PCI for Unprotected Left Main Coronary Artery Stenosis

Current Recommendation for unprotected LMCA Stenosis

- Class IIb C in ESC guideline (2005) and Class III in ACC guideline (2006) in patients eligible for CABG
- Class III is the conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/ effective and in some cases may be harmful.

Evidence of the Superiority of CABG Very Old Study

Trial	Enroll	F/U	Survival rate		P
	Medicine	CABG			
Veteran	1972-	3.5 years	65%	88%	0.01
Administration Cooperative Study	1974		N=43	N=48	
European Coronary	1973-	5 years	62%	93%	<0.05
Surgical Study	1976		N=31	N=28	
Coronary Artery	1974-	4 years	63%	88%	<0.0001
Surgery Study	1979		N=309	N=1,183	
Pooled data	1972-	3.5-5	62%	88%	<0.0001
	1979	years	N=405	N=1,259	

Unprotected left main stenting is still premature in general practice...

Compare to Surgery,

High Mortality in PCI?

Low Event Rate in Low Risk Group

One year Clinical Outcomes of ULTIMA Registry

(%)	All (n=279)	Low Risk
Death	24.2	3.4
Cardiac Death	20.2	3.4
MI	9.8	2.3
CABG	9.4	11.4
Repeat PCI	24.2	20.4
Death or MI	27.8	3.4
Death/MI/CABG	34.6	16.9

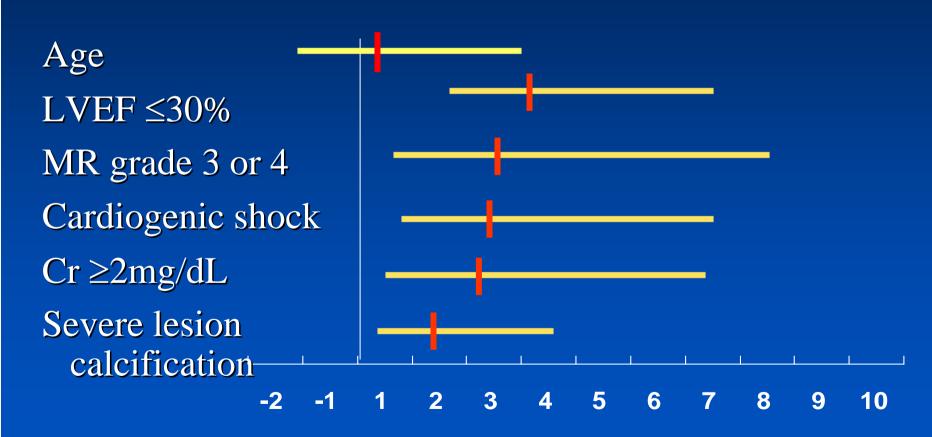
ULTIMA, Circulation 2001;104:1609





Relative Risk of Mortality in LMCA Stenting

ULTIMA Registry (279 pts)



Nalysnyk L, Heart 2003, 89:767,





In-hospital Outcomes

310 pts, Elective Unprotected left main stenting in highly selected groups of patients who have normal left ventricular function (mea age 56 yrs)

Procedural Success Rate: 99%

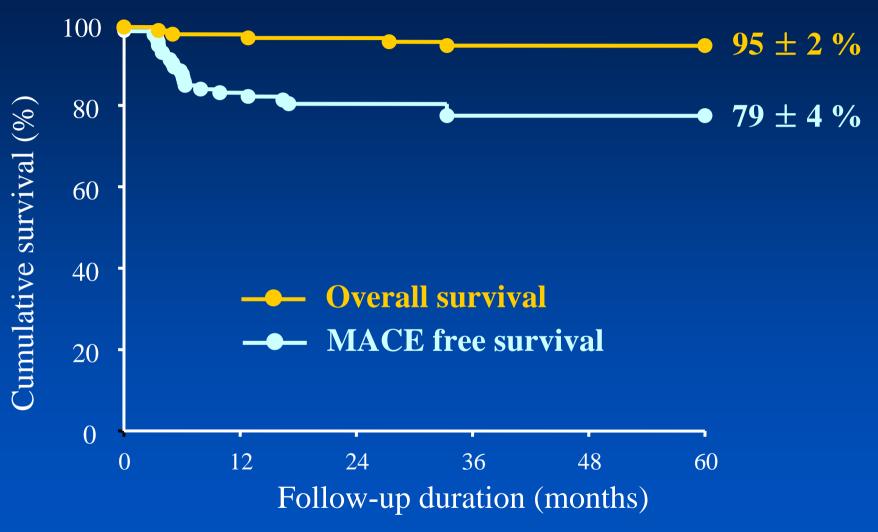
Acute closure	0
Subacute thrombosis	1 (0.5%)
Death	0
Q-MI	0
Emergent CABG	0

Park SJ, Am J Cardiol 2003





Survival for 5 years



Park SJ, Am J Cardiol 2003



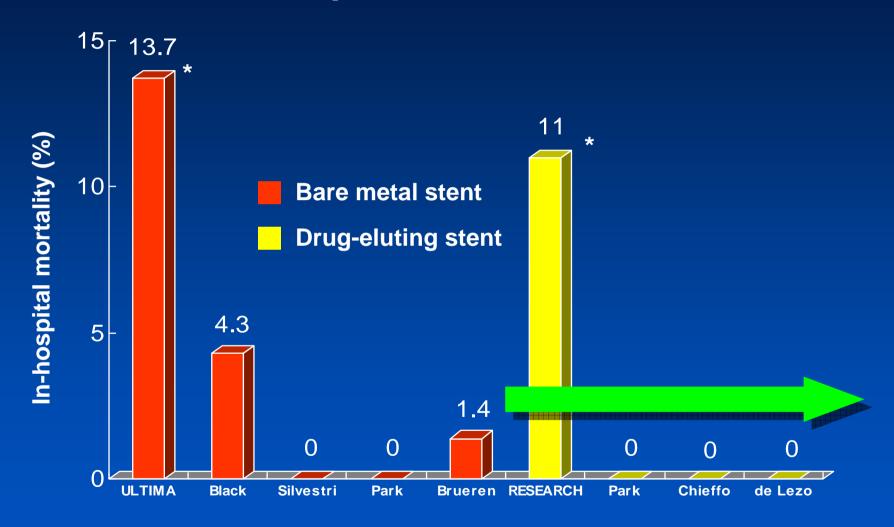
Risk of Mortality in Unprotected Left main stenting

May be mainly related with clinical variables - what patients are...

