

Randomized Trial of Atopaxar in the Treatment of Patients With Coronary Artery Disease

The Lessons From Antagonizing the Cellular Effect of Thrombin—Coronary Artery Disease Trial

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Background—Thrombin is a key mediator of platelet activation. Atopaxar is a reversible protease-activated receptor-1 antagonist that interferes with thrombin-mediated platelet effects. The phase II Lessons From Antagonizing the Cellular Effect of Thrombin—Coronary Artery Disease (LANCELOT-CAD) trial examined the safety and tolerability of prolonged therapy with atopaxar in subjects with CAD.

Methods and Results—Subjects with a qualifying history were randomized in a double-blind fashion to 3 dosing regimens of atopaxar (50, 100, or 200 mg daily) or matching placebo for 24 weeks and followed up for an additional 4 weeks. The key safety end points were bleeding according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Thrombolysis in Myocardial Infarction (TIMI) classifications. Secondary objectives included platelet aggregation and major adverse cardiac events. Seven hundred and twenty subjects were randomized. Overall bleeding rates tended to be higher with atopaxar compared with placebo by CURE criteria (placebo, 0.6%; atopaxar, 3.9%; relative risk, 6.82, $P=0.03$; 50 mg, 3.9%; 100 mg, 1.7%; 200 mg, 5.9%; P for trend=0.01) and TIMI criteria (placebo, 6.8%; atopaxar, 10.3%; relative risk, 1.52, $P=0.17$; 50 mg, 9.9%; 100 mg, 8.1%; 200 mg, 12.9%; P for trend=0.07). There was no difference in major bleeding. Major adverse cardiac events were numerically lower in the atopaxar subjects. All atopaxar regimens achieved high levels of platelet inhibition. A transient elevation in liver transaminases and dose-dependent QTc prolongation without apparent complications were observed in higher-dose atopaxar treatment groups.

Conclusions—In this dose-ranging study of patients with CAD, treatment with atopaxar resulted in platelet inhibition, more minor bleeding, and numerically but not statistically fewer ischemic events. Larger-scale trials are needed to determine whether these patterns translate into clinically meaningful effects.

Clinical Trial Registration—URL: <http://www.ClinicalTrials.gov>. Unique identifier: NCT00312052.

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Key Words: anticoagulants ■ blood platelets ■ clinical trials ■ coronary artery disease
■ platelet aggregation inhibitors ■ stroke

The addition of the P2Y₁₂ antagonist clopidogrel to augment aspirin has demonstrated clear benefit in patients with acute coronary syndromes (ACS),^{1,2} with even more intensive P2Y₁₂ blockade demonstrating even greater reductions in cardiovascular ischemic events, but with more

bleeding.³⁻⁵ However, the benefit of intensification of antiplatelet therapy in the secondary prevention of patients with chronic manifestations of coronary heart disease is less certain. The largest trial of more intensive antiplatelet therapy, Clopidogrel for High Atherosclerotic Risk and Ischemic

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Stabilization Management and Avoidance (CHARISMA), found that the addition of clopidogrel to aspirin in patients with or at high risk for developing atherosclerotic vascular disease did not significantly improve overall clinical outcomes.⁶ However, subsequent analysis of the CHARISMA trial suggested that patients with symptomatic vascular disease, particularly with prior myocardial infarctions, had a substantial benefit from intensification of antiplatelet therapy.⁷ Compared with ACS, patients with chronic coronary artery disease (CAD) are at lower immediate risk for recurrent ischemic events; therefore, clinicians caring for patients with chronic CAD may be less tolerant of bleeding side effects when balancing the risks and benefits of intensification of therapy.

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For these reasons, additional targets for antiplatelet therapy in chronic CAD are desirable. One promising target is inhibition of the protease-activated receptor-1 (PAR-1).⁸ Thrombin is a serine protease that plays multiple roles in the hemostatic process and is a potent activator of platelets at the site of arterial thrombotic events.⁹ Protease-activated receptor-1 is the principal receptor on human platelets responsible for activation by thrombin.¹⁰ Although circulating thrombin is broadly active in hemostasis, platelet aggregation stimulated by thrombin interaction with PAR-1 is less involved in primary hemostasis^{11,12}; therefore, therapies selectively targeting this receptor may be particularly attractive in chronic CAD. One such PAR-1 inhibitor, vorapaxar (SCH 530348), is currently in phase III development and is being tested in chronic atherosclerosis¹³ and ACS.¹⁴

Atopaxar (E5555) is a novel, potent, selective, more rapidly reversible small-molecule selective PAR-1 antagonist that has demonstrated substantial antiplatelet effect in healthy volunteers beyond therapy with aspirin and clopidogrel.¹⁵ We sought to evaluate the safety and tolerability of various doses of atopaxar in patients with chronic CAD in the Lessons From Antagonizing the Cellular Effect of Thrombin (LANCELOT)-CAD Trial. This trial was conducted in parallel with a phase II trial of atopaxar in patients with ACS, the LANCELOT-ACS trial (www.clinicaltrials.gov; unique identifier, NCT00548587).

Methods

Study Design and Participants

The LANCELOT-CAD trial was a multicenter, randomized, double-blind, placebo-controlled trial of atopaxar versus placebo that randomized 720 subjects at 136 study centers in 11 countries between September 13, 2007, and August 14, 2009. Subjects 45 to 80 years of age with a history of high-risk CAD were eligible for the study. High-risk CAD was defined as CAD manifest by any of the following: (1) previous ACS (including myocardial infarction or unstable angina) at least 4 weeks previously, (2) percutaneous coronary revascularization at least 12 weeks previously, and (3) angina with documented ischemia by provocative testing or angiographically evident CAD (>70%) and at least 1 high-risk indicator (high-sensitivity C-reactive protein >3.0 mg/L, diabetes mellitus, peripheral arterial disease, stroke [>1 year earlier], or carotid arterial disease) at the time of enrollment. Subjects must have been receiving antiplatelet therapy with aspirin (75 to 325 mg daily) and/or a thienopyridine (clopidogrel or ticlopidine) for 1 month before screening.

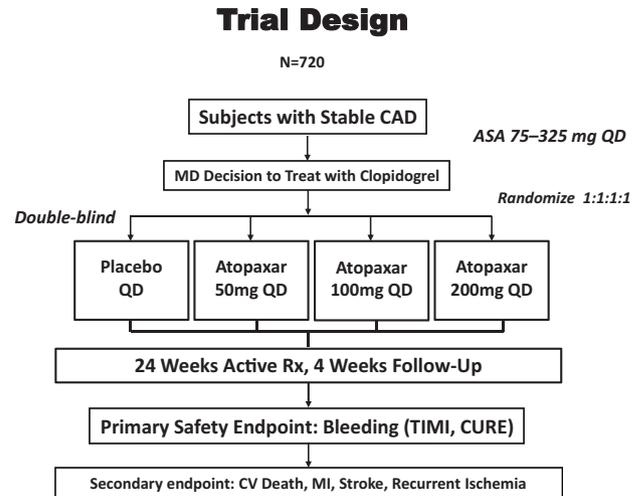


Figure 1. Protocol design for Lessons From Antagonizing the Cellular Effect of Thrombin-Coronary Artery Disease (LANCELOT-CAD). ASA indicates aspirin; QD, once daily; MACE, major adverse cardiovascular events; CV, cardiovascular; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; and CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events.

