    - 37-75 YO, previous MI or previous or current angina, revascularization
  - Reduction of LDL-C: 77 vs 101 mg/dL
  - PEP: first MACE – death from CHD, NFNP related MI, resus. Cardiac arrest, fatal or NF stroke

Table 2. Estimated Hazard Ratio for Individual Components of the Primary and Secondary Efficacy Outcomes.*

Outcome	10 mg of Atorvastatin (N=5006)	80 mg of Atorvastatin (N=4995)	Hazard Ratio (95% CI)	P Value
	no. with first event (%)			
Primary outcome				
Total major cardiovascular events	548 (10.9)	434 (8.7)	0.78 (0.69–0.89)	<0.001
Death from CHD	127 (2.5)	101 (2.0)	0.80 (0.61–1.03)	0.09
Nonfatal, non–procedure-related myocardial infarction	308 (6.2)	243 (4.9)	0.78 (0.66–0.93)	0.004
Resuscitation after cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56–1.67)	0.89
Fatal or nonfatal stroke	155 (3.1)	117 (2.3)	0.75 (0.59–0.96)	0.02
Secondary outcomes				
Major coronary event†	418 (8.3)	334 (6.7)	0.80 (0.69–0.92)	0.002
Cerebrovascular event‡	250 (5.0)	196 (3.9)	0.77 (0.64–0.93)	0.007
Hospitalization for congestive heart failure	164 (3.3)	122 (2.4)	0.74 (0.59–0.94)	0.01
Peripheral-artery disease§	282 (5.6)	275 (5.5)	0.97 (0.83–1.15)	0.76
Death from any cause	282 (5.6)	284 (5.7)	1.01 (0.85–1.19)	0.92
Any cardiovascular event	1677 (33.5)	1405 (28.1)	0.81 (0.75–0.87)	<0.001
Any coronary event¶	1326 (26.5)	1078 (21.6)	0.79 (0.73–0.86)	<0.001

LaRosa JC. N Engl J Med 2005;352:1425-35.

