The SELECT-ACS Trial

Effects of the P-selectin antagonist inclacumab on myocardial damage after PCI for NSTEMI

Jean-Claude Tardif MD
Montreal Heart Institute
University of Montreal

on behalf of the SELECT-ACS steering committee

Background

- Myocardial damage is common after PCI, due in part to inflammation and platelet activation.
- P-selectin, a cell adhesion molecule expressed on activated endothelial cells and platelets, plays a critical role in leukocyte and platelet rolling.
- Animal studies have suggested that inhibition of P-selectin decreases neutrophil and platelet adhesion, macrophage accumulation and neointimal formation after injury.

Inclacumab

- Fully human recombinant monoclonal IgG4 antibody
- Mutated Fc portion, elimination of effector functions by IgG4 conversion and L235E mutation
- High selectivity (3000 fold) for P-selectin vs E- and L-selectin
- No adverse findings in non-clinical safety profiling
- Anti-inflammatory + antithrombotic effects: in vitro assays, ex vivo human flow system, in vivo inflammation model
- Reduction in CD11b expression on neutrophils

Study objective

To determine the efficacy of inclacumab in reducing myocardial damage during percutaneous coronary intervention (PCI) in patients with non-ST elevation MI (NSTEMI)

Study design

- 18-85 years
- NSTEMI
- TnI or CK-MB above 99th percentile
- Scheduled for cath and ad hoc PCI

Randomization

- Placebo (1 infusion)
- Inclacumab 5 mg/kg (1 infusion)
- Inclacumab 20 mg/kg (1 infusion)

Screening

Coronary angio Ad hoc PCI	TnI + CK-MB 8, 16, 24 hours	Safety visits 30 and 120 days

NSTEMI Study drug infusion 1-24 hrs pre-PCI

Montreal Heart Institute Coordinating Center | MHICC

Exclusion criteria

- PCI within past 72 hours, recent thrombolysis
- Recent cerebral vascular disease or stroke
- Bleeding disorders, blood dyscrasia
- Severe uncontrolled hypertension
- Prior CABG surgery
- Active or chronic infection
- Severe inflammatory or auto-immune disease
- Uncontrolled diabetes
- Hepatic failure, severe renal failure