Key exclusion criteria included increased risk of bleeding (bleeding diathesis, major trauma or surgery within 30 days, pathological bleeding within 6 months, history of intracranial or retinal hemorrhage, stroke or transient ischemic attack within 1 year, known intracranial vascular pathology, international normalized ratio >1.5, partial thromboplastin time >1.5 times the upper limit of normal [ULN], platelet count <100 000 per μ L, hemoglobin <10 g/dL), New York Heart Association class III or IV congestive heart failure, cardiovascular instability as evidenced by events or cardiovascular medication dose modifications within 30 days of screening, surgery within 30 days of screening or planned during the course of the study, alanine aminotransferase or aspartate aminotransferase >3 times the ULN, total bilirubin >1.5 times the ULN, and creatinine clearance <30 mL/min. The following medications were prohibited during the 30 days before screening and for the duration of the study: oral antiplatelet agents other than aspirin (\leq 325 mg daily), clopidogrel (75 mg daily), or ticlopidine (250 mg twice daily); oral anticoagulants; fibrinolytics; long-term nonsteroidal antiinflammatory drugs or cyclooxygenase-2 inhibitors; potent and moderate CYP 3A4 inhibitors; or other investigational agents. All subjects had to provide written informed consent. The study was performed in accordance with local institutional review or ethics regulations and was registered (www.clinicaltrials.gov; number, NCT00312052).

Study Procedures

The trial was conducted in 4 periods: screening (day -21 to -1), baseline (day 1), treatment (day 1 to week 24), and follow-up off study medication (week 24 to 28). Subjects were randomly assigned at baseline to either placebo or 1 of 3 dosing regimens of atopaxar (50, 100, or 200 mg daily) in a 1:1:1:1 fashion (Figure 1). The initial design of the study planned for 600 subjects to be randomized. During the course of the study, fewer patients had participated in the platelet study than anticipated, and enrollment was increased to 720 subjects to allow inclusion of the full population of 80 subjects planned to be enrolled in the pharmacokinetic/pharmacodynamic substudy. Subjects were to be evaluated at baseline; weeks 1, 2, and 4; and every 4 weeks thereafter until week 28. At each visit, subjects had assessment of clinical end points and adverse events, physical examinations, laboratory testing, and resting 12-lead ECG. For subjects in the pharmacodynamic study, additional visits for assessment of drug levels and platelet function measures were held during week 25. Platelet aggregation was assessed in 80 subjects by light transmission aggregometry to thrombin receptor-activating peptide

15 $\mu\text{mol/L}$ at selected study sites with appropriate facilities. Tracings were verified by blinded reviewers at Java Clinical Research (Dublin, Ireland). Results are expressed as percent inhibition of final platelet aggregation. An independent Data Monitoring Committee reviewed unblinded safety information at predefined time points to ensure the safety of subjects participating in the study.

Study Outcomes

The primary objective of the study was to assess the safety of atropaxar compared with placebo. The key measures were the proportion of subjects with any bleeding event meeting Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Thrombolysis in Myocardial Infarction (TIMI) criteria through week 24. CURE bleeding events were further subclassified as major (life-threatening or non-life-threatening) or minor according to standard designations. The TIMI bleeding criteria were classified as major, minor, and minimal (requiring medical attention or not requiring medical attention). Comparisons are made between the placebo group, each atropaxar treatment group, and the combined atropaxar group.

The key secondary end point of the study was to assess the efficacy of atropaxar compared with placebo by comparing the proportion of subjects with major adverse cardiovascular events (MACEs) through week 24. The MACEs were defined as the composite of cardiovascular death, myocardial infarction, stroke, or refractory ischemia. Additional secondary efficacy end points included the individual components of the MACE composite. Additional secondary study measures included platelet function test results, ECG parameters (including QT interval [QTc]), safety laboratory values, and adverse events.

Clinical events were adjudicated by an independent Clinical Events Committee at the Cleveland Clinic Cardiovascular Coordinating Center by physicians unaware of the treatment assignments.

Statistical Considerations

The study was designed as a dose-ranging pilot study to evaluate the safety and tolerability of atropaxar and to inform decision making regarding a large trial powered for clinical events. By definition, such a trial is not powered for modest differences in either efficacy or safety events. An original sample size of 600 subjects would provide 80% power to detect a 64% reduction in high-sensitivity C-reactive protein.

Efficacy analyses were conducted in the intention-to-treat cohort, which included all randomized subjects who signed informed consent and had any follow-up visit. Two of 720 subjects did not meet these criteria, and are not included in the intention-to-treat population. Safety analyses were planned to be performed in a safety cohort receiving at least 1 dose of study medication, although all subjects in the intention-to-treat cohort met the criteria for the safety cohort.

Baseline characteristics are presented as counts and percentages for categorical variables and means (SDs) for continuous variables. Clinical events are incidences, presented as proportions for the placebo group, the combined atropaxar group, and each individual dosing group, and expressed as a relative risk (RR) estimate accompanied by a 2-sided exact *P* value and exact 95% confidence limits based on the Agresti-Min method. The exact Cochran-Armitage trend test was used to assess for trends across the active treatment arms. All tests were performed as 2 sided, and an α level of 0.05 was considered significant. No multiplicity corrections were performed. Statistical analyses were performed with SAS software (SAS Institute, Inc., Cary, NC).

The study was funded by Eisai Incorporated (Tokyo, Japan). The study was designed as a collaborative effort between the Steering Committee and the sponsor. The academic authors wrote all drafts of the manuscript and take responsibility for its content. The TIMI Study Group received the full trial database and independently verified key analyses (C.F.C.). The sponsor was, by contract, allowed to review the manuscript and provide comments but had no editorial authority.

Results

Subjects and Disposition

Overall, 720 subjects were randomized, including 1 subject who withdrew consent after the baseline visit and 1 subject

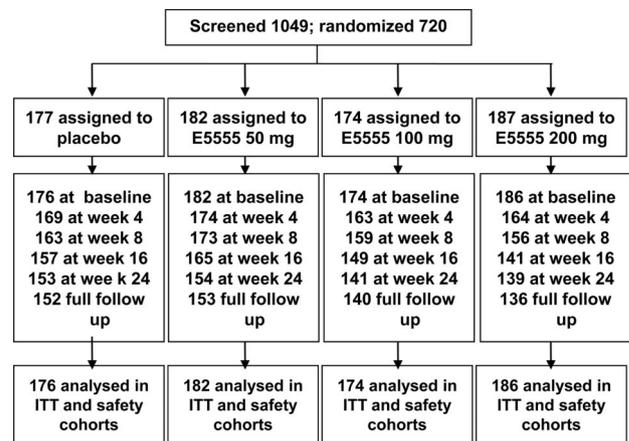


Figure 2. Consort diagram. Flow of subjects through the Thrombolysis in Myocardial Infarction (TIMI) trial indicating the number of subjects with follow-up at the given time points and the number included in analytic cohorts.

who was discontinued by the investigator at the baseline visit. All remaining subjects received at least 1 dose of study drug; therefore, the intention-to-treat and safety populations consist of 718 subjects (Figure 2). The duration of complete follow-up by treatment arm is displayed in Figure 2. A total of 6 subjects were lost to follow-up during the study.