DUAAL trial

- **Amlod 10 mg vs lipitor 80 mg vs both for anti-ischemic effect**

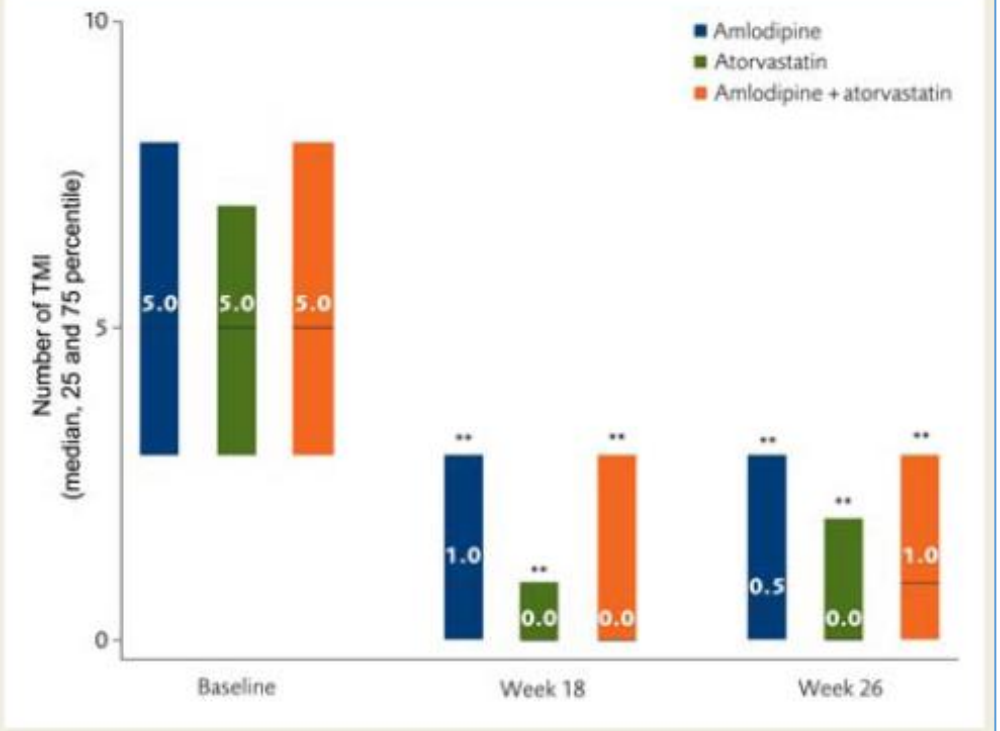


Figure 3 Median number of transient myocardial ischaemia episodes/week, recorded