ORIGINAL RESEARCH

Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention According to Timing of Infusion: Insights From the SELECT-ACS Trial

Barbara E. Stähli, MD, MBA;* Catherine Gebhard, MD;* Valérie Duchatelle, MD; Daniel Cournoyer, MSc; Thibaut Petroni, MD; Jean-François Tanguay, MD; Stephen Robb, MD; Jessica Mann, MD, PhD; Marie-Claude Guertin, PhD; R. Scott Wright, MD; Philippe L. L'Allier, MD; Jean-Claude Tardif, MD

***Background*—**The Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST-Segment Elevation Myocardial Infarction (SELECT-ACS) trial suggested beneficial effects of inclacumab, a monoclonal antibody directed against P-selectin, on periprocedural myocardial damage. This study evaluated the effect of inclacumab on myocardial damage according to varying time intervals between study drug infusion and percutaneous coronary intervention (PCI).

***Methods and Results*—**Patients (n=544) enrolled in the SELECT-ACS trial and randomized to receive 1 infusion of placebo or inclacumab (5 or 20 mg/kg, administered between 1 and 24 hours before PCI) were divided according to the time interval between study drug infusion and PCI. The primary end point was the change in troponin I from baseline at 16 and 24 hours after PCI. In patients receiving inclacumab 20 mg/kg with a short (less than median) time interval between infusion and PCI, placebo-adjusted geometric mean percent changes in troponin I, creatine kinase–myocardial band, and peak troponin I at 24 hours were −45.6% (P=0.005), −30.7% (P=0.01), and −37.3% (P=0.02), respectively. No significant changes were observed in patients with a long (greater than median) time interval between infusion and PCI. Placebo-adjusted geometric mean percent changes in troponin I and creatine kinase–myocardial band were −43.5% (P=0.02) and −26.0% (P=0.07), respectively, when inclacumab 20 mg/kg was administered between 1 and 3 hours before PCI, whereas the drug had no effect with longer intervals.

***Conclusions*—**Inclacumab 20 mg/kg significantly reduces myocardial damage after PCI in patients with non–ST-segment elevation myocardial infarction, and benefits are larger when the infusion is administered <3 hours before PCI.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01327183. **(*J Am Heart Assoc*. 2016;5: e004255 doi: 10.1161/JAHA.116.004255)**

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Myocardial damage is frequently observed in patients undergoing percutaneous coronary intervention (PCI) and has been associated with worse outcomes.[1,2] Although different treatment strategies have been developed to reduce myocardial injury after coronary revascularization,[3–5] the high incidence highlights the need for novel therapeutic concepts. Pathophysiological mechanisms of periprocedural myocardial injury are incompletely understood, and activation of inflammation and platelets, along with distal embolization and microvascular obstruction, seem to play a pivotal role.[1,6,7] P-selectin is a cell adhesion molecule that is expressed on activated endothelial cells and platelets, and known to mediate leukocyte recruitment and promote the formation of procoagulant microparticles.[8–10] Recent research has indicated that P-selectin appears to be involved in the pathogenesis of myocardial damage in acute coronary syndromes and during PCI.[11–15] The SELECT-ACS (Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST-Segment Elevation Myocardial

From the Montreal Heart Institute, Université de Montréal, Montreal, Canada (B.E.S., C.G., V.D., T.P., J.-F.T., P.L.L., J.-C.T.); Montreal Health Innovations Coordinating Center (MHICC), Montreal, Canada (D.C., M.-C.G.); Hoffmann-La Roche, Basel, Switzerland (S.R., J.M.); Mayo Clinic, Rochester, MN (R.S.W).

*Dr Stähli and Dr Gebhard are co-first authors.

Correspondence to: Jean-Claude Tardif, MD, Montreal Heart Institute, 5000 Belanger Street, Montreal, Canada H1T 1C8. E-mail: jean-claude.tardif@icm-mhi.org

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Infarction) trial suggested beneficial effects of inclacumab, a monoclonal antibody directed against P-selectin, on myocardial damage after PCI in patients with non–ST-segment elevation myocardial infarction (NSTEMI).[14] In this trial, inclacumab (5 and 20 mg/kg) was administered as a single intravenous infusion between 1 and 24 hours before PCI.