Baseline and Procedural Characteristics

The baseline characteristics (Table 1) were balanced across treatment arms. Because of the enrichment criteria, prior diabetes mellitus and stroke were common. Patients were well treated with nearly universal use of aspirin, and $\approx 40\%$ of subjects received clopidogrel. Guideline-based therapies, β -blockers, inhibitors of the renin-angiotensin-aldosterone system, and lipid-lowering agents were used in most subjects.

Safety and Tolerability

The results of the key safety analyses are shown in Table 2 and Figure 3. Similar results were observed with both bleeding criteria. When bleeding was categorized with the CURE bleeding criteria, there was a higher rate of bleeding with atropaxar than placebo (3.9% versus 0.6%; RR, 6.82; 95% confidence interval, 1.17 to 94.0; $P=0.03$), with a trend toward more bleeding across higher doses of atropaxar (P for trend=0.01). There was no difference in CURE major bleeding (Table 2).

Bleeding assessed by the TIMI criteria showed a tendency toward higher rates of overall bleeding with atropaxar than placebo (10.3% versus 6.8%; RR, 1.52; 95% confidence interval, 0.85 to 2.76; $P=0.17$). Indeed, a general pattern of greater bleeding with higher doses of atropaxar (P for trend across doses=0.072) was also observed, with the highest rate of bleeding in subjects randomized to 200 mg daily. However, this excess in bleeding was nearly completely driven by TIMI minimal bleeding. There was no difference observed in TIMI major or TIMI minor bleeding; rates of such events were low in all treatment groups. A total of 3 subjects across all atropaxar therapy arms had TIMI major bleeding (0.6%), including 1 subject with hemorrhagic stroke in the 200-mg dose group. Examination of a subset of TIMI minimal bleeds,

Table 1. Baseline Characteristics

	Atopaxar					Study Total (n=720)
	Placebo (n=177)	50 mg (n=182)	100 mg (n=174)	200 mg (n=187)	Active Total (n=543)	
Demographics, %						
Age ≥65 y, %	47	48	42	49	47	47
Age (median), y	63	64	62	64	64	64
Weight (median), kg	86	90	90	89	90	89
White race, %	98	93	95	94	94	95
Women, %	24	25	25	22	24	24
Prior MI, %	62	65	64	62	64	63
Prior PCI, %	62	63	62	66	64	63
Prior CABG, %	46	37	45	42	41	43
Known coronary stenosis >70%, %	72	75	78	75	76	75
Prior stroke/TIA, %	11	9	12	11	11	11
Diabetes mellitus, %	63	71	64	69	68	67
Prior CHF, %	16	14	12	17	14	15
Current smoker, %	15	19	17	24	20	19
Concomitant medications, %						
Aspirin	95	90	95	91	92	93
Clopidogrel	36	44	34	42	40	39
RAA agents	80	79	81	83	81	81
β-blockers	78	85	79	75	80	79
CCB	28	32	25	33	30	29
Lipid lowering	93	93	97	95	95	94
Region of enrollment, %						
WE/NA	79	77	78	79	78	78
EE	14	15	16	15	15	15
Asia Pacific	7	8	7	6	7	7

MI indicates myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; CHF, congestive heart failure; RAA, rennin-angiotensin-aldosterone agents; CCB, calcium channel blockers; WE, Western Europe; NA, North America; and EE, Eastern Europe.

those requiring medical evaluation or treatment, demonstrated a higher rate in atopaxar-treated patients, particularly in subjects receiving the highest-dose regimen. The size of the trial precludes meaningful subgroup analysis of bleeding. In an exploratory analysis, patients receiving aspirin and clopidogrel had higher absolute rates of TIMI bleeding, and the point estimate of the RR was greater with atopaxar compared with placebo (13.6 versus 7.7; RR, 1.8; 95% confidence interval, 0.8 to 4.4; $P=0.21$) compared with those treated without clopidogrel (8.1 versus 6.3; RR, 1.3; 95% confidence interval, 0.6 to 2.8; $P=0.56$), although no interaction between treatments was observed.

More subjects discontinued study treatment in the atopaxar treatment groups overall than in placebo treatment (Table 2). However no significant difference was observed in the discontinuation of study drug for treatment emergent adverse events or bleeding.

Efficacy

Major adverse cardiovascular events were infrequent overall, as would be expected in a chronic CAD population. Efficacy results are summarized in Table 2 and Figure 4. There was no

significant difference in the combined MACE end point between the combined atopaxar treatment arms and placebo (2.6% versus 4.6%; RR, 0.57; 95% confidence interval, 0.25 to 1.35; $P=0.20$). However, each atopaxar dosing arm had numerically fewer MACEs than placebo. There was no apparent relationship of higher atopaxar doses with improved efficacy because the lowest event rate occurred in the lowest (50 mg) treatment arm. A single subject died of pancreatic cancer during the study 47 days after discontinuation of study therapy. No cardiovascular deaths were observed. The majority of clinical events were recurrent ischemia, which demonstrated a pattern of efficacy similar to the overall composite. No significant differences were observed in markers of inflammation between active treatment and placebo.

Platelet Function Testing and Inflammatory Markers

A total of 80 subjects participated in the platelet function testing portion of LANCELOT-CAD. Treatment with atopaxar resulted in dose-dependent inhibition of thrombin receptor-activating peptide stimulated platelet aggregation (Figure 5). With single first doses of 100 or 200 mg atopaxar,

Table 2. Key Safety (Bleeding) and Efficacy (Major Adverse Cardiac Events) and Tolerability End Points

