



The Effects of Pre-Procedural Statin Treatment in **PCI & CABG** Patients

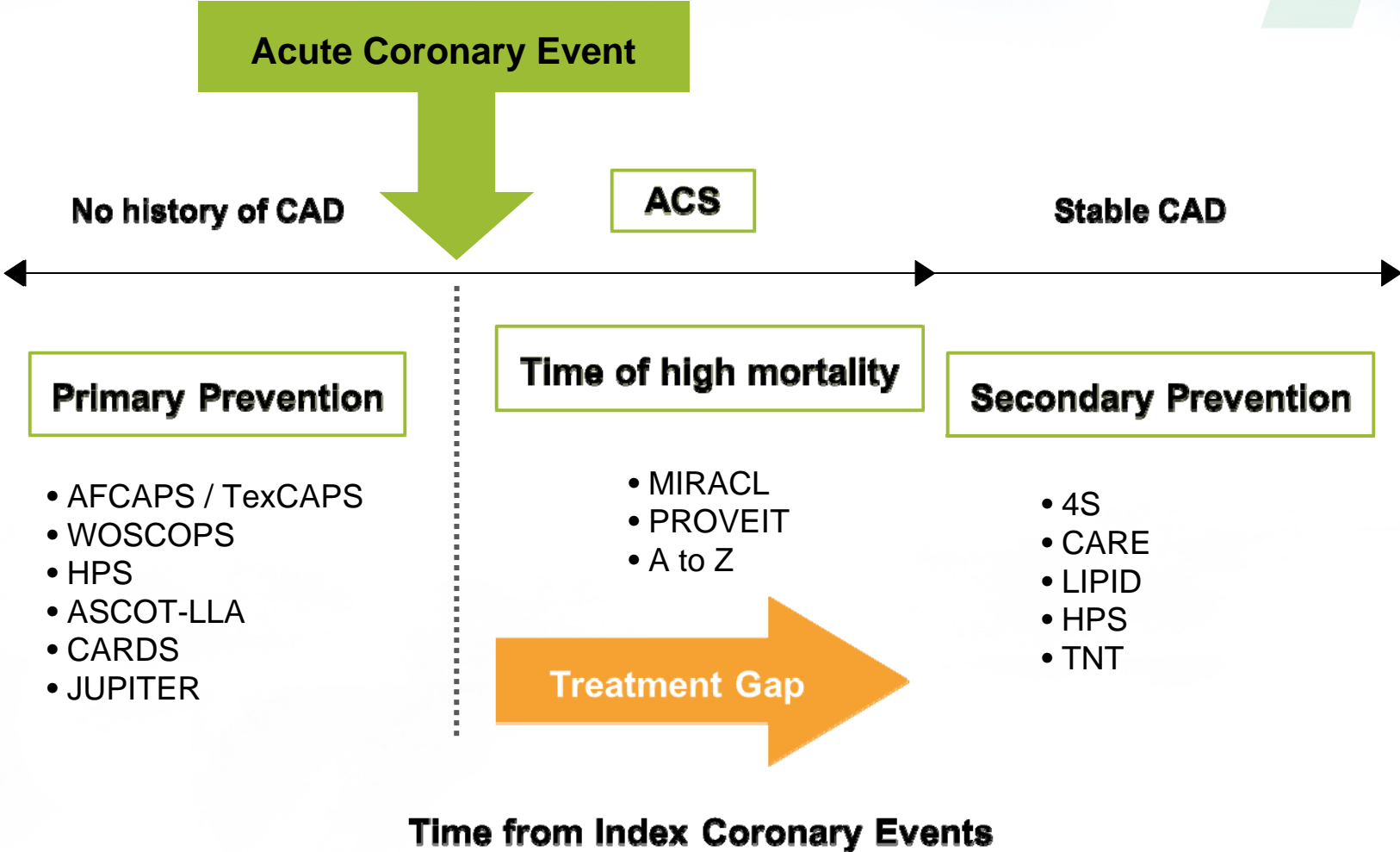
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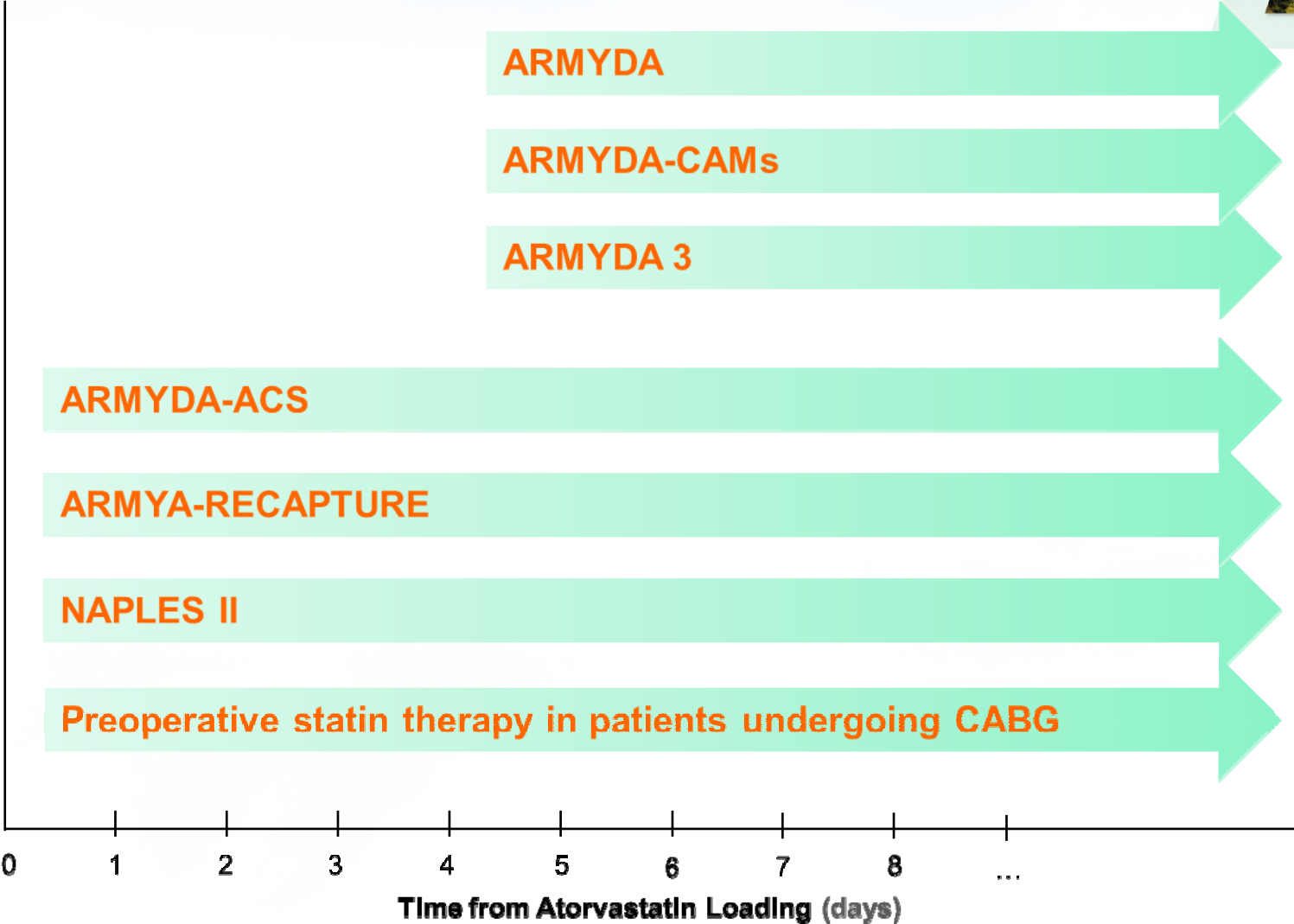


**Quantum Leap in *Statin Therapy*
in Patients *Undergoing PCI***

Randomized Controlled Studies of Lipid-Lowering Therapy in Patients with ACS



Latest Trials on ACS....