Patients selection is important for lower mortality and good clinical outcomes

In the era of DES...

In-Hospital Mortality Low in the patients at a low risk!

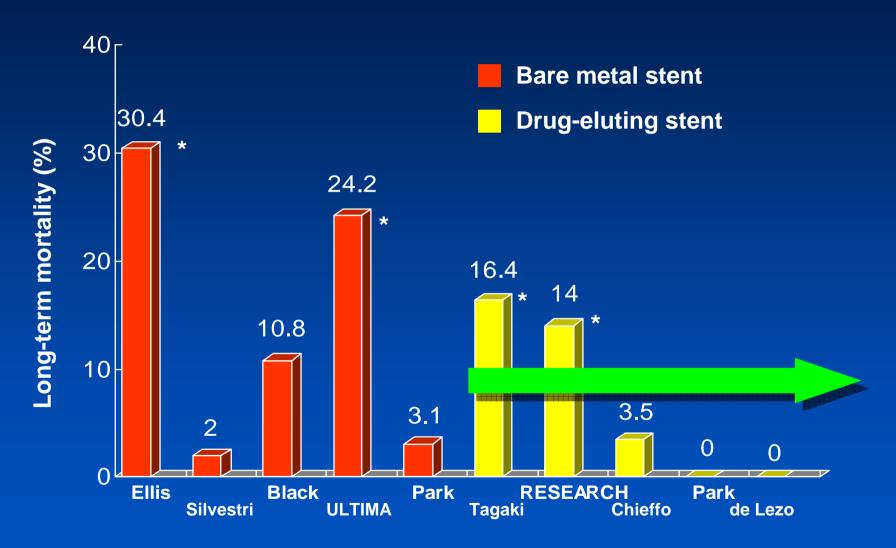


* High-risk surgical candidates



Long-term Mortality (after 6 Mo)

Acceptable in the patients at a low risk!



* High-risk surgical candidates



Predictors of Death/ MI in Unprotected LM stenting

324 patients

who underwent elective coronary stenting for the treatment of unprotected LMCA (DES 176, BMS 148 Pts)

* Exclusion of ST elevation MI within 24 hours

AMC data





Overall Incidence of Death/ MI 13.0% (42 patients).

In-Hopspital

- Periprocedural MI *: 334 pts (10.2%)
 - Death or SAT:None

Clinical F/U

(98%, median 26 months)

- Deaths: 5 pts (1.6 %)
 4 cardiac
 1 non-cardiac
- Non-fatal MI : 4 pts (1.2%)

TLR: 36 pts (11.1%), 16 PCI, 20 CABG

* CKMB rise >3times



Baseline Characteristics

Variables	Death/MI (n=42)	No death/MI (n=282)	Р
Age (yrs)	60.6±11.4	58.5±12.0	0.309
Men	30 (71.4%)	194 (68.8%)	0.730
Diabetes mellitus	8 (19.0%)	72 (25.5%)	0.363
Hypercholesterolemia (>200mg/dL)	11 (26.2%)	61 (21.6%)	0.507
Smoking	15 (35.7%)	85 (30.1%)	0.466
Hypertension	15 (35.7%)	123 (43.6%)	0.334
Previous PCI	5 (11.9%)	44 (15.6%)	0.649
Previous CABG	1 (2.4%)	1 (0.4%)	0.243



Clinical Characteristics

Variables	Death/MI (n=42)	No death/MI (n=282)	P
LVEF (%)	62.0 (55.0-66.0)	62.0 (59.0-66.0)	0.456
ACS	26 (61.9%)	133 (47.2%)	0.075
Renal failure	0 (0%)	4 (1.4%)	1.000
EuroSCORE	3.0 (2.0-6.0)	2.0 (1.0-4.0)	0.022
Parsonnet score	7.0 (6.0-13.0)	7.0 (6.0-8.3)	0.175
CRP (mg/dL)	2.4 (1.1-3.9)	2.0 (0.9-4.0)	0.736
Lipoprotein(a) (mg/L)	20.9 (12.1-35.4)	21.5 (9.4-37.2)	0.888
Homocysteine (μmol/L)	12.7 (9.9-15.0)	12.4 (10.2-15.1)	0.778



Angiographic Characteristics

Variables	Death/MI (n=42)	No death/MI (n=282)	P
Bifurcation involvement	29 (69.0%)	157 (55.7%)	0.102
Multivessel (≥ 2) except for the left main	29 (69.0%)	137 (48.6%)	0.013
Reference diameter (mm)	3.56±0.80	3.69±0.70	0.314
Pre-procedural MLD (mm)	1.28±0.61	1.48±0.66	0.066
Post-procedural MLD (mm)	3.52±0.65	3.72±0.64	0.069
Lesion length (mm)	12.1 (9.1-35.4)	11.8 (8.0-18.4)	0.133

CVRF

Procedural Characteristics

Variables	Death/MI (n=42)	No death/MI (n=282)	Р
Multivessel PCI	23 (54.8%)	119 (42.2%)	0.126
Stenting in the side branch	9 (21.4%)	62 (22.0%)	0.935
Total stent length (mm)	18.0 (13.0-42.8)	18.0 (12.0-23.0)	0.089
Used stents at the LMCA	1.0 (1.0-1.3)	1.0 (1.0-1.0)	0.956
Number of total used stents	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.015
Debulking atherectomy	8 (19.0%)	53 (18.8%)	0.969
Rotablating atherectomy	0 (0%)	4 (1.4%)	1.000



