Platelets play a key role in patients with an acute coronary syndrome, particularly in the early phases of the disease.1,2 Activated platelets release thromboxane A 2 (TXA 2), adenosine diphosphate (ADP), adenosine triphosphate, and thrombin, stimulating platelet activation and aggregation processes.3 Antiplatelet therapy is the cornerstone of treatment for patients with coronary artery disease.4 Currently, the combination of aspirin, an irreversible inhibitor of cyclooxygenase and a P2Y 12-ADP receptor inhibitor, is the antiplatelet treatment of choice in patients with acute coronary syndrome, where a fast and strong platelet inhibition is needed.5,6

Clopidogrel, the most worldwide used P2Y 12-ADP receptor antagonist, presents some limitations, such as high inter- and intraindividual variability or slow onset of action, despite loading dose (LD), which has been related with an increase of cardiovascular events.7-9 This finding has been overcome with new ADP-antagonists, like prasugrel or ticagrelor,10,11 However, evidence is lacking about the effects of achieving faster and stronger cyclooxygenase inhibition with intravenous lysine acetylsalicylate (LA) compared with oral aspirin on prasugrel-inhibited platelets.

Background—Prasugrel and ticagrelor, new P2Y 12-adenosine diphosphate receptor antagonists, are associated with greater pharmacodynamic inhibition and reduction of cardiovascular events compared with clopidogrel in patients with an acute coronary syndrome. However, evidence is lacking about the effects of achieving faster and stronger cyclooxygenase inhibition with intravenous lysine acetylsalicylate (LA) compared with oral aspirin on prasugrel-inhibited platelets.

Methods and Results—This was a prospective, randomized, single-center, open, 2-period crossover platelet function study conducted in 30 healthy volunteers. Subjects were randomly assigned to receive a loading dose of intravenous LA 450 mg plus oral prasugrel 60 mg or loading dose of aspirin 300 mg plus prasugrel 60 mg orally in a crossover fashion after a 2-week washout period between treatments. Platelet function was evaluated at baseline, 30 minutes, 1 h, 4 h, and 24 h using light transmission aggregometry and vasodilator-stimulated phosphoprotein phosphorylation. The primary end point of the study, inhibition of platelet aggregation after arachidonic acid 1.5 mmol/L at 30 minutes, was significantly higher in subjects treated with LA compared with aspirin: 85.3% versus 44.3%, respectively, P=0.003. This differential effect was observed at 1 hour (P=0.002) and 4 hours (P=0.048), but not at 24 hours. Subjects treated with LA presented less variability and faster and greater inhibition of platelet aggregation with arachidonic acid compared with aspirin.

Conclusions—The administration of intravenous LA resulted in a significant reduction of platelet reactivity compared with oral aspirin on prasugrel-inhibited platelets. Loading dose of LA achieves an earlier platelet inhibition and with less variability than aspirin.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02243137. (Circ Cardiovasc Interv. 2015;8:e002281. DOI: 10.1161/CIRCINTERVENTIONS.114.002281.)

Key Words: acute coronary syndrome ■ aspirin ■ lysine acetylsalicylate ■ platelet
WHAT IS KNOWN

- Antiplatelet therapy is the cornerstone of treatment for patients with an acute coronary syndrome.
- Currently, combination of an inhibitor of cyclooxygenase and a P2Y₁₂-adenosin diphosphate receptor inhibitor is the antiplatelet treatment of choice in patients with an acute coronary syndrome.
- New P2Y₁₂-adenosin diphosphate receptor antagonists (prasugrel and ticagrelor) have shown greater and faster platelet inhibition with less variability than clopidogrel, with clinical implications.
- Oral enteric-coated aspirin is the recommended cyclooxygenase inhibitor in patients with an acute coronary syndrome, and intravenous use only when oral ingestion is not possible.

