Dual Antiplatelet Therapy after Percutaneous Coronary Intervention in Acute Ischemic Patients at High Bleeding Risk

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Abstract:

The appropriate duration of dual antiplatelet therapy in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent remains unclear.

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Introduction:

Patients with a history of acute coronary syndrome (ACS) remain at increased risk of ischemic events long term. Data from the Global Registry of Acute Coronary Events (GRACE) showed that more than half (53.6%) of ACS patients were re-hospitalized at least once during the 5-year follow-up period after discharge ***(1).***

During the immediate 2 years after ACS, 7.1% of patients died, 6.3% experienced heart failure, and 4.4% experienced reinfarction, despite treatment aimed at secondary prevention. In another global registry, Reduction of Atherothrombosis for Continued Health (REACH), almost a fifth of patients with a prior myocardial infarction (MI) either died or experienced another MI or a stroke over the following 4 years, with the greatest risk in those who had had an event within the year prior to enrollment ***(2).***

Platelet Activation:

Platelets play a pivotal role in the pathogenesis of ACS. While activation of circulating platelets is essential for normal hemostasis in response to vascular injury, their activation and aggregation in the context of atherosclerotic plaque rupture or erosion promote pathological thrombus formation ***(3).***

Atherosclerotic plaque and thrombi may occlude the blood vessels, thereby blocking the supply of oxygen to the tissues and resulting in an ischemic event. When the coronary arteries are affected, this can result in stable or unstable angina, depending on the degree and nature of the blockage; if the ischemia is severe, the outcome is MI and necrosis ***(1).***

Multiple cellular pathways participate in the activation and aggregation of platelets at the site of endothelial disruption and represent pharmacological targets for the acute and long-term treatment of atherothrombosis. Secondary prevention strategies for ACS patients currently focus on the inhibition of three key platelet activation pathways: thromboxane A2 (TXA-2) generation via cyclooxygenase-1 (COX-1); adenosine diphosphate (ADP)-mediated activation of the P2Y12 receptor; and thrombin-mediated activation of protease-activated receptor-1 (PAR-1) ***(4).***

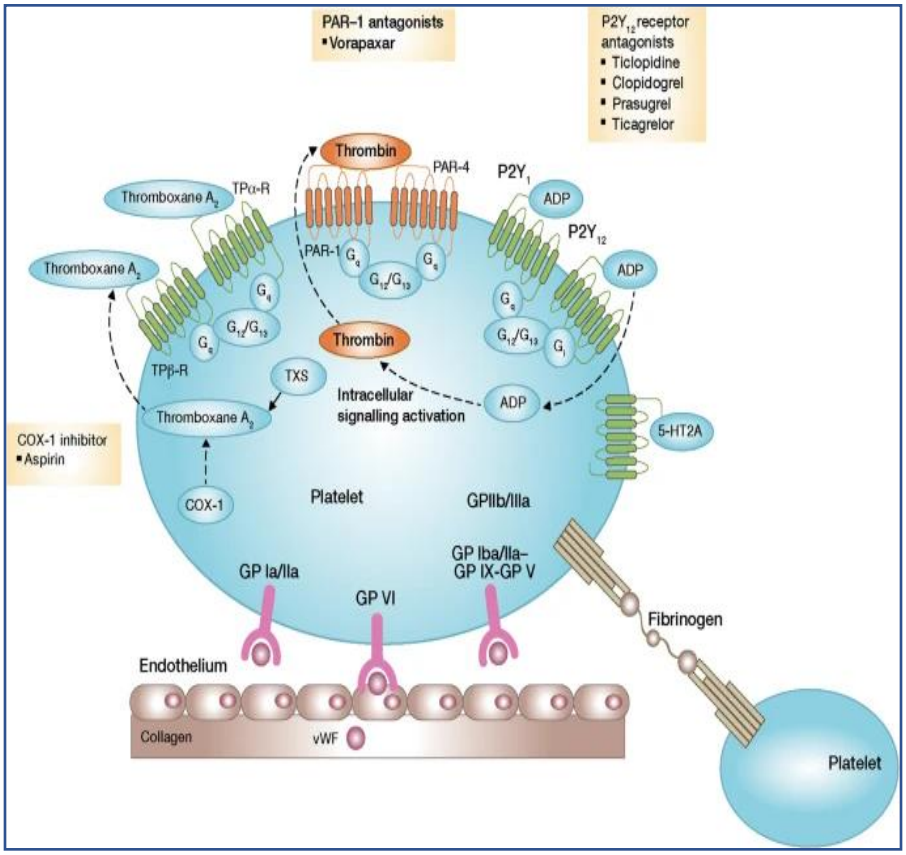

Figure (1): Cellular targets for oral antiplatelet agents. ADP adenosine diphosphate, COX cyclooxygenase, GP glycoprotein, PAR protease-activated receptor, vWF von Willebrand factor***(2).***

