Count Down to…

COMBAT

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

Roxana Mehran, MD
Associate Professor of Medicine

The Cardiovascular Research Foundation
Columbia University Medical Center

COMBAT - Background

Un-protected LM PCI – Challenges to overcome

- Acute Procedural/in-hospital Complications
  - Operator expertise/Technique
  - In-hospital mortality from 2% in low risk, to 21% in high risk (ULTIMA registry)
- Stent Thrombosis
  - May be fatal, as high as 2.5% in bifurcation disease
  - Rate is unknown, not examined in DES era systematically
- Restenosis (up to one year)
  - Pre-DES: 7.3% (Black), 34% (Ultima registry)
  - DES: 3% (Lefevre, et al.), 19% (Chieffo et al.), 30% (Teirstein, et al.)
- Long-term Safety and efficacy compared to CABG

Factors to be Considered in LM Intervention

Prognostic Factors

- Emergency Vs. Elective Intervention
- High-Risk Vs. Low-Risk Patient

Technical Considerations

- Isolated LM vs. LM + other major epicardial vessels
- Aorto-ostial/Shaft location vs. Bifurcation/Trifurcation
  - Technique for bifurcation treatment
    - •Crush
    - •Culotte
    - •V stenting
    - •T stenting
    - •Final kissing balloon inflation
- Use of Support Devices
- Use of Debulking Devices
- Use of IVUS

COMBAT - Background

Un-protected LM CABG – Challenges to overcome

- Acute Procedural/in-hospital Complications
  - In-hospital CVA and Mortality higher than PCI Neurologic complications rarely reported
- Graft Patency
  - Use of SVG conduits vs. Arterial conduits, not examined systematically
  - Unexpectedly high failure rate (defined as >75% DS) in PREVENT IV (SVGs - 28% per patient)
- Long-term safety and efficacy compared to PCI with DES is unknown

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

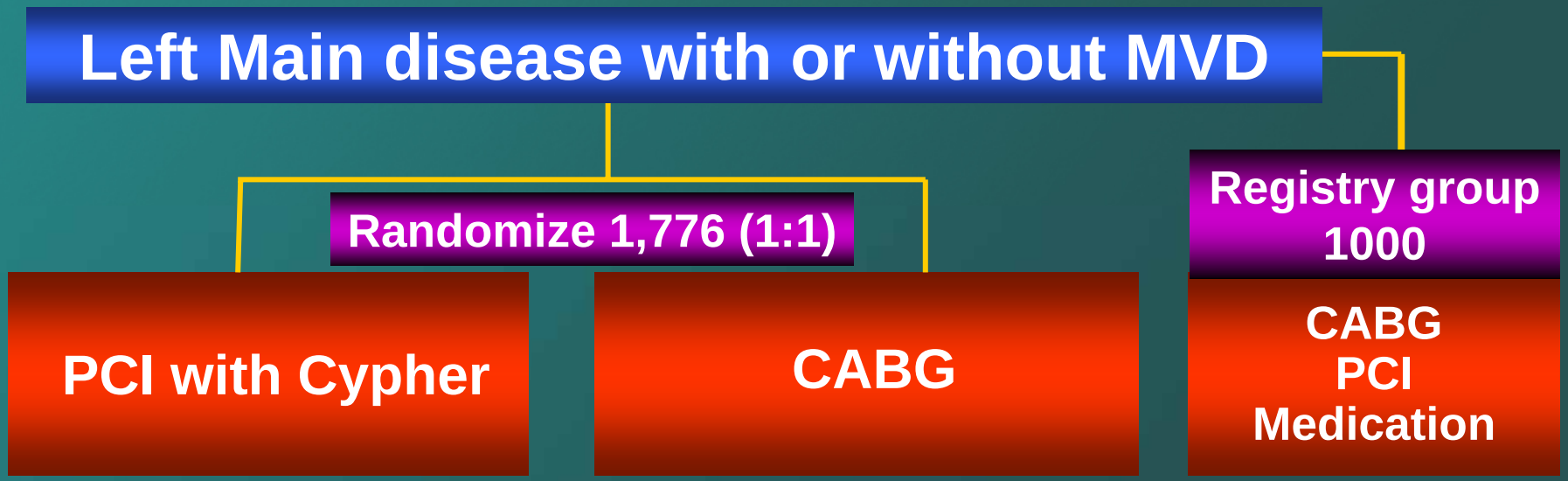
In patients with CAD involving the LM (with or without additional epicardial CAD – MVD), PCI with the Cypher™ stent, compared to CABG, will be safe and effective, resulting in:

