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

Stephen D. Wiviott, MD; Marcus D. Flather, MD; Michelle L. O’Donoghue, MD, MPH; Shinya Goto, MD; Desmond J. Fitzgerald, MD; Fernando Cura, MD; Philip Aylward, BM, BCh, PhD; Victor Guetta, MD; Dariusz Dudek, MD; Charles F. Contant, PhD; Dominick J. Angiolillo, MD, PhD; Deepak L. Bhatt, MD, MPH; on behalf of the LANCELOT–CAD Investigators

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 using 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
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. 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. 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.

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). 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. Protease-activated receptor-1 is the principal receptor on human platelets responsible for activation by thrombin. Although circulating thrombin is broadly active in hemostasis, platelet aggregation stimulated by thrombin interaction with PAR-1 is less involved in primary hemostasis; 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 atherosclerosis and ACS.

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. 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 (at least 4 weeks previously, (2) percutaneous coronary revascularization (1) previous ACS (including myocardial infarction or unstable angina)

**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...
Study Outcomes

The primary objective of the study was to assess the safety of atopaxar 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 atopaxar treatment group, and the combined atopaxar group.

The key secondary end point of the study was to assess the efficacy of atopaxar 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 safety studies 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 atopaxar 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 atopaxar 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 Cochrane-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 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 ≈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 atopaxar 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 atopaxar (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 atopaxar 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 atopaxar (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 atopaxar 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>
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<th>Dose Group</th>
<th>Randomized Subjects</th>
<th>Follow-Up</th>
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<td>182</td>
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<td>Placebo analyses</td>
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<tr>
<td>Atopaxar 100 mg</td>
<td>184</td>
<td>184</td>
<td>Placebo analyses</td>
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<tr>
<td>Atopaxar 200 mg</td>
<td>187</td>
<td>187</td>
<td>Placebo analyses</td>
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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.

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Randomized Subjects</th>
<th>Follow-Up</th>
<th>Bleeding Analysis</th>
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<td>Atopaxar 200 mg</td>
<td>187</td>
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<td>Placebo analyses</td>
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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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=176), n (%)</th>
<th>Atopaxar, n (%)</th>
<th>50 mg (n=182)</th>
<th>100 mg (n=174)</th>
<th>200 mg (n=186)</th>
<th>Active Total (n=542)</th>
<th>P</th>
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<tr>
<td>Any CURE bleeding</td>
<td>1 (0.6)</td>
<td>7 (3.9)</td>
<td>3 (1.7)</td>
<td>11 (5.9)</td>
<td>21 (3.9)</td>
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<td></td>
<td>P=0.04</td>
<td>P=0.33</td>
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<td>RR = 6.82 (1.17–94.0)</td>
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<td>Major</td>
<td>0 (0)</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>5 (0.9)</td>
<td>0.14</td>
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<tr>
<td></td>
<td>P=0.21</td>
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<td>P=0.11</td>
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<td>P=0.22</td>
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<tr>
<td>Minor</td>
<td>1 (0.6)</td>
<td>5 (2.8)</td>
<td>3 (1.7)</td>
<td>8 (4.3)</td>
<td>16 (3.0)</td>
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<td></td>
<td>P=0.13</td>
<td>P=0.33</td>
<td>P=0.02</td>
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<td>RR = 5.0 (0.89–69.7)</td>
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<tr>
<td>Any TIMI bleeding</td>
<td>12 (6.8)</td>
<td>18 (9.9)</td>
<td>14 (8.1)</td>
<td>24 (12.9)</td>
<td>56 (10.3)</td>
<td>0.072</td>
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<td></td>
<td>P=0.31</td>
<td>P=0.69</td>
<td>P=0.053</td>
<td></td>
<td></td>
<td>RR = 1.52 (0.85–2.76)</td>
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<tr>
<td>Major</td>
<td>0 (0)</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
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<td>P=0.38</td>
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<tr>
<td>Minor</td>
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<td>1 (0.6)</td>
<td>0 (0)</td>
<td>2 (1.1)</td>
<td>3 (0.55)</td>
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<td></td>
<td>P=0.52</td>
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<td>P=0.23</td>
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<tr>
<td>Minimal</td>
<td>12 (6.8)</td>
<td>15 (8.2)</td>
<td>14 (8.1)</td>
<td>21 (11.3)</td>
<td>50 (9.2)</td>
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<tr>
<td></td>
<td>P=0.63</td>
<td>P=0.69</td>
<td>P=0.14</td>
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<td>Minimal requiring medical attention</td>
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<td>6 (3.3)</td>
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<td>P=0.07</td>
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<td>RR = 6.49 (1.12–89.5)</td>
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<tr>
<td>Bleeding resulting in study drug discontinuation</td>
<td>1 (0.6)</td>
<td>3 (1.65)</td>
<td>0 (0)</td>
<td>3 (1.61)</td>
<td>6 (1.1)</td>
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<td>P=0.52</td>
<td>P=0.53</td>
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<td>RR = 1.95 (0.30–24.5)</td>
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<td>MACE</td>
<td>8 (4.6)</td>
<td>3 (1.7)</td>
<td>5 (2.9)</td>
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<td>P=0.13</td>
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<td>RR = 0.57 (0.25–1.35)</td>
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<tr>
<td>Myocardial infarction</td>
<td>2 (1.1)</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
<td>1 (0.5)</td>
<td>4 (0.7)</td>
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<tr>
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<td>P=0.60</td>
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<td>1 (0.5)</td>
<td>1 (0.2)</td>
<td>0.26</td>
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<tr>
<td>Recurrent ischemia</td>
<td>6 (3.4)</td>
<td>2 (1.1)</td>
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<td>Recurrent ischemia requiring revascularization</td>
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<td>P=1.0</td>
<td>P=0.15</td>
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<td></td>
<td>RR = 0.65 (0.14–3.22)</td>
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(Continued)
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-