Oral Antiplatelet Agents:

Aspirin:

The benefit of aspirin therapy for secondary prevention of ischemic events in patients at high risk for atherothrombosis is well established. Aspirin irreversibly acetylates COX-1, inhibiting formation of the pro-thrombotic mediator TXA-2 from arachidonic acid. Its antiplatelet effects occur rapidly, and it takes 3–4 days for complete recovery of platelet aggregation after stopping treatment ***(3).***

Aspirin remains a first-line, foundation treatment for prevention of ischemic events after ACS, and a daily maintenance dose of 75–100 mg is recommended indefinitely.

Lower aspirin doses are preferred because higher doses (≥ 160 mg) are usually associated with increased bleeding risk without an improvement in ischemic outcomes ***(1).***

As aspirin cannot prevent platelet activation via other pathways, combination therapy with another oral antiplatelet agent is usually recommended, and the combined use of aspirin and P2Y12 inhibitors has been shown to provide additive inhibition of platelet activation. Aspirin resistance, i.e., a lower-than-normal platelet inhibitory effect, has been reported in some patient populations, and may be addressed by increasing the frequency of intake and/or combination with other antiplatelet agents***(5).***

- Clopidogrel:

Ticlopidine and clopidogrel represent the first and second generation of P2Y12 inhibitors, respectively, and both belong to the thienopyridine class of antiplatelet drugs that selectively and irreversibly prevent binding of ADP to the P2Y12 receptor. While effective as an antiplatelet agent, the use of ticlopidine is associated with potentially serious adverse effects, including bone marrow suppression; therefore, clopidogrel is currently the most widely used P2Y12 inhibitor***(6).***

Clopidogrel is a prodrug, requiring hepatic conversion via cytochrome (CYP) P450 enzymes to produce an active metabolite. This means it can take up to 8 h after a loading dose of clopidogrel to achieve significant platelet inhibitory effects. Clopidogrel responsiveness may be diminished by concomitant administration of drugs that competitively inhibit its activation by CYP enzymes, such as proton pump inhibitors ***(4).***

As binding of the clopidogrel metabolite to the P2Y12 receptor is irreversible, restoration of platelet function is delayed until the body produces new platelets. Therefore, clopidogrel should be discontinued at least 5 days prior to elective surgery ***(7).***

Dual antiplatelet therapy, predominantly with clopidogrel and aspirin, has been the backbone of secondary prevention of recurrent ischemic events in ACS patients for over a decade. Many trials demonstrated a relative risk reduction in major adverse cardiovascular (CV) events (MACE) (death from CV causes, non-fatal MI, or stroke) in non-ST-elevation (NSTE)-ACS patients treated with clopidogrel plus aspirin versus aspirin alone for 12 months following ACS***(3).***

The benefit of clopidogrel was maintained from 2 h post-administration to the end of follow-up and was largely accounted for by a reduction in the risk of non-fatal MI. Subsequent studies confirmed the secondary prevention benefit of clopidogrel plus aspirin in patients with ST-elevation MI (STEMI) managed with fibrinolytics and in the setting of elective percutaneous coronary intervention (PCI)***(1).***

However, it is well recognized that there is a considerable degree of inter-individual variability in response to clopidogrel as a result of multiple factors, including age, diabetes mellitus, drug–drug interactions, and genetic polymorphisms (particularly those affecting CYP2C19, the principal enzyme group involved in its metabolic activation) ***(7).***

A review of 15 prospective studies noted that approximately 25% of patients were clopidogrel non-responders according to ADP aggregation testing; they exhibited high on-treatment platelet reactivity (HPR), which was associated with a 3.5-fold greater risk of recurrent ischemic events***(8).***