This study aimed to evaluate the effects of inclacumab on periprocedural myocardial damage according to varying time intervals between study drug infusion and PCI. Favorable effects of inclacumab in patients with NSTEMI would support the concept of targeting the P-selectin pathway for the reduction of myocardial damage during PCI and would contribute to the optimization of the study drug regimen.

Methods

The SELECT-ACS Study Design

Details of the SELECT-ACS trial were published previously.[14] The SELECT-ACS study was a multicenter, randomized, double-blind, placebo-controlled trial (NCT01327183) evaluating the efficacy and safety of inclacumab (RO4905417; F. Hoffmann-La Roche) in patients with NSTEMI undergoing PCI. A total of 544 patients presenting with NSTEMI and scheduled for coronary angiography and PCI were enrolled at 66 centers located in Canada, the United States, Poland, and the Netherlands. Patients were randomized at a 1:1:1 ratio to receive inclacumab 5 mg/kg, inclacumab 20 mg/kg, or placebo. The study drug or placebo was administered as a single 1-hour infusion between 1 and 24 hours before PCI. Troponin I (TnI) and creatine kinase–myocardial band (CK-MB) levels were measured at baseline and at 8, 16, and 24 hours after PCI (or at discharge if patients were discharged before the last time point). The efficacy population (n=322) comprised patients who received the study drug or placebo, underwent PCI, and had TnI levels measured at both baseline and follow-up. The study was coordinated by the Montreal Health Innovations Coordinating Center, a division of the Montreal Heart Institute. The protocol was approved by the institutional review board at each participating center, and all participants enrolled in the study provided written informed consent.

Outcomes

The primary efficacy endpoint was the change in TnI from baseline at 16 and 24 hours after PCI (or at discharge if patients were discharged before the last time point). The secondary endpoints were the peak TnI, the area under the curve for TnI over 24 hours, the change in TnI from baseline at 8 hours, and the changes in CK-MB from baseline at 8, 16, and 24 hours after PCI. Data on the time interval between study drug infusion and PCI were available for 321 patients. Comparisons were made between patients with a short (less than median) and a long (greater than median) time interval between study drug infusion and PCI and between patients receiving the study drug or placebo 1 to 3, 3 to 4, and >4 hours before PCI.

Statistical Analysis

Continuous variables are presented as mean±SD or median and interquartile range. Categorical variables are given as frequencies. For inclacumab 5 and 20 mg/kg, treatment groups with varying time intervals between study drug infusion and PCI were compared with placebo using appropriate contrast and log transformation to account for the skewed distribution. Log transformation was performed for TnI, CK-MB, peak TnI, and area under the curve for TnI. The study end points were analyzed using an ANCOVA model including treatment group (placebo, inclacumab 5 mg/kg, and inclacumab 20 mg/kg) and time interval (categorized as short and long time interval or as 1–3, 3–4, and >4 hours) as main effects and adjusting for baseline biomarker levels, known diabetes mellitus (the stratification factor of the SELECT-ACS trial), and differences ($P \leq 0.10$) in procedural characteristics between the short and long time interval groups. The dataset was not split, and the ANCOVA models were not applied separately in the short and long time interval groups. The area under the curve for TnI over 24 hours was analyzed using an ANOVA model including treatment group (placebo, inclacumab 5 mg/kg, and inclacumab 20 mg/kg) and time interval (categorized as short and long time interval or as 1–3, 3–4, and >4 hours) as main effects and adjusting for known diabetes mellitus and differences in procedural characteristics. Differences between treatment and placebo groups were described through placebo-adjusted geometric mean percent change, and the geometric mean was obtained by the antilog of log-transformed data. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute).

Results

Patient Characteristics

Baseline clinical and procedural characteristics are summarized in Tables 1 and 2. Patients were mostly white (96.0%) and male (78.8%). In both the placebo and inclacumab 5 mg/kg groups, baseline characteristics did not differ between patients with short and long time intervals between study drug infusion and PCI. In the inclacumab 20 mg/kg group, the number of vessels treated per patient was slightly lower in patients with a short versus long time interval (1.1±0.2 versus 1.2±0.4, P=0.049). The median time interval between study drug infusion and PCI was 202 minutes (interquartile