- 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

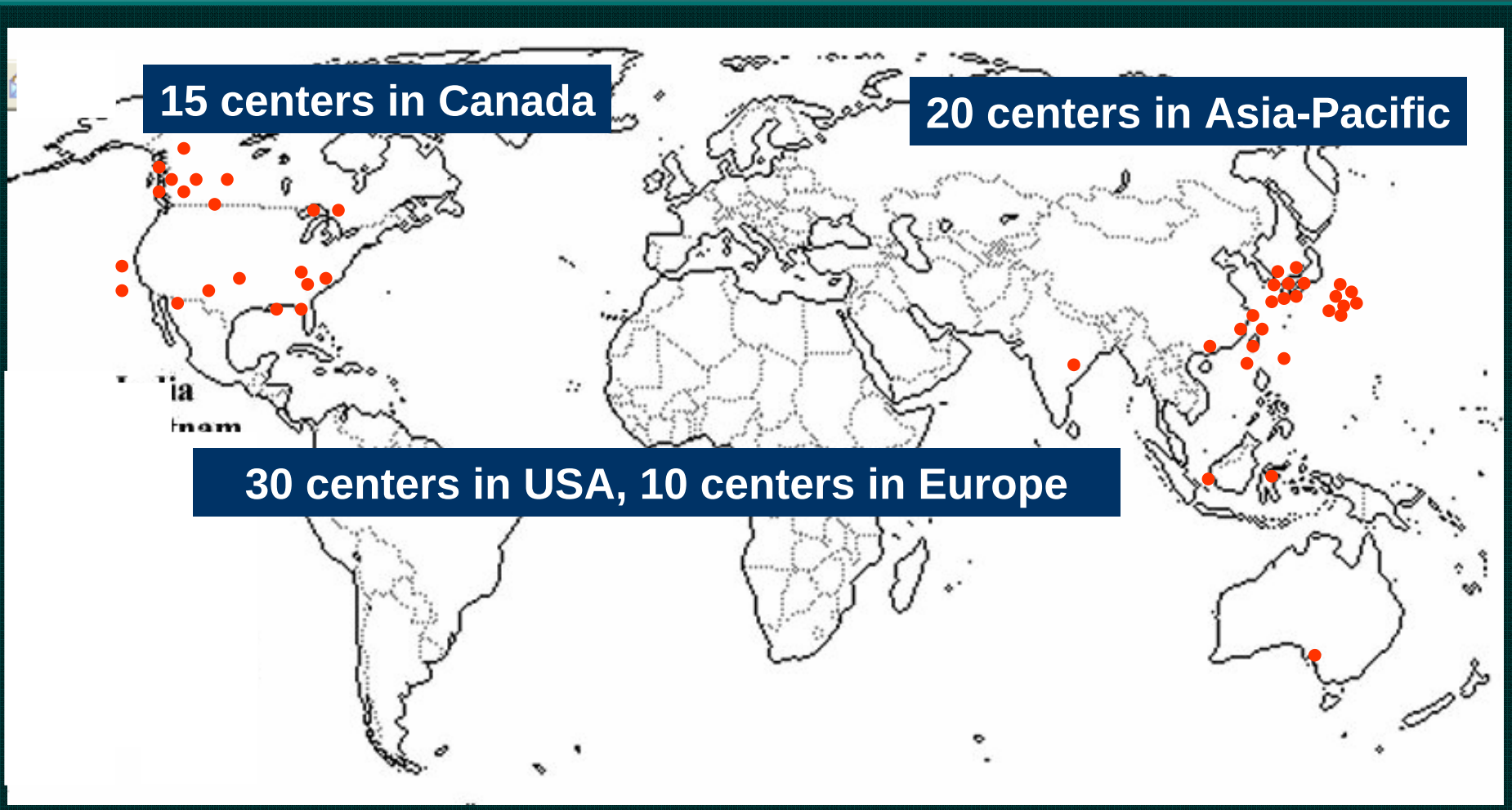
*COM*parison of *B*ypass surgery and *A*ngioplas*T*y Using Sirolimus Electing Stent in Patients with Left Main Coronary Disease



