Intracellular calcium modulation During AMI Reperfusion: CASTEMI and EVOLVE

I.K. Jang, MD

Associate Professor of Medicine
Harvard Medical School
Massachusetts General Hospital

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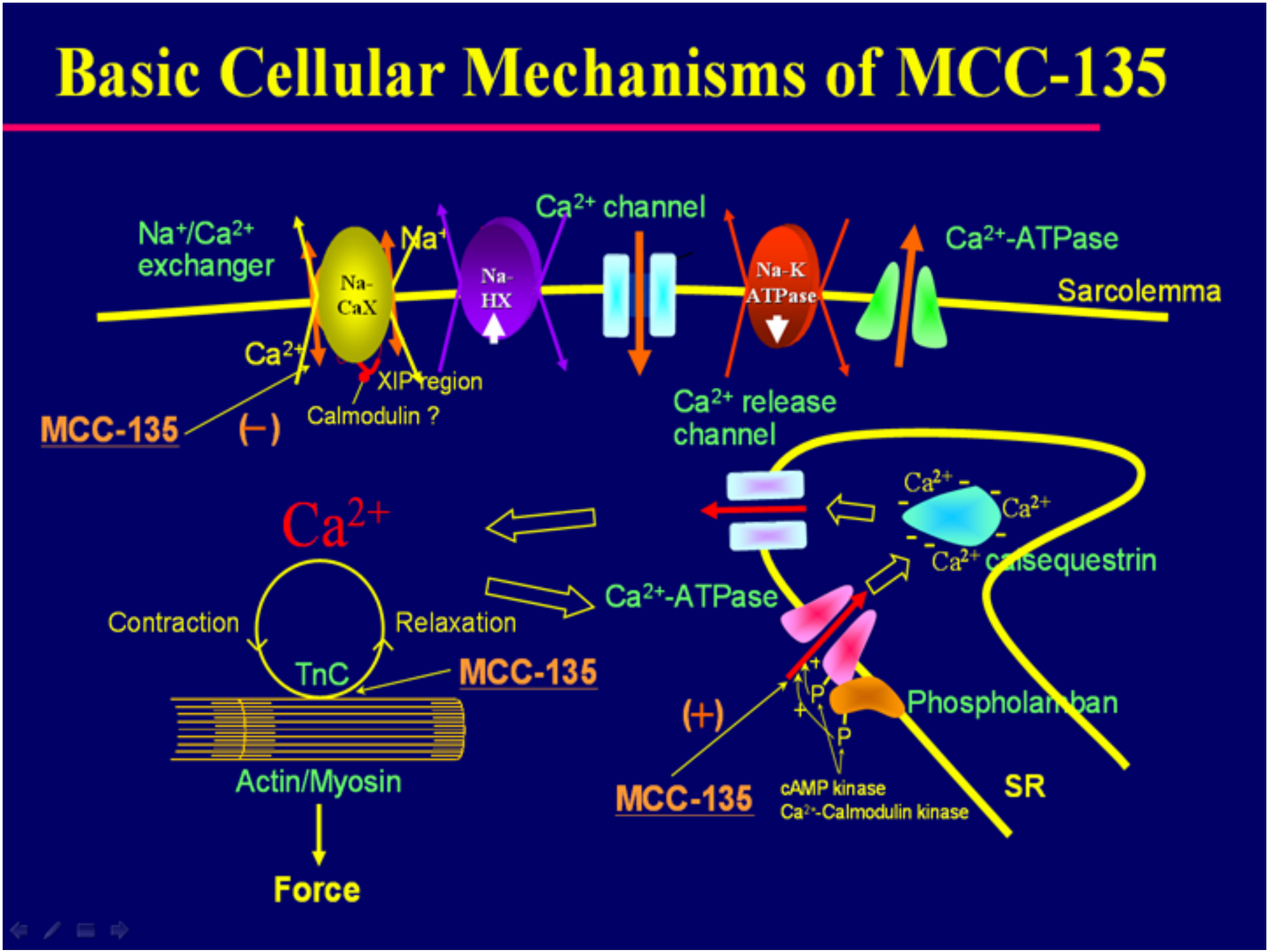
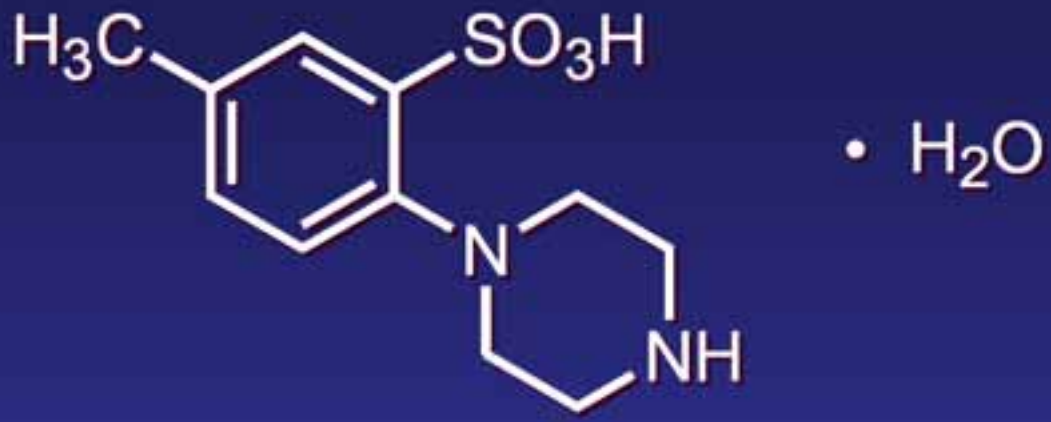
Basic Cellular Mechanisms of MCC-135



