Over the past decades, antiplatelet therapy has evolved from the relatively weak oral agent aspirin to additional oral and parenteral agents with greater antiplatelet activity. One example of a successful agent is the second-generation thienopyridine clopidogrel. Clopidogrel inhibits platelet P2Y12 receptors and given with aspirin, which inhibits cyclooxygenase-1 enzyme, composes the actual standard of care of dual antiplatelet therapy. Dual antiplatelet therapy is recommended by the American College of Cardiology/American Heart Association, American College of Chest Physicians, and the European Society of Cardiology (ESC) for patients undergoing percutaneous coronary intervention (PCI) and patients with ST-elevated myocardial infarction (STEMI) or unstable angina (UA)/non-STEMI (NSTEMI). A common point of emphasis in these guidelines is the recommendation to provide a clopidogrel loading dose (LD) before PCI, although uncertainty remains in these recommendations on the optimal dose and optimal timing of administration.

Whereas the American College of Cardiology/American Heart Association UA/NSTEMI guidelines recommend a 300-mg clopidogrel LD, they acknowledge that although the supporting evidence is much weaker than that for a 300-mg LD, a higher dose of 600 or 900 mg may be more beneficial in some circumstances. The PCI guidelines recommend a 600-mg clopidogrel LD before or during the procedure. The ESC guidelines suggest that a 600-mg LD may be initiated immediately after the first medical contact for invasively managed patients with NSTEMI. Unfortunately, there are no clinical data and, therefore, no recommendation on the maintenance dose (MD) during the acute phase or chronic phase.

The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS 7) trial is the first large-scale, randomized trial to compare 2 strategies: high-dose clopidogrel (600-mg LD/150-mg MD) versus standard-dose clopidogrel (300-mg LD/75-mg MD) to assess the added benefit of a higher platelet inhibition of P2Y12 receptors on ischemic events. In a factorial design, the trial also evaluated 2 strategies of high-dose aspirin (300 to 325 mg) versus a low dose (75 to 100 mg) to assess the risk/benefit of different aspirin dosage regimens. This trial sheds new light on what could be the standard oral antiplatelet therapy of non-ST-elevation acute coronary syndrome (NSTE-ACS). In this review, the results of CURRENT-OASIS 7 were considered in light of the existing biological and clinical data that support the 2 hypotheses tested by this pivotal trial that should certainly influence physicians in their care of patients with NSTE-ACS.

1. Clopidogrel 300 mg/75 mg in Standard Dual Antiplatelet Therapy

Clopidogrel is a prodrug that needs to be metabolized by cytochromes in the liver to produce the active metabolite that finally binds irreversibly to P2Y12 platelet receptors and, therefore, inhibits platelet aggregation. The first particularity of clopidogrel is a slow onset of action that reaches a steady state only after several days when administered at a dose of 75 mg/d without loading. Pharmacodynamic studies in healthy volunteers and then in patients with ACS showed that a single 300-mg LD of clopidogrel could be used to shorten the time to maximal platelet inhibition. Therefore, this regimen (300-mg LD followed by 75-mg MD) was legitimately tested versus placebo in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial and demonstrated a clinical benefit, in an ACS population managed conservatively, most of the time. Indeed, 12,562 patients with UA/NSTEMI were randomized within 24 hours of symptom onset to receive either a 300-mg clopidogrel LD (n=6529) or placebo (n=6303) followed by a 75-mg/d clopidogrel MD and 75 to 325 mg aspirin daily for 3 to 12 months (mean duration, 9 months). Death, MI, or stroke was reduced by 20% in patients who received clopidogrel (95% CI, 10% to 28%; P<0.001). In the PCI-CURE trial, a predefined postrandomization subgroup of patients undergoing PCI, the relative risk reduction associated with clopidogrel was 31% (95% CI, 13% to 46%; P=0.002). After the CURE trial, these finding were confirmed in subset analyses of other studies conducted in NSTE-ACS.