Efficacy and safety endpoints

Primary efficacy endpoint

- Change in troponin I at 16 and 24 hours post-PCI

Secondary efficacy endpoints

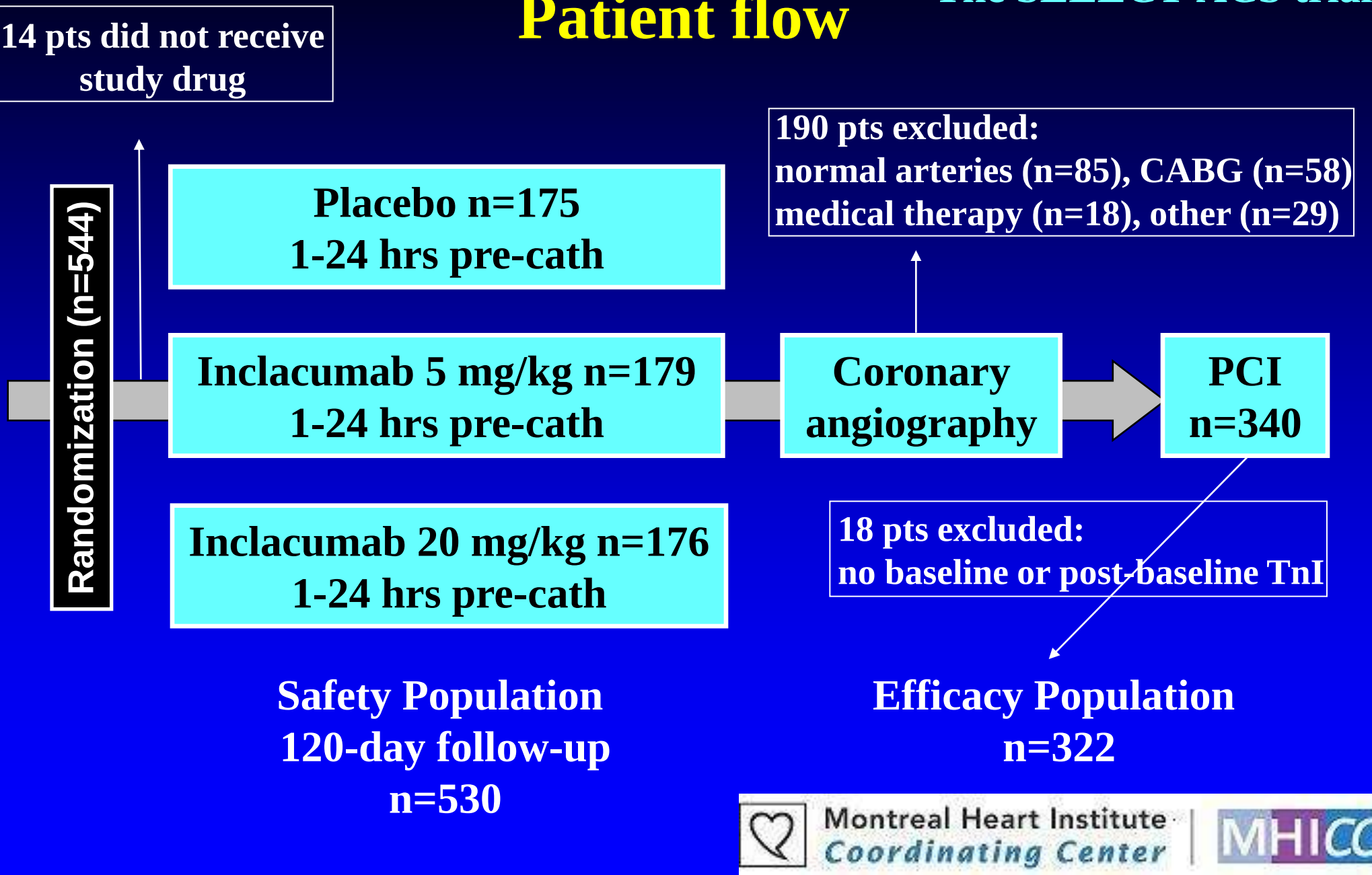
- Peak troponin I (TnI) post-PCI
- Area under the curve for TnI over 24 hours
- Change in TnI at 8 hours post-PCI
- Changes in CK-MB at 8, 16 and 24 hrs post-PCI

Safety analysis (in all patients who received infusion)

- AEs, lab results, physical exam, vital signs, ECG

Patient flow

The SELECT-ACS trial



Montreal Heart Institute Coordinating Center | MHICC

Baseline characteristics

	Placebo (n = 115)	Inclacumab 5 mg/kg (n = 95)	Inclacumab 20 mg/kg (n = 112)
Age (yrs, median)	60.9	63.1	59.8
Men (%)	79.1	77.9	79.5
Caucasians (%)	95.7	95.8	96.4
Diabetes (%)	20.9	24.2	23.2
Duration of PCI (min)	20.0	22.0	25.5
Ref. vess. diameter (mm)	3.0	3.0	3.0
Total stent length (mm)	22.0	20.0	22.0
Drug-eluting stent (%)	59.2	58.6	56.5
Bare metal stent (%)	35.4	35.3	39.1

Concomitant medications

	Placebo (n = 115)	Inclacumab 5 mg/kg (n = 95)	Inclacumab 20 mg/kg (n = 112)
P2Y12 inh. pre-PCI (%)	79.8	78.5	81.8
Gp 2b3a antagonists (%)	17.4	16.8	19.6
Aspirin (%)	96.6	91.1	92.0
Statins (%)	96.0	94.4	94.9
ACE inhibitors (%)	75.4	71.5	79.0
ARBs (%)	14.3	19.0	9.7
Beta-blockers (%)	90.3	90.5	92.0

