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REVIEW

Oral Antiplatelet Therapy in Acute Coronary Syndromes: Recent Developments

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ABSTRACT

The purpose of this article is to summarize the current knowledge about treatment with oral platelet inhibitors in patients with acute coronary syndrome (ACS). Antiplatelet therapy has been shown to improve the prognosis of patients with ACS with ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation ACS (NSTE-ACS). Aspirin should be given with a loading dose of 250–500 mg, followed by 75–100 mg/day. Dual antiplatelet therapy is recommended for all patients with ACS for 12 months regardless of the initial revascularization strategy. Clopidogrel should be administered at first medical contact in STEMI with a loading dose of 600 mg. In patients with ACS and percutaneous coronary intervention (PCI) 2×75 mg clopidogrel should be given daily over 7 days, while in all other patients 75 mg per day appears to be sufficient. The two newer adenosine diphosphate-receptor antagonists prasugrel and ticagrelor lead to a more rapid and effective inhibition of platelet aggregation compared with clopidogrel, which was associated with an improved clinical outcome in two large randomized studies. Prasugrel is indicated in patients with ACS undergoing PCI and was most effective in diabetics and in patients with STEMI. In the recent TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes trial in medically treated patients with NSTE-ACS, prasugrel did not significantly reduce ischemic events compared with clopidogrel. Ticagrelor has been studied in the whole spectrum of ACS patients and reduced cardiovascular and total mortality in comparison with clopidogrel. The greatest benefit has been observed in patients with planned conservative treatment and in patients with impaired renal function. Expanding antiplatelet therapy from dual to triple therapy including a platelet thrombin

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receptor antagonist in the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome trial was not associated with a significant reduction in the primary combined endpoint but an increase in bleeding complications. However, in the **T**hrombin **R**eceptor **A**ntagonist in **S**econdary **P**revention of atherothrombotic ischemic events study in patients with prior myocardial infarction, vorapaxar on top of standard antiplatelet therapy was effective.

Keywords: Acute coronary syndromes; Antiplatelets; Cardiology; Clopidogrel; Prasugrel; Ticagrelor

INTRODUCTION

Despite an early invasive strategy and revascularization therapy, mortality and morbidity in patients with acute coronary syndromes (ACS) with ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation ACS (NSTE-ACS) remain high. Antiplatelet therapy is a cornerstone of acute and long-term therapy in patients with ACS [1, 2]. Numerous trials have been performed to determine the optimal timing, optimal dose and optimal duration of various combinations of antiplatelet drugs. This manuscript summarizes the current status of antiplatelet treatment in patients with ACS with STEMI and NSTE-ACS.

ASPIRIN

Aspirin is one of the most frequently studied drugs and has been shown to improve prognosis in patients with STEMI and NSTE-ACS [3]. With a loading dose of 250–500 mg (orally or, as preferred in Europe, intravenously), inhibition of the cyclooxygenase A and attenuation of thromboxane A_2 is achieved within minutes. While in the US a maintenance dose of 325 mg has been preferred, in most European countries 100 mg is the standard. In the large Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS (CURRENT-OASIS) 7 trial [4] a dose of 75–100 mg was as effective as 300–325 mg with respect to ischemic events after 30 days, but associated with a reduction in minor bleedings (Table 1). It should be acknowledged that patients in the CURRENT-OASIS 7 trial were a low-risk group, indicated by the low combined endpoint rate of 4.3% after 30 days [4]. Therefore, it cannot be ruled out

Table 1 Results of the CURRENT-OASIS 7 study [4]

Aspirin dose	75–100 mg	300–325 mg	*P* value
Total group	$n = 12{,}579$	$n = 12{,}507$	–
CV death	2.3%	2.1%	NS
Myocardial infarction	2.1%	2.0%	NS
Stroke	0.5%	0.6%	NS
Combined endpoint	4.4%	4.2%	0.6 (NS)
Major bleeding	2.3%	2.3%	NS
Minor bleeding	4.4%	5.0%	0.04
Patients with PCI	$n = 8{,}639$	$n = 8{,}624$	
CV death	2.0%	1.8%	NS
Myocardial infarction	2.4%	2.3%	NS
Stroke	0.3%	0.4%	NS
Combined endpoint	4.2%	4.1%	NS
Major bleeding	1.3%	1.5%	NS

CURRENT OASIS Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS, *CV* cardiovascular, *NS* nonsignificant, *PCI* percutaneous coronary intervention

that higher doses of aspirin might be beneficial in higher risk ACS populations. However, in the majority of patients a maintenance dose of 75–100 mg aspirin is certainly sufficient.