Procedural Characteristics

Variables	Death/MI (n=42)	No death/MI (n=282)	Р
Cutting balloon angioplasty	2 (4.8%)	8 (2.8%)	0.501
Direct stenting	10 (23.8%)	88 (31.2%)	0.330
Maximal device diameter (mm)	4.19±0.52	4.44±0.59	0.120
Intra-aortic balloon pump	8 (19.0%)	16 (5.7%)	0.002
Glycoprotein IIb/IIIa inhibitor	8 (19.0%)	13 (4.6%)	< 0.001
Guidance of IVUS	30 (71.4%)	202 (71.6%)	0.978
DES (Sirolimus-eluting stent)	23 (54.8%)	153 (54.3%)	0.951



Major Predictors of Death/MI in Unprotected LM stenting

By Multivariate Analysis

1.	High	EuroS	CO	RE	(>6)
		Luius			(20)

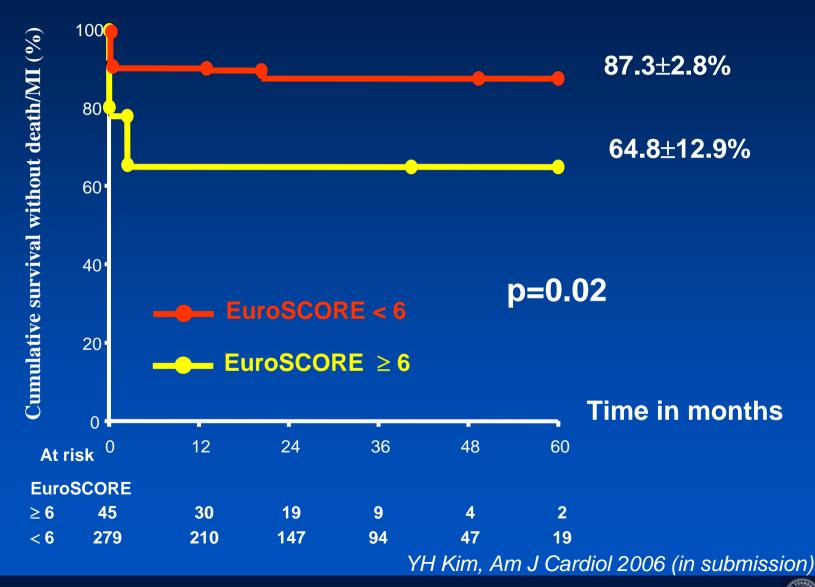
2. No. of total used stents

3. Use of GP IIb/IIIa inhibitor

Hazard ratio	95% CI	P value
3.362	1.181 – 9.574	0.023
1.792	1.021 - 3.146	0.042
8.640	2.722 - 27.418	< 0.001



MI-free Survival Curve



Risk of Mortality in Unprotected Left main stenting

May be mainly related with clinical variables - what patients are rather than what lesions are ...

Unprotected left main stenting is still premature in general practice,

Unprotected left main bifurcation stenting is very challenging and good invited target for PCI in near future...

DES for Ostial or Shaft LMCA Stenosis?

Experience of Asan Medical Center

Ostial and Shaft LM PCI 51 patients

Lesion length, mm

Reference, mm

Used stent

IVUS guidance

Acute gain, mm

Late loss, mm

Restenosis

TLR

Stent thrombosis

 9.3 ± 5.4

 3.49 ± 0.53

Single in all pts

41 (80%)

 2.18 ± 0.66

 0.10 ± 0.23

1/38 (2.6%)

1 (2.0%)

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SJ Park, J Am Coll Cardiol 2005; 45:351-5



DES for Ostial or Shaft LMCA Stenosis

No Mortality

2.6% Restenosis

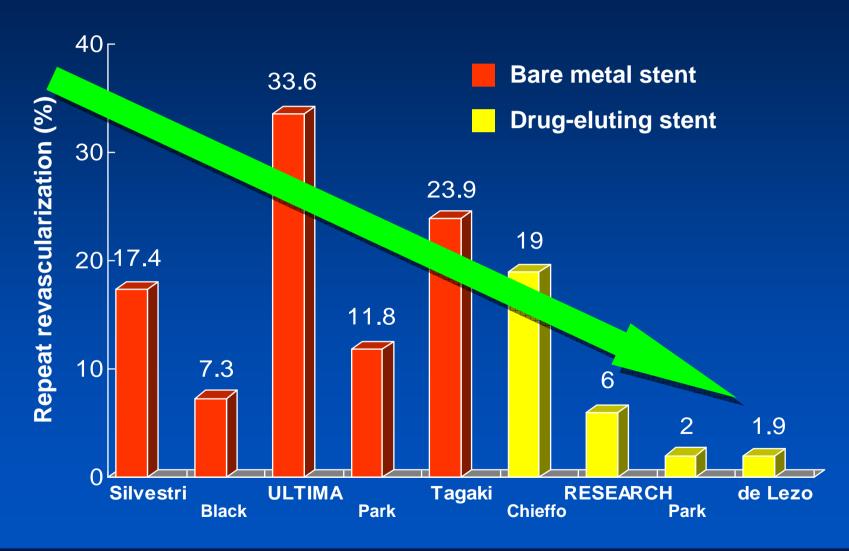
2% TLR

Would be an effective alternative and even better compare to surgery...

What about DES for Bifurcation LMCA Stenosis?

This is more challenging even in the DES era...

Significant Reduction of TLR with DES Unprotected Left main stenting



But, the TLR rates of DES remains diverse.