The previous review is supported by data from the National Institutes of Health (NIH)-funded Implementing GeNomics In pracTicE (IGNITE) network study, which found that in patients with a non-functional allele, the risk of MACE was significantly greater with clopidogrel compared with other antiplatelet therapies ***(8).***

Consequently, the clopidogrel prescribing information contains a boxed warning about higher CV event rates in poor metabolizers. The third-generation P2Y12 inhibitors, prasugrel and ticagrelor, were developed with the aim of addressing the slow onset and heterogeneous platelet inhibiting properties of clopidogrel, and the Clinical Pharmacogenetics Implementation Consortium and the institutions involved in the IGNITE project collectively recommend that patients with poor or intermediate metabolizer phenotypes should be given treatment other than clopidogrel, such as prasugrel or ticagrelor. It should be noted that a clinical study exploring CYP2C19 genotype-guided therapy after PCI is ongoing and these recommendations are based on clinical opinion and experience rather than clinical trial evidence ***(2).***

Newer P2Y12 Inhibitors:

- **Prasugrel:**

Like clopidogrel, prasugrel is a thienopyridine and, therefore, blocks ADP binding to the P2Y12 receptor irreversibly. It is also a prodrug, requiring metabolic activation, but has a faster onset of action than clopidogrel. It is recommended that prasugrel is stopped at least 7 days prior to elective coronary artery bypass graft (CABG) surgery (class I recommendation), but shorter delays may be reasonable in patients referred for urgent CABG (class IIb recommendation) ***(9).***

Many studies established prasugrel as superior to clopidogrel for the secondary prevention of recurrent ischemic events following ACS, in patients managed with PCI ***(6).***

Dual antiplatelet therapy with prasugrel and aspirin can reduce the incidence of death from CV causes, non-fatal MI, or non-fatal stroke compared with clopidogrel and aspirin. Several studies cleared that rates of stent thrombosis were also lower for prasugrel plus aspirin compared with clopidogrel plus aspirin, but rates of TIMI-defined non–CABG-related major bleeding were significantly greater in the prasugrel-treated versus clopidogrel-treated group, including life-threatening and fatal bleeding***(5).***

However, considering both ischemic and bleeding events, the net clinical benefit was in favor of prasugrel. A subgroup analysis of TRITON-TIMI 38 identified an excess of intracranial bleeding with prasugrel treatment in patients with a prior stroke or transient ischemic attack (TIA), which resulted in net harm. There was also no net benefit of prasugrel in patients aged 75 years or older or those weighing less than 60 kg. As a result of these observations, the prasugrel prescribing information contains a boxed warning against its use in patients with active pathological bleeding or a history of TIA or stroke, and provisos concerning its use in older and lighter patients ***(2).***

Another analysis from TRITON-TIMI confirmed a consistent net clinical benefit of prasugrel from randomization to day 3, and from day 3 until the end of the trial. Also, among patients who experienced a non-fatal event during the trial, there was a significant reduction in both recurrent events and subsequent CV death with prasugrel versus clopidogrel. It should be noted that these are landmark analyses and further studies are needed to confirm these findings ***(10).***

In contrast to TRITON-TIMI 38, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial failed to show superiority of prasugrel over clopidogrel (both on top of aspirin) in NSTE-ACS patients managed with medical therapy alone ***(11).***

At 17 months, the composite rate of CV death, MI, and stroke with prasugrel treatment was 13.9 versus 16.0% with clopidogrel treatment. Although there were higher rates of minor and moderate bleeding among patients receiving prasugrel, there was no significant increase in the rate of severe, major, or life-threatening bleeding, despite a treatment duration up to 30 months. In this study, patients > 75 years or < 60 kg body weight received a reduced dose of prasugrel (5 mg rather than 10 mg); all patients received the same dose of clopidogrel (75 mg) ***(11).***

- **Ticagrelor:**

Ticagrelor is the first in a new class of agents called cyclopentyltriazolopyrimidines that reversibly inhibits the P2Y12 receptor by binding at a different site. It does not block ADP binding per se but inhibits platelet activation by blocking ADP-induced signal transduction. Unlike prasugrel, ticagrelor is a direct-acting agent with a faster onset of action than clopidogrel. Furthermore, it has a faster offset of action as a result of its reversible effects ***(1).***

It is recommended that ticagrelor is stopped at least 5 days prior to elective CABG surgery (class I recommendation), but shorter delays may be reasonable in patients referred for urgent CABG (class IIb recommendation) ***(12).***

