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An update of dual antiplatelet therapy

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Abstract
Since platelet activation and aggregation play a major role in thrombus formation in lumen of coronary arteries, they constitute a main target in treatment of stable ischemic heart disease and acute coronary syndromes. Antiplatelet therapy should be commenced as early as possible within the current indications in order to reduce the risk of both acute ischemic complications and recurrent atherothrombotic events. Platelet functions can be inhibited by three classes of drugs having different mechanisms of action, namely acetylsalicylic acid, P_2Y_{12} inhibitors, and glycoprotein IIb/IIIa antagonists. Dual antiplatelet therapy (acetylsalicylic acid and P_2Y_{12} inhibitors) have recently been a hot topic of research with the advent of stents in recent years. Multiple regimens of antiplatelet and anticoagulation therapy have been used in the past in patients undergoing percutaneous coronary intervention. The optimal duration of dual antiplatelet therapy after drug-eluting stent implantation is unclear. Many clinicians have pushed for prolonged dual antiplatelet therapy — beyond 12 months — on the assumption that extended therapy reduces recurrent cardiovascular events. Despite the established guidelines, there is not a clear consensus about how to manage antiplatelet therapy. New antiplatelet agents have been developed for patients at high risk of thrombosis. Their benefits in terms of mortality and major cardiovascular events have been demonstrated, but some concerns remain regarding the possible increase in bleeding.The aim of this review was to summarize the current literature containing the potential solutions to problems related to indications and duration of dual antiplatelet therapy and its interaction with other medications.

Keywords: Dual Antiplatelet Therapy; Drug Eluting Stent; P_2Y_{12} Inhibitors; Proton Pump Inhibitors.

INTRODUCTION

Platelets play a major role in pathological thrombosis due to their capacity to adhere to damaged walls as well as they serve as a vital part of normal hemostasis. They manifest themselves as a result of fragmentation of cytoplasms of megakaryocytes on bone marrow, and their life span in circulation is 10 days in average. 10^{11} platelets are reproduced on a daily basis under physiological conditions while this may increase up to 10 times in case of a rising need (1).

Antiplatelet therapy is a commonly-adopted procedure for treatment and prevention of myocardial infarction (MI) and percutaneous coronary interventions (PCI) as well as neurological cases such as transient ischemic attacks and strokes, peripheral arterial diseases, anti-phospholipid syndrome, and hematological cases such as hyperactive platelet syndrome.

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Effect Mechanisms of Anti-Platelet Agents

Platelet activation is comprised of many steps starting with interaction of platelets with robust endothelium. Thrombus formation takes places in 3 stages. The first step is the initial phase which is followed by diffusion and tightening stages. At the first stage, platelets form a layer on collagen matrix under the endothelium. Von Willebrand factor (vWF) and P-selection of endothelium surface molecule play a role in contact of platelets with endothelium and settlement in the subendothelium. The fact that Von Willebrand factor is binding to the glycoprotein Ib receptor serves as a critical point of adhesion (2-3). Collagen underneath the endothelium directly interacts with glycoprotein VI and Ia receptors on platelets, stimulates platelets, ADP and TxA2 receptors, and consequently GP IIb/IIIa receptor is activated. This receptor is rapidly and tightly bound to fibrinogen and causes platelets to form a potent and robust thrombus (4). Formed by calcium from prothrombin via prothrombin activator, thrombin takes effect over the receptor (PAR-1) activated by protease. That thrombin integrates fibrinogen into fibrin makes thrombus formation even more tight.

Current Antiplatelet Agents

Activity of acetylsalicylic acid (ASA), which is one of the most common agents put to use for antiplatelet therapy, is limited to the irreversible acetylation of thrombocyte cyclooxygenase-1 which serves as a potent stimulant of

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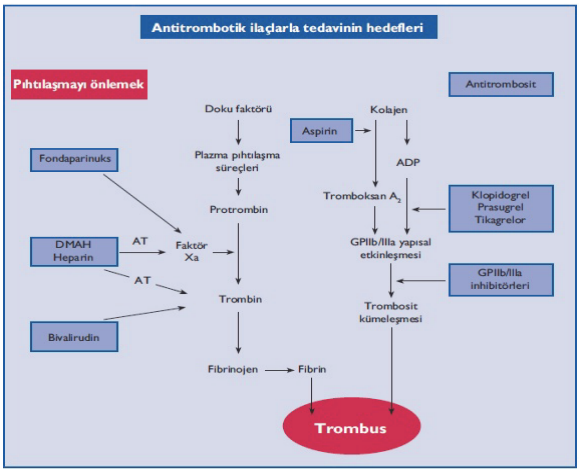
thrombocyte aggregation and hinders thromboxane A2 formation. Thienopiridines block the signal of P2Y12 receptor and inhibit the platelet activation via ADP, and limit the transformation of glycoprotein IIb-IIIa into its active form. Binding of two platelets to each other is achieved through GPIIb/IIIa integrin receptor. GP IIb/IIIa antagonists inhibit the platelet activation through direct inhibition of glycoprotein IIb/IIIa integrin receptor, and block the final common pathway of platelet aggregation (5). Enabling to transform fibrinogen into fibrin, thrombin provides the irreversible binding of two platelets to each other. Thanks to this effect, thrombin plays an essential role in thrombus formation and serves as the most effective one among all thrombocyte activators (collagen, ADP, TxA2, thrombin, epinephrine etc.) (2-6). Thrombin receptor antagonists and new P2Y12 inhibitors are acknowledged as major novelties in antiplatelet therapy (Figure 1).

