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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

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Objectives The study aimed to evaluate inclacumab for the reduction of myocardial damage during a percutaneous coronary intervention (PCI) in patients with non–ST-segment elevation myocardial infarction.

Background P-selectin is an adhesion molecule involved in interactions between endothelial cells, platelets, and leukocytes. Inclacumab is a recombinant monoclonal antibody against P-selectin, with potential anti-inflammatory, antithrombotic, and antiatherogenic properties.

Methods Patients (N = 544) with non–ST-segment elevation myocardial infarction scheduled for coronary angiography and possible ad hoc PCI were randomized to receive 1 pre-procedural infusion of inclacumab 5 or 20 mg/kg or placebo. The primary endpoint, evaluated in patients who underwent PCI, received study medication, and had available efficacy data (n = 322), was the change in troponin I from baseline at 16 and 24 h after PCI.

Results There was no effect of inclacumab 5 mg/kg. Placebo-adjusted geometric mean percent changes in troponin I with inclacumab 20 mg/kg were −24.4% at 24 h ($p = 0.05$) and −22.4% at 16 h ($p = 0.07$). Peak troponin I was reduced by 23.8% ($p = 0.05$) and area under the curve over 24 h by 33.9% ($p = 0.08$). Creatine kinase-myocardial band yielded similar results, with changes of −17.4% at 24 h ($p = 0.06$) and −16.3% at 16 h ($p = 0.09$). The incidence of creatine kinase-myocardial band increases >3 times the upper limit of normal within 24 h was 18.3% and 8.9% in the placebo and inclacumab 20-mg/kg groups, respectively ($p = 0.05$). Placebo-adjusted changes in soluble P-selectin level were −9.5% ($p = 0.25$) and −22.0% ($p < 0.01$) with inclacumab 5 and 20 mg/kg. There was no significant difference in adverse events between groups.

Conclusions Inclacumab appears to reduce myocardial damage after PCI in patients with non–ST-segment elevation myocardial infarction. (A Study of RO4905417 in Patients With Non ST-Elevation Myocardial Infarction [Non-STEMI] Undergoing Percutaneous Coronary Intervention; NCT01327183) (J Am Coll Cardiol 2013;61:2048–55) © 2013 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is a widely used revascularization procedure for patients with stable and unstable coronary artery disease, but varying degrees of periprocedural myocardial damage (often relatively minor) occurs in as many as 50% of patients, even after a seemingly

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uneventful PCI (1–3). Although the pathophysiology of post-PCI myocardial damage is multifactorial, inflammation and platelet activation appear to play pivotal roles (4–7). P-selectin, a cell adhesion molecule expressed on activated endothelial cells and platelets, plays a critical role in leukocyte tethering and rolling on the vessel wall and subsequent diapedesis through interactions with P-selectin glycoprotein ligand 1 (8). It also promotes platelet rolling and adhesion to the activated vessel wall. When expressed on the cell surface, P-selectin therefore affects both the inflammatory and thrombotic cascades, induces formation of procoagulant microparticles, and mediates microparticle and leukocyte recruitment to thrombi, which collectively promotes both leukocyte recruitment to activated endothelium and thrombus growth and stabilization (9). Studies in mice, rats, and pigs have suggested that inhibition of P-selectin with either an anti–P-selectin monoclonal antibody or P-selectin glycoprotein ligand 1–immunoglobulin complex can significantly decrease neutrophil and platelet adhesion, macrophage accumulation, and neointimal formation after arterial injury (10–13). Inclacumab is a highly specific human recombinant monoclonal antibody against P-selectin, which has been shown to reduce CD11b expression (known to increase after PCI [14]) on neutrophils in a concentration-dependent fashion (data on file, F. Hoffmann-La Roche). The SELECT-ACS (Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST-Elevation Myocardial Infarction) clinical trial was designed to determine the efficacy of inclacumab in reducing myocardial damage during PCI in patients with non–ST-segment elevation myocardial infarction (NSTEMI). We hypothesized that inclacumab would reduce myocardial damage through the effects of P-selectin inhibition on both the inflammatory and thrombotic cascades.