### Table 2. Continued

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<th>Placebo (n=176), n (%)</th>
<th>Atopaxar, n (%)</th>
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<td>29 (15.9)</td>
<td>34 (19.5)</td>
<td>50 (26.9)</td>
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<td>Study drug discontinuation for AE</td>
<td>11 (6.3)</td>
<td>18 (9.9)</td>
<td>18 (10.3)</td>
<td>21 (11.3)</td>
<td>57 (10.5)</td>
<td>0.15</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>P=0.21</td>
<td>P=0.18</td>
<td>P=0.09</td>
<td>P=0.09</td>
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</table>

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.

### TIMI Criteria Bleeding

![TIMI Criteria Bleeding](image)

**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.
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 highsensitivity C-reactive protein, placental growth factor, myeloperoxidase, and interleukin-6,-18, and -1. 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
nonsevere bleeding, as evidenced by higher rates of TIMI major bleeding were demonstrated with prasugrel.4 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 QTcF (Table 4) were observed in both placebo and atopaxar–treated subjects, with no differences between doses or placebo.17

**Table 3. Incidence of Liver Function Abnormalities During Study**

<table>
<thead>
<tr>
<th>Placebo (n = 176)</th>
<th>Atopaxar, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg (n = 182)</td>
<td></td>
</tr>
<tr>
<td>100 mg (n = 174)</td>
<td></td>
</tr>
<tr>
<td>200 mg (n = 186)</td>
<td></td>
</tr>
<tr>
<td><strong>ALT ≥3×ULN</strong></td>
<td>0 (2.1)</td>
</tr>
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<td><strong>ALT &gt;5×ULN</strong></td>
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</tr>
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<td><strong>ALT &gt;8×ULN</strong></td>
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<tr>
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<td>&gt;1.5×ULN</td>
<td>1 (0.6)</td>
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<td>&gt;2×ULN</td>
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ALT, alanine aminotransferase; ULN, upper limit of normal; and AST, aspartate aminotransferase.

Of note, a significant increase in liver transaminases was observed among patients treated with atopaxar (Table 3). Increases in transaminases were frequently noted 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 QTcF (Table 4) were observed in both placebo and atopaxar–treated subjects, with no differences between doses or placebo.17

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

<table>
<thead>
<tr>
<th>Atopaxar</th>
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<tbody>
<tr>
<td>Placebo (n = 175)</td>
</tr>
<tr>
<td>Mean (SD)</td>
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<tr>
<td>&gt;450 ms, %</td>
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*Active total vs placebo.*

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 QTcF (Table 4) were observed in both placebo and atopaxar–treated subjects, with no differences between doses or placebo.17

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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, 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
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 atopaxar groups than in the placebo group. There was no suggestion of improved efficacy with higher-dose atopaxar, 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 atopaxar (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 atopaxar that make this agent a potentially attractive PAR-1 antagonist for clinical practice. With higher-dose atopaxar, 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 atopaxar 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 atopaxar demonstrated the pharmacodynamic reversibility of the drug, with complete offset apparent by 3 days with 50 mg and 7 days with 100 mg atopaxar. 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 atopaxar, 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 atopaxar, meets the goals of a successful phase II clinical trial of a novel antiplatelet agent. This study has defined 50 to 200 mg atopaxar 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) - E. 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) - J. Dudek, South Africa - L. Burgess, Sweden - O. Hansen, United Kingdom (11) - M. Flather, United States (309) - D.L. Bhatt.