Meta-Analysis of Pre-procedural Statin Treatment

[Design] Pre-Procedural Statin Therapy : A Meta-Analysis of Randomized Trials



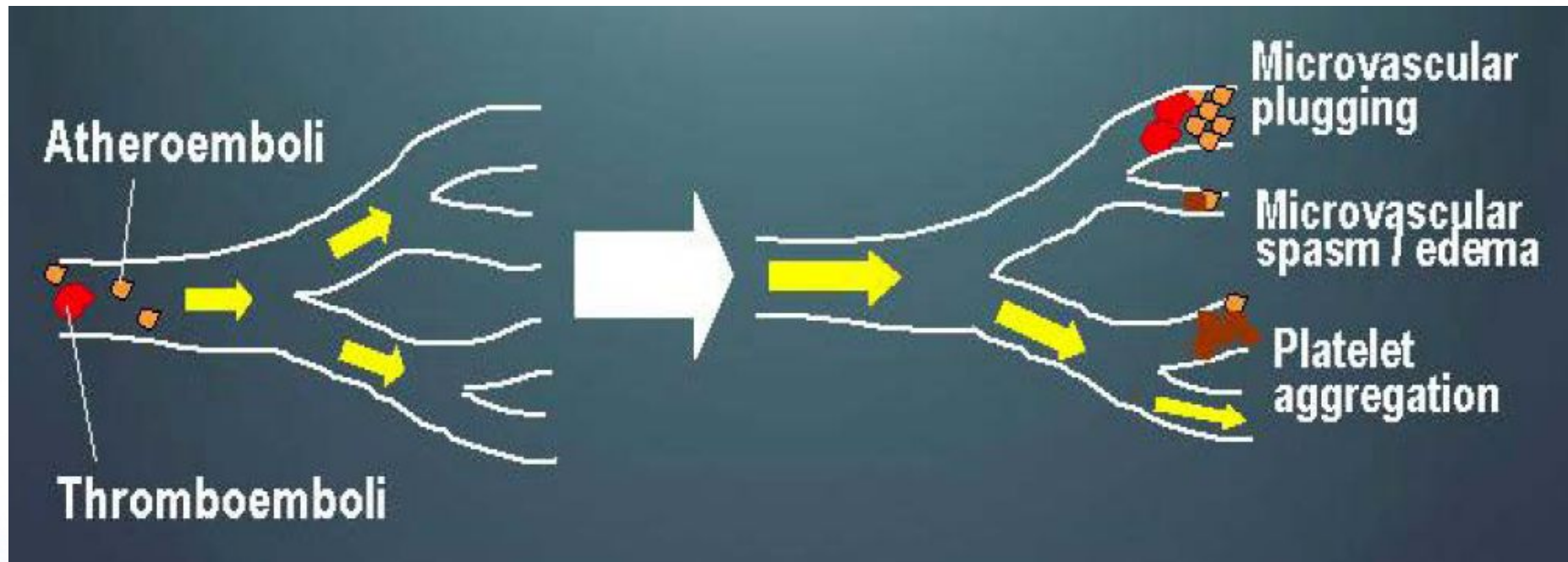
First Author / Trial (Ref. #)	Year	Patients, n	Age, yrs	DM, %	Patient Population	Follow-Up Duration
Yun et al. (18)	2009	225/220	64/63	33/30	Urgent PCI for ACS	30 days
Veselka et al. (19)	2009	100/100	68/64	26/25	Elective PCI	1 day
NAPLES II (20)	2009	338/330	64/65	39/37	Elective PCI	1 day
Jia et al. (21)	2009	113/115	65/66	19/22	Urgent PCI for ACS*	1 day
ARMYDA-RECAPTURE(22)	2009	192/191	66/66	37/35	Elective PCI or urgent PCI for ACS+	30 days
ARMYDA-ACS (23)	2007	86/85	64/67	29/33	Urgent PCI for ACS	30 days
Kinoshita et al. (24)	2007	21/21	66/67	NR	Elective PCI	6 months
Bozbas et al. (25)	2007	29/34	57/62	17/21	Elective PCI	1 day
ARMYDA (12)	2004	76/77	64/65	27/19	Elective PCI	30 days
Briguori et al. (26)	2004	226/225	63/62	25/19	Elective PCI	1 day
Ji et al. (27)	2009	71/69	65/66	38/38	Elective off-pump CABG	13 days
Berkan et al. (28)	2009	23/23	65/68	35/39	Elective CABG	30 days
Mannacio et al. (29)	2008	100/100	61/59	0/0	Elective CABG	23 days
Song et al. (30)	2008	62/62	62/64	47/52	Elective off-pump CABG	30 days
Tamayo et al. (31)	2008	22/22	68/68	27/41	Elective CABG	2.5 days
ARMYDA-3 (32)	2006	101/99	66/67	32/42	Elective CABG	30 days
Chello et al. (33)	2006	20/20	66/64	0/0	Elective CABG	7 days
Christenson et al. (34)	1999	40/37	63/64	23/24	Elective CABG	12 days
DECREASE-III (13)	2009	250/247	66/66	22/17	Elective vascular surgery	30 days
DECREASE-IV (35)	2009	265/268	65/66	12/9	Elective noncardiac surgery	30 days
Durazzo et al. (36)	2004	50/50	66/68	18/16	Elective vascular surgery	6 months

[Design] Pre-Procedural Statin Therapy : A Meta-Analysis of Randomized Trials

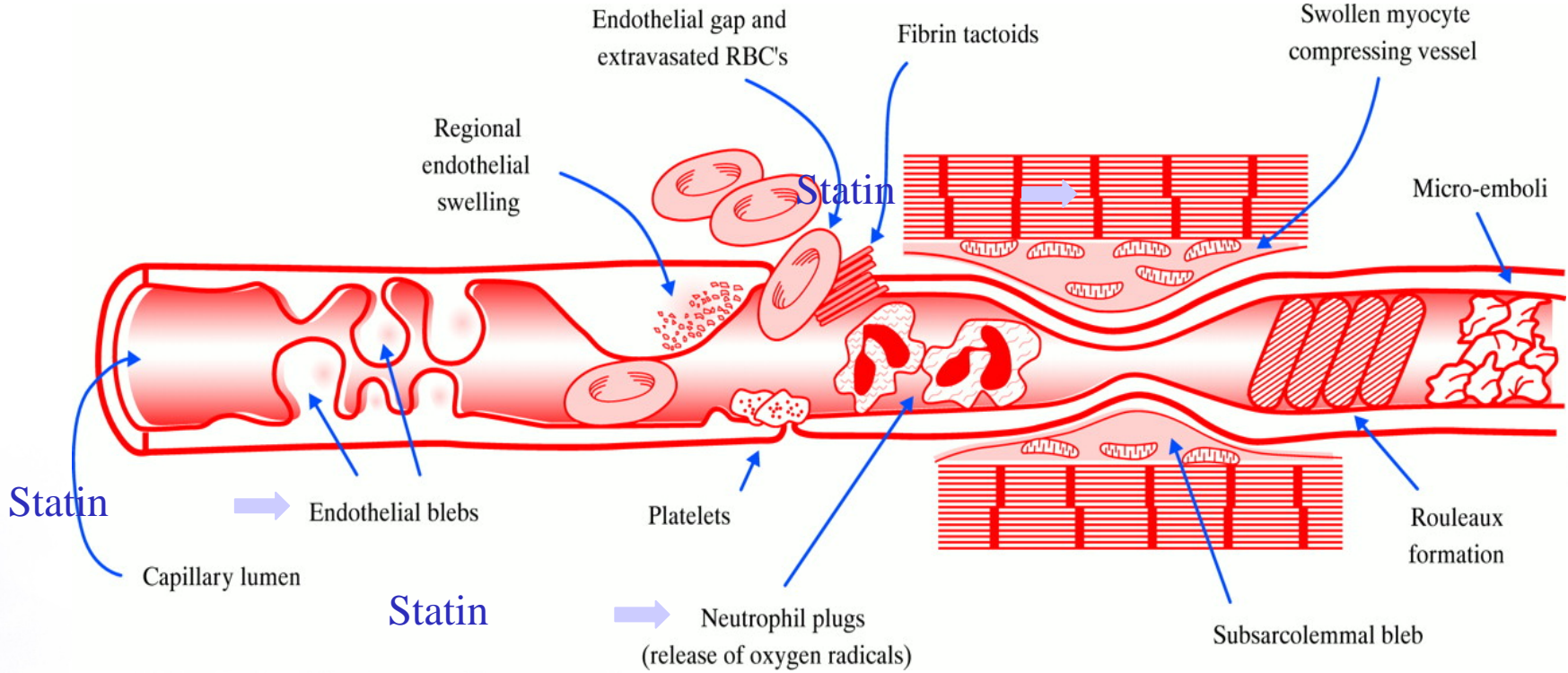


First Author / Trial (Ref. #)	Trial Primary Outcome	Generation Treatment Assignment	Blinded Outcome Assessment	Completeness of Follow-Up (%)
Yun et al. (18)	Post-procedure MI	ND	ND	100/100
Veselka et al. (19)	Post-procedure MI	ND	No	100/100
NAPLES II (20)	Post-procedure MI	Computer-generated	ND	100/100
Jia et al. (21)	Post-procedure MI	ND	ND	100/100
ARMYDA-RECAPTURE (22)	Adverse events	Random number	Double blind*	100/100
ARMYDA-ACS (23)	Adverse events	Random number	Yes	100/100
Kinoshita et al. (24)	Post-procedure MI	ND	ND	95/100
Bozbas et al. (25)	Post-procedure MI	ND	ND	100/100
ARMYDA (12)	Post-procedure MI	ND	Double blind*	100/100
Briguori et al. (26)	Q-wave MI	Computer-generated	No	100/100
Ji et al. (27)	Atrial fibrillation	Computer-generated	Yes	100/100
Berkan et al. (28)	Inflammatory markers	ND	Double blind*	100/100
Mannacio et al. (29)	Post-operative MI	Computer-generated	Double blind*	100/100
Song et al. (30)	Atrial fibrillation	Random number	ND	100/100
Tamayo et al. (31)	Inflammatory markers	ND	ND	100/100
ARMYDA-3 (32)	Atrial fibrillation	Computer-generated	Yes	100/100
Chello et al. (33)	Inflammatory markers	ND	Double blind*	100/100
Christenson et al. (34)	Thrombocytosis	ND	ND	100/100
DECREASE-III (13)	Myocardial ischemia	Computer-generated	ND	ND
DECREASE-IV (35)	Adverse events	Computer-generated	No	ND
Durazzo et al. (36)	Adverse events	Computer-generated	Yes	100/100

