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Oral Immunosuppressive Therapy to Prevent In-Stent Restenosis

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Alfredo E. Rodriguez declares no conflicts of interest

Possible role of long-term medical therapies to prevent restenosis following percutaneous coronary intervention

SUMMARY AND RECOMMENDATIONS — Some long-term medical therapies have evidence of efficacy in reducing restenosis. However, for four possibly effective oral drugs (cilostazol , pioglitazone or rosiglitazone , and sirolimus), the reduction in late lumen loss may be significantly less than that achieved with a drug-eluting stent [66]. In light of the DECLARE-LONG II trial, other therapies such as cilostazol may add incremental benefit when co-administered following drug-eluting stent implantation. (See 'Cilostazol' above.)

In the CREST trial of cilostazol , for example, the degree of late lumen loss, although significantly less than in the placebo arm [12], was greater than that seen in trials of drug-eluting stents (0.57 mm in CREST versus 0.24 mm in SIRIUS and 0.23 mm in TAXUS IV) [14,15]. A greater degree of late lumen loss was also noted with oral sirolimus in ORAR II compared to a sirolimus-eluting stent in SIRIUS (0.66 mm versus 0.24 mm) [14,18].

- We recommend **against** using any of the oral therapies cited above to prevent restenosis (Grade 1B). Antiplatelet therapy is primarily given to prevent stent thrombosis and for secondary prevention of cardiovascular disease. (See 'Possibly effective' above and "Coronary artery stent thrombosis: Incidence and risk factors" .)

It is possible that oral therapy in addition to a drug-eluting stent might be beneficial in high-risk lesions (eg, small vessels and long lesions). However, this hypothesis must be confirmed in randomized trials.

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UpToDate

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ORAL TREATMENT TO PREVENT RESTENOSIS

LACK of INFORMATION??

BACKGROUND

Marx SO et al. Rapamycin-FKBP inhibits cell cycle regulators of proliferation invascular smooth muscle cell. Circ Res 1995;76:412.

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ORAL TREATMENT TO PREVENT RESTENOSIS

NEGATIVE RESULTS??

All ORAL TREATMENT TRIALS

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Positive Results

1. Versaci F et al. Immunosuppressive therapy for the prevention of restenosis after coronary artery stent implantation (IMPRESS Study). J Am Coll Cardiol 2002;40:1935e1942.
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Randomized Clinical Trials
(8/8 positive)

SIROLIMUS

Hausleiter J et al. OSIRIS TRIAL. Circulation 2004;110:790e795.
Rodriguez AE et al. ORAR 2 TRIAL J Am Coll Cardiol 2006;47:1522e1529.
Rodríguez AE et al. ORAR 3 TRIAL. Euro Intervention 2009;5:255e264.
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PREDNISONE

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COLCHICINE

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Systematic Review
(2/2 positive)

Dasari TW et al. Systematic review of effectiveness of oral sirolimus after bare-metal stenting of coronary arteries for prevention of in-stent restenosis. Am J Cardiol. 2013 Nov 1;112(9):1322-7.
Sardar P et al. Steroids for the prevention of restenosis in bare-metal stents--a systematic review and meta-analysis. J Invasive Cardiol 2012;24(3):98-103.

Rationality of OIM Therapies After BMS

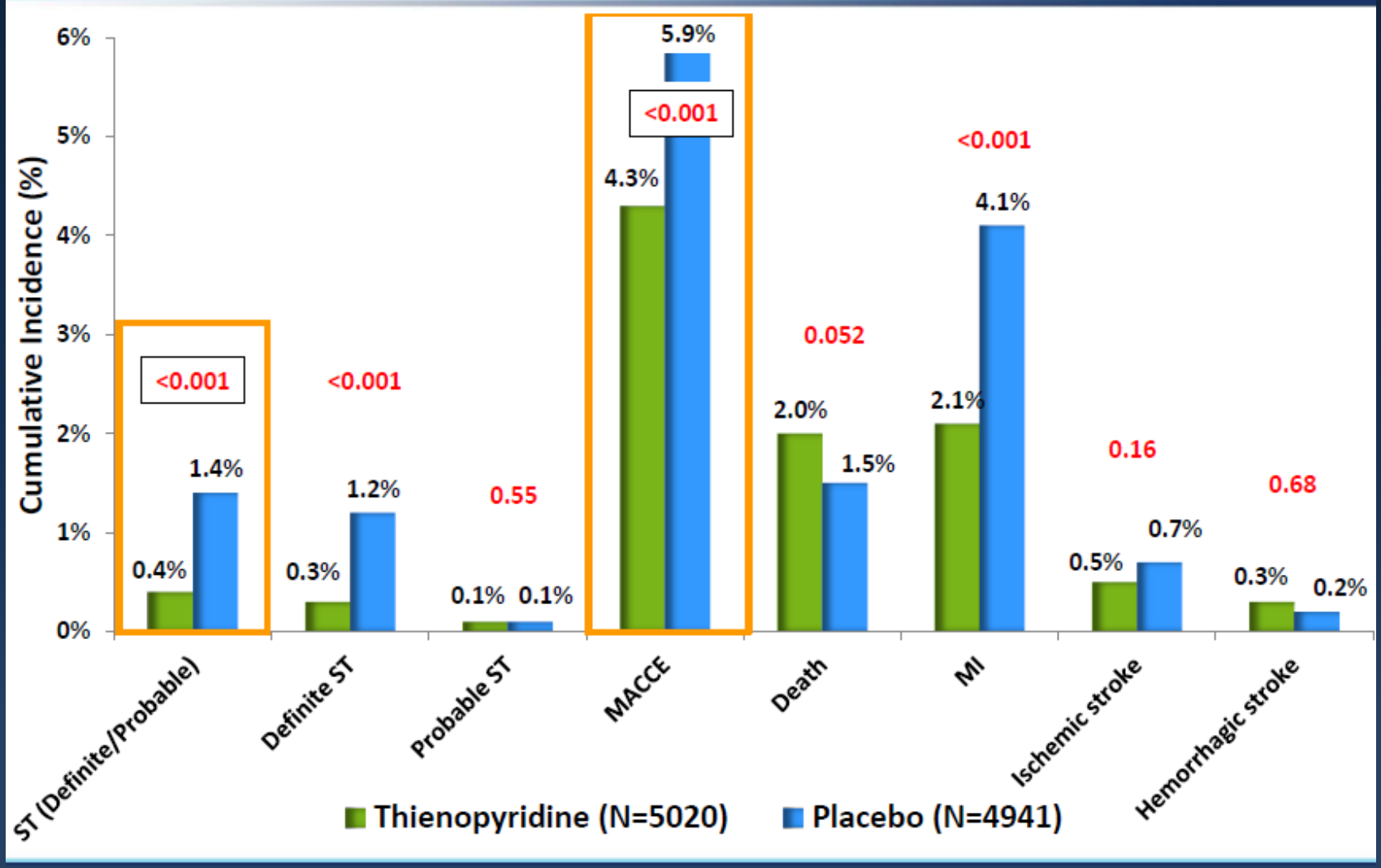
- *#Notwithstanding the undisputed merits of DES to prevent restenosis, BMS have not been abandoned.*
- *#Concerns about a higher risk of bleeding or noncompliance with the mandatory DAPT therapy suggest some relative contraindications to DES in PCI-patients with specific clinical and socioeconomic conditions.*
- *#Despite socio economic considerations are more relevant in certain geographic areas, BMS*
- *are still used in one fourth of patients receiving a PCI in the US and these patients are at high risk of restenosis.*

Cassese, S, Rodriguez AE et al. Atherosclerosis. 2014 Dec;237(2):410-7

- Drug Eluting Stents and Bleeding Risk with Long Term Use of DAPT

Co-Primary Effectiveness End Points & Components: 12-30 Months

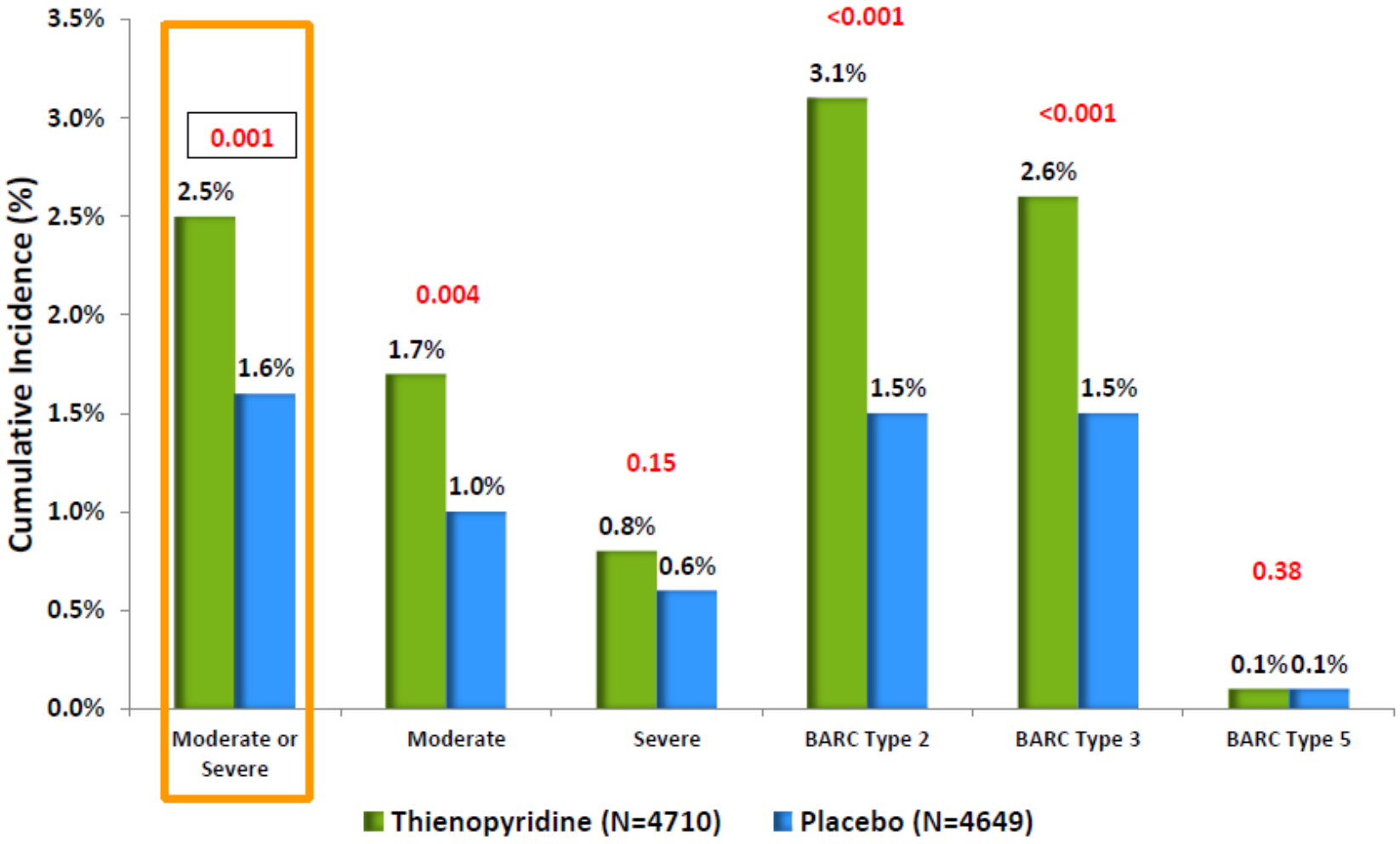
DAPT STUDY

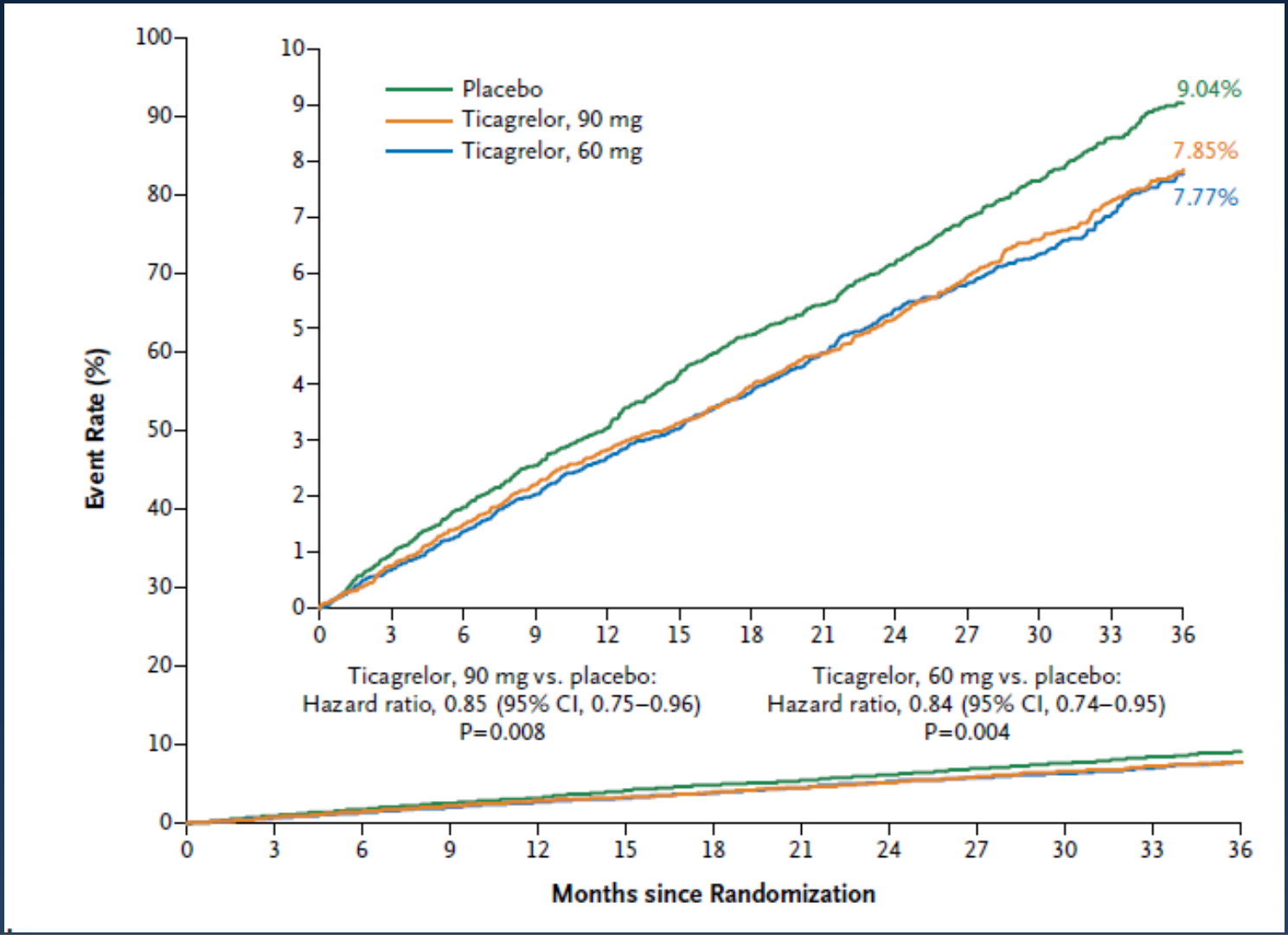


L Mauri AHA NEJM , November 16, 2014,

Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

DAPT STUDY





Kaplan–Meier Rates of Cardiovascular Death, Myocardial Infarction, and Stroke through 3 Years, According to Study Group.

M. Bonaca et al. N Engl J Med 2015;372:1791-800

End Point	Ticagrelor, 90 mg (N=6988)	Ticagrelor, 60 mg (N=6958)	Placebo (N=6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
			number (percent)				
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42)	<0.001	3.08 (2.12–4.48)	<0.001
Bleeding leading to study-drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29)	<0.001	4.40 (3.48–5.57)	<0.001
[redacted] intracranial hemorrhage	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
[redacted]	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
[redacted]	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64)	0.26	0.97 (0.37–2.51)	0.94
[redacted]	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00
Other adverse event							
Dyspnea	1205 (18.93)	987 (15.84)	383 (6.38)	3.55 (3.16–3.98)	<0.001	2.81 (2.50–3.17)	<0.001
Event leading to study-drug discontinuation	430 (6.50)	297 (4.55)	51 (0.79)	8.89 (6.65–11.88)	<0.001	6.06 (4.50–8.15)	<0.001
Serious adverse event	22 (0.41)	23 (0.45)	9 (0.15)	2.68 (1.24–5.83)	0.01	2.70 (1.25–5.84)	0.01
[redacted]	166 (3.30)	173 (3.43)	161 (2.89)	1.17 (0.94–1.46)	0.15	1.17 (0.94–1.45)	0.15
[redacted]	107 (2.04)	121 (2.32)	106 (1.98)	1.15 (0.88–1.50)	0.31	1.24 (0.96–1.61)	0.10
Gout	115 (2.28)	101 (1.97)	74 (1.51)	1.77 (1.32–2.37)	<0.001	1.48 (1.10–2.00)	0.01

Safety End Points as 3-Year Kaplan–Meier Estimates

M. Bonaca et al. N Engl J Med 2015;372:1791-800

Randomized Clinical Trials
(8/8 positive)

SIROLIMUS

Hausleiter J et al. OSIRIS TRIAL. Circulation 2004;110:790e795.
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Sardar P et al. Steroids for the prevention of restenosis in bare-metal stents--a systematic review and meta-analysis. J Invasive Cardiol 2012;24(3):98-103.

1274 patients
Screened for inclusion in ORAR III

485 patients met clinical exclusion criteria:

AMI < 24 hours.
Participation in another trial.
Refuses to be included in the trial
Commorbidities

102 patients met angiographic exclusion criteria:
Target vessel size <2.5 mm (visual)
Chronic total occlusion
Non significant CAD
Diffuse CAD
ISR

487 p ded, unabl with mult DES

200 patients included in ORAR III RCT

OR+BMS 100 pts

1° Gen. DES 100 pts

Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

Comparison of Cost-Effectiveness of Oral Rapamycin Plus Bare-Metal Stents Versus First Generation of Drug-Eluting Stents 5 years FU from ORAR 3 RCT

BACKGROUND

Results from one (*EuroIntervention. 2009 Jun;5(2):255-6*) and three years (*Catheter Cardiovasc Interv 2012;80:385e394*) of FU were published and showed that the strategy of OR plus BMS has no significant differences in MACE or TVR in comparison with DES therapy, although costs were significantly higher with DES.

