COMBAT- Revised Protocol

Randomized COMparison of Bypass Surgery versus AngioplasTy using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease

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COMBAT Trial – Study Design

- 1,776 patients with LM CAD randomized to DES with Cypher™ or CABG
- Post approval (Cypher™ commercialized)
- Study Sponsor:
  - Cordis, Johnson and Johnson, Warren, NJ
- Funding
  - Cordis, Johnson and Johnson, Warren, NJ
- Physician-Directed Study:
  - Independent Executive Committee of Cardiologists, Surgeons and Interventionalists

COMBAT: Hypothesis

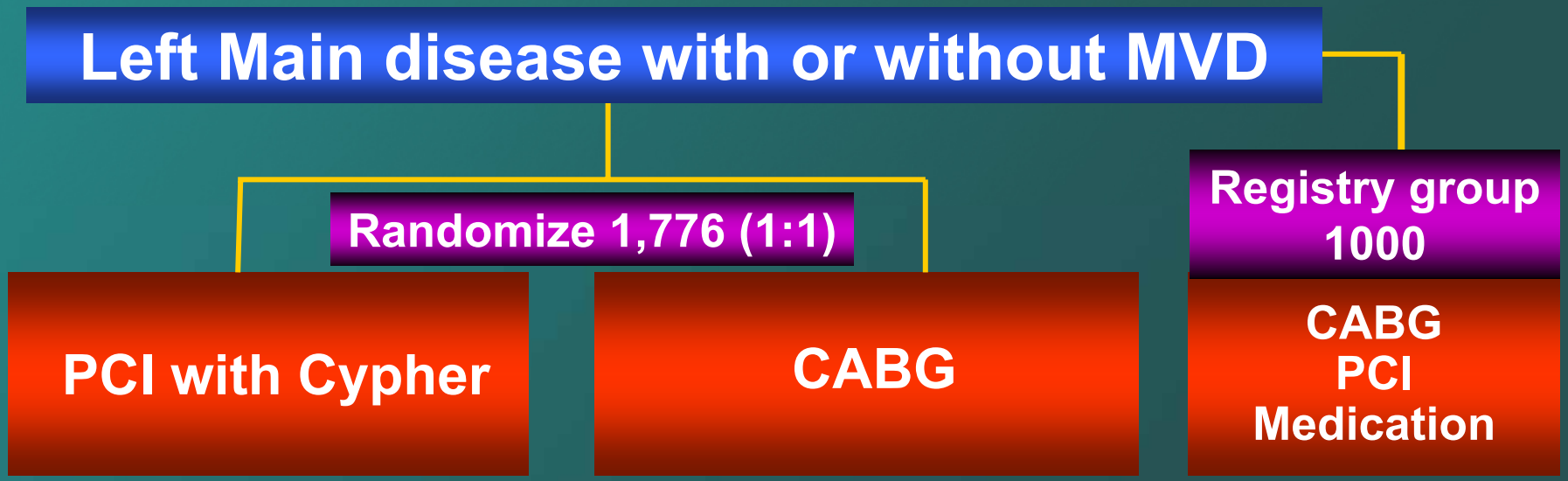
In patients with CAD involving the LM (with or without additional epicardial CAD – MVD), PCI with the Cypher™ stent, compared to CABG, will be safe and effective, resulting in:

- similar rates of major adverse events (all cause mortality, MI, and CVA) at two years - primary endpoint