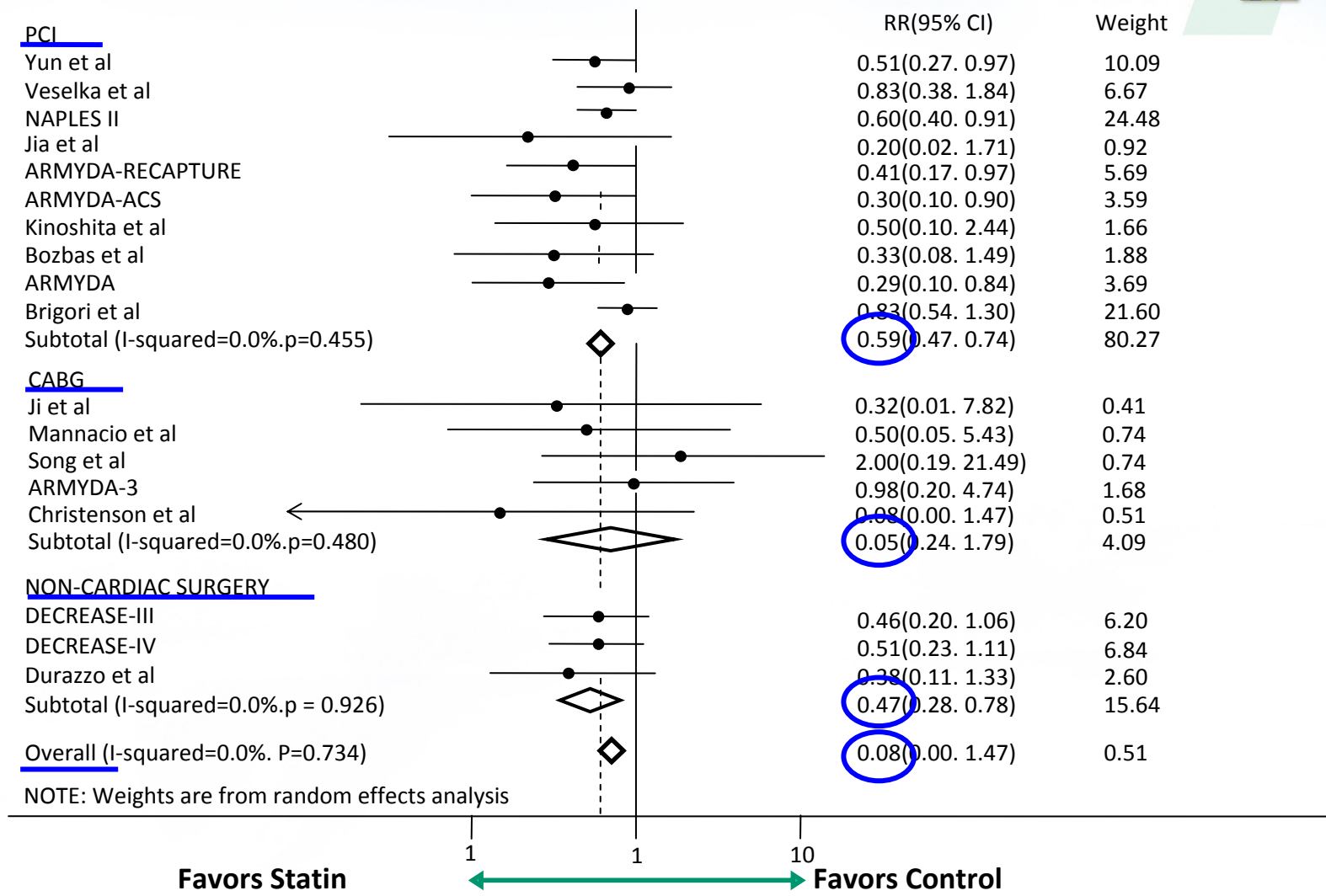
Background



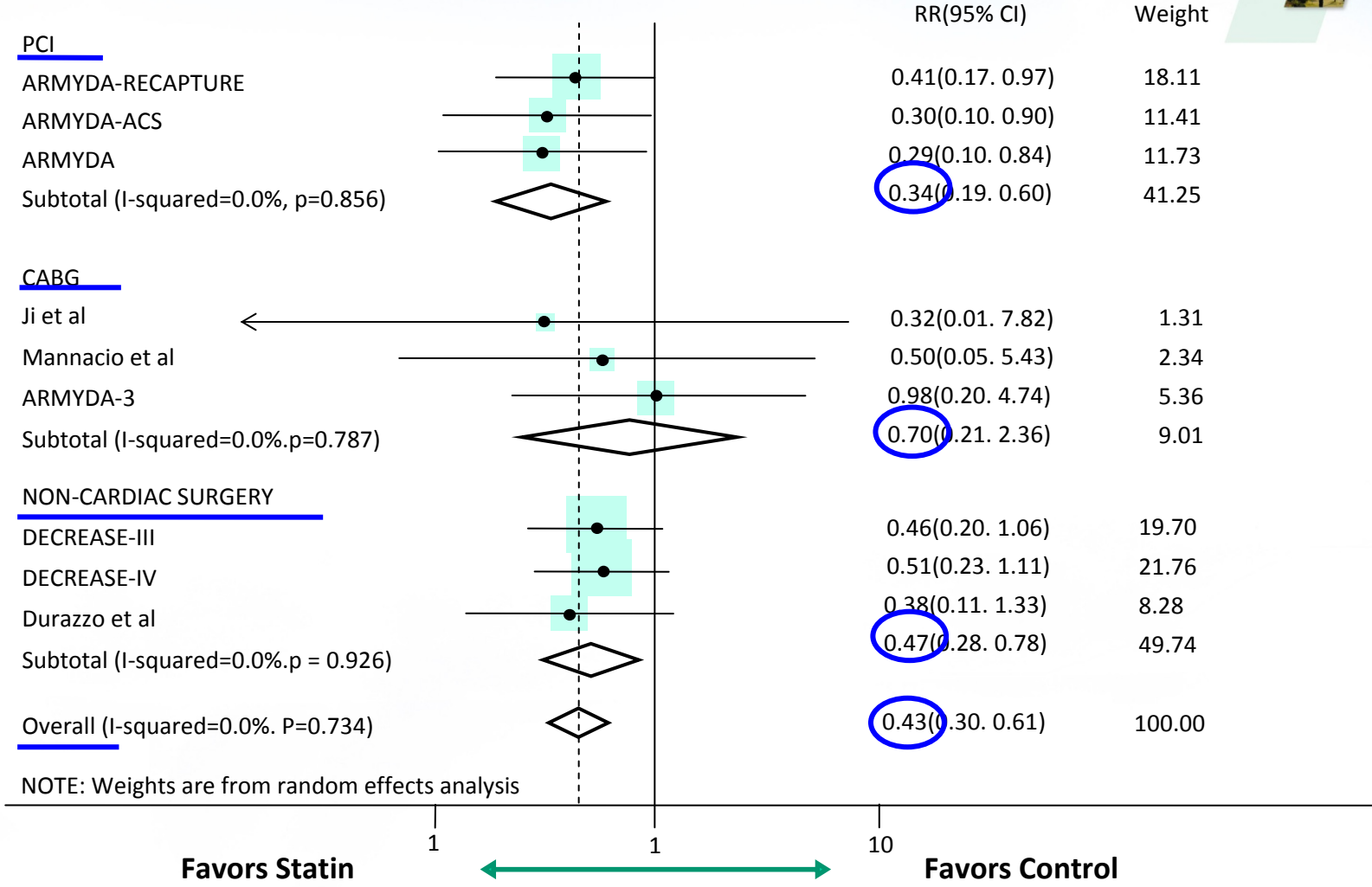
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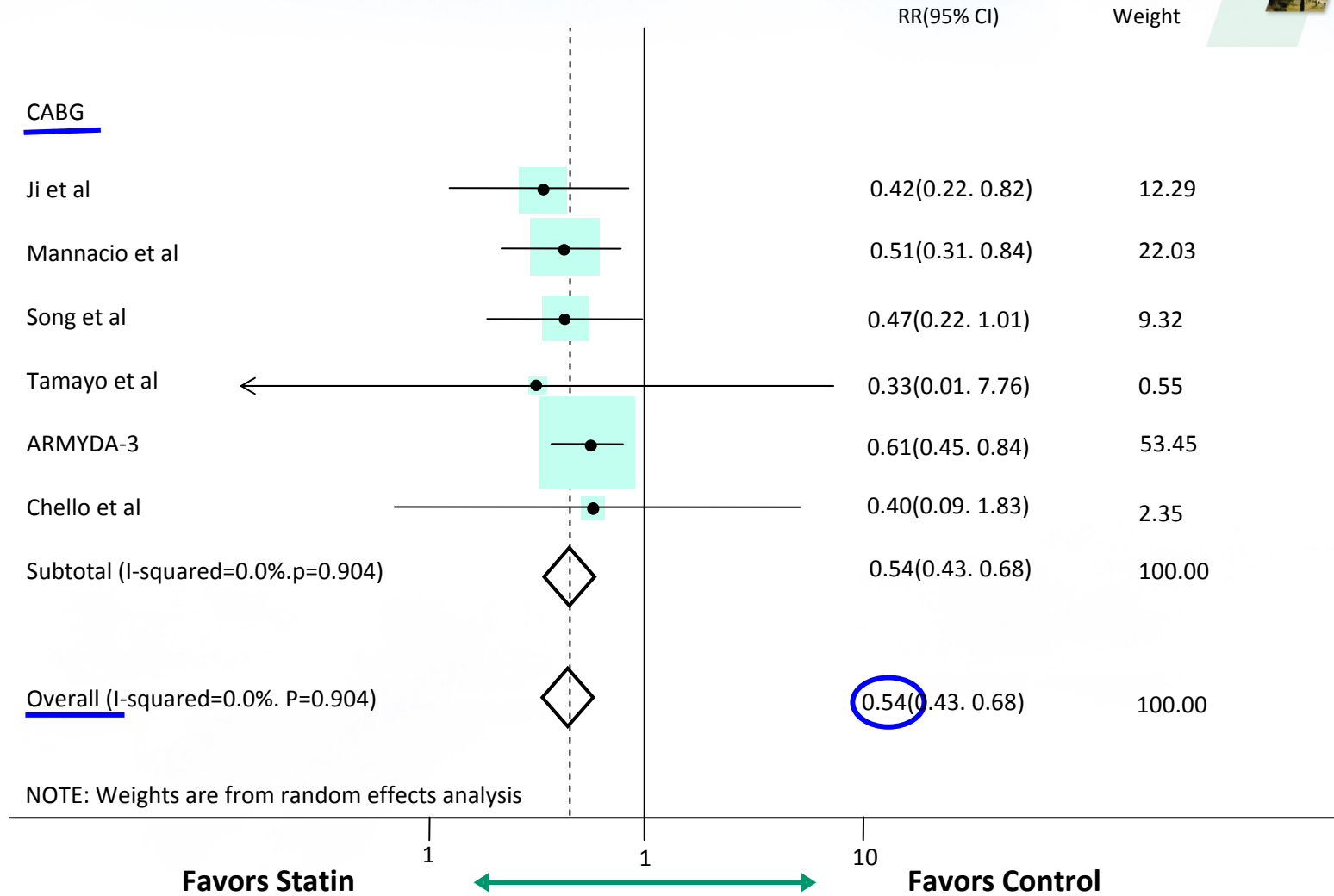
[Result] Post-Procedural Myocardial Infarction



[Result] Post-Procedural Myocardial Infarction in Placebo-Controlled Trials



[Result] Post-Procedural Atrial Fibrillation



[Conclusion] Meta-analysis of Pre-procedural Statin Therapy

- **A short-term statin pretreatment** prior to PCI and Non-cardiac surgery may improve post-procedural MI in ACS patients
- **Reloading** with high dose Atorvastatin is associated with improved clinical outcome **in patients on chronic statin therapy** undergoing PCI: ARMYDA-RECAPTURE result
- Early reduction in clinical events may be related more to **pleiotropic effects** (ex. greater reduction in inflammation).
- Statins contribute to plaque stability and/or regression through a number of lipid-dependent and -independent (pleiotropic) mechanisms (e.g. ↓ inflammation).