The pivotal ticagrelor trial was Platelet Inhibition and Patient Outcomes (PLATO), which evaluated the efficacy and safety of dual therapy with ticagrelor or clopidogrel plus aspirin for the reduction of CV events

in patients hospitalized for either STEMI or moderate- to high-risk NSTE-ACS ***(12).***

In contrast to TRITON-TIMI 38, patients were included whether or not an invasive strategy was planned. The study found that ticagrelor reduced the composite primary endpoint of CV death, MI, and stroke by 16% at 12 months compared with clopidogrel, but at the expense of an increase in the rate of PLATO- or TIMI-defined non–CABG-related major bleeding***(2).***

The individual endpoints of recurrent MI and CV death were also reduced in the ticagrelor group compared with clopidogrel in many studies. Moreover, ticagrelor treatment was associated with a significant reduction in the rate of death by any cause, rates of both first and recurrent ischemic events, and rates of stent thrombosis ***(13).***

A real-world evidence study conducted in Sweden (Swedish Web system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies [SWEDEHEART]) and including over 45,000 ACS patients, subsequently reported outcomes for ticagrelor versus clopidogrel that were consistent with those found in PLATO ***(14).***

Outcomes with ticagrelor versus clopidogrel in PLATO were consistent across subgroups of patients with STEMI or NSTE-ACS, and those managed with either PCI or medical therapy alone. Similarly, outcomes were consistent in older patients, those with low body weight, and those with prior TIA or non-hemorrhagic stroke ***(12).***

However, ticagrelor efficacy was found to differ according to region, with a reduced benefit in terms of the primary endpoint in patients based in North America compared with the rest of the world. As a greater proportion of patients in North America were reported to take high-dose aspirin maintenance therapy (median $\geq$ 300 mg/day), a negative interaction between ticagrelor and high-dose aspirin was proposed as a possible explanation for this disparity, but no definitive explanation exists for these findings ***(15).***

As a result, ticagrelor maintenance therapy is recommended to be taken with low aspirin doses of 75–100 mg/day. The ticagrelor prescribing information also warns against concomitant aspirin doses exceeding 100 mg, and contraindicates the use of ticagrelor in patients with active pathological bleeding or history of intracranial hemorrhage ***(3).***

- **Prasugrel Versus Ticagrelor:**

There are currently limited data comparing the efficacy and safety of ticagrelor and prasugrel in ACS patients. The results of the first head-to-head randomized clinical trial (Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-18 [PRAGUE-18]) were published recently ***(16).***

This open-label, phase IV study aimed to enroll 2500 patients with acute MI undergoing PCI in tertiary centers in the Czech Republic. However, early outcome analysis (up to 1 month post-event) of 1230 patients found no significant difference between prasugrel and ticagrelor (both plus aspirin) for the composite primary endpoint of death, re-infarction, urgent target vessel revascularization, stroke, serious bleeding requiring transfusion, or prolonging hospitalization at 7 days, nor in the key secondary endpoint of CV death, non-fatal MI, or stroke at 30 days ***(16).***

Consequently, the trial was terminated early for 'lack of utility'. The 1-year follow-up also found no significant differences between prasugrel and ticagrelor with regard to efficacy or bleeding. The primary endpoint (CV death, MI or stroke at 1 year) was 6.6% in the prasugrel group and 5.7% in the ticagrelor group ***(16).***

An earlier meta-analysis of randomized trials of prasugrel and ticagrelor also showed no significant differences between treatments in the rates of CV death, MI or stroke, or non–CABG-related major bleeding. This is an indirect comparative analysis. Recent pharmacodynamic studies suggest that there is little difference between prasugrel and ticagrelor in terms of timing and degree of platelet inhibition. However, these studies have looked at only short-term pharmacodynamic effects after drug loading***(2).***

Other studies suggest that there may be a variable response with prasugrel when used long term or in patients with STEMI, influenced by older age and prior aspirin use. The open-label Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 (ISAR-REACT 5) trial (NCT01944800) compared the clinical effects of ticagrelor and prasugrel for up to 12 months in approximately 4000 ACS patients with a planned invasive strategy ***(17).***

In the absence of the contraindications referred to above, the most recent guidelines for maintenance treatment with dual antiplatelet therapy give a class IIa recommendation for the use of prasugrel or ticagrelor in preference to clopidogrel in ACS (NSTE-ACS or STEMI) patients who have undergone coronary stent implantation***(1).***