Change in troponin I at 24 hours

Troponin I (TnI)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean I.Q.R.	1.03 0.24-4.69	0.71 0.17-3.44	0.82 0.19-3.73
24 hours post-PCI	1.76	1.21	0.99
Change from baseline[1]	57.7%	55.5%	19.1%
Placebo-adjusted change[2] 95% C.I. p-value	-- --	-1.4% (-26.7, 32.7) 0.93	-24.4% (-43.1, 0.4) 0.05

[1]Adjusted geometric mean %change (based on repeated ANCOVA model).
[2]Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

Montreal Heart Institute Coordinating Center | MHICC

Change in troponin I at 16 hours

Troponin I (TnI)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean I.Q.R.	1.03 0.24-4.69	0.71 0.17-3.44	0.82 0.19-3.73
16 hours post-PCI	1.74	1.30	1.09
Change from baseline[1]	77.4%	71.3%	37.6
Placebo-adjusted change[2] 95% C.I. p-value	-- --	-3.4% (-27.2, 28.2) 0.81	-22.4% (-40.8, 1.7) 0.07

[1]Adjusted geometric mean %change (based on repeated ANCOVA model).
[2]Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

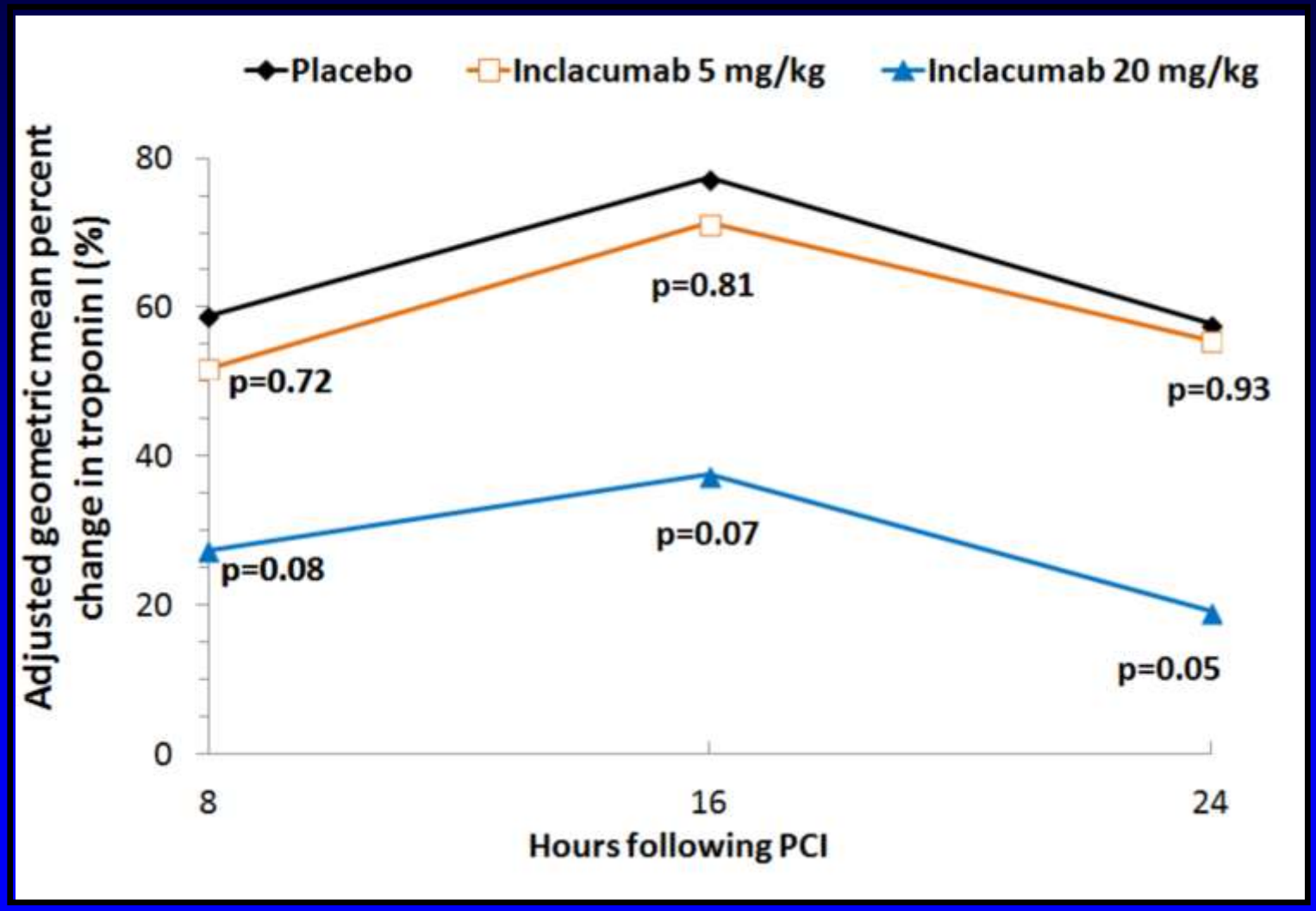
Montreal Heart Institute Coordinating Center | MHICC