CALDARET (MCC-135)

5-methyl-2-(piperazin-1-yl) benzenesulfonic acid monohydrate:

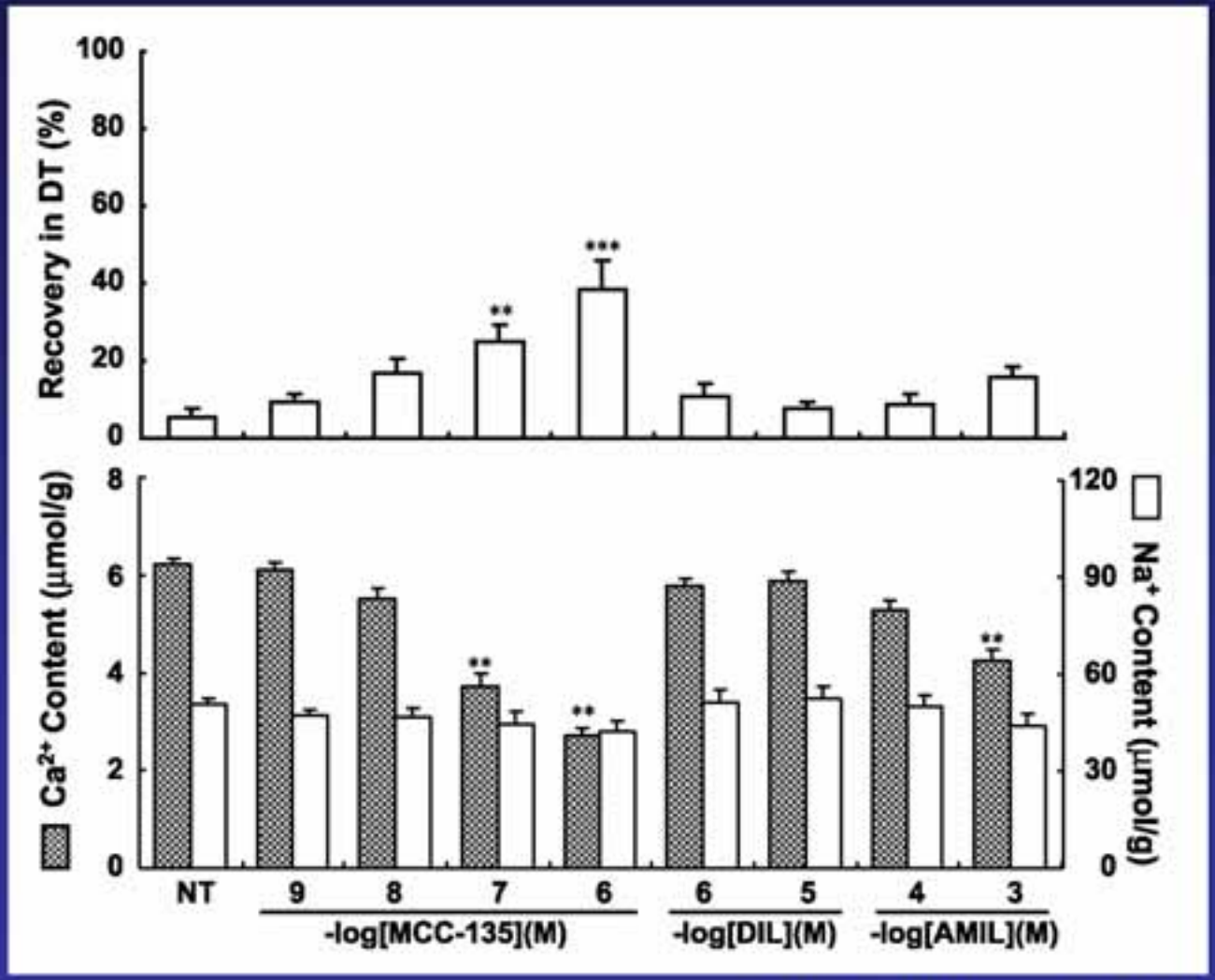


- MCC-135 is a novel compound which enhances the sequestration of calcium by the sarcoplasmic reticulum and inhibits Na/Ca exchnager.
- **In animal models, MCC-135 reduced infarct size and improved LV function during and after resolution of ischemia**