by ambulatory electrocardiographic 48 h monitoring. $^{**}P < 0.001$ vs. baseline. TMI, transient myocardial ischaemia.

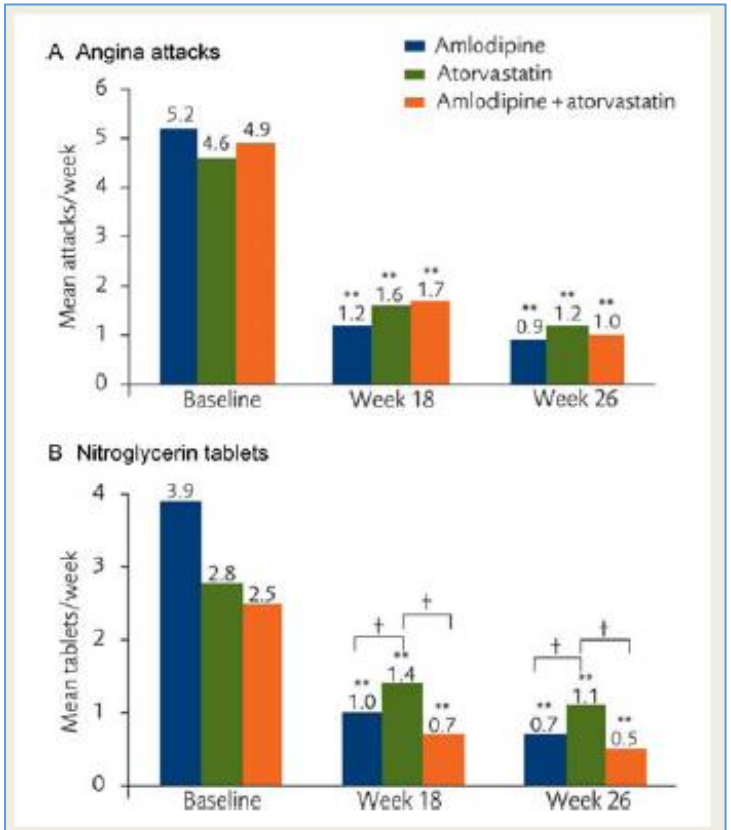
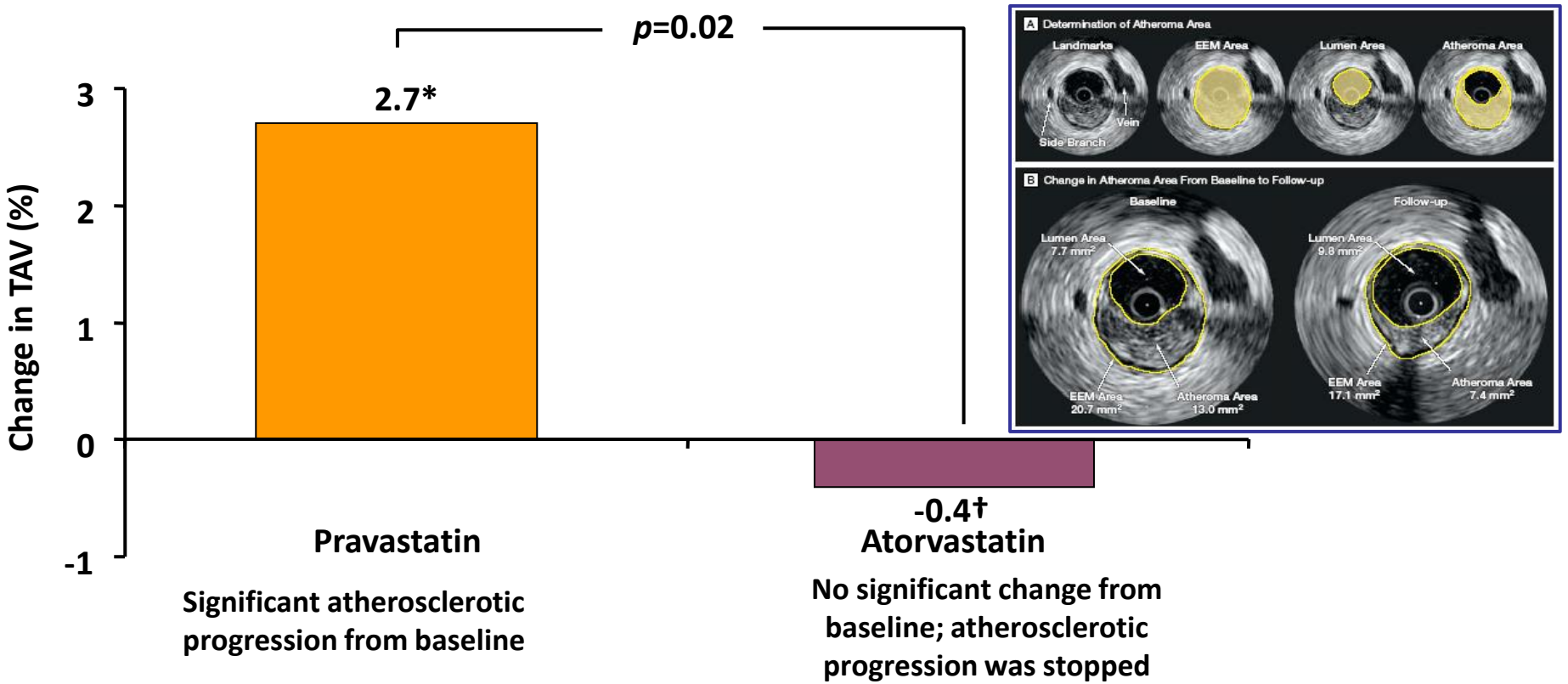