Table 1. Baseline Characteristics

	Placebo			Inclacumab (5 mg/kg)			Inclacumab (20 mg/kg)			
	Short Time Interval (n=56)	Long Time Interval (n=59)	*P* Value	Short Time Interval (n=48)	Long Time Interval (n=47)	*P* Value	Short Time Interval (n=56)	Long Time Interval (n=55)	*P* Value	*P* Value*
Age, y	59.7 (54.2–66.6)	61.4 (55.4–66.6)	0.66	61.5 (56.7–69.4)	65.4 (54.6–71.9)	0.45	60.4 (53.8–68.4)	59.0 (51.9–68.6)	0.87	1.00
Male	76.8	81.4	0.54	75.0	80.9	0.49	85.7	72.7	0.10	0.22
Race										
White	98.2	93.2		95.8	95.7		92.9	100.0		
Asian	0.0	0.0		0.0	0.0		1.7	0.0		
Black or African American	1.8	5.1		4.2	4.3		5.4	0.0		
Other	0.0	1.7		0.0	0.0		0.0	0.0		
Body mass index, kg/m^2	29.3 (26.3–32.2)	28.4 (25.8–31.5)	0.38	27.4 (25.0–31.1)	27.9 (24.8–31.3)	0.66	29.0 (26.6–32.1)	28.9 (25.5–32.1)	0.78	0.92
Diabetes mellitus	19.6	22.0	0.75	20.8	27.7	0.44	23.2	21.8	0.86	0.65
P2Y12 antagonists before PCI	76.8	82.8	0.43	74.5	82.6	0.34	83.6	80.0	0.62	0.37
Glycoprotein IIb/IIIa antagonists	16.1	18.6	0.72	20.8	12.8	0.29	19.6	20.0	0.96	0.63
Aspirin	94.6	94.9	0.95	93.8	89.4	0.44	92.9	87.3	0.33	0.69
Statins	94.6	96.6	0.61	95.8	95.7	0.98	96.4	94.6	0.64	0.65
Angiotensin-converting enzyme inhibitors	78.6	67.8	0.20	75.0	66.0	0.36	75.0	81.8	0.39	0.67
Angiotensin II receptor antagonists	12.5	18.6	0.39	20.8	14.9	0.37	12.5	5.5	0.21	0.95
Beta blockers	89.3	93.2	0.46	93.8	85.1	0.18	85.7	96.4	0.07	0.57
GRACE risk score, %	109 (93–121)	111 (99–133)	0.54	109 (93–121)	112 (95–133)	0.20	103 (96–119)	105 (90–123)	0.95	0.46

Values are median (interquartile range) or percentages. GRACE indicates Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention.
*For comparisons between the placebo and inclacumab 20 mg/kg short time interval groups.

range 154–323 minutes) and was similar among treatment groups, with 205 minutes (interquartile range 160–300 minutes), 195 minutes (interquartile range 145–390 minutes), and 200 minutes (interquartile range 160–361 minutes) in the placebo, inclacumab 5 mg/kg, and inclacumab 20 mg/kg groups, respectively.

Effects of Inclacumab 5 mg/kg on Myocardial Damage

Inclacumab 5 mg/kg had no effect on periprocedural myocardial damage irrespective of the time interval between study drug infusion and PCI. Placebo-adjusted geometric mean percentage changes in TnI from baseline at 16 and 24 hours were 12.1% (*P*=0.57) and 0.6% (*P*=0.98), respectively, in patients with a short time interval and −13.4% (*P*=0.48) and −17.8% (*P*=0.36), respectively, in those with a long time interval between study drug infusion and PCI. Corresponding changes in CK-MB at 16 and 24 hours were −4.9% (*P*=0.75) and −8.0% (*P*=0.59), respectively, in patients with a short time interval and −6.2% (*P*=0.68) and −9.6% (*P*=0.50), respectively, in those with a long time interval. The placebo-adjusted geometric mean percent changes in peak TnI were 11.3% (*P*=0.60) and −11.6% (*P*=0.55) in the short and long time interval groups, respectively, and corresponding changes in the area under the curve for TnI over 24 hours were −39.6 (*P*=0.14) and −13.1% (*P*=0.68), respectively.