Effect of MCC-135 on Na^+/Ca^{2+} Exchanger

- Isolated rat heart
- Perfused with Krebs buffer solution containing monensin (5uM) for 10 min (increases intracellular Na^+, activating Na^+/Ca^{2+} exchanger)
- No flow 15 min → 30 min reperfusion
- MCC-135 or control drugs added during reperfusion

MCC -135 Inhibits Monensin-Induced Ca^{2+} Overload and Improved Developed Tension (DT)

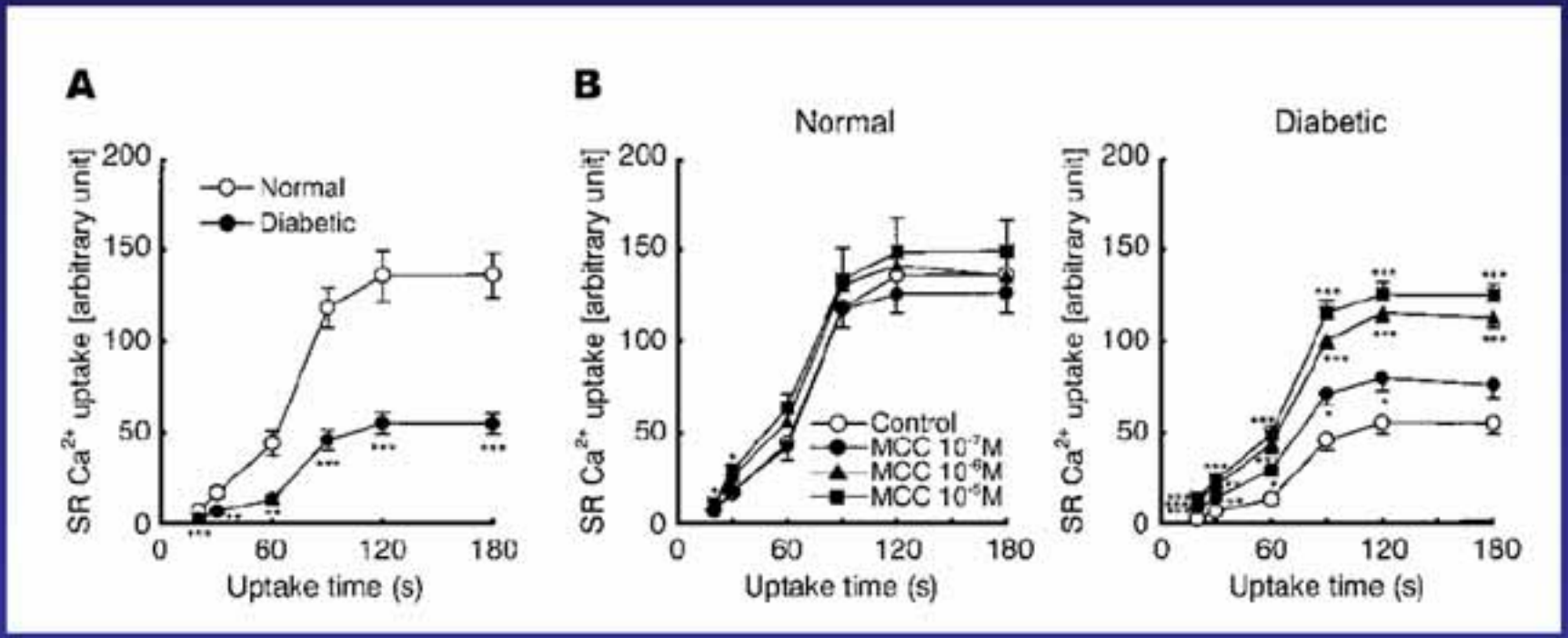


Eur J Pharmacol 2004;499:179

Effect of MCC-135 on SR Function

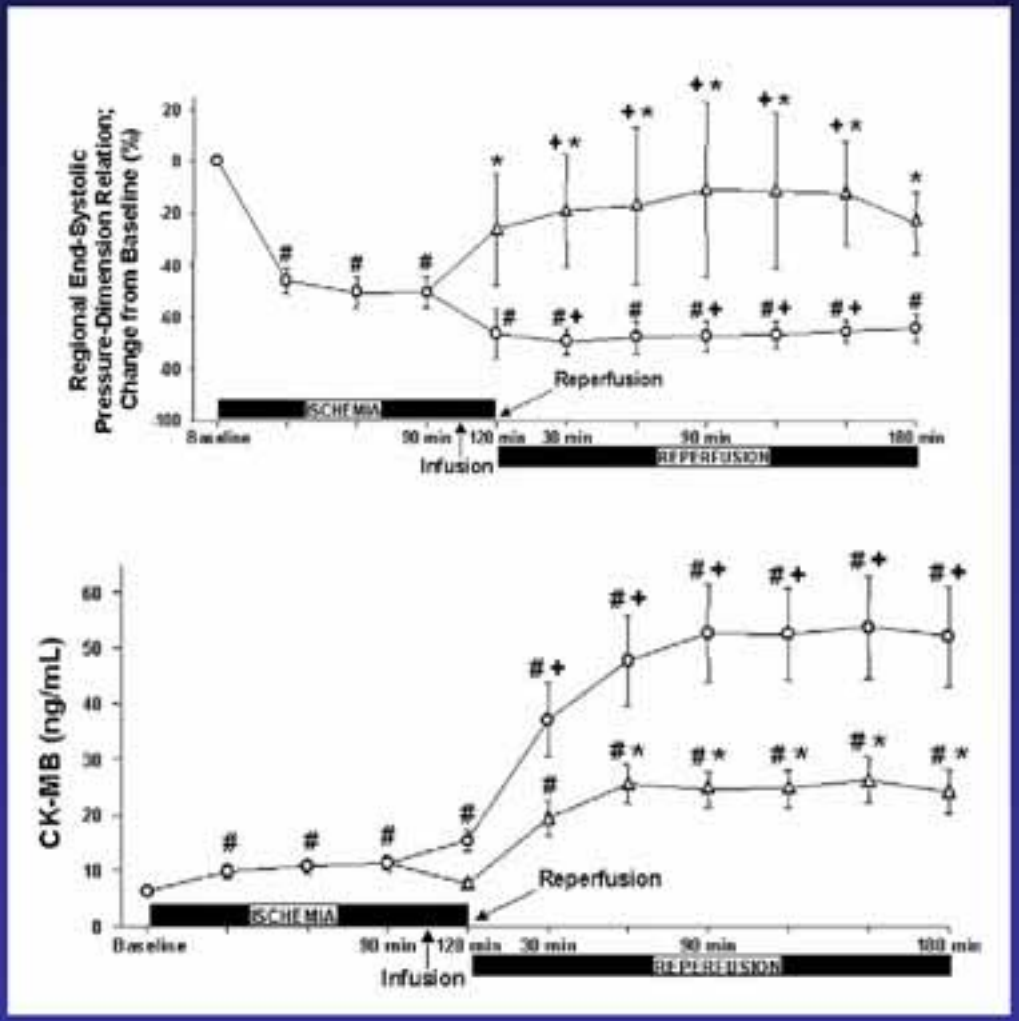
- Diabetic cardiomyopathic rats produced by streptozotocin
- Skinned LV papillary muscles with Preserved SR
- Load Ca^{2+} in the presence and absence of MCC-135
- SR Ca^{2+} uptake assessed by caffeine-induced contraction

MCC-135 Increased SR Ca^{2+} Uptake in Diabetic Rats



J Pharmacol Exp Ther 2001;298:1161

Effect of MCC-135 on Myocardial Function and Infarct Size



Effect of i.v. administration of MCC-135 (300 μg/kg/hr) on regional function and cardiac marker (CK-MB) in pigs. Values are mean±S.E.M. #p<0.05 vs baseline, +p<0.05 vs ischemia, *p<0.05 vs control. (circle=control, n=11; triangle=MCC, n=7)

IV administration of MCC-135 leads to a reduction in infarct size and improvement of LV regional function.

Ann Thorac Surg 2003;76:2054

MCC-135 Summary

- Novel mechanism: Decrease cytosolic Ca^{2+}
  - *Inhibits Na^{+}/Ca^{2+} exchanger*
  - *Increases uptake of Ca^{2+} into SR*
- Reduces infarct size and increases function in animal models of MI

Development of MCC-135

- As MCC-135 has cardio-protective efficacy during ischemia/reperfusion, "treatment of STEMI" was proposed.
- CASTEMI (E05) was performed in Europe/ Israel in Large STEMI (Σ ST $\geq$ 10mm) patients.
- EVOLVE (A02) was recently completed in broader patients population with higher dose levels.