Figure 1. Purpose of therapy through antithrombotic drugs



Acetylsalicylic Acid (ASA)

Dating back to thirty years ago and remaining in effect as of today, all the up-to-date studies have proved that ASA decreases the prevalence of mortality or recurrent MI in stable and unstable coronary artery diseases. ASA is a standardized therapy which has been administered for years in stable angina pectoris (SAP), unstable angina pectoris and non-ST-segment elevation myocardial infarction (NSTEMI). Since ASA safely inhibits cyclooxygenase-1 (COX-1), it does not require to follow up its effects except for cases where drug resistance may offer help for treatment planning. non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen can reversibly block COX-1, and irreversibly inhibit ASA leading to potential prothrombotic effects through COX-2 inhibition. NSAIDs should be avoided as they may increase the risk of ischemic events (8). ASA is the most common antithrombotic drug to treat cardiovascular diseases while its safety and the "ASA resistance" issues into question as some patients have experienced vascular thromboembolic events following ASA therapy. Laboratory tests refer to some terms such as "incomplete-responders", "poor-responders", and "ASA failure" for cases where ASA effect is poor or insufficient. The term "ASA non-responders" was proposed instead of "ASA resistance" for cases where platelet aggregation persists even though ASA sufficiently inhibits the thromboxane synthesis. ASA resistance can be evaluated by clinical or laboratory characteristics. While the main reason behind ASA resistance has yet to be fully unrevealed, many mechanisms including genetic abnormalities play a role in this regard. It is of critical importance to prospectively investigate the ASA resistance before initiating a long-term antiplatelet therapy with ASA. Many studies have proved that the use of ASA prior to an acute event for patients with acute coronary syndromes (ACS) is associated with positive outcomes such as less NSTEMI and a smaller infarct site growth (9-10). Despite all these apparently positive findings, there are also some studies which show that ASA use prior to an acute event results in worse long-term outcomes for patients (11). As a result of ESSENCE study, it was determined that 84% of the patients were previously administered with ASA, and these patients were found out to have more mortality, MI, need for urgent revascularization and the use of enoxaparin was deemed more suitable (12). This may stand for ASA resistance and the need for a more effective antiplatelet therapy in such cases.

Reference to ASA in Current Guidelines

The role played by ASA for stable ischemic heart diseases and ACS patients, and Class-1 indications are presented in Table 1.

Table 1. Reference to ASA in Current Guidelines

- 75-150 mg ASA is recommended before elective PCI. (ESC SAP- 2013)
- Daily low-dose ASA is recommended for stable patients. (ESC SAP- 2013)
- ASA should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it. (ACC/AHA NSTEMI-2012)
- ASA 162 to 325 mg should be given before primary PCI. (ACC/AHA STEMI-2013)
- After PCI, ASA should be continued indefinitely. (ACC/AHA STEMI-2013)

Thienopiridines

1-Ticlopidine: It takes effect through the ADP-dependent pathway of platelet activation. It requires transformation into an active form after orally administration. It takes permanent effect against platelet protein as a ADP receptor or a part of a platelet membrane associated with an ADP receptor, and inhibits platelet aggregation induced by ADP. Ticlopidine may lead to severe neutropenia for 1% of patients which is reversible upon a frequent discontinuation of medication. Very rarely, thrombotic thrombocytopenic purpura may manifest itself at a rate of 0.02% within 2 to 8 weeks following the ticlopidine therapy. In recent years, its use has declined due to neutropenia and thrombocytopenia accompanied by ticlopidine while the use of its derivative called clopidogrel, which allows for no side effect, has been increasingly administered. In case it is used along with ASA, clopidogrel is proved to show similar effects with ticlopidine in preventing stent thrombosis (13).

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2-Clopidogrel: It is the most commonly-used member of thienopiridine class of drugs that inhibits adenosine diphosphate P2Y12 receptor. Its effect in clinical use of ticlopidine is proven whereas its side-effect profile lies with the clopidogrel thienopiridine class of drugs with a more benign and a faster onset of action. What structurally differs in clopidogrel from ticlopidine is the fact that it has an additional carboxymethyl group. This similarity in chemical structure shows that many functional characteristics of clopidogrel is similar with that of ticlopidine. Clopidogrel, which is inactive in vitro, is metabolically activated by liver cytochrome P4503A4 enzyme. It is irreversibly bound to P2Y12 ADP receptor located on this active metabolite platelet membrane, and it makes the receptor inactive all the time. This procedure biochemically takes place when the clopidogrel repeats the disulphide bond on the receptor. The inactivation of this receptor results in inhibition of dose-dependent platelet aggregation. The elimination half life of an active metabolite is 8 hours. As it is the case for ASA, it is possible to fix platelet functions by means of thrombocyte infusions or waiting for the formation of a new platelet in case of absence of active drug.