After multiple biological studies on the response to a 300-mg LD of clopidogrel, cardiologists noted another particularity: the large interindividual variability of its effect.
Indeed, the platelet inhibition obtained with a 300-mg LD follows a Gaussian distribution, with patients having a limited or sometimes absent response (hyporesponsiveness) to the drug, whereas others have a hyperresponse.\(^{19}\)

In a first period, studies have focused on the poor response to clopidogrel, which has been extensively studied with different tests, agonists, and definitions. The response to the drug was linked to recurrent ischemic events in ACS or PCI, with higher rates of stent thrombosis. The causes for this hyporesponsiveness have been identified with a genetic determinant, the CYP2C19\(^*2\) variant (odds ratio [OR], 2.75), and clinical determinants, such as diabetes (OR, 1.75), hyporesponsiveness have been identified with a genetic determinant, the CYP2C19\(^*2\) variant (odds ratio [OR], 2.75), and clinical determinants, such as diabetes (OR, 1.75), increasing age (OR, 1.03 per year), and body mass index (OR, 1.06 per kg/m\(^2\)). Then, in a second, more recent period, cardiologists noticed that bleeding and transfusion used in patients with ACS treated with dual antiplatelet therapy had a major impact on mortality comparable to the impact of recurrent ischemic events.\(^{20}\) Therefore, attention focused on the increased bleeding risk associated with higher doses of or more potent antiplatelet agents. Here again, the biological interindividual variability in the response to clopidogrel (genetically driven or not) seems to play a role.\(^{21}\)

### 2. What Are the Data That Support the Use of LDs >300 mg?

Overall, the goals of higher clopidogrel LD (>300 mg) have been to achieve a faster onset of inhibition of platelet aggregation with a higher degree of inhibition to reduce the incidence of hyporesponsiveness and the incidence of recurrent ischemic events, all while preserving or limiting the bleeding risk to acceptable levels. Pharmacodynamic studies have shown that compared to a 300-mg clopidogrel LD, a higher LD achieves greater levels of platelet inhibition and equivalent levels of inhibition in a shorter time period (Table 1).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>LD of Clopidogrel Tested</th>
<th>Biological End Point</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-CHOICE(^{22})</td>
<td>2005</td>
<td>60</td>
<td>300 mg vs 600 mg</td>
<td>MPA (5 and 20 (\mu)mol/L ADP) at baseline and 4 h post-LD</td>
<td>No evaluation of relative inhibition</td>
</tr>
<tr>
<td>ALBION(^{23})</td>
<td>2006</td>
<td>103</td>
<td>300 mg vs 600 mg</td>
<td>IPA (20 (\mu)mol/L ADP) at baseline and 0.5, 1, 2, 3, 4, 5, 6, and 24 h post-LD</td>
<td>Additional surrogate end point with troponin I release</td>
</tr>
<tr>
<td>PRINC(^{24})</td>
<td>2008</td>
<td>60</td>
<td>600 mg vs 1200 mg</td>
<td>% inhibition at 2, 4, and 7 h post-LD</td>
<td>Two separate administrations of a 600-mg LD</td>
</tr>
<tr>
<td>PREPAIR(^{25})</td>
<td>2008</td>
<td>148</td>
<td>300 mg vs 600 mg vs 1200 mg (600 mg (\times 2))</td>
<td>MPA and RPA (5 and 20 (\mu)mol/L ADP at baseline and before angiography</td>
<td>Two separate administrations of a 600-mg LD</td>
</tr>
<tr>
<td>RELOAD(^{26})</td>
<td>2008</td>
<td>166</td>
<td>300 mg vs 900 mg</td>
<td>IRPA (5, 10, and 20 (\mu)mol/L ADP), PRU and % inhibition at baseline, 4 and 24 h post-LD</td>
<td>Patients under chronic clopidogrel treatment</td>
</tr>
</tbody>
</table>

IPA indicates inhibition of platelet aggregation; IRPA, relative inhibition of platelet inhibition; LTA, light transmittance aggregometry; MPA, maximum platelet aggregation; PRINC, Plavix Response in Coronary Intervention; RPA, residual platelet aggregation; VN, Verify Now.