CECI
CENTRO DE ESTUDIOS EN CARDIOLOGIA INTERVENCIONISTA

Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

METHODS

From January 2006 to September 2007 in three hospitals in Buenos Aires, Argentina, 200 patients pts were randomized either to OR (n=100) or DES (n=100). **OR was given as a bolus of 10 mg the day before PCI followed by daily doses of 3 mg during the following 13 days.**

DES group received clopidogrel for at least one year and OR group for one month. DES used in the trial were Paclitaxel (Boston Scientific), Sirolimus (Cordis) and Zotarolimus (Medtronic) eluting stents, all commercially available in Argentina. **Follow Up angiogram was only clinically indicated.**

Costs expressed in US dollars, included procedural, hospitalization, medications at hospital, repeat revascularization procedures at follow up and professional fees.

Clinical Exclusion Criteria were AMI in the last 24 hours, in-stent restenosis, previous PCI in the last six months and short life expectancy.

Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

Comparison of Cost-Effectiveness of Oral Rapamycin Plus Bare-Metal Stents Versus First Generation of Drug-Eluting Stents 5 years FU from ORAR 3 RCT

The **primary end point** was to compare overall costs (included in-hospital and follow-up) of both revascularization strategies (OR and DES) at 1, **3** and 5 years follow-up. This was selected on the hypothesis of similar efficacy for both strategies.

Secondary end points included safety end points defined by a composite of death from any cause, myocardial infarction (MI) or stroke (MACE). Target Vessel Revascularization (TVR) and Target Lesion Revascularization (TLR) were analyzed separately as efficacy end points and were not included as part of the MACE definition.
Target vessel failure (TVF) was defined as cardiac death, MI and TVR.

CECI
CENTRO DE ESTUDIOS EN CARDIOLOGIA INTERVENCIONISTA

Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

5 years FU from ORAR 3 RCT

Baseline Clinical, Demographic and Angiographic Characteristics (cont)

Characteristics n (%)	OR+BMS (n=100 pts)	DES (n=100 pts)	P value
Age (years)	62.1 +/- 10.1	63.4 +/- 10.6	0.30
Age > 65 years	40%	48%	0.31
Male gender	83 (83.0%)	81 (81.0%)	1.00
Hypertension	69 (69.0%)	72 (72.0%)	0.93
Dyslipemia	71 (71.0%)	81 (81.0%)	0.61
Current smokers	21 (21.0%)	17 (17.0%)	0.67
Diabetes Mellitus	**24 (24.0%)**	**33 (33.0%)**	**0.36**
Previous CVA	2 (2.0%)	2 (2.0%)	1.00
Previous MI	26 (26.0%)	33 (33.0%)	0.51
Previous Coronary Revascularization	12 (12.0%)	13 (13.0%)	1.00
Unstable Angina (ACC/AHA class)	62 (62.0%)	56 (56.0%)	0.74
Stent diameter (mm)	2.78 +/- 0.4	2.76 +/- 0.4	0.66
MVD	48 (48%)	51 (51%)	0.90
EuroSCORE	3.63 +/- 2.7	3.41 +/-2.6	0.56

Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

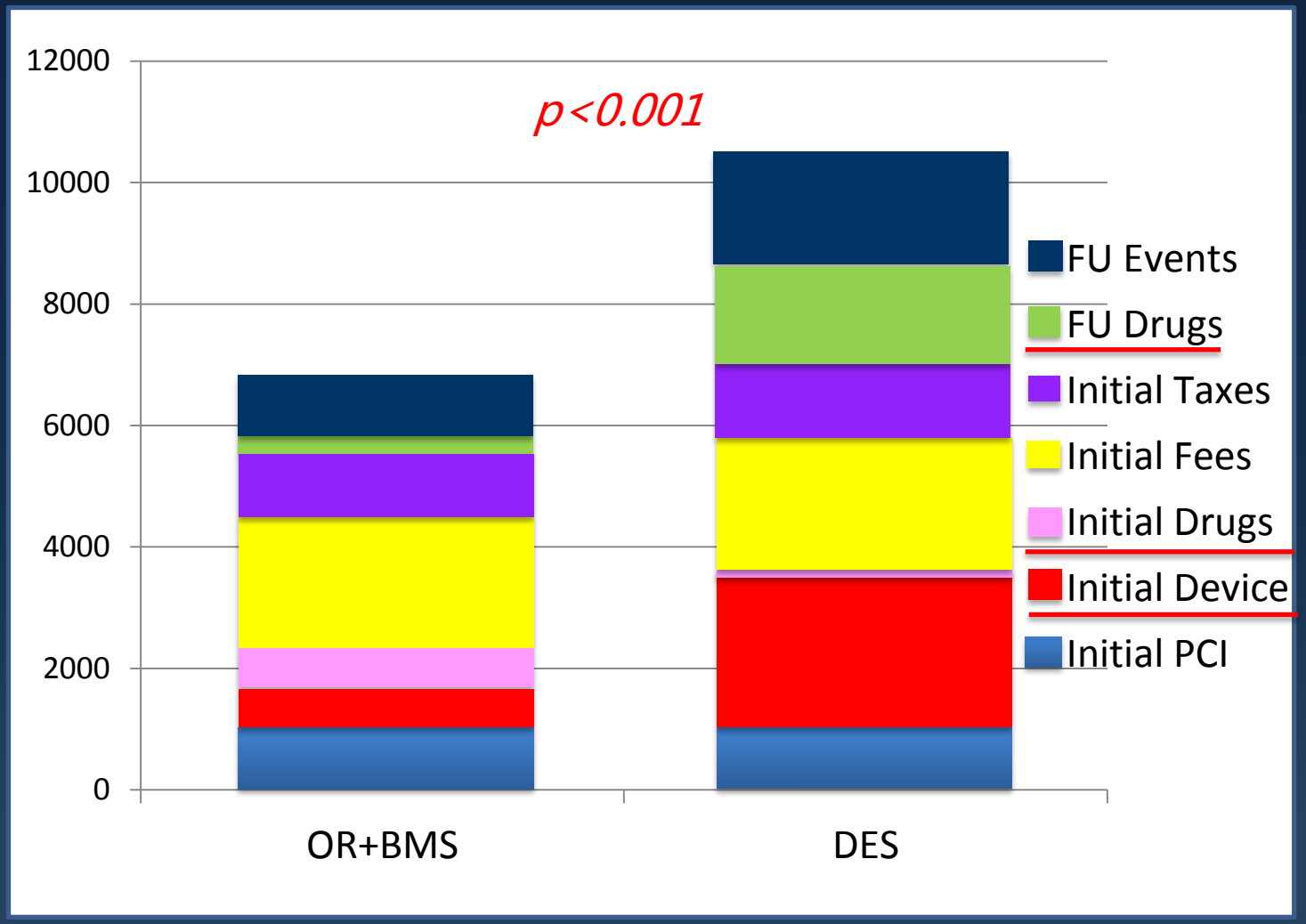
5 years FU from ORAR 3 RCT

Baseline Clinical, Demographic and Angiographic Characteristics (cont)

Characteristics n (%)	OR+BMS (n=100 pts)	DES (n=100 pts)	P value
N° of treated vessels	131	142	0.70
N° of treated lesions	158	170	0.75
N° of stents per patient	1.71	1.76	0.91
Reference diameter < 2.5 mm	**36.1%**	**28.2%**	**0.32**
Overlapping stents per vessel	**24.4% (32/131)**	**14.8% (21/142)**	**0.28**
Stent length (mm)	19.1 +/- 4.3	21.4 +/- 5.2	0.001
Stent diameter (mm)	2.78 +/- 0.4	2.76 +/- 0.4	0.66

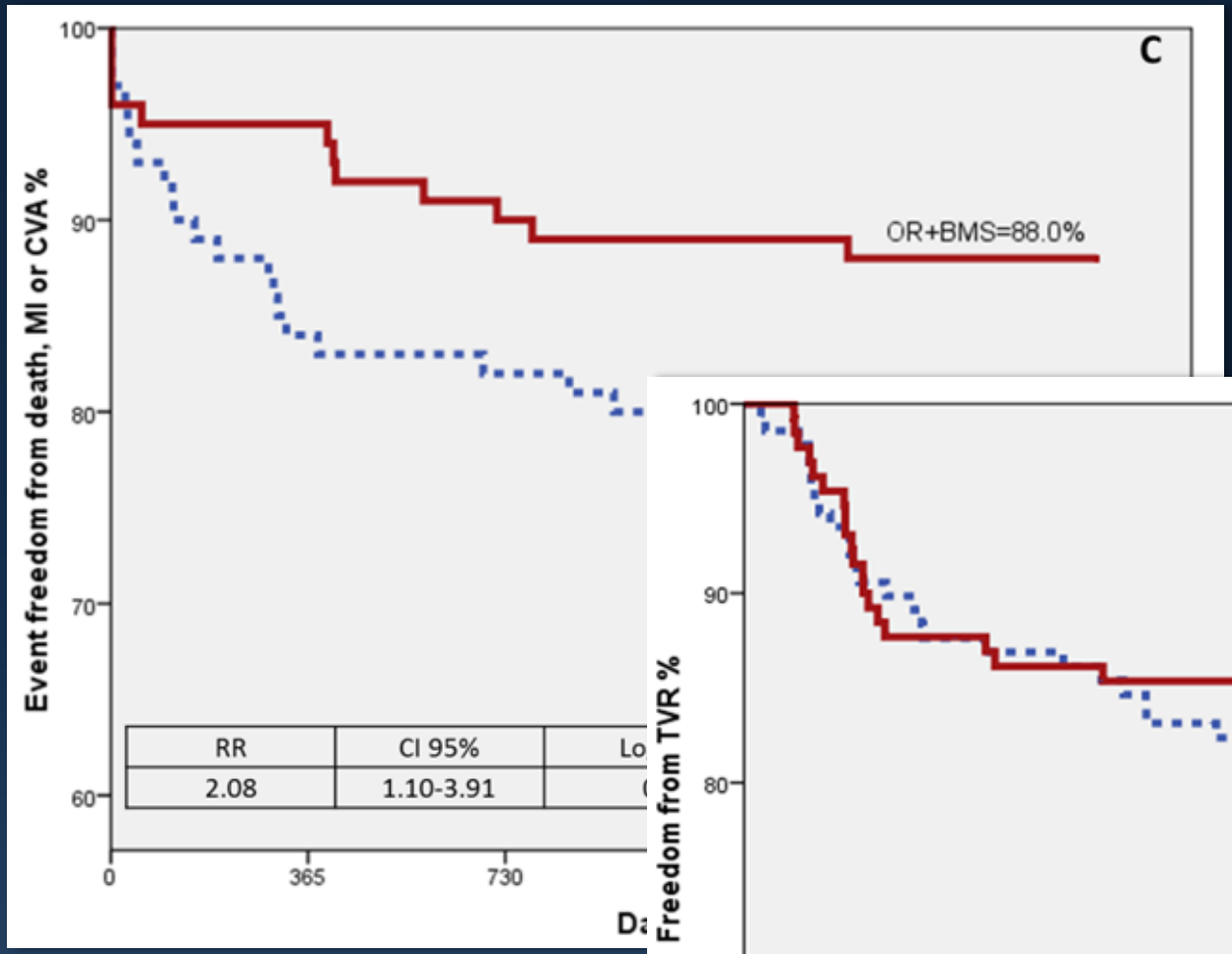
Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

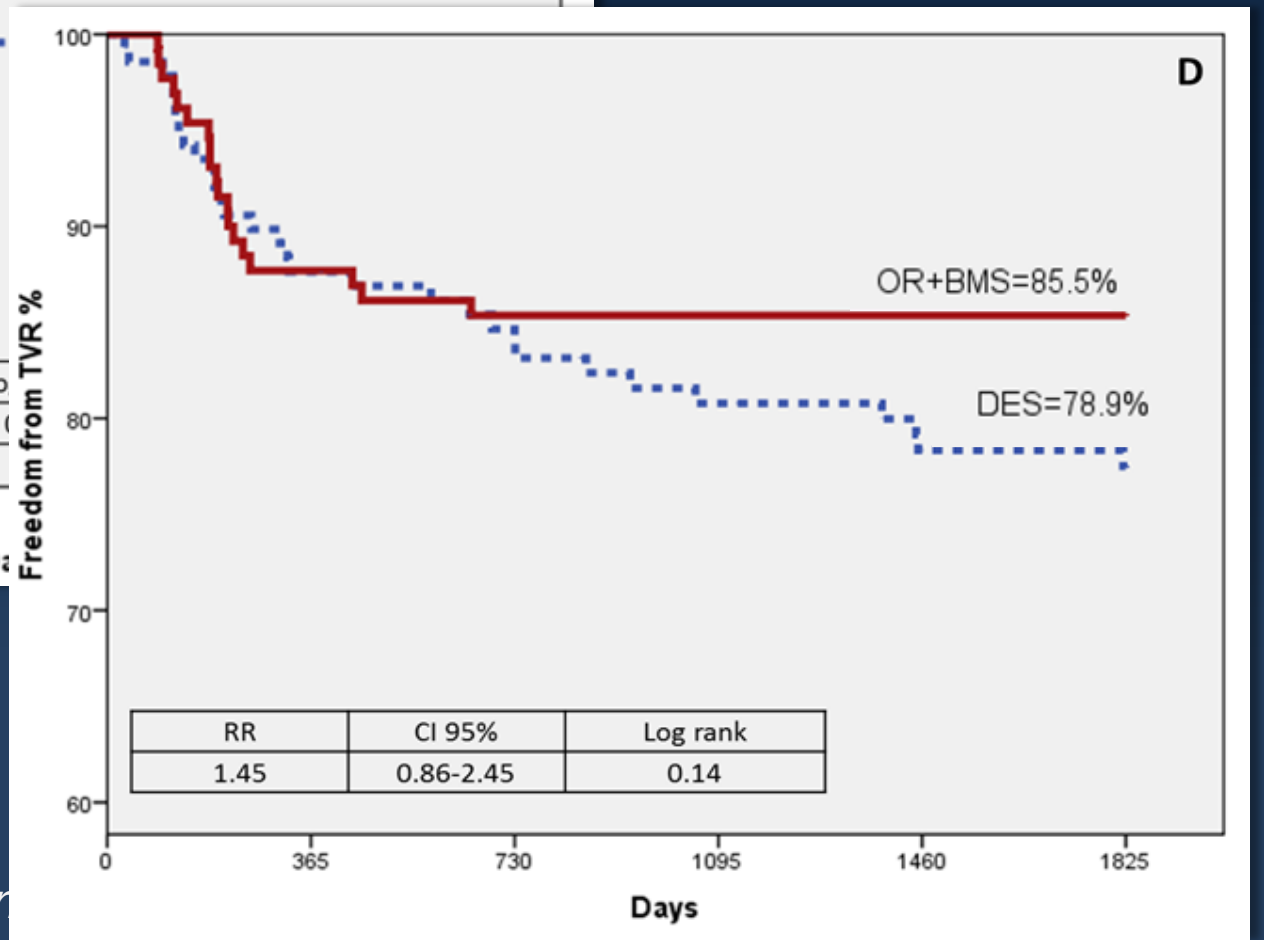
COSTS during ORAR 3 RCT.



Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

Kaplan Meier survival curves in ORAR 3 RCT





Event progression during ORAR 3 RCT

Incidence of clinical endpoints at 1 and 5 years of follow up.						
Event	OR+BMS n=100 (%)	DES n=100 (%)	RR	CI 95%		Chi^2
				Inferior	Superior	
TVF						
0-1 years	21 (21.0)	23 (23.0)	1.09	0.64	1.84	0.73
1-5 years	5 (5.0)	13 (13.0)	2.6	0.96	7.02	0.08
0-5 years	26 (26.0)	36 (32.0)	1.38	0.90	2.11	0.08
TLR						
0-1 years	11/158 (7.0)	14/170 (8.2)	1.18	0.55	2.52	0.84
1-5 years	5/158 (3.1)	16/170 (9.4)	2.95	1.10	7.87	0.03
0-5 years	16/158 (10.1)	30/170 (17.6)	1.74	0.98	3.07	0.05
TVR						
0-1 years	14/131 (10.6)	15/ 142 (10.5)	0.98	0.49	1.96	0.86
1-5 years	5/131 (3.8)	15/142 (10.5)	2.78	1.04	7.46	0.02
0-5 years	19/131 (14.5)	30/142 (21.1)	1.45	0.86	2.45	0.16

LATE CATCH-UP after 1 year…

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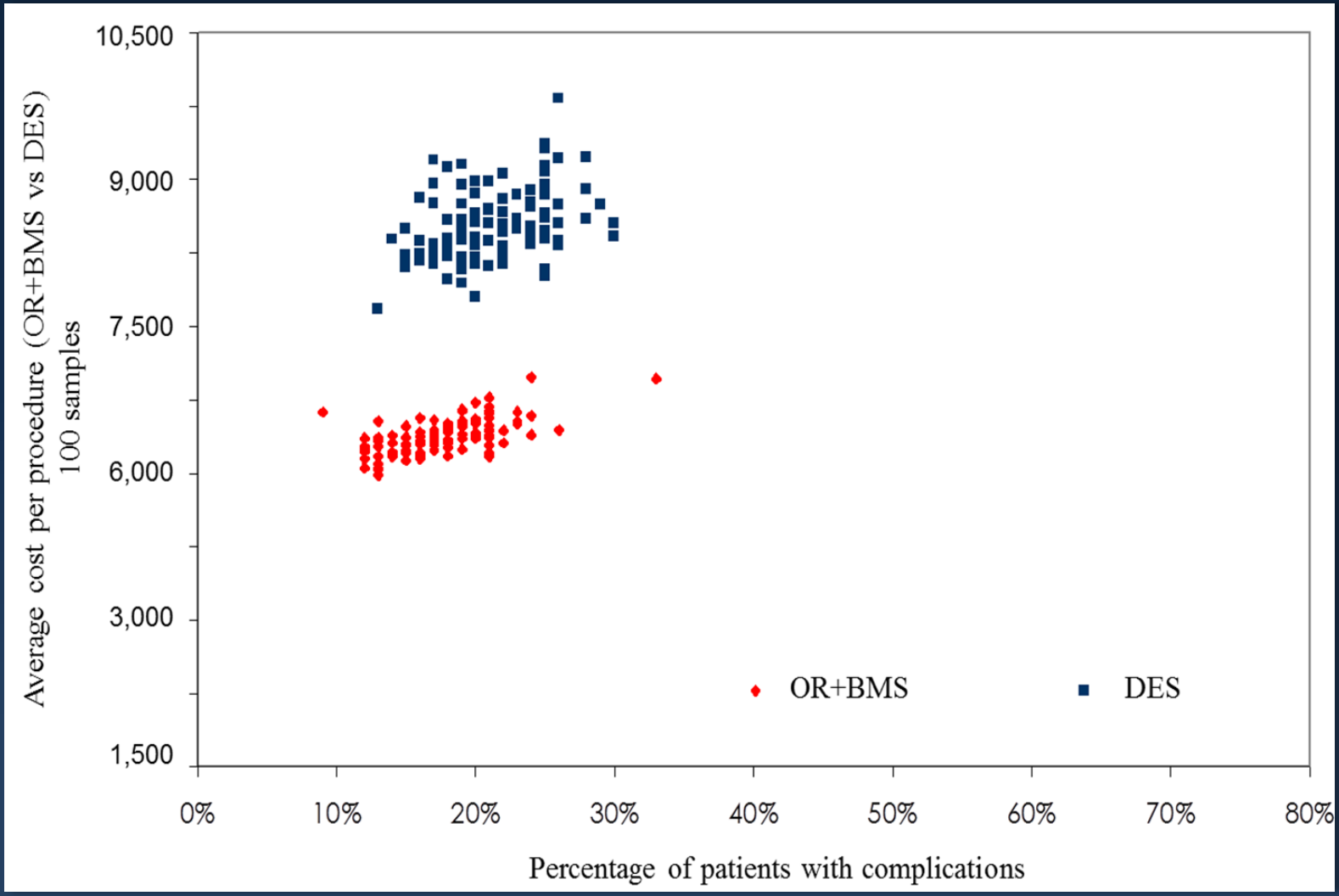
Bootstrap analysis in patients with cardiac adverse events in both groups ORAR 3 RCT



Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

Clinical Outcome according to AGE in ORAR 3 RCT

	Patients < 65 years			Patients ≥ 65 years		
	OR	DES	P	OR	DES	P
	n=60 (%)	n=52 (%)		n=40 (%)	n=48 (%)	
Death	2 (3.3)	5 (9.6)	0.32	4 (10.0)	11 (22.9)	0.10
MI	6 (10.0)	6 (11.5)	0.79	0 (0.0)	6 (12.5)	0.05
Death+MI+CVA	8(13.3)	11 (21.2)	0.27	4 (10.0)	14 (29.2)	0.026
TVF	16 (26.7)	15 (28.8)	0.79	10 (25.0)	21 (43.8)	0.06
TVR	12/81 (14.8)	12/69 (17.4)	0.66	7/50 (14.0)	18/73 (24.6)	0.17
TLR	9/97 (9.3)	12/82 (14.6)	0.26	7/61 (11.5)	18/88 (20.5)	0.14

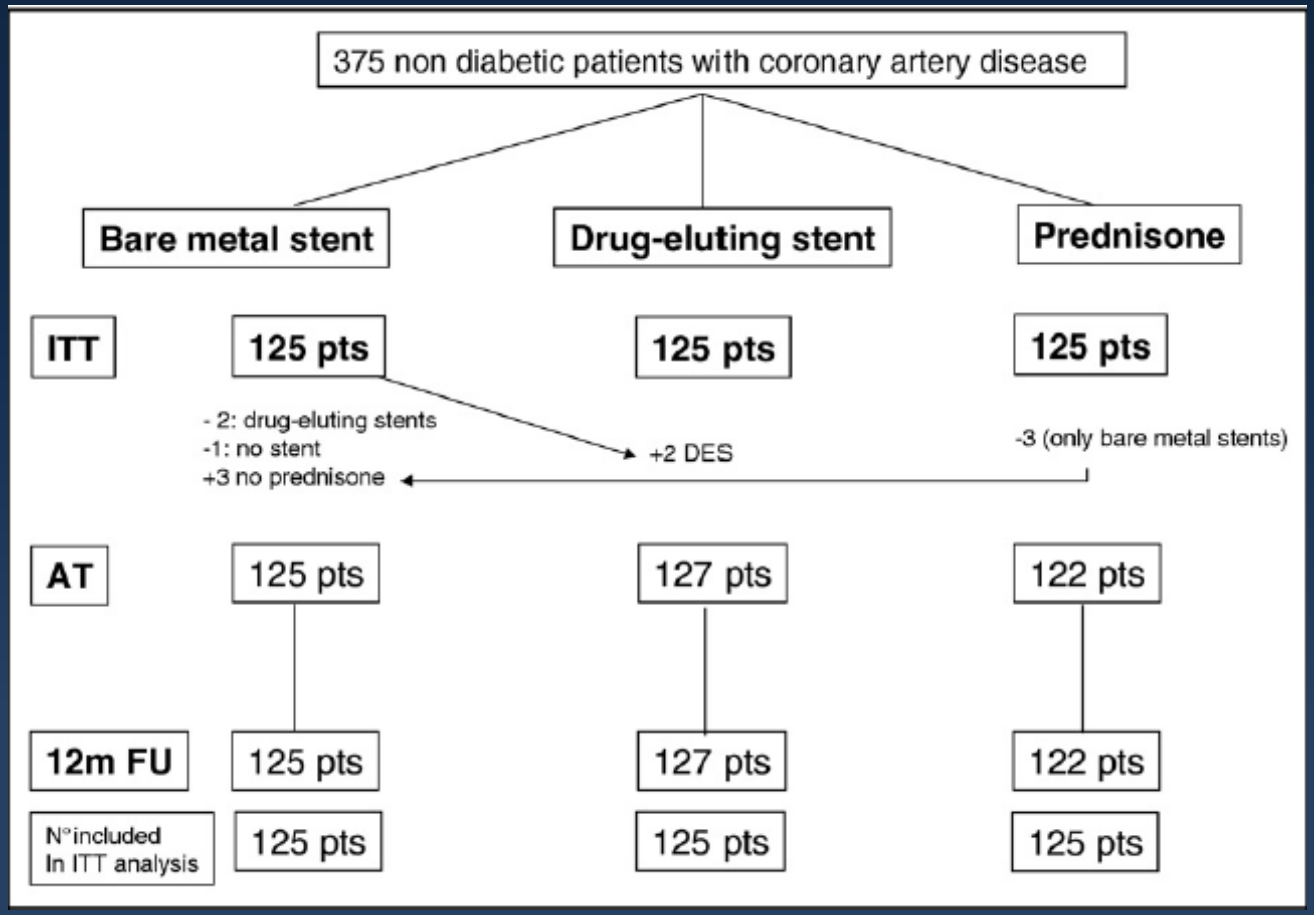
Is here room for OIT??

Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

PREDNISONE Randomized Clinical Trials

Trial	*Design and setting*	*Year of publication*	*Patients*	*OIT drug*	*OIT time interval*	*Stents used in the control arm*	*Primary clinical endpoints*	*Primary angiographic endpoints*	*Secondary endpoints*	*Follow-up (median, days)*
CEREA DES[25]	Multicenter, three arms, BMS- and DES-controlled, de novo and ISR lesions	2011	375	Prednisone	Post-procedure out to 40 days after index PCI (decalage)	BMS or PES, SES	12-month MACE*-free survival	N/A	N/A	330
IMPRESS[24]	Multicenter, two arms, placebo-controlled, persistent elevated CRP levels post-procedure, de novo lesions	2002	83	Prednisone	72h to 45 days after index PCI (decalage)	BMS	12-month event-free survival rate§	6-month restenosis, LLL‖	N/A	360

Long-term clinical follow-up of the multicenter, randomized study to test immunosuppressive therapy with oral prednisone for the prevention of restenosis after percutaneous coronary interventions: Cortisone plus BMS or DES veRsus BMS alone to EliminAte Restenosis (CEREA-DES)



Ribichini F et al. Eur Heart J. 2013 Jun;34(23):1740-8.

CEREA-DES
Long-term clinical events

Follow-up period	BMS	Prednisone	DES	*p1*	*p2*
1–4 years (%)					
All death	1 (0.8)	2 (1.6)	3 (2.4)	1	0.62
Cardiac death	1 (0.8)	2 (1.6)	3 (2.4)	1	0.62
MI	0	0	3 (2.4)	1	0.06
TVR	7 (5.6)	2 (1.6)	5 (4)	0.20	0.90
TLR	2 (1.6)	1 (0.8)	4 (3.2)	1	0.70
Non-TVR	4 (3.2)	3 (2.4)	7 (5.6)	1	0.62
All Revascularizations	11 (8.8)	5 (4)	12 (9.6)	0.30	1
All MACEs	8 (6.4)	4 (3.2)	11 (8.8)	0.60	0.86
4 years (%)					
All death	2 (1.6)	2 (1.6)	3 (2.4)	1	1
Cardiac death	2 (1.6)	2 (1.6)	3 (2.4)	1	1
MI	4 (3.2)	1 (0.8)	4 (3.2)	0.40	1
TVR	29 (23.2)	17 (13.6)	19 (15.2)	0.08	0.20
TLR	17 (13.6)	11 (8.8)	8 (6.4)	0.40	0.10
Non-TVR	9 (7.2)	6 (4.8)	15 (12)	0.90	0.30
Very late stent thrombosis (definite)	0	0	3 (2.4)	1	0.06
Very late stent thrombosis (possible)	0	0	4 (3.2)	1	0.02
Dual antiplatelet therapy	6 (4.8)	4 (3.2)	29 (23.2)	0.68	<0.001
Non-TLR + non-TVR	21 (16.8)	12 (9.6)	26 (20.8)	0.06	0.4
All MACEs	35 (28)	20 (16)	26 (20.8)	0.04	0.38

Ribichini F et al. Eur Heart J. 2013 Jun;34(23):1740-8.

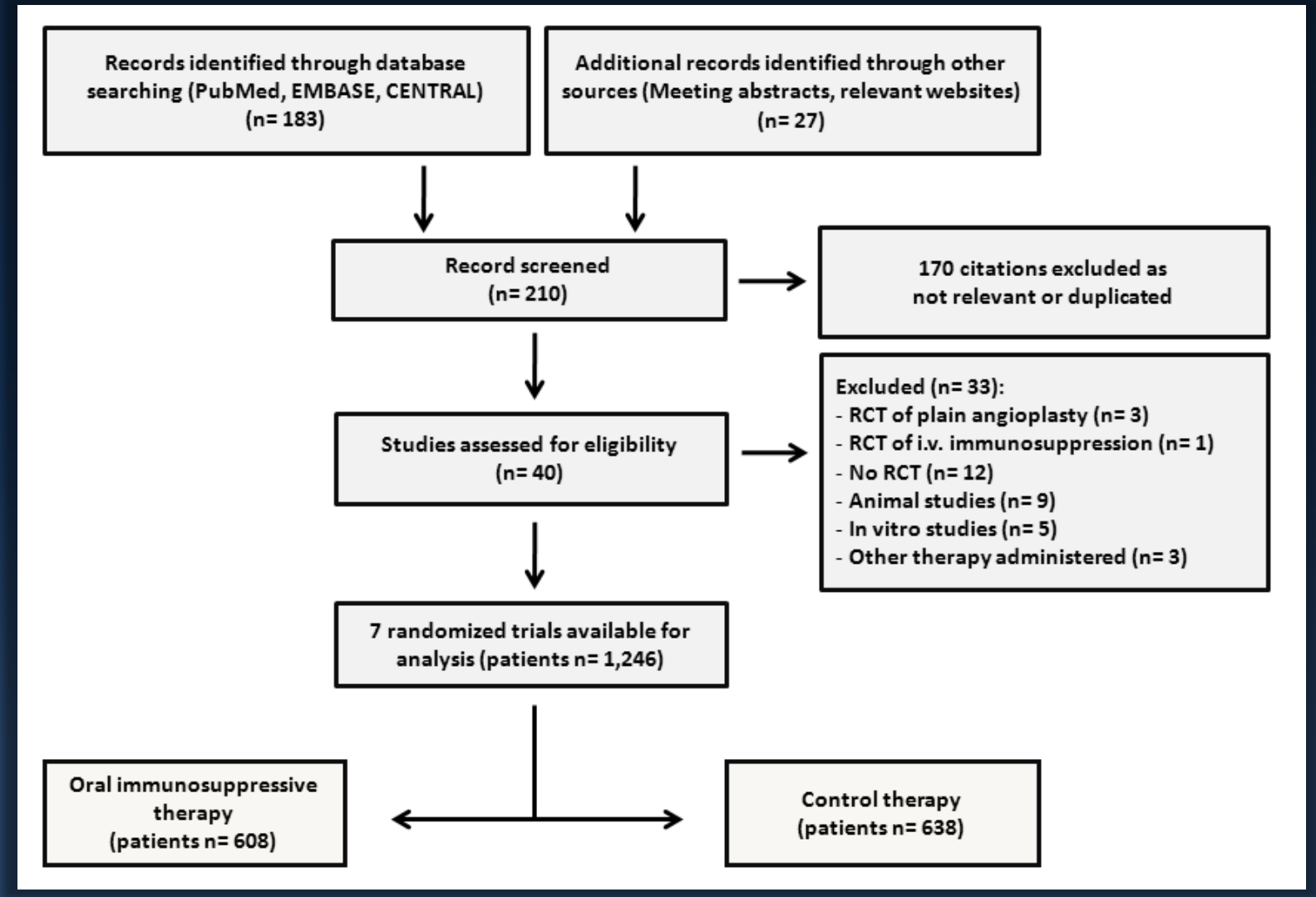
ORAI iMmunosuppressive therapy to prevent in-Stent rEstenosiS (RAMSES) cooperation: a patient-level meta-analysis of randomized trials

Cassese S, De Luca G, Ribichini F, Cernigliaro C, Sansa M, Versaci F, Proietti I, Stankovic G, Stojkovic S, Fernandez-Pereira C, Tomai F, Vassanelli C, Antoniucci D, Serruys PW, Kastrati A, **Rodriguez AE.**

Atherosclerosis. 2014 Dec;237(2):410-7

RAMSES meta-analysis

PRISMA flow chart for the trial selection process.



Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

RAMSES meta-analysis

RAMSES population

5 RCT
OIT+BMS
Vs.
BMS

- Prednisone → **IMPRESS** (41 vs 43)
- Rapamycin → **Cernigliaro et al** (54 vs 54); **ORAR II** (50 vs 50); **Stojkovic et al** (35 vs 37); **OSIRIS** (203 vs 102)

1 RCT
OIT+BMS
Vs.
DES

- Rapamycin → **ORAR III** (100 vs 100)

1 RCT
OIT+BMS
Vs.
DES
Vs.
BMS

- Prednisone → **CEREA-DES** (125 vs 125 vs 125)

Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

RAMSES meta-analysis

Trial	Random sequence generation	Blinding of participants	Blinding of outcome assessment*	Description of incomplete outcome data	Sample size calculation	Trial funding
CEREA DES	Yes (computer-generated)	No	Yes (Independent CEC)	Yes (flow diagram)	Yes (superiority design)	Yes (Public health research grant)
Cernigliaro et al.	Yes (computer-generated)	Yes	Yes (Independent CEC)	Yes (flow diagram)	Yes (superiority design)	No (Investigator driven)
IMPRESS	Yes (computer-generated)	Yes	Yes (Independent CEC)	Yes	Yes (superiority design)	No (Investigator driven)
ORAR II	Yes (central random list)	No	Yes (Independent CEC)	Yes	Yes (superiority design)	No (Investigator driven)
ORAR III	Yes (central random list)	Yes	Yes (Independent CEC)	Yes (flow diagram)	Yes (non-inferiority design)	No (Investigator driven)
OSIRIS	Yes (central random list)	Yes	Yes (Independent CEC)	Yes	Yes (superiority design)	No (Investigator driven)
Stojkovic et al.	Yes	No	Yes (Independent CEC)	Yes	Yes (superiority design)	No (Investigator driven)

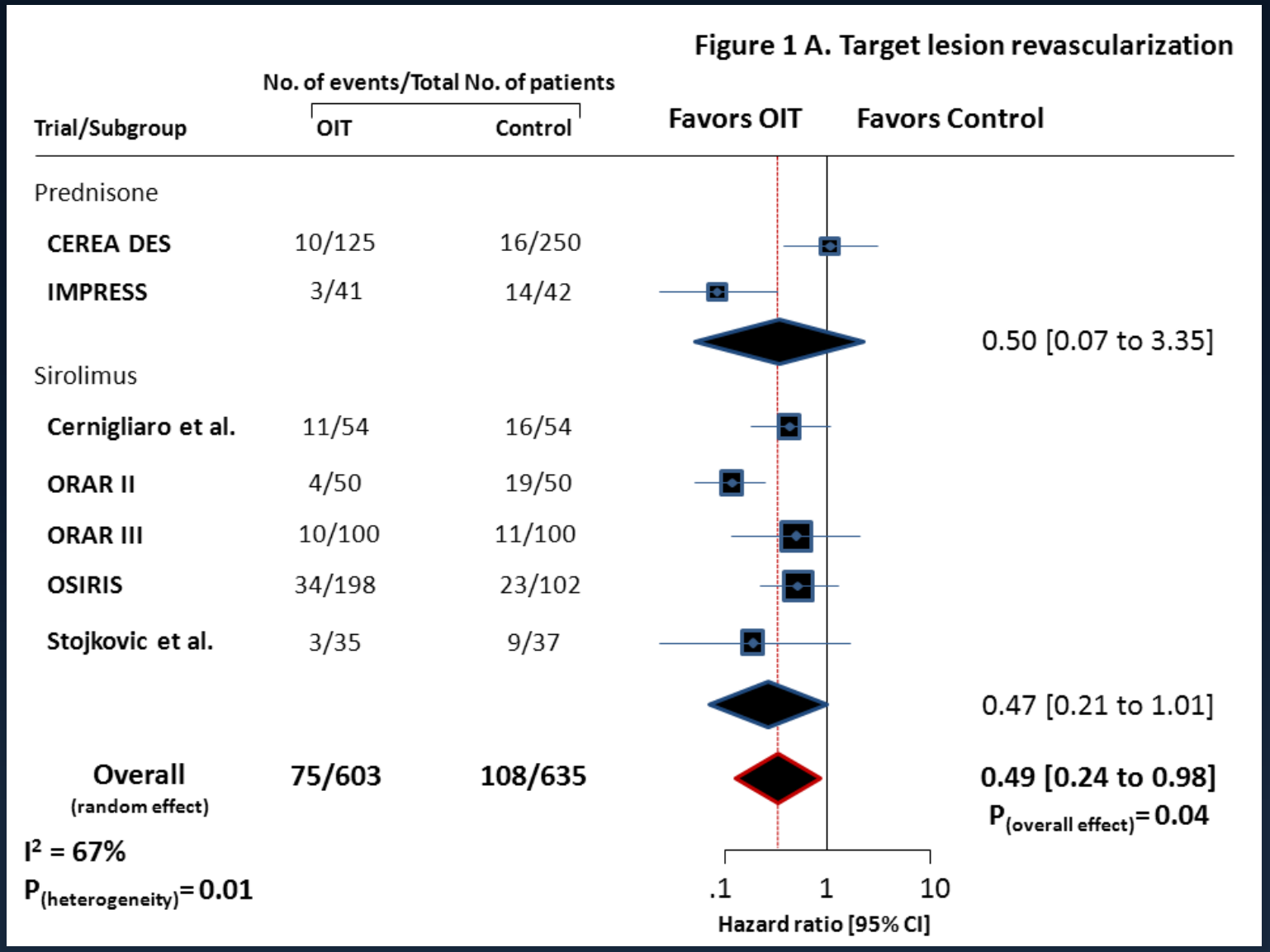
Assessment of risk of bias

Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

End Points

- #Primary endpoints were target lesion revascularization (TLR) and the composite of death/myocardial infarction (MI).
- # Secondary endpoints were death, MI, stent thrombosis (ST) and in-stent late lumen loss at angiographic surveillance.
- #All endpoints were evaluated according to per protocol definitions and events count was hierarchical, considering always the most severe event when more than one occurred.