Effects of Inclacumab 20 mg/kg on Myocardial Damage

Effects of inclacumab 20 mg/kg on periprocedural myocardial damage differed according to the time interval between study drug infusion and PCI. In patients with a short time interval (less than the median of 202 minutes), inclacumab resulted in significant placebo-adjusted geometric mean percent changes in TnI at 16 and at 24 hours of −34.9% (*P*=0.03) and −45.6% (*P*=0.005), respectively, whereas it had

Table 2. Procedural Characteristics

	Placebo			Inclacumab (5 mg/kg)			Inclacumab (20 mg/kg)			
	Short Time Interval (n=56)	Long Time Interval (n=59)	*P* Value	Short Time Interval (n=48)	Long Time Interval (n=47)	*P* Value	Short Time Interval (n=56)	Long Time Interval (n=55)	*P* Value	*P* Value*
Duration of PCI, minutes	20.0 (12.5–35.5)	23.0 (14.0–41.0)	0.22	20.0 (12.5–38.0)	24.0 (13.0–36.0)	0.75	20.5 (15.0–37.0)	29.0 (16.0–45.0)	0.23	0.50
Number of vessels treated per patient	1.1±0.4	1.1±0.3	0.94	1.0±0.2	1.1±0.4	0.19	1.1±0.2	1.2±0.4	0.049	0.28
Reference vessel diameter, mm†	3.0 (2.5–3.5)	3.0 (2.7–3.5)	0.40	3.0 (2.5–3.5)	3.0 (2.8–3.5)	0.07	3.0 (2.5–3.1)	3.0 (2.5–3.5)	0.34	0.87
Bifurcation lesion, %	16.1	17.0	0.89	10.4	23.4	0.09	19.6	16.4	0.65	0.61
Loss of side branch during the procedure, %	3.6	3.4		0.0	0.0		1.8	0.0		0.52
Transient no-reflow, %	1.8	3.4	0.59	4.2	6.4	0.62	8.9	3.6	0.27	0.13
Total stent length, mm	n=52	n=56		n=43	n=45		n=54	n=54		
	23.0 (15.0–30.0)	21.0 (15.0–32.5)	0.91	18.0 (15.0–30.0)	20.0 (18.0–28.0)	0.34	23.0 (15.0–30.0)	21.0 (16.0–33.0)	0.15	0.57
Stent type, number of stents	n=71	n=76		n=56	n=60		n=64	n=73		
Drug-eluting, %	64.8	54.0	0.37	53.6	63.3	0.36	46.9	64.4	0.10	0.049
Bare metal, %	29.6	40.8		37.5	33.3		46.8	32.9		
None, %	5.6	5.2		8.9	3.4		6.3	2.7		

Values are median (interquartile range), mean±SD or percentages. PCI indicates percutaneous coronary intervention.
*For comparisons between the placebo and inclacumab 20 mg/kg short time interval groups.
†Reference vessel diameter was evaluated visually on coronary angiograms.

no effect in patients with a long time interval (Table 3). Corresponding changes in CK-MB at 16 and 24 hours were −26.0% (*P*=0.049) and −30.7% (*P*=0.01), respectively, in patients with a short time interval and −9.8% (*P*=0.49) and −15.7% (*P*=0.25), respectively, in those with a long time interval (Table 4). When adjusting for sex, use of P2Y12 antagonists, use of glycoprotein IIb/IIIa antagonists, and transient "no-reflow" phenomenon, the trends remained the same.

When dividing patients into 3 groups according to the time interval between study drug infusion and PCI, placebo-adjusted geometric mean percent changes in TnI and CK-MB at 24 hours were −43.5% (*P*=0.02) and −26.0% (*P*=0.07), respectively, when inclacumab 20 mg/kg was administered between 1 and 3 hours before PCI, whereas infusions between 3 and 4 hours and >4 hours before PCI had no effect (Table 5).

Inclacumab 20 mg/kg was associated with a significant placebo-adjusted geometric mean percent change in peak TnI levels (−37.3%, *P*=0.02) in patients with a short time interval (less than the median of 202 minutes), whereas it did not exert any effect on those with a long time interval (−15.6%, *P*=0.39). The placebo-adjusted geometric mean percent changes in the area under the curve for TnI over the 24-hour period after PCI were −48.2 (*P*=0.047) and −32.4% (*P*=0.23) in the short and the long time interval groups, respectively.