- similar rates of ischemic TVR and MAE at two years - secondary endpoints

COMBAT Randomized Trial

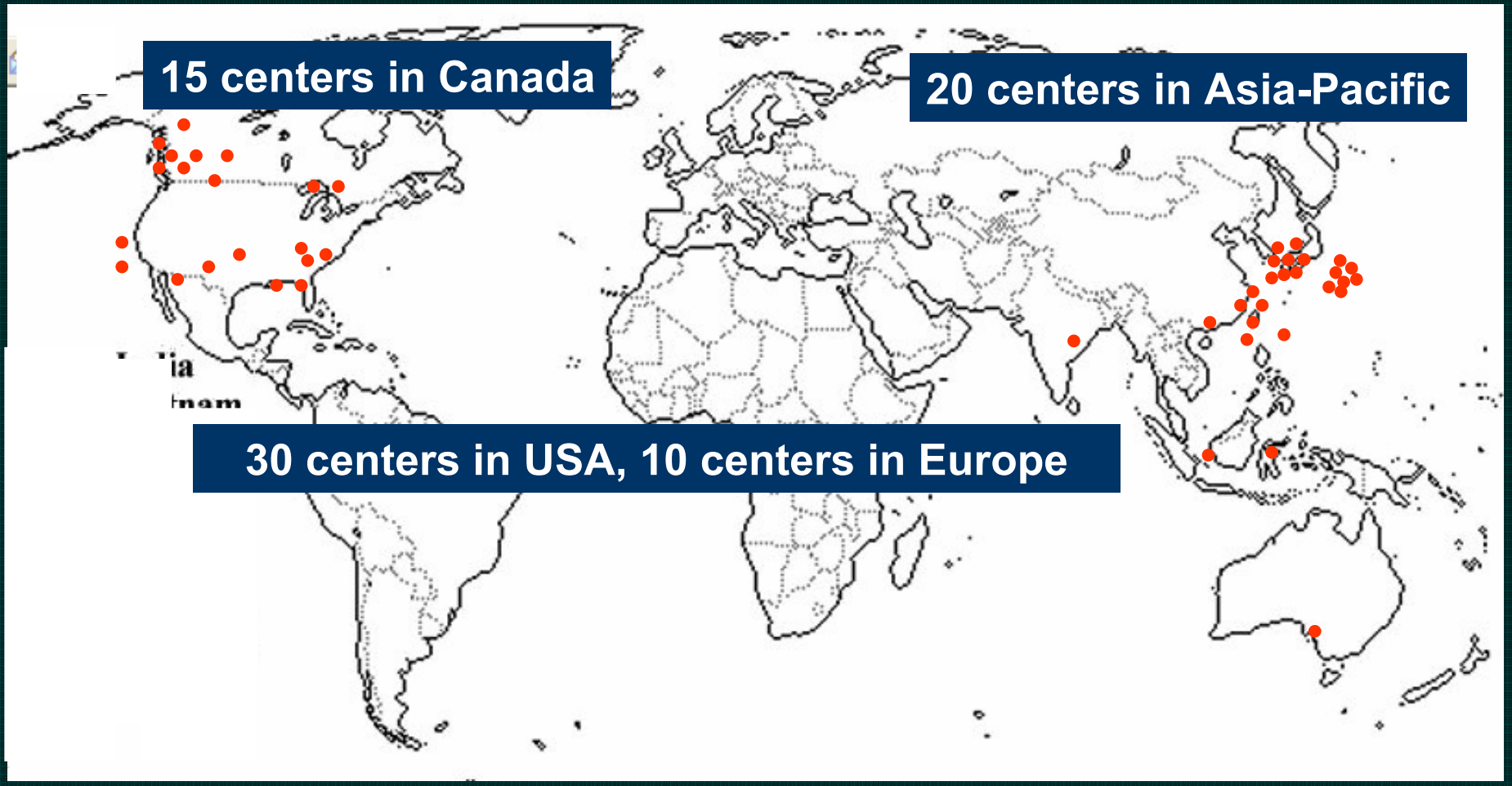
*COM*parison of *B*ypass surgery and *A*ngioplas*T*y Using Sirolimus Electing Stent in Patients with Left Main Coronary Disease



PRIMARY Endpoint: 2-year death, MI, and stroke
SECONDARY Endpoints: 6-mo angio, 2-yr and 5-yr MAE and TVR

PI: Seung-Jung Park, Martin B. Leon
75 centers from Asia-Pacific, USA, Canada and EU

75 Investigator Centers in Asia, North America, and Europe



COMBAT Study Factors

Committees

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

Study coordination:
Seung-Jung Park, MD
Young-Hak Kim, MD,
CVRF, Seoul, Korea

Roxana Mehran, MD
Stuart Pocock, PhD
CRF, NYC, USA

Angio, IVUS, and ECG core labs:
Cardiovascular Research Foundation, NYC

COMBAT Study Factors

Executive Committee

Martin B. Leon (co-Chair)
Park SJ (co-Chair)
Spencer King
Steve Ellis
David Faxon
Peter Berger
Michael Mack
Eric Rose
Eric Schampaert
Jeffrey W. Moses
Paul Teirstein
Gregg W. Stone
Gary S. Mintz