WHAT THE STUDY ADDS

- Intravenous lysine acetylsalicylate achieves an earlier and higher cyclooxygenase inhibition compared with oral aspirin.
- This faster reduction in platelet aggregation is achieved, despite these platelets presenting a potent adenosin diphosphate–dependent inhibition by prasugrel.
- Contrary to oral aspirin, subjects treated with intravenous lysine acetylsalicylate presented less inter- and intravariability in platelet inhibition.
- Because a more rapid marked platelet inhibition is needed in patients presenting with an acute myocardial infarction, the results of this study could have clinical implications.

Study Design

The ECCLIPSE (Impact of intravenous Lysine Acetylsalicylate versus oral Aspirin on Prasugrel inhibited platelets) trial was a prospective, randomized, single-center, open, 2-period crossover platelet function study in healthy volunteers. Subjects included were recruited from university students and healthcare professionals. To be enrolled, subjects fulfilled all inclusion criteria: age between 18 and 60 years, body mass index between 19 and 29 kg/m², and normal platelet function (defined as maximal platelet aggregation after stimuli with 20 μM ADP and 1.5 mmol/L arachidonic acid >70%). Active smokers, pregnant or childbearing women, subjects with known drug allergies, coronary artery disease and showed similar or higher effectiveness on platelet inhibition with LA. These studies assessed oral administration of LA, but there are not data evaluating the effects of intravenous LA that could lead to a faster and higher platelet inhibition than oral dosage. This fact is especially important in the setting of ST-segment–elevation acute myocardial infarction patients, where early platelet inhibition is associated with a reduction in cardiovascular events.

Therefore, the present study aims to analyze the effects of combined administration of intravenous LA plus prasugrel versus aspirin plus prasugrel orally on platelet aggregation and to assess whether the administration of these different drug regimens affect the time to onset of platelet inhibition.

Methods

Platelet Function Testing

Blood samples were collected from an antecubital vein using a 21-gauge needle after randomization and each of the previously specified set time points. First 3 mL of blood was discharged to avoid spontaneous platelet activation. All samples were processed within 1 hour by researchers that were blinded to the treatment assigned.

Platelet Aggregation

Platelet aggregation was assessed using light transmittance aggregometry as previously described. In brief, light transmittance aggregometry was performed in platelet-rich plasma by the turbidometric method in a 4-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown, Pennsylvania) according to standard protocols. The platelet-rich plasma was obtained as a supernatant after centrifugation of citrated blood at 800 rpm for 10 minutes and platelet-poor plasma was obtained after a second centrifugation of samples at 2500 rpm for 10 minutes. Light transmission was adjusted to 0% with platelet-rich plasma and to 100% with platelet-poor plasma for each measurement. Curves were recorded during 5 minutes, and platelet aggregation was determined as the maximal percent change in light transmittance using platelet-poor plasma as a reference. ADP 20 μM was used to assess P2Y₁₂-dependent pathway aggregation, arachidonic acid (AA) 1.5 mmol/L was used to study the response to cyclooxygenase-2, and thrombin receptor-activated peptide (TRAP) 25 μM were used to stimulate thrombin-dependent platelet aggregation. Inhibition of platelet aggregation (IPA) was defined as the relative percent decrease in maximal aggregation and was

personal history of bleeding, or any relevant medical condition using any medication within 14 days before study participation or taking aspirin, nonsteroidal anti-inflammatory drugs, or other drugs known to affect platelet function in the last 21 days were excluded.

Subjects who met all criteria for enrollment were randomly assigned to receive an LD of LA (450 mg intravenous) plus prasugrel (60 mg orally) or LD of aspirin (300 mg orally) plus prasugrel (60 mg orally). The medication was administered after fasting (at least 10 hours). Platelet function studies were performed at baseline, 30 minutes, 1 hour, 4 hours, and 24 hours after LD. After 2-week washout period, the same procedures were performed while taking the other treatment combination under research. The study design algorithm is shown in Figure 1.

This protocol was approved by the local Ethics Review Committee and complied with the Declaration of Helsinki. All subjects gave their written informed consent before undergoing any study procedure or receiving any study treatment. A clinical research organization was contracted to hold the data and perform the data analysis after data lock. An independent data safety monitoring committee was instituted for adjudication of adverse clinical events. A simple randomization was performed using a computer-randomization with STATA 12.0.