	Placebo (n=176), n (%)	Atopaxar, n (%)				Active Total (n=542)	P
		50 mg (n=182)	100 mg (n=174)	200 mg (n=186)			
Safety							
Any CURE bleeding	1 (0.6)	7 (3.9) P=0.04	3 (1.7) P=0.33	11 (5.9) P=0.004	21 (3.9) RR = 6.82 (1.17–94.0) P=0.03		0.010
Major	0 (0)	2 (1.1) P=0.21	0 (0) ...	3 (1.6) P=0.11	5 (0.9) ...		0.14
Minor	1 (0.6)	5 (2.8) P=0.13	3 (1.7) P=0.33	8 (4.3) P=0.02	16 (3.0) RR = 5.2 (0.89–69.7) P=0.08		0.039
Any TIMI bleeding	12 (6.8)	18 (9.9) P=0.31	14 (8.1) P=0.69	24 (12.9) P=0.053	56 (10.3) RR = 1.52 (0.85–2.76) P=0.17		0.072
Major	0 (0)	2 (1.1) P=0.21	0 (0) ...	1 (0.5) P=0.52	3 (0.6) ...		0.86
Minor	0 (0)	1 (0.6) P=0.52	0 (0) ...	2 (1.1) P=0.23	3 (0.55) ...		0.18
Minimal	12 (6.8)	15 (8.2) P=0.63	14 (8.1) P=0.69	21 (11.3) P=0.14	50 (9.2) P=0.33		0.14
Minimal requiring medical attention	1 (0.6)	6 (3.3) P=0.07	3 (1.7) P=0.33	11 (5.9) P=0.004	20 (3.7) RR = 6.49 (1.12–89.5) P=0.03		0.006
Bleeding resulting in study drug discontinuation	1 (0.6)	3 (1.65) P=0.53	0 (0) P=0.52	3 (1.61) P=0.53	6 (1.1) RR = 1.95 (0.30–24.5) P=0.59		0.78
Efficacy							
MACE	8 (4.6)	3 (1.7) P=0.13	5 (2.9) P=0.53	6 (3.2) P=0.54	14 (2.6) RR = 0.57 (0.25–1.35) P=0.20		0.77
CV death	0 (0)	0 (0) ...	0 (0) ...	0 (0) ...	0 (0)
Myocardial infarction	2 (1.1)	1 (0.6) P=0.60	2 (1.2) P=1.0	1 (0.5) P=0.6	4 (0.7) P=0.73		0.69
Stroke	0 (0) ...	0 (0) ...	0 (0) ...	1 (0.5) P=0.52	1 (0.2) ...		0.26
Recurrent ischemia	6 (3.4)	2 (1.1) P=0.14	3 (1.7) P=0.37	4 (2.2) P=0.53	9 (1.7) RR = 0.49 (0.18–1.36) P=0.17		0.67
Recurrent ischemia requiring revascularization	2 (1.1)	2 (1.1) P=1.0	2 (1.1) P=1.0	0 (0) P=0.15	4 (0.7) RR = 0.65 (0.14–3.22) P=0.73		0.23

(Continued)

Table 2. Continued

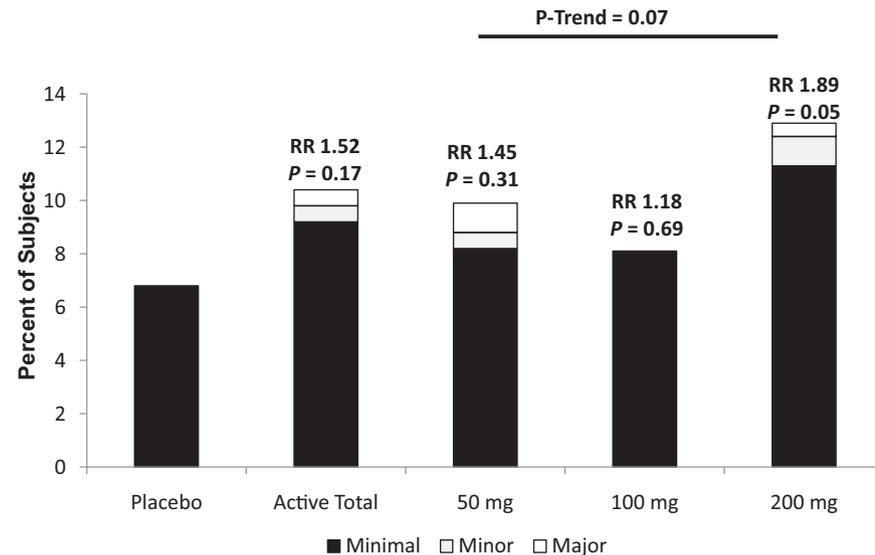
	Placebo (n=176), n (%)	Atopaxar, n (%)				P
		50 mg (n=182)	100 mg (n=174)	200 mg (n=186)	Active Total (n=542)	
Tolerability						
Discontinued from Study	24 (13.6)	29 (15.9) <i>P</i> =0.56	34 (19.5) <i>P</i> =0.14	50 (26.9) <i>P</i> =0.002	113 (20.8) <i>P</i> =0.03	<0.001
Study drug discontinuation for AE	11 (6.3)	18 (9.9) <i>P</i> =0.21	18 (10.3) <i>P</i> =0.18	21 (11.3) <i>P</i> =0.09	57 (10.5) <i>P</i> =0.09	0.15

CURE indicates Clopidogrel in Unstable Angina to Prevent Recurrent Events; CI, confidence interval; TIMI, Thrombolysis in Myocardial Infarction; MACE, major adverse cardiovascular events; CV, cardiovascular; and AE, adverse events. *P* versus placebo, active total lists. Relative risk (RR), 95% confidence interval (in parentheses), and *P* value indicates RR and CI were not calculable owing to a 0 cell in the comparator group.

rapid and nearly complete inhibition of platelet aggregation (IPA) was achieved within 4 to 6 hours. With these doses of atopaxar, 90% and 96% mean IPA, respectively, was achieved, and high levels were maintained for 24 hours. In subjects treated with 50 mg, 38% IPA was achieved by 4 to 6 hours, but inhibition diminished over time and was indistinguishable from placebo by 24 hours. After 2 weeks (and

through 7 weeks) of daily dosing, all treatment groups had high levels of IPA with nearly complete inhibition of thrombin receptor-activating peptide-induced platelet aggregation, although in contrast with 100- and 200-mg dosing, 50-mg dosing continued to have a demonstrable daily dosing effect, with peak and trough levels differing after each daily dose. At study completion, offset was observed with each dose regi-

TIMI Criteria Bleeding



CURE Criteria Bleeding

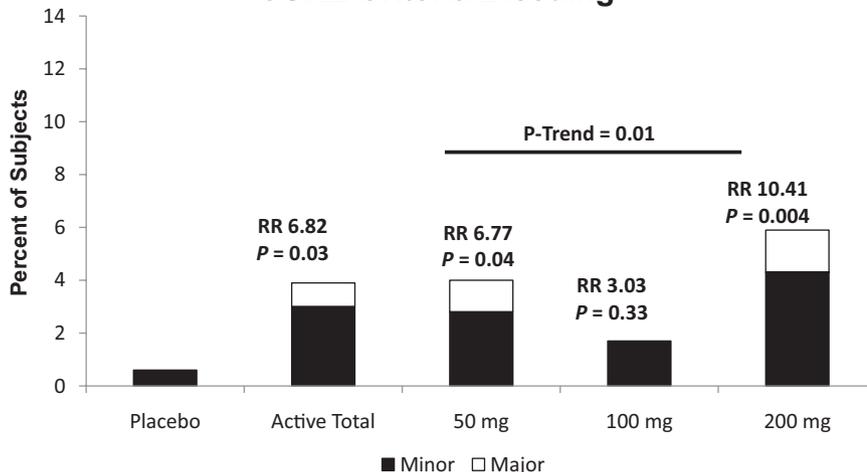


Figure 3. Safety events. Top, Percent of subjects with bleeding events using Thrombolysis in Myocardial Infarction (TIMI) criteria. *P* values are listed for overall (major, minor, or minimal) in each treatment group. **Bottom,** Percent of subjects with bleeding events using Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) criteria. *P* values are listed for overall (major or minor) in each treatment group. Individual relative risks and *P* values are in comparison to placebo. Trend *P* values are across all groups.