Perioperative Statin Therapy in Patients Undergoing CABG

Perioperative Cardiac Medical Therapy

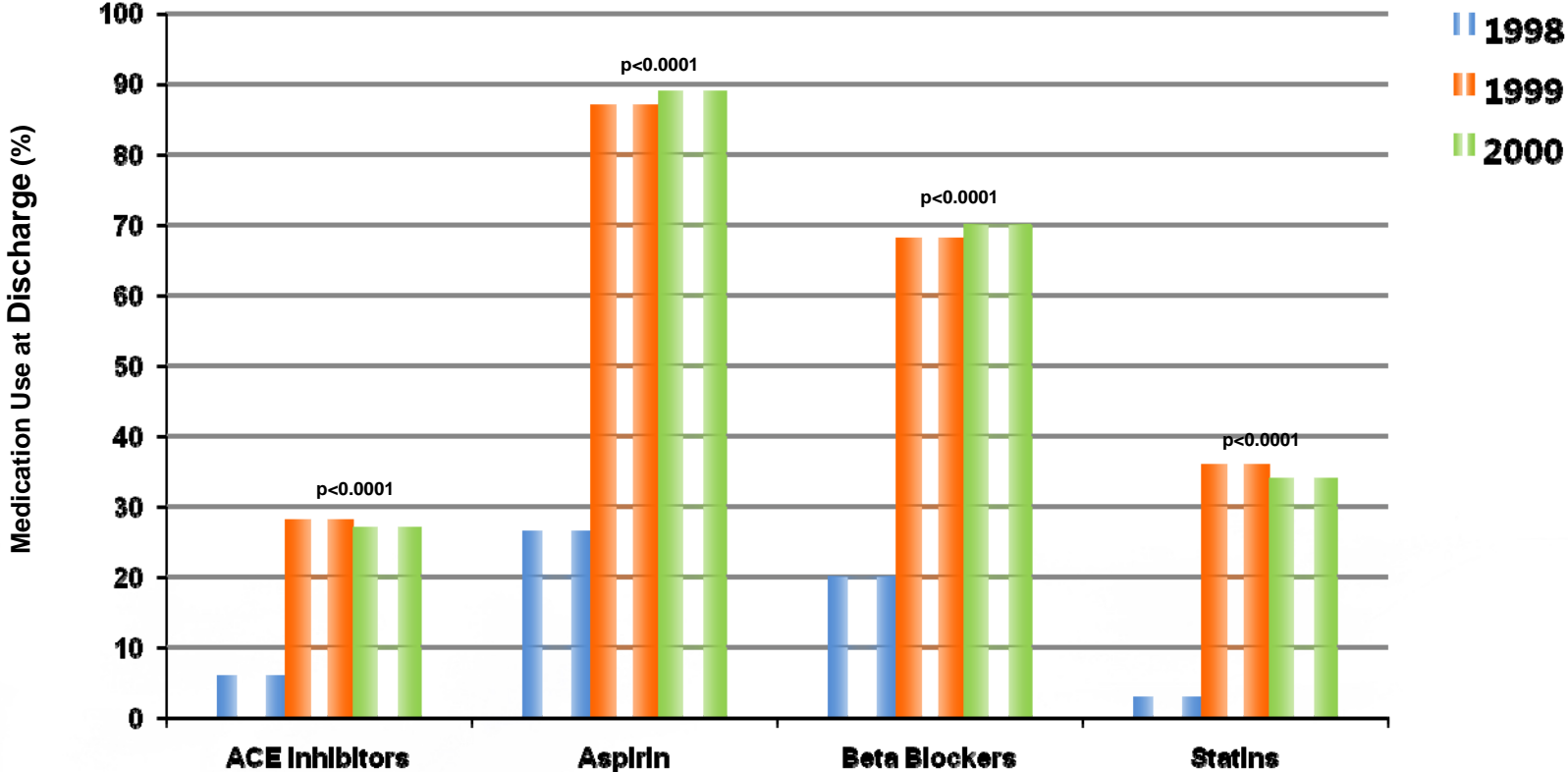


Frequency of Medication Use by Class During Hospitalization Among 2389 Patients Undergoing Coronary Artery Bypass Graft Surgery

Medication class (%)	Anytime (n = 2389)	Admission (n = 1537) ●	Presurgery (n = 949) ●★	1 Day Before Surgery (n = 2389) ●	Day of Surgery (n = 2389)	1 Day After Surgery (n = 2384) ▲	Postsurgery (n = 2384) ▲	Discharge (n = 2331) ■
ACE inhibitors	41.7	20.0	33.4	25.8	8.9	16.0	22.7	23.0
Aspirin	95.2	24.6	41.4	23.4	43.0	67.4	80.4	74.0
Beta blocker	89.6	35.0	52.4	44.6	42.9	50.2	67.2	58.9
Statins	42.4	17.5	30.0	21.6	8.9	19.0	29.2	28.2

- Patients who had surgery on the day of admission were excluded from the admission and presurgery analyses.
- ★ Patients who had surgery on the day after admission were excluded from the presurgery analyses.
- ▲ Patients who died on the day of surgery were excluded from the day after surgery and postsurgery analyses.
- Patients who died were excluded from the discharge medication analyses.

Medication at Discharge by Year





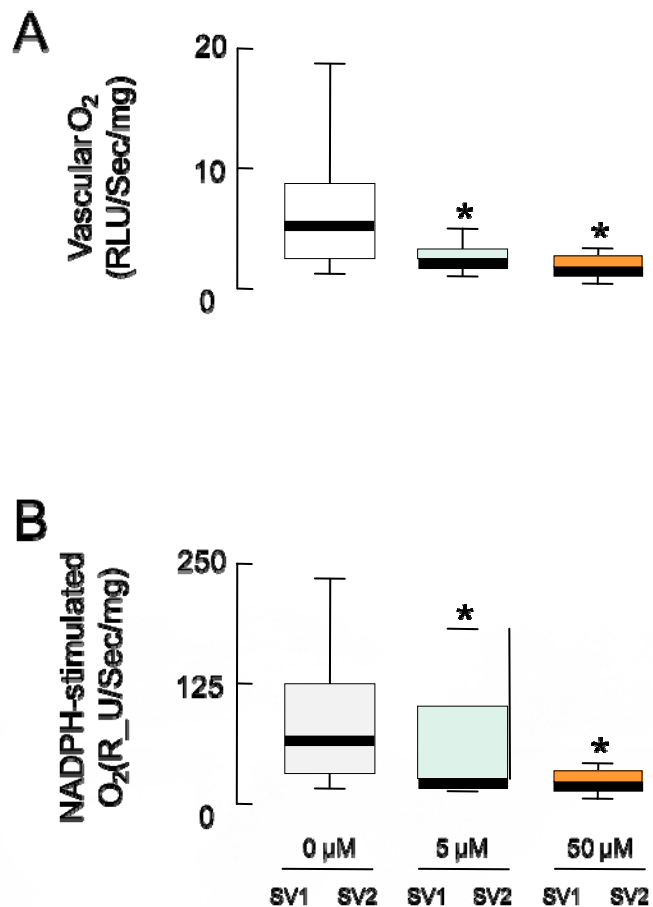
***Studies on **Mechanism** by Statin of
Beneficial Effects Relating CABG Surgery***

Statin's Beneficial Effects on Atherosclerosis and Cardiovascular Events

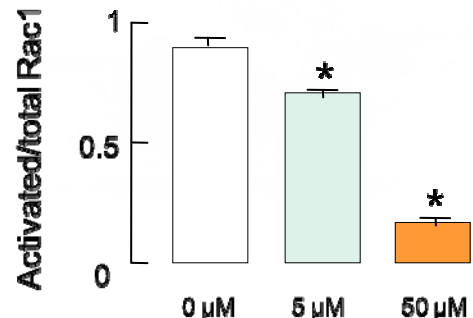
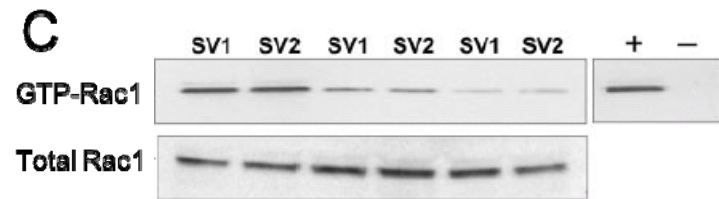


- Down regulation of the inflammatory cascade
- stabilization of the endothelial cell
- attenuation of oxidative damage
- decreasing thrombotic risk
- plaque stabilization

Mechanism of Protective Effect by Preop. Atorvastatin in Pts Undergoing CABG Surgery



- Short-term treatment with Atorvastatin 40mg/d before CABG rapidly improves redox state in saphenous vein grafts, by inhibiting vascular Rac1-mediated activation of NADPH-oxidase



Preop. Atorvastatin Decreased Inflammation Parameters in Pts Undergoing CABG



- Preoperative Atorvastatin treatment in patients undergoing elective CABG decreased inflammation parameters and could be effective in preventing systemic inflammatory response syndrome.

Post-operative data for patients who underwent elective coronary artery bypass grafting with (group 1) or without (group 2) pre-operative 20mg/day Atorvastatin

Post-operative measure	Group 1 (n = 20)	Group 2 (n = 20)	Statistical significance
Length of stay in intensive care unit (days)	2.0 (1.0)	3.5 (2.5)	p = 0.046
Intubation time (h)	8.0 (5.5)	7.0 (10.25)	NS
PO2 (mmHg)	93.8 ± 22.93	86.0 ± 20.99	NS
PCO2 (mmHg)	36.45 ± 3.64	37.8 ± 3.67	NS
SaO2 (%)	97.0 (3.75)	95.4 (3.25)	NS
Length of hospital stay (days)	7.0 (1.0)	8.0 (1.75)	NS

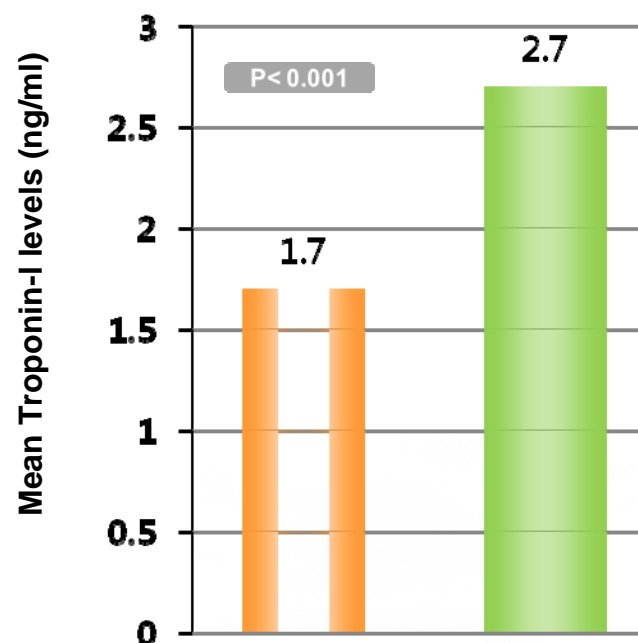
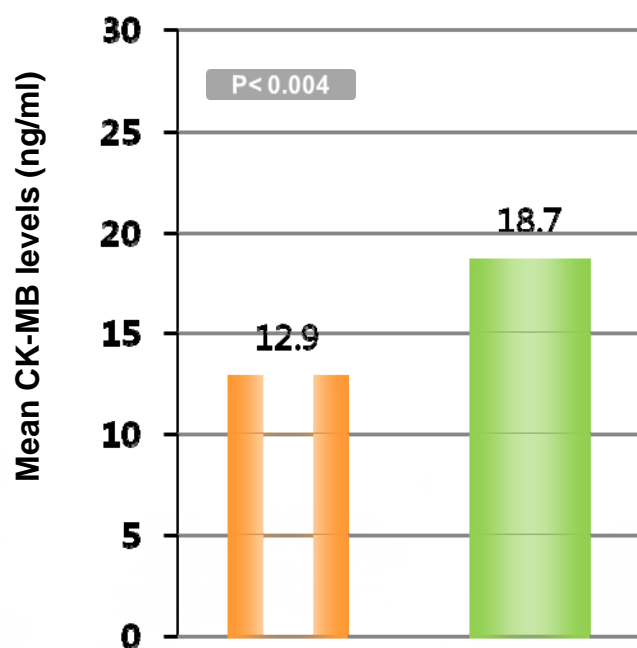
Data shown are median (interquartile range) or mean ± SD unless stated otherwise.