Figure 1. Flow diagram of the study. LD indicates loading dose.
Lysine Acetylsalicylate and Platelet Function

Table. Platelet Function Profiles According to Treatment Assigned

<table>
<thead>
<tr>
<th></th>
<th>Lysine Acetylsalicylate (n=30)</th>
<th>Aspirin (n=29)</th>
<th>Lysine Acetylsalicylate Group, Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PR, %</td>
<td>80.1±9.9</td>
<td>82.8±12.0</td>
<td>−2.7 (−8.4 to 3.1)</td>
<td>0.352</td>
</tr>
<tr>
<td>IPA 30 min, %</td>
<td>85.3±7.2</td>
<td>44.3±32.6</td>
<td>30.2 (11.1 to 49.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>IPA 1 h, %</td>
<td>84.7±5.7</td>
<td>54.0±28.2</td>
<td>27.7 (10.4 to 45.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>IPA 4 h, %</td>
<td>86.8±7.0</td>
<td>70.0±28.2</td>
<td>17.5 (0.1 to 35.0)</td>
<td>0.048</td>
</tr>
<tr>
<td>IPA 24 h, %</td>
<td>88.4±6.6</td>
<td>90.4±5.5</td>
<td>−2.9 (−7.6 to 1.7)</td>
<td>0.209</td>
</tr>
<tr>
<td>ADP 20 μM, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PR, %</td>
<td>72.1±11.4</td>
<td>75.6±10.4</td>
<td>−3.5 (−9.1 to 2.2)</td>
<td>0.236</td>
</tr>
<tr>
<td>IPA 30 min, %</td>
<td>70.0±24.6</td>
<td>60.6±33.6</td>
<td>6.9 (−16.4 to 30.2)</td>
<td>0.554</td>
</tr>
<tr>
<td>IPA 1 h, %</td>
<td>84.2±12.3</td>
<td>84.4±10.9</td>
<td>−6.5 (−15.5 to 2.5)</td>
<td>0.153</td>
</tr>
<tr>
<td>IPA 4 h, %</td>
<td>87.2±11.8</td>
<td>89.7±8.6</td>
<td>−4.4 (−12.2 to 3.4)</td>
<td>0.260</td>
</tr>
<tr>
<td>IPA 24 h, %</td>
<td>83.5±13.3</td>
<td>83.6±9.4</td>
<td>−4.4 (−14.0 to 5.1)</td>
<td>0.355</td>
</tr>
<tr>
<td>TRAP 25 μM, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PR, %</td>
<td>76.3±7.7</td>
<td>76.6±6.8</td>
<td>1.2 (−2.6 to 5.0)</td>
<td>0.526</td>
</tr>
<tr>
<td>IPA 30 min, %</td>
<td>19.5±12.6</td>
<td>10.0±19.1</td>
<td>9.1 (6.0 to 32.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>IPA 1 h, %</td>
<td>22.0±14.9</td>
<td>13.6±12.4</td>
<td>8.4 (−1.5 to 20.9)</td>
<td>0.089</td>
</tr>
<tr>
<td>IPA 4 h, %</td>
<td>24.5±17.5</td>
<td>19.4±21.0</td>
<td>13.8 (−2.2 to 29.8)</td>
<td>0.089</td>
</tr>
<tr>
<td>IPA 24 h, %</td>
<td>24.5±15.9</td>
<td>21.9±21.6</td>
<td>0.85 (−15.5 to 17.2)</td>
<td>0.917</td>
</tr>
<tr>
<td>PRI, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76.8±22.7</td>
<td>77.4±13.2</td>
<td>−0.6 (−10.4 to 9.1)</td>
<td>0.895</td>
</tr>
<tr>
<td>30 min</td>
<td>15.1±18.3</td>
<td>15.7±21.3</td>
<td>6.6 (−7.2 to 22.8)</td>
<td>0.300</td>
</tr>
<tr>
<td>1 h</td>
<td>6.6±9.4</td>
<td>4.0±6.8</td>
<td>2.5 (−1.9 to 6.9)</td>
<td>0.265</td>
</tr>
<tr>
<td>4 h</td>
<td>4.9±8.5</td>
<td>8.4±18.0</td>
<td>−1.2 (−12.0 to 9.5)</td>
<td>0.820</td>
</tr>
<tr>
<td>24 h</td>
<td>10.0±10.9</td>
<td>9.0±8.9</td>
<td>1.0 (−6.1 to 9.2)</td>
<td>0.690</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation. IPA was defined as the relative percent decrease in maximal aggregation and was calculated as (baseline platelet reactivity−platelet reactivity at the different timepoints of the study)/baseline platelet reactivity×100. AA indicates arachidonic acid; ADP, adenosin diphosphate; IPA, inhibition of platelet aggregation; LA, lysine acetylsalicylate; PR, platelet reactivity; PRI, platelet P2Y12 reactivity index; and TRAP, thrombin receptor-activated peptide.