Figure 5 (*A*) Mean angina attacks/week and (*B*) mean number of nitroglycerin tablets/week, based on patients' diaries. $^{**}P < 0.001$ vs. baseline; $^{\dagger}P < 0.05$ change from baseline between groups.

Deanfield JE. Eur Heart J 2010;31:2650-9.

Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)

- **Atorvastatin 80 mg VS Pravsstatin 40 mg for 18 months**



*Progression vs baseline (*P*=0.001); †No change vs baseline (*P*=0.98)

Nissen SE. JAMA 2004;291:1071-80.

ZIPANGU with angioscopy and IVUS

- **Ezetimibe 10 mg vs placebo on atorvastatin 10-20 mg**
  - LDL-C : 103±28 to 63±18 mg/dL vs 100±28 to 75±17 mg/dL

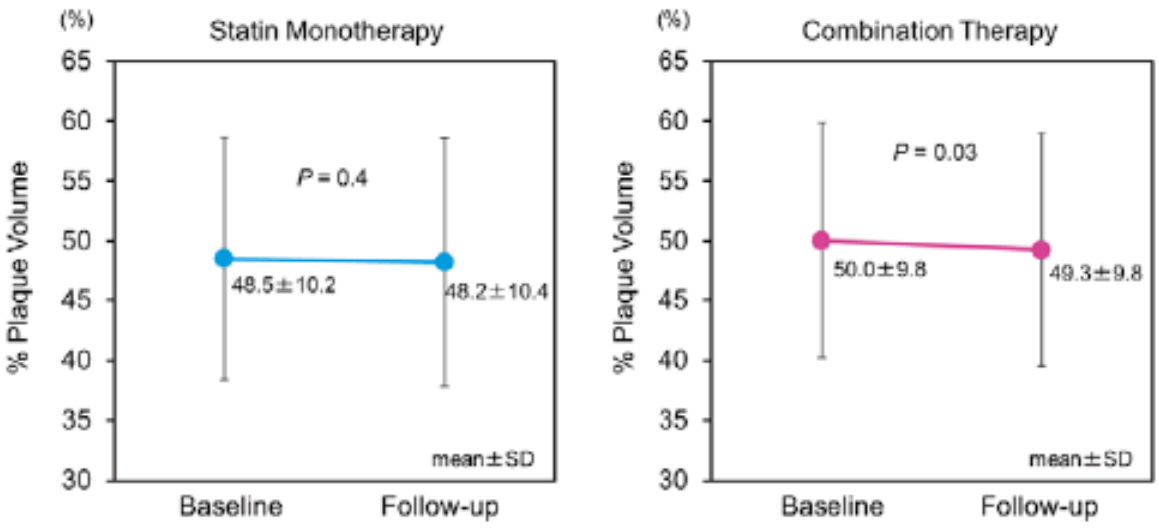


Figure 3. Changes in %plaque volume from baseline to follow-up. The %plaque volume did not change from baseline to follow-up in the monotherapy group (48.5±10.2% vs. 48.2±10.4%, P=0.4), but decreased significantly in the combination therapy group (50.0±9.8% vs. 49.3±9.8%, P=0.03).

Ueda Y. Circ J 2017;81:1611-9.