PO2 partial pressure of oxygen; PCO2, partial pressure of carbon dioxide; SaO2, arterial oxygen saturation; NS, not statistically significant (P > 0.05)

Preop. Atorvastatin on Myocardial Ischemia Markers After on-Pump CABG



- Preop. Atorvastatin treatment results in significant reductions of myocardial markers after on-pump CABG operation



■ Atorvastatin pretreatment
■ No Atorvastatin pretreatment



Preoperative Statin Therapy & CABG surgery

Preop. Statin : Independent Predictor of Mortality



- Independent predictors of in-hospital mortality following CABG surgery

	Coefficient	p value
All patients		
Atrial arrhythmia history	0.84	< 0.001
Congestive heart failure history	0.87	< 0.001
Age (years)	0.06	< 0.001
Redo procedure	1.20	0.009
Preoperative AMI	0.84	0.005
Insulin dependent diabetes	0.85	0.009
Tobacco past/current	0.77	0.024
Female gender	0.56	0.066
High Risk Patients		
Insulin dependent diabetes	1.10	0.070
Preoperative statin use	1.07	0.030

AMI : acute myocardial infarction.

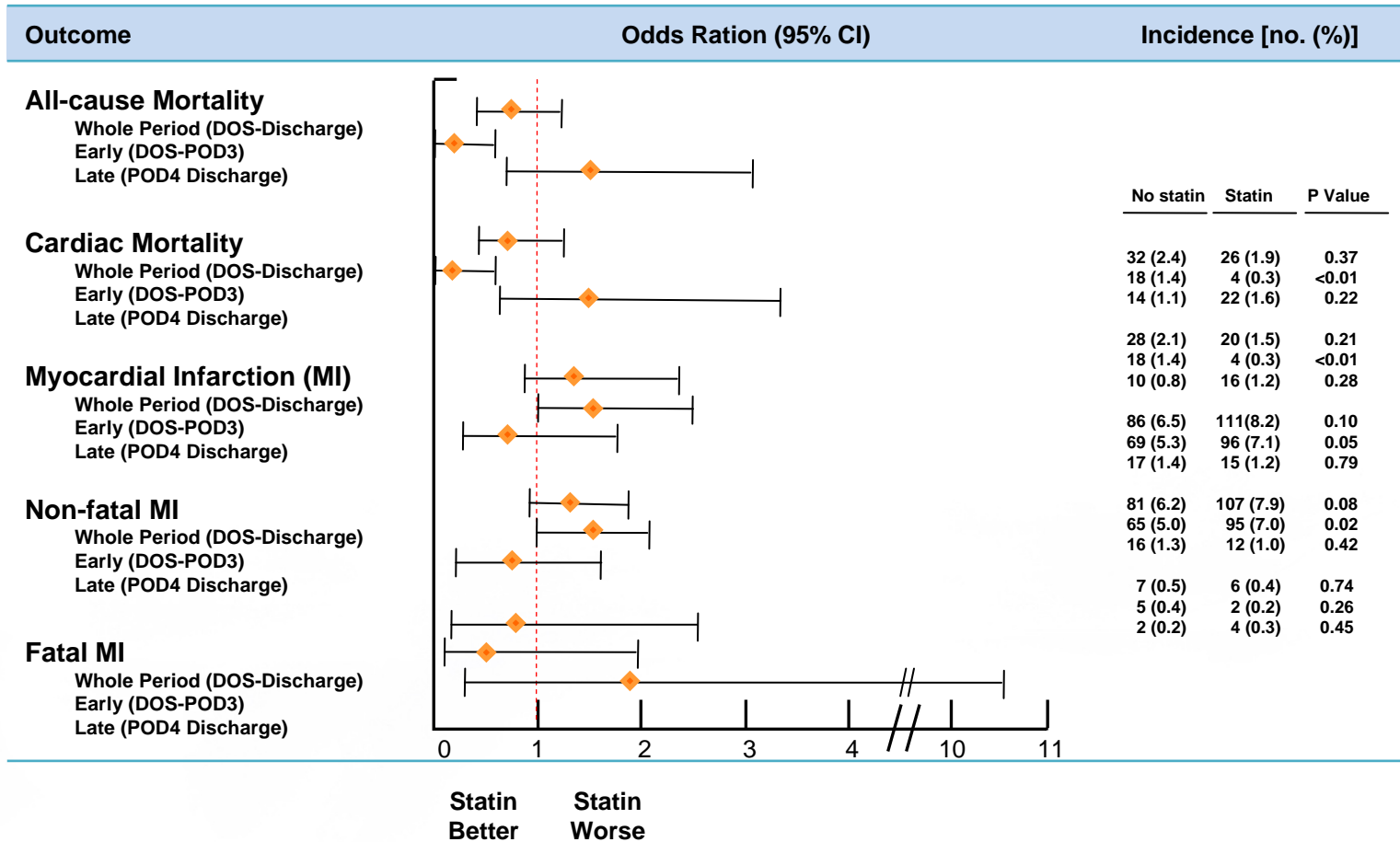
Retrospective cohort, Pt population: isolated CABG surgery

Preoperative statin use is associated with lower operative mortality in high-risk patients



Preop. Statin & Mortality

- Preop. Statin use reduced cardiac mortality after primary, elective CABG

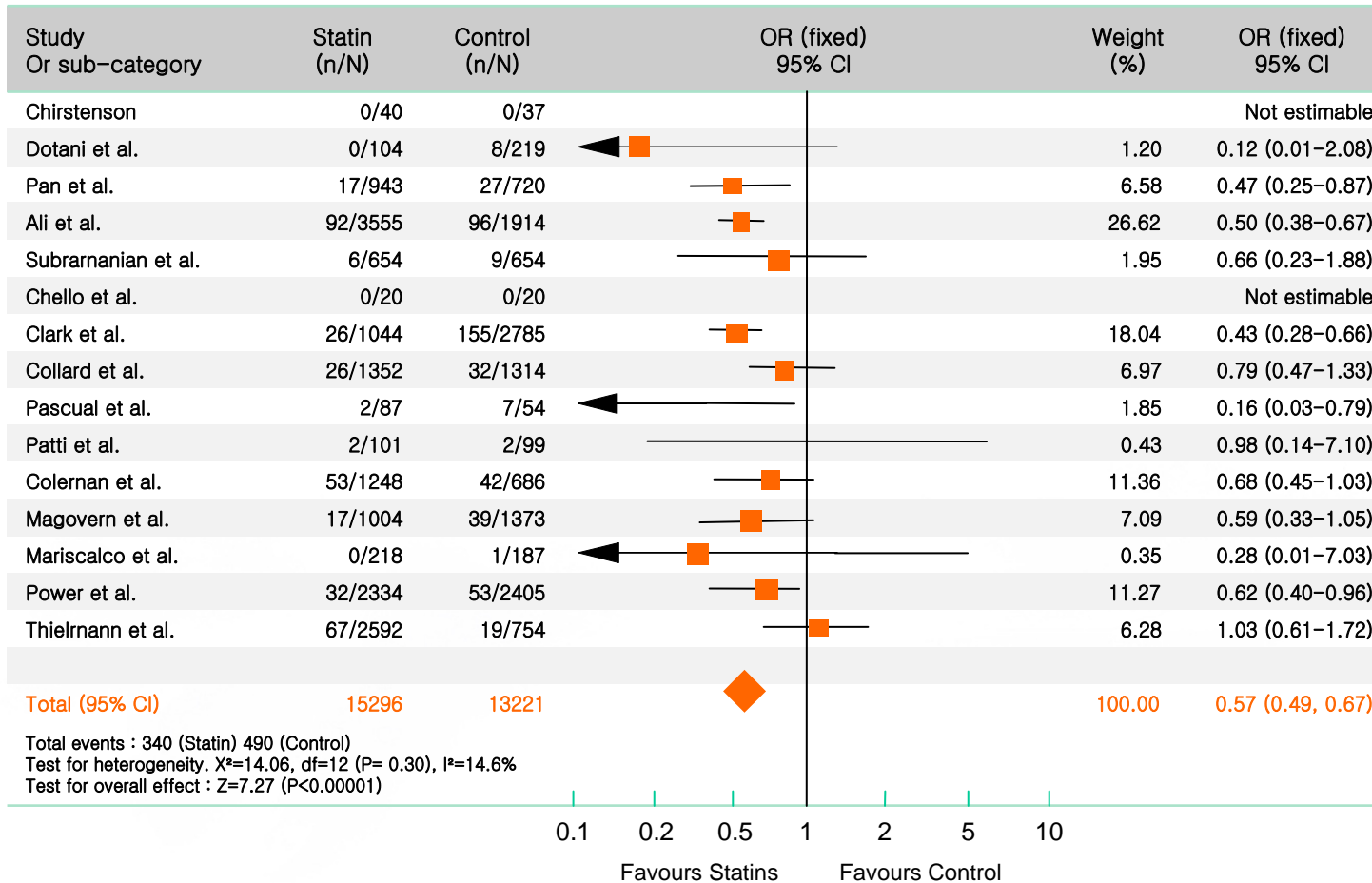


Statin Better Statin Worse



Preop. Statin & Mortality : Meta-Analysis

- Preoperative statin use and the incidence of early all-cause mortality after cardiac surgery