Platelet P2Y12 Reactivity Index

The platelet P2Y12 reactivity index (PRI) was determined through assessment of vasodilator stimulated phosphoprotein (VASP) phosphorylation according to standard protocols. In brief, VASP phosphorylation was measured by quantitative flow cytometry (Gallios cytometer Beckman Coulter, Miami, Florida) using commercially available labeled monoclonal antibodies (Biocytex Inc., Marseille, France). The PRI was calculated after measuring the mean fluorescence intensity of VASP phosphorylation levels following challenge with prostaglandin E1 and prostaglandin E1 plus ADP. Prostaglandin E1 increases VASP phosphorylation levels through stimulation of adenylate cyclase, whereas ADP binding to purinergic receptors leads to inhibition of adenylate cyclase. Therefore, the addition of ADP to prostaglandin E1-stimulated platelets reduces levels of prostaglandin E1−induced VASP phosphorylation. Elevated PRI values are indicative of upregulation of the P2Y12 signaling pathway.

Primary End Point and Sample Size

The primary end point of the study was the IPA responses to AA 1.5 mmol/L stimuli by light transmission aggregometry 30 minutes after administration of study drugs. Secondary end points were the IPA at baseline, 1 hour, 4 hours, and 24 hours after AA 1.5 mmol/L, IPA after ADP 20 μM, TRAP 25 μM, and the PRI through the sequence. To estimate the sample size, and according to previous pharmacodynamics studies, we hypothesized a 27% mean reduction in the primary end point after treatment with intravenous LA compared with oral aspirin. Therefore, at least 30 subjects would be required to provide a 80% power to detect statistical differences between groups with a 2-sided α level of 0.05.

Statistical Analysis

Normally distributed continuous variables are presented as mean±standard deviation. Variables were analyzed for a normal distribution with the Kolmogorov–Smirnov test. Categorical variables are expressed as frequencies and percentages. Confidence intervals (CI) and all test of statistical significance for treatment comparisons were evaluated at a 2-tailed significance level of 0.05.

All statistical comparisons of platelet function between intravenous LA and oral aspirin for the primary and secondary end points with continuous variables were conducted using a linear mixed-effect model for repeated measures. In this model, baseline levels of platelet function were considered as covariance, healthy subjects as random effects, and treatment group, sequence, and treatment-group-by-sequence (treatment by period interaction to test for carryover effects) as fixed effects. Combined data of the 2 periods of the study were assessed. All analyses of platelet function were conducted in all randomized subjects who received at least one dose of study drug. Statistical analysis was performed using SPSS/PC 17 (SPSS Inc, Chicago, IL).

Results

Patient Population

A total of 51 subjects were screened and 30 were randomly assigned to either intravenous LA versus oral aspirin (aged
Of these 30 subjects, and after 2-weeks washout period, 29 completed the second treatment period. One subject who was initially assigned to the LA group in the first treatment period was found to have an exclusion criterion (prior diagnosis of pituitary microadenoma) and did not crossover to aspirin. Only one insignificant bleeding in the LA group was reported.