Antonio Colombo
Junbo Ge
Young-hak Kim
Takeshi Kimura
Jae-Won Lee
Ian Meredith
Yoshihisa Nakagawa
Ross Prpic
Takaheko Suzuki
David O. Williams
George Dangas
Roxana Mehran
Dennis Donohoe

COMBAT Trial

Study Support & Managing Committees

- Executive Committee
- Country Leaders
- Clinical Events Committee
- Angiographic Core Lab
- IVUS Core Lab
- ECG Core Lab
- Data Safety Monitoring Board (DSMB)

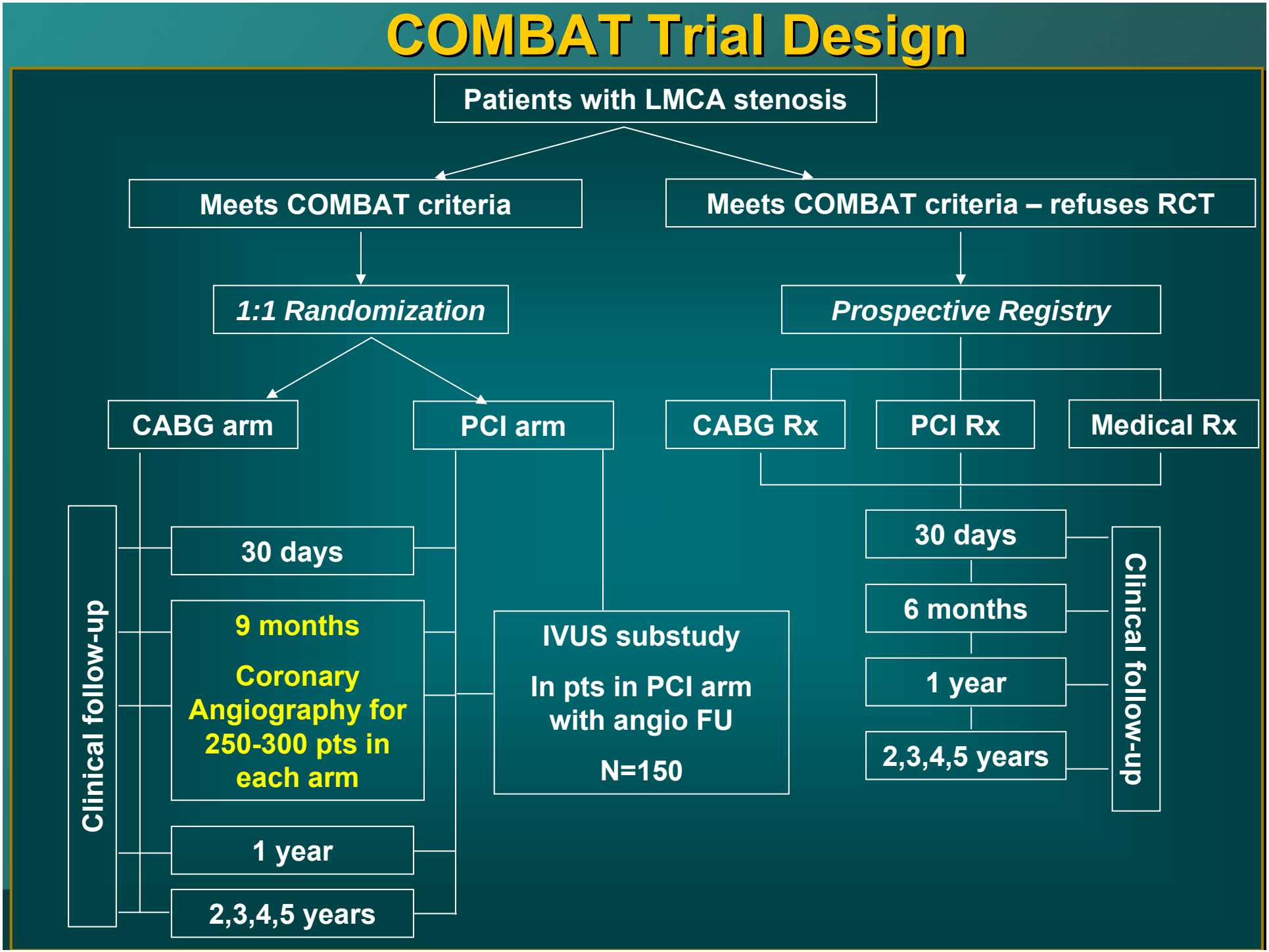
COMBAT Trial: Objective

To compare the safety and efficacy of Sirolimus-eluting balloon expandable stents (Cordis-Johnson & Johnson, Warren, NJ, USA) vs. the accepted standard of care, CABG, for the treatment of unprotected LMCA stenoses.

COMBAT Trial: Methodology

Prospective
Open label
Multicenter
Dual arm
Randomized

COMBAT Trial Design



COMBAT Trial: Primary Endpoint

The composite of death (all cause mortality), myocardial infarction (Q-wave and NQWMI) and major stroke at a mean of 2-year follow-up (all > 1 yr FU).

COMBAT Trial: Key Secondary Endpoints

- MACCE 1: The composite of death, MI, stroke and ischemia-driven left main TVR at a mean of 2 years follow-up.
- MACCE 2: The composite of death, MI, stroke and ischemia-driven TVR of any vessel at a mean of 2 years follow-up.

COMBAT Trial:
Secondary Safety and Efficacy Endpoints

- Cumulative major adverse cardiac and cerebrovascular events (all cause death, MI, stroke and ischemic TVR)
- Cardiac death;
- Myocardial infarction;
- Stroke;
- Target vessel revascularization;
- Stent thrombosis for the PCI arm;
- Ischemic TLR

F/U

- 30 days
- 6 months
- 1 year
- 2 years
- 3 years
- 4 years
- 5 years

COMBAT Trial: Additional Secondary Outcomes

- Non-target vessel revascularization
- Angiographic parameters in PCI arm
  - In-segment Binary RS, late loss
  - In-stent Binary RS, late loss
- Angiographic graft patency; DS<75% with TIMI 3 flow
- Re-hospitalizations
- Angina status
- Quality of life
- Use of cardiac medications

COMBAT Trial: Entry Criteria