Preop. Statin & Clinical Outcomes : Meta-Analysis



- Preoperative statin use and the incidence of clinical outcomes

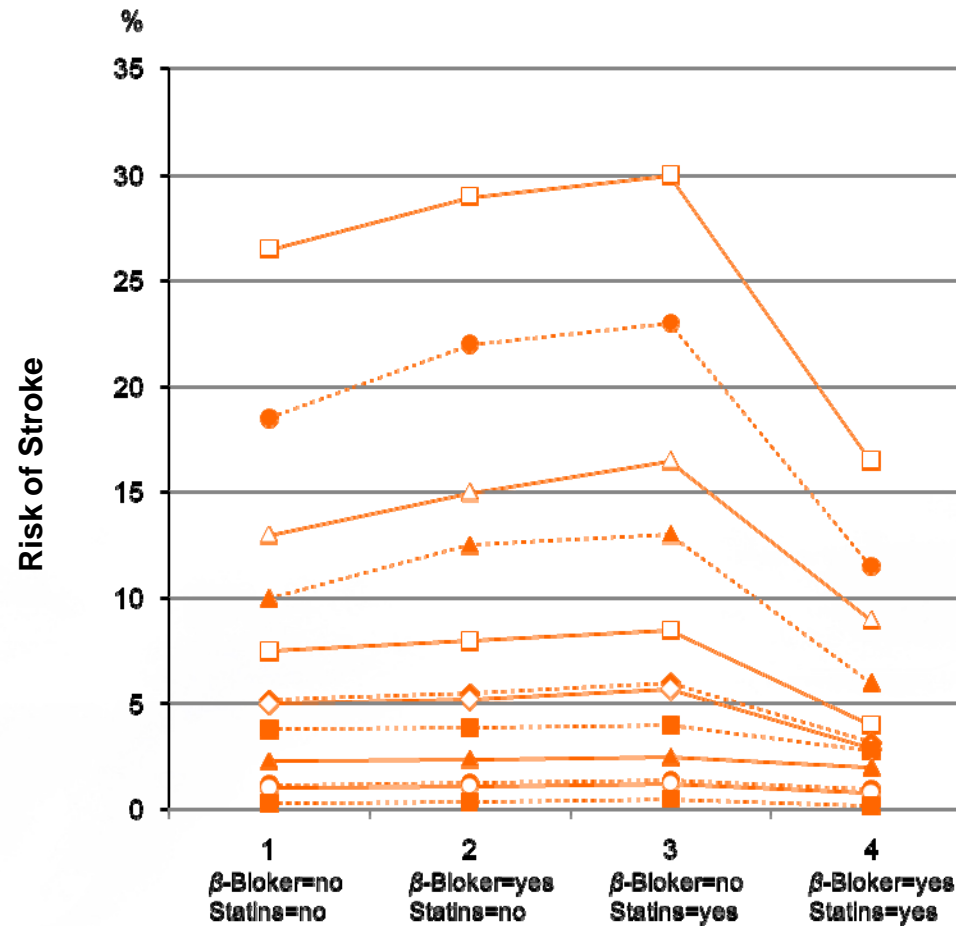
Outcome	Sample size (N)	Treatment group % (N)	Incidence % (N)	Absolute RR %	X ² test (P-value)
Mortality	28 517	Statin : 53.6% (15 296) Control : 46.4% (13 221)	2.2% (340) 3.7% (490)	1.5%	<0.0001
Myocardial Infarction	14 330	Statin : 62.9% (9012) Control : 37.1% (5318)	4.2% (380) 3.9% (208)	-0.3%	0.373
Atrial fibrillation	7643	Statin : 52.7% (4027) Control : 47.3% (3616)	24.9% (1004) 29.2% (1056)	4.3%	<0.0001
Stroke	16 390	Statin : 61.0% (10 003) Control : 39.0% (6387)	2.1% (212) 2.9% (187)	0.8%	0.001
Renal failure	6408	Statin : 66.1% (4236) Control : 33.9% (2172)	3.9% (165) 4.5% (97)	0.6%	0.275

■ Statin ■ Control



Preop. Statin & Stroke Risk

- Combination of statin and beta-blockers decreased stroke risk at 30 days after CABG surgery





Statin Therapy and Postoperative AF

Preop. Atorvastatin & Postop. AF in Armyda-3 Study (1)

- Atorvastatin 40 mg/day, initiated 1 wk before elective cardiac surgery with cardiopulmonary bypass, significantly decreases postoperative AF.
- Postoperative Atrial fibrillation occurred in 35 (35%) of 101 patients in the Atorvastatin arm versus 56 (57%) of 99 patients in the placebo arm (P0.003).

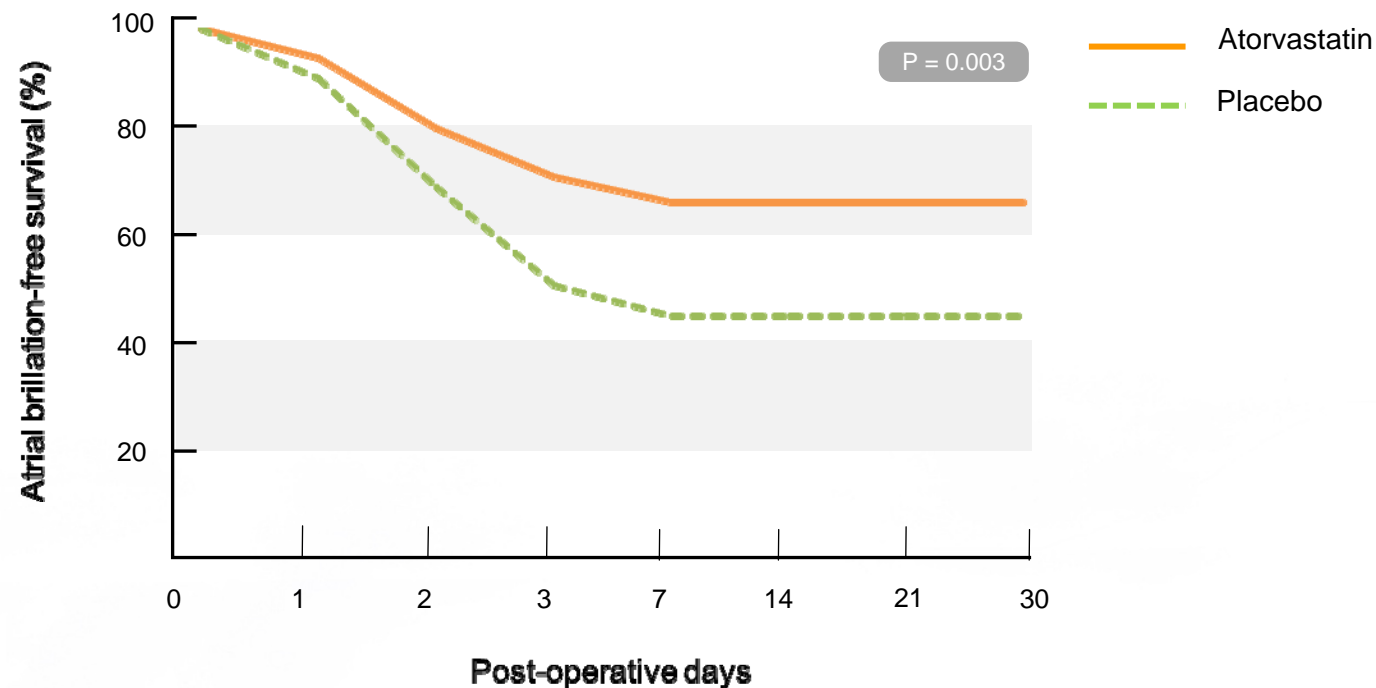
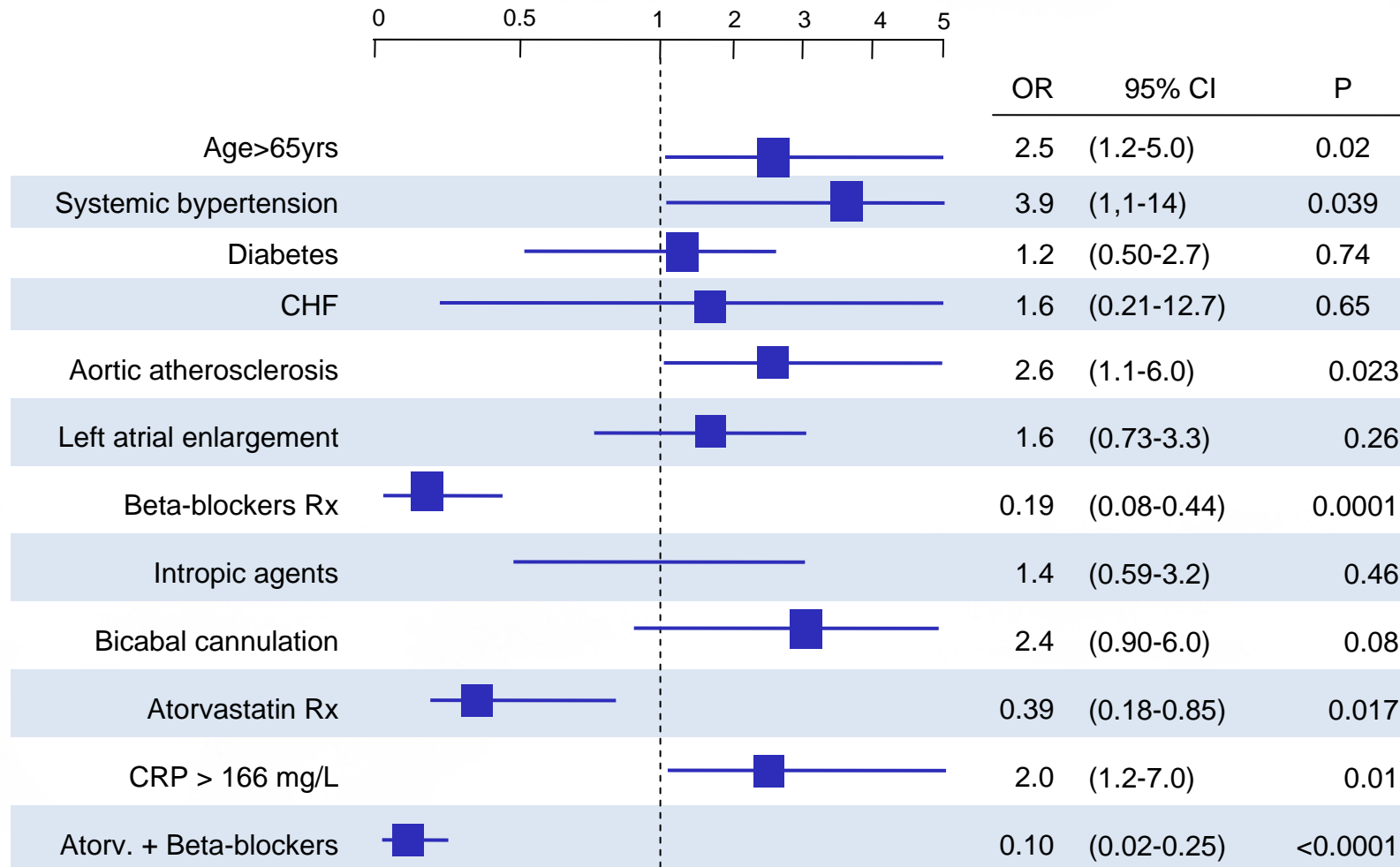


Figure2. Actuarial curves of 30 day atrial fibrillation-free survival in the 2 arms.