Loading regimens higher than 900 mg also have been tested, usually with 2 separate administrations. In the randomized Plavix Response in Coronary Intervention study, patients who received 2 600-mg clopidogrel boluses 2 hours apart had significantly greater levels of platelet inhibition than patients who received a single 600-mg bolus.\(^{24}\) The same concept also was explored in the PREPAIR study,\(^{25}\) where patients were randomly assigned to receive 1 of the following 3 treatment regimens: (1) clopidogrel 300-mg LD the day before \((\geq 15\) hours) plus 75 mg on the morning of the procedure, (2) clopidogrel 600-mg LD on the morning of the procedure \((\geq 2\) hours), or (3) clopidogrel 600-mg LD the day before and a new 600-mg LD the morning of the procedure. Several ex vivo platelet aggregation measures were examined, and for all parameters, the group that received the double 600-mg LD achieved the greatest level of platelet inhibition.

In the Reload With Clopidogrel Before Coronary Angioplasty in Subjects Treated Long Term With Dual Antiplatelet Therapy (RELOAD) trial, patients taking 75 mg/d clopidogrel for \(>7\) days were randomized to receive an initial clopidogrel LD of 300, 600, or 900 mg.\(^{26}\) Four hours after the
initial dose, patients were given a second LD such that the total dose equaled 900 mg (eg, those who received an initial dose of 300 mg received a second dose of 600 mg). Platelet inhibition was assessed before the provision of each LD and 4 and 24 hours after the initial dose. A dose-response effect was noted following the first LD such that the inhibition of residual platelet aggregation was greatest with 900 mg and lowest with 300 mg and the rate of hyporesponders was significantly lower among patients who received a 900-mg LD. These results show that a 900-mg clopidogrel LD is superior to 300 or 600 mg to reduce poor clopidogrel response in patients already taking 75 mg/d clopidogrel. Importantly, it also demonstrates that in this dose range of 900 mg, there is no limitation due to intestinal absorption.

All these studies suggested that high LD is efficient in terms of pharmacodynamic response resulting in a higher and faster platelet inhibition, reducing but not totally overcoming poor responsiveness. In these small biological trials, higher LD appeared to be safe because there were no excess bleeding events, but they clearly did not have the power to conclude on clinical outcomes.

Beyond poor individual response, there is also evidence that the higher LD may overcome potential drug-drug interactions that were demonstrated ex vivo with atorvastatin with the 300-mg clopidogrel LD but not with the 600-mg LD. Similarly, higher LD of clopidogrel may help to overcome the potential adverse interaction of clopidogrel with proton pump inhibitors that was demonstrated ex vivo by the Omeprazole Clopidogrel Aspirin study with decreased platelet reactivity measured by vasodilator-stimulated phosphoprotein on concomitant administration of omeprazole and a 300-mg LD of clopidogrel and as absent in a second study in which patients received a 600-mg LD of clopidogrel. Finally, the hypothesis that higher and faster inhibition would improve clinical outcomes was supported by the findings of recent clinical trials demonstrating a reduction of ischemic events with 2 more potent ADP receptor blockers (P2Y12 inhibitors), namely prasugrel and ticagrelor, when compared with the standard dual antiplatelet therapy using clopidogrel for ACS.