- At each participating site, there will be at least three co-PIs: an interventional cardiologist, a cardiothoracic surgeon, and a neurologist.
- Consecutive patients presenting at participating centers will be evaluated for the entry into the study.
- Eligible patients with unprotected LMCA stenosis with (~80%) or without (~20%) multivessel disease and anatomy suitable for both PCI and CABG will be randomized to either procedure following angiographic assessment.

COMBAT Trial: Entry Criteria

- Only sirolimus-eluting stents should be used in patients during the course of the trial (unless other drug-eluting stents or bare metal stents are required to complete a successful percutaneous revascularization procedure).
- In all cases, the final decision regarding eligibility for randomization in the trial of all target vessels (LMCA and possible additional vessels), including ability to treat with either PCI or CABG will be the responsibility of both the interventional cardiologist (co-investigator at the site) and the cardiothoracic surgeon (co-investigator at the site), based upon clinical factors and review of the initial angiogram. The interventionalist and cardiothoracic surgeon at each site will prospectively document in the subjects chart their intentions of which vessels are revascularization targets including the LM and other diseased vessels, and the fact that they met the eligibility criteria for the study.

COMBAT Trial: Inclusion Criteria

- Age > 18;
- Significant unprotected LMCA stenosis (>50% DS by visual estimate ± IVUS) **AND** any additional target lesions (if present) with >50% DS (visual estimate);
- Stable or unstable angina or atypical chest pain or no symptoms but documented myocardial ischemia, LMCA amenable to **BOTH** PCI (with SES) or CABG;
- Lesions outside LMCA (if present) potentially treatable with **BOTH** PCI (w or w/o SES) and CABG;
- The patient agrees to the study protocol and the schedule of clinical and angiographic follow-up, and provides informed, written consent.