	Colombo A	Serruys PW	Park SJ
Number	85	95 (15 protected)	102
DES used	Cypher	Cypher+Taxus	Cypher
Technical success (%)	100	99	100
In-hospital			
Cardiac death	0	1 (1%)	0
MI (Q and Non-Q)	5 (5.9%)	1 (1%)	7 (6.9%)
CABG	0	0	0
Long-term	6-Mo	1-Yr	1-Yr
Cardiac death	3 (3.5%)	13 (14%)	0
MI	0	4 (4%)	0
TLR	12 (14.1%)	6 (6%)	2 (2.0%)



Different % of LMCA bifurcation PCI were included

	Colombo A	Serruys PW	Park SJ
Patient	85	95	102
Age	63.2±11.7	64±12	60.3±11.1
Male	70 (84.3%)	66%	87 (71.9%)
Diabetes mellitus	18 (21.2%)	30%	29 (84.4%)
Ejection fraction, %	51.1±11	41±14	60.4±8.4
Acute MI	NA	17%	10 (9.8%)
Cardiogenic shock	NA	9%	0
Multivessel disease	NA	80%	59 (58.4%)
Distal location	69 (81.2%)	65%	72 (70.6%)



Antonio likes two stenting stategy because bifurcation stenting is his unique invention!

	Colombo A	Serruys PW	Park SJ
Reference, mm	3.73±0.6	3.25±0.5	3.46±0.65
MLD, pre, mm	1.34 ± 0.5	1.09 ± 0.44	1.31±0.57
Treated lesions or multi-vessel PCI	2.9±1.6	NA	43 (42.2%)
Stent length, mm	24.3±12	24±13	26.6±18.1
DCA, mm	2 (2.3%)	0	3 (2.9%)
MLD, post, mm	3.3±0.6	2.83±0.49	3.36±0.47
Bifurcation stenting	51 (74%)	40%	29 (41%)
Culotte	5 (10%)	36%	0
T technique	4 (8%)	44%	1 (3%)
Crush	30 (59%)	12%	11 (38%)
Kissing	12 (24%)	8%	17 (59%)



However, a high TLR rate has been paid for the complex stenting strategy

	Colombo A	Serruys PW	Park SJ
Bifurcation stenting	51 (74%)	40%	29 (41%)
Culotte	5 (10%)	36%	0
T technique	4 (8%)	44%	1 (3%)
Crush	30 (59%)	12%	11 (38%)
Kissing	12 (24%)	8%	17 (59%)
TLR	12 (14.1%)	6 (6%)	2 (2.0%)

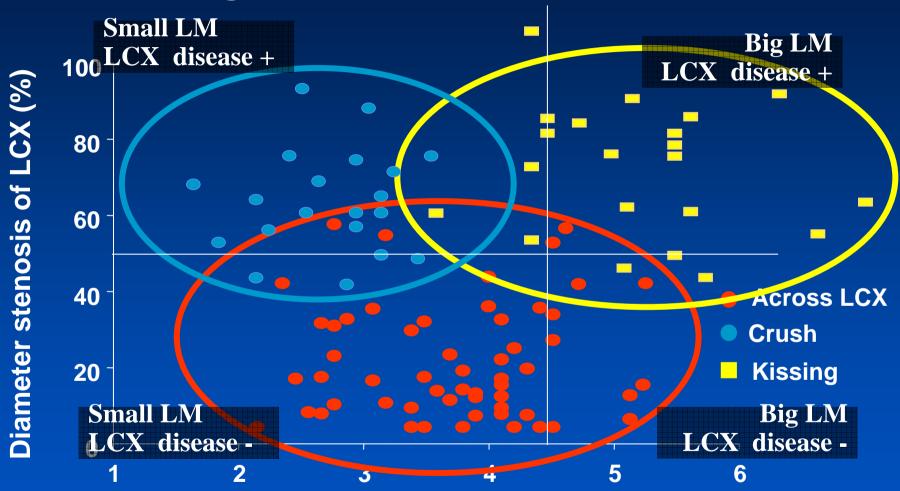
Recommended Treatment Strategy for LMCA bifurcation lesions

Stenting Cross-over (provisional T stenting)

Kissing Stenting Stent Crushing

Different Treatment in AMC

According to LM size and LCX involvement



Reference diameter of LMCA (mm)



Baseline Data

Characteristic	Stent Cross-over	Complex tech.	P value
Patients	67	49	
Age, yr	59.6±12.0	60.6±8.5	0.604
Males	48 (71.6)	38 (77.6)	0.473
Cardiac risk factors			
Hypertension	34 (50.7)	17 (34.7)	0.085
Diabetes mellitus	24 (35.8)	11 (22.4)	0.121
Hypercholesterolemia	17 (25.4)	8 (16.3)	0.242
Current smoking	13 (19.4)	15 (30.6)	0.163
Previous PCI	8 (11.9)	9 (18.4)	0.334
ACS	34 (50.7)	29 (52.2)	0.368
Multivessel involvement	46 (68.7)	42 (85.7)	0.047
Left ventricular EF, %	59.2±8.0	61.5±7.3	0.110

YH Kim, Am J Cardiol 2006 (in press)





Procedural Data

Characteristic	Cross-over.	Complex tech.	P value
Patients	67	49	
Multiple lesion intervention	25 (37.3)	18 (36.7)	0.949
Debulking atherectomy	4 (6.0)	3 (6.1)	0.973
Use of GP IIb/IIIa inhibitor	3 (4.5)	9 (18.4)	0.027
Intravascular ultrasound guidance	60 (89.6)	43 (87.8)	0.762
Stent length in LM, mm	31.8±19.3	35.4±18.3	0.314
Stents used per lesion	1.4±0.7	2.6±0.8	< 0.001
Use of IABP	5 (7.5)	2 (4.1)	0.697