Discussion

This study showed that inclacumab 20 mg/kg significantly reduces periprocedural myocardial damage in patients with NSTEMI undergoing PCI, with benefits being larger when the study drug was administered between 1 and 3 hours before PCI. These results support therapeutic concepts targeting P-selectin–dependent pathways in patients with acute coronary syndromes.

P-Selectin and Myocardial Damage After PCI

Periprocedural myocardial injury is seen in up to 50% of coronary interventions and, being associated more with difficult PCI procedures, occurs mostly in patients with large plaque volumes, high thrombus burden, and complex coronary

Table 3. Change in Troponin I at 16 and 24 Hours After PCI in Patients With Short and Long Time Intervals Between Study Drug Infusion and PCI

	Short (Less Than Median) Time Interval			Long (Greater Than Median) Time Interval		
	Placebo	Inclacumab (5 mg/kg)	Inclacumab (20 mg/kg)	Placebo	Inclacumab (5 mg/kg)	Inclacumab (20 mg/kg)
Baseline GM (IQR)	1.12 (0.26–5.90)	0.56 (0.11–2.99)	0.91 (0.18–4.32)	0.96 (0.22–4.23)	0.89 (0.25, 4.18)	0.71 (0.19–3.05)
16 hours after PCI GM	2.01 (n=56)	1.35 (n=48)	1.15 (n=54)	1.51 (n=58)	1.25 (n=46)	1.01 (n=53)
Adjusted GM percentage change from baseline to 16 hours	133.3	161.6	51.8	89.8	64.4	57.3
Placebo-adjusted GM percentage change at 16 hours		12.1	−34.9		−13.4	−17.1
95% CI		−24.7 to 67.0	−55.8 to −4.2		−41.7 to 28.7	−43.6 to 21.7
P value		0.57	0.03		0.48	0.34
24 hours after PCI GM	2.23 (n=50)	1.35	1.00 (n=52)	1.41 (n=54)	1.10 (n=47)	0.95 (n=48)
Adjusted GM percentage change from baseline to 24 hours	179.5	181.1	52.0	104.9	68.5	63.6
Placebo-adjusted GM percentage change at 24 hours		0.57	−45.6		−17.8	−20.2
95% CI		−35.2 to 56.0	−64.4 to −16.9		−46.2 to 25.5	−47.7 to 21.9
P value		0.98	0.005		0.36	0.30

GM indicates geometric mean; IQR, interquartile range; PCI, percutaneous coronary intervention.

anatomy.[1,16,17] Although occurring mostly silently, even minor postprocedural elevations of cardiac biomarkers have been associated with adverse outcomes.[17,18] Inflammation and platelet activation play a critical role in the pathogenesis of myocardial damage following coronary interventions.[6,7] Inhibiting P-selectin–dependent functions such as platelet activation and leukocyte recruitment has initially emerged as a promising therapeutic approach in preventing neointimal formation.[10,19–21] Based on encouraging results from animal models of myocardial ischemia–reperfusion injury and phase I clinical studies,[22–25] the recent SELECT-ACS trial has then extended the concept of targeting P-selectin pathways to patients with acute coronary syndromes undergoing PCI and demonstrated the efficacy of the P-selectin antagonist inclacumab in reducing periprocedural myocardial damage.[14]

Inclacumab Effects on Myocardial Damage After PCI

Our study demonstrated that the largest benefits in reducing periprocedural myocardial damage were achieved when inclacumab was given between 1 and 3 hours before PCI. This observation may at least in part explain the modest statistical significance of inclacumab effects observed in the SELECT-ACS trial, in which the study drug was administered within 24 hours before PCI.[14] Pathophysiological mechanisms linking the time point of drug administration to inclacumab effects are not yet known. Given the long half-life of inclacumab comparable to that of other human IgG antibodies and the persistent inhibition of platelet–leukocyte aggregates demonstrated after inclacumab administration,[24,25] alternative signaling cascades involving rapidly activated pathways and short-term effects at maximum drug concentrations achieved at the end of the infusion may have accounted for these findings. Furthermore, cross-reactivity of inclacumab with other receptors, similar to the observations reported for different drugs including glycoprotein IIb/IIIa antagonists,[26,27] may come into play. This raises the question of whether shorter (<1 hour) time intervals between study drug infusion and PCI or continuous infusions administered throughout the procedure, along with intracoronary infusion methods, would have caused an even larger effect. Further studies are needed to fully elucidate pharmacokinetic profiles of inclacumab in patients presenting with acute coronary syndromes and undergoing PCI and to prospectively compare different treatment regimens. In addition, one might speculate that a shorter time interval between study drug administration and PCI mirrors a shorter time interval between symptom onset