3. What Is the Benefit of Higher Doses of Clopidogrel in Clinical Trials?

Several small-numbered randomized trials aimed to demonstrate a clinical benefit of higher LD of clopidogrel in the setting of PCI (Table 2). In the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA-2) study, patients receiving a 600-mg LD of clopidogrel 4 to 8 hours before the procedure showed a 52% relative risk reduction of the study composite end point (death, MI, or target vessel revascularization) at 30 days compared with patients receiving a 300-mg LD. The benefit of the Amaryda-2 study was entirely due to a reduction of periprocedural MI, and no bleeding excess was reported, but this study was not sized to show differences in hard end points. In another study, Cuisset et al demonstrated that a 600-mg clopidogrel LD 12 hours before PCI decreased the persistence of high posttreatment platelet reactivity measured by aggregometry compared with patients receiving a 300-mg LD (15% versus 25%; P=0.03) and decreased the rate of major CV events (MACE) at 1-month follow-up (5% versus 12%; P=0.02). Bonello et al showed that individualized therapy with higher LD of clopidogrel (up to a total dose of 2.4 g of clopidogrel) guided by platelet function test (vasodilator-stimulated phosphoprotein) could improve the prognosis of patients who displayed hyporespones to an initial 600-mg LD of clopidogrel in terms of stent thrombosis at 1 month (0.5% versus 4.2%; P<0.01), with a similar risk of bleeding (4% versus 5%). The Amaryda-RELOAD study evaluated the safety and the effectiveness of a 600-mg LD of clopidogrel administrated 4 to 8 hours before PCI versus placebo in patients on chronic clopidogrel therapy (>10 days) undergoing PCI. The primary composite end point (30-day incidence of MACE) was not significantly different between the 2 strategies (6.7% versus 8.8%; P=0.50) with no increase of bleeding in the reload arm (6% in both groups), whereas the ACS subgroup did benefit from the clopidogrel reloading with a lower MACE rate compared with the no-reloading group (6.4 versus 16.3%; P=0.033), generating the hypothesis that patients with ACS might be the best target for a reloading strategy.

The CURRENT-OASIS 7 trial is the first large-scale randomized trial to compare 2 doses of clopidogrel, large enough to assess the added benefit of a double dose on ischemic events and able to evaluate the safety with an estimation of bleeding risk. The trial tested whether a double-dose regimen of clopidogrel (600-mg LD followed by 150-mg MD from day 2 to day 7, then 75-mg MD) was superior to a standard-dose regimen of clopidogrel (300-mg LD followed by 75-mg MD) in preventing CV death, MI, or

Table 2. Prospective Randomized Studies Comparing Different LD of Clopidogrel on Clinical End Points

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Population</th>
<th>LD of Clopidogrel Tested</th>
<th>Clinical End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARMYDA-2</td>
<td>2005</td>
<td>255</td>
<td>Elective PCI and</td>
<td>300 mg vs 600 mg</td>
<td>Death, MI, or TVR at 30 days</td>
</tr>
<tr>
<td>Cuisset et al</td>
<td>2006</td>
<td>292</td>
<td>NSTE-ACS</td>
<td>300 mg vs 600 mg</td>
<td>Death, stent thrombosis, recurrent ACS, and stroke at 30 days</td>
</tr>
<tr>
<td>Bonello et al</td>
<td>2009</td>
<td>429</td>
<td>Electro PCI and</td>
<td>600 mg vs repeated bolus of 600 mg</td>
<td>Stent thrombosis at 30 days</td>
</tr>
<tr>
<td>ARMYDA-RELOAD</td>
<td>2010</td>
<td>503</td>
<td>NSTE-ACS</td>
<td>Placebo vs 600 mg in patients under chronic clopidogrel therapy</td>
<td>Death, MI, or TVR at 30 days</td>
</tr>
<tr>
<td>CURRENT-OASIS 7</td>
<td>2010</td>
<td>25 086</td>
<td>NSTE-ACS</td>
<td>300 mg vs 600 mg</td>
<td>Death, MI, and stroke at 30 days</td>
</tr>
</tbody>
</table>

TVR indicates target vessel revascularization.
stroke at 30 days in patients with NSTE-ACS who were treated with an early invasive strategy. An amendment to the protocol while the study was ongoing extended the recruitment to primary PCI of patients with STEMI, and the final population regroups a broad range of patients with ACS. The safety of the clopidogrel double-dose regimen also was compared to the standard-dose regimen in terms of thrombolysis in myocardial infarction (TIMI) major bleeding. This clopidogrel part of the study is double blind.