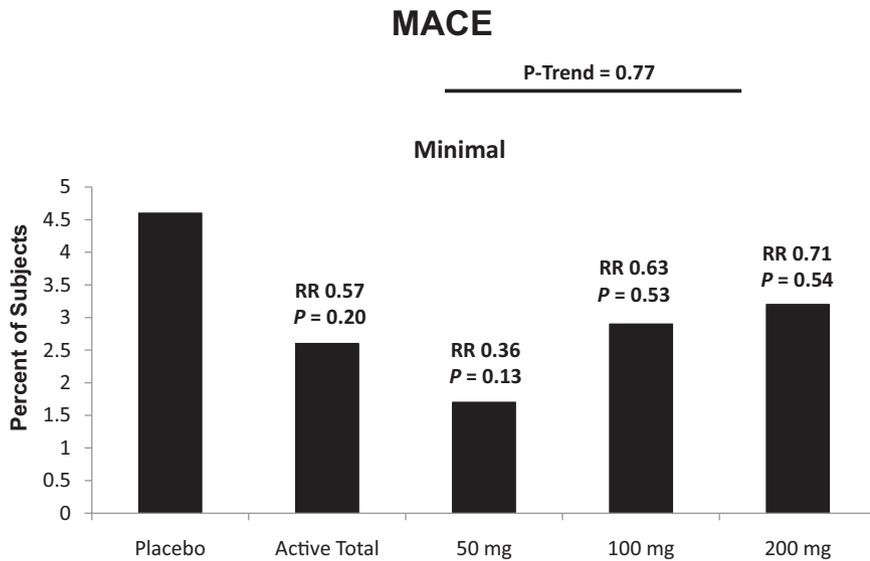


Figure 4. Efficacy events. Comparison of major adverse cardiovascular events (MACEs) by treatment group. Individual relative risks (RRs) and *P* values are in comparison to placebo. Trend *P* values are across all groups.

men. By day 3 after the final dose, subjects receiving 50 mg were indistinguishable from placebo-treated subjects, whereas 100 and 200 mg remained with high levels of antiplatelet activity. By day 7 after treatment cessation, patients treated with 100 mg atopaxar had levels of IPA similar to those of placebo-treated subjects, whereas subjects receiving 200 mg remained with significantly higher levels of IPA.

Markers of inflammation were measured in the entire study population. Overall, there were no consistent trends for an anti-inflammatory effect of atopaxar as measured by high-sensitivity C-reactive protein, placental growth factor, myeloperoxidase, and interleukin-6, -18, and -1 β . The platelet-inflammatory biomarker CD-40 ligand tended to be lower in atopaxar-treated patients.

Adverse Effects

Two significant, off-target effects were noted. First, patients treated with atopaxar tended to have more frequent elevation of liver enzymes (Table 3). Elevations of alanine aminotransferase >3 times the ULN and >5 times the ULN were observed more frequently than with placebo treatment, particularly with higher-dose atopaxar. These elevations most

commonly occurred at week 8, and tended to be transient. No subject developed liver failure or laboratory values meeting the Hy's law (alanine aminotransferase >3 times the ULN and total bilirubin >2 times the ULN).

In addition, there were modest increases in QTcF with the active treatment compared with placebo (Table 4), particularly in the higher-dose atopaxar arms. However, prolongations beyond 500 milliseconds and prolongations of >30 and >60 milliseconds were infrequent, and no consistent patterns of treatment-related excess emerged.

Discussion

We report the primary results of the LANCELOT-CAD trial, the largest reported study of a PAR-1 antagonist in a chronic CAD population. Escalating doses of atopaxar appeared to result in more overall bleeding in a dose-dependent fashion, but severe bleeding was infrequent in all treatment groups and was not increased with atopaxar. Although not powered for clinical efficacy events, patients treated with atopaxar had numerically fewer ischemic events during the course of the trial, without a clear dose-response relationship. Platelet

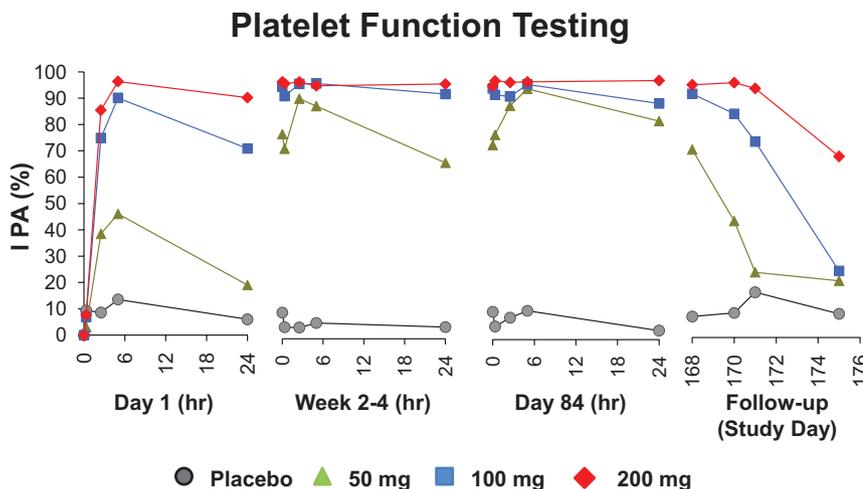


Figure 5. Platelet inhibition. Percent inhibition of platelet aggregation (IPA) to thrombin receptor-activating peptide (15 μ mol/L) at each time point. Number of subjects with evaluable baseline: placebo, 15; 50 mg, 14; 100 mg, 15; and 200 mg, 19.