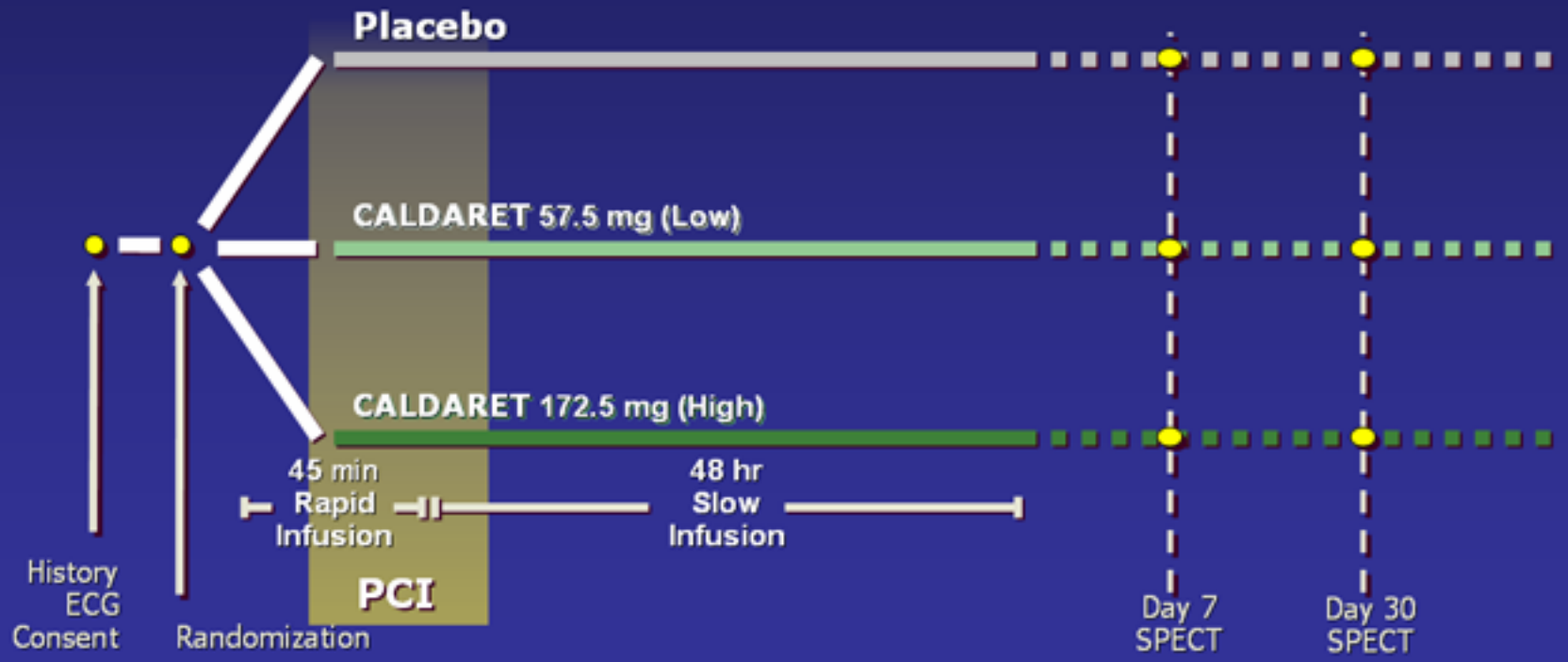
CALDARET in ST Elevation MI (CASTEMI)

Population: 387 patients were enrolled,
247 had TIMI 0/1 flow (target population)