COMBAT Trial: Key Exclusion Criteria

- LVEF < 30%
- Cardiogenic shock
- Prior CABG or valve surgery
- Creatinine ≥ 2.5 mg/dL
- Hepatic dysfunction
- Acute MI within 7 days
- Any previous PCI of LM, ostial LAD or ostial LCx
- Previous PCI of any other vessels in last 12 months
- Intention to treat 2 or more CTOs

COMBAT: Registry

- Patients with unprotected LMCA disease ≥50% who meet all inclusion and exclusion criteria, but are not enrolled due to patient or physician preference, will be included in a prospective registry (not exceeding 1000 patients) with 5-year follow-up similar to the randomized patients (but without obligatory angiographic follow-up in these patients)

- Informed consent must be obtained from these first 1000 patients included in this study for the full follow-up in-hospital, 1 month, 3 months, 9 months, 1, 2, 3, 4, and five years.

COMBAT: Statistical Methods

- All primary and secondary endpoints will be analyzed both on an intent-to-treat basis (all patients analyzed as part of their assigned treatment group) and on a per protocol basis (patients analyzed as part of their assigned treatment group only if they actually received their assigned treatment).
- The principal analyses will be by intention to treat.
- Randomizing 1,776 patients 1:1 to SES compared to CABG affords 80% power to show non-inferiority for the primary triple endpoint of 2-year death, MI or stroke using a test for the comparison of two exponential survival curves.
- The assumed event rates are 12% at two years with an absolute delta for non-inferiority of 4%, equivalent to a hazard ratio of 1.365.

Assumptions

2-year event rates All LM disease	CABG	DES
MAE (death, MI, CVA)	12%	12%
Ischemic TVR	10%	10%*
MAE + TVR	18%	18%

*Accept a larger delta for non-inferiority

Sample Size for Different Rates of MAE at 2 years for *80% Power* with α=0.05

Delta	Event rate	Number of patients per group	Total number of patients
3.0%	10.0%	1249	2498
4.0%	10.0%	708	1416
5.0%	10.0%	457	914
6.0%	10.0%	321	642
3.0%	12.0%	1460	2920
4.0%	12.0%	888	1776
5.0%	12.0%	531	1062
6.0%	12.0%	372	744
3.0%	15.0%	1758	3516
4.0%	15.0%	992	1984
5.0%	15.0%	637	1274
6.0%	15.0%	444	888

COMBAT Trial: Sample Size Calculation

- Randomizing 1,776 patients 1:1 to SES vs. CABG provides 80% power to show non-inferiority for the primary endpoint of 2 year MAE.
- Event rate assumption of 12% in each arm. Delta for non-inferiority of 4%. One-sided alpha error of 0.05, HR=1.365.
- Sample size increased to 1,776 patients (888 per arm) to account for expected 5% loss to follow-up at 2 years.

Statistical Analysis and Power

- **LM patients:**
  - Secondary two-year non-inferiority objective (MAE + Ischemic TVR):
    - Rates assumed to be 18% in both arms
    - delta = 9%
    - α=0.05
    - >99% power to demonstrate non-inferiority for using a 1-sided binomial test of proportions

COMBAT Trial: Stratification

To ensure balance among the strata, the randomization will be stratified by the following factors:

- **Lesion location (ostial and shaft vs. bifurcation);**
- **Diabetes mellitus;**
- **Enrolling site.**

COMBAT Trial
Adjunctive Pharmacological Therapy: PCI Arm

Aspirin: 300-325 mg PO at least 24 hours peri-PCI & during the in-hospital phase; 75-81 mg PO per day, or as per local standard of care as an out-patient

Thienopyridine: 600 mg PO loading dose of Clopidogrel or 500 mg of Ticlopidine at least 24 hours before the PCI; 75 mg of Clopidogrel or 500 mg of Ticlopidine post-PCI for at least 1 year

During PCI, either **unfractionated heparin or bivalirudin** is administered to discretion of the operator.

Platelet glycoprotein IIb/IIIa inhibitor abciximab or integrilin is left to discretion of the operator.