Preop. Atorvastatin & Postop. AF in ARMYDA-3 Study (2)

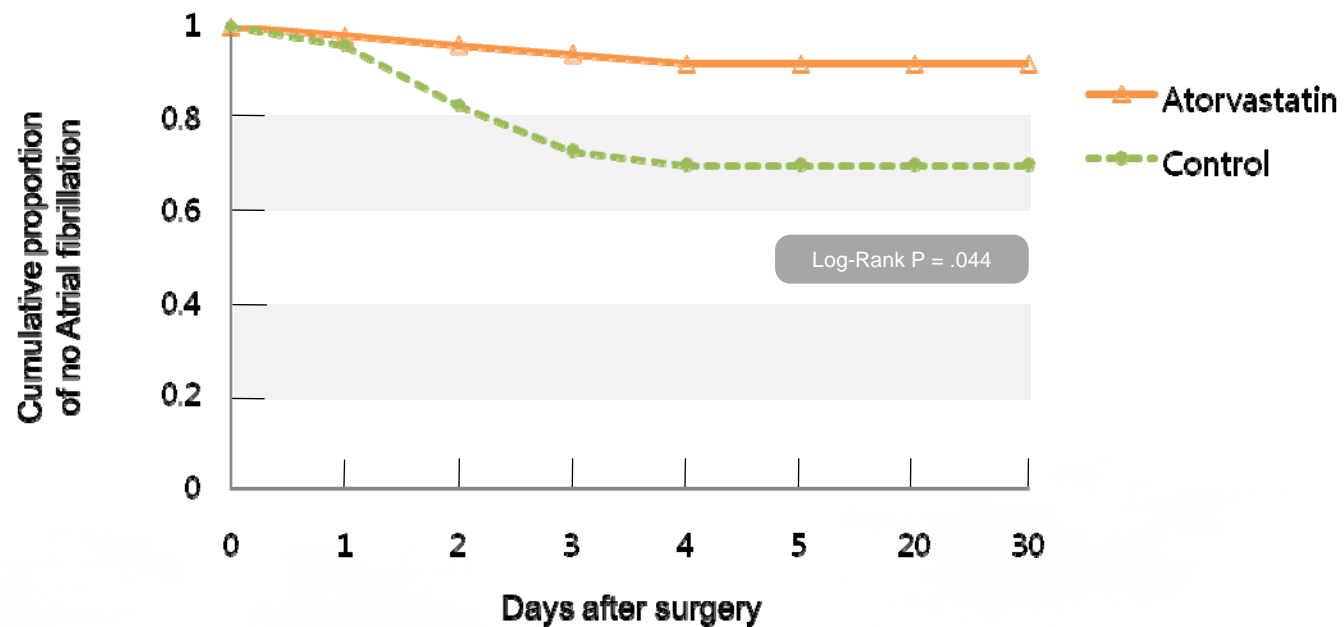
Odds ratio for post-operative Atrial fibrillation





Preop. Atorvastatin & Postop. AF

- Preop. Atorvastatin significantly reduced the occurrence of post operative AF after off-pump CABG.

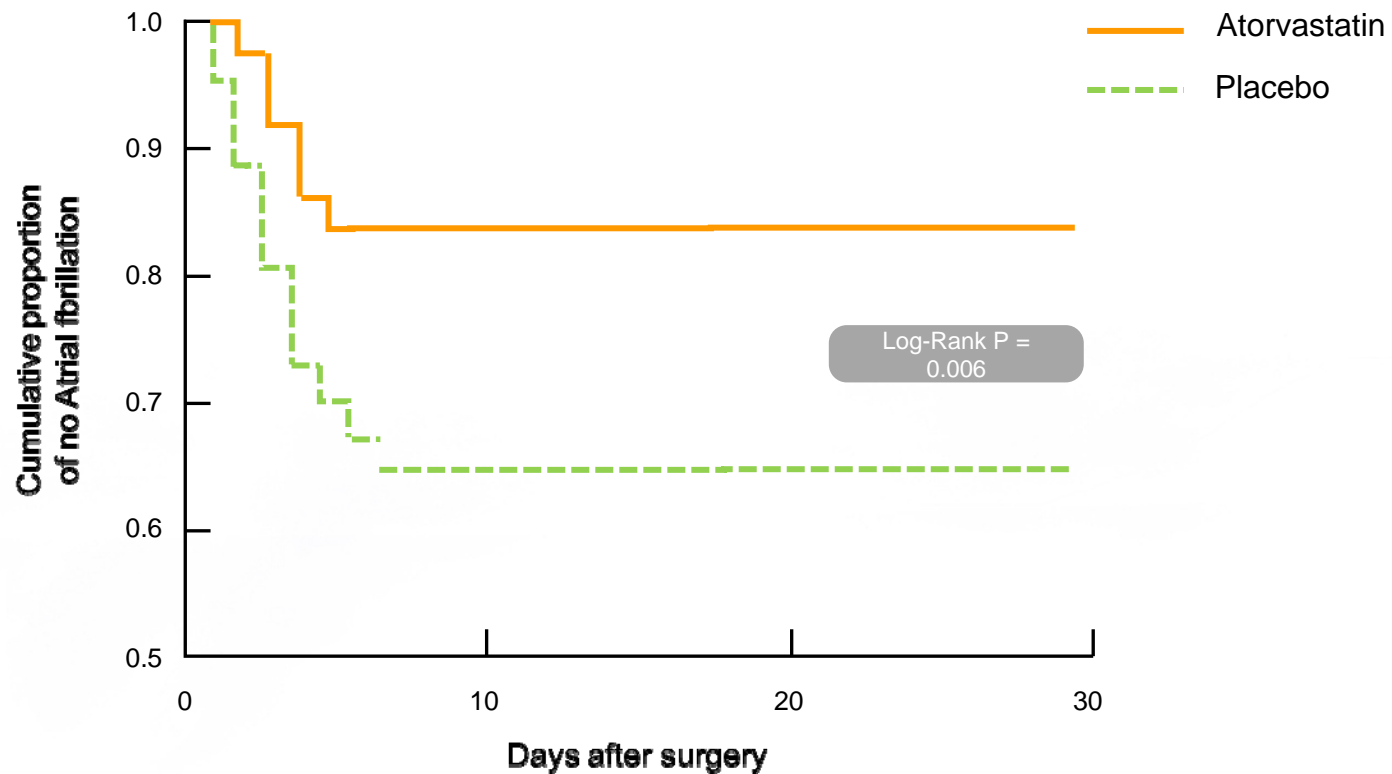


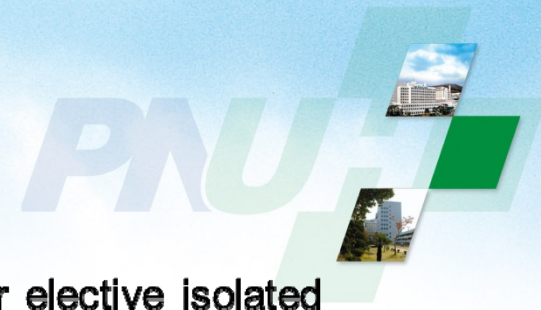
Primary Outcome	Control(n=62)	Lipitor(n=62)	P value
Incidence of postoperative AF (30 day follow up)	17 (27%)	8 (13%)	0.04



Preop. Atorvastatin & Postop. AF in China

- Atorvastatin 20 mg/day, 1 wk before elective off-pump CABG and continued in the postoperative period, significantly decreases post operative AF.
- Atorvastatin 49 patients (20 mg, 7 days before op) vs Control 51 patients (placebo)
- Primary Endpoint: Atrial fibrillation





Preop. statin & Postop. AF in Japan

- Preop. statin significantly reduces the incidence of AF after elective isolated off-pump CABG in Japanese pts.

Table 5. Multivariate Predictors of Postoperative Atrial Fibrillation

	OR	95%CI	P value
Statin	0.49	0.22-0.81	0.01
Age *	1.33	1.04-1.69	0.02
Transfusion	2.21	1.38-3.55	0.01

* OR per 10-year increase.
OR, odds ratio; CI, condence interval.

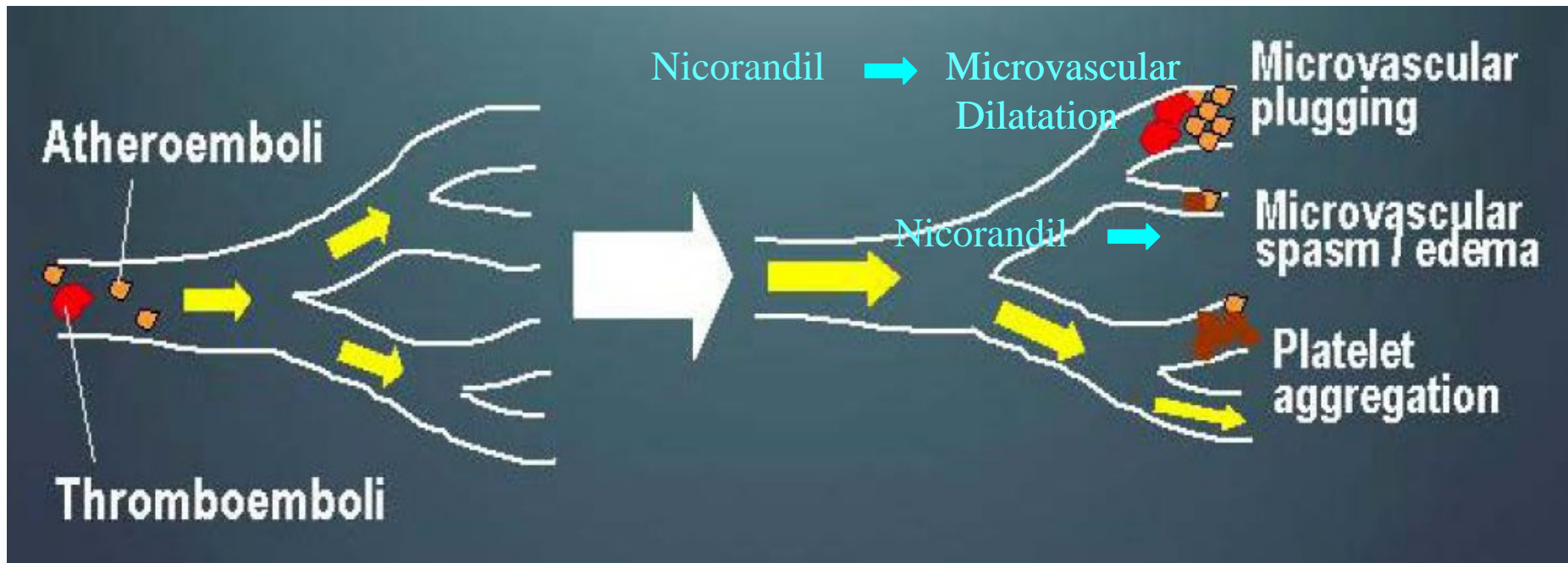


The Effect of Intra-coronary Nicorandil prior to Reperfusion in Acute ST Segment Elevation Myocardial Infarction