Table 4. Change in Creatine Kinase–Myocardial Band at 16 and 24 Hours After PCI in Patients With Short and Long Time Intervals Between Study Drug Infusion and PCI

	Short (Less Than Median) Time Interval			Long (Greater Than Median) Time Interval		
	Placebo	Inclacumab (5 mg/kg)	Inclacumab (20 mg/kg)	Placebo	Inclacumab (5 mg/kg)	Inclacumab (20 mg/kg)
Baseline GM (IQR)	10.76 (3.95–30.00)	7.41 (2.40, 21.65)	7.99 (2.75–17.85)	8.37 (3.20–21.30)	7.68 (3.30–12.90)	7.71 (3.30–14.50)
16 hours after PCI GM	10.96 (n=56)	8.36 (n=48)	7.10 (n=54)	8.40 (n=58)	7.50 (n=46)	7.33 (n=53)
Adjusted GM percent change from baseline to 16 hours	31.0	24.6	−3.0	12.8	5.8	1.8
Placebo-adjusted GM percent change at 16 hours		−4.9	−26.0		−6.2	−9.8
95% CI		−30.0 to 29.2	−45.1 to −0.2		−30.9 to 27.3	−33.0 to 21.3
P value		0.75	0.049		0.68	0.49
24 hours after PCI GM	8.99 (n=50)	6.96 (n=45)	5.56 (n=52)	7.30 (n=54)	6.22 (n=47)	6.02 (n=49)
Adjusted GM percent change from baseline to 24 hours	26.6	16.5	−12.3	12.2	1.4	−5.4
Placebo-adjusted GM percent change at 24 hours		−8.0	−30.7		−9.6	−15.7
95% CI		−32.1 to 24.7	−48.4 to −7.0		−32.6 to 21.2	−37.0 to 12.9
P value		0.59	0.01		0.50	0.25

GM indicates geometric mean; IQR, interquartile range; PCI, percutaneous coronary intervention.

Table 5. Changes in Troponin I and CK-MB at 24 Hours After PCI According to Different Time Intervals Between Study Drug Infusion and PCI

	Troponin I			CK-MB		
Time Interval	<3 Hours	3–4 Hours	>4 Hours	<3 Hours	3–4 Hours	>4 Hours
Inclacumab 5 mg/kg						
Patients, n	39	17	36	39	17	36
Adjusted GM percent change from baseline to 24 hours	174.5	119.5	67.4	13.7	17.4	0.8
Placebo-adjusted GM percent change at 24 hours	0.77	−20.4	−11.2	−10.5	−6.8	−6.9
95% CI	−37.7 to 62.9	−59.5 to 56.4	−46.0 to 46.0	−35.8 to 24.9	−41.7 to 49.1	−34.1 to 31.4
P value	0.97	0.51	0.64	0.51	0.77	0.68
Inclacumab 20 mg/kg						
Patients, n	41	23	36	41	24	36
Adjusted GM percent change from baseline to 24 hours	54.0	63.6	58.6	−6.0	−12.9	−8.4
Placebo-adjusted GM percent change at 24 hours	−43.5	−40.7	−15.9	−26.0	−30.9	−15.4
95% CI	−64.8 to −9.3	−68.1 to 10.3	−49.0 to 38.7	−46.7 to 2.8	−54.9 to 5.8	−40.2 to 19.6
P value	0.02	0.10	0.50	0.07	0.09	0.34

CK-MB indicates creatine kinase-myocardial band; GM, geometric mean.

and PCI, and that patients with a longer time interval between infusion and PCI were those who presented at a later myocardial infarction stage when inclacumab may have exerted less pronounced effects. However, data on symptom duration were not collected in the SELECT-ACS trial. Although concomitant evidence-based therapies were balanced between treatment and placebo groups and between patients with a short and a long time interval between study drug infusion and PCI, drug interactions between inclacumab and standard of care medications cannot be ruled out completely.