ADENOSINE DIPHOSPHATE-RECEPTOR ANTAGONISTS

Current guidelines recommend dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP)-receptor antagonist after STEMI and NSTE-ACS [1, 2]. The ADP-receptor antagonist clopidogrel is labeled in a loading dose of 300 mg and a maintenance dose of 75 mg in patients with NSTE-ACS. This recommendation is based on the results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial [5]. However, a 600 mg loading dose is associated with a faster onset and higher level of platelet aggregation inhibition [6]. In the already mentioned CURRENT-OASIS 7 trial, the 600 mg loading dose followed by 2×75 mg daily over 7 days reduced ischemic events in patients with ACS treated with percutaneous coronary intervention (PCI), compared with the standard dose [7]. In the patients without PCI there was no benefit of the double-dose clopidogrel [4] (Table 2).

The optimal timing of initiation of clopidogrel therapy is still a matter of debate. In patients with STEMI and planned primary PCI the results of a small randomized trial [8] and large registries [9] suggest that the loading dose should be given at first medical contact, preferably in the prehospital phase in the ambulance. Since only very few patients with STEMI will be referred for immediate coronary artery bypass surgery, the risk of severe bleeding is not significantly increased with the prehospital loading dose.

Table 2 Results of the CURRENT-OASIS 7 study comparing two clopidogrel regimens [4]

Clopidogrel dose	300/ 75 mg	600/ 2 × 75 mg	*P* value
Total group	$n = 12{,}520$	$n = 12{,}566$	
CV death	2.2%	2.1%	NS
Myocardial infarction	2.2%	1.9%	0.09 (NS)
Stroke	0.5%	0.5%	NS
Combined endpoint	4.4%	4.2%	0.6 (NS)
Major bleeding	2.0%	2.5%	0.01
Patients with PCI	$n = 8{,}703$	$n = 8{,}560$	
CV death	1.9%	1.9%	NS
Myocardial infarction	2.6%	2.0%	0.01
Stroke	0.4%	0.4%	NS
Combined endpoint	4.5%	3.9%	0.04
Major bleeding	1.1%	1.6%	0.01

CURRENT-OASIS Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS, *CV* cardiovascular, *NS* nonsignificant, *PCI* percutaneous coronary intervention

Clopidogrel has several drawbacks: the delayed onset of action, the large interindividual variability in platelet response, and its irreversible effect on platelet inhibition [6]. The first two points are due to the two-stage activation process of clopidogrel, involving a number of cytochrome P450 isoenzymes, which are susceptible to drug–drug interactions and genetic polymorphisms. Patients with genetic polymorphisms have a reduced or a lack of metabolism of clopidogrel, and might therefore be good candidates for treatment with newer compounds [10].

Two new compounds, the nonreversible thienopyridine prasugrel and the reversible

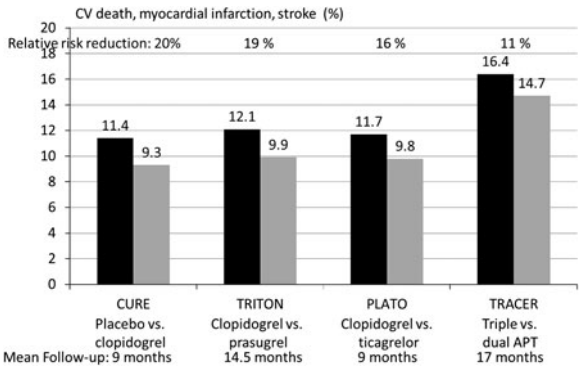

Fig. 1 Incidence of the combined clinical endpoint of cardiovascular death, myocardial infarction, and stroke in large randomized clinical trials comparing oral antiplatelet therapies in patients with acute coronary syndrome. *APT* antiplatelet therapy, *CURE* clopidogrel in unstable angina to prevent recurrent events trial, *CV* cardiovascular, *PLATO* PLATelet inhibition and patient outcomes, *TRACER* thrombin receptor antagonist for clinical event reduction in acute coronary syndrome, *TRITON-TIMI* TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction

cyclopentyl-triazolo-pyrimidine, ticagrelor, lead to a faster and more potent ADP-receptor inhibition, compared with clopidogrel [11, 12]. While prasugrel needs only one metabolization step, ticagrelor is an active drug which does not need metabolization to become active. In two large trials they were compared with the standard clopidogrel dose (300 mg loading dose followed by 75 mg) and were able to reduce the primary endpoint of cardiovascular death, myocardial infarction, and stroke significantly [13, 14] (Fig. 1). While the benefit of prasugrel in the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN (TRITON) with Prasugrel–Thrombolysis In Myocardial Infarction (TIMI; TRITON-TIMI 38) occurred early, the timing of benefit with ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial was somewhat delayed, but constantly growing over time.