Methods

Study design and procedures. This prospective, international, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of inclacumab (RO4905417, F. Hoffmann-La Roche) in patients with NSTEMI scheduled for coronary angiography and PCI. The study was coordinated by the Montreal Heart Institute Coordinating Center. Patients reviewed and signed an informed consent form approved by the institutional review boards of the study sites before any study-related procedures. Patient screening was performed up to 3 days before PCI, followed by treatment involving a single infusion of inclacumab (5 or 20 mg/kg) or placebo before PCI. Patients were monitored for 24 h for efficacy and 120 days for safety evaluations (Fig. 1). Troponin I (TnI) and creatine kinase-myocardial band (CK-MB) levels were measured in a central laboratory.

Abbreviations and Acronyms

ANCOVA = analysis of covariance
AUC = area under the curve
CK-MB = creatine kinase-myocardial band
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
TnI = troponin I

The study drug was administered between 1 and 24 h before PCI over a 1-h infusion period. Patients were randomized in a 1:1:1 ratio to 3 treatment arms: inclacumab 5 mg/kg, inclacumab 20 mg/kg, or placebo. A stratified randomization was used to account for the presence or absence of known diabetes to ensure equal distribution within the randomized groups. A randomization schedule was generated using SAS statistical software version 9.3 (SAS Institute, Cary, North Carolina). Patients received concomitant evidence-based therapies as currently recommended by the American College of Cardiology/American Heart Association guidelines. This included the administration of aspirin, a P2Y12 inhibitor, lipid-lowering medications (preferably a statin), and a renin-angiotensin system inhibitor as deemed necessary by the investigator. Patients were assessed at baseline and at 8, 16, and 24 h post-PCI or at the time of discharge if patients were discharged before the last time point. All patients returned 30 and 120 days post-infusion for follow-up safety visits that included the assessment of adverse events, routine clinical laboratory tests, physical examination, and electrocardiograms. A subset of the enrolled patients (n = 177) willing to participate in an optional substudy had additional blood samples collected at baseline and at 8 h post-PCI for the measurement of plasma-soluble P-selectin levels using a specific enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, Minnesota).

Study population. A total of 544 patients at 66 centers located in Canada, the United States, Poland, and the Netherlands were enrolled in this study. Patients were included in the study if they were between 18 and 85 years old, were diagnosed with NSTEMI as defined by the American College of Cardiology/American Heart Association guidelines, and scheduled for coronary angiography and possible ad hoc PCI. Reasons for exclusion were PCI within the past 72 h; recent thrombolytic therapy; recent cerebrovascular disease or stroke; bleeding disorders; significant blood dyscrasia; severe uncontrolled hypertension; previous coronary artery bypass graft surgery; active or recent chronic bacterial, parasitic, or viral infection; uncontrolled diabetes mellitus; intercurrent infection; severe renal failure; hepatic failure; severe active inflammatory or immune-mediated disease; pregnancy or planned pregnancy; or any other condition or disease that would render the patient unsuitable for the study in the opinion of the investigator. Patients