Surprisingly, in this study of 25 086 patients with ACS, no significant difference was observed at 30 days for the primary objective, which occurred in 4.2% of individuals receiving the double-dose regimen compared to 4.4% in those who received the standard doses (hazard ratio [HR], 0.94; 95% CI, 0.83 to 1.06; P=0.3). This trial failed to meet its primary end point, which theoretically limits further subgroup analysis. The interpretation of the results published 1 year after the presentation at the ESC conference in 2009 slightly differs on an important statistical issue.38 Indeed, when analyzing the results from the subgroup of 17 263 patients with ACS who underwent PCI, the double-dose regimen led to a nominal 25% decrease in CV events (3.9% versus 4.5%; HR, 0.85; 95% CI, 0.74 to 0.99; P=0.039).39 However, the P value for interaction was 0.03 and did not meet the prespecified criteria (P<0.01) to consider these results as statistically significant.

Therefore, the only clearly real statistically significant benefit was the 32% reduction in the risk of stent thrombosis (1.6% versus 2.3%; HR, 0.68; 95% CI, 0.55 to 0.85; P<0.001). In contrast, the 7823 patients with ACS who did not undergo PCI because no significant coronary artery disease (CAD) was identified or because they had severe CAD requiring coronary artery bypass graft (CABG) surgery or just medical treatment had a 14% trend toward more CV events (4.9% versus 4.3%; HR, 1.14; P=0.2), results that also could be a play of chance because they share the same P value for interaction.

Interestingly, although the success of clopidogrel at a standard-dose regimen against placebo in the CURE trial was driven by the benefit obtained in a population mostly medically treated, this type of patients did not benefit from higher doses of clopidogrel in CURRENT. These results suggest that the dose of clopidogrel should not be the same for patients with ACS treated with or without PCI. Such a hypothesis seems to be confirmed by the good clinical results obtained with prasugrel in Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON)32 and ticagrelor in Platelet Inhibition and Patient Outcomes (PLATO) PCI trial,33 showing that platelet inhibition should be more aggressive in patients with ACS undergoing PCI.

4. How Can We Explain the Limited Clinical Benefit in the CURRENT Trial?

After exposing the results of biological studies showing improvement in the speed of action, the level of inhibition and diminution in the rate of hyporesponders with the 600-mg doses of clopidogrel and even diminution of periprocedural MI or stent thrombosis in small randomized studies, it is not easy to interpret the globally negative results of the CURRENT trial. Nevertheless several hypotheses can emerge.

When comparing the 3 major contemporary ACS trials (TRITON, PLATO, and CURRENT), the CURRENT trial design can be compared to the PLATO trial design, at least for the overall population, because both included a broad range of patients with ACS, with ≈30% being medically treated. Having the same comparator, the 2 major remaining differences in these 2 trials are (1) the level of platelet inhibition obtained by theitive 180-mg LD of ticagrelor compared with clopidogrel and (2) the duration of the high-MD regimen (ticagrelor 90 mg BID for 12 months versus clopidogrel 150 mg for 7 days).

First, despite its impressive number of patients (25 086 patients with ACS), the CURRENT trial might have failed to demonstrate a benefit in the reduction of ischemic events simply because of a lack of power. This lack of power was obviously not in the number of patients in this large and robust trial; rather, the lack of power was in the double-dose clopidogrel regimen compared with the standard dual antiplatelet therapy. We know from biological studies that the level of inhibition obtained by a 600-mg LD of clopidogrel is higher than 300 mg but is inferior from the one obtained by 900 mg and far from the one obtained with 180 mg of ticagrelor or 60 mg of prasugrel (Figure 1). In the first 30 days of the PLATO and TRITON trials, there was a clear early benefit in the primary end point, with these drugs providing a higher and more sustained level of platelet inhibition, whereas in the CURRENT trial, the event rates were almost identical (HR, 0.96; 95% CI, 0.85 to 1.08; P=0.47) (Figure 2). When we look closely at the curves, the benefit of ticagrelor and especially prasugrel seems to occur within the first 7 days, suggesting that in this crucial period for thrombotic events, clopidogrel was not efficient enough to
demonstrate an early difference in terms of events in the overall population (Figure 3).