QCA Analysis at Main Vessel

	Cross-over	Complex tech.	p
Patients	67	49	
Follow-up CAG	57 (85)	41 (85)	
Proximal RVD, mm	3.61±0.72	3.77±0.74	0.240
Distal RVD, mm	2.81±0.60	2.75±0.45	0.557
MLD, mm			
Before procedure	1.11±0.47	1.01±0.47	0.269
After procedure	2.97±0.52	2.98±0.36	0.931
At follow-up	2.91±0.53	2.56±0.67	0.006
Lesion length, mm	25.8±17.1	26.2±14.5	0.918
Acute gain, mm	1.86±0.58	1.96±0.45	0.295
Late loss, mm	0.13±0.40	0.42 ± 0.63	0.009



QCA Analysis at Circumflex Artery

	Cross-over	Complex tech.	p
Patients	67	49	
Follow-up CAG	57 (85)	41 (85)	
Distal RVD, mm	2.78±0.66	2.64±0.49	0.209
MLD, mm			
Before procedure	2.25±0.76	1.39±0.64	< 0.001
After procedure	2.21±0.77	2.65±0.40	< 0.001
At follow-up	1.98±0.80	1.97±0.81	0.958
Acute gain, mm	-0.04±0.66	1.26±0.60	< 0.001
Late loss, mm	0.20±0.59	0.69±0.72	<0.001





IVUS Analysis at Distal LMCA

	Cross-over	Complex tech.	p	
Patients	46	39		
Before procedure				
EEM CSA, mm ²	21.7±6.0	20.6±4.0	0.391	
Lumen CSA, mm ²	6.2±2.2	4.8±1.7	0.003	
Plaque burden, %	70.8±8.9	76.1±9.1	0.012	
After procedure				
EEM CSA, mm ²	23.9±5.7	24.0±3.9	0.905	
Lumen CSA, mm ²	11.7±2.7	12.5±2.7	0.191	
Plaque burden, %	50.2±8.4	47.7±8.8	0.184	

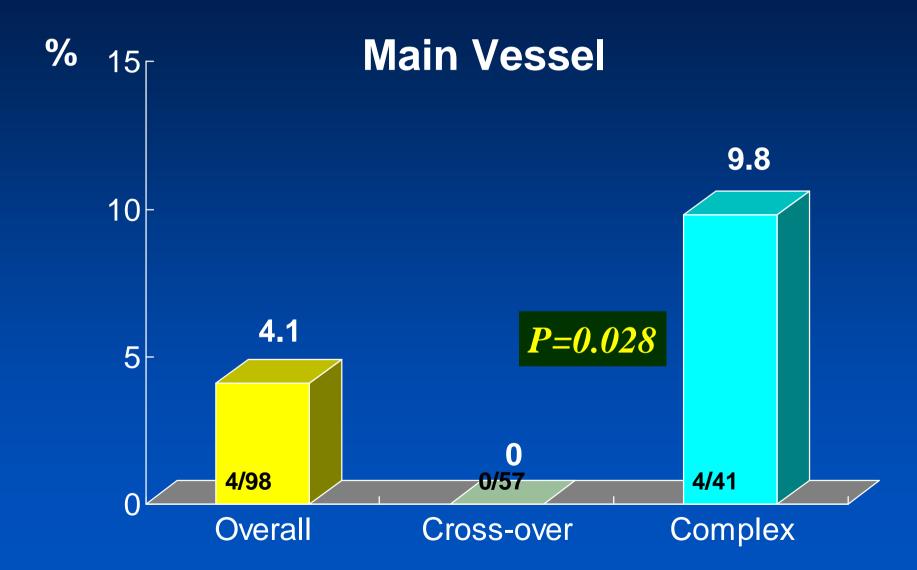
IVUS Analysis at Ostial LAD Under-expansion in complex stenting

	Cross-over	Complex tech.	p
Patients	46	39	
Before procedure			
EEM CSA, mm ²	15.2±4.4	14.4±3.3	0.339
Lumen CSA, mm ²	4.5±2.0	4.2±1.8	0.548
Plaque burden, %	69.7±11.8	70.6±9.9	0.707
After procedure			
EEM CSA, mm ²	18.2±4.0	17.7±2.6	0.523
Lumen CSA, mm ²	9.7±2.0	8.0±1.7	< 0.001
Plaque burden, %	45.8±10.2	54.8±7.5	< 0.001