investigator for a past Roche-sponsored trial. Dr. Tanguay is a consultant to Roche. Dr. Wright is a research consultant to Roche/Genentech, 3M, and Sanofi Regeneron, and is a consultant to Gilead. Dr. Ibrahim is a proctor and consultant for St. Jude and Gore. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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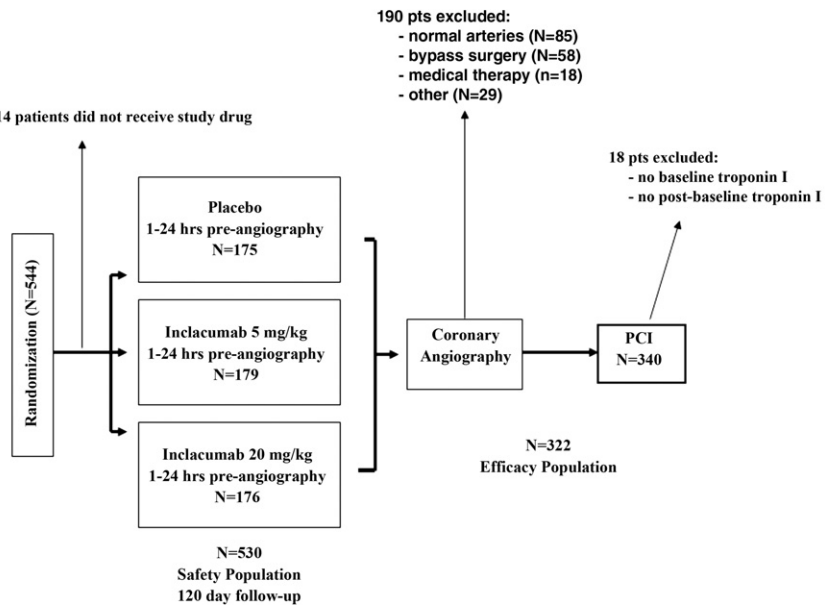

Figure 1 **Overview of Study Design and Patient Disposition**

A total of 544 patients were enrolled in the study. A total of 322 patients received study medication, underwent percutaneous coronary intervention (PCI) and had troponin I levels available at both baseline and follow up (efficacy population). Safety analyses were performed on all patients who received study medication regardless of whether or not they proceeded to PCI (n = 530).

who were randomized to receive the study drug (or placebo) infusion but did not undergo the planned PCI procedure were not evaluated for efficacy, but were followed for safety assessments.

Study endpoints. Efficacy analyses were conducted in patients who received the study drug (or placebo) infusion, underwent PCI, and had TnI levels available at both baseline and follow-up. The primary efficacy endpoint was the change from baseline in TnI evaluated at both 16 and 24 h (or time of discharge, whichever was earlier) post-PCI. The secondary endpoints of this study were the peak TnI post-PCI, the area under the curve (AUC) for TnI over the 24-h period after PCI, the change from baseline in TnI at 8 h post-PCI, and the changes from baseline in CK-MB at 8, 16, and 24 h post-PCI.

Safety analyses were performed on all patients who received study medication regardless of whether they proceeded to PCI. Safety was assessed through reporting of adverse events, clinical laboratory test results, and physical examination including vital signs and 12-lead electrocardiograms.

Statistical analysis. Baseline, efficacy, and safety data are reported using descriptive statistics. Mean, SD, median, and minimum and maximum are presented for continuous variables; count and frequency are presented for categorical variables. The primary endpoint was analyzed using a repeated-measures analysis of covariance (ANCOVA) adjusting for baseline value of TnI and for the stratification factor (presence or absence of diabetes before acute coronary syndrome). Each active treatment group was compared with placebo using appropriate contrasts. The secondary endpoints expressed as changes from baseline were analyzed using a similar repeated-measures ANCOVA model. Comparisons of peak TnI between active treatment and placebo groups were conducted using an ANCOVA model adjusting for baseline TnI and diabetes. The 24-h AUC for TnI was analyzed using an analysis of variance model adjusting for diabetes. Change from baseline to 8 h post-PCI in soluble P-selectin levels, available in a subgroup of patients, was analyzed using an ANCOVA model adjusting for baseline level and diabetes.

A log transformation was applied to these efficacy endpoints because of skewed distribution. Differences between the active treatment and placebo groups were therefore described through placebo-adjusted geometric mean percent change. The geometric mean is obtained by the antilog of log-transformed data. Placebo-adjusted geometric mean percent change at 24 h is equal to [(geometric mean for change at 24 h with inclacumab − geometric mean for change at 24 h with placebo)/ geometric mean for change at 24 h with placebo] × 100.

All testing was 2 sided and conducted at the 0.05 significance level. No adjustments were made for multiple comparisons. Statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute).