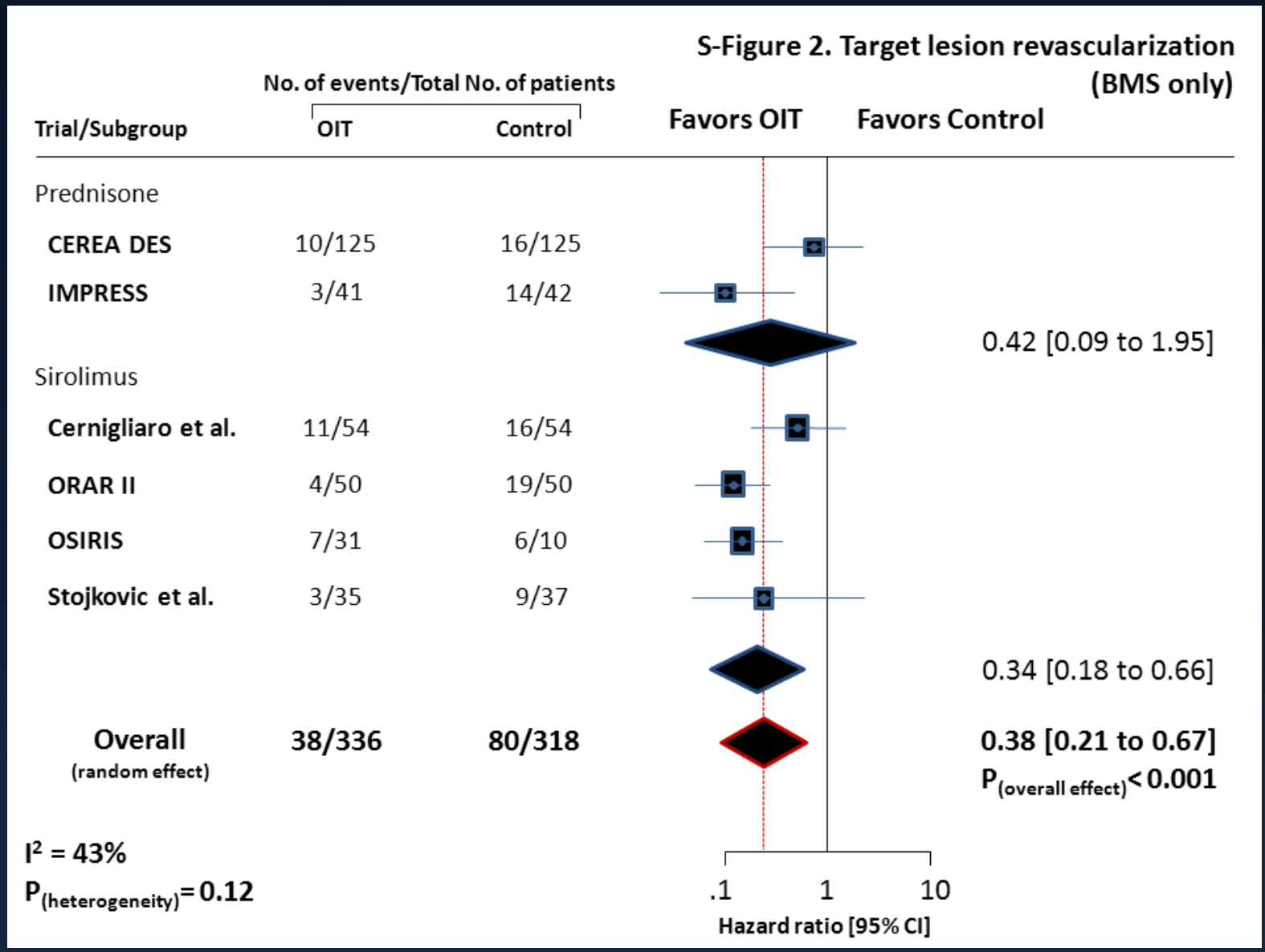
RAMSES meta-analysis



Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

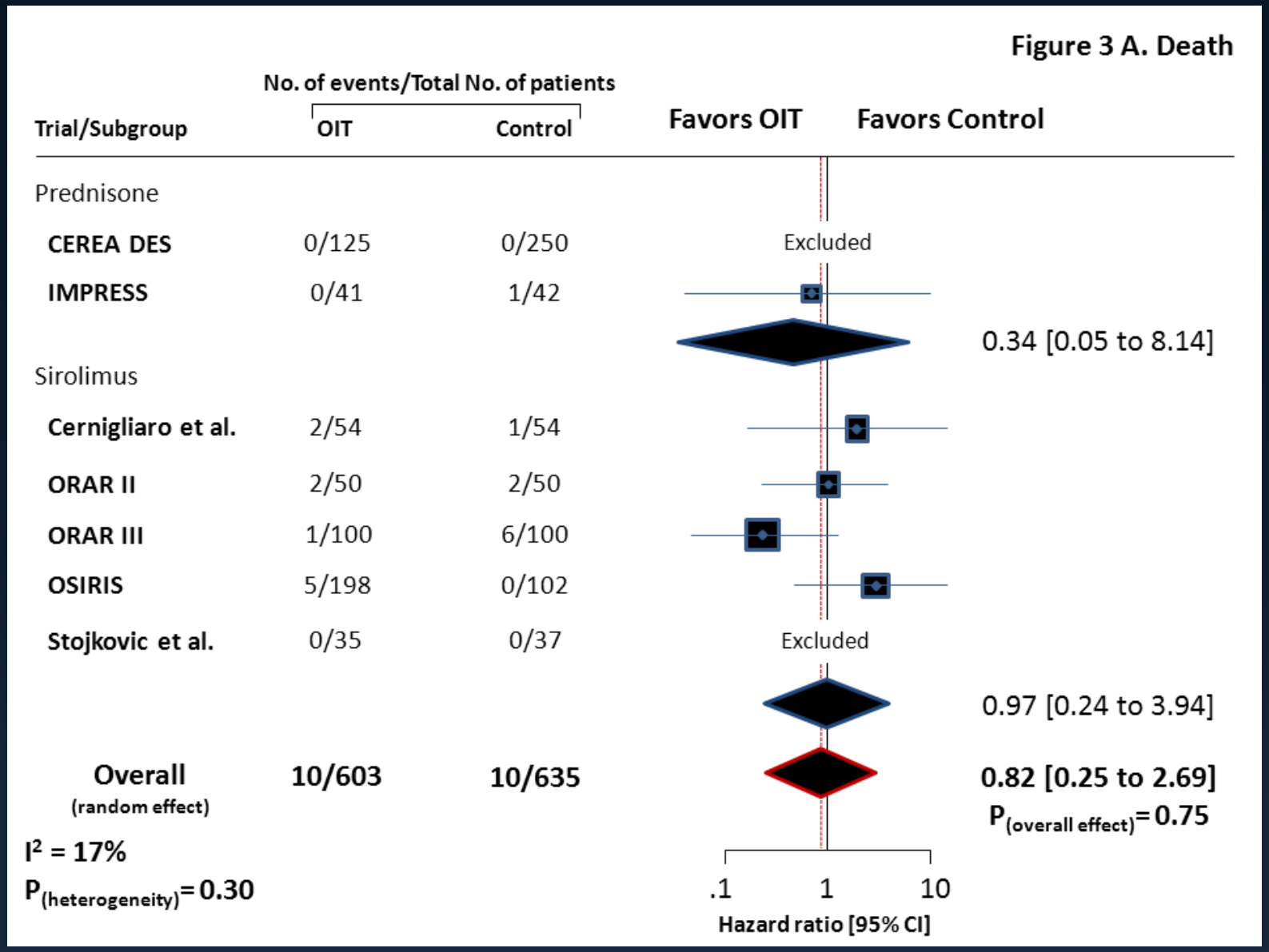
RAMSES meta-analysis

Analysis of TLR for BMS+OIT versus BMS



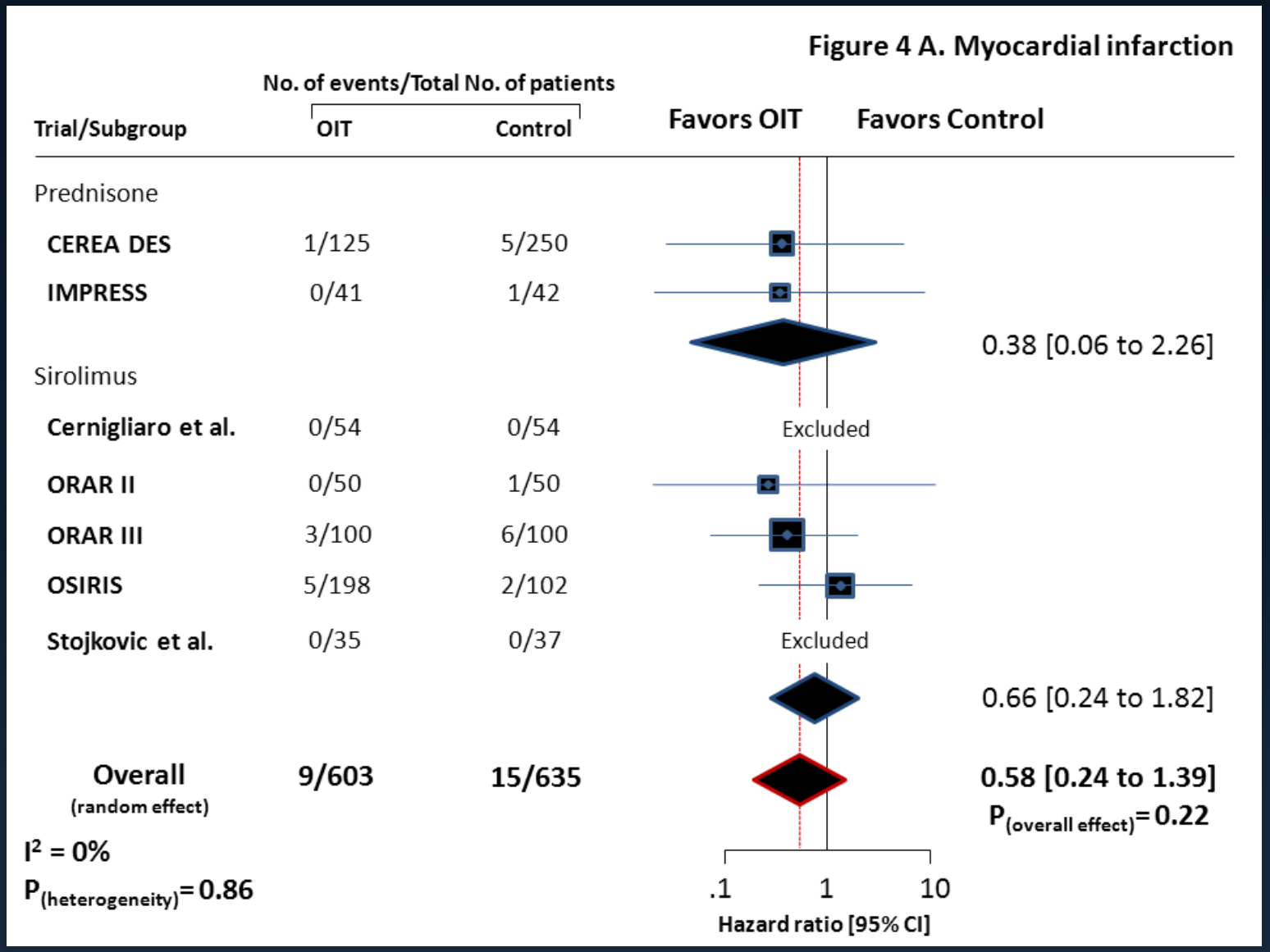
Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

RAMSES meta-analysis



Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

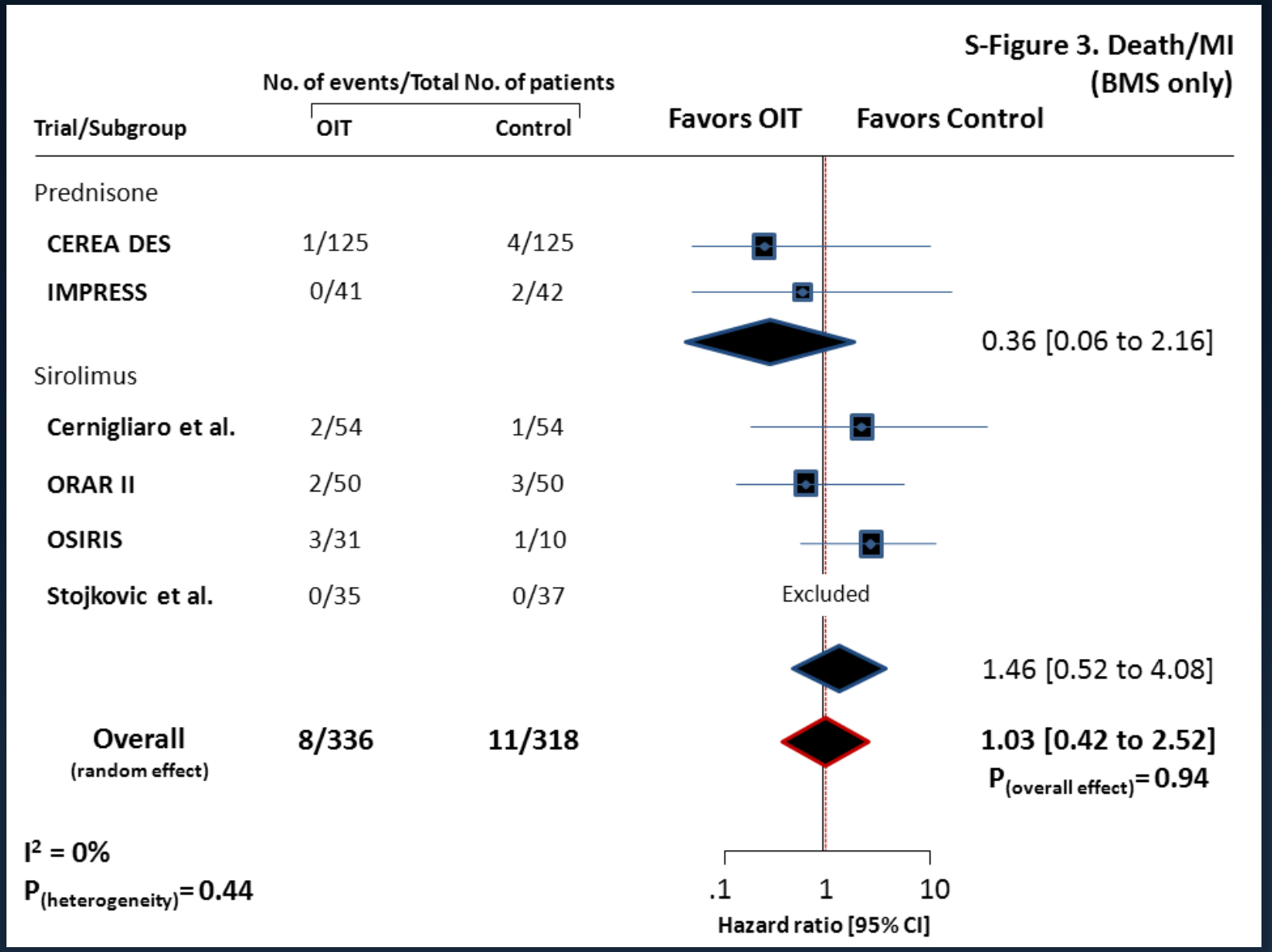
RAMSES meta-analysis



Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

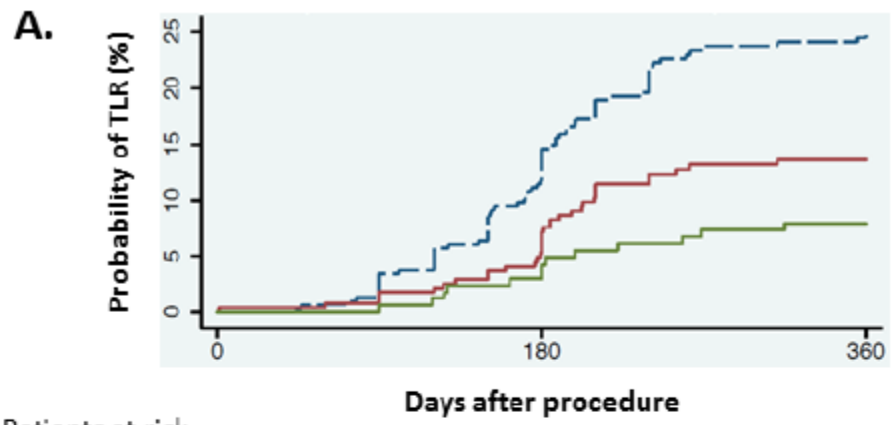
RAMSES meta-analysis

Analysis of death/MI for BMS+OIT versus BMS.



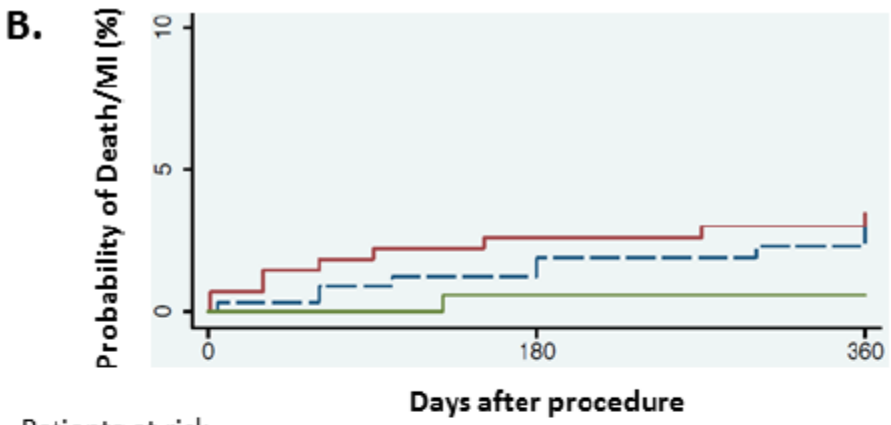
Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

Survival curves for primary and secondary endpoints according to the treatment received (BMS+OIT [prednisone or sirolimus] or BMS).