Ticagrelor (but not prasugrel) is recommended over clopidogrel in NSTE-ACS patients managed with medical therapy alone. Other possible considerations in choice of agent include the dosing regimen and adverse event profile. Prasugrel is administered once daily and ticagrelor twice daily, which may have some bearing on patient compliance ***(4).***

In addition, ticagrelor is the only P2Y12 inhibitor that is currently licensed (according to prescribing information) to be crushed and mixed with water, and either drunk or given by nasogastric tube, for patients with difficulty swallowing. Finally, both drugs carry an increased risk of bleeding (including life-threatening or fatal bleeding in the case of prasugrel), and ticagrelor is associated with an increased risk of dyspnea ***(4).***

- **Vorapaxar:**

Vorapaxar is a novel oral PAR-1 antagonist that inhibits thrombin-mediated platelet activation, which is independent of the ADP- and TXA-2-mediated pathways. Therefore, residual platelet activation is feasible despite dual inhibition of COX-1 and P2Y12, raising the question of whether 'triple therapy' would be beneficial ***(5).***

The phase III study Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) investigated the efficacy and safety of vorapaxar versus placebo in NSTE-ACS patients receiving aspirin and clopidogrel, but was terminated early due to increased major bleeding with vorapaxar, including more than a three-fold increase in the rate of intracranial bleeding. There was also no apparent benefit of vorapaxar in reducing CV events ***(2).***

Indeed, vorapaxar has been approved by the US Food and Drug Administration (FDA) for secondary prevention in patients with prior MI or PAD, in combination with aspirin and/or clopidogrel, but is contraindicated in patients with a history of stroke, TIA or intracranial hemorrhage, or with active pathological bleeding ***(6).***

The prescribing information also warns that consideration should be given to factors that increase the risk of bleeding, including older age and low body weight. The European guidelines recommend that ischemic and bleeding risk should be thoroughly assessed before prescribing vorapaxar with aspirin and clopidogrel ***(18).***

However, the current US guidelines for the management of patients with NSTE-ACS and STEMI, and duration of dual antiplatelet therapy in coronary artery disease (CAD), do not refer to vorapaxar***(7).***

Optimal Duration of Treatment:

- Guidelines:

The US guidelines for ACS broadly recommend that dual antiplatelet therapy be continued for 12 months after the index event, followed by aspirin monotherapy. An American College of Cardiology (ACC)/American Heart Association (AHA) guideline focused update on the duration of dual antiplatelet therapy in patients with CAD was published recently, taking into account existing guideline recommendations and the results of a systematic review of randomized clinical trials ***(19).***

This opinion gives a class I recommendation for 12 months of treatment with low-dose aspirin (81 mg, range 75–100 mg) and a P2Y12 inhibitor in four specific groups of patients with an acute or recent coronary event (STEMI or NSTE-ACS), excluding those with specific contraindications to any of the drugs ***(19).***

These four ACS groups (with dual antiplatelet therapy recommendations) are (1) all medically managed patients (aspirin plus clopidogrel or ticagrelor); (2) STEMI patients treated with a fibrinolytic (aspirin plus clopidogrel); (3) patients who have undergone PCI with a drug-eluting stent

(DES) or bare-metal stent (BMS) (clopidogrel, prasugrel, or ticagrelor); and (4) patients who have undergone CABG (resume treatment post-surgery and continue to 1 year) ***(3).***

In the first three of these groups, the guidelines also give a class IIb recommendation that prolonging dual antiplatelet therapy beyond 12 months may be reasonable. Conversely, dual antiplatelet therapy may be reasonable for just 6 months in patients with significant overt bleeding or at high bleeding risk (e.g., treatment with oral anticoagulant) or at increased risk of severe bleeding complication (e.g., major intracranial surgery) ***(5).***

In patients with stable ischemic heart disease, the guidelines state that it may be reasonable to discontinue dual antiplatelet therapy sooner in PCI patients treated with 'newer-generation' DES (e.g., everolimus- or zotarolimus-eluting stents), as they are associated with a lower risk of stent thrombosis and MI compared with older DES types (e.g., sirolimus- and paclitaxel-eluting stents) ***(1).***