Sample size estimation. The sample size was based on the comparison of 2 means of TnI with an alpha level of 0.05. The calculation of sample size used previously published data on troponin after PCI (15) based on log-transformed data that showed that the average SD of log TnI the first

Table 1 Patient Demographics and Baseline Characteristics

	Placebo (n = 115)	Inclacumab 5 mg/kg (n = 95)	Inclacumab 20 mg/kg (n = 112)	All (N = 322)
Age, yrs	60.9 (54.4–66.6)	63.1 (55.4–70.6)	59.8 (53.4–68.7)	61.1 (54.5–69.0)
Sex				
Male	79.1	77.9	79.5	78.9
Female	20.9	22.1	20.5	21.1
Race				
White	95.7	95.8	96.4	96.0
Asian	0.0	0.0	0.9	0.3
Black or African American	3.5	4.2	2.7	3.4
Other	0.9	0.0	0.0	0.3
Diabetes, %	20.9	24.2	23.2	22.7
Duration of PCI, min	20.0 (14.0–40.0)	22.0 (13.0–36.0)	25.5 (16.0–40.0)	23.0 (15.0–40.0)
No. of vessels treated/patient	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Reference vessel diameter, mm*	3.0 (2.5–3.5)	3.0 (2.5–3.5)	3.0 (2.5–3.4)	3.0 (2.5–3.5)
Total stent length, mm	n = 108	n = 88	n = 109	n = 305
	22.0 (15.0–30.0)	20.0 (16.0–29.0)	22.0 (16.0–30.0)	20.0 (15.0–30.0)
Stent type, no. of stents	n = 147	n = 116	n = 138	n = 401
Drug-eluting	59.2	58.6	56.5	58.1
Bare-metal	35.4	35.3	39.1	36.7
None	5.4	6.0	4.3	5.2
P2Y12 antagonist before PCI	79.8	78.5	81.8	80.1
Glycoprotein IIb/IIIa antagonist	17.4	16.8	19.6	18.0
Aspirin	96.6	91.1	92.0	93.2
Statins	96.0	94.4	94.9	95.1
Angiotensin-converting enzyme inhibitors	75.4	71.5	79.0	75.3
Angiotensin II receptor antagonists	14.3	19.0	9.7	14.3
Beta-blockers	90.3	90.5	92.0	90.9

Values are median (interquartile range) or %. *Reference vessel diameter was evaluated visually in the catheterization laboratory.
PCI = percutaneous coronary intervention.

24 h after PCI was 1.5 and that the geometric mean in the placebo group was ~1.0 ng/ml. To detect a 40% reduction in TnI, the study required 137 patients per group (411 total). Because it was estimated that 20% of the randomized patients might not be eligible to undergo PCI and to ensure that sufficient numbers of patients would be randomized, treated, and undergo PCI, 172 patients per group (516 total) were targeted for enrollment.

Results

A total of 322 patients received study medication, underwent PCI, and had TnI levels available at both baseline and follow-up (see Fig. 1 for patient disposition). The population was primarily white (96.0%) and male (78.9%), with a median age of 61.1 years. Most patients received drug-eluting (58.1%) or bare metal (36.7%) stents during PCI. There were no differences in baseline characteristics among the 3 treatment groups (n = 115 for placebo, n = 95 for inclacumab 5 mg/kg, n = 112 for inclacumab 20 mg/kg) (Table 1).

Efficacy of inclacumab 5 mg/kg. Treatment with inclacumab 5 mg/kg did not demonstrate any effect on reducing periprocedural myocardial damage. There was no statistically significant effect on the placebo-adjusted geometric mean percent changes from baseline in TnI at 16 h post-PCI (−3.4%, p = 0.81), in TnI at 24 h post-PCI (−1.4%, p = 0.93), in peak TnI (−1.5%, p = 0.92), in the AUC over 24 h for TnI (−27.2%, p = 0.19), and in CK-MB at 16 h (−7.0%, p = 0.50) and at 24 h (−4.7%, p = 0.64) post-PCI after pre-treatment with inclacumab 5 mg/kg (Tables 2 and 3).