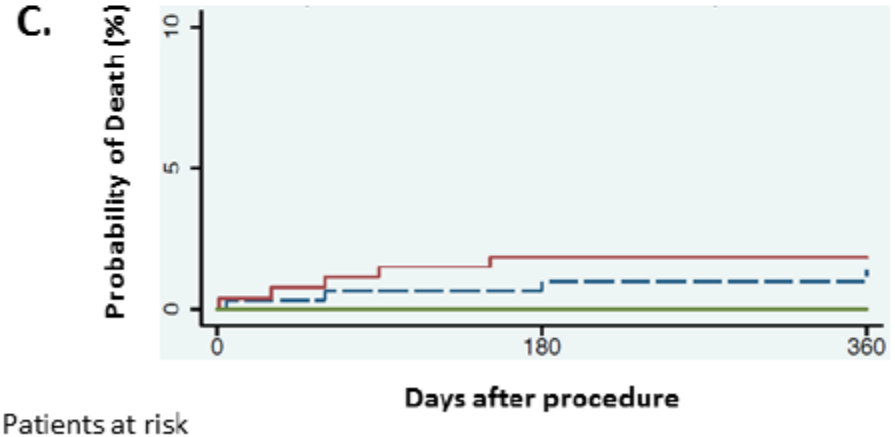
Patients at risk

Prednisone	166	161	153
Sirolimus	437	403	310
BMS	318	277	197



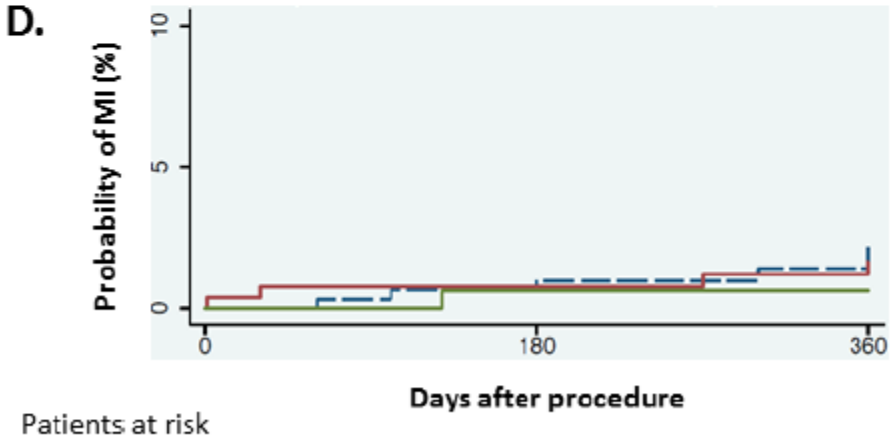
Patients at risk

Prednisone	166	163	162
Sirolimus	437	419	363
BMS	318	303	242



Patients at risk

Prednisone	166	166	165
Sirolimus	437	425	369
BMS	318	305	245

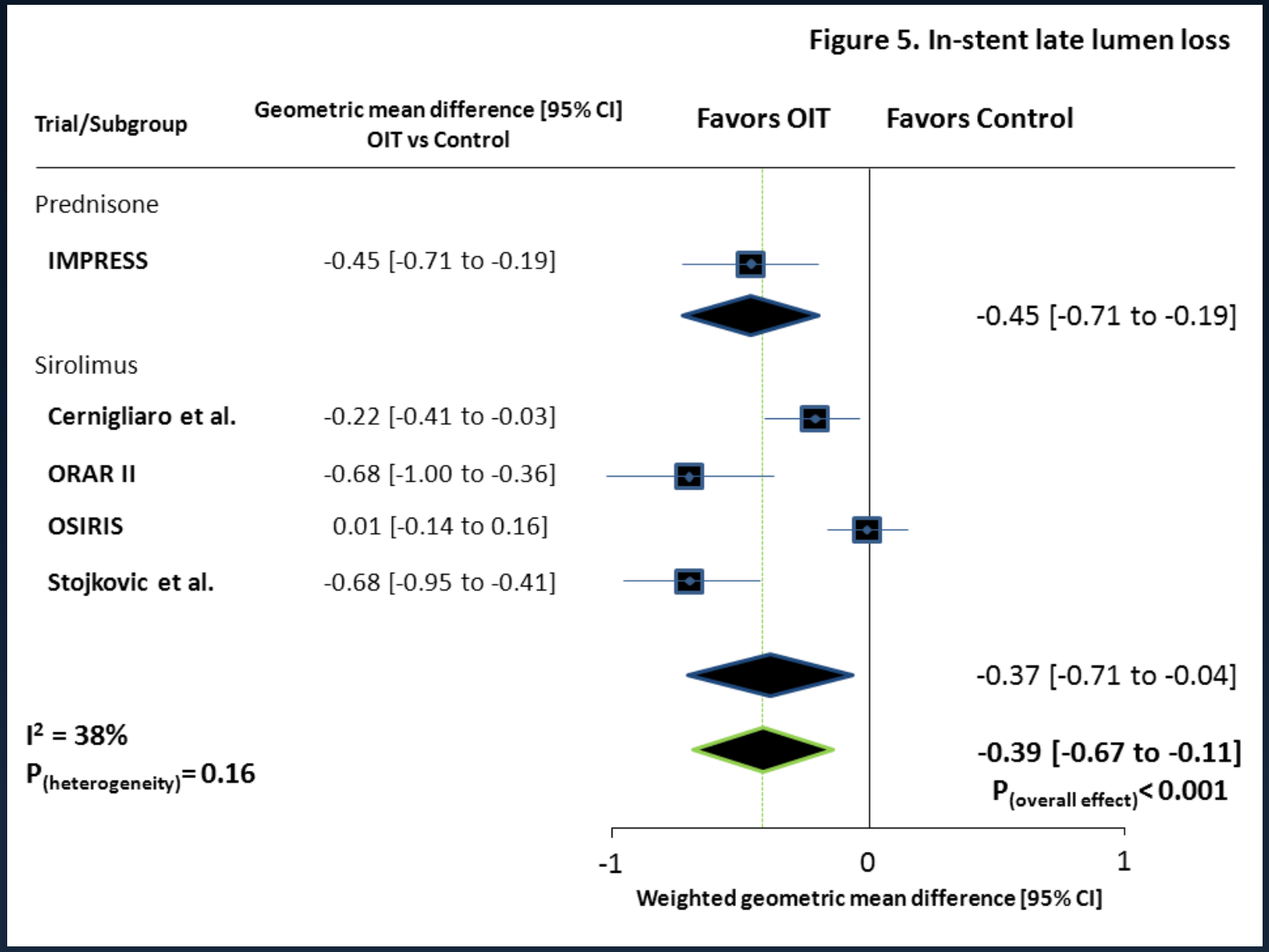


Patients at risk

Prednisone	166	163	161
Sirolimus	437	423	368
BMS	318	303	242

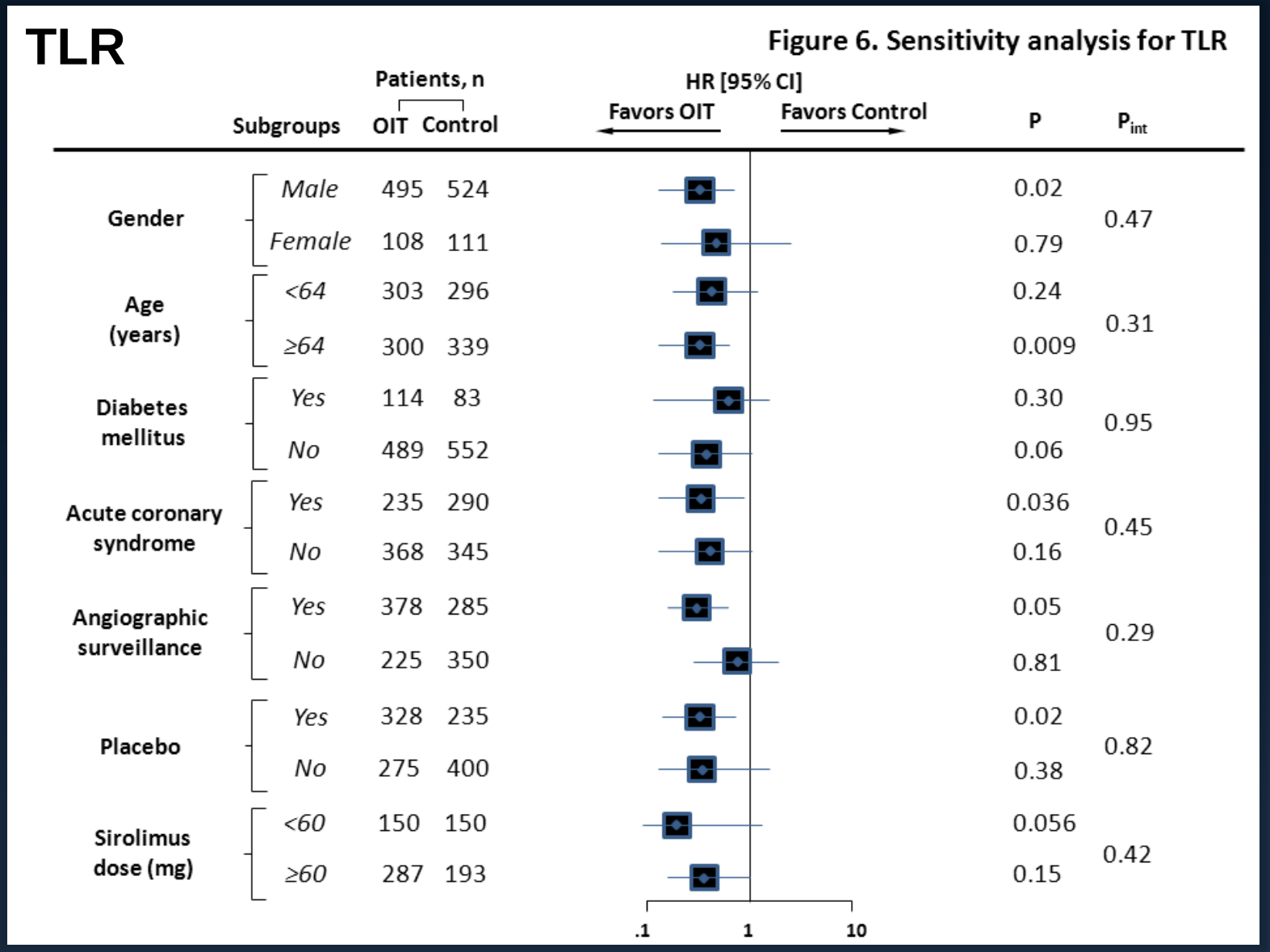
Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

RAMSES meta-analysis



Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

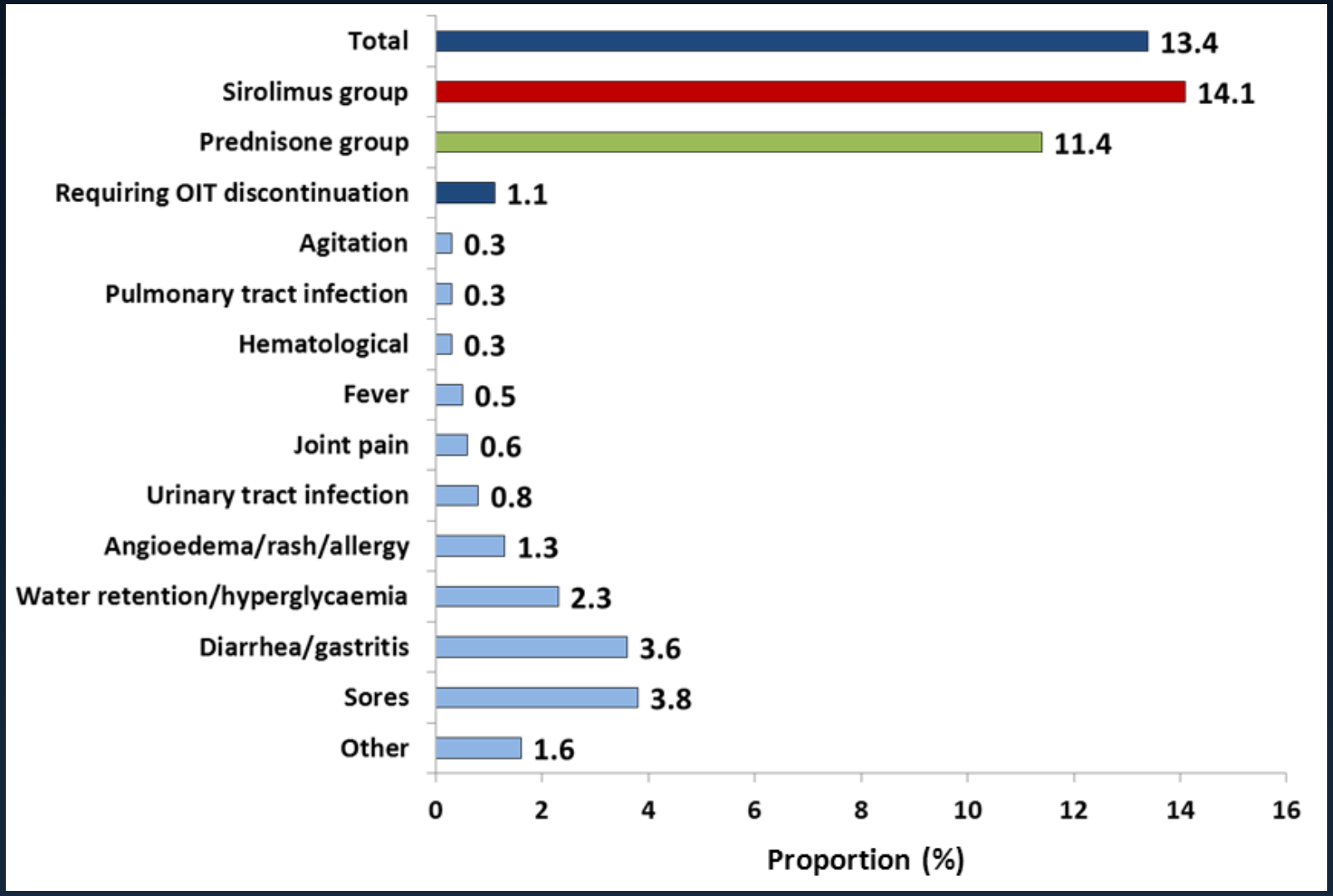
RAMSES meta-analysis



Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

RAMSES meta-analysis

Side effects associated with OIT



Cassese, Kastrati, Rodriguez et al. Atherosclerosis. 2014 Dec;237(2):410-7

Colchicine Treatment for the Prevention of Bare-Metal Stent Restenosis in Diabetic Patients

- Double blind, prospective, placebo controlled study included 196 diabetic pt treated with BMS randomly asigned to colchicine 0.5 mg (n=100) or placebo (n=96) twice daily for 6 months.
- Angiography and IVUS to monitor restenosis 6 months after initial procedure.
- Well ballanced demographic and angiographic baseline characteristics.
- 16% of adverse events in colchicine group (diarrhea or nausea) vs 7% in placebo.

Results at 6 months of FU

	Colchicine (n = 100)	Controls (n = 96)	*P* Value
In-Stent Restenosis	16%	33%	0.007
Late Lumen Loss, mm	0.4	0.9	< 0.01
MLD, mm	2.8	2.3	< 0.01

Deftereos S et al. J Am Coll Cardiol. 2013 Apr 23;61(16):1679-85.