Table 3. Incidence of Liver Function Abnormalities During Study

	Placebo (n=176), n (%)	Atopaxar, n (%)			P
		50 mg (n=182)	100 mg (n=174)	200 mg (n=186)	
ALT $\geq 3 \times$ ULN	0	2 (1.1)	5 (2.9)	11 (5.9)	<0.0001
ALT $> 5 \times$ ULN	0	0	3 (1.7)	6 (3.2)	0.0015
ALT $> 8 \times$ ULN	0	0	1 (0.6)	1 (0.5)	0.38
AST $> 3 \times$ ULN	0	2 (1.1)	3 (1.7)	7 (3.8)	0.0041
AST $> 5 \times$ ULN	0	0	3 (1.7)	1 (0.5)	0.42
AST $> 8 \times$ ULN	0	0	2 (1.1)	0	1.00
Total bilirubin $> 1.5 \times$ ULN	1 (0.6)	2 (1.1)	0 (0)	2 (1.1)	0.77
Total bilirubin $> 2 \times$ ULN	0 (0)	0 (0)	0 (0)	1 (0.5)	0.26

ALT, alanine aminotransferase; ULN, upper limit of normal; and AST, aspartate aminotransferase.

function studies revealed that atopaxar inhibits thrombin receptor-activating peptide-induced platelet aggregation to high levels in a dose-dependent and reversible fashion. At higher doses (100 and 200 mg), subjects treated with atopaxar had higher rates of elevations of liver enzymes and modest prolongation of QTcF, but without clinical adverse outcomes. These findings are consistent with previously reported data for atopaxar in 263 subjects with CAD studied with a similar design in Japan in the Japanese LANCELOT-CAD trial.¹⁶

The primary goal of LANCELOT-CAD was to assess the safety and tolerability of atopaxar in patients with stable CAD. The key safety metric was bleeding. Neither a significant increase nor a clear trend was observed in TIMI major, TIMI minor, or CURE major bleeding, although few overall events were observed. There was a signal for increased nonsevere bleeding, as evidenced by higher rates of TIMI minor and aggregate TIMI or CURE bleeding episodes, particularly among those receiving the highest dose, 200 mg/d. These data suggest that the range of doses tested in LANCELOT-CAD are biologically active and relevant in the clinical setting and may help guide dose selection for future study.

The Safety of SCH 530348 in Subjects Undergoing Non-Emergent Percutaneous Coronary Intervention (TRA-PCI)

study with vorapaxar reported similar data with numerically increasing rates of TIMI major or minor bleeding with escalating doses but no significant difference from placebo.¹⁷ Mechanistic data from preliminary investigations suggest that PAR-1 antagonism should not promote pathological bleeding or prolong bleeding time.¹² How then do we integrate these findings with the basic mechanisms? Data from the early clinical experiences with vorapaxar, and now with atopaxar, are not conclusive at this time, with small numbers of patients exposed and few serious bleeding episodes reported, so it remains possible that these agents will not increase overall severe bleeding. The lack of clear increases in severe bleeding with either agent is encouraging for the clinical future of PAR-1 antagonism in general and for these compounds. In LANCELOT-CAD, the trend toward greater rates of nonsevere bleeding could be a harbinger of risk for more severe bleeding in larger-scale trials. For instance, no significant difference in TIMI major or minor bleeding with prasugrel compared with clopidogrel was observed in the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 phase II trial, but higher rates of nonserious bleeding were observed.¹⁸ In the well-powered phase III Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON)-TIMI 38, increased rates of TIMI major bleeding were demonstrated with prasugrel.⁴ Although PAR-1 signaling may not play a major role in primary hemostasis, inhibiting this pathway in the setting of aspirin and thienopyridine therapy may accentuate the effects of inhibiting yet another key platelet signaling. Larger trials powered for meaningful differences in clinically significant bleeding events are needed to understand how the basic mechanism of PAR-1 antagonists will translate to clinical tolerability. Such trials are now ongoing with vorapaxar and should serve to prove or refute this conceptual framework of separation between anti-ischemic efficacy and bleeding risk.^{13,14}

Additional and unexpected safety signals emerged from the trial data. Increases in liver transaminases were seen more frequently in patients treated with atopaxar compared with placebo; this appeared to be dose dependent, with the highest rates of liver function abnormalities seen in the highest-dose atopaxar treated patients. Importantly, no subjects experienced severe liver dysfunction, and none met the Hy's law (> 3 times the ULN and total bilirubin > 2 times the ULN). Similarly, dose-related but modest levels of prolongation of

Table 4. Incidence of QTcF Abnormalities at Week 24 or Last Observation Carried Forward

	Placebo (n = 175)	Atopaxar			Active Total (n = 526)	P*
		50 mg (n = 181)	100 mg (n = 168)	200 mg (n = 177)		
Mean (SD)	415 (29)	410 (28)	416 (31)	414 (30)	413 (30)	0.67
> 450 ms, %	19 (11)	13 (7)	17 (10)	18 (10)	48 (9)	0.55
> 500 ms, %	3 (1.7)	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)	0.37
Change from baseline						
Mean (SD)	0.4 (20)	0.8 (22)	2.7 (23)	2.4 (24)	1.9 (23)	0.67
> 30 ms, %	8 (4.6)	15 (8.3)	14 (8.3)	18 (10.2)	47 (8.9)	0.07
> 60 ms, %	1 (0.6)	2 (1.1)	3 (1.8)	3 (1.7)	8 (1.5)	0.46

*Active total vs placebo.

QTcF were observed. Although few patients developed clinically significant prolonged QTcF, such signals in phase II trials deserve further exploration in dedicated studies and large-scale clinical trials. However, with small numbers of patients treated, these data raise a possible concern and require careful monitoring in larger-scale clinical trials to assess the true clinical importance.

The LANCELOT-CAD trial was not powered to detect a difference in MACEs, and, indeed, no significant difference was seen. However, rates of efficacy end points, particularly recurrent ischemia, were lower in all atropaxar groups than in the placebo group. There was no suggestion of improved efficacy with higher-dose atropaxar, with the lowest rate of MACEs observed in the 50-mg treatment arm. Although conclusions drawn from limited data should be viewed cautiously, one interpretation is that lower doses of atropaxar (50 to 100 mg) may be as effective as higher doses with a better overall safety and pharmacological profile, particularly in patients with chronic CAD in whom clinical event rates are low and the safety and tolerability of therapies may contribute to a greater extent to the risk/benefit profile than in the setting of ACS.

The platelet function study results highlight some of the key features of atropaxar that make this agent a potentially attractive PAR-1 antagonist for clinical practice. With higher-dose atropaxar, nearly complete inhibition of thrombin receptor-activating peptide-induced platelet aggregation was achieved within hours. These high levels of platelet inhibition were sustained throughout the treatment period. In contrast, 50 mg atropaxar resulted in modest levels of early platelet inhibition that was initially not sustained in the period immediately before the next dose, but achieved higher levels with repeated dosing. The lower doses of atropaxar demonstrated the pharmacodynamic reversibility of the drug, with complete offset apparent by 3 days with 50 mg and 7 days with 100 mg atropaxar. In contrast, studied doses of vorapaxar were reported to have a 50% platelet recovery after 4 weeks.¹² The dynamic range of effects of these doses suggests that it may be possible to achieve different goals with atropaxar, depending on the clinical circumstances (ie, rapid inhibition in the setting of ACS or percutaneous coronary intervention) and the ability to achieve relatively rapid offset in the setting of chronic therapy in the event of bleeding or need for elective surgery. Biomarker analyses did not support a clinically meaningful antiinflammatory effect in this setting.