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Yung Woo Shin, MD

Background



Methods



- **Seventy-three patients with acute ST segment elevation myocardial infarction were randomly assigned to the nicorandil group (n=37) or a control group (n=36) all patients had a PCI.**
- **In the nicorandil group, 4 mg of intra-coronary nicorandil was infused directly into the infarct area prior to reperfusion (2 mg before ballooning, 2 mg before stenting).**



Results

Results

Baseline Clinical Characteristics

N (73)	Nicorandil(n=37)	Control(N=36)	p Value
Age(years)	56.4 ± 13	60.2 ± 12	0.214
Male	31(83.8%)	30(83.3%)	0.579
Hypertension	19(51.4%)	24(66.7%)	0.285
Diabetes mellitus	10(27.0%)	13(36.1%)	0.404
Smoking	32(86.5%)	25(69.3%)	0.078
Previous MI*	2(5.4%)	3(8.3%)	0.473
Previous angioplasty	1 (2.7%)	1 (2.7%)	0.337
Medication			
Aspirin	37(100%)	36(100%)	1.0
Clopidogrel	37(100%)	36(100%)	1.0
Cilostazole	7(18.9%)	9(25%)	0.11
Statin	35(94.6%)	34(94.4%)	0.35
Gp# lib/IIIa inhibitor	5(13.5%)	5(13.9%)	0.84
ACEI¶	24(67.6%)	22(61.1%)	0.76
ARB§	10(27.2%)	12(33.3%)	0.65
Hepain	37(100%)	36(100%)	1.0
Beta blocker	23(62.2%)	20(55.6%)	0.45

MI* : myocardial infarction Gp# : glycoprotein ACEI¶ : angiotensin converting enzyme inhibitor ARB§ : angiotensin receptor blocker

Results

Angiographic characteristics

N (73)	Nicorandil(n=37)	Control(N=36)	p Value
Culprit lesion*			
LAD	20(54.1%)	20(55.6%)	0.719
LCX	2(5.4%)	8(22.2%)	
RCA	14(37.8%)	9(25.0%)	
RI	1(2.7%)	1(2.8%)	
Three vessel disease	7(18.9%)	4(11.1%)	0.351
Lesion type			
B2	16(43.2%)	12(33.3%)	0.384
C	21(56.8%)	24(66.7%)	
Thrombus score			
3	10(27.2%)	15(41.7%)	0.281
5	27(72.8%)	21(58.3%)	
Pre-TIMI grade			
0	27(72.9%)	21(58.3%)	0.188
1	0	0	
2	8(29.6%)	9(25.0%)	0.733
3	2(5.4%)	6(16.7%)	

•LAD : Left anterior descending artery LCX : left circumflex artery RCA : Right coronary artery
 RI : Ramus intermedius

Results

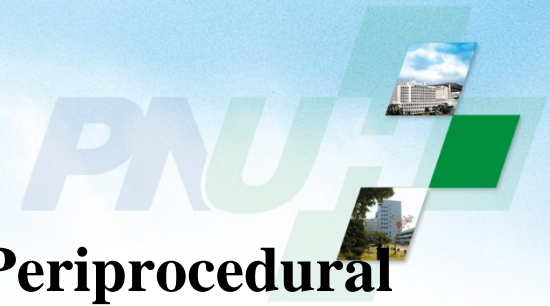
PCI data and Laboratory findings

N (73)	Nicorandil(n=37)	Control(N=36)	p Value
Peak CK-MB	313.5	295.3	0.538
Peak Troponin-I	110.3	83.1	0.442
Type of Stent			
Cypher	14(37.8%)	19(52.8%)	
Taxus	14(37.8%)	11(30.6%)	0.205
Endeavor	1(2.7%)	2(5.6%)	
Bare metal	3(8.5%)	0	
PTCA only	5(13.2%)	4(11.1%)	
Post-TIMI grade			
0	1(2.7%)	2(5.2%)	0.538
1	1(2.7%)	4(10.4%)	0.155
2	0	3(8.3%)	0.173
3	35(94.6%)	27(75.0%)	0.019
Myocardial blush grade			
1	0	5(13.9%)	0.019
2	11(29.7%)	10(27.8%)	0.854
3	26(70.3%)	21(58.3%)	0.287
Composite end point			
No-reflow	1(2.7%)	2(5.2%)	0.538
Slow flow	1(2.7%)	4(10.4%)	0.155
Ventricular arrhythmia	0	2(5.2%)	0.146
Re-myocardial infarction	1(2.7%)	0	0.321

Results



- Significant difference in the **composite endpoint (No-reflow, slow flow, ventricular arrhythmia)** in the nicorandil group
- **The post TIMI grade 3** was higher in the nicorandil group
- **The myocardial perfusion grade 1** was not observed in the nicorandil group
- Major adverse cardiac events in hospital and in 30 days were similar between two groups



The Effect of Intra-coronary Nicorandil on Periprocedural Myocardial Infarction Prior to Elective Percutaneous Coronary Intervention in Stable and Unstable Angina

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The Effect of Intra-coronary Nicorandil on Periprocedural MI

- Subjects

The study group was comprised of ninety patients of **stable or unstable AP with long LAD lesion, normal cardiac enzyme level** who visited the emergency department or OPD of our hospital for chest pain between November 2007 and June 2009.

- Procedure

Subjects in the **Nicorandil Group were administrated 2 mg intracoronary nicorandil** prior to percutaneous transluminal coronary angioplasty and an **additional dose of 2 mg intracoronary nicorandil in the long LAD lesion before stent implantation**. A minimum 3 minutes interval was observed between the first and second dose of nicorandil to reduce adverse effects. Then one or more DES was implanted for the treatment of de novo lesions of the LAD.

The Effect of Intra-coronary Nicorandil on Periprocedural MI

- Cardiac enzymes

After successful PCI, blood was collected just before PCI and 6, 12, 18, 24, 36 and 48 h after PCI for measuring the concentrations of **CK-MB and cTnl**.

- Analysis of Coronary Angiography

The angiograms after stent implantation of all study patients were taken. One of the main reason of PMI is **side branch occlusion**, so side branches were analyzed. **More than 1 mm in diameter** were estimated, including **septal branches and diagonal branches** and described by three status; **branch occlusion, narrowing, TIMI flow reduction**. The side branch was considered narrowed when there was a $> 50\%$ stenosis after stent placement and reduction of TIMI flow more than a grade 1 at any time after stent placement was defined as "TIMI flow reduction".

The Effect of Intra-coronary Nicorandil on Periprocedural MI :

Baseline clinical characteristics

N(90)	Nicorandil(N=41)	Control(N=49)	p value
Stable AP	21(51.2%)	29(59.2%)	0.449
Age(years)	66.2 ± 9	65.3 ± 10	0.654
Male	20(48.8%)	33(67.3%)	0.075
Hypertension	27(65.9%)	30(61.2%)	0.650
Diabetes mellitus	15(36.6%)	15(30.6%)	0.549
Smoking	14(34.1%)	14(28.6%)	0.569
Family Hx of MI	7(17.1%)	5(10.2%)	0.340
Previous MI	5(12.2%)	1(2%)	0.054
Previous angioplasty	3(7.3%)	0(0%)	0.054
CKD*	2(4.9%)	0(0%)	0.118
Dyslipidemia	9(22.0%)	9(18.4%)	0.672
Total cholesterol	182.5 ± 31.8	193.9 ± 35.9	0.118
LDL	118.18 ± 26.3	119.67 ± 34.9	0.835
HDL	41.15 ± 9.5	43.4 ± 11.64	0.347
Creatinine	1.02 ± 0.53	1.04 ± 0.23	0.8
hsCRP	0.788 ± 2.0	0.448 ± 0.5	0.287

The Effect of Intra-coronary Nicorandil on Periprocedural MI.

Post-PCI peak cardiac enzyme & side branch analysis of LAD after PCI

N(90)	Nicorandil(N=41)	Control(N=49)	p value
Peak CK-MB ($\mu\text{g/L}$)	2.51 \pm 1.96	1.85 \pm 1.79	0.099
Peak Troponin I (ng/mL)	0.53 \pm 0.67	0.34 \pm 0.54	0.196
Rates of side branch occlusion	5.3%	2%	0.276
Rates of side branch narrowing	21.3%	6%	0.017
Rates of TIMI grade reduction	2.6%	6%	0.292
Jail Index[#]	0.076 \pm 0.21	0.073 \pm 0.19	0.951

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Clinical outcomes

N(90)	Nicorandil(N=41)	Control(N=49)	p value
In-hospital outcomes			
Death	0	0	-
TLR	1(2.4%)	0	0.272
STEMI	1(2.4%)	0	0.272
CVA#	1(2.4%)	0	0.272
6 month follow-up outcomes			
Death	0	0	-
TLR	1(2.4%)	0	-
STEMI	1(2.4%)	0	-
CVA	1(2.4%)	0	-

Conclusions

- Preoperative statin therapy was associated with survival and other clinical benefits (AF, thromobis and stroke) for patients undergoing CABG
- Available data is encouraging preoperative **statin therapy to reduce the risk of mortality** for patients undergoing CABG
- Preoperative statin therapy should be considered for most patients undergoing CABG, to reduce the incidence and/or clinical sequelae of Artrial fibrillation