ORAL TREATMENT TO PREVENT RESTENOSIS

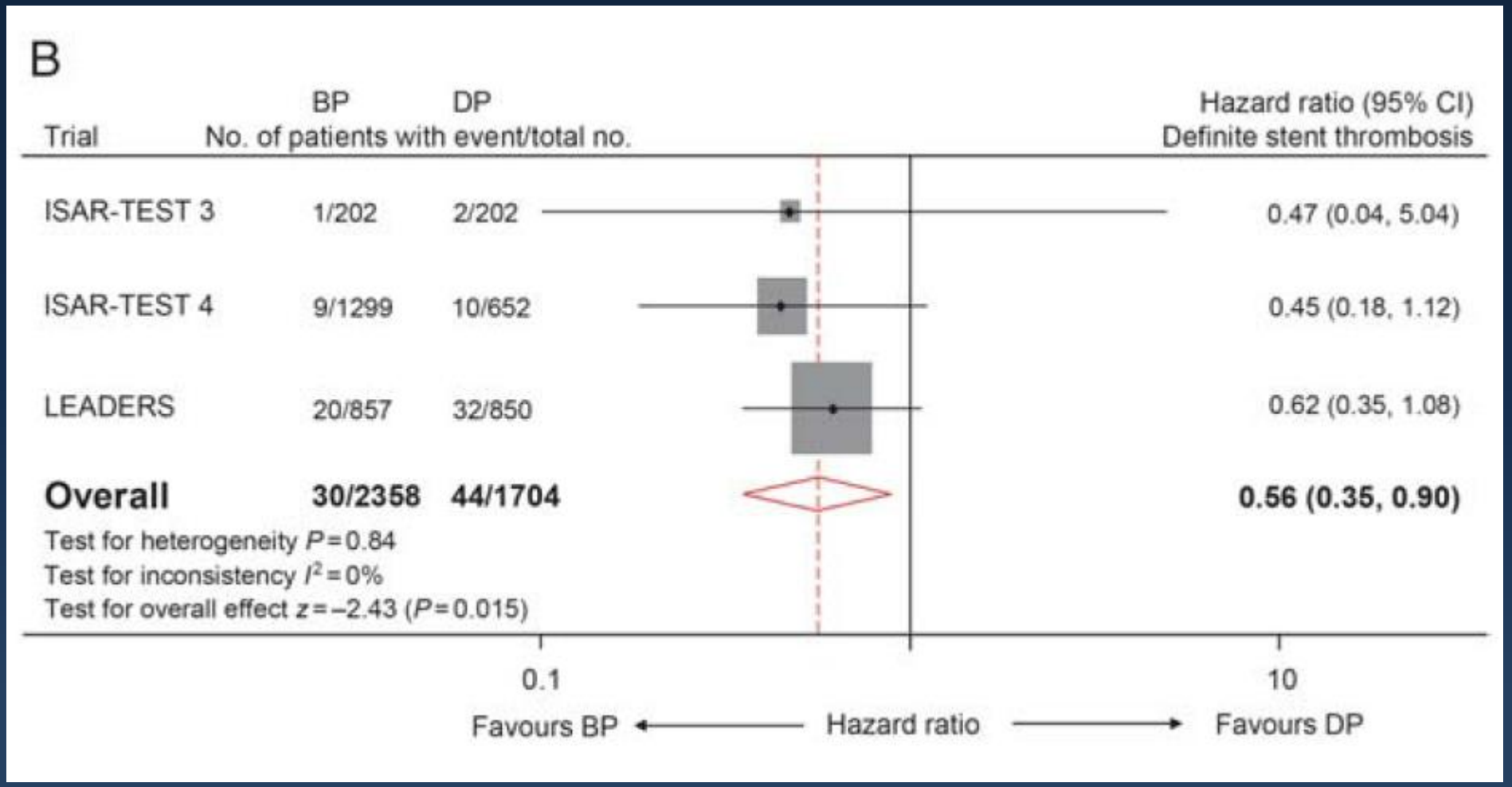
Pooled data from ORAR 3 (5 yrs FU) and CEREA-DES (4 yrs FU)
Rapamycin/Prednisone+BMS vs Cypher, Taxus & Endeavor

	OIT (225 p)	DES (225 p)	P value
Death	8/225	19/225	0.02
MI	7/225	16/225	0.04
TLR	27/350	38/360	0.2
SET	2/225	16/225	<0.001
Very Late SET	1/225	11/225	0.002

Rodriguez AE et al. Am J Cardiol. 2014 Mar 1;113(5):815-21

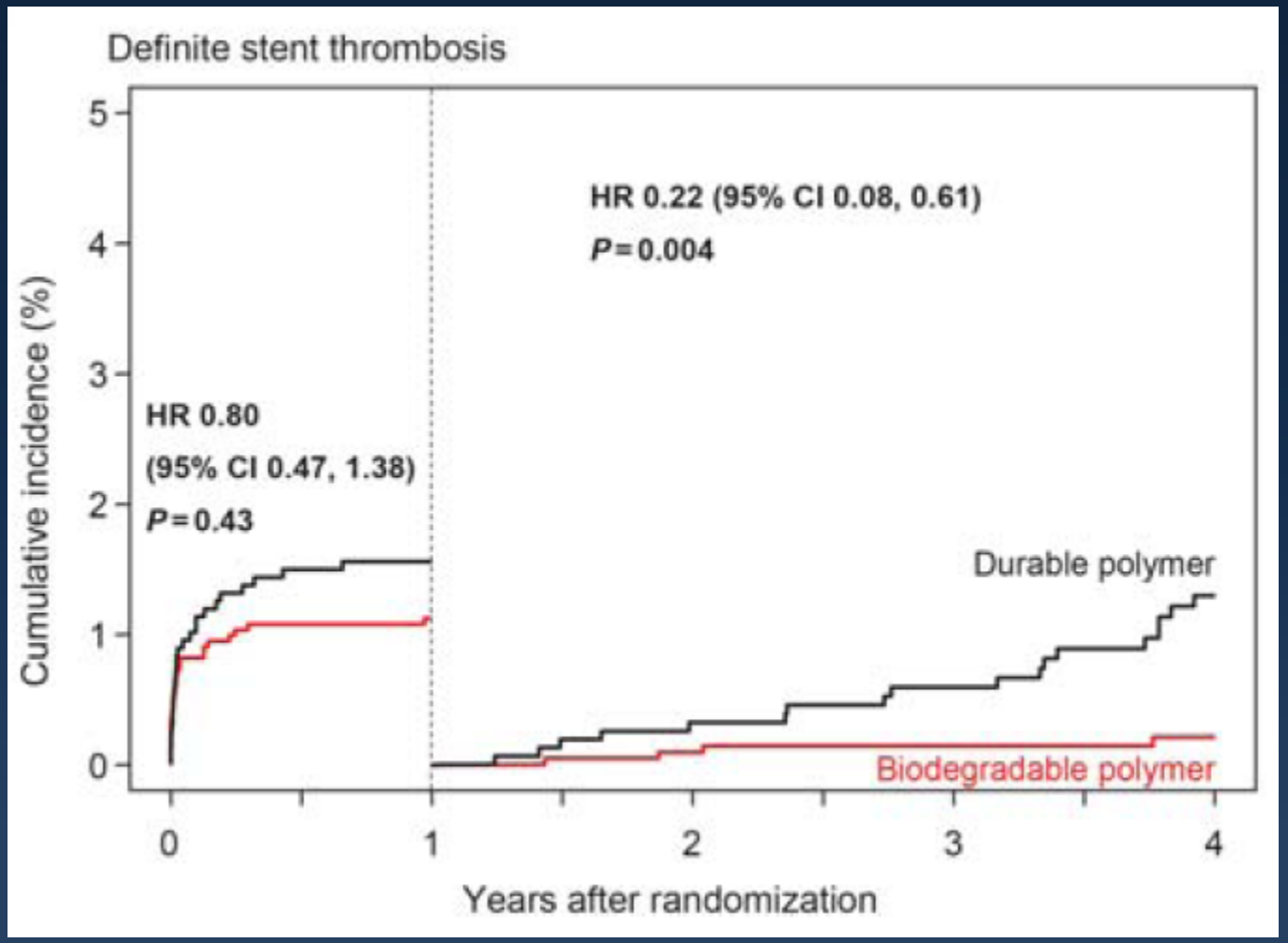
Ribichini F et al. Eur Heart J. 2013 Jun;34(23):1740-8.

Stent thrombosis and new DES generations
Biodegradable polymers



GG Stefanini, RA Byrne, PW Serruys et al.
Eur Heart J. 2012 May;33(10):1214-22

Stent thrombosis and new DES generations
Biodegradable polymers



GG Stefanini, RA Byrne, PW Serruys et al.
Eur Heart J. 2012 May;33(10):1214-22

	SES (n=73 Lesions)	PES (n=85 Lesions)	CoCr-EES (n=46 Lesions)	*P* Value CoCr-EES vs SES	*P* Value CoCr-EES vs PES
No. of histological sections evaluated	479	578	300		
No. of stent struts evaluated	4546	6037	3873		
External elastic lamina area, mm^2	14.2±5.1	14.1±5.6	12.5±5.0	0.010	0.089
Stent area, mm^2	6.7±2.2	7.2±3.2	6.2±2.4	0.15	0.034
Underlying plaque area, mm^2	7.5±3.9	6.9±3.3	6.3±3.1	0.16	0.34
Mean neointimal thickness, mm	0.09 (0.04–0.18)	0.11 (0.06–0.19)	0.09 (0.03–0.18)	0.89	0.32
Maximum neointimal thickness, mm	0.19 (0.08–0.32)	0.26 (0.17–0.35)	0.20 (0.10–0.39)	0.93	0.13
Uncovered struts, %	18.0 (0–51.4)	18.7 (7.1–44.4)	2.6 (0–7.1)	<0.0005	<0.0005
Prevalence of >30% uncovered struts*	44 (60)	57 (67)	9 (20)	<0.0005	<0.0005
Struts with fibrin, %	29.9 (12.1–59.9)	51.1 (36.9–72.9)	8.5 (0–28.2)	0.001	<0.0005
Inflammation score†	1.00 (0.33–2.00)	1.00 (0.13–1.44)	0.26 (0–0.60)	<0.0005	0.006
Maximum number of eosinophils per strut‡	0 (0–9.5)	0 (0–2.0)	0 (0–1.3)	0.009	0.59
Struts with giant cells, %	16.7 (9.5–41.4)	3.0 (0–9.0)	7.5 (3.3–18.2)	0.002	0.001
Prevalence of malapposition	12 (16)	15 (18)	2 (4)	0.065	0.043
Prevalence of hypersensitivity reaction§	6 (8)	0 (0)	0 (0)	0.081	…
Prevalence of neoatherosclerosis‖	25/72 (35)	15/78 (19)	12/41 (29)	0.91	0.19
Foamy macrophage clusters	8/72 (11)	13/78 (17)	8/41 (20)	0.15	0.69
Fibroatheroma	15/72 (21)	2/78 (3)	4/41 (10)	0.32	0.13
TCFA/in-stent plaque rupture§	2/72 (2)	0/78 (0)	0/41 (0)	0.52	…
Distribution of neoatherosclerosis‖¶					
None/focal/diffuse	47/10/15	63/11/4	29/7/5	Ref/0.62/0.48	Ref/0.47/0.13
Prevalence of calcification within the neointima‖	14/72 (19)	4/78 (5)	3/41 (7)	0.048	0.88

F Otsuka, Finn A, Virmani R et al. ***Circultation*** 2014; 129:211-223

Prevalence of Neoatherosclerosis

	SES (n=73 Lesions)	PES (n=85 Lesions)	CoCr-EES (n=46 Lesions)	*P* Value CoCr-EES vs SES	*P* Value CoCr-EES vs PES
No. of histological sections evaluated	479	578	300		
No. of stent struts evaluated	4546	6037	3873		
Prevalence of neoatherosclerosis‖	25/72 (35)	15/78 (19)	12/41 (29)	0.91	0.19
Foamy macrophage clusters	8/72 (11)	13/78 (17)	8/41 (20)	0.15	0.69
Fibroatheroma	15/72 (21)	2/78 (3)	4/41 (10)	0.32	0.13
TCFA/in-stent plaque rupture§	2/72 (2)	0/78 (0)	0/41 (0)	0.52	…
Distribution of neoatherosclerosis‖¶					
None/focal/diffuse	47/10/15	63/11/4	29/7/5	Ref/0.62/0.48	Ref/0.47/0.13
Prevalence of calcification within the neointima‖	14/72 (19)	4/78 (5)	3/41 (7)	0.048	0.88

F Otsuka, Finn A, Virmani R et al. ***Circultation*** 2014; 129:211-223

Conclusions

- *1#.Notwithstanding that latest DES designs are significantly more safer than previous ones, BMS implantation during PCI have not been abandoned and are expected to grow in the next 5 years.*

- *2#. Oral Immunosuppressive therapy (OI) after BMS implantation significantly reduced restenosis rates compared to BMS alone. The reduction was driven by less late lumen loss with OI.*

- *3#. Taking into consideration the randomized data, rapamycin and prednisone appear to be the most promising in this setting. However, prednisone cannot be used in diabetics which limits its use.*

- *4#. The use of oral agents to reduce restenosis should be considered in all patients with relative contraindications for DES implantation.*

- *5#.We believe that the guidelines should be amended to include these agents in certain specific situations*

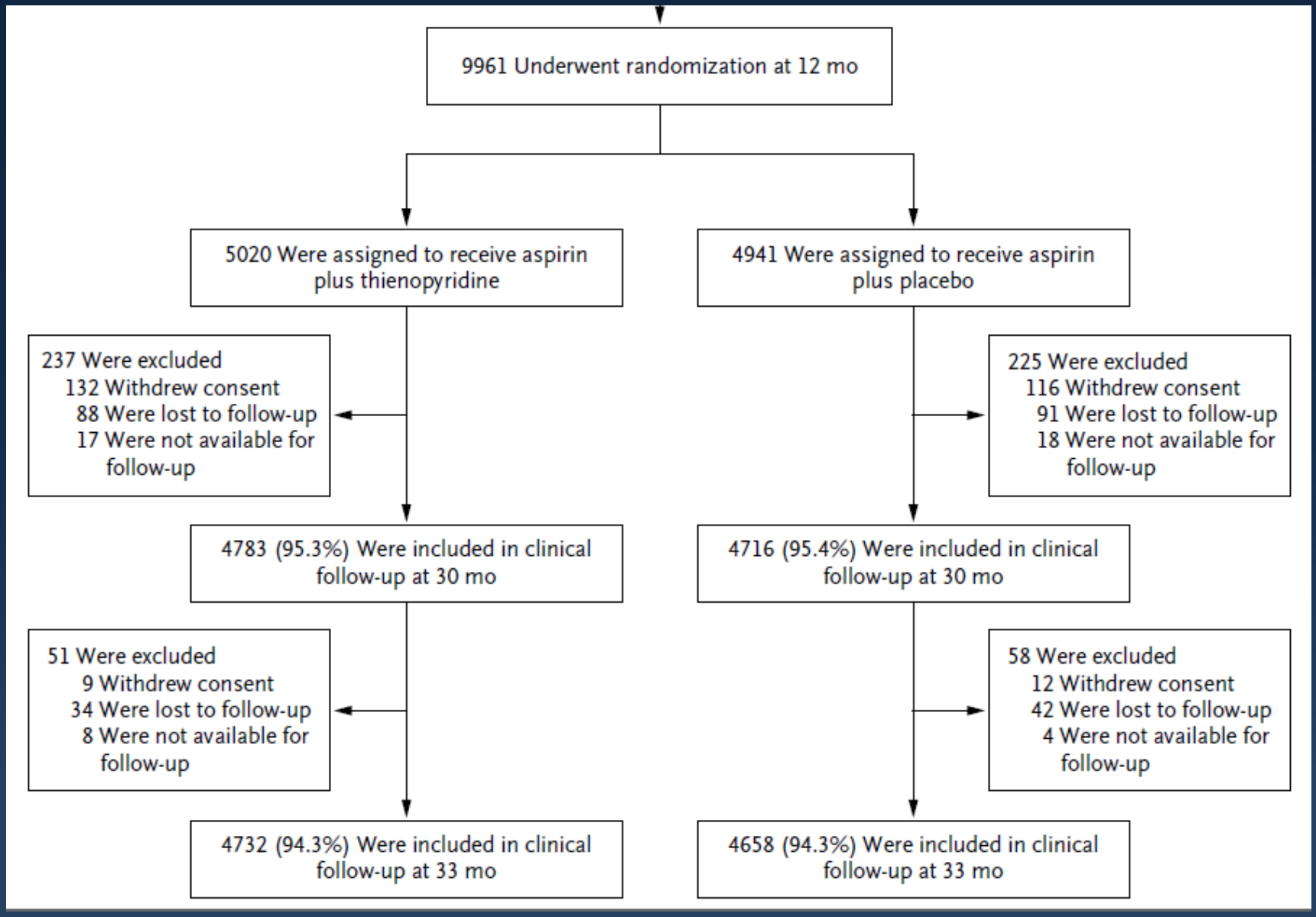
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2014 VOL. 371 NO. 23

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

DAPT duration – DAPT Trial



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

Objectives

DAPT STUDY

- To determine whether dual antiplatelet therapy beyond 12 months is associated with reduction in **stent thrombosis** and/or **major adverse cardiovascular and cerebrovascular events**
- To determine the impact of dual antiplatelet therapy beyond 12 months on **moderate or severe bleeding**

In a broadly inclusive population treated with coronary stents

Primary End Points

DAPT STUDY

Two powered co-primary effectiveness end points

- **Definite or probable stent thrombosis**
  (Academic Research Consortium definition)
- **Major adverse cardiovascular or cerebrovascular events**
  (MACCE, death, MI or stroke)

Powered primary safety end point

- **Moderate or severe bleeding**
  (Global Utilization of Streptokinase and TPA for Occluded Arteries classification [GUSTO])

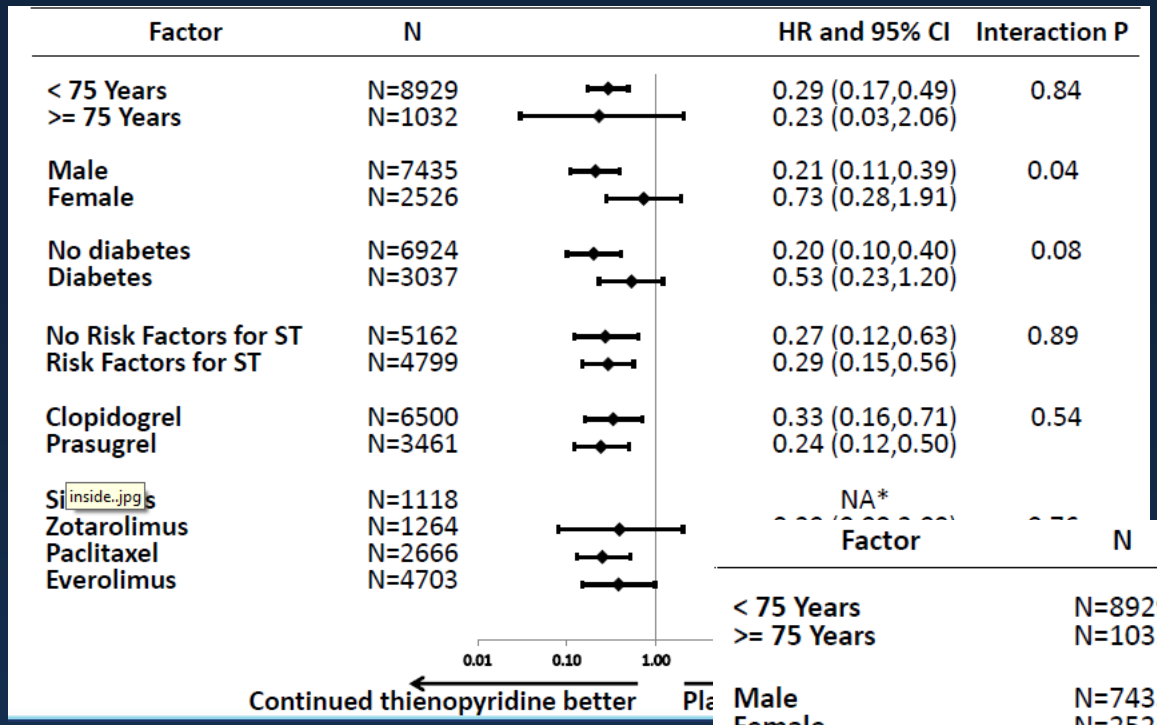
Primary analysis period = drug treatment period of 12-30 m