General Guidelines for PCI

- Complete revascularization (PCI in vessels ≥2.5mm and lesions >50% diameter stenosis) is strongly recommended, but it is not mandatory
- A multi-staged procedure is allowed
- IVUS or any other monitoring devices are allowed

General Guidelines for PCI

- Only the Cypher stent is allowed
- Use of adjunctive therapy (such as DCA, atherectomy, GP IIb/IIIa inhibitor, or IABP) is left to the operator's decision.
- Clopidogrel or ticlopidine for at least 12 months (75mg/day after loading dose of 600mg) and indefinite use of aspirin (200-360mg/day).

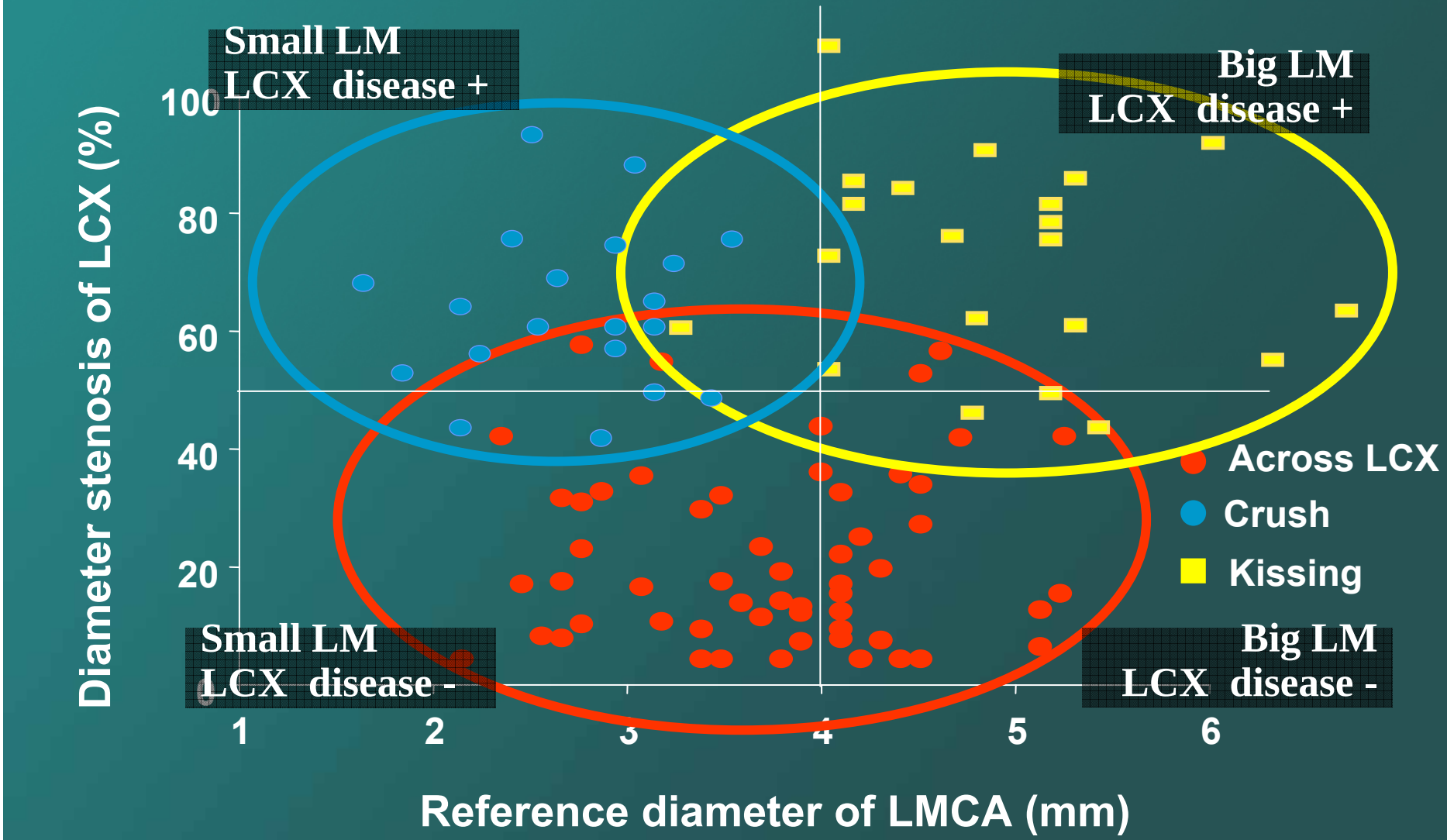
Recommended Treatment Strategy for LM bifurcation lesions