Change in peak troponin I and AUC

Troponin I (TnI)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Peak TnI geometric mean	2.09	1.56	1.34
Placebo-adjusted change[1] 95% C.I. p-value	--	-1.5% (-26.3, 31.6) 0.92	-23.8% (-42.2, 0.5) 0.05
Area under the curve	40.37	28.87	26.35
Placebo-adjusted change 95% C.I. p-value	-- --	-27.2% (-54.8, 17.2) 0.19	-33.9% (-58.1, 4.3) 0.08

[1]Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

Percent change in troponin I over time



Change at 24 hrs with inclacumab 20 mg/kg vs pbo: diabetics -33.2%, non-diabetics -31.6% (p=0.03)

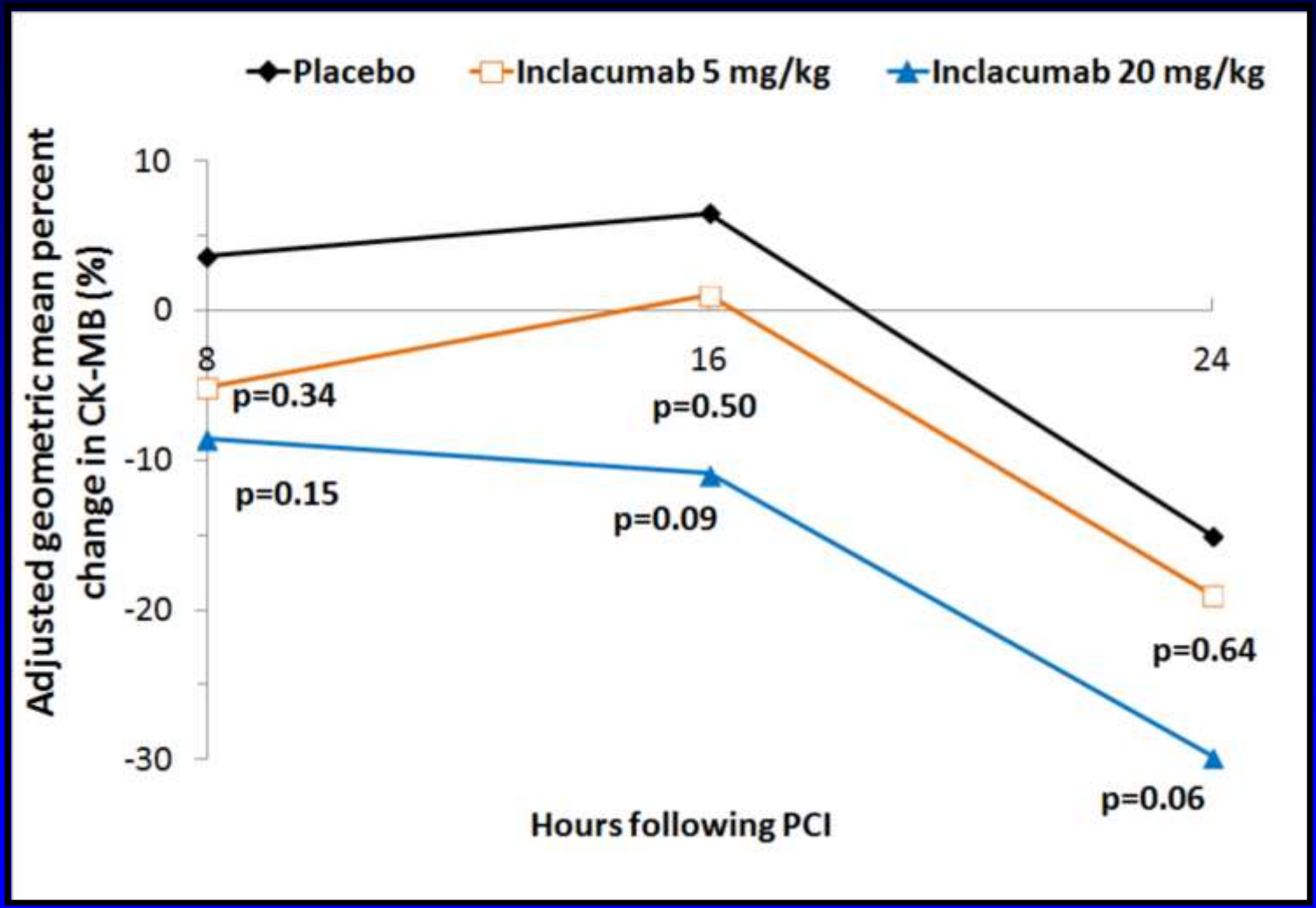
Montreal Heart Institute Coordinating Center | MHICC