Primary analysis cohort: randomized DES-treated subjects

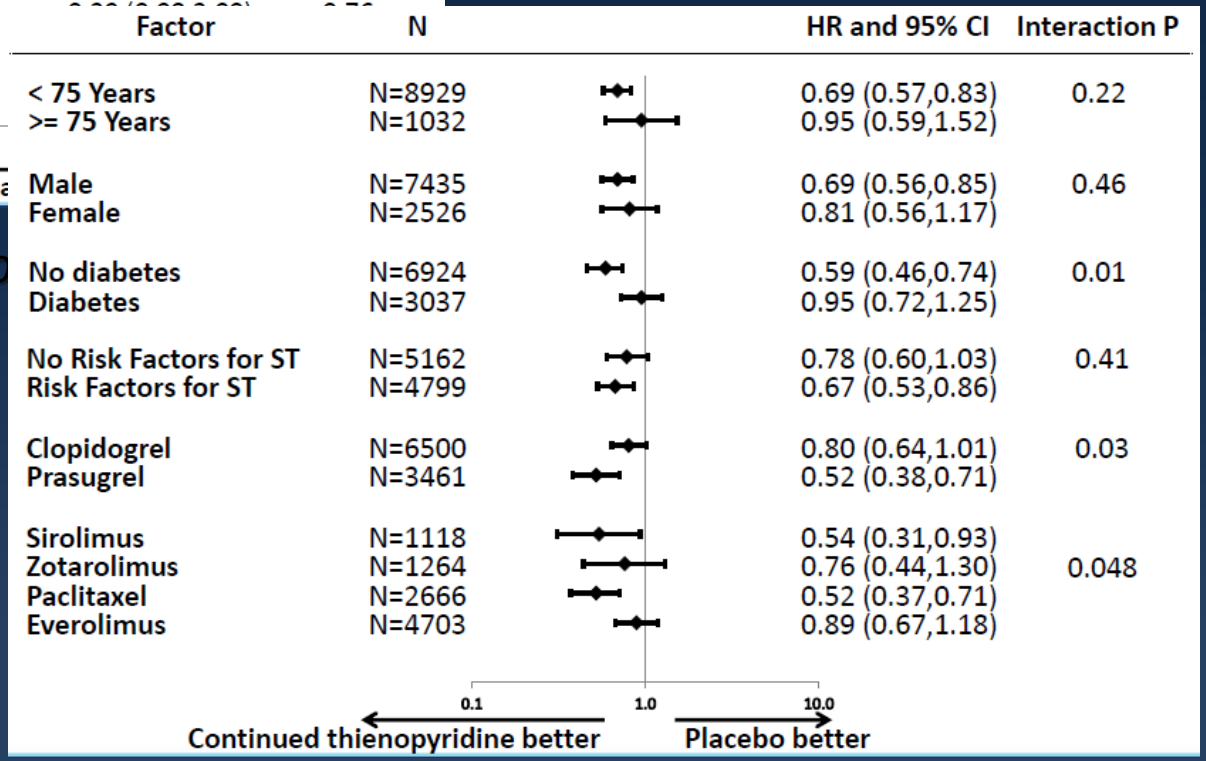
Baseline Characteristics

	Thienopyridine N=5020	Placebo N=4941	P-value
Age (years)	61.8	61.6	0.24
Female	24.7%	26.0%	0.15
Race – Non White	8.9%	8.6%	0.67
Ethnicity-Hispanic or Latino	3.2%	3.3%	0.91
Weight – kg	91.5	91.5	0.93
BMI	30.5	30.6	0.92
Diabetes Mellitus	31.1%	30.1%	0.28
Hypertension	75.8%	74.0%	0.03
Cigarette Smoker	24.6%	24.7%	0.91
Prior PCI	30.4%	31.0%	0.50
Prior CABG	11.3%	11.8%	0.49
NSTEMI	15.5%	15.5%	0.93
STEMI	10.6%	10.3%	0.65
Number of Treated Vessels	1.11	1.12	0.60
Number of Stents	1.47	1.45	0.23
Total Stent Length (mm)	27.7	27.4	0.43
Stent Diameter <3mm (min per subject	46.6%	46.4%	0.99

DAPT duration – DAPT Trial



Stent thrombo



MACCE

Bleeding End Point during Month 12 to Month 30

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 7, 2015 VOL. 372 NO. 19

Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer Bansilal, M.D., M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Pierre Theroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D., Shinya Goto, M.D., Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H., for the PEGASUS-TIMI 54 Steering Committee and Investigators*

DAPT duration – PEGASUS TIMI 54 Trial

Characteristic	Ticagrelor, 90 mg (N=7050)	Ticagrelor, 60 mg (N=7045)	Placebo (N=7067)
Age — yr	65.4±8.4	65.2±8.4	65.4±8.3
Female sex — no. (%)	1682 (23.9)	1661 (23.6)	1717 (24.3)
White race — no. (%)†	6126 (86.9)	6077 (86.3)	6124 (86.7)
Weight — kg	82.0±16.7	82.0±17.0	81.8±16.6
Hypertension — no. (%)	5462 (77.5)	5461 (77.5)	5484 (77.6)
Hypercholesterolemia — no. (%)	5410 (76.7)	5380 (76.4)	5451 (77.1)
Current smoker — no. (%)	1187 (16.8)	1206 (17.1)	1143 (16.2)
Diabetes mellitus — no. (%)	2241 (31.8)	2308 (32.8)	2257 (31.9)
Multivessel coronary artery disease — no./total no. (%)	4155/7049 (58.9)	4190/7042 (59.5)	4213/7067 (59.6)
History of PCI — no./total no. (%)‡	5852/7049 (83.0)	5879/7044 (83.5)	5837/7066 (82.6)
>1 Prior myocardial infarction — no. (%)	1143 (16.2)	1168 (16.6)	1188 (16.8)
Peripheral-artery disease — no. (%)	371 (5.3)	368 (5.2)	404 (5.7)
Estimated glomerular filtration rate <60 ml/min/1.73 m^2 — no./total no. (%)§	1653/6958 (23.8)	1547/6955 (22.2)	1649/6985 (23.6)
Qualifying event¶			
Years since myocardial infarction			
Median	1.7	1.7	1.7
Interquartile range	1.2–2.3	1.2–2.3	1.2–2.3
Type of myocardial infarction — no. (%)			
STEMI	3763/7043 (53.4)	3757/7035 (53.4)	3809/7057 (54.0)
NSTEMI	2898/7043 (41.1)	2842/7035 (40.4)	2843/7057 (40.3)
Unknown type	382/7043 (5.4)	436/7035 (6.2)	405/7057 (5.7)

M. Bonaca et al. N Engl J Med 2015;372:1791-800

End Point	Ticagrelor, 90 mg (N=7050)	Ticagrelor, 60 mg (N=7045)	Placebo (N=7067)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Cardiovascular death, myocardial infarction, or stroke	493 (7.85)	487 (7.77)	578 (9.04)	0.85 (0.75–0.96)	0.008	0.84 (0.74–0.95)	0.004
Death from coronary heart disease, myocardial infarction, or stroke	438 (6.99)	445 (7.09)	535 (8.33)	0.82 (0.72–0.93)	0.002	0.83 (0.73–0.94)	0.003
Cardiovascular death or myocardial infarction	424 (6.79)	422 (6.77)	497 (7.81)	0.85 (0.75–0.97)	0.01	0.85 (0.74–0.96)	0.01
Death from coronary heart disease or myocardial infarction	350 (5.59)	360 (5.75)	429 (6.68)	0.81 (0.71–0.94)	0.004	0.84 (0.73–0.96)	0.01
Cardiovascular death	182 (2.94)	174 (2.86)	210 (3.39)	0.87 (0.71–1.06)	0.15	0.83 (0.68–1.01)	0.07
Death from coronary heart disease	97 (1.53)	106 (1.72)	132 (2.08)	0.73 (0.56–0.95)	0.02	0.80 (0.62–1.04)	0.09
Myocardial infarction	275 (4.40)	285 (4.53)	338 (5.25)	0.81 (0.69–0.95)	0.01	0.84 (0.72–0.98)	0.03
Stroke							
Any	100 (1.61)	91 (1.47)	122 (1.94)	0.82 (0.63–1.07)	0.14	0.75 (0.57–0.98)	0.03
Ischemic	88 (1.41)	78 (1.28)	103 (1.65)	0.85 (0.64–1.14)	0.28	0.76 (0.56–1.02)	0.06
Death from any cause	326 (5.15)	289 (4.69)	326 (5.16)	1.00 (0.86–1.16)	0.99	0.89 (0.76–1.04)	0.14

Efficacy End Points as 3-Year Kaplan–Meier Estimates

M. Bonaca et al. N Engl J Med 2015;372:1791-800

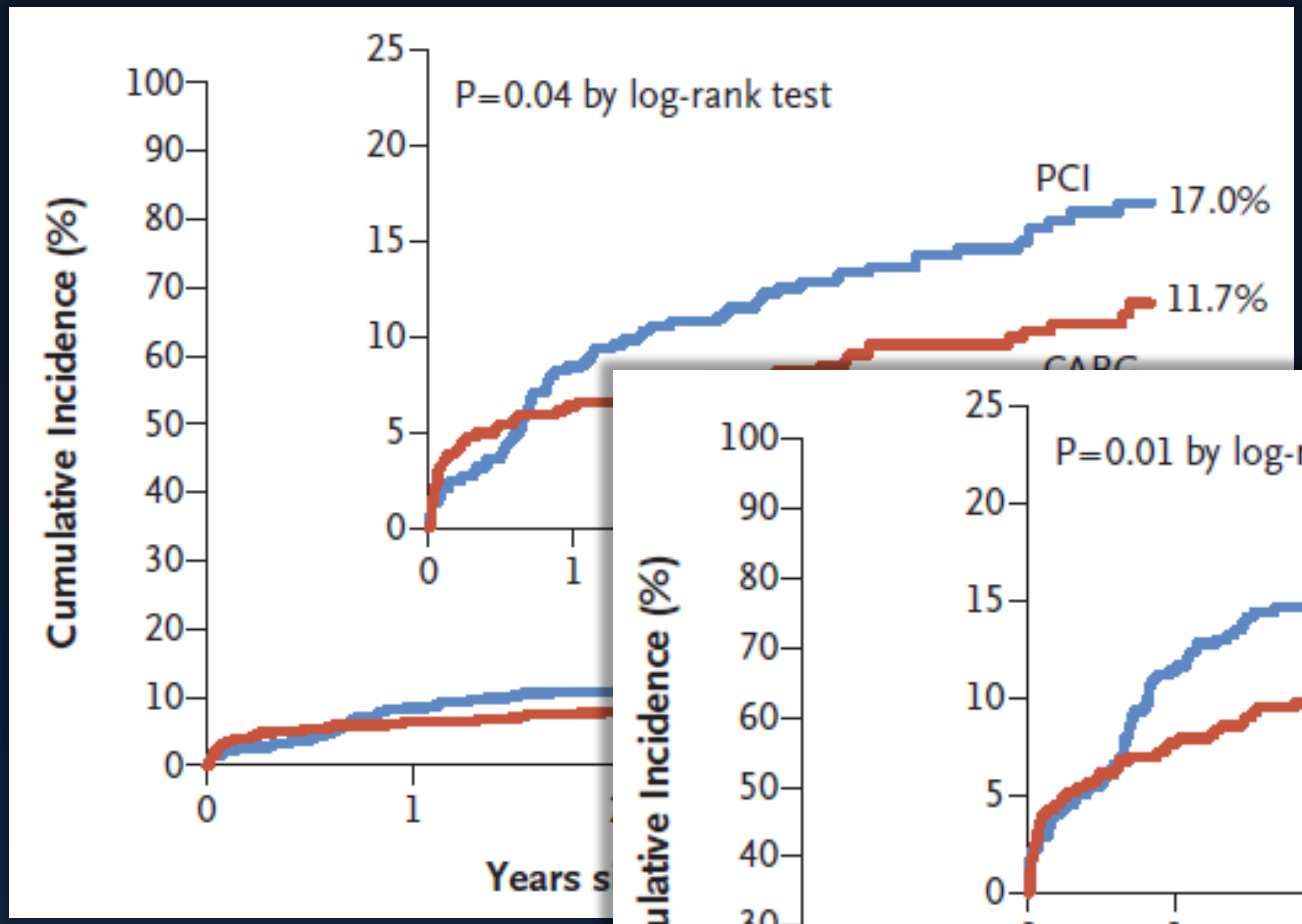
The NEW ENGLAND JOURNAL of MEDICINE

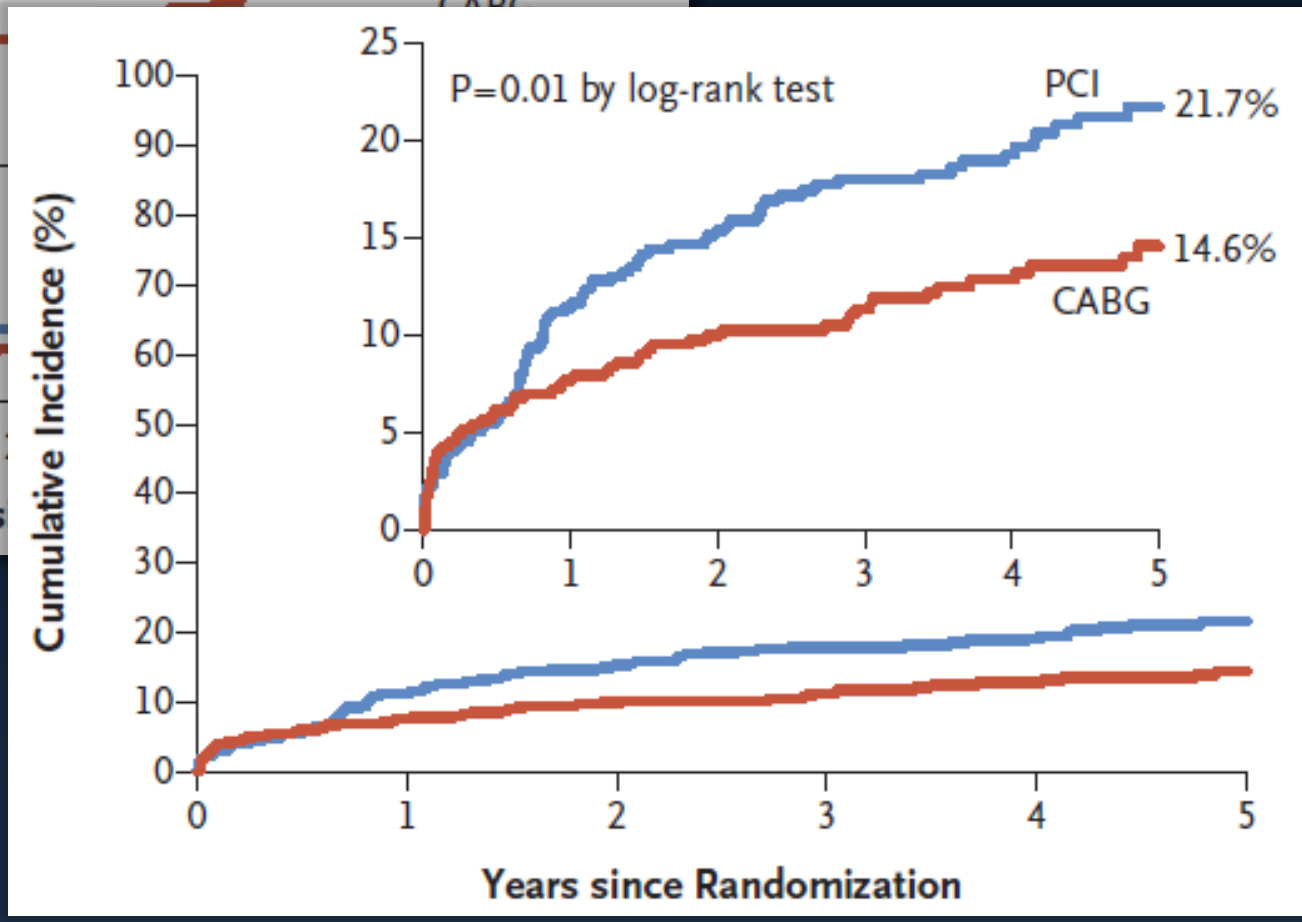
ORIGINAL ARTICLE

Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease

Seung-Jung Park, M.D., Ph.D., Jung-Min Ahn, M.D., Young-Hak Kim, M.D., Duk-Woo Park, M.D., Sung-Cheol Yun, Ph.D., Jong-Young Lee, M.D., Soo-Jin Kang, M.D., Seung-Whan Lee, M.D., Cheol Whan Lee, M.D., Seong-Wook Park, M.D., Suk Jung Choo, M.D., Cheol Hyun Chung, M.D., Jae Won Lee, M.D., David J. Cohen, M.D., Alan C. Yeung, M.D., Seung Ho Hur, M.D., Ki Bae Seung, M.D., Tae Hoon Ahn, M.D., Hyuck Moon Kwon, M.D., Do-Sun Lim, M.D., Seung-Woon Rha, M.D., Myung-Ho Jeong, M.D., Bong-Ki Lee, M.D., Damras Tresukosol, M.D., Guo Sheng Fu, M.D., and Tiong Kiam Ong, M.D., for the BEST Trial Investigators*

Death, MI or TVR





Death, MI, CVA or TVR

SJ Park et al. N Engl J Med 2015; 372:1204-1212

Long-Term Clinical End Points after Randomization, According to Study Group

End Point	PCI (N=438)	CABG (N=442)	Hazard Ratio (95% CI)†	P Value‡
	number (percent)			
Death				
Any cause	29 (6.6)	22 (5.0)	1.34 (0.77–2.34)	0.30
Cardiac cause	18 (4.1)	16 (3.6)	1.15 (0.58–2.25)	0.69
Noncardiac cause	11 (2.5)	6 (1.4)	1.87 (0.69–5.05)	0.21
Myocardial infarction				
Any	21 (4.8)	12 (2.7)	1.76 (0.87–3.58)	0.11
Stroke				
Any	11 (2.5)	13 (2.9)	0.86 (0.39–1.93)	0.72
Death, myocardial infarction, or stroke	52 (11.9)	42 (9.5)	1.26 (0.84–1.89)	0.26
Repeat revascularization				
Any	48 (11.0)	24 (5.4)	2.09 (1.28–3.41)	0.003
Target vessel	31 (7.1)	17 (3.8)	1·88 (1.04–3.40)	0.03
Target lesion	25 (5.7)	17 (3.8)	1.51 (0.82–2.80)	0.19
New lesion	24 (5.5)	10 (2.3)	2.47 (1.18–5.17)	0.01
Bleeding				
TIMI major bleeding§	30 (6.8)	132 (29.9)	0.20 (0.14–0.30)	<0.001

SJ Park et al. N Engl J Med 2015; 372:1204-1212

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2007 VOL. 357 NO. 20

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

TIMI Bleeding End Points in the Overall Cohort at 15 Months
TRITON TIMI 38 Trial

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

CONCLUSIONS

In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups. (ClinicalTrials.gov number, NCT00097591.)