Efficacy of inclacumab 20 mg/kg. Treatment with inclacumab 20 mg/kg resulted in placebo-adjusted geometric mean percent changes in TnI of −24.4% at 24 h (p = 0.05) (Table 2, Fig. 2) and −22.4% at 16 h (p = 0.07). The addition of the patients who had cardiac biomarker measurements but did not receive the infusion to the analysis of the primary endpoint yielded identical results. Peak TnI and the AUC for TnI were also lower compared with placebo (−23.8%, p = 0.05 and −33.9%, p = 0.08, respectively (Table 3). Likewise, inclacumab was associated with placebo-adjusted geometric mean percent changes in CK-MB of −17.4% at 24 h (p = 0.06) and −16.3% at 16 h (p = 0.09) (Fig. 3). The incidence of increases in CK-MB greater than 3 times the upper limit of normal was 18.3% in the placebo group and 8.9% with inclacumab 20 mg/kg (p = 0.05).

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Table 2 Primary Efficacy Parameters: Change in Troponin I at 16 and 24 h

Troponin I	Placebo (n = 115)	Inclacumab 5 mg/kg (n = 95)	Inclacumab 20 mg/kg (n = 112)
Baseline GM (interquartile range)	1.03 (0.24–4.69)	0.71 (0.17–3.44)	0.82 (0.19–3.73)
16 h post-PCI GM	1.74 (n = 114)	1.30 (n = 94)	1.09 (n = 108)
Adjusted GM percent change from baseline to 16 h	77.4	71.3	37.6
Placebo-adjusted GM percent change at 16 h	—	−3.4	−22.4
95% CI		−27.2 to 28.2	−40.8 to 1.7
p value		0.81	0.07
24 h post-PCI GM	1.76 (n = 104)	1.21 (n = 92)	0.99 (n = 101)
Adjusted GM percent change from baseline to 24 h	57.7	55.5	19.1
Placebo-adjusted GM percent change at 24 h	—	−1.4	−24.4
95% CI		(−26.7 to 32.7)	(−43.1 to 0.4)
p value		0.93	0.05
Placebo-adjusted GM percent change at 24 h			
Diabetic patients		−29.0 (n = 23)	−33.2 (n = 24)
95% CI		−63.5 to 38.0	−65.4 to 29.0
p value		0.31	0.23
Nondiabetic patients		−4.2 (n = 69)	−31.6 (n = 77)
95% CI		−32.5 to 36.0	−51.3 to −3.9
p value		0.81	0.03
Periprocedural IIb/IIIa inhibition		43.4% (n = 15)	−12.3% (n = 20)
95% CI		−32.1 to 202.5	−56.2 to 75.5
p value		0.34	0.71
No periprocedural IIb/IIIa inhibition		−18.5% (n = 77)	−36.1% (n = 81)
95% CI		−41.9 to 14.1	−54.1 to −11.0
p value		0.23	0.01

CI = confidence interval; GM = geometric mean; PCI = percutaneous coronary intervention.

The effect of inclacumab 20 mg/kg was similar in patients with or without diabetes. Placebo-adjusted changes in TnI at 16 and 24 h were −29.0% (p = 0.03) and −36.1% (p = 0.01), respectively, in patients not treated with glycoprotein 2b3a inhibitors (n = 264) and −0.8% (p = 0.98) and −12.3%, respectively (p = 0.71) in the others (n = 58). Corresponding changes in CK-MB were −20.3% (p = 0.05) and −23.1% (p = 0.02) without background 2b3a inhibition and +6.9% (p = 0.78) and −17.8% (p = 0.42) in those also treated with a IIb/IIIa inhibitor.

Safety. Overall, 22.6% of the patients who received study medication (N = 530) reported at least 1 serious adverse event, and the percentages of serious adverse events were 18.3%, 24.0%, and 25.6% in the placebo, inclacumab 5 mg/kg, and 20 mg/kg groups, respectively (Table 4). Most adverse events were of mild or moderate intensity and resolved without sequelae. Overall, the pattern and nature of adverse events were similar in the placebo and the active treatment groups. No clinically significant or dose-related abnormalities were found on electrocardiography or vital signs, and no dose-related abnormalities were reported in laboratory parameters. There were no apparent effects on infection rates or bleeding. The number of major adverse cardiovascular events, including deaths, nonfatal myocardial infarctions, strokes, and cardiac arrests (reported events were independently adjudicated), was small. There were 0, 4, and 2 deaths in the placebo, inclacumab 5 mg/kg, and inclacumab 20 mg/kg groups, respectively.