There were important differences in design and patients between the two trials. In TRITON-TIMI 38 only ADP-receptor antagonist-naïve patients with NSTE-ACS and known coronary artery anatomy undergoing PCI and patients with STEMI scheduled for primary PCI were included. In contrast, in the PLATO trial, patients with the whole spectrum of ACS, regardless of the initial strategy were enrolled. Half of the patients were already pretreated with clopidogrel. Therefore, the results of these two trials cannot be compared directly. The 1-year cardiovascular mortality was lower in TRITON-TIMI 38 compared with PLATO (2.2% vs. 4.5%). The PLATO trial included a higher-risk group of ACS patients. However, in the PLATO trial a significant reduction in cardiovascular mortality (4.0% vs. 5.1%, $P = 0.001$) and all-cause mortality (4.5% vs. 5.9%, $P = 0.0003$) was observed. Patients with an impaired renal function had particular benefit from ticagrelor [15]. An important subgroup was the patients undergoing coronary artery bypass surgery [16]. Here, ticagrelor reduced total mortality from 9.7% to 4.7% ($P < 0.01$), without an increase in major bleeding complications. Patients with an intended conservative therapy also benefitted from ticagrelor [14]. The question as to whether ticagrelor should be given at first medical contact in patients with STEMI scheduled for primary PCI is currently being investigated in the randomized Administration of Ticagrelor in the Catheterization Lab or in the Ambulance for New sT elevation myocardial Infarction to open the Coronary artery (ATLANTIC) trial.

The results with prasugrel were particularly impressive in patients with STEMI [17] and with diabetes mellitus [18]. A subgroup in which prasugrel was associated with an unfavorable outcome are the patients with prior stroke/transient ischemic attack (TIA). In these patients, prasugrel is contraindicated.

Elderly patients (>75 years of age) and patients with lower body weight (<60 kg) had no benefit, and an increase in bleeding complications. It is likely that in these patients a lower dose of 5 mg prasugrel would be more appropriate. In the recently published TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial [19] a reduction of the prasugrel dose to 5 mg in the elderly and patients with a low body weight was associated with a somewhat higher but not statistically different bleeding complication, compared with clopidogrel. In this large clinical study, medically managed patients with NSTE-ACS were randomized in the subacute phase to prasugrel or clopidogrel. The primary endpoint was not statistically different between the two groups. However, in patients with angiographically documented coronary artery disease, prasugrel reduced the combined endpoint from 16.5% to 12.8% ($P = 0.001$). Another randomized study, A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction: ACCOAST seeking to determine the optimal timing of prasugrel in patients with NSTE-ACS scheduled for coronary angiography has been stopped prematurely, due to an increase in bleedings in the patients with a 30 mg loading dose before angiography [20]. Therefore, the optimal timepoint for administration of the loading dose of prasugrel in NSTE-ACS seems to be after visualization of coronary anatomy and the decision to proceed to PCI.

Both studies have been criticized because of the low loading dose of clopidogrel (300 mg), which certainly is associated with a delayed onset of action compared with the 600 mg dose [6]. This applies somewhat more to the TRITON-TIMI 38 study where all patients were ADP-receptor antagonist naïve. However, in the CURRENT-OASIS 7 trial the differences between the 300 and 600 mg loading dose were overall statistically negative [3] and not in the magnitude observed between prasugrel and clopidogrel in the TRITON-TIMI 38 trial [13]. In the ACAPULCO study, the 600 mg loading dose of clopidogrel was not as effective as prasugrel in patients with ACS [11]. In the PLATO trial the benefit of ticagrelor was somewhat delayed and the curves continued to diverge during the follow-up period, so a significant contribution of the loading dose is unlikely. In addition, almost half of the patients had received a clopidogrel loading dose before randomization, and in patients undergoing PCI an additional dose of 300 mg clopidogrel was given. The most recent ACS European guidelines [1] recommend clopidogrel only if prasugrel or ticagrelor are not available, while the American guidelines do not support the use of the new compounds so strongly [2].