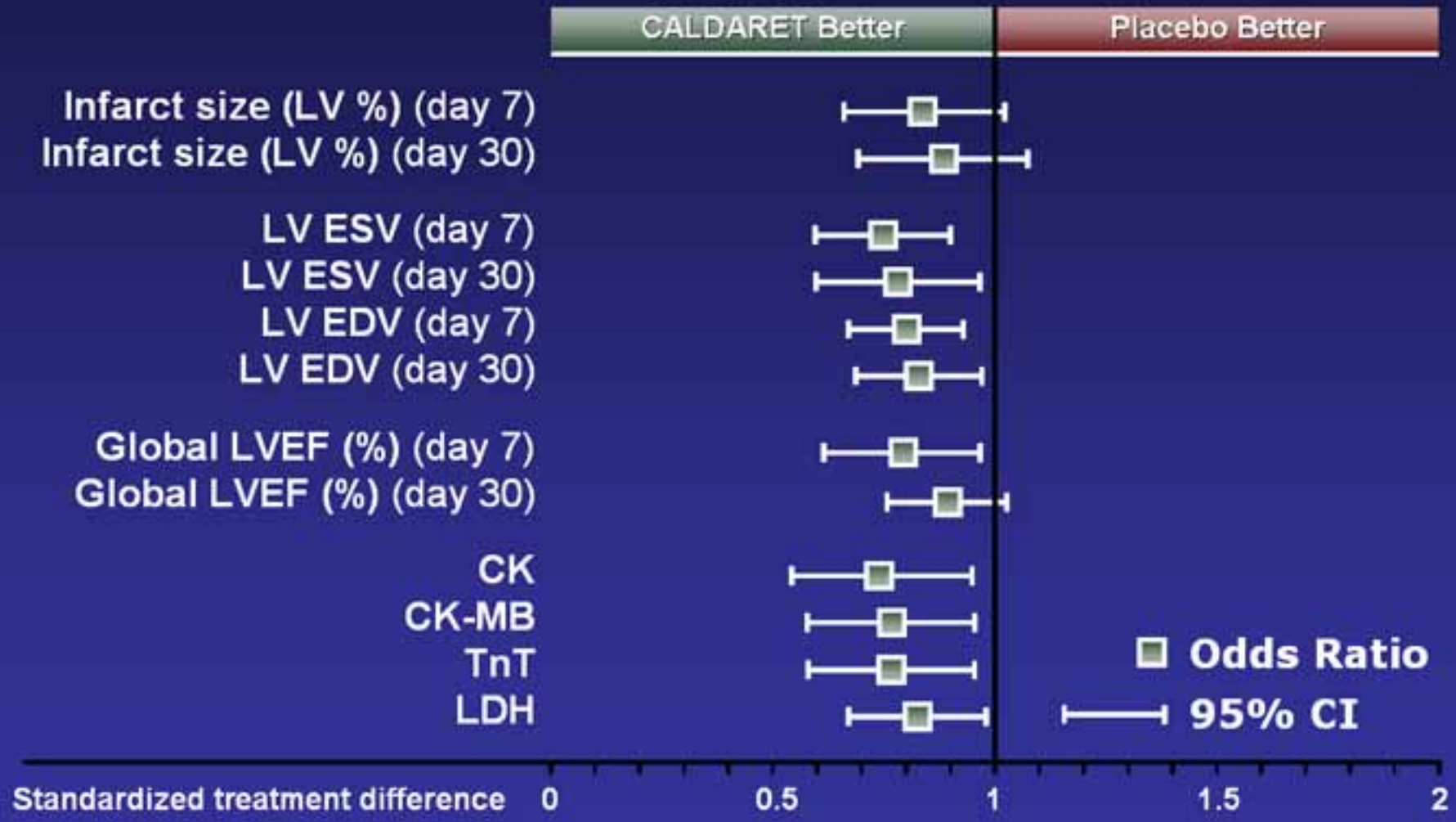
Total Mortality: 2.3%

Primary end point: SPECT Infarct Size - day 7

Study Design



172.5mg CALDARET vs Placebo in Patients with Anterior MI and TIMI 0/1 flow



CASTEMI

- *CASTEMI* showed similar infarct sizes for both CALDARET and placebo in the overall STEMI population.
- However, in patients with anterior MI CALDARET caused significant reductions in all cardiac markers as well as LV end diastolic and end systolic volumes with increase in ejection fraction.
- It was well tolerated without hemodynamic, biochemical or ECG abnormalities