Plasma soluble P-selectin levels. In the subset of patients participating in the optional substudy (n = 177), only the higher dose of inclacumab demonstrated a significant effect on soluble P-selectin levels at 8 h. Placebo-adjusted geometric mean percent changes were −9.5% with inclacumab 5 mg/kg (n = 53, p = 0.25) and −22.0% with inclacumab 20 mg/kg (n = 63, p < 0.01) (Fig. 4).

Discussion

This randomized, placebo-controlled international multicenter phase 2 study tested the specific P-selectin monoclonal antibody inclacumab given as a single injection before coronary angiography and ad hoc PCI in patients with NSTEMI. Inclacumab at a dose of 20 mg/kg was found to consistently reduce TnI and CK-MB levels post-PCI, although the results were of borderline statistical significance. Similarly, the incidence of CK-MB increases >3 times the upper limit of normal was reduced with inclacumab 20 mg/kg compared with placebo. Inclacumab at the same dose was also found to reduce significantly the plasma level of soluble P-selectin. These are encouraging results supporting beneficial biological effects of this P-selectin antagonist, which need to be confirmed in a larger clinical trial.

Table 3 Secondary Efficacy Parameters: Changes in Troponin I and CK-MB

	Placebo (n = 115)	Inclacumab 5 mg/kg (n = 95)	Inclacumab 20 mg/kg (n = 112)
CK-MB			
Baseline geometric mean (IQR)	9.46 (3.60–23.70)	7.54 (2.70–15.50)	7.97 (3.10–17.85)
8 h post-PCI GM	9.29 (n = 113)	7.28 (n = 93)	7.25 (n = 110)
Adjusted GM percent change from baseline to 8 h	3.6	−5.1	−8.6
Placebo-adjusted GM percent change at 8 h	—	−8.5	−11.9
95% CI		−23.6 to 9.7	−25.8 to 4.8
p value		0.34	0.15
16 h post-PCI GM	9.57 (n = 114)	7.93 (n = 94)	7.29 (n = 108)
Adjusted GM percent change from baseline to 16 h	6.5	−1.0	−10.9
Placebo-adjusted GM percent change at 16 h	—	−7.0	−16.3
95% CI	—	−25.0 to 15.2	−31.9 to 2.7
p value		0.50	0.09
24 h post-PCI GM	8.07 (n = 104)	6.57 (n = 92)	5.83 (n = 102)
Adjusted GM percent change from baseline to 24 h	−15.0	−19.0	−29.8
Placebo-adjusted GM percent change at 24 h	—	−4.7	−17.4
95% CI	—	−22.3 to 16.9	−32.1 to 0.4
p value		0.64	0.06
Peak TnI geometric mean	2.09	1.56	1.34
Placebo-adjusted GM percent change in peak TnI	—	−1.5	−23.8
95% CI		−26.3 to 31.6	−42.2 to 0.5
p value		0.92	0.05
TnI area under the curve GM	40.37	28.87	26.35
Placebo-adjusted GM percent change in TnI area under the curve (over 24 h)	—	−27.2	−33.9
95% CI		−54.8 to 17.2	−58.1 to 4.3
p value		0.19	0.08
Adjusted GM percent change in TnI from baseline to 8 h	58.9	51.8	27.4
Placebo-adjusted GM percent change in TnI at 8 h	—	−4.5	−19.8
95% CI	—	−25.9 to 23.2	−37.1 to 2.3
p value		0.72	0.08

CK-MB = creatine kinase-myocardial band; TnI = troponin I; other abbreviations as in Tables 1 and 2.