Study Limitations

This study has the limitations of a post hoc analysis, and larger trials randomizing patients to different treatment regimens are needed to confirm these results. Although procedural complexity as reflected by the duration of PCI did not differ between groups, and adjustments for specific procedural characteristics including number of vessels treated and stent type implanted were performed, other aspects such as plaque burden and coronary dissection/perforation which might have affected the endpoints were not addressed. Further, as patients with NSTEMI undergoing interventional treatment were included in the SELECT-ACS trial, these findings cannot be extrapolated to patients presenting with stable coronary artery disease or ST-segment elevation myocardial infarction, and potential inclacumab effects in patients treated medically need to be assessed in future studies.

Conclusion

Inclacumab 20 mg/kg significantly reduces postprocedural myocardial damage in patients with NSTEMI, with the largest benefits observed when the drug is administered between 1 and 3 hours before PCI. The results of this study provide a strong rationale to further define the role of a P-selectin–based therapy in patients presenting with acute coronary syndromes.

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Disclosures

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References

1. Babu GG, Walker JM, Yellon DM, Hausenloy DJ. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. *Eur Heart J*. 2011;32:23–31.
2. Roe MT, Mahaffey KW, Kilaru R, Alexander JH, Akkerhuis KM, Simoons ML, Harrington RA, Tardiff BE, Granger CB, Ohman EM, Moliterno DJ, Lincoff AM, Armstrong PW, Van de Werf F, Califf RM, Topol EJ. Creatine kinase-MB elevation after percutaneous coronary intervention predicts adverse outcomes in patients with acute coronary syndromes. *Eur Heart J*. 2004;25:313–321.
3. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, Montinaro A, Di Sciascio G. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol*. 2007;49:1272–1278.
4. Tardif JC, L'Allier PL, Gregoire J, Ibrahim R, McFadden G, Kostuk W, Knudtson M, Labinaz M, Waksman R, Pepine CJ, Macaulay C, Guertin MC, Lucas A. A randomized controlled, phase 2 trial of the viral serpin Serp-1 in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2010;3:543–548.
5. Bonz AW, Lengenfelder B, Strotmann J, Held S, Turschner O, Harre K, Wacker C, Waller C, Kochsiek N, Meesmann M, Neyses L, Schanzenbacher P, Ertl G, Voelker W. Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol*. 2002;40:662–668.
6. Mickelson JK, Lakkis NM, Villarreal-Levy G, Hughes BJ, Smith CW. Leukocyte activation with platelet adhesion after coronary angioplasty: a mechanism for recurrent disease? *J Am Coll Cardiol*. 1996;28:345–353.
7. Serrano CV Jr, Ramires JA, Venturinelli M, Arie S, D'Amico E, Zweier JL, Pileggi F, da Luz PL. Coronary angioplasty results in leukocyte and platelet activation with adhesion molecule expression. Evidence of inflammatory responses in coronary angioplasty. *J Am Coll Cardiol*. 1997;29:1276–1283.
8. Celi A, Pellegrini G, Lorenzet R, De Blasi A, Ready N, Furie BC, Furie B. P-selectin induces the expression of tissue factor on monocytes. *Proc Natl Acad Sci USA*. 1994;91:8767–8771.
9. Bevilacqua MP, Nelson RM. Selectins. *J Clin Invest*. 1993;91:379–387.
10. Wagner DD, Burger PC. Platelets in inflammation and thrombosis. *Arterioscler Thromb Vasc Biol*. 2003;23:2131–2137.
11. Wang J, Zhang S, Jin Y, Qin G, Yu L, Zhang J. Elevated levels of platelet-monocyte aggregates and related circulating biomarkers in patients with acute coronary syndrome. *Int J Cardiol*. 2007;115:361–365.
12. Ikeda H, Takajo Y, Ichiki K, Ueno T, Maki S, Noda T, Sugi K, Imaizumi T. Increased soluble form of P-selectin in patients with unstable angina. *Circulation*. 1995;92:1693–1696.
13. Yazici M, Demircan S, Durna K, Yasar E, Sahin M. Relationship between myocardial injury and soluble P-selectin in non-ST elevation acute coronary syndromes. *Circ J*. 2005;69:530–535.
14. Tardif JC, Tanguay JF, Wright RS, Duchatelle V, Petroni T, Gregoire JC, Ibrahim R, Heinonen TM, Robb S, Bertrand OF, Cournoyer D, Johnson D, Mann J, Guertin MC, L'Allier PL. Effects of the P-selectin antagonist inclacumab on myocardial damage after percutaneous coronary intervention for non-ST-segment elevation myocardial infarction: results of the SELECT-ACS trial. *J Am Coll Cardiol*. 2013;61:2048–2055.
15. Stähli BE, Tardif JC, Carrier M, Gallo R, Emery RW, Robb S, Cournoyer D, Blondeau L, Johnson D, Mann J, Lespérance J, Guertin MC, L'Allier PL. Effects