EVOLVE

EValuation Of MCC-135 (caldaret) for LV salvagE in AMI

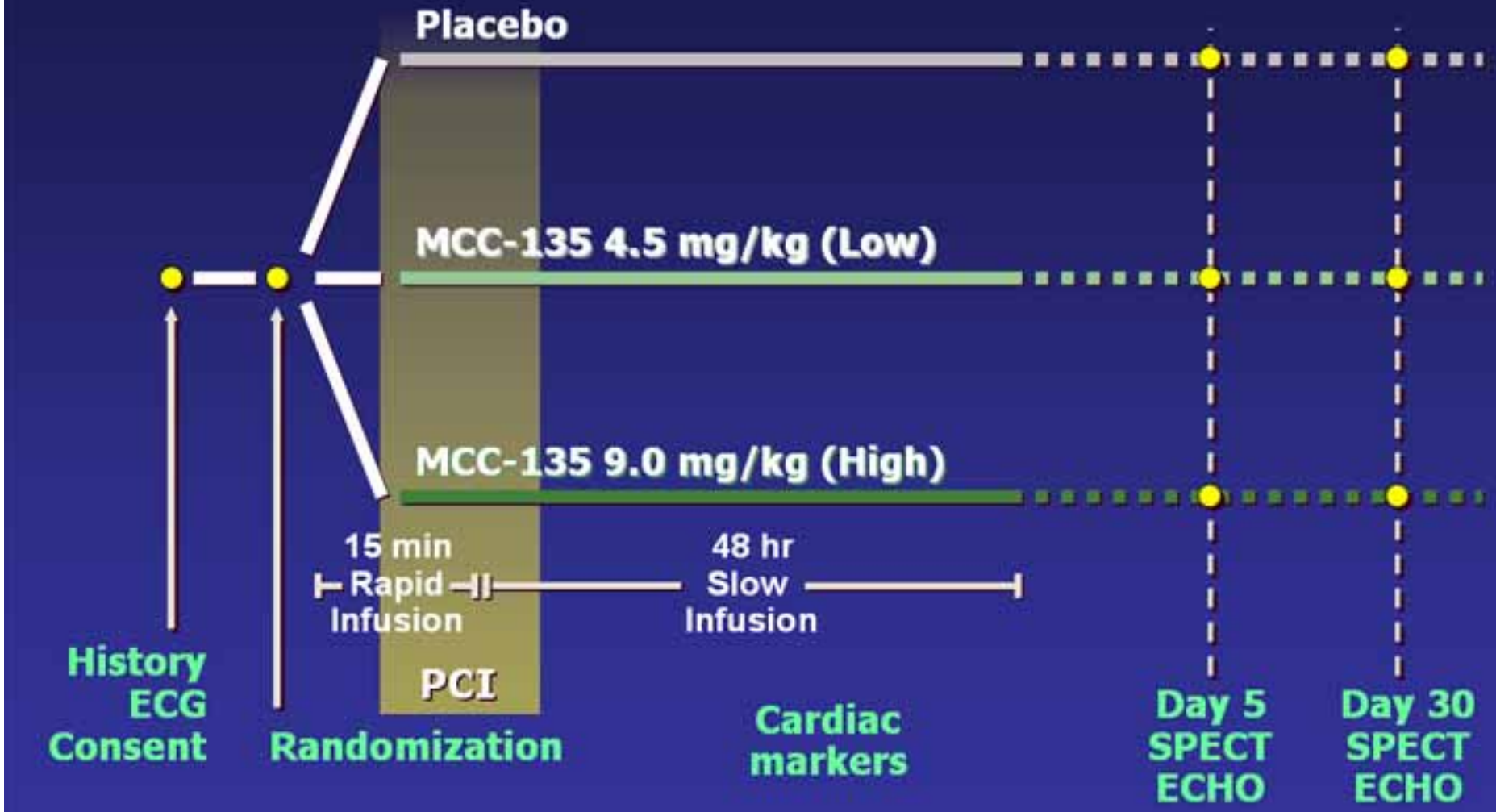
Aims of A02 Trial

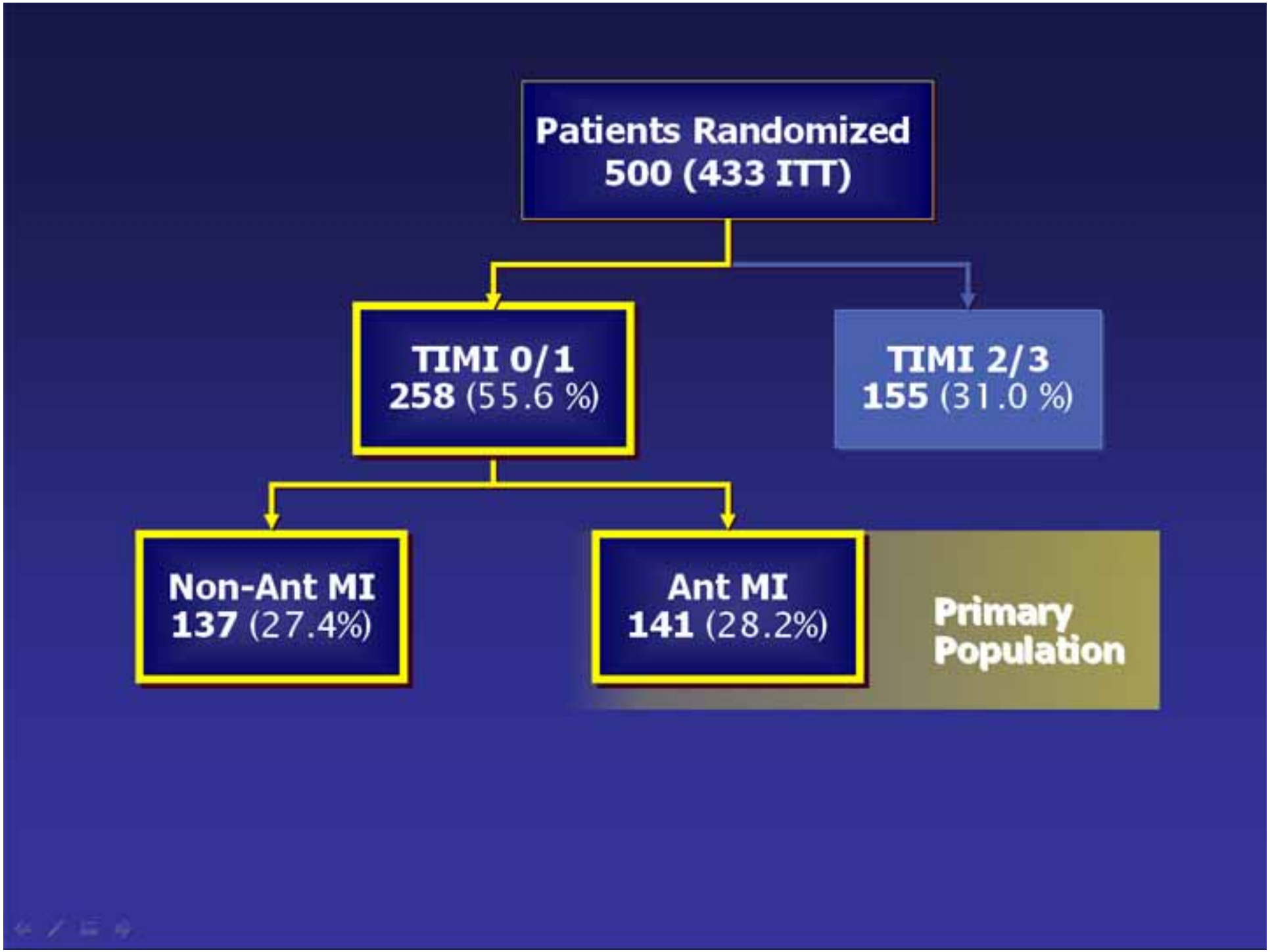
- To explore ***higher*** *doses* of MCC-135 compared to E05 in patients with acute STEMI undergoing primary PCI
- To investigate the safety and efficacy of MCC-135 in a ***broader*** *patient population* compared to E05 trial
- To investigate salvage index using Day 1 SPECT and Echo

