

ANTIPLATELETS GUIDELINES IN ENDOVASCULAR TREATMENT OF INTRACRANIAL ANEURYSMS: RECOMMENDATIONS FROM MALAYSIAN NEUROINTERVENTIONAL SOCIETY (MyNIS)

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INTRODUCTION

The landscape of periprocedural antiplatelet therapy has witnessed significant evolution alongside advancements in the endovascular management of intracranial aneurysms. This includes the introduction of flow-diverting stents, intracranial stents, intrasaccular devices, and stent-assisted coiling. Traditionally, a dual antiplatelet therapy (DAPT) regimen involving Aspirin and Clopidogrel has been widely adopted due to its established safety and efficacy. However, recent studies have identified alternative antiplatelet agents such as Ticagrelor, Tirofiban, or Prasugrel, which have demonstrated comparable efficacy and safety profiles. Endorsed by the Malaysian Society of Interventional Neuroradiology (MYNIS), this guideline aims to assist Interventional Neuroradiologists (INRs) and other physicians involved in treatment in selecting the most appropriate antiplatelet therapy for patients undergoing interventional procedures.

COX-1 INHIBITORS

Aspirin

Aspirin, also known as acetylsalicylic acid (ASA), functions as an irreversible inhibitor of cyclooxygenase-1 (COX-1), thereby impeding the production of thromboxane A₂. Even with daily doses as low as 75 mg, Aspirin achieves complete inactivation of COX-1 within platelets due to its irreversible binding and the fact that platelets do not synthesize new proteins during their 7- to 10-day lifespan. This characteristic renders Aspirin an ideal antiplatelet agent, characterized by a stable half-life and predictable therapeutic response, particularly in preventing thromboembolism in the treatment of unruptured intracranial aneurysms. Its onset of action typically occurs within 15–30 minutes, and the plasma half-life of Aspirin is approximately 15–20 minutes.

Original trials involving intracranial flow diverters utilized daily maintenance doses ranging from 100 mg to 325 mg of Aspirin, while a standard dosage of 325 mg per day is commonly employed for intracranial stents and flow-diverting devices. Research suggests that Aspirin may contribute to the reduction of aneurysmal degradation and inflammation of the aneurysmal wall, in addition to promoting endothelial progenitor cell mobilization. Common side effects of Aspirin administration include gastritis and ulceration attributed to its non-selective COX blockade.

P2Y₁₂ INHIBITORS

Clopidogrel

Clopidogrel, a thienopyridine compound, functions by irreversibly inhibiting the platelet P2Y₁₂ adenosine diphosphate receptor, thereby reducing platelet aggregation. Additionally, it impedes platelet aggregation by other platelet agonists such as thromboxane A₂ and thrombin by diminishing the amplification effect of ADP released from platelet-dense granules. With a half-life spanning 7–8 hours and an onset of action typically ranging from 2 to 4 hours, Clopidogrel is commonly administered in a loading dose of 300 to 600 mg, complemented by a daily dosage of 75 mg.

The combination of Clopidogrel with Aspirin as part of dual antiplatelet therapy (DAPT) is a widely adopted practice in endovascular aneurysm treatment. However, a major concern with Clopidogrel is its nature as a prodrug, necessitating enzymatic conversion to active metabolites for its antiplatelet effects to manifest. Consequently, loading doses are often required to achieve rapid efficacy. Various factors, including drug interactions, polymorphisms within the CYP450 enzyme family, and smoking status, can contribute to a significant proportion of individuals showing an inadequate response to Clopidogrel treatment.

Prasugrel

Prasugrel is a newer generation thienopyridine, functions by inhibiting the P2Y₁₂ receptor and has a half-life ranging from 2 to 15 hours. In comparison to Clopidogrel, it offers a faster onset of action and increased efficacy. Prasugrel undergoes more efficient conversion to its active metabolites and exhibits reduced dependence on CYP enzymes compared to Clopidogrel. Prasugrel is primarily used for patients undergoing intracranial flow diversion, especially when Clopidogrel fails to produce an adequate response due to altered hepatic metabolism. The duration of action of Prasugrel is similar to other thienopyridines, involving irreversible binding to ADP receptors. The standard dosing regimen is a 60 mg loading dose followed by a once-daily maintenance dose of 10 mg (or 5 mg if the patient weighs less than 60 kg). Prasugrel is associated with an increased risk of major bleeding and is contraindicated in patients with acute stroke due to the increased risk of hemorrhagic transformation.

Ticagrelor

Ticagrelor is a reversible inhibitor of P2Y₁₂ receptors, belonging to the thienopyridine class, similar to Clopidogrel and Prasugrel. It has a median onset of action of 1.3–2 hours, a half-life of 4.6–6.3 hours, and becomes undetectable in plasma after 20 hours. Unlike Clopidogrel, Ticagrelor does not require hepatic metabolism for activation, making it effective for patients with genetic resistance to Clopidogrel due to CYP2C19 enzyme alterations. Ticagrelor is considered a safe and efficacious alternative to Clopidogrel, typically administered with a loading dose of 180 mg and a maintenance dose of 90 mg twice daily for 3–6 months.

GLYCOPROTEIN IIB/IIIA AGENTS

Tirofiban

Tirofiban, a glycoprotein IIb/IIIa receptor antagonist, binds reversibly to the GPIIb/IIIa receptor and has a plasma half-life of 2.5 hours. It is helpful in preventing platelet aggregation and thrombosis, particularly in acute ischemic stroke and during endovascular treatments. Administered intravenously, Tirofiban achieves more than 90% inhibition of ADP-induced platelet aggregation within 10–40 minutes with a 0.4 µg/kg loading infusion, followed by a maintenance infusion of 0.1 µg/kg/min. Platelet function returns to near baseline in 90% of patients within 4–8 hours after discontinuing the infusion. Similar to Eptifibatide, Tirofiban is renally cleared and requires dose adjustment in patients with impaired renal function; however, it can be effectively cleared by hemodialysis.