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

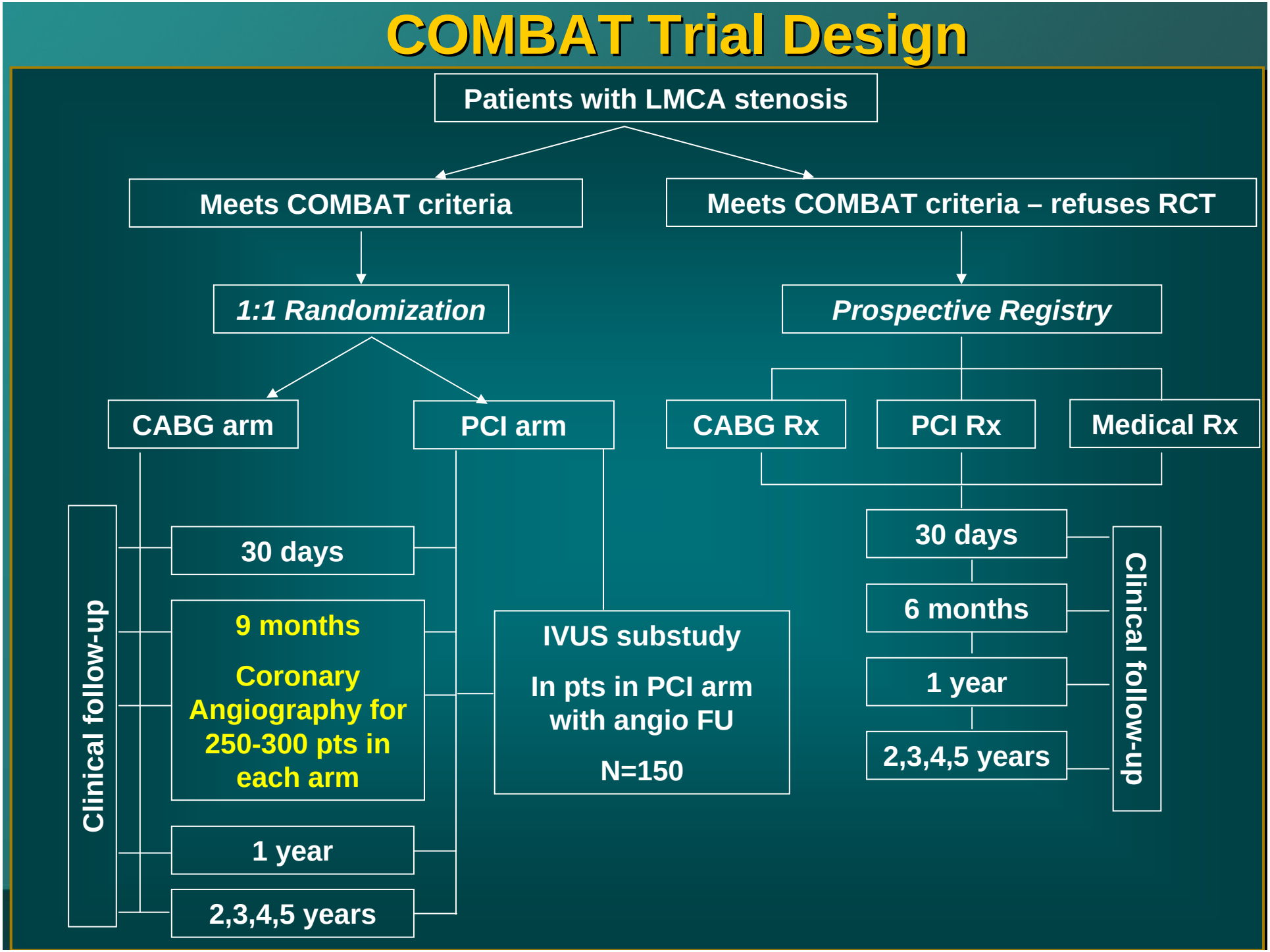
Antonio Colombo
Junbo Ge
Young-hak Kim
Takeshi Kimura
Jae-Won Lee
Ian Meredith
Yoshihisa Nakagawa
Ross Prpic
Takaheko Suzuki
David O. Williams
George Dangas
Roxana Mehran
Dennis Donohoe

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 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: 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