Then, was the 7-day duration of double MD of clopidogrel a good choice? There are few data in the literature supporting the increase of the MD of clopidogrel, and they all arise from biological studies. Few studies have assessed the antiplatelet effect of a 150-mg daily MD of clopidogrel,40–41 and 1 recent study that involved patients with STEMI showed that doubling the MD of clopidogrel (to 150 mg/d) during 30 days increased the degree of platelet inhibition and decreased the rate of hyporesponders to the drug. There is no information available on the long-term benefit of 150 versus 75 mg of clopidogrel. In the landmark analysis of TRITON and PLATO, there was an exact same additional 20% relative reduction of ischemic events during the MD period (30 days to 12 or 15 months) for both trials for ticagrelor (HR, 0.80; 95% CI, 0.70 to 0.91; P<0.001) and for prasugrel (HR, 0.80; 95% CI, 0.70 to 0.91; P=0.003), clearly suggesting that there is a benefit of a higher MD for a longer period than 7 days, at least on the ischemic side (Figure 4), and subsequently leading to the conclusion that the period of 7 days with 150 mg of clopidogrel in the CURRENT trial may have been too short.

Furthermore, the heterogeneity in the results of CURRENT suggests that the dose of clopidogrel should not be the same for PCI and non-PCI patients. When analyzing the benefits of a higher platelet inhibition for patients with ACS undergoing PCI in the CURRENT trial, they are in the same line as those of the TRITON trial (99% PCI patients) and the PLATO-Invasive subgroup and clearly demonstrate that in PCI patients, a more rapid and potent antiplatelet therapy is necessary.

Finally, the clopidogrel regimen used in CURRENT led to an apparent paradoxical result that is the nonsignificant 14% increase of ischemic events in patients with ACS treated medically. Of the 7823 patients who did not undergo PCI, 45% (3520) had no significant CAD (normal or <70% stenosis), 24% had CABG surgery, and 31% were not candidates for any type of revascularization, all types of patients where there is no rationale for higher and more rapid platelet inhibition. Apparently, patients with no significant CAD presented a surprising unexplained and almost significant 67% relative increase ischemic risk with the double-dose regimen (1.7% versus 1.0%; HR, 1.67; P=0.09)12.

What are the most likely explanations for the globally negative result of CURRENT? First, would CURRENT have had a design similar to the TRITON design (limited to PCI patients), it may have been a positive study. Second, clopidogrel 600 mg certainly provides a too-low degree of platelet inhibition in PCI patients who deserve higher doses of clopidogrel as shown in the previous smaller studies that used, for example, a 900-mg or a double LD of 600 mg (eg, 1 before catheterization and 1 at the time of PCI); this also is confirmed now by the studies with prasugrel and ticagrelor. Third, 600 mg is probably a too-high dose of clopidogrel in patients who do not need strong platelet inhibition for their medical management and even more unnecessary in patients who do not have significant CAD or need to go to CABG surgery rapidly.

5. What Is the Impact of Higher Doses of Clopidogrel on Bleeding?

In the CURRENT-OASIS 7 trial, increasing the dose of clopidogrel not only had a limited impact on ischemic events, but, surprisingly for many, also increased major bleeding by 24% based on the CURRENT definition (2.5% versus 2.0%; HR, 1.24; 95% CI, 1.05 to 1.46; P=0.01); a similar relative

![Figure 2. Rate of ischemic events (CV death, MI, stroke) at 30 days in patients with ACS in the CURRENT, TRITON, and PLATO trials. Comparator was the standard dual antiplatelet therapy for the 3 studies (light gray bars). K-M indicates Kaplan-Meier.](image)