Eptifibatide

Eptifibatide, a cyclic heptapeptide derived from rattlesnake venom, reversibly binds to the GPIIb/IIIa receptor and has a plasma half-life of 1.5–2.5 hours. A bolus dose of 180 µg/kg achieves over 80% inhibition of platelet function within 15 minutes. An infusion of 0.5–0.75 µg/kg/min decreases platelet function after 4–6 hours, the time required to reach a steady state. This delay can be mitigated by administering a second 180 µg/kg bolus within 10 minutes after the first. Less than 50% of platelet aggregation inhibition remains 4 hours after stopping the infusion. Eptifibatide is renally cleared and requires dosage adjustment in patients with a creatinine clearance of less than 50 ml/min. It is particularly useful for proximal thrombus or in-stent occlusions during aneurysm coil embolization, with no reported hemorrhagic complications or worsening of pre-existing subarachnoid hemorrhage, although it may be less effective for distal thrombi.

CLINICAL SCENARIO

CASE 1

Elective procedure with no intra-operative complication, e.g unruptured intracranial aneurysm for flow diverter stent placement

Pre-procedure:

Oral Aspirin 300-325mg and Clopidogrel 300-600mg given 5-7 days prior to the procedure

Post-procedure:

Oral Aspirin 75-100mg daily for 12 months and Clopidogrel 75mg daily for 3-6 months; *or*

Oral Aspirin 75-100mg daily for 12 months and Ticagrelor 90mg BD for 3-6 months

CASE 2

Emergency procedure with no intra-operative complication, e.g ruptured intracranial aneurysm for flow diverter stent or stent and coiling placement

Pre-procedure:

Oral Aspirin 300-325mg or IV Aspirin 500mg, and Clopidogrel 300-600mg prior to the procedure

Post-procedure:

Oral Aspirin 75-100mg daily for 12 months and Clopidogrel 75mg daily for 3-6 months; *or*

Oral Aspirin 75-100mg daily for 12 months and Ticagrelor 90mg BD for 3-6 months

CASE 3

Elective procedure with intra-operative thrombosis, e.g placement of flow diverter in unruptured intracranial aneurysm complicated with thrombosis.

Pre-procedure:

Oral Aspirin 300-325mg and Clopidogrel 300-600mg given 5-7 days prior to the procedure

Intra-procedure:

Tirofiban 12µg/kg loading infusion over 30 minutes

Post-procedure:

IV infusion of Tirofiban 0.1µg/kg/min for 12-24 hours; *and*

Oral Aspirin 75-100mg daily for 12 months and Clopidogrel 75mg daily for 3-6 months; *or*

Oral Aspirin 75-100mg daily for 12 months and Ticagrelor 90mg BD for 3-6 months

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TABLE LEGEND:

Table 1: Summary of pharmacokinetic and pharmacodynamics of commonly used antiplatelet agents

Antiplatelet Agents	Mechanism of action	Half-life	Onset of action	Consideration	Side effects
Aspirin	COX-1 inhibitor	15–20min in plasma	15-30min	Effect on platelets 8–10 days given irreversibility of COX inhibition	Bleeding. Gastrointestinal upset
Clopidogrel	Irreversible P2Y12 inhibitor	7-8h	2-4h	Requires hepatic metabolism, potential genetic resistance (CYP2C19 variations)	Bleeding. Marrow suppression. Thrombotic thrombocytopenic purpura
Prasugrel	Irreversible P2Y12 inhibitor	2-15h	30min	Effects last 8–10 days. Rapid onset of action due to fast conversion to active metabolites	Bleeding
Ticagrelor	Reversible P2Y12 inhibitor	4.6-6.3h	1.3-2h	Not affected by CYP polymorphisms	Bleeding. Respiratory discomfort
Tirofiban	Reversible GPIIb/IIIa receptor antagonist	2.5h	10-40min	Given IV or IA. Needs renal adjustment	Bleeding. Thrombocytopenia
Eptifibatide	Reversible GPIIb/IIIa receptor antagonist	1.5-2.5h	15min	Given IV or IA. Needs renal adjustment	Bleeding. Thrombocytopenia

Table 2: Recommended antiplatelet regimes and dosage

Antiplatelet Agents	Dosage		Duration
	Loading	Maintenance	
Elective			
Aspirin	300-325mg	75-100mg daily	5-7 days prior, then continue minimum for 12 months
Clopidogrel	300-600mg	75mg daily	5-7 days prior, then continue for 3-6 months
Prasugrel	30-60mg	5-10mg daily	3-6 months
Ticagrelor	180mg	90mg twice daily	3-6 months
Emergency			
Aspirin	Oral: 75-325mg IV: 500mg Rectal: 120-300mg	75-100mg daily	STAT, then continue minimum for 12 months
Clopidogrel	300-600mg	75mg daily	STAT, then continue for 3-6 months
Prasugrel	30-60mg	5-10mg daily	3-6 months
Ticagrelor	180mg	90mg twice daily	3-6 months
Rescue Therapy			
Tirofiban	12µg/kg for 30 min	0.1µg/kg/min	IV or IA bolus, followed by infusion 12-24 hours
Eptifibatide	180µg/kg for 1-2 min	1-2µg/kg/min	IV or IA bolus, followed by infusion 12-24 hours