Overall, the LANCELOT-CAD trial, by providing data about on- and off-target safety measures, a suggestion of clinical efficacy, and the pharmacology of atropaxar, meets the goals of a successful phase II clinical trial of a novel antiplatelet agent. This study has defined 50 to 200 mg atropaxar as a dynamic range that provides high levels of inhibition of platelet aggregation with dose-dependent onset and offset and, as a result of both efficacy and safety results, provides guidance for potential future investigation. Only large-scale, well-powered clinical trials will determine whether these findings translate into a clinically important target to improve the care of patients with cardiovascular diseases.

Appendix

The members of the Operations and Steering Committees of the LANCELOT-ACS trial were as follows (local investigators listed separately in the online-only Data Supplement Appendix). The number of subjects enrolled in each enrolling country listed in parentheses. D.L. Bhatt (Principal Investigator); M.D. Flather (Co-Principal Investigator); M.L. O'Donoghue (Investigator); S.D. Wiviott (Investigator). **Steering Committee:** Argentina (60) - F. Cura, Australia (52) - P. Aylward, Belgium (14) - D. Schoors, Canada (135) - S. Goodman, Czech Republic - P. Jansky, France - G. Montalescot, Germany (8) - U. Zeymer, Hungary (30) - M. Keltai, Italy - M. Valgimigli, Israel (15) - V. Guetta, Netherlands (9) - A. Withagen, Poland (77) - D. Dudek, South Africa - L. Burgess, Sweden - O. Hansen, United Kingdom (11) - M. Flather, United States (309) - D.L. Bhatt. **ECG Core Lab:** S. Goodman. **Platelet Function Core Lab:** D. Fitzgerald. **Data Safety Monitoring Board:** R. Becker (Chair), F. Spencer, K. Lee, F. Verheugt, J. Weitz, C.P. Cannon (1st meeting only). **Clinical Events Committee:** Chairs: A. Askari, V. Menon. Members: I. Ahmad, M. Akhtar, B. Austin, E. Gorodeski, C. Sila, Staff: N. Pasca, K. Brown, L. Schultz, Cleveland Clinic.

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Disclosures

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CLINICAL PERSPECTIVE

Thrombin is a key mediator of platelet activation in acute coronary syndromes. Atopaxar is a reversible protease-activated receptor antagonist that interferes with thrombin mediated platelet effects. The phase II Lessons From Antagonizing the Cellular Effect of Thrombin–Coronary Artery Disease (LANCLOT–CAD) trial examined the safety and tolerability of prolonged therapy with atopaxar in subjects with CAD. Seven hundred and twenty subjects were randomized in a double-blind fashion to 1 of 3 dosing regimens of atopaxar (50, 100, or 200 mg daily) or matching placebo for 24 weeks and followed up for an additional 4 weeks. Overall bleeding rates tended to be higher with atopaxar compared with placebo by Clopidogrel in Unstable Angina to Prevent Recurrent Events and Thrombolysis in Myocardial Infarction criteria without a difference in major bleeding by either category. All atopaxar regimens achieved high levels of platelet inhibition with dose-dependent rapid onset and offset. Major adverse cardiac events tended to be less frequent with atopaxar, but the trial was not powered for clinical events, and statistically significant differences were not observed. Atopaxar was generally well tolerated, but QTc prolongations and liver transaminase elevations without clinical sequelae were observed with higher-dose atopaxar. Although these data are encouraging, larger-scale trials are needed to determine the clinical efficacy and safety of protease-activated receptor-1 antagonism in patients with atherosclerotic vascular disease.

On-Line Supplementary Appendix: LANCELOT CAD sites with at least one subject enrolled:

Argentina: E. Blumberg, F. Cura, J. Fuselli, O. D. Manuale, E. Perna, A. Sosa Liprandi, **Australia:** C. Beauloye, P. Carroll, D. Colquhoun, A. Dart, J. Horowitz, J. Karrasch, L. Mahar, D. Roberts, A. Sinhal, J. Waites, **Belgium:** J. Dens, D. El Allaf, D. Schoors, **Canada:** M. Baird, M. Boulianne, P. Costi, I. Dattani, D. Hambly, T. Huynh, S. Jolly, S. Kouz, R. Labonté, G. Moe, S. Nawaz, M. O'Mahony, Y. Pesant, P. Thérout, L. Title, **Germany:** O. Bruder, M. Buerke, R. Erbel, J. Harenberg, H. Heuer, S. Kaab, S. Konstantinides, M. Oeff, U. Tebbe, U. Zeymer, **Hungary:** M. Keltai, R. Kiss, L. Márk, A. Ronaszeki, T. A. Sipos, A. Vértes, **Israel:** S. Banai, M. Gellerman, S. Gottlieb, M. Shechter, A. Solodky, **Netherlands:** M. Daniels, F.R. den Hartog, M. van Hessen, R. Van Stralen, A. Voogel, A. Withagen, **Poland:** J. Bychowski, D. Dudek, P. Kolodziej, J. Kopaczewski, A. Korzeniowski, P. Kurek, W. Piotrowski, L. Polonski, Z. Reszka, M. Trusz-Gluza, P. Wojewoda, **United Kingdom:** M. Flather, R. MacWalter, M. Pye, D. Roberts, S. Saltissi, R. Senior, **United States:** J. Anderson, D. Angiolillo, R. Ashley Jr, S. Bailey, M. Barber, E. Bates, S. Benjamin, S. Bimson, J. Bisognano, G. Brooks, J. Clower, III, Y. Cohen, N. Dashevsky, P. Dugano-Daphnis, W. Ellison, R. Foster, W. George, J. Gilbert, I. Gilchrist, R. Giusti, E. Goudreau, F. Gredler, D. Gupta, T. Hack, E. Hage-Korban, H. Herrmann, D. Hotchkiss, R. Jackson, D. Jinich, A. Kabour, Z. S. Kahn, Y. Katsnelson, R. Katz, M. Litt, H. Lui, P. R. Myers, V. Nadar, R. Nielsen, S. Oparil, P. Ouyang, G. E. Platt, R. Prasad, C. Rodriguez-Fierro, A. Salacata, N. Sandoval, M. Sharma, J. Soufer, A. Sprague, F. St. Goar, N. K. Tahirkheli, U. Thadani, S. Thew, K. J. Tucker, K. Vora, S. Wagner, W. Wainwright, R. Weiss, W. Wu

새로운 항혈소판제 'Atopaxar'를 포함한 삼제요법은 과연 효과적이고 안전한가?