Up-to-date guidelines recommend the use of clopidogrel for 1 years irrespective of stent implantation for ACS patients. CAPRIE study (Clopidogrel versus ASA Patients at risk of Ischemic Events) compared clopidogrel+ASA with primary outcome points (ischemic stroke, ME, mortality caused by vascular factors) for high-risk patients. The study reports that the use of clopidogrel decreases the cardiovascular events 8.7% (14). Carried out in a randomized way for patients with complaints of ACS, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) and COMMIT/CCS 2 (Clopidogrel and Metaprolol in Myocardial Infarction Trials) studies show that a combination of ASA and clopidogrel rather than ASA on its own significantly decreases secondary endpoints caused by recurrent MI and cardiovascular mortality (15,16). The results of PCI-CURE sub-group's study strongly corroborates administering clopidogrel preloading and continuing to do so for a long time for ACS patients except for STEMI regardless of whether a PCI is made or not (17). CLARITY-TIMI 28 study (Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28) compared clopidogrel (75 mg/day following 300 mg of loading dose) with placebo in addition to the standard therapy including ASA for patients about whom a fibrinolytic therapy is opted for. According to the follow-up results of the groups for 30 days, the group of clopidogrel achieved a relatively 20% decrease in combined mortality outcomes caused by urgent revascularization, recurrent MI and cardiovascular nortality (18). Tackling patients who were deemed suitable for PCI, the analysis over PCI-CLARITY sub-group proved the effect of clopidogrel on patients who undergo PCI (19).

Recurrent MI rates still are at a high level in spite of a dual antiplatelet therapy administered through ASA and clopidogrel. Resulting from pathways where genetic polymorphism and clopidogrel are metabolized, drug-drug interactions block the platelet inhibition at the same rate for all patients (20, 21). CURRENT–OASIS 7 (Clopidogrel and ASA Optimal Dose Usage to Reduce Recurrent Events−Seventh Organization to Assess Strategies in Ischemic Syndromes) study (22) compared the use of clopidogrel in a standard dose (75 mg) with the use of clopidogrel in a double dose (150 mg) to maximize the platelet inhibition, and the anticipated benefit could not be yielded to a satisfactory extent. The fact that a part of the patients experienced some thrombotic events in spite of a dual antiplatelet therapy shifted the focus on looking into variability of responses to clopidogrel and poor P2Y12 inhibition for some patients. In spite of clopidogrel therapy, the increase platelet activity is related to undesired events. In this case, a of high dose of clopidogrel or another potent antiplatelet drug would be the choice for therapy. A great deal of mechanisms have been put forth to look into clopidogrel resistance or non-response while some of them argued that genetic factors play a major role in non-response to clopidogrel therapy. Many mechanisms have been held accountable for the development of resistance to clopidogrel. Such mechanisms are divided into two main groups: external and internal. External mechanisms are comprised of insufficient drug dose and changes in absorption and metabolism caused by non-compliance to therapy, use of low dose and increased body surface area that lead to a decline in clopidogrel bio-availability, and drug interactions that affect bio-transformation of a drug (23). Internal mechanisms are differences among individuals in terms of P2Y12 receptor's gene and other gene polymorphism as well as CYP 3A enzyme system's metabolic activity.

Various options of therapy have been brought forward given the variability of responses to clopidogrel therapy and the prevalence of recurrent ischemic events for patients not responding to therapy. Current guidelines recommend for the analysis of response to clopidogrel through various tests when it comes to a case where stent thrombosis may be mortal for a patient with a coronary stent (unprotected left main coronary and left main coronary bifurcation etc.). In case the inhibition for thrombocyte aggregation is below 50% as a result of such tests, it is recommended to use clopidogrel for 150 mg/day rather than 75 mg as a class IIb indication whereas there is no sufficient data to corroborate this procedure (24). While patients with no sufficient response to clopidogrel pose a high risk for ischemic complications that may manifest themselves following PCI, there is no easily-performed test with high reliability to detect resistance to antithrombocyte drugs. A recently-released study reported that the response to clopidogrel was tested by a simple and rapid test (point-of-care) for patients treated with a drug-eluting stent (DES), and that the prevalence of ischemic events including stent thrombosis turned out to be higher for patients with high activity of thrombocyte in spite of clopidogrel therapy. However, a significant part of the patients showed no sign of any ischemic event even though no-response to clopidogrel was on a high level (25). Until we are equipped with results of randomized prospective studies on new tests and alternative means of therapy, it is not recommended to perform a routine

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antithrombocyte drug resistance test prior to any PCI. With that being said, current tests suffice to find out the response to clopidogrel for patients who may be mortal due to ischemic complications in particular (left main coronary interventions, interventions on single remaining patent coronary artery).
The quest for an agent with a potent effect and less risks of bleeding following acute coronary syndromes and a coronary artery stenting procedure has led us to studies on new antiplatelet agents. Characteristics of an ideal antiplatelet agent are presented in Table 2.

Table 2. Characteristics of An Ideal Antiplatelet Agent

1- Predictable hemodynamic characteristics
2- Requires no monitoring to follow up
3- Fast onset of action
4- Rapid termination of effects or equipped with an antidote.
5- Potent thrombotic effect
6- Low risk
7- Cost effective
8- Easily-administered