![Figure 3. Early benefit of a more-potent regimen of antiplatelet agents on the Kaplan-Meier estimated cumulative rate of ischemic events (CV death, MI, stroke) at 30 days in patients with ACS in the CURRENT, TRITON, and PLATO trials. Comparator was the standard dual antiplatelet therapy for the 3 studies (dotted gray lines). The gray zone delimits the first 7 days of treatment.](image)
26% increase of major bleeding was observed with the more stringent TIMI definition (1.7% versus 1.3%; HR, 1.296; 95% CI, 1.03 to 1.54; \( P \leq 0.005 \)). Severe bleeding (CURRENT definition) also was increased by 22% with the double-dose regimen (1.9% versus 1.6%; HR, 1.22; 95% CI, 1.03 to 1.54; \( P = 0.01 \)). Therefore, the chosen strategy of a short (1-week) treatment period with 150 mg, for safety reasons, also failed in the CURRENT trial because it translated in a 26% relative increase in non-CABG TIMI major bleeding, an increase of similar magnitude to what was seen with prasugrel (25%) and ticagrelor (22%) (Figure 5A). Reassuringly, there was no increase in the rate of fatal bleeding and intracranial hemorrhage with the double-dose regimen (Figure 5B), and bleeding complications seem to be driven by the need for red blood cell transfusion (2.2% versus 1.7%; HR, 1.28; 95% CI, 1.07 to 1.54; \( P = 0.01 \)), a condition that affects prognosis itself through various mechanisms, including the increase of platelet aggregation.44

6. What Did We Know About Doses of Aspirin in Patients With NSTE-ACS?
The optimal dose of aspirin in NSTE-ACS is debated, with variance in guidelines and practice. The dose of aspirin currently used in patients with ACS varies among regions of the world. In North America, higher doses of aspirin (≥300 mg) are commonly used, whereas in Europe, lower doses (≤100 mg) are favored. The lack of a relationship between increasing aspirin dose and improved efficacy has been uniformly observed, and if anything, the trend in benefit has favored lower doses that are associated with lower gastrointestinal sides effects and bleeding.45,46 Indeed, in a pooled analysis of 11 clinical trials, including 5228 patients randomized to aspirin or placebo following a transient ischemic attack or stroke, similar efficacy was found for aspirin doses ranging from 50 to 1500 mg daily.36 The Antithrombotic Trialists’ Collaboration also found no relationship between dose and efficacy, and the greatest risk reduction was found with doses from 75 to 150 mg.37 An evaluation of aspirin versus placebo in ACS found lower doses of aspirin to be associated with better outcomes.38 Lower doses also have been associated with improved safety as shown in a metaanalysis in which doses <100 mg/d were associated with a significantly lower rate of major bleeding events than doses >200 mg/d (1.56%; 95% CI, 1.2% to 1.9%; versus 2.29%; 95% CI, 1.9% to 7.0%; \( P = 0.0001 \)).49 However, in another analysis, no relationship was found between aspirin dose and gastrointestinal bleeding.40 The question of aspirin doses in ACS has been reevaluated by the second randomization in CURRENT-OASIS 7.

7. What Impact Does of the CURRENT-OASIS 7 Trial Have on the Aspirin Dose?
In CURRENT-OASIS 7, all patients received an LD of 300 mg of aspirin the first day and were assigned on the second day in an open-label manner to 300 to 325 mg of aspirin once daily or 75 to 100 mg of aspirin once daily for 30 days. In terms of efficacy, there was no significant difference in the primary outcome or its components, although there was a numeric reduction with the higher dose of aspirin. A limitation of this open-label part of the study is that we do not know the aspirin status before randomization (chronic treatment and dose) and how compliance to the recommended randomized dose was followed by the patients, compliance to aspirin therapy being a major issue for its efficacy.47,48 Compared with low-dose aspirin, aspirin doses of 300 to 325 mg did not result in any significant differences in the primary outcome and in major bleeding (whatever the definition). The some-
randomized trials suggest that a regimen providing a more
term with the positive results of the TRITON and PLATO
catheterization facilities.

strategy already recommended and used in many centers with
OASIS 7 PCI substudy suggest that higher doses of clopi-
antiplatelet agent. However, the data of the CURRENT-
significant benefit of higher doses of one or the other oral
blind for the evaluation of clopidogrel dosing and open label
what surprising good safety of high-dose aspirin may be
related to the short-term use of these higher doses compared
with previous studies that reported safety concerns with high
doses. Finally, the results on the aspirin doses in CURRENT
are likely to have little impact on physicians who will not find
a good reason to change their practice.