Myocardial damage after PCI. PCI can induce an inflammatory response (16,17), even during apparently uneventful procedures. Damage to the vascular wall during intervention leads to activation of endothelial cells, leukocytes, and platelets (6,7,16,17). Statins have been shown in small clinical studies to reduce TnI release after PCI, both in patients with stable coronary disease and after ACS (18–21), and this benefit has been attributed to their anti-inflammatory activity. Similarly, an anti-inflammatory viral serpin has been shown to reduce the release of myocardial damage markers after PCI in a small clinical trial (15). P-selectin antagonism has been shown in multiple animal studies to decrease the adhesion of neutrophils and platelets and the accumulation of macrophages after arterial injury (10–13). More specifically, inclacumab reduces neutrophil activation (CD11b expression) and platelet-leukocyte aggregates by as much as 95% (data on file, F. Hoffmann-La Roche). The latter effect on platelet-leukocyte aggregates may contribute to a reduction in the risk of microembolization during PCI and could account at least in part for the reduction in levels of myocardial damage markers seen in patients treated with inclacumab 20 mg/kg.

Safety of inclacumab. Inclacumab appeared to have been tolerated well in the SELECT-ACS trial, although the percentage of patients with serious adverse events was

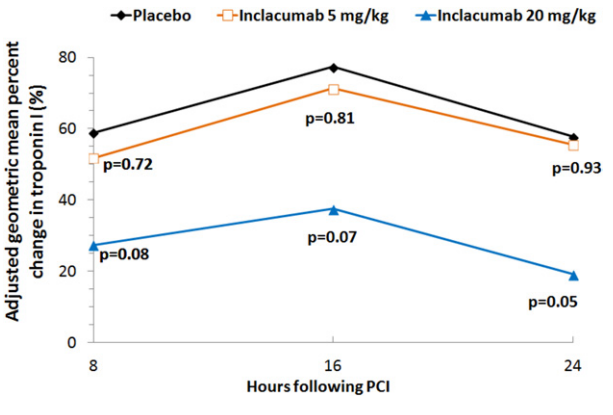

Figure 2 Percent Change in Troponin I Over Time

The **black line** represents placebo, the **orange line** represents inclacumab 5 mg/kg, and the **blue line** represents inclacumab 20 mg/kg. PCI = percutaneous coronary intervention.

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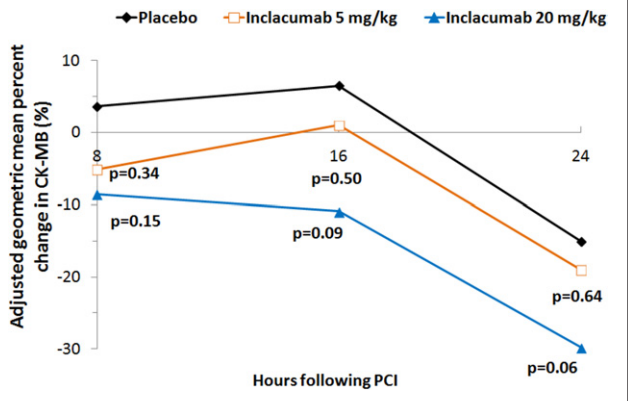

Figure 3 Percent Change in CK-MB Over Time

The **black line** represents placebo, the **orange line** represents inclacumab 5 mg/kg, and the **blue line** represents inclacumab 20 mg/kg. CK-MB = creatine kinase-myocardial band; PCI = percutaneous coronary intervention.

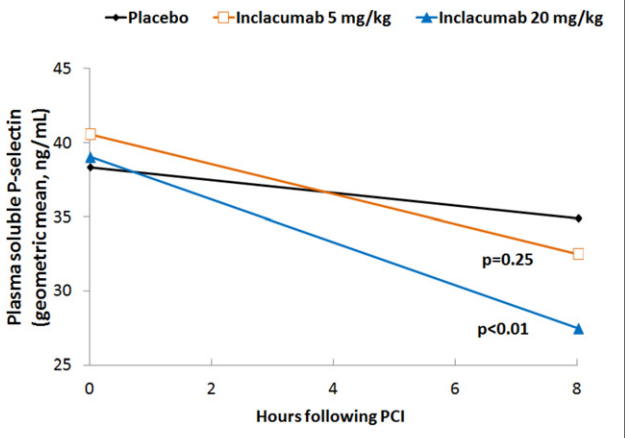

Figure 4 Change in Plasma-Soluble P-Selectin at 8 h Post-PCI

The **black line** represents placebo, the **orange line** represents inclacumab 5 mg/kg, and the **blue line** represents inclacumab 20 mg/kg. PCI = percutaneous coronary intervention.