3-Prasugrel: Prasugrel is an oral 3rd generation thienopiridine that blocks thrombocyte ADP P2Y12 receptor specific and irreversible. It is 10 times more effective than clopidogrel while platelet responses among patients vary less. There is no interaction with proton pump inhibitors (PPI) and CYP2C19 gene code polymorphism. JUMBO TIMI Phase II dosage study made a comparison for 904 patients administered with either elective or urgent PCI. 30-day major adverse cardiac events were less common in prasugrel group while it put forth significant clinical responses when compared to clopidogrel, and it was well tolerated with no difference in prevalence of bleeding (26) PRINCIPLE TIMI 44 study showed that the prasugrel group yielded more platelet inhibition and less resistance on hour 6 when compared to a high dose of clopidogrel (600 mg loading) (27). TRITON-TIMI-38 study made a comparison between prasugrel administered on 60 mg of loading dose at first and on 10 mg dose later on, and clopidogrel administered on 300 mg of loading dose and 75 mg daily dose for patients to be administered with a primary PCI following coronary angiography and who suffered from ST-Elevation MI (STEMI) but not administered with clopidogrel or recently underwent STEMI or Non-ST Elevation MI (NSTEMI) patients with moderate to high risks. 11.2% of patients administered with clopidogrel and 9.3% of patients administered with prasugrel yielded primary composite outcomes (mortality caused by cardiovascular factors, non-fatal MI or stroke), and the MI risk declined to a significant extent (28). A definite or potential stent thrombosis (as defined by ARC) in all patient cohorts declined to a significant extent in prasugrel group when compared to clopidogrel group while life-threating bleeding significantly increased. A greater benefit was yielded for diabetic patients without any increase in bleeding risks. No difference was detected in terms of the drug effectiveness among patients with (CrCl <60 ml/min.) or without (CrCl >60 mL/min.) a renal disorder. This study showed that it yields no clinical benefit for patients with an age of ≥75 or low body weight (<60 kg), and that it is detrimental to patients with a history of stroke/transient ischemic attack (TIA). While Canadian and American guidelines recommend to sustain 5 mg/day for patients over 75 years of age or below 60 kg in weight in an effort to mitigate the risk of bleeding, such recommendations are based on pharmacokinetics and they have yet to be validated by clinical trials (29-30). Recently concluded, the randomized double-blind TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study did not opt for PCI, instead administered all of 7243 medically-monitored patients with ASA for 100 mg, and randomized to clopidogrel and prasugrel branch. The two groups proved no significant difference in terms of composite cardiovascular outcomes (mortality caused by cardiovascular factors, non-terminal MI, non-terminal stroke) while no significant difference was detected for major bleeding, either (31). Given the results of this study, it is concluded that prasugrel is not superior to clopidogrel for medically-treated ACS patients.

4-Ticagrelor: It is an oral and reversible P2Y12 antagonist. It offers a direct effect without any need for sit-P450 bio-transformation unlike clopidogrel and prasugrel. Its fast onset of action is effective (a full P2Y12 receptor inhibition 2 hours after the intake) while its half life accounts for 12 hours, and it shows low affinity for a P2Y12 receptor. It is non-thienopiridine and a member of cyclopentyl-triazole-pyrimidine which is a new class of antiplatelet. ONSET/OFFSET phase II study (32) detected a faster and a full P2Y12 receptor inhibition when compared to clopidogrel. RESPOND phase II study (33) yielded an effective platelet inhibition through ticagrelor for all the patients who previously did or did not response to clopidogrel. DISPERSE and DISPERSE-2 phase II dosage studies (34) reported an increase in total bleeding when compared to clopidogrel when used for 90 and 180 mg 2x1 but detected no difference in ischemic events. Carried out in an effort to prove effectiveness and reliability, Phase III clinical trial named PLATO (Study of Platelet Inhibition and Patient Outcomes), randomized patients who suffer from NSTEMI with a planned invasive therapy and moderate to high risks or STEMI patients with a planned primary PCI to clopidogrel with 300 mg of loading dose, 75 mg of maintenance dose or ticagrelor with 180 mg of loading dose and 90 mg of maintenance dose for twice a day. 12-month follow-up pointed out that the prevalence of a primary composite activity outcome (cardiovascular-dependent mortality, MI or stroke) in all patient cohorts was 11.7% in clopidogrel group while it decreased to 9.8% in ticagrelor group. The cardiovascular-dependent mortality rate significantly decreased from 5.1% to 4% while the MI rate, which previously stood at 6.9%, decreased to 5%. No significant difference was identified in the number of stroke cases. The definite stent thrombosis rate decreased from 1.9% to 1.3% ($p< 0.01$) while the total mortality rate decreased from 5.9% to 4.5% ($p<0.001$). Clopidogrel and ticagrelor groups proved no significant difference between each other in terms of major bleeding rates. Major bleeding events, which are not dependent on coronary artery bypass grafting surgery

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(CABG), accounted for 3.8% for clopidogrel group and 4.5% for ticagrelor group. Major bleeding rates associated with CABG are similar for ticagrelor and clopidogrel groups. While the total terminal intracranial bleeding rates were higher in ticagrelor group, the groups proved no difference in terms of terminal bleeding rates (35). Other than an increase in small-scale bleeding events or major bleeding events not associated with CABG, the adverse effects of ticagrelor include dyspnea, an increase in prevalence of ventricular pauses, and asymptomatic increases on uric acid levels (36). Triggered by ticagrelor, dyspnea manifests itself most commonly (up to 15%) within the first week of therapy. While dyspnea can be transient, it may be rarely severe to an extent where therapy would have to be halted. Ticagrelor-associated ventricular pauses are usually in asymptomatic nocturnal sinoatrial forms. The mechanism of dyspnea and ventricular pauses has yet to be found out.