Conclusions
The large, randomized CURRENT-OASIS 7 trial, double
blind for the evaluation of clopidogrel dosing and open label
for the evaluation of aspirin dosing, failed to demonstrate a
significant benefit of higher doses of one or the other oral
antiplatelet agent. However, the data of the CURRENT-
OASIS 7 PCI substudy suggest that higher doses of clopi-
dogrel might benefit the patient undergoing rapid PCI, a
strategy already recommended and used in many centers with
catheterization facilities.

The data of the CURRENT-OASIS 7 trial put into perspec-
tive with the positive results of the TRITON and PLATO
randomized trials suggest that a regimen providing a more
potent P2Y12 inhibition than a 300-mg LD of clopidogrel in
the acute phase followed by an MD of 75 mg in the chronic
phase is particularly beneficial to patients with ACS under-
going PCI. In patients with comorbidities, uncertain diagno-
sis, or at high bleeding risk when the initial strategy is a
medical management without catheterization or planned PCI,
clopidogrel 300 mg/75 mg remains, to date, the optimal
antiplatelet approach.

Disclosures
Dr Silvain has received research grants from Sanofi-Aventis,
Daichi-Sankyo, Eli Lilly, INSERM, Fédération Française de Cardi-
ologie, and Société Française de Cardiologie; consultant fees from
Daichi-Sankyo and Eli Lilly; and lecture fees from AstraZeneca,
Daichi-Sankyo, and Eli Lilly. Dr Collet has received research grants
from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Guerbet Med-
ical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fonda-
tion of France, INSERM, Fédération Française de Cardiologie, and
Société Française de Cardiologie; consulting fees from Sanofi-
Aventis, Eli Lilly, and Bristol-Myers Squibb; and lecture fees from
Bristol-Myers Squibb, Sanofi-Aventis, and Eli Lilly. Dr Montalescot
has received research grants from Bristol-Myers Squibb, Sanofi-
Aventis, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific,
Cordis, Stago, Centocor, Fondation de France, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie;
consulting fees from Sanofi-Aventis, Eli Lilly, Bristol-Myers Squibb, The Medicines Company, and Schering Plough; and lectures
fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Merck
Sharpe & Dohme, Cordis, GlaxoSmithKline, and Schering Plough.
Dr Montalescot was one of the members of the steering committee of
the CURRENT-OASIS 7 trial.

References
1. Duffy B, Bhatt DL. Antiplatelet agents in patients undergoing percuta-
neous coronary intervention: how many and how much? Am J Cardiolog-
2. Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and
3. Michelson AD. P2Y12 antagonism: promises and challenges. Arte-
V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG,
Tabaro M, Verheugt F, Weidinger F, Weis M, Vahanian A, Camm J, De
Caterina R, Dean V, Dickstein K, Funck-Brentano C, Heilmann I, Kris-
tensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P,
Zamorano JL, Aguirre FV, Al-Attar N, Alegria E, Andreotti F, Benzer W,
Breithardt O, Danchin N, Di Mario C, Dudek D, Gelb D, Halvorsen S,
Kaufmann P, Kornowski R, Lip GY, Rutten F. Management of acute
myocardial infarction in patients presenting with persistent ST-segment
elevation: the Task Force on the Management of ST-Segment Elevation
Acute Myocardial Infarction of the European Society of Cardiology. Eur
5. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-
Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W.
Guidelines for the diagnosis and treatment of non-ST-segment elevation
Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Stone GW, Wijns W.
Guidelines for percutaneous coronary interventions. The Task Force for
summary: American College of Chest Physicians Evidence-Based
AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW,
Nishimura R, Ornato JP, Page RL, Riegel B, American College of Cardiology, American Heart Association Task Force on Practice
Guidelines (Writing Committee to Revise the 2002 Guidelines for the


Key Words: acute coronary syndrome ▪ platelet aggregation inhibitors
Optimal Use of Thienopyridines in Non-ST-Elevation Acute Coronary Syndrome Following CURRENT-OASIS 7

Johanne Silvain, Anne Bellemain-Appaix, Olivier Barthélémy, Farzin Beygui, Jean-Philippe Collet and Gilles Montalescot

_Circ Cardiovasc Interv._ 2011;4:95-103
doi: 10.1161/CIRCINTERVENTIONS.109.910406
_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/4/1/95