E05 vs. A02 Trial

	E05: CASTEMI	A02: EVOLVE
Inclusion Criteria	Sum ST Elevation > 10 mm on ECG	Anterior Large Inferior First MI only
Doses	57.5 mg/48 hrs 172.5 mg/48 hrs	4.5 mg/kg/48 hrs 9.0 mg/kg/48 hrs
Rapid Infusion	45 min	15 min
Primary Analysis	Day 7	Day 5
Sub-studies	NA	SPECT, ECHO

Study Design




Patients Randomized
500 (433 ITT)
TIMI 0/1
258 (55.6 %)
TIMI 2/3
155 (31.0 %)
Non-Ant MI
137 (27.4%)
Ant MI
141 (28.2%)
Primary Population

Endpoints

Primary:

- LVEF measured by SPECT at day 5 in anterior MI with TIMI 0/1 patients

Secondary:

- Infarct size measured by SPECT, ECHO and cardiac markers
- LV volume and function by SPECT and ECHO: LVEDV, LVESV
- Safety and tolerability

Baseline Data

Demographics
Safety Population

	4.5 mg/kg	9.0mg/kg	Placebo
Age (Years) (mean ± SD)	59.8 ± 12.6	59.3 ± 11.7	58.5 ± 12.3
Gender (Male)	131 (80.4%)	115 (77.7%)	113 (72.0%)
Race (Caucasian)	148 (90.8%)	136 (91.9%)	142 (90.4%)
Body weight (kg) (mean ± SD)	82.8 ± 16.6	83.0 ± 17.2	83.5 ± 17.6

Cardiac History (1)
Anterior TIMI 0/1, Safety Population

	4.5 mg/kg	9.0 mg/kg	Placebo
Myocardial Infarction	4 (2.5%)	3 (2.0%)	6 (3.8%)
Hypertension	74 (45.4%)	76 (51.4%)	70 (44.6%)
TIA	2 (1.2%)	3 (2.0%)	0 (0.0%)
Cerebrovascular Accident	5 (3.1%)	4 (2.7%)	3 (1.9%)
Diabetes Mellitus (Non-Insulin)	11 (21.2%) 28 (17.2%)	8 (21.1%) 25 (16.9%)	6 (11.8%) 17 (10.8%)
Coronary Artery Disease	15 (9.2%)	18 (12.2%)	18 (11.5%)

Cardiac History (2)
Safety Population

	4.5 mg/kg	9.0 mg/kg	Placebo
Peripheral Vascular Disease	9 (5.5%)	8 (5.4%)	9 (5.7%)
Lipidemia	53 (32.5%)	45 (30.4%)	54 (34.4%)
Family History of Heart Attack	49 (30.1%)	50 (33.8%)	51 (32.5%)
Smoking History	91 (55.8%)	91 (61.5%)	99 (63.1%)

Myocardial Infarct Location
Safety Population

	4.5 mg/kg	9.0 mg/kg	Placebo
Anterior	83 (50.9%)	73 (49.3%)	81 (51.6%)
Non-Anterior	80 (49.1%)	75 (50.7%)	76 (48.4%)

Summed ST-elevation

Anterior TIMI 0/1, Safety Population

	4.5 mg/kg	9.0 mg/kg	Placebo
Summed ST elevation (mean ± SD)	14.4 ± 7.1 12.6 ± 7.0	16.8 ± 9.7 12.6 ± 7.7	18.0 ± 13.1 13.2 ± 9.5

Baseline Killip Class

Anterior TIMI 0/1, Safety Population

	4.5 mg/kg	9.0 mg/kg	Placebo
Class I	47 (90.4%) 150 (92.0%)	32 (84.2%) 133 (89.9%)	49 (96.1%) 150 (95.5%)
Class II	5 (9.6%) 12 (7.4%)	6 (15.8%) 14 (9.5%)	2 (3.9%) 7 (4.5%)
Class III	0 (0.0%) 0 (0.0%)	0 (0.0%) 1 (0.7%)	0 (0.0%) 0 (0.0%)

Baseline Procedures
Safety Population

(mean ± SD)	4.5 mg/kg	9.0 mg/kg	Placebo
Onset of symptoms to hospitalization (hrs)	1.9 ± 1.32	1.8 ± 1.27	1.8 ± 1.31
Hospitalization to study drug infusion (hrs)	1.5 ± 2.26	1.5 ± 1.60	1.4 ± 1.34
Start of study drug infusion to PCI therapy (hrs)	0.4 ± 0.34	0.3 ± 0.34	0.4 ± 0.35

Final Results

ESC in Barcelona