DAPT for IHD

- **Complex means no unified answer in population level.**

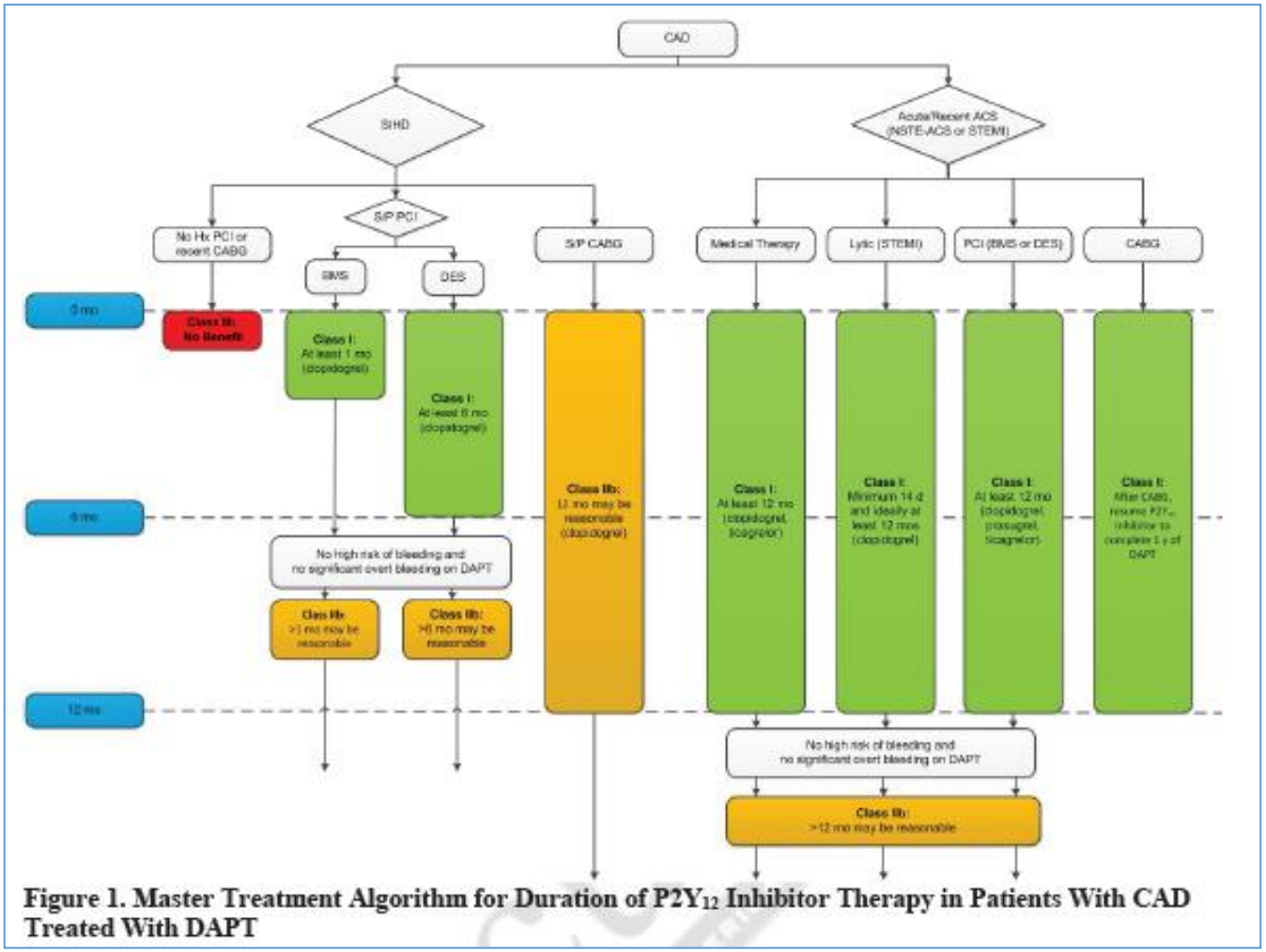


Figure 1. Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT

Bittl JA. J Am Coll Cardiol 2016;68:1116-39.

What we have for stable CAD beyond Statin

- **COMPASS, CANTOS, FOURIER, ODYSSEY, PEGASUS**
  - vascular dose rivaroxaban, low dose ticagreleor
  - Canakinumab
  - PCSk9 inhibitor: evolocumab, alirocumab

Table 1 Stable coronary artery disease - new advances in secondary prevention, overview

Variable	COMPASS	CANTOS	FOURIER	ODYSSEY	PEGASUS-TIMI 54
n	27,395	10,061	27,564	18,924	21,162
Population	Stable CAD	h/o MI, hs-CRP level ≥2 mg/L	established CV disease	ACS 1–12 months prior to randomization and on high-intensive statin therapy	h/o MI 1–3 years prior + additional risk feature
FU-time	23 months (mean)	3.7 years (median)	2.2 years (median)	2.8 years (median)	33 months (median)
Concept	Anti-thrombotic	Anti-inflammatory	lipid-lowering	lipid-lowering	anti-thrombotic/anti-platelet
Substance/dosage	Rivaroxaban 5 mg bid mono *vs.* rivaroxaban 2.5 mg bid + ASA *vs.* ASA mono	Canakinumab 50, 150 and 300 mg *vs.* placebo	Evolocumab 140 mg Q2W or 420 mg QM *vs.* placebo	Alirocumab 75 or 150 mg Q2W s.c. *vs.* placebo	Ticagrelor 60 or 90 mg bid *vs.* placebo
Adverse effects	Increased bleeding defined by ISTH (HR 1.70; 95% CI: 1.40–2.05; P<0.001)	Neutropenia, thrombocytopenia, infection	no significant side effects *vs.* placebo	local injection side reaction	increase of TIMI major bleeding (HR 2.32, 95% CI: 1.68–3.21, P<0.001)
Mortality (from any cause)	Rivaroxaban + ASA: 3.42%; placebo: 4.14%	Canakinumab 150 mg: 2.73%; placebo: 2.97%	Evolocumab (all dosages): 3.2%; placebo: 3.1%	Alirocumab: 3.5%; placebo: 4.1%	Ticagrelor 60 mg bid: 4.7%; placebo: 5.2%

Kalbacher D. Ann Transl Med 2018;6:323.

Conclusion

- **Effects of medications for sCAD**
- **Aspirin**
  - reduction of MI, but ambiguity in mortality reduction and high bleeding
- **ADP receptor blocker**
  - limited evidence in this area, alternative for aspirin
- **Beta blocker**
  - loosing the evidence of MACE reduction
  - much better in reduction of ischemic episode
- **ACE inhibitor**
  - effective in specific situation, e.g. hypertension, HF and DM
- **Statin**
  - only drug of proven efficacy in reduction of MACE, even more mortality
- **Definition of sCAD**
  - each study has own definition
  - ISCHEMIA trial will give us more detailed definition for sCAD

Thank you for your time.

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