권 준 교수 인하대병원 심장내과

Summary

배경

Thrombin은 혈소판 활성화에 중요한 매개체 역할을 하는데, atopaxar은 단백질분해효소 활성수용체 1(protease activated receptor-1, PAR-1)에 대한 가역적 길항제로 thrombin 매개성 혈소판 활성화를 억제한다. 이번 Phase II Lessons From Antagonizing the Cellular Effect of Thrombin-Coronary Artery Disease(LANCELOT-CAD) 임상연구는 atopaxar를 장기적으로 복용하고 있는 관동맥질환자를 대상으로 atopaxar 치료의 안전성과 내약성을 살펴보고자 하였다.

방법 및 결과

자격심사를 거친 환자들은 atopaxar 용량(1일 50, 100, or 200mg)에 따라 3개의 복용군과 위약군으로 이중맹검 방식으로 무작위 배정된 후 24주간 투약하였으며, 그 후 4주간 더 추적관찰하였다. 확인하고자 한 중요한 안전성 증점은 CURE(Clopidogrel in Unstable Angina to Prevent Recurrent Events)와 TIMI(Thrombolysis in Myocardial Infarction) 분류에 따른 출혈 부작용이었으며, 2차 목적으로 혈소판 응집반응과 심장사건 발생을 관찰하였다. 총 11개국 136개 센터에서 720명의 환자가 모집되었으

며, 전체적으로 위약군에 비하여 atopaxar 복용군에서 CURE(위약군, 0.6%; atopaxar 복용군, 3.9%; relative risk, 6.82; $P=0.03$; 50mg, 3.9%; 100mg, 1.7%; 200mg, 5.9%; P for trend=0.01)와 TIMI 분류(위약군, 6.8%; atopaxar 복용군, 10.3%; relative risk, 1.52; $P=0.17$; 50mg, 9.9%; 100mg, 8.1%; 200mg, 12.9%; P for trend=0.07)에 따른 출혈 발생 빈도가 모두 높은 것으로 나타났다. 그러나 대출혈 발생 빈도는 유의한 차이를 보이지 않았다. 주요 심장사건 발생 빈도는 atopaxar 복용군에서 수적으로 적었다. 세 가지 atopaxar 요법 모두 혈소판 억제효과가 상당히 높은 것으로 나타났으며, 고용량 복용군에서는 일시적 간효소 수치 증가와 용량에 의존적인 QTc 연장이 관찰되었다.

결론

관동맥질환자에서의 atopaxar 선량범위 연구결과 atopaxar 치료 후 혈소판 억제효과는 증가되며, 통계적 의의는 없지만 허혈성 사건 발생이 수적으로 감소하고, 소출혈 발생빈도는 증가하였다. 그러나 이러한 결과들에 대한 임상적 의의를 얻기 위해서는 더 많은 환자들을 대상으로 한 대규모 임상연구가 필요할 것으로 사료된다.

Commentary

혈소판은 죽상혈전증(atherothrombosis) 발생 기전에 중심적 역할을 한다. 따라서 죽상동맥경화증 환자의 가장 중요한 치료 타겟이다. 현재 급성 관동맥증후군이나 협심증 환자의 치료 가이드라인에 아스피린과 P2Y12 수용체 길항제 등의 항혈소판제가 포함되어 있다. 그러나 기존의 항혈소판제는 혈소판 활성화에 또 하나의 중요한 매개체가 되는 thrombin 수용체를 차단하지 못한다. 따라서 기존의 항혈소판제 치료에도 불구하고 혈소판은 여전히 thrombin 수용체를 통한 활성화 가능성을 가지게 된다. 이는 아마도 관동맥질환자에서 기존의 2제 요법 치료에도 불구하고 혈소판 활성화로 인한 심혈관사건이 발생하는 이유로 생각된다. Thrombin은 혈소판 표면에 있는 PAR-1 수용체에 대한 매개체 역할을 통하여 혈소판을 활성화한다. 따라서 PAR-1 수용체를 차단함으로써 thrombin 매개성 혈소판 활성화를 억제할 수 있음이 제시된 바 있으며, atopaxar가 이에 해당되는 새로운 항혈소판제이다. Atopaxar는 생체 내 시험연구를 통해서 강력하고 빠르게 그리고 가역적으로 PAR-1 수용체를 억제함으로써 출혈시간의 연장 없이 아스피린과 clopidogrel 이상의 항혈소판 효과를 가지고 있음이 규명된 바 있다.

본 LANCELOT-CAD 연구는 Phase II 임상연구로 주목적은 관동맥질환자들을 대상으로 세 가지 용량(50mg, 100mg, 200mg)의 atopaxar 치료에 대한 안전성과 내약성을 보고자 한 연구이다. 안전성의 주 척도는 출혈인데 전체적으로 위약군에 비해 atopaxar 복용군에서 특히, 고용량군에서 출혈 발생빈도가 증가하는 것으로 나타났다. 대출혈 발생빈도는 유의한 차이를 보이지 않았다. 그러나 본 연구의 atopaxar 복용군에서의 소출혈 발생빈도 증가라는 결과를 가볍게 보지 말아야 할 것으로 생각된다. 왜냐하면, 과거에도 phase II JUMBO-TIMI 26 임상연구에서 위약군에 비하여 prasgurel 복용군에서 단지 경증 출혈 발생빈도가 높은 것으로 나타났음에도 불구하고, phase III TRITON-TIMI 38 임상연구에서는 prasgurel 복용군에서 TIMI 대출혈 발생빈도가 높은 것

으로 나타난 바 있기 때문이다. 안전성에서 우려할 만한 다른 사건들은 고용량 환자에서 일시적으로 증가한 간효소 수치와 비록 수는 작지만 용량에 의존적으로 나타난 QTc 연장이다. 이러한 두 가지 부작용 모두 대규모 임상연구를 통해 조심스럽게 확인해봐야 할 것으로 사료된다.

주요 심장사건 발생 빈도는 atopaxar 복용군에서 수적으로 낮게 나왔을 뿐 통계적으로 유의하지 않았으며, 본 연구가 임상적 사건 발생을 보기 위한 효과적인 연구가 아니라 점을 감안한다면 이 결과에 크게 의미를 둘 필요는 없는 것으로 판단된다. 그럼에도 불구하고 모든 atopaxar 복용군에서 반복적인 허혈증상이 위약군보다 적게 나타난 것은 다소 고무적인 결과라 할 수 있다. 마지막으로, 혈소판 억제효과는 세 가지 용량 모두에서 증가하였으며 작용 발현 및 회복 시간은 용량에 의존적인 것으로 나타났다.

본 연구결과는 새로운 항혈소판제에 대한 Phase II 임상연구 목적이 잘 부합되는 성공적인 결과인 동시에 죽상혈전증 치료에 있어 기존의 2제 요법에 추가적인 항혈소판 치료제로써의 atopaxar의 매력과 가능성을 보여준 연구결과이기도 하다. 그러나 이번 연구결과에서 제시된 atopaxar의 효용 가능성에 대한 임상적 적용을 위해서는 향후 더 많은 환자들을 대상으로 한 대규모의 임상연구가 필요할 것으로 사료된다.