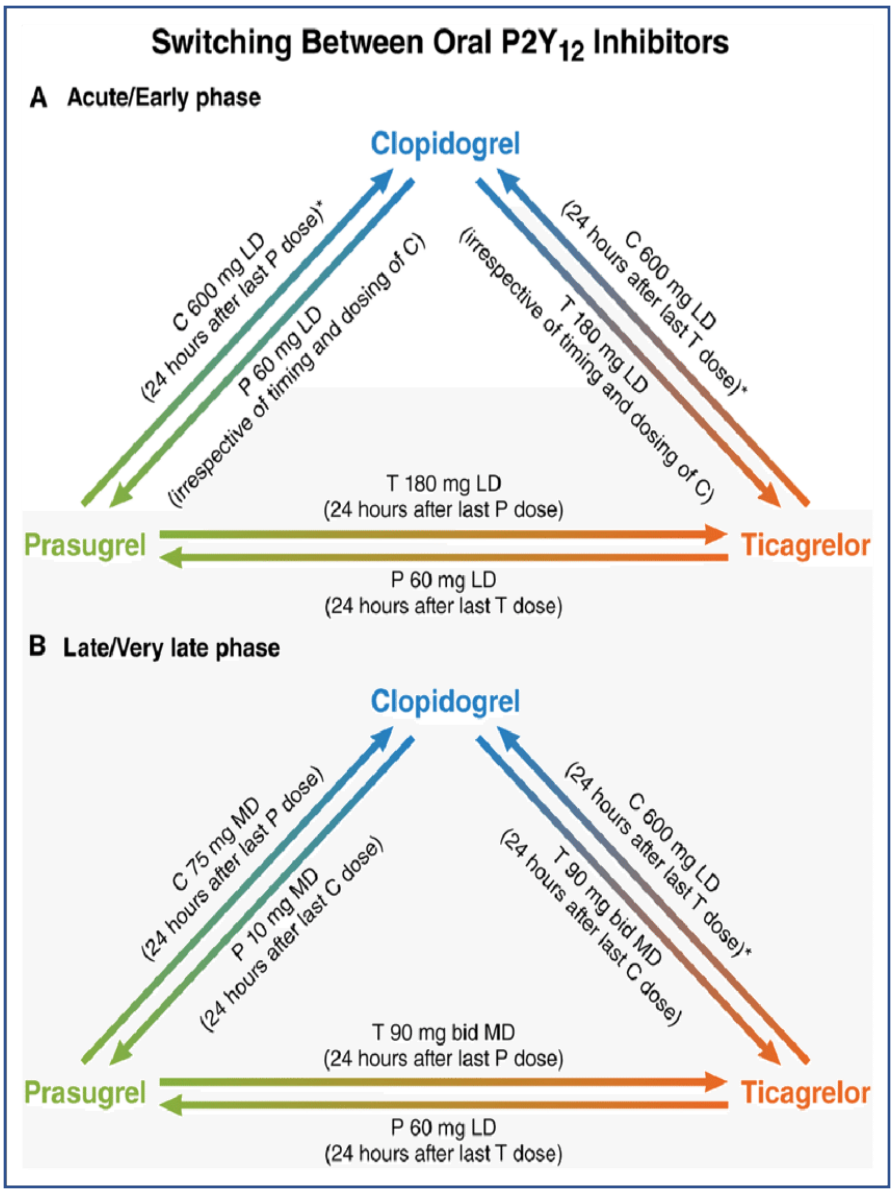

Figure (2): Consensus recommendations on switching between oral P2Y 12 inhibitors. A, Switching between oral agents in the acute/early phase. In the acute/early phase (≤30 days from the index event), switching should occur with the administration of a loading dose (LD) in most cases, with the exception of patients who are deescalating therapy because of bleeding or bleeding concerns, in whom a maintenance dose (MD) of clopidogrel (C) should be considered. Timing of switching should be 24 hours after the last dose of a given drug, with the exception of when escalating to prasugrel (P) or ticagrelor (T), when the LD can be given regardless of the timing and dosing of the previous clopidogrel regimen. *Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns. B, Switching between oral agents in the late/very late phase. In the late/very late phase (>30 days from the index event), switching should occur with the administration of an MD 24 hours after the last dose of a given drug, with the exception of patients changing from ticagrelor to prasugrel therapy, for whom an LD should be considered. De-escalation from ticagrelor to clopidogrel should occur with administration of an LD 24 hours after the last dose of ticagrelor (but in patients in whom de-escalation occurs because of bleeding or bleeding concerns, an MD of clopidogrel should be considered). *Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns ***(20).***