**Platelet Function Profiles**

There were no differences in platelet function at baseline between LA plus prasugrel and aspirin plus prasugrel groups with all platelet function test assessed (Table). The combination of the data of the 2 periods of the study shows that the primary end point of the study, IPA at 30 minutes after AA 1.5 mmol/L, was significantly higher in subjects treated with LA compared with aspirin: 85.3%±7.2% versus 44.3%±32.6%, respectively; mean difference 30.2 (95% CI, 11.1–49.3), \( P = 0.003 \). This differential effect was observed at 1 hour (84.7%±5.7% versus 54.0%±28.2%; mean difference 30.7; 95% CI, 10.4–45.1; \( P = 0.002 \)) and 4 hours (86.8%±7.0% versus 70.0%±28.2%; mean difference 17.5; 95% CI, 0.1–35.0; \( P = 0.048 \)), but not at 24 hours (88.4%±6.6% versus 90.4%±5.5%; mean difference −2.9; 95% CI, −7.6 to 1.7; \( P = 0.209 \)) (Figure 2A).

Platelet function profiles according to P2Y12-dependent pathway aggregation were shown in Figure 2B. There were no differences between LA and aspirin groups assessed by ADP 20 \( \mu \)M at any time point (\( P = \text{NS} \)). These results were similar when exploring platelet activation with PRI (Figure 2C). When thrombin-dependent platelet aggregation was analyzed with TRAP 25 \( \mu \)M, subjects treated with LA showed a significant reduction in platelet function at 30 minutes (19.5%±12.6% versus 10.0%±19.1%; mean difference 9.5; 95% CI, 6.0–32.1; \( P = 0.005 \)) and a trend at 1 hour (22.0%±14.9% versus 13.6%±12.4%; mean difference 6.5; 95% CI, −2.2 to 20.9; \( P = 0.089 \)) and at 4 hours (24.5%±31.1% versus 19.4%±21.0%; mean difference 5.4; 95% CI, −0.8 to 11.6; \( P = 0.089 \)), but not at 24 hours (24.5%±15.9% versus 21.9%±21.6%; mean difference 0.85; 95% CI, −15.5 to 17.2; \( P = 0.917 \)) when compared with aspirin group (Figure 2D). Figure 3 shows the
aggregation tracing curves at 30 minutes after stimuli with AA and TRAP in both groups. The earlier and faster effect of LA compared with aspirin is achieved at 30 minutes with AA and TRAP stimuli, but no differences were found with ADP. No statistically significant differences were also observed by sequence, period, or the treatment-by-period interaction, which suggest no carryover effect with all platelet function test, including the primary end point (Figure 4).

Figure 5 shows individual subject antiplatelet response after AA 1.5 mmol/L at baseline, 30 minutes, 1 hour, 4 hours, and 24 hours. Subjects treated with LA presented less variability and faster and greater decrease in platelet inhibition compared with aspirin group.

Discussion

The ECCLIPSE study is the first randomized trial to analyze the pharmacodynamic effects of intravenous LA plus oral prasugrel compared with aspirin plus prasugrel orally in healthy volunteers. In particular, the results of the study show that intravenous LA was associated with higher platelet inhibition than oral aspirin group. Further, the administration of intravenous LA resulted in a rapid and marked reduction on platelet reactivity by 30 minutes compared with oral aspirin and these differences maintained in the first 4 hours after LD. Finally, LA achieved a more consistent platelet inhibition and less inter- and intraindividual variability.