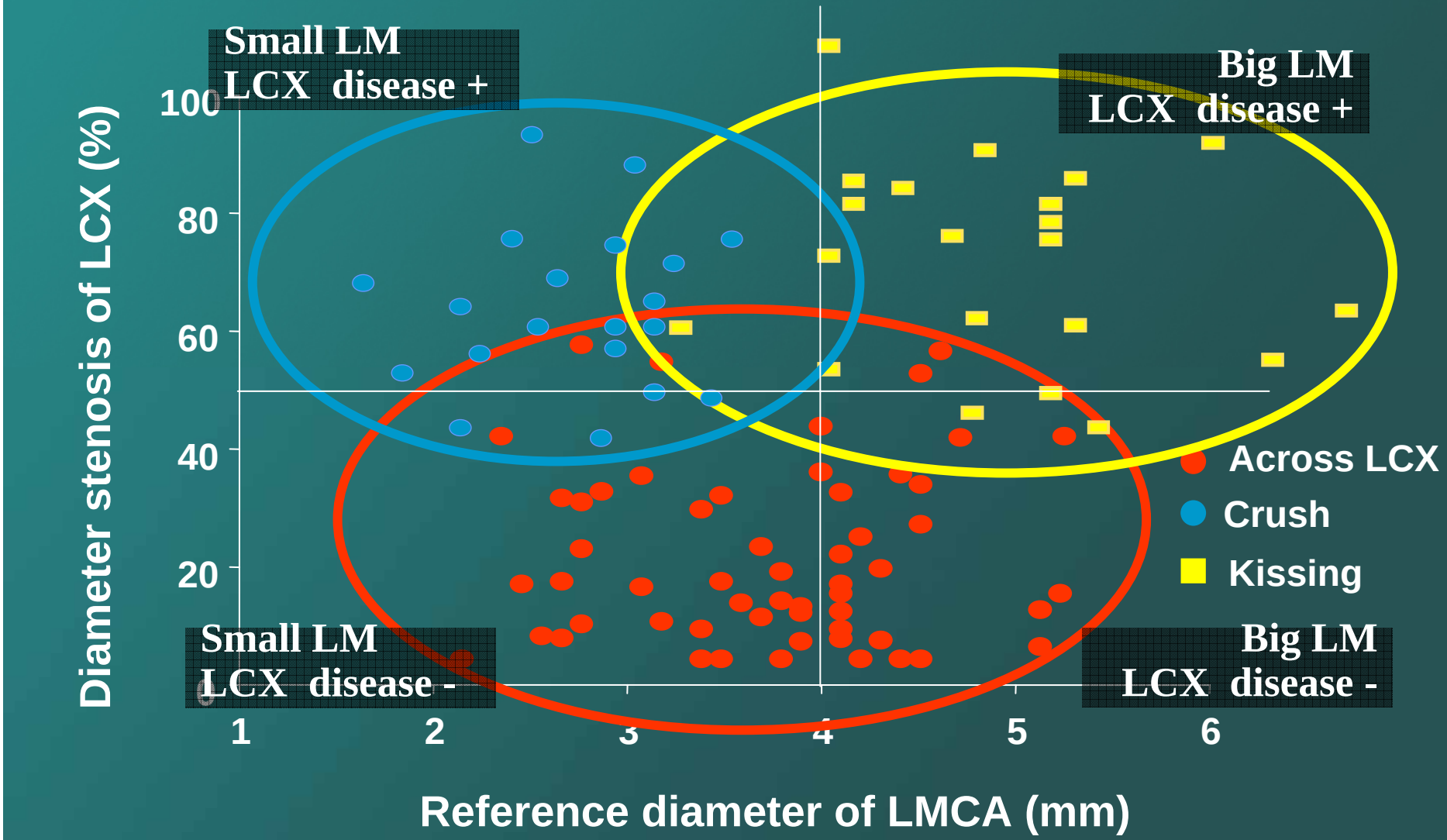
- Patients with unprotected LMCA disease ≥50% who meet all inclusion and exclusion criteria, but are not enrolled due to patient or physician preference, will be included in a prospective registry (not exceeding 1000 patients) with 5-year follow-up similar to the randomized patients (but without obligatory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

Different Treatment According to LM size and LCX involvement



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

- **“Mom, you can’t go to Korea, because you will be in tomorrow, while I am still in yesterday!”**

  Katerina Dangas- age 6

- **Well she is right, here in Korea you are definitely in the future for treatment of Left Main Disease…**