Evidence:

Data from a number of clinical trials and recent meta-analyses indicated that extending dual antiplatelet therapy beyond 12 months may be beneficial in some patients. Other studies have looked at shorter term dual antiplatelet therapy ***(4).***

A subgroup analysis from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial in patients with prior MI found that ~ 2 years of treatment with clopidogrel plus aspirin reduced the rate of ischemic events by almost a quarter compared with aspirin therapy alone; however, the trial failed to meet its primary endpoint, showing no benefit in patients with clinically evident CV disease or multiple risk factors ***(21).***

The duration of dual antiplatelet therapy following DES placement has been evaluated in a decision-analytic Markov model. For the subgroup of patients with ACS, the authors found that only a 2% absolute reduction in MACE would be needed for 30 months of treatment with dual antiplatelet therapy to be preferable to 12 months followed by aspirin alone, including consideration of bleeding risk ***(22).***

However, a number of meta-analyses of randomized trials have generally shown that short-term (< 6 months) versus long-term (> 12 months) dual antiplatelet therapy after second-generation DES placement has similar rates of mortality and ischemic events, but with a lower rate of overall bleeding, particularly in low-risk patients***(2).***

The authors concluded that while shorter treatment may be safe and effective in some cases, high-risk patients may require a tailored approach. An analysis of 4190 patients from the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) registry found that only around 10% of patients treated with DES have either a low thrombotic/high bleeding risk or a high thrombotic/low bleeding risk. Thus, identification of a high thrombosis/low bleeding risk or low thrombosis/high bleeding risk population is challenging ***(23).***

A large, randomized, multicenter, open-label trial is currently assessing the hypothesis that 6 months of dual antiplatelet therapy after DES implantation is not inferior to 12 month dual antiplatelet therapy with regard to clinical outcomes. The final results of the study, known as the Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in ST-elevation Myocardial Infarction (DAPT-STEMI), are awaited, but should hopefully help answer the question of whether short- or long-term dual antiplatelet therapy is preferential in patients with DES implantation ***(24).***

Risk Stratification:

In order to identify patients most likely to benefit from more intensive antiplatelet therapy, identification of characteristics associated with increased mortality, CV event recurrence, and bleeding is crucial ***(2).***

Bleeding risk:

Bleeding risk is the primary safety issue associated with antiplatelet treatment and must be balanced against the reduction in ischemic risk when selecting therapy. Analysis of a prospective, real-world, Italian registry found that the main reason for continuing dual antiplatelet therapy beyond 12 months in patients following an ACS was low bleeding risk, more so than high ischemic risk ***(25).***

Major bleeding events during hospitalization for ACS are an independent predictor of adverse outcomes at 6 months and 1 year post–index event. An analysis of the PLATO trial found that spontaneous major bleeding events were associated with similar mortality rates (short and long term) as spontaneous ischemic events in patients with ACS receiving dual antiplatelet therapy ***(26).***

A further study evaluated the average daily ischemic rate and the average daily bleeding rate in 3602 patients with STEMI enrolled in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) study. The study found that while both rates decreased over time after the primary PCI, the daily risk of ischemia was greater than the daily risk of bleeding after 30 days. To complicate matters, many factors that increase ischemic risk also increase the risk of bleeding ***(27).***

Post-discharge risk scores currently include GRACE and the more recent risk model using data from the long-tErm follow-up of antithrombotic management Patterns In acute CORonary (EPICOR) study, which predict mortality at 6 months and 1 year following ACS, respectively ***(28).***

Most recently, a 'DAPT score' has been developed, using data from the DAPT study to assess the potential benefits and harms of continuing dual antiplatelet therapy beyond 1 year in patients undergoing PCI. This risk score has the advantage of evaluating both thrombotic and bleeding risk, with positive or negative points assigned for each of the components. Patients with scores ≥ 2 were found to have a reduced risk of ischemic events and smaller increases in bleeding during extended dual antiplatelet therapy, compared with those with scores < 2 ***(29).***

In another analysis looking at subgroups of patients with or without prior MI before coronary stent implantation, among patients with DAPT scores ≥ 2, continued thienopyridine therapy versus aspirin alone was associated with significant reductions in MI/stent thrombosis: prior MI 2.7 versus 6.0%, $p < 0.001$; no MI 2.6 versus 5.2%, $p = 0.002$, with comparable bleeding rates***(30).***