The main result of this study states that the effect achieved with intravenous LA is earlier and higher than oral aspirin. This finding could be explained by the pharmacokinetic effect of aspirin. Thus, Gurfinkel et al showed that the onset of platelet inhibition with oral aspirin (320 mg) was slower than the inhibition achieved with oral LA (320 mg) in patients with stable coronary artery disease.\textsuperscript{15} Nevertheless, in this study, both treatments achieved similar platelet inhibition at 60 minutes; in the ECCLIPSE trial, differences in platelet inhibition with intravenous LA is higher than oral aspirin not only at 30 minutes, but also at 60 minutes. Therefore, intravenous LA could contribute to reach greater and broader reduction of platelet aggregation, despite these platelets presented a potent ADP-dependent inhibition by prasugrel. Whether this effect is enough to reach clinical benefits is unknown. In fact, some reports have suggested that clinical benefits of aspirin as an antithrombotic agent are achieved with inhibition levels exceeding 95% in response to AA,\textsuperscript{23,24} although the test used to assess platelet function were different in our study compared with previously reported.\textsuperscript{15}

Interestingly, LA not only increased platelet inhibition when cyclooxygenase pathway was assessed, but also showed an early reduction in the thrombin-dependent platelet pathway.
aggregation. This unexpected finding could suggest the effect of LA in the inhibition of different platelet activation pathways. In fact, an additive effect on platelet inhibition is observed when a more effective antithrombotic strategy is used to achieve an earlier antplatelet effect.25 However, it also could be explained by the high variability of the platelet function assays and the marginal differences in both groups at just one time point (30 minutes).26

Current investigation concentrates on the field of P2Y12-ADP platelet receptor inhibition. Prasugrel and ticagrelor are characterized by more prompt, potent, and predictable antiplatelet effects and greater clinical efficacy than clopidogrel.10,11 However, these drugs also present limitations, including a delayed antplatelet effect, particularly in the setting of ST-segment–elevation acute myocardial infarction.27–29 In the ECCLIPSE trial, intravenous LA achieved a platelet inhibition higher than 82% by 30 minutes after LD, meanwhile oral aspirin only inhibited 44%. Moreover, aspirin only achieved 70% platelet inhibition at 4 hours. These findings could have clinical implications because recent reports have showed that high aspirin treatment platelet reactivity is associated with a higher risk for cardiovascular outcomes.30 In fact, a more rapid and marked platelet inhibition with ticagrelor, in prehospital ST-segment–elevation acute myocardial infarction patients, could be associated with a significant reduction in stent thrombosis.31 Therefore, the findings of ECCLIPSE trial show that, despite of a high prasugrel platelet inhibition, intravenous LA could reduce platelet reactivity faster and stronger, which could have clinical implications.

This study has some limitations. First, the trial enrolled healthy volunteers, and this fact may limit the generalization to clinical patient population with cardiovascular disease. Second, the relation between clinical outcomes and the speed of onset and magnitude of platelet inhibition with LA is unknown. Finally, the present study was not designed to evaluate maintenance doses. However, protocol design and statistical analyses reinforced the value of the results obtained, which suggested a pharmacodynamic benefit of intravenous LA compared with oral aspirin.

In conclusion, the present study demonstrates that the administration of intravenous LA plus oral prasugrel resulted in a significantly reduction of platelet reactivity compared with aspirin plus prasugrel orally. LA achieves a faster onset of platelet inhibition, with less intra- and interindividual variability than aspirin.

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**Disclosures**

Dr Vivas reports honoraria for lectures and consulting for Eli Lilly and Company and Daiichi Sankyo, Inc. Dr Núñez-Gil reports honoraria for lectures for Eli Lilly and Company and Daiichi Sankyo, Inc. Dr Macaya reports honoraria for lectures and consulting for Eli Lilly and Company and Daiichi Sankyo, Inc. Dr Fernández-Ortiz reports honoraria for lectures and consulting for Eli Lilly and Company and Daiichi Sankyo, Inc. The other authors report no conflicts.

**References**


Impact of Intravenous Lysine Acetylsalicylate Versus Oral Aspirin on Prasugrel-Inhibited Platelets: Results of a Prospective, Randomized, Crossover Study (the ECCLIPSE Trial)

David Vivas, Agustín Martín, Esther Bernardo, María Aranzazu Ortega-Pozzi, Gabriela Tirado, Cristina Fernández, Isidre Vilacosta, Iván Núñez-Gil, Carlos Macaya and Antonio Fernández-Ortiz

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