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.

Sources of Funding

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Disclosures

Dr Wiviott has received research funding from Eli Lilly, Daiichi Sankyo, and Schering Plough; consulting fees from Bristol Myers Squibb, Sanofi-aventis, AstraZeneca, ARENA, Medco; and independent continuing medical education speaking fees from Eli Lilly, Daiichi Sankyo, and Schering Plough. Dr Flather has received honoraria for participation at meetings related to the development of atopaxar and receives research grants and honoraria for speaker meetings and advisory boards from Sanofi-aventis, Bristol Myers Squibb, Eli Lilly, Daiichi Sankyo, Novartis, and GlaxoSmithKline. Dr O’Donoghue receives research grants from GlaxoSmithKline and Eisai and honoraria from Eli Lilly and Daiichi Sankyo (continuing medical education only). Dr Gozi has received research grants and honoraria from Sanofi-aventis, Eisai, and Otsuka and consulting fees from Merck and Eisai. Dr Fitzgerald reports honoraria from Eisai. Dr Aylward reports research grants and honoraria from Merck, and speakers bureau funding from Eisai, AstraZeneca, Boehringer Ingelheim, Sanofi-aventis, Merck, and Pfizer. Dr Dominick Angelillo reports honoraria for lectures from Bristol Myers Squibb, Sanofi-aventis, Eli Lilly and Co, and Daiichi Sankyo, Inc; consulting fees from Bristol-Myers Squibb, Sanofi-aventis, Eli Lilly Co, and Daiichi Sankyo, Inc, The Medicines Company, Portola, Novartis, Medicare, Accuremetric, Arena Pharmaceuticals, Merck, Evolva, and AstraZeneca; and research grants from GlaxoSmithKline, Bristol Myers Squibb, Sanofi-aventis, Otsuka, Boston Scientific, Eli Lilly and Co, Daiichi Sankyo, Inc, The Medicines Company, Portola, Accuremetrics, Schering-Plough, AstraZeneca, Eisai, and Johnson & Johnson. Dr Bhatt receives research grants from AstraZeneca, Bristol-Myers Squibb, Eisai, Sanofi-aventis, and The Medicines Company. The other authors report no conflicts.

References


**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 (LANCELOT–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.
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

Stephen D. Wiviott, Marcus D. Flather, Michelle L. O'Donoghue, Shinya Goto, Desmond J. Fitzgerald, Fernando Cura, Philip Aylward, Victor Guetta, Dariusz Dudek, Charles F. Contant, Dominick J. Angiolillo and Deepak L. Bhatt

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

새로운 항혈소판제 ‘Atopaxar’를 포함한 삼계요법은 과연 효과적이고 안전한가?

권 준 교수 인하대병원 심장내과

Summary

배경
Thrombin은 혈소판 활성화에 중대한 역할을 하는데, atopaxar는 단백분해효소 활성화수용체 1(protease activated receptor-1, PAR-1)에 대한 가역적 결합체로 thrombin 항성 제소산 활성화를 억제한다. 이번 Phase II Lessons From Antagonizing the Cellular Effect of Thrombin-Coronary Artery Disease(LANCELOT-CAD) 임상연구는 atopaxar를 장기적으로 복용하고 있는 임상
매질환자를 대상으로, atopaxar 치료의 안전성과 효능성
을 실험보고자 하였다.

방법 및 결과
자극심사를 거친 환자들은 atopaxar 용량(1일 50, 100, or 200mg)에 따라 3개의 복용군과 위약군으로 이중명
검 방식으로 무작위 배정된 후 24주간 투약하였으며, 그 후 4주간 더 추적관찰하였다. 확인하고자 한 중증의
안정성 병증은 CURE(Clopidogrel in Unstable Angina to Prevent Recurrent Events)와 TIMI(Thrombolysis in Myocardial Infarction) 분류에 따른 출혈 부작용이었으
며, 2차 목표로 혈소판 용접반응과 심장사전 발생을 관
찰하였다.

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 발생률이 모두 높은 것으로 나타났다. 그러나 대조
군 발생 반도는 유의한 차이를 보이지 않았다. 주요 심장
사전 발생 반도는 atopaxar 복용군에서 수적으로 적었다.
세 가지 atopaxar 요법 모두 혈소판 역제효과가 상당히
높은 것으로 나타났으며, 고용량 복용군에서는 일시적
간호소 수치 증가와 용량에 의존적인 Qτc 연장이 관찰되
았다.