numerically higher in those treated with inclacumab. Despite the role of the P-selectin pathway in the interactions between endothelium, leukocytes, and platelets, inclacumab was not associated with infections and bleeding. The number of major adverse cardiovascular events was small; 4 deaths occurred in the inclacumab 5 mg/kg group, 2 in the inclacumab 20 mg/kg group, and none in the placebo group. There was also a numerical excess of myocardial infarctions (4, 7, and 2 myocardial infarctions, respectively) reported as cardiovascular events; the significance of this in unclear and could have been related to the way in which periprocedural myocardial infarctions were reported by some investigators or to the play of chance. Indeed, the incidence of CK-MB increases >3 times the upper limit of normal was reduced in the inclacumab 20 mg/kg group compared with the placebo group (8.9% vs. 18.3%).

Study limitations. Efficacy analyses were conducted in patients who received the infusion, underwent PCI, and had TnI levels available at baseline and follow-up; this was not an intention-to-treat analysis involving all patients randomized in the study. The amount of myocardium at risk was not specifically measured in this study. Also, we did not collect the time between hospital admission and PCI. The SELECT-ACS trial was not powered for the evaluation of clinical endpoints. Although TnI and CK-MB are reliable biomarkers of myocardial damage, the clinical significance of post-PCI elevations remains open to

Table 4 Safety Summary

	Placebo (n = 175)	Inclacumab 5 mg/kg (n = 179)	Inclacumab 20 mg/kg (n = 176)	All (N = 530)
No. of treatment emergent SAEs	49	63	66	178
Patients with at least 1 treatment emergent SAE	32 (18.3)	43 (24.0)	45 (25.6)	120 (22.6)
Patients with SAE leading to study drug interruption or withdrawal	0 (0.0)	1 (0.6)	4 (2.3)	5 (0.9)
No. treatment emergent AEs	332	396	330	1,058
Patients with treatment emergent infection	21 (12.0)	19 (10.6)	19 (10.8)	59 (11.1)
Patients with AE occurring within 24 h of infusion start	57 (32.6)	61 (34.1)	56 (31.8)	174 (32.8)
Patients with bleeding at up to 30 days	6 (3.4)	9 (5.0)	5 (2.8)	20 (3.8)
Patients with bleeding at up to 120 days	9 (5.1)	11 (6.1)	7 (4.0)	27 (5.1)
Occurrence of major bleed at 120 days	3 (1.7)	1 (0.6)	2 (1.1)	6 (1.1)
All-cause death	0	4	2	6
Nonfatal MI*	2	4	7	13
Stroke	0	0	1	1
Hospitalized for ACS >24 h	2	1	1	4
Resuscitated cardiac arrest	1	2	1	4
Patients with at least 1 revascularization procedure	20	31	22	73
Patients with hospitalization for CHF	0	2	0	2
Renal failure	1	1	1	3

Values are n or n (%). *Some periprocedural myocardial infarctions were reported as nonfatal MIs according to the investigator's judgment.
ACS = acute coronary syndrome; AE = adverse event; CHF = congestive heart failure; MI = myocardial infarction; SAE = serious adverse event.

debate. Nevertheless, this study supports that P-selectin antagonism with inclacumab has favorable biological effects in patients with NSTEMI undergoing PCI. Although only the higher dose of inclacumab provided benefits on myocardial damage biomarkers, the results were concordant with the reduction in soluble levels of P-selectin with the 20 mg/kg dose.

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.

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Key Words: inclacumab ■ myocardial infarction ■ percutaneous coronary intervention ■ P-selectin.