5-Cangrelor: Cangrelor is an intravenous (IV) ATP analog and a potent reversible P2Y12 receptor inhibitor. Unlike clopidogrel, prasugrel and ticagrelor, it has a direct effect by means of intravenous administration, and it does not have to be transformed from liver to an active metabolite. Due to its extremely fast onset of action (a few seconds), extremely fast duration of action (20 mins.) and short half life (3-6 mins.), it becomes attractive for cases that require PCI and an urgent surgery. CHAMPION-PCI (Comparing Cangrelor to Clopidogrel in Subjects Who Require PCI) study is a randomized and multicentre study including 8877 stable coronary artery patients, and patients with acute coronary syndrome while CHAMPION-PLATFORM study was performed on 5362 patients, with complaints of unstable angina pectoris (USAP) and NSTEMI, by administering them with IV bolus in line with coronary angiography test results prior to PCI, and infusion cangrelor or placebo for 2 hours.. CHAMPION-PCI study reported a non-significant increase in major bleeding for cangrelor group while CHAMPION-PLATFORM study put forth a significant decrease in mortality and stent thrombosis and a significant increase in major bleeding for cangrelor group (37,38).

General characteristics of thienopiridines are presented in Table 3. The references to thienopiridines in current guidelines are presented in Table 4, 5 and 6.

Table 3. General characteristics of thienopiridines

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg orally then75mg a day	60 mg orally then 10mg a day	180 mg orally then 90 mg twice a day	30 µg/kg bolus and 4 µg/kg/min infusion
Dosing in CKD				
Stage 3	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Stage 4	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Stage 5	Use only for selected indications	No dose adjustment	No dose adjustment	No dose adjustment
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with variable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading dose effect	2–6 hours	30 min	30 min	2 min
Duration of effect	3-10 days	7-10 days	3-5 days	1-2 hours
Withdrawal before surgery	5 days	7 days	5 days	1 hour
Plasma half life	30-60 min	30-60 min	6-12 hours	5-10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes - inactive metabolite only

Table 4. Recommendations of Antiplatelet Therapy for Stable Coronary Artery Disease (ESC SAP- 2013)

Class-I Indications
- A loading dose of a clopidogrel should be given before elective PCI

Class-2a Indications
- Prasugrel and ticagrelor should be given for stent thrombosis under clopidogrel theraphy

Class-2b Indications
- Prasugrel and ticagrelor should be given for high risk patients before elective PCI

Class-3 Indications
- Clopidogrel should not be administered for unknown coronary anatomy
- Prasugrel and ticagrelor should not be given for elective low risk PCI

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Table-5. Recommendations of Antiplatelet Therapy for NSTEMI (ACC/AHA NSTEMI-2012)

Class I

- A loading dose followed by daily maintenance dose of either clopidogrel, prasugrel (in PCI treated patients) or ticagrelor should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major GI intolerance
- Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected should receive dual antiplatelet therapy on presentation.
- Before PCI: Clopidogrel, ticagrelor, IV GP IIb/IIIa inhibitor
- At the time of PCI: Clopidogrel, prasugrel, ticagrelor, IV GP IIb/IIIa inhibitor
- For UA/NSTEMI patients in whom an initial conservative (ie, noninvasive) strategy is selected, clopidogrel or ticagrelor (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for up to 12 months
- A loading dose of P2Y12 receptor inhibitor therapy is recommended for UA/NSTEMI patients for whom PCI is planned one of the following regimens should be used:

1. Clopidogrel 600 mg should be given as early as possible before or at the time of PCI or
2. Prasugrel 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI or 3.Ticagrelor 180 mg should be given as early as possible before or at the time of PCI

- If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by, P2Y12 receptor inhibitor therapy, earlier discontinuation should be considered

Class 2a

- For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with aspirin, a P2Y12 receptor inhibitor (clopidogrel or ticagrelor), and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa inhibitor before diagnostic angiography
- For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier than planned catheterization or PCI

Class 2b

- For UA/NSTEMI patients in whom an initial conservative (ie, noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy
- Prasugrel 60 mg may be considered for administration promptly upon presentation in patients with UA/NSTEMI for whom PCI is planned, before definition of coronary anatomy if both the risk for bleeding is low and the need for CABG is considered unlikely
- The use of upstream GP IIb/IIIa inhibitors may be considered in high-risk UA/NSTEMI patients already receiving aspirin and a P2Y12 receptor inhibitor (clopidogrel or ticagrelor) who are selected for an invasive strategy, such as those with elevated troponin levels, diabetes, or significant ST-segment depression, and who are not otherwise at high risk for bleeding In patients with definite UA/NSTEMI undergoing PCI as part of an early invasive strategy, the use of a loading dose of clopidogrel of 600 mg, followed by a higher maintenance dose of 150 mg daily for 6 days, then 75 mg daily may be reasonable in patients not considered at high risk for bleeding

Class 3

- In UA/NSTEMI patients with a prior history of stroke and/or TIA for whom PCI is planned, prasugrel* is potentially harmful as part of a dual antiplatelet therapy regimen

Table 6. Recommendations of Antiplatelet Therapy for STEMI (ACC/AHA STEMI-2013)

Class 1

- A loading dose of a P2Y12 receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:
  - Clopidogrel 600 mg
  - Prasugrel 60 mg
  - Ticagrelor 180 mg

  P2Y12 inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (bare-metal or drug-eluting) during primary PCI using the following maintenance doses
  - Clopidogrel 75 mg daily
  - Prasugrel 10 mg daily
  - Ticagrelor 90 mg twice a day

Class 2b

- Continuation of a P2Y12 inhibitor beyond 1 year may be considered in patients undergoing drug-eluting stent placement

Class 3

- Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack

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Current Guidelines and Unsettled Questions

In the light of current information and guidelines, the hope to form an effective antiplatelet activity has been restored upon the inclusion of new antiplatelet agents into clinical trials whereas it is a fact that clinicians have yet to reach a consensus over an effective and reliable platelet inhibition.