결론
관동맥질환자에서의 atopaxar 선량범위 연구결과
atopaxar 치료 후 혈소판 역제효과는 증가하였으며,
통계적
의의는 없지만 혈행성 사전 발생이 수적으로 감소하고,
소출혈 발생반도는 증가하였다. 그러나 이러한 결과들에
대한 임상적 의의를 얻기 위해서는 더 많은 환자들을 대
상으로 한 대규모 임상연구가 필요할 것으로 사료된다.
Commentary

혈소판은 성혈혈관(atherothrombosis) 발생 기전에 중
심적 역할을 한다. 따라서 성혈중증후군 환자의 가장
중요한 치료 타깃이다. 현재 급성 관동맥경화증과 혈
심증 환자의 치료 가이드라인에 아스피린과 P2Y12 수용
체 결정제 등이 혈소판 작용을 완화시키는 효과가 있
다. 그러나 기
존의 항혈소판제는 혈소판 활성을 예 예사한 중요한 위
해가 되는 thrombin 수용체를 차단하지 못한다. 따라서
기존의 항혈소판제 치료에도 불구하고 혈소판은 여전
히 thrombin 수용체를 통해 활성화 가능성을 가지게 된
다. 이는 아마도 관동맥질환에서 기존의 2차 요법 치료
에도 불구하고 혈소판 활성화로 인한 심혈관사건이 발
생하는 이유로 생각된다. Thrombin은 혈소판 표면에 있
는 PAR-1 수용체에 대한 매개체 역할을 통하여 혈소판
을 활성화한다. 따라서 PAR-1 수용체를 차단함으로써
thrombin 매개된 혈소판 활성화를 억제할 수 있으며, atopia
pax가 이에 대응되는 새로운 항혈
소판제이다. AtoPax는 생물 내 시험 연구를 통해서 강력
하고итель적으로 PAR-1 수용체를 억제함
으로써 출혈시간의 연장 없이 아스피린과 dopidorg의 이
상의 항혈소판 효과를 가지고 있어 규명된 바 있다.
본 LANCELOT-CAD 연구는 Phase II 임상연구로 주목
적인 관동맥질환환자들을 대상으로 세 가지 용량(30mg, 100mg, 200mg)의 atopax의 치료에 대한 안전성과 내
악성을 보고한 연구이다. 안전성의 주 척도는 출혈인
데 전체적으로 위약군에 비해 atopax 복용군에서 특
히, 고용량군에서 출혈 발생빈도가 증가하는 것으로 나
타났지만, 대출혈 발생빈도는 유의한 차이를 보이지 않
았다. 그러나 본 연구의 atopax 복용군에서의 소출혈
발생빈도 증가라는 결과를 가볍게 보지 않아야 할으
로 생각된다. 때문에, 과거에도 phase II JUMBO–TIMI 26
임상연구에서 위약군에 비하여 prasugrel 복용군에
서 단지 경중 출혈 발생빈도가 높은 것으로 나타났음에
도 불구하고, phase III TRITON–TIMI 38 임상연구에서는
prasugrel 복용군에서 TIMI 대출혈 발생빈도가 높은 것
으로 나타난 바 있기에 때문이다. 안전성에서 우려할 만한
다른 사건들은 고용량 환자에서 일시적으로 증가한 간
효소 수치와 비록 수는 작지만 용량에 의존적으로 나타
난 QTC 연장이 있다. 이러한 두 가지 부작용 모두 대규모 임
상연구를 통해 조심스럽게 확인해야 할 것으로 사료된
다. 주요 심장사건 발생 비도는 atopax 복용군에서 수적으
로 낮게 나온을 뿐 통계적으로 유의하지 않았으며, 본 연
구가 임상적 사건 발생을 보기 위한 효과적인 연구가 아니라
면 검증할수록 이런 결과에 크게 의의를 두 필요는 없
는 것으로 판단된다. 그럼에도 불구하고 모든 atopax 복
용군에서 부작용이 현저한 하혈증상이 보이거나 보행
되는 것은 다르게 두고 결과에 미치는 영향은 유의적인 것으로 나타났다.
본 연구결과는 새로운 항혈소판제에 대한 Phase II 임상
연구 목적이 잘 부합되는 성공적인 결과인 동시에 작용
활성화한 기존의 2차 요법에 추가적인 항혈소
판 치료제로서의 atopax의 메커니즘과 가능성과 보고된 연
구결과는 이와 같다. 그러나 이번 연구결과에서 제시된
atopax의 효용 가능성에 대한 임상적 적용을 위해서는
향후 더 많은 환자들을 대상으로 한 대규모의 임상연구
가 필요할 것으로 사료된다.