Change in CK-MB at 24 hours

CK-MB	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean I.Q.R.	9.46 3.60-23.70	7.54 2.70-15.50	7.97 3.10-17.85
24 hours post-PCI	8.07	6.57	5.83
Change from baseline[1]	-15.0%	-19.0%	-29.8
Placebo-adjusted change[2] 95% C.I. p-value	-- --	-4.7% (-22.3, 16.9) 0.64	-17.4% (-32.1, 0.4) 0.06

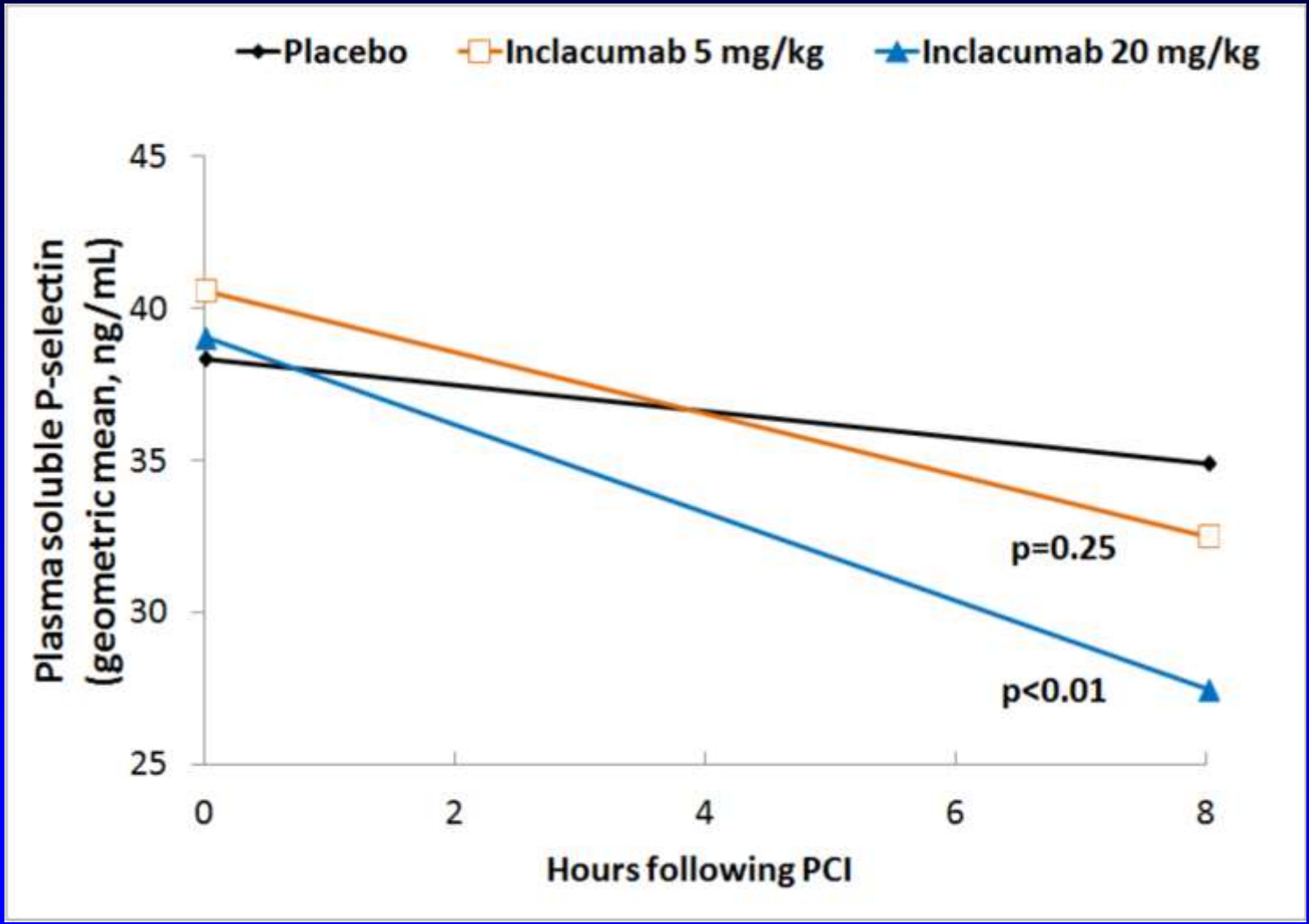
[1] Adjusted geometric mean %change (based on repeated ANCOVA model).
[2] Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

Percent change in CK-MB over time



Incidence of CK-MB increases >3 X ULN:
placebo 18.3%, inclacumab 20 mg/kg 8.9% (p=0.05)

Plasma soluble P-selectin level after PCI



Placebo-adjusted GM percent change:
-22.0% with inclacumab 20 mg/kg (p<0.01)

Montreal Heart Institute Coordinating Center | MHICC

Safety summary

The SELECT-ACS trial

	Placebo (n = 175)		Inclacumab 5 mg/kg (n = 179)		Inclacumab 20 mg/kg (n = 176)	
	n	%	n	%	n	%
Serious adverse events	32	18.3	43	24.0	45	25.6
Adverse events	106	60.6	111	62.0	112	63.6
Infection	21	12.0	19	10.6	19	10.8
Bleeding up to 120 days	9	5.1	11	6.1	7	4.0
All-cause death	0		4		2	
*Non-fatal MI	2		4		7	
Stroke	0		0		1	
Hospitalization for ACS	2		1		1	
Resuscitated cardiac arrest	1		2		1	
Revascularization procedures	20		31		22	

**Some peri-PCI MIs were reported as non-fatal MIs according to investigator's judgement*

Limitations

- Efficacy analyses were conducted in patients who received the infusion, underwent PCI and had TnI levels available at baseline and follow-up.
- Several results were of borderline statistical significance.
- Study not powered for evaluation of clinical endpoints.
- While TnI and CK-MB are reliable biomarkers of myocardial damage, the clinical significance of post-PCI elevations remains open to debate.

Conclusions

- The consistency of our data suggests that the P-selectin antagonist inclacumab reduces myocardial damage after PCI in patients with NSTEMI.
- Further clinical investigation will be required to determine the clinical value (benefit or harm) of inclacumab in patients presenting with myocardial infarction whether or not they undergo PCI.

JACC publication available on-line