Stenting Cross-over
(provisional T stenting)

Kissing Stenting

Stent Crushing

Different Treatment According to LM size and LCX involvement



COMBAT Trial: Staged PCI

- A staged procedure may be either planned or provisional.
- After the 1st stage, the next planned stage should be performed within 45 days of randomization, and all planned staged procedures must be completed within 60 days of randomization.
- The 30-day follow-up visit occurs 30 ± 7 days following the day of the final stage of a staged index PCI.

COMBAT Trial: CABG Procedure

- Once the patient is randomly assigned to CABG, the procedure must be performed no later than 14 days after randomization.
- The use of an internal mammary artery to the left anterior descending is strongly recommended in all patients.
- The choice of surgical approach- cardiopulmonary bypass and cardioplegic arrest (conventional CABG) or "beating heart" (off-pump CABG) - is left to the individual surgeon's judgment.

COMBAT Trial: Peri-Procedural Treatment and Management in the CABG Arm

Before CABG:

- Patients continue aspirin therapy until the day of surgery;
- Clopidogrel/ticlopidine should be discontinued 5 days prior to elective CABG;
- Platelet GP IIb/IIIa inhibitors should be stopped 1 day before CABG.

Post-CABG:

- Oral aspirin therapy 75-81 mg PO per day, or as per local standard of care;
- Clopidogrel 75 mg daily for at least 1 year is strongly recommended.

COMBAT Trial: Post-Procedural Management in Both Arms

- Cardiovascular risk-factor modification:
  - nutrition
  - exercise
  - smoking cessation.
- Management of hypertension: all patients will be treated with an ACE inhibitor (or if intolerant, an angiotensin receptor blocker and a β-blocker with goal: for BP less than 130/80.
- Lipid management: use of statins to reach an LDL cholesterol < 70 mg/dl. Addition of fibrates or niacin to achieve ADA targets for the HDL cholesterol (>45 mg/dl in men and > 55 mg/dl in women) and triglyceride targets (<150 mg/dl).
- Hemoglobin A1c and lipid profile be conducted at least every 6-12 months for the duration of the study.

COMBAT Trial: MI Definitions for Both Arms

- MI: within 7 days post index PCI or index CABG
  - CK-MB elevation >5x upper limit of normal AND
  - Chest pain suggestive of ischemia OR
  - ECG changes indicative of ischemia (ST segment elevation or depression, development of pathologic Q waves in ≥2 contiguous leads on the ECG, or new LBBB).
- MI more than 7 days post PCI or CABG and in patients undergoing medical management
  - Typical rise and gradual fall of troponin or more rapid rise and fall of CK-MB for detecting myocardial necrosis with at least one of the following:
    - Typical or atypical symptoms of ischemia;
    - Development of pathologic Q waves in ≥2 contiguous leads on the ECG, or new LBBB; OR
    - ECG changes indicative of ischemia (ST segment elevation or depression);
    - Troponin rise is defined any value exceeding the upper limit of normal for the specific institution.
    - CK-MB rise is defined as at least 2 values exceeding the upper limit of normal for the specific institution.

COMBAT Trial

Study Timeline:

- **Study Preparation:**
  - May 2005 – April 2006
- **IDE Submission:**
  - May 2006
- **First Patient Enrolled:**
  - July 2006

COMBAT Trial

Study Timeline (continued):

- Last Patient Enrolled:
  - January 2008
- Last Patient 30-day Follow-up:
  - February 2008
- Last Patient 12 month Follow-up:
  - February 2009, assuming that mean follow-up of two years is reached

COMBAT Monitoring Plan:

- Pts with primary endpoint events ⇒ monitor 100% of all data fields
- Pts without primary endpoint events
  - Monitor random 15% of the first 500 patients (all data)
    - If error rate is <25%, then monitor 15% of the study population
    - If error rate is >25% ⇒ increase monitoring by 10% increments