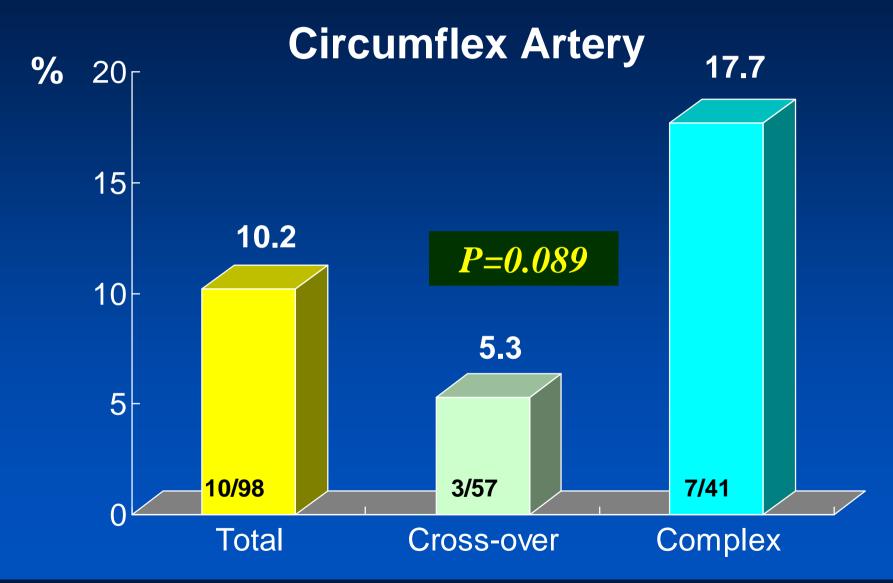


Restenosis Rate of Bifurcation

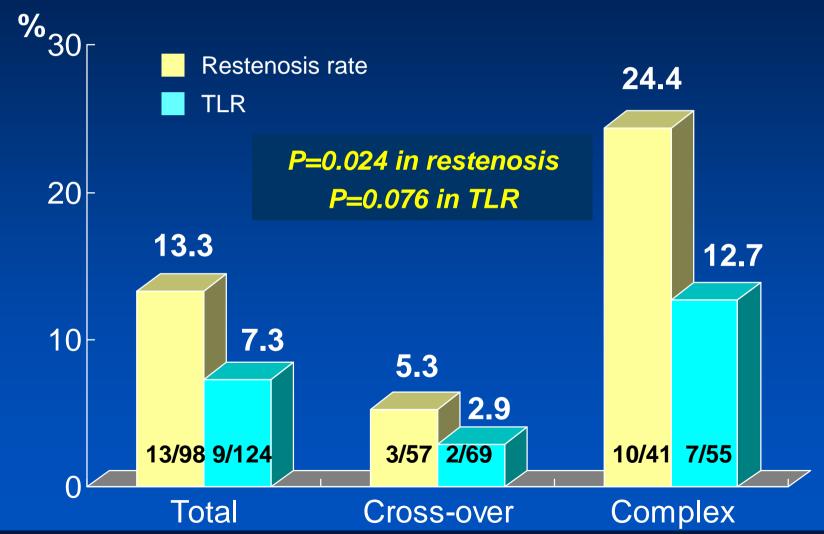


AMC data

Restenosis Rate of Bifurcation



Rates of Restenosis and TLR **Total 124 bifurcation LMCA**



Two Different Complex Strategies

What about Kissing vs. Stent Crushing?

QCA Analysis at Main Vessel

	Kissing stenting	Stent Crushing	p
Patients	24	25	
Follow-up CAG	20 (83)	21 (84)	
Proximal RVD, mm	4.09±0.69	3.46±0.65	0.002
Distal RVD, mm	2.92±0.42	2.59±0.42	0.009
MLD, mm			
Before procedure	0.91±0.52	1.12±0.40	0.111
After procedure	2.97±0.35	2.99±0.37	0.837
At follow-up	2.58±0.70	2.54±0.66	0.865
Lesion length, mm	23.7±13.3	28.6±15.4	0.253
Acute gain, mm	2.06±0.40	1.87±0.49	0.138
Late loss, mm	0.39±0.67	0.44±0.61	0.790





QCA Analysis at LCX

	Kissing stenting	Stent Crushing	p
Patients	24	25	
Follow-up CAG	20 (83)	21 (84)	
Distal RVD, mm	2.73±0.56	2.56±0.40	0.229
MLD, mm			
Before procedure	1.48±0.78	1.30±0.47	0.332
After procedure	2.70±0.36	2.60±0.44	0.387
At follow-up	2.03±0.78	1.91±0.85	0.646
Acute gain, mm	1.22±0.72	1.30±0.46	0.645
Late loss, mm	0.72±0.56	0.67±0.85	0.824
Restenosis	3 (15.0)	4 (19.0)	1.000



IVUS Finding at the LMCA

Variable	Cross over (n=43)	Kissing (n=18)	Crushing (n=16)	P value
Before procedure				
EEM area (mm ²)	21.7±6.0	21.5±3.7	19.7±4.2	0.404
Lumen area (mm²)	6.2±2.2 *	4.6±2.1	5.0±1.3	0.010
Plaque area (mm²)	15.5±5.1	16.9±3.7	14.7±4.6	0.360
Plaque burden (%)	70.8±8.9 *	78.6±8.7	73.4±8.9	0.011
After procedure				
EEM area (mm ²)	23.9±5.7	25.1±3.6	22.7±3.9	0.334
Lumen area (mm²)	11.7±2.7	13.0±3.1	11.9±2.0	0.172
Plaque area (mm²)	12.1±4.4	12.0±2.9	10.9±3.0	0.465
Plaque burden (%)	50.2±8.4	48.1±10.0	47.2±7.4	0.399

^{*} p<0.05/3 between cross-over and Crush, † between cross-over and Kissing, ‡ between Crush and Kissing



IVUS Finding at the Ostial LAD

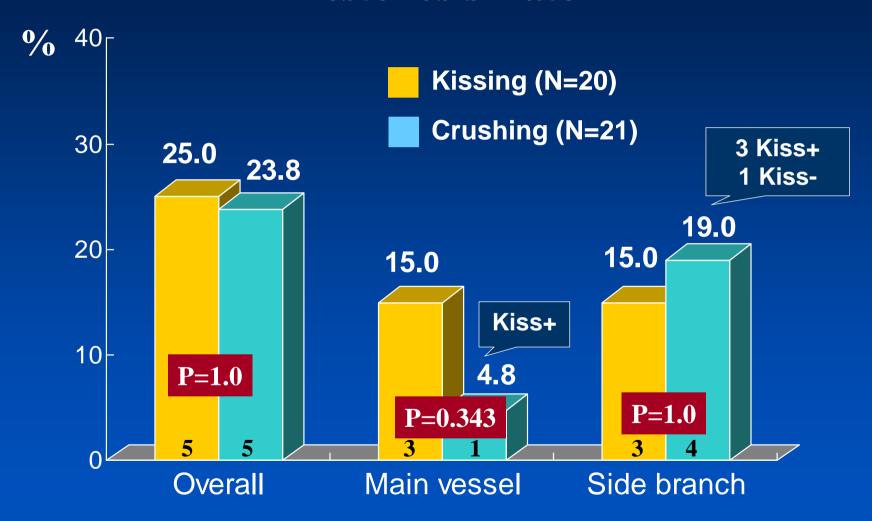
Variable	Cross over (n=43)	Kissing (n=18)	Crushing (n=16)	P value
Before procedure				
EEM area (mm²)	15.2±4.4	14.9±3.1	13.7±3.6	0.450
Lumen area (mm²)	4.5±2.0	4.2±1.8	4.2±1.9	0.831
Plaque area (mm²)	10.8±4.1	10.7±3.0	9.5±2.5	0.475
Plaque burden (%)	70.0±11.8	71.6±10.6	69.5±9.2	0.796
After procedure				
EEM area (mm²)	18.2±4.0	18.1±2.2	17.2±3.0	0.615
Lumen area (mm²)	9.7±2.0 *,†	7.7±1.7	8.3±1.7	< 0.001
Plaque area (mm²)	8.5±3.1 *	10.4±1.9	8.9±2.0	0.024
Plaque burden (%)	45.8±10.2 *,	57.7±7.5 ‡	51.6±6.3	< 0.001