Argumentative subjects, past and ongoing studies are summarized as follows:

1-Is it possible to administer with prasugrel pre-treatment for NSTEMI patients prior to imaging of coronary artery anatomy?

Even though administering pre-treatment through P2Y12 antagonists prior to percutaneous coronary interventions is an effective method of treatment covered by guidelines, it is concluded that this would not yield the anticipated benefit as it would increase the bleeding risk when the bleeding risk and ischemic complications are considered in tandem. Carried out on this subject, ACCOAST (A Comparison of prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction) is a randomized double-blind study and randomized to prasugrel, pre-treatment and placebo branches prior to imaging of coronary anatomy for NSTEMI patients. The pre-treatment group was administered with 30 mg additional dose in case of any PCI indication following 30 mg prasugrel loading while the group with no pre-treatment was administered with placebo, and 60 mg prasugrel loading in case of any PCI indication. While the two groups proved no significant difference in terms of cardiovascular mortality, MI, stroke and need for urgent revascularization, 7-day follow-up revealed that all TIMI (Thrombolysis in Myocardial Infarction) major bleeding rates increased by 2 folds in the pre-treatment group and by 3 to 6 folds in life-threatening forms of bleeding (39). In conclusion, administering pre-treatment through prasugrel prior to coronary angiography within the first 48 hours following the admission of NSTEMI patients is not effective or reliable.

2- Is it possible to customize an antiplatelet therapy?

The pharmacodynamic response to clopidogrel depending on factors such as genotype polymorphism varies to a significant extent. Some patients may show signs of increase thrombocyte activity even though they are administered with clopidogrel on sufficient doses. The definition of clopidogrel resistance is controversial whereas it is divided into two. The first one is laboratory clopidogrel resistance, and defined as insufficient in vitro antithrombocyte effect. The other one is clinical clopidogrel resistance. It is proved that a high level of thrombocyte reactivity after a clopidogrel treatment is associated with an increase in risks for stent thrombosis (40, 41). While genetic tests are not routinely performed in clinical practices, thrombocyte function tests are performed in an attempt to define those with an insufficient response to clopidogrel (42). Angiolillo et al. (43) showed that CYP3A4 gene polymorphism alters thrombocyte activation for patients administered with clopidogrel, and that this may curb the effectiveness of clopidogrel for such patients. In a recently-released study, Collet et al. (44) showed that CYP2C19*2 gene polymorphism is associated with negative prognosis and stent thrombosis for patients with a history of MI at an early age (<45 age) and administered with clopidogrel. The same cytochrome was analyzed by TRITON-TIMI 38 study for patients who carry a P 450 genetic variant and are administered with clopidogrel. The active metabolite of clopidogrel for patients carrying a genetic variant was less than of those carrying no such genetic variant. The thrombocyte inhibition turned out to be less while cardiovascular events including stent thrombosis seemed to be in a higher prevalence (45). Lau et al. (46) reported that the response to clopidogrel depends on metabolic activity of CYP3A4 enzyme. The activity of this enzyme that turns clopidogrel into an active form was found to be low for patients with no sufficient platelet inhibition through clopidogrel in particular. Interestingly, clopidogrel antiplatelet activity seemed to recover as they were administered with rifampicin that increases the activity of this enzyme.

While tests on platelet reactivity planned to be made in a bedside mode seem to be a new hope for resistance to clopidogrel, studies have yet to detect a significant clinical outcome. ARCTIC (Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care) study reported that platelet reactivity and genetic tests are not effective in customizing an antiplatelet therapy, and that no significant difference has been made in risks for stent thrombosis (47). In today's world, performing thrombocyte function tests on a routine basis is not recommended for ACS patients treated with clopidogrel.

3- Is it possible to enhance effectiveness if we carry out more platelet receptor blockages?

The effect of inhibiting more than one aggregation pathway on decreasing ischemic complications has been analyzed and some new drugs such as vorapaxar have been put forth. Vorapaxar is a PAR-1 (protease-activated receptor) antagonist and it inhibits the platelet aggregation selectively induced by thrombin. Platelet inhibition through thrombin has been viewed as a more reliable way. TRACER (Executive and Steering Committees The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) study reported that the addition of vorapaxar to the standard dual antiplatelet therapy for NSTEMI patients yielded no significant decline in cardiovascular mortality, MI and stroke, and increased all bleeding rates including intracranial bleedings (48). This approach is currently avoided due to the fact that it gives rise to an increase in bleeding rates.

4- How reliable can an antiplatelet agent with a fast onset and duration of action be?

Administering a pre-treatment with P2Y12 receptor antagonists decreases the number of ischemic complications while increasing bleeding complications for patients about whom CABG is opted. Therefore, the quest for an antiplatelet agent that is equipped with a wide range of reliability and fast onset and duration of

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action is ongoing. IV is an ATP analog while cangrelor, which is a potent and reversible P2Y12 receptor inhibitor, stands out among others with its fast onset and duration of action. As cited before, CHAMPION-PCI study reported a non-significant increase in major bleeding for cangrelor group while CHAMPION-PLATFORM study put forth a significant decrease in mortality and stent thrombosis and a significant increase in major bleeding for cangrelor group (37,38). Serving as one of the most current studies with regard to cangrelor, CHAMPION-PHOENIX (Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events) is a double-blind, randomized and placebo-controlled study that is randomized to clopidogrel loading dose compliant with cangrelor and guideline recommendations for 1145 patients with a planned urgent or elective PCI through IV bolus or infusion. The risk of stent thrombosis proved a statistically significant decline after 48 hours while life-threatening bleeding rates did not increase (49). Cangrelor is of importance for patients that may need an urgent CABG as it offers a fast onset and during of action.