SD Wiviott et al. N Engl J Med 2007; 357:2001-2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

Safety of the Study Drugs
PLATO TRIAL

CONCLUSIONS

In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non–procedure-related bleeding. (ClinicalTrials.gov number, NCT00391872.)

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Primary safety end points — no./total no. (%)				
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33
Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001

L Wallentin et al. N Engl J Med 2009; 361:1045-1057

Comparison of the incidence of dyspnea in patients treated with reversible P2Y12 inhibitors and patients treated with clopidogrel

Study drug (reversible $P2Y_{12}$ inhibitor)	Patients (total n)	Dose	Duration of treatment	A Percent of dyspnea in study drug group	B Percent of dyspnea in clopidorel group	A/B	Study (reference)
Ticagrelor*	Patients with atherosclerosis (200)	50 mg b.i.d. 100 mg b.i.d. 200 mg b.i.d. 400 mg q.d.	28 d 28 d 28 d 28 d	10 10 16 20	0 0 0 0	∞ ∞ ∞ ∞	DISPERSE (4)
Ticagrelor	NSTE-ACS (990)	90 mg b.i.d. 180 mg b.i.d.	12 wk 12 wk	10.5 15.8	6.4 6.4	1.64 2.47	DISPERSE-2 (5)
Ticagrelor#	Stable CAD (123)	90 mg b.i.d.	6 wk	38.6	9.3	4.15	ONSET/OFFSET (6,7)
Ticagrelor	Stable CAD (98)	90 mg b.i.d.	14 d	13	4	3.25	RESPOND (8)
Ticagrelor	ACS (18,624)	90 mg b.i.d.	12 mo	13.8	7.8	1.77	PLATO (3)
Cangrelor§	ACS (8,877)	4 µg/Kg/min IV	2–4 h	1	0.4	2.5	CHAMPION-PCI (10)
Elinogrel	Nonurgent PCI (626)	100 mg b.i.d. 150 mg b.i.d.	120 d 120 d	12.4 12.1	3.8 3.8	3.26 3.18	INNOVATE-PCI (11)

Cattaneo M, Faioni EM.. Thromb Haemost. 2012 Dec;108(6):1031-6

First, some decisions to make…

Clinical setting

- *STEMI*
- *Non STEMI ACS*
- *Elective PCI*

PCI complexity

- *Small vessels*
- *bifurcations*
- *Long lesions*
- *Lack of intravascular ultrasound*

Patients characteristics

- *Diabetics*
- *Elderly*
- *Renal failure*
- *Comorbirities*

DES choice

- *SES*
- *EES*
- *ZES*
- *DES generation (s) …. and etc*

Costs

Healthcare System

This will influence in dual antiplatelet therapy election and duration

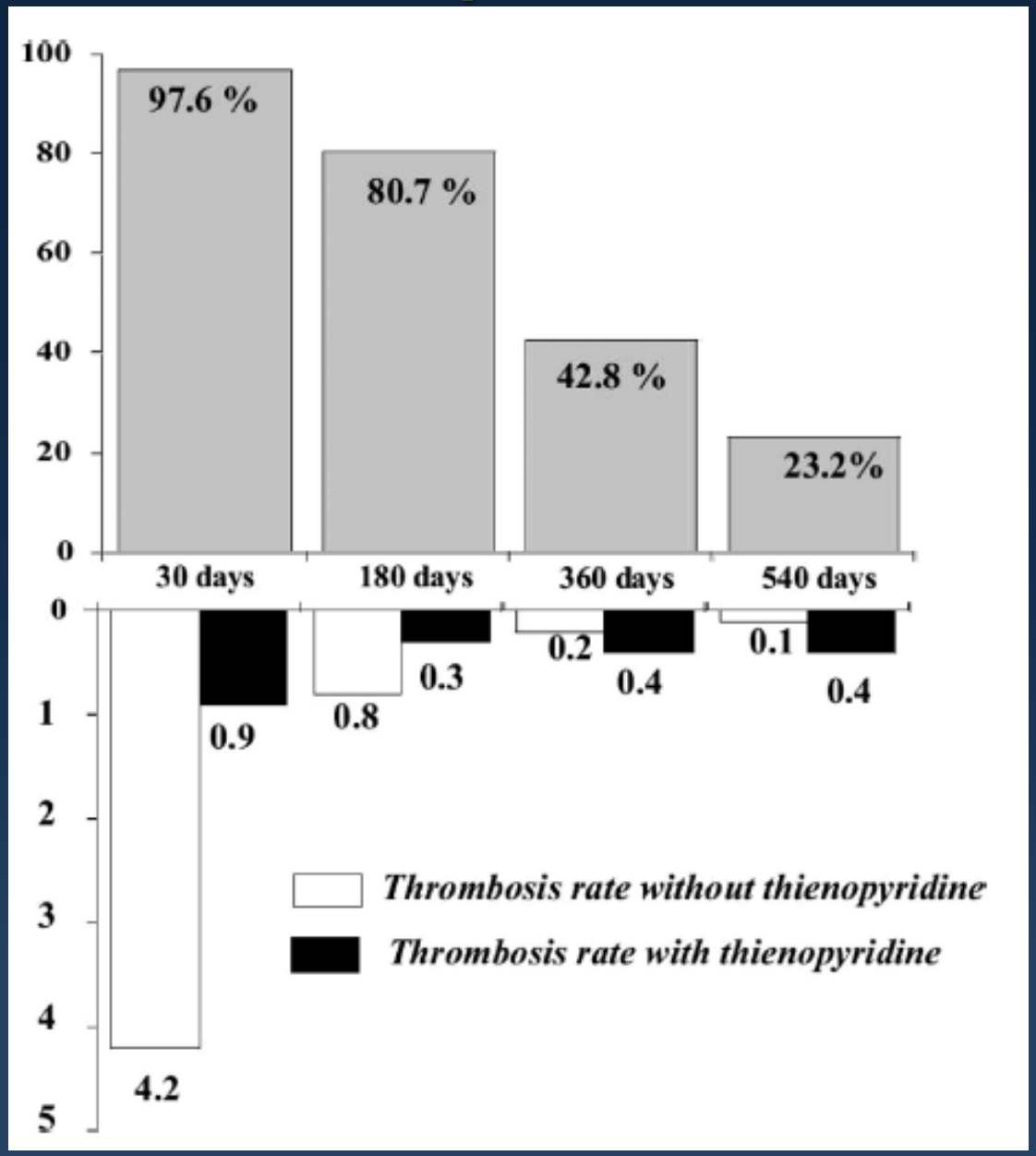
Potential predisposing factors for stent thrombosis

- Plaque rupture of adjecent lesion
- Incomplete endothelization
- Noncompliance with DAPT
- Clopidogrel nonresponsiveness
- Small vessels
- Long lesions
- Bifurcations
- Lack of intravascular ultrasound guidance
- Hypersensivity to drug or polymer
- Diabetes
- Renal failure
- Low ejection fraction
- Prior brachytherapy
- Incomplete stent apposition

When using DES + long DAPT we must take in account some variables…

Colombo A and Gerber RT. Circ Cardiovasc Interv. 2008;1:226-232

Relationship between DAPT and thrombosis

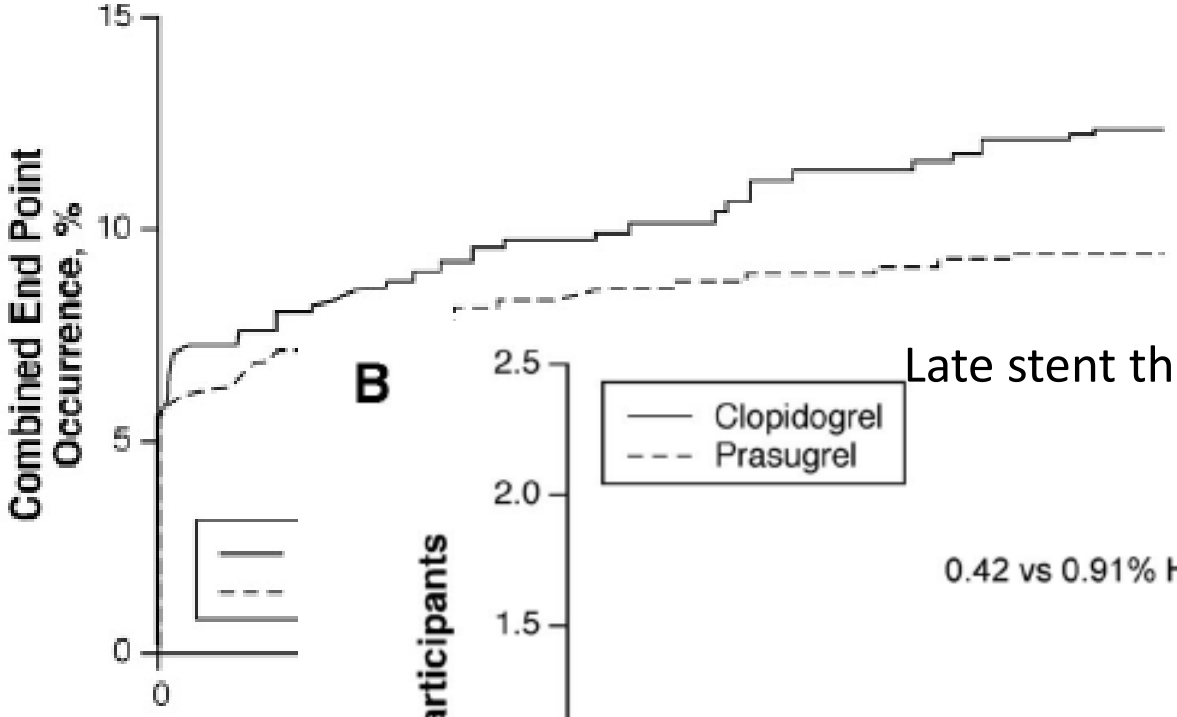


Patients on DAPT

Thrombosis rate % with and without DAPT

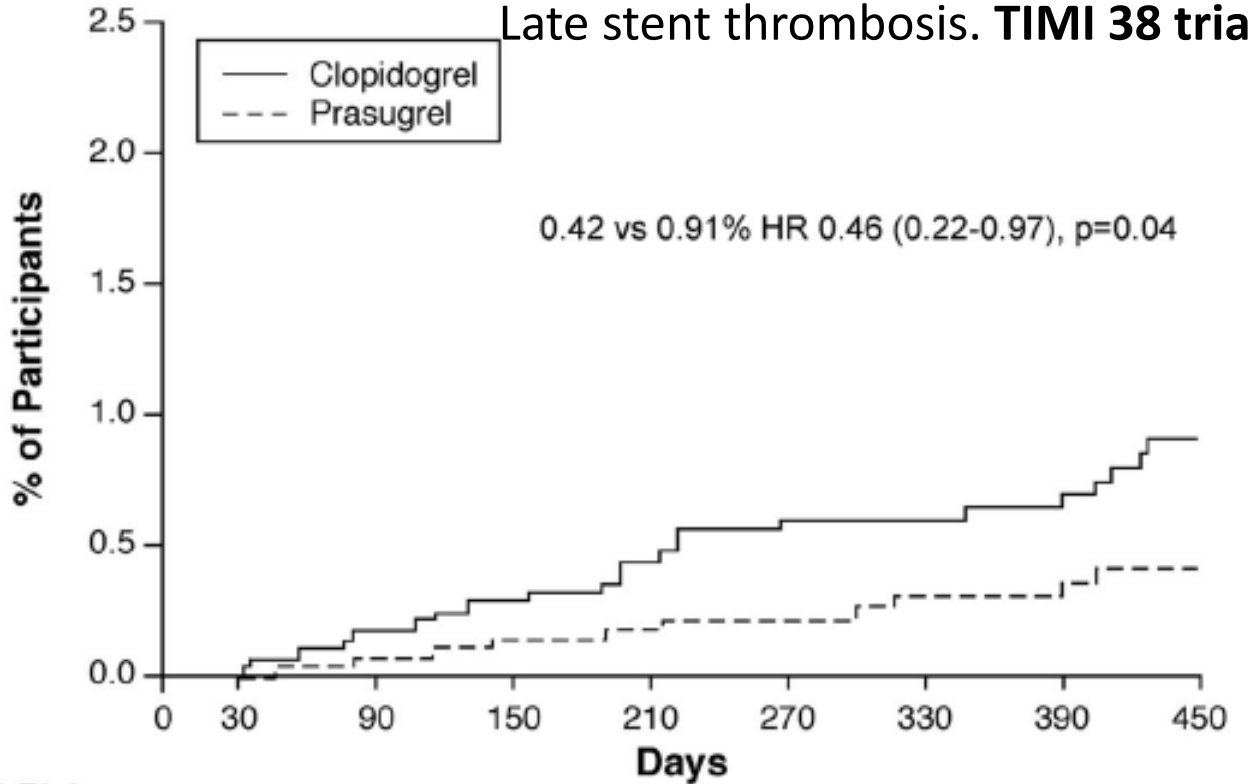
Colombo A and Gerber RT. Circ Cardiovasc Interv. 2008;1:226-232

Death/MI or CVA Relative risk reduction for clopidogrel compared with placebo 26.9% (95% CI, 3.9% to 44.4%, p=0.02) (**CREDO TRIAL**)



No. at Risk	
Placebo	1063
Clopidogrel	1053

Late stent thrombosis. **TIMI 38 trial**

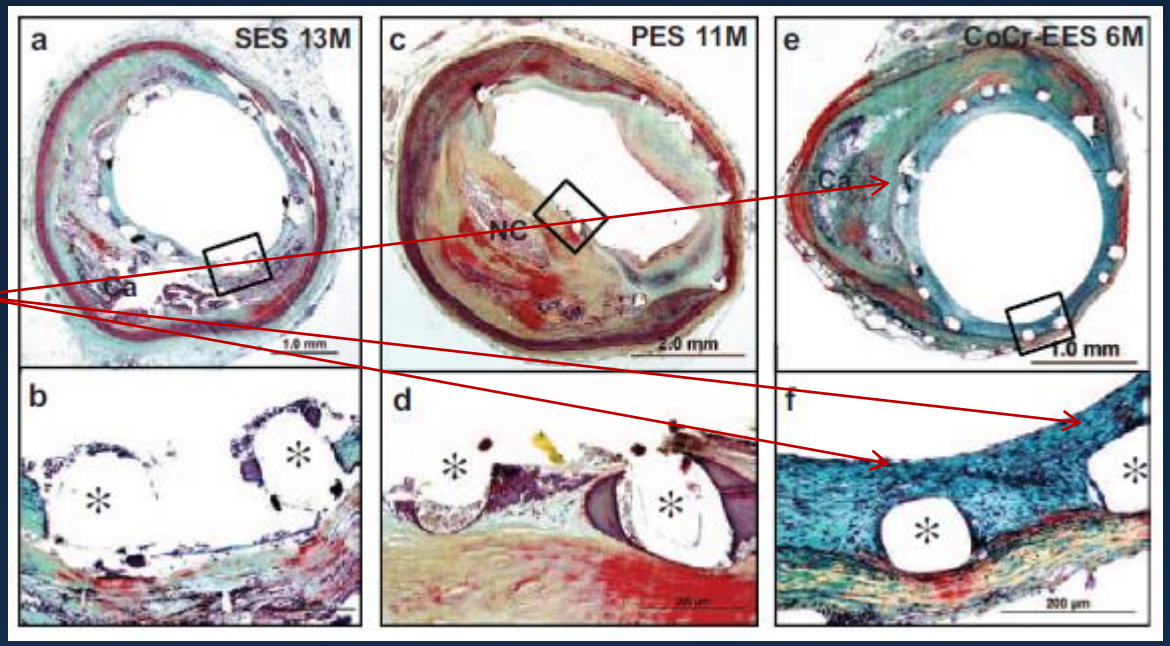


No. at Risk								
Prasugrel	2802	2774	2753	2512	2360	2186	1859	1336
Clopidogrel	2806	2772	2751	2520	2400	2225	1922	1379

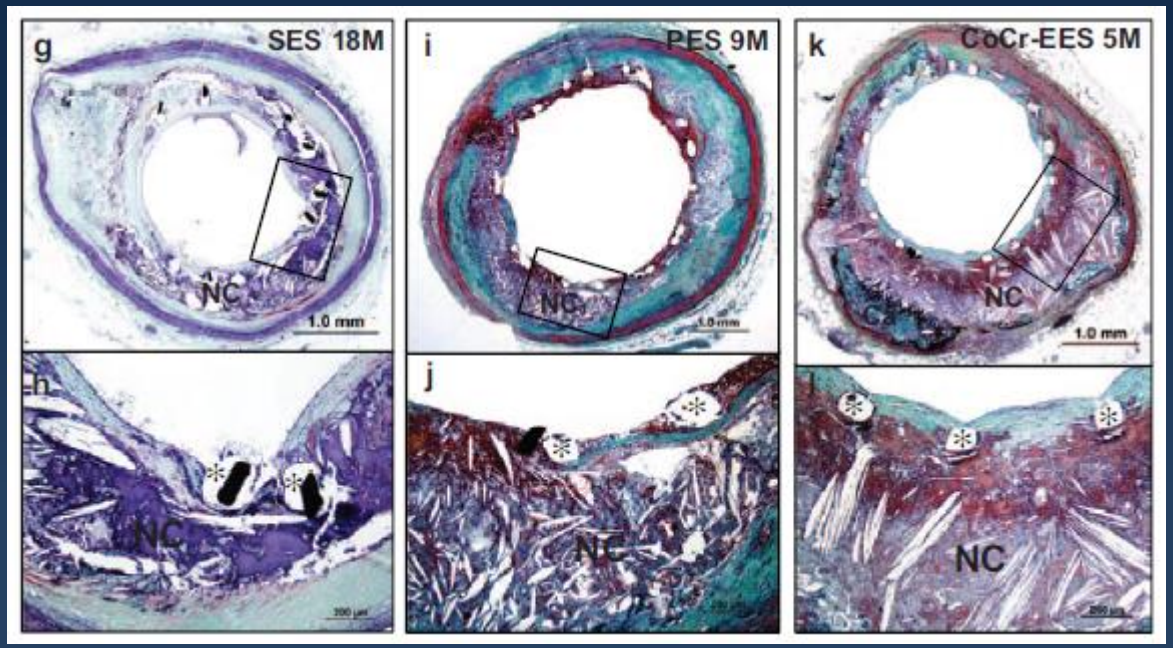
AK Chhatriwalla and DL Bhatt. Circ Cardiovasc Interv. 2008;1:217-225

DES for Stable CAD

Neointimal growth, underlying fibroatheroma and All struts are covered with proteoglycan-rich neointima with absence of fibrin.



DES for ACS



F Otsuka, Finn A, Virmani R et al. ***Circulation*** 2014; 129:211-223

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