^{*} p<0.05/3 between cross-over and Crush, † between cross-over and Kissing, ‡ between Crush and Kissing

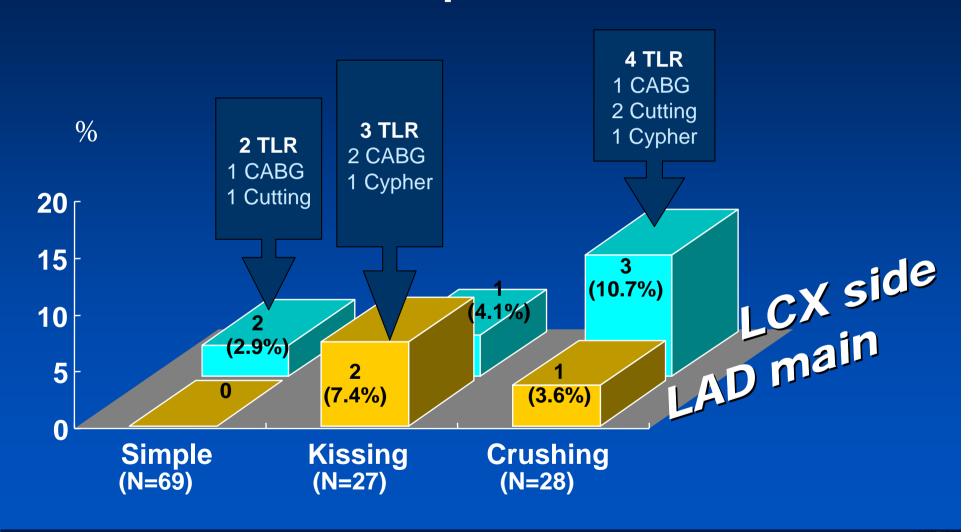


Kissing vs. Crush

Restenosis Rate



TLR: 7.3% in LMCA Bifurcation PCI 9/124 patients



Stenting Technique at LM Bifurcation Lesions

- Both the presence of ostial LCX disease (diameter stenosis ≥50%) and the LMCA size by angiographic and IVUS examinations were two important considerations in selecting the stenting strategy.
- Compared to the complex stenting approach, the simple approach (stenting cross-over) was technically easier and appeared to be more effective in improving long-term outcomes for lesions with normal or diminutive LCX.

How to Prove it?

COMBAT Randomized Trial

<u>COM</u>parison of <u>Bypass surgery and <u>Angioplas Ty</u> using sirolimus electing stent in patients with left main coronary disease</u>

Left Main disease with or without MVD
Up to 75 cardiac centers

Randomize over 1,776 (1:1)

CABG N=888 Registry group 1,000

CABG PCI Medication

Primary Endpoint: 2-year death, MI, and stroke
Key Secondary Endpoints: MACCE including primary end point and
ischemia-driven TLR