5- What would be the optimal length of time for antiplatelet therapy when it comes to new generation DES?

The release of DES has decreased the prevalence of restenosis events to a certain extent while it brings about the risk of late stent thrombosis. The need to make use of a long-term dual antiplatelet therapy makes the choice of patients important as they are to be administered with drug-eluting stents. A great deal of studies have been carried out thus far pertaining to the dual antiplatelet therapy following the implantation of a drug-eluting stent. Drawn up in line with such studies, current guidelines recommend for dual antiplatelet therapy for all patients for 1 month after the implantation of a bare metal stent (BMS) with stable angina, for 6 to 12 months after a DES implantation and for 1 year after the ACS irrespective of revascularization strategies (50-52).

In line with the current data, it is deduced that some patient populations (e.g.; those with a high risk for thromboembolic events, and patients who previously underwent implantation of sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES)) may gain benefit from the dual antiplatelet therapy that extend for more than 1 year. The downside of this strategy is that rates of severe bleeding complications increase in time. Recent data suggest that a 6-month DAPT is likely to be sufficient as the correlation between the interruption of dual antiplatelet therapy (DAPT) and late and very late stent thrombosis is extremely weak.

Keeping the length of time for the use of dual antiplatelet under 12 months would lead to a decline in bleeding risk, and thus an increase in ischemic endpoints would be a concern even though they would have to target points. Carried out on this topic, EXCELLENT study (the Efficacy of Xience/Promus vs. Cypher to Reduce Late Loss After Stenting) compared the use of DAPT for 6 months and the use of DAPT for 12 months after a first and second generation DES implantation for 1443 patients with SAP, NSTEMI/USAP or an ischemic event. Both therapy branches showed signs of non-inferiority in terms of cardiovascular mortality, MI and stent thrombosis that are primary outcomes. The study is viewed as a limited one since it ignores to analyze the need for recurrent revascularization and excludes high-risk patients (53). RESET study (Real Safety and Efficacy of 3-month DAPT following Endeavor zotarolimus-eluting stent implantation) compared the use of dual antiplatelet for 3 months with the use of dual antiplatelet for 12 months for patients implanted with a zotarolimus-eluting stent and reported that 3-month use of dual antiplatelet turned out to be non-inferior in terms of cardiovascular mortality, MI, stent thrombosis, target revascularization and bleeding outcomes (54). OPTIMIZE study (Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents) compared the use of DAPT for 3 months with the use of DAPT for 12 months for stable and low-risk ACS patients following a 2nd generation DES implantation, and reported that 3-month use of DAPT was non-inferior in terms of mortality, MI, stroke and major bleeding while the stent thrombosis rates were similar after 3 months (55).

Once ischemic endpoints were what was concerned about, some researchers thought that the extension of time for dual antiplatelet therapy could be a solution and thus carried out studies accordingly. Once we take a look at current research papers on the subject, a meta-analysis over 4 preceding studies (REAL/ZEST-LATE, PRODIGY, EXCELLENT, RESET) was conducted in 2012 and it was concluded that the extension of time for the standard 12-month DAPT would yield no benefit for MI, mortality or stent thrombosis, and contrarily increase the risk of TIMI-major bleeding (56). The early results of the ARCTIC-INTERRUPTION study (Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: rationale and design of the assessment with a double randomization of a fixed dose versus a monitoring-guided dose of ASA and clopidogrel after DES implantation, and treatment interruption versus continuation, 1 year after stenting) pointed to no benefit in terms of ischemic events (MI, ST and urgent revascularization) for patients undergoing DAPT for more than 1 year, and suggested that the extension of time for DAPT was associated with an increase in major and minor bleeding risks (57).

It is required to carry out more large-scaled studies to eliminate paradoxical increases in ischemic complications even though it is a fact that keeping the length of time for dual antiplatelet therapy after a DES implantation under 12 months would mitigate the number of bleeding complications for the elderly as the most-concerned group of people for bleeding complication, and patients with tendency to bleeding and a history of DAPT and hemorrhagic complications.

The ongoing studies on this topic are summarized in Table 7.

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Table 7. Ongoing clinical trials for optimal dual antiplatelet therapy after DES

Trial	Patient (n)	Stent Type	Dual antiplatelet	Primary endpoints	Follow up
DAPT[58]	20645	BMS,DES	12 vs 30 months	Death,MI,stroke	30 mo.
ISAR-SAFE[59]	6000	DES	6 vs 12 months	Death,MI,stroke, ST TIMI-major bleeding	15 mo.
Nobori-DAPT	4598	Biolimus Stent	6 vs 18 months	Death,non-fatal MI,stroke, major bleeding	18 mo.
SECURITY	4000	2. generation DES	6 vs 12 months	6-24. month ST	24 mo.
OPTIDUAL[60]	1966	DES	12 vs >12 months	Non-fatal MI,stroke, major bleeding	36 mo.
EDUCATE	2500	ZES	12 vs 30 months	Death,MI,ST, bleeding	24-36 mo.
DAPT-STEMI	1100	DES	6 vs 12 months	All-cause death,MI, revascularization, stroke, major bleeding	24 mo.
ISAR-CAUTION	3000	DES	6. months, rapid or slow offset	Cardiac death, MI, ST, stroke, major bleeding, hospitalization for acute coronary syndrome	3 mo.