Among patients with DAPT scores < 2, continued thienopyridine therapy versus aspirin alone was associated with significantly increased bleeding, but no ischemic benefit, in patients with or without prior MI. Therefore, while the DAPT score may still require further evaluation in other patient cohorts, it has thus far been shown to enhance the prediction ***(30).***

Many authors identified ten significant predictors of severe/life-threatening/ moderate bleeding (age, sex, weight, NSTEMI [vs. unstable angina], angiography performed at randomization, prior peptic ulcer disease, baseline creatinine, baseline systolic blood pressure, baseline hemoglobin and angiography before randomization) and five significant predictors of TIMI major/minor bleed (age, female sex, baseline creatinine, baseline hemoglobin and angiography before randomization), which could be used to reliably predict bleeding risk in patients receiving dual antiplatelet therapy after hospitalization for ACS ***(1).***

A number of individual patient factors are also recognized to increase the risk of CV events and/or bleeding, which may also have an impact on the relative benefits of dual antiplatelet therapy, as summarized briefly below. The risk of adverse events following an ACS also progressively increases with multiple risk factors. For these patients, more aggressive secondary prevention strategies, such as longer dual antiplatelet therapy, may be required ***(3).***

****TIMI and GUSTO scores for assessment of bleeding :***

The TIMI bleeding classification is a laboratory-based scale while the GUSTO bleeding classification is a clinically based scale .The TIMI definition of bleeding uses four categories: major, minor, minimal, and none. The GUSTO bleeding definition also uses four categories: severe or life-threatening, moderate, mild, and none. The PURSUIT investigators used both definitions to classify bleeding events. The PARAGON investigators defined bleeding complications as major or life-threatening, and intermediate. Major or life-threatening bleeding was defined as any intracranial hemorrhage or bleeding leading to hemodynamic compromise requiring intervention. Intermediate bleeding was defined as bleeding requiring transfusion or a decrease in hemoglobin 5 g/dl or more (or decrease in hematocrit ≥15% when hemoglobin was unavailable).

Key Elements of the TIMI and GUSTO Bleeding scores :

TIMI Bleeding Classification (7)

Major	Intracranial hemorrhage or a ≥5 g/dl decrease in the hemoglobin concentration or a ≥15% absolute decrease in the hematocrit
Minor	Observed blood loss: ≥3 g/dl decrease in the hemoglobin concentration or ≥10% decrease in the hematocrit
	No observed blood loss: ≥4 g/dl decrease in the hemoglobin concentration or ≥12% decrease in the hematocrit
Minimal	Any clinically overt sign of hemorrhage (including imaging) that is associated with a <3 g/dl decrease in the hemoglobin concentration or <9% decrease in the hematocrit

GUSTO Bleeding Classification (8)	
Severe or life-threatening	Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in hemodynamic compromise
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding

GUSTO = Global Strategies for Opening Occluded Coronary Arteries; TIMI = Thrombolysis In Myocardial Infarction**.(31)**

- **Diabetes Mellitus:**

Patients with diabetes mellitus have an increased risk of mortality and ischemic events, and a generally poorer prognosis following ACS, compared with non-diabetic patients. Patients receiving insulin therapy appear to be at further risk than those who do not require insulin. Moreover, diabetic patients have been shown to have hyper-reactive platelets and reduced response to antiplatelet therapy compared with non-diabetic patients ***(32).***

- **Renal Dysfunction:**

A significant proportion of patients with ACS have renal dysfunction, associated with poorer short- and long-term ischemic outcomes. However, renal dysfunction is associated with an increased risk of bleeding, complicating the net benefit–risk profile of potential antiplatelet therapy. There is also evidence that a severe reduction in glomerular filtration rate may be a determinant of high residual platelet reactivity during clopidogrel maintenance therapy, and that the newer P2Y12 inhibitors may overcome this problem ***(4).***

- **Polyvascular Disease:**

Patients with vascular disease in more than one arterial bed are at a greater risk for ischemic events and have poorer prognosis following ACS ***(33).***

- **Age:**

Increasing age is associated with increased CV events and bleeding risk, reduced response to antiplatelet therapy, and a higher rate of HPR ***(1).***

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