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, proceeded by a loading dose of 300-600mg given 5 days prior to the procedure. 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.

$P2Y_{12}$ 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.

The P2Y12 reaction units (PRU) test, for example the VerifyNow system, is vital for assessing the effectiveness of antiplatelet therapy with P2Y12 receptor inhibitors like Clopidogrel. By measuring the inhibition of platelet aggregation after stimulation with ADP, the PRU test helps determine if a patient is responding adequately to Clopidogrel. The target therapeutic range is 60–240 PRU, indicating sufficient platelet inhibition to prevent thrombotic events, which is crucial during procedures like stent placements.

Identifying non-responsive patients early allows clinicians to adjust dosages or switch to alternative medications such as Ticagrelor or Prasugrel, ensuring optimal antiplatelet therapy and reducing the risk of complications.

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.

Cangrelor

Cangrelor is an ATP analogue that inhibits ADP-mediated platelet aggregation by binding to the P2Y12 receptor. It is not a prodrug and is active immediately after IV administration, with a short half-life of 3–6 minutes. Cangrelor's effects are dose-dependent, with doses up to 4 μg/kg/min inhibiting platelet aggregation and increasing bleeding time. The antiplatelet effect is reversed within 20 minutes after infusion cessation. In cardiology, a common dosing protocol includes a 30 μg/kg IV bolus followed by a 4 μg/kg/min IV infusion. Lower doses, such as a 5 μg/kg bolus followed by 0.75–1 μg/kg/min infusion, have also been used. While evidence for Cangrelor in neurointerventional procedures is limited, it shows promise for high-risk patients and procedures. It has been effective in treating ruptured and unruptured aneurysms, with a hemorrhagic complication rate of around 4%.

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.

Abciximab

Abciximab, a monoclonal antibody targeting the GPIIb/IIIa receptor, is used to inhibit platelet adhesion and aggregation. It is administered intravenously (IV) or intraarterially (IA) and has a short half-life of 10-30 minutes, though it remains platelet-bound for 15 days. A bolus of 250 μg/kg inhibits more than 80% of platelet aggregation within 15 minutes. It can be reversed partially with platelet infusion in emergencies. Dosing regimens include 4-10 mg boluses for thrombus removal and 0.25 mg/kg IA loading followed by 0.125 μg/kg/min infusion for thrombus dissolution. Profound thrombocytopenia has been reported, thus monitoring of platelet is recommended following bolus of Abciximab.

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 100mg and Clopidogrel 75mg daily for 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 100mg and Clopidogrel 75mg daily for 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	MIMS
Aspirin	COX-1 inhibitor	15–20min in plasma	15-30min	Effect on platelets 8–10 days given irreversibility of COX inhibition	Bleeding Gastrointestinal upset	A
Clopidogrel	Irreversible P2Y12 inhibitor	7-8h	2-4h	Requires hepatic metabolism, potential genetic resistance (CYP2C19 variations)	Bleeding Marrow suppression. Thrombotic thrombocytopenic purpura	B
Prasugrel	Irreversible P2Y12 inhibitor	2-15h	30min	Effects last 8–10 days. Rapid onset of action due to fast conversion to active metabolites	Bleeding	B
Ticagrelor	Reversible P2Y12 inhibitor	4.6-6.3h	1.3-2h	Not affected by CYP polymorphisms	Bleeding Respiratory discomfort	B
Cangrelor	Reversible P2Y12 inhibitor	3-6min	Immediate	Requires IV administration	Bleeding Dyspnea	A*
Tirofiban	Reversible GPIIb/IIIa receptor antagonist	2.5h	10-40min	Given IV or IA. Needs renal adjustment	Bleeding Thrombocytopenia	B
Eptifibatide	Reversible GPIIb/IIIa receptor antagonist	1.5-2.5h	15min	Given IV or IA. Needs renal adjustment	Bleeding Thrombocytopenia	B
Abciximab	Reversible GPIIb/IIIa receptor antagonist	10-30min	Immediate	Requires IV or IA administration	Bleeding Thrombocytopenia Hypotension	A*

Table 2: Recommended antiplatelet regimes and dosage

Antiplatelet Agents	Dosage		Duration
	Loading	Maintenance	
Elective			
Aspirin	100mg daily	75-100mg daily	5-7 days prior, then continue minimum for 12 months
Clopidogrel	75mg daily	75mg daily	5-7 days prior, then continue for 3-6 months
Prasugrel	30-60mg	5-10mg daily	1 day prior, then maintenance for 3-6 months
Ticagrelor	180mg	90mg twice daily	1 day prior, then maintenance for 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	STAT, then continue for 3-6 months
Ticagrelor	180mg	90mg twice daily	STAT, then continue for 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