6- How are we supposed to make use of dual antiplatelet therapy for patients with an indication to have used oral anticoagulants?

5-7% of patients with a history of percutaneous coronary intervention has an indication for anticoagulants. Patients, who are required to undergo ASA, thienopiridine and warfarin as well as triple oral antithrombotic therapy (TOAT), seem to be characterized by atrial fibrillation, mechanical cardiac valve replacement, left ventricular mural thrombus, and venous thromboembolism (61). The need for PCI is the most common indication for patients diagnosed with Atrial Fibrillation (AF). There are many questions, concerns and challenges over the length of time for the triple therapy, its benefits, risks and alternatives. Such questions lead to perspectives renewed in line with newly-approved antiplatelet and anticoagulant agents. The main goal is to eliminate thrombosis-dependent cardiovascular events while mitigating the number of potential bleeding complications.

For patients with AF following an ACS and implanted with a BMS, current guidelines recommend for TOAT for the first 4 weeks and then warfarin+clopidogrel until 12 months or warfarin only after 100 mg/day of ASA, and 6-months TOAT for patients implanted with a DES, and then warfarin+clopidogrel or 100 mg/day of ASA until 12 months, and warfarin only after 12 months (62). Triple antiplatelet-dependent bleeding complications are life threatening whereas their impact on mortality and morbidity following a PCI is huge. The length of a triple therapy is the most important step to keep this complication under control while this matter remains to be widely discussed. It is imperative to take account of the bleeding risks that may emerge during and after the procedure for patients using oral anticoagulants (OAC), and draw up an anticoagulation plan by paying regard to the balance between the urgency of the procedure and the bleeding risk. Recently carried out on this topic, WOEST study (Use of clopidogrel with or without ASA in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention) reported that a dual therapy (Clopidogrel-OAC) rather than a triple therapy (ASA-clopidogrel-OAC) significantly decrease major bleeding rates and increased the number of thrombotic events for patients who had to use oral anticoagulants and previously undergo a PCI (63). The fact that the patient population is small-scaled is one of the limitations to this study, and it is required to carry out wider-scaled and randomized studies to incorporate it into current guidelines.

7- Is there any new study on the interaction between clopidogrel and proton pump inhibitors?

As for acute coronary syndromes, the most common side-effect of clopidogrel is gastrointestinal bleeding as it is the most widely-used agent to mitigate the number of recurrent cardiovascular events for patients administered with a medical or percutaneous coronary intervention. Aspirin can lead to gastroduodenal damages due to direct impact on gastric epithelium and synthesis inhibition of prostaglandin in gastric mucosa as well as clopidogrel antiplatelet effects, anti-angiogenic effects, thrombocyte inhibition, and decrease in excretion of platelet-derivative growth factors that may lead to coagulation and angiogenesis (64). The American College of Cardiology Foundation Task Force (ACCF), American College of Gastroenterology (ACG) and the American Heart Association (AHA) released a consensus to prescribe NSAII, COX-2 inhibitors, ASA or clopidogrel and proton pump inhibitors (PPI) for patients at risk since the common use of clopidogrel creates tendency to gastric erosion and bleeding. Among risk factors for gastric bleeding are history of an ulcer complication, peptic ulcer, gastrointestinal system (GIS) bleeding, dual antiplatelet therapy (DAPT), age over 60, use of corticosteroid, dyspepsia or gastroesophageal reflux disease (GERD) and gastric bleeding (64). PPIs are one of the most widely-administered drugs around the world. Omeprazole, lansoprazole and rabeprazole can inhibit cytochrome P4502C19. Thus, they can alter pharmacokinetics of clopidogrel and lead to adverse cardiac outcomes (65). Carried out on this topic, CREDO study (Clopidogrel for the Reduction of events During Observation) reported no detrimental effect for the combination of PPI and clopidogrel (66). As a part of the COGENT–1 (the Clopidogrel and the Optimization of Gastrointestinal Events) study, coronary artery patients administered with a dual therapy of ASA-clopidogrel were also administered with PPI (20 mg omeprazole) and

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compared to a placebo group while no difference was reported between the two groups in terms of ischemic complications. Gastrointestinal bleeding complications, on the other hand, significantly decreased in the omeprazole group. PRINCIPLE TIMI-44 (Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation) and TRITON TIMI-38 studies reported that PPIs pharmacodynamically interacts with clopidogrel much more than with prasugrel. Another striking output of the studies was the fact that the clinical endpoints of PPI therapy including omeprazole and pantoprazole remained unaffected (67). The use of PPI is not limited in the light of current studies while it is recommended to administer PPI by taking account of benefits and damages for patients with a favorable indication and a high risk of bleeding.

Antiplatelet agents are drugs that are immediately administered for ischemic complications while bleeding complications constitute a major problem. Carried out upon the introduction of new antiplatelet agents in clinical practices, new large-scaled studies have risen hopes to come up with an ideal antiplatelet agent. These drugs, which can shape algorithms of antithrombocyte therapy in the future, offer major proven advantages. Among the superior aspects of these drugs to clopidogrel is less resistance, the need for a shorter period of time to take effect, less drug interaction, bleeding, direct impact and reversible effect. Major changes to be made in current guidelines require wider-scaled and randomized studies.

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