of P-selectin antagonist inclacumab in patients undergoing coronary artery bypass graft surgery. SELECT CABG Trial. *J Am Coll Cardiol*. 2016;67:343–352.

16. Cuculi F, Lim CC, Banning AP. Periprocedural myocardial injury during elective percutaneous coronary intervention: is it important and how can it be prevented? *Heart*. 2010;96:736–740.
17. Nienhuis MB, Ottervanger JP, Bilo HJ, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: a meta-analysis. *Catheter Cardiovasc Interv*. 2008;71:318–324.
18. Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol*. 2003;42:1406–1411.
19. Hayashi S, Watanabe N, Nakazawa K, Suzuki J, Tsushima K, Tamatani T, Sakamoto S, Isobe M. Roles of P-selectin in inflammation, neointimal formation, and vascular remodeling in balloon-injured rat carotid arteries. *Circulation*. 2000;102:1710–1717.
20. Tanguay JF, Geoffroy P, Sirois MG, Libersan D, Kumar A, Schaub RG, Merhi Y. Prevention of in-stent restenosis via reduction of thrombo-inflammatory reactions with recombinant P-selectin glycoprotein ligand-1. *Thromb Haemost*. 2004;91:1186–1193.
21. Phillips JW, Barringhaus KG, Sanders JM, Hesselbacher SE, Czarnik AC, Manka D, Vestweber D, Ley K, Sarembock IJ. Single injection of P-selectin or P-selectin glycoprotein ligand-1 monoclonal antibody blocks neointima formation after arterial injury in apolipoprotein E-deficient mice. *Circulation*. 2003;107:2244–2249.
22. Fukushima S, Coppen SR, Varela-Carver A, Yamahara K, Sarathchandra P, Smolenski RT, Yacoub MH, Suzuki K. A novel strategy for myocardial protection by combined antibody therapy inhibiting both P-selectin and intercellular adhesion molecule-1 via retrograde intracoronary route. *Circulation*. 2006;114:I251–I256.
23. Weyrich AS, Ma XY, Lefer DJ, Albertine KH, Lefer AM. In vivo neutralization of P-selectin protects feline heart and endothelium in myocardial ischemia and reperfusion injury. *J Clin Invest*. 1993;91:2620–2629.
24. Kling D, Stucki C, Kronenberg S, Tuerck D, Rheaume E, Tardif JC, Gaudreault J, Schmitt C. Pharmacological control of platelet-leukocyte interactions by the human anti-P-selectin antibody inclacumab–preclinical and clinical studies. *Thromb Res*. 2013;131:401–410.
25. Schmitt C, Abt M, Ciorciaro C, Kling D, Jamois C, Schick E, Solier C, Benghozi R, Gaudreault J. First-in-man study with inclacumab, a human monoclonal antibody against P-selectin. *J Cardiovasc Pharmacol*. 2015;65:611–619.
26. Simon DI, Xu H, Ortlepp S, Rogers C, Rao NK. 7E3 monoclonal antibody directed against the platelet glycoprotein IIb/IIIa cross-reacts with the leukocyte integrin Mac-1 and blocks adhesion to fibrinogen and ICAM-1. *Arterioscler Thromb Vasc Biol*. 1997;17:528–535.
27. Lincoff AM, Kereiakes DJ, Mascelli MA, Deckelbaum LI, Barnathan ES, Patel KK, Frederick B, Nakada MT, Topol EJ. Abciximab suppresses the rise in levels of circulating inflammatory markers after percutaneous coronary revascularization. *Circulation*. 2001;104:163–167.