Elinogrel is a reversible ADP-receptor antagonist which is available both in the intravenous and oral form. Therefore, it seems attractive for the treatment of ACS patients avoiding the problem of oral application in the acute phase, especially in patients who are not able to digest drugs (postresuscitation, intubation, vomiting, etc.). Elinogrel has been studied in a small pilot trial in patients with primary PCI for STEMI [21] and in a somewhat larger phase 2 study in patients with elective PCI [22]. Larger clinical trials are needed to determine the value of this new compound.

In summary, the newer ADP-receptor antagonists, prasugrel and ticagrelor, are able to achieve a more rapid and effective inhibition of platelet aggregation compared with clopidogrel. This is associated with a 1.9–2.2% absolute and 16–19% relative-risk reduction for

ischemic events, but with an increase of TIMI major noncoronary artery bypass graft (CABG)-related bleeding of 0.6%. Data looking at these new compounds in patients with the need for oral anticoagulation is lacking, therefore in those patients clopidogrel should be given. Other patient populations where we need more data regarding safety and efficacy of the new drugs are the elderly, patients with prior stroke (especially hemorrhagic stroke), and those with severe comorbidities, who were not included in the large randomized trials. For these patients, real-world data from large well-performed registries are needed to determine the safety and efficacy in clinical practice.

PLATELET THROMBIN RECEPTOR ANTAGONISTS

One of the most potent activators of platelet activation is thrombin. Thrombin activates platelets through two protease-activated receptors, PAR-1 and PAR-4. The inhibition of the PAR-1 receptor has been found to result in potent inhibition of thrombin-mediated platelet activation but appears to preserve primary hemostatic function [23]. Thus, selective PAR-1 inhibitors seem attractive substances for the treatment of patients with ACS. Recently, the results of a large clinical trial with vorapaxar, an oral PAR-1 antagonist, were reported [23]. Patients with ACS <24 h duration treated with standard therapy were given vorapaxar or placebo, and followed for a mean of 500 days. More than 98% of patients were on aspirin and 91% received clopidogrel. Therefore, this trial explored triple versus double antiplatelet therapy. While the primary endpoint of cardiac death, myocardial infarction, stroke, rehospitalization, or urgent coronary revascularization was not significantly reduced (18.5% vs. 19.9%, $P = 0.07$), the main secondary endpoint of cardiac death, myocardial infarction, and stroke occurred significantly less frequently with vorapaxar (14.7% vs. 16.4%, $P = 0.03$) (Fig. 1). The rate of TIMI major bleeding complications was increased with vorapaxar (3.1% with vorapaxar vs. 2.1% with placebo, $P < 0.01$). In the **T**hrombin **R**eceptor **A**ntagonist in **S**econdary **P**revention of atherothrombotic ischemic events (TRA-2P) study in patients randomized in the subacute or chronic phase after myocardial infarction, vorapaxar reduced the combined endpoint compared with placebo from 9.7% to 8.1% ($P < 0.001$) [24].

In summary, vorapaxar seems an attractive new alternative in the spectrum of antiplatelet agents used in patients with ACS. Further research is needed to define the place of vorapaxar in the treatment of ACS patients. So far, it is the only antiplatelet therapy which has shown a benefit as an add-on to aspirin >12 months after the acute event [24]. In the acute and subacute phases it has only been tested as add-on to dual antiplatelet therapy; therefore, it would be of interest to have a direct comparison with an ADP-receptor antagonist in patients with a baseline therapy of aspirin after ACS.

Another PAR-1 inhibitor, atopaxar, has been studied in two small trials in patients with ACS [25, 26]. It decreased ischemia on holter monitoring and was associated with a nonsignificant increase in the rate of major TIMI bleeding complications [25]. So far, no large clinical study has been performed with this compound.

THE PROBLEM OF BLEEDING DEFINITIONS

In recent years it has become clear that not only the ischemic events but also bleeding

contribute to the mortality of patients with ACS. If antiplatelet treatment becomes more intense and effective, this is usually associated with an increase in bleeding complications. In order to be able to compare the efficacy and safety of new antiplatelet regimens, a unique definition of bleeding complications would be desirable [27]. Unfortunately, large clinical trials have used different definitions for bleedings [28]. In Table 3, bleeding complications in the different large clinical trials with oral antiplatelet therapy for ACS patients are summarized.