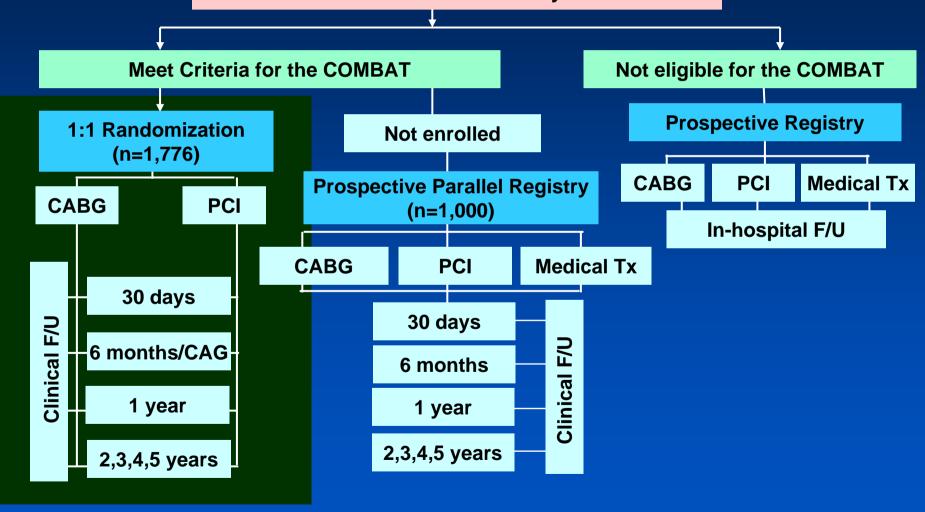
PI: Seung-Jung Park, Martin B. Leon

PCI with SES

N=888

Flow Chart of Study

Patients with >50% LMCA stenosis by visual estimate



Study Progress of the COMBAT

2004 2005 2006

Nov Sep

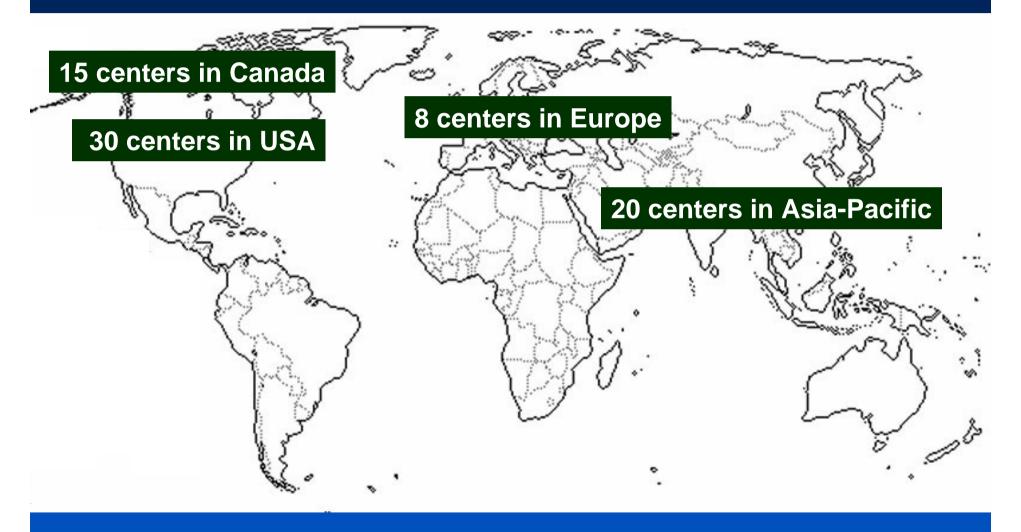
Pre-COMBAT

: Run-in study

- Which patients can be treatable with both PCI or CABG (COMBAT randomization)?
- Which patient population continues to be solely eligible for CABG (CABG only)?
- Which characterize high risk operative patients not eligible for CABG (PCI only)?
- Are we ready to initiate a comparison study in multicenters (peer-review)?
- What will be the results of COMBAT (outcome expectation)?

COMBAT

Up to 75 Centers in Asia, North America, and Europe



Study Coordination & Investigating Centers

Principal Investigator:

Seung-Jung Park, MD, Asan Medical Center, Seoul, Korea Martin B. Leon, MD, Colombia University Hospital, USA

Data Coordinating Center: Roxana Mehran, MD, CRF, NY

QCA Core Lab: Alexandra J. Lansky, MD. CRF, NY

ECG Core Lab: George Dangas, MD, CRF, NY

Data Safety Monitoring Board: Bernard Gersh, MD

Clinical Event Committee

Study End Points Primary end point

- Composite of
 - All cause death
 - Myocardial infarction (both Q and non-Q)
 - Stroke

• Primary end point will be analyzed both on an intention-to-treat basis at a mean of 2 years F/U

Study End Points Key Secondary end points

Analysis at a mean of 2 years follow-up

- MACCE 1, composite of
 - All cause death
 - Myocardial infarction
 - Stroke
 - Ischemia-driven left main TVR
- MACCE 2, composite of
 - MACCE 1
 - Any ischemia-driven TVR

Study End Points Other Secondary end points

- The composite of death, MI and stroke at 30 days to five years
- MACCE 1 at 30 days and yearly to five years
- MACCE 2 at 30 days and yearly to five years
- Componet of MACCE at 30 days and yearly to five years
- Stent thrombosis for the PCI arm to five years
- Analysis segment and in-stent binary restenosis at 9 month Analysis segment and in-stent late loss at 9 month Angina status at 2 years
- Follow-up in-stent, in-segment Intimal hyperplasia volume by IVUS
- Incidence of stent malapposition, strut fracture, and peri-stent remodeling by IVUS
- Graft patency in patient undergoing CABG at 9 month
- Non-target vessel revascularization yearly to five years
- Cardiac re-hospitalizations
- Quality of life measurements
- Use of cardiac medications



Randomization

- 1:1 randomization
 - Stent arm: SES (CypherTM, J & J) implantation
 - CABG arm
- The randomization will be stratified by
 - Diabetes mellitus
 - Enrolling site
- No site more than 75 patients.

Inclusion Criteria

Patients must fulfill all of the followings

- 1. At least 18 years of age
- 2. LM stenosis > 50% by visual estimate
- 3. Patients with angina or documented ischemia, amendable to both stent-assisted PCI or bypass surgery
- 4. Lesions outside LMCA potentially treatable with both PCI and CABG
- 5. Agreement to informed written consent

Exclusion Criteria

- 1. Hypersensitivity to antiplatelet drug/ stent/ contrast agent
- 2. Systemic sirolimus use within 12 months
- 3. Female of childbearing potential
- 4. History of bleeding diathesis/coagulopathy/refusal of transfusion
- 5. History of intracranial lesion (mass, aneurysm, etc)
- 6. CVA for the past 6 months or any permanent deficit
- 7. GI bleeding within the last 2 months or major surgery within 6 weeks
- 8. Platelet < 100,000 cells/mm³ or Hgb < 10g/dL
- 9. Extensive peripheral vascular disease
- 10. Elective surgery requiring cessation of thienopyridines for the first 6 months





Exclusion Criteria

- 12. Previous enrollment of this trial
- 13. Active participation in other study
- 14. Left ventricular ejection fraction < 30%
- 15. Prior CABG
- 16. Prior valve surgery
- 17. Patients who need major surgery
- 18. Creatinine $\geq 2.5 \text{mg/dL}$ or dependence on dialysis
- 19. Severe hepatic dysfunction (≥ 3 times normal reference values)
- 20. AMI within 1 week
- 21. Any previous PCI of a LMCA or ostial LAD or ostial LCX
- 22. Any previous PCI within 1 year or previous any brachytherapy
- 23. Intention to treat more than one totally occluded major epicardial vessel



COMBAT Randomized Trial

<u>COM</u>parison of <u>Bypass surgery and <u>Angioplas</u> Ty using sirolimus electing stent in patients with left main coronary disease</u>

PCI can be an alternative to CABG in unprotected LMCA stenosis in the near future.