In Fig. 2 the non-CABG-related major bleeding rates after 30 days are depicted. Looking at Table 3 and Fig. 2 it becomes clear that the rate of CABG procedures and the definition of bleeding complications contribute majorly to the bleeding rates. Therefore, it seems rather difficult to compare bleeding complication rates between the trials. The commonly used comparator therapy was aspirin and the standard therapy was clopidogrel (300/75 mg). With this therapy, bleeding rates were by far not identical in the trials, again underscoring the problems of comparing therapies indirectly. Overall, the results show that a more effective platelet inhibition is associated with higher bleeding rates.

Table 3 Bleeding complications in different trials with clopidogrel 300 mg loading dose and 75 mg maintenance dose as comparator

CURE 9 months	**Placebo**	**Clopidogrel 300 mg/75 mg**	***P* value**
CURE bleeding	2.7%	3.7%	<0.01
TIMI major bleeding	1.2%	1.1%	NS
CURRENT-OASIS 7 30 days	Clopidogrel 300 mg/75 mg	Clopidogrel 600 mg/150 mg	
CURRENT-OASIS 7 major	2.0%	2.5%	<0.01
Non-CABG TIMI major	1.3%	1.7%	<0.01
TRITON-TIMI 38 15 months	Clopidogrel 300 mg/75 mg	Prasugrel	
TIMI major	1.9%	2.5%	0.03
Non-CABG TIMI major	1.8%	2.4%	0.03
PLATO 12 months	Clopidogrel 300 mg/75 mg	Ticagrelor	
PLATO defintion	11.2%	11.6%	NS
Non-CABG TIMI major	2.0%	2.6%	0.02
TRACER	Dual APT	Dual APT + vorapaxar	
GUSTO severe or moderate	4.5%	6.1%	<0.01
Non-CABG TIMI major	1.1%	2.0%	<0.01

APT antiplatelet therapy, *CABG* coronary artery bypass graft, *CURE* Clopidogrel in Unstable Angina to Prevent Recurrent Events trial, *CURRENT-OASIS* Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS, *GUSTO, NS* nonsignificant, *PLATO* PLATelet inhibition and patient Outcomes, *TIMI* thrombolysis in myocardial infarction, *TRACER* Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome, *TRITON-TIMI 38* TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction

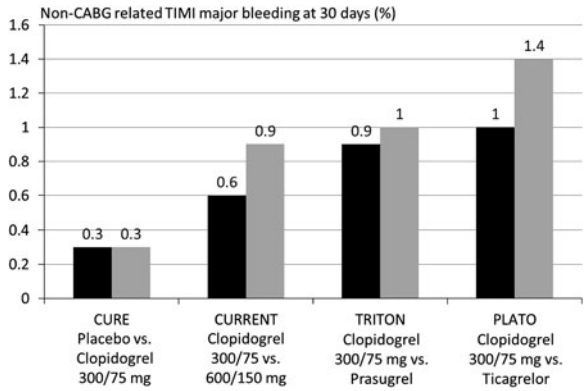

Fig. 2 Incidence of noncoronary artery bypass graft related major bleeding complications after 30 days in trials involving the standard clopidogrel dose of 300/75 mg in one randomized group. *CABG* coronary artery bypass graft, *CURE* clopidogrel in unstable angina to prevent recurrent events trial, *CURRENT-OASIS* Clopidogrel optimal loading dose usage to reduce recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS, *PLATO* PLATelet inhibition and patient Outcomes, *TIMI* thrombolysis in myocardial infarction, *TRITON-TIMI* TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction

BEDSIDE MONITORING FOR THE ADJUSTMENT OF ANTIPLATELET THERAPY

There are numerous reports about the predictive value of a high on-treatment platelet reactivity in clopidogrel-treated patients for ischemic events. However, trials aiming to adjust ADP-receptor therapy with various platelet function tests were all negative [29]. The most recent one, the ARCTIC trial, measured platelet function with the VeryNow Assay™, (Accumetrics, San Diego, CA, USA) in patients undergoing PCI [29]. Adjustment of antiplatelet therapy compared with standard treatment did not reduce the primary ischemic endpoint or bleeding complications. Therefore, so far there seems to be no indication for the monitoring of platelet function in patients treated with various antiplatelet regimens.

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