WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 10, 27-38. Review Article ISSN 2277– 7105

CLOPIDOGREL THERAPY IN STROKE PATIENTS

Karima Samlan*

Master of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga.

Article Received on
25 June 2019,

Revised on 15 July 2019,
Accepted on 04 August 2019,

DOI: 10.20959/wjpr201910-15550

***Corresponding Author**
Karima Samlan
Master of Clinical Pharmacy,
Faculty of Pharmacy,
Universitas Airlangga.

I. INTRODUCTION

Cerebrovascular disease or stroke is the second leading cause of death worldwide.[1] Stroke is a syndrome due to disrupted blood flow in the brain causing sudden neurological deficit, at least for 24 hours. Stroke is the main manifestation of cerebrovascular disease, the all types of vascular diseases in the brain.[2]

Stroke is the main cause of mortality and morbidity. Cerebral infarct (ischaemic stroke) due to arterial occlusion is the most common type of stroke, but an ischaemic condition also contributes to the pathophysiology of primary intra-cerebral and subarachnoid haemorrhage.[3]

Stroke is divided into ischaemic (accounting for 87% stroke) and haemorrhagic (13%) stroke. Ischaemic stroke, both the thrombolytic or embolic stroke, is a progression of sudden focal neurological deficit due to inadequate blood supply to the brain area. Thrombolytic occlusion happens when the thrombus was formed in the artery of the brain. While embolic stroke happens when a thrombus, from in or outside cerebral vascularization, ruptured and occluded the cerebral vascularization. The extra-cerebral emboli usually arises from the heart, called cardio-embolic stroke.[1]

Haemorrhagic stroke arises from central nerves system (CNS) haemorrhage including subarachnoid haemorrhage (SAH), intra-cerebral haemorrhage (ICH), and subdural hematome. SAH is a sudden haemorrhage between in the inner and middle part of meningeal layers, due to trauma, ruptured cerebral aneurysm, or arteriovenous malformation (AVM). ICH is a direct haemorrhage in brain parenchyma, usually due to uncontrolled hypertension. The subdural hematoma arises from subdural layer bleeding and mostly due to the head injury.

II. Risk Factors and Classification

Risk factors assessment for ischaemic and haemorrhagic stroke is an important component of stroke prevention, diagnosis, and treatment. The main target of long term ischaemic stroke management includes the primary prevention (the first stroke prevention) and recurrent stroke prevention by risk factors reduction and modification. Ischaemic stroke risk factors are modifiable and non-modifiable (Figure 1). The patients had to assess and modify their risk factors, if possible, to lower the risk of stroke event and/or recurrency.[4,5]

Figure 1: Modifiable and non-modifiable risk factors of ischaemic stroke.

There are two main ischaemic cerebral events: transient ischaemic attack (TIA) and ischaemic stroke (cerebral infarct). TIA is a temporary neurological dysfunction arises from focal area of the brain, spinal cord, or retina ischaemic without any acute infarction. TIA has a rapid onset and short duration, less than 1 hour and usually not longer than 30 minutes. The symptom varies depend on the brain area involved. But, there is no deficit residue after the event. The classic definition of TIA is based on the duration, less than 24 hours; any

symptom that lasts more than 24 hours is categorized as ischaemic stroke. Modified neuroimaging techniques showed that clinical symptoms that last more than 1 hour are an ischaemic stroke based on the evidence of tissue infarct. Using classic definition of TIA is potentially misclassifying one third cases. So, TIA definition had changed by dismiss the duration factor to support the diagnosis and classification of the event.[6] TIA is also an acute ischaemic stroke risk factor, accounting for approximately 15% cases of acute ischaemic stroke; so, the prevention of TIA and ischaemic stroke is similar.[7]

Ischaemic stroke is similar to TIA; except for the tissue injury and infarction, and deficit residue found in many patients after the event. A tissue definition based on the existence of cerebral infarct had approved as cerebral infarct definition including brain, spinal cord, and retinal cell permanent injury based on neuropathology, neuroimaging, and clinical evidences.[8]

III. Pathophysiology

In ischaemic stroke there is blood supply disruption in the brain due to thrombus or emboli. The diminished cerebral blood flow leads to tissue hypo-perfusion, hypoxia, and cell deaths. Thrombus formation usually started by lipid deposit in the vessels causing blood flow turbulence. This event leads to vessels injury and exposes vascular collagen to the blood. The vessels injury trigger thrombocyte aggregation due to sub-endothelium exposure. Thrombocytes release adenosine diphosphate (ADP) causing platelet aggregation and consolidation. Thromboxane A2 also contributes to the thrombocyte aggregation and vasoconstriction. The vessels injury activate the coagulation cascade to produce thrombin that turns fibrinogen to fibrin causing clot formation from fibrin molecules, thrombocytes, and blood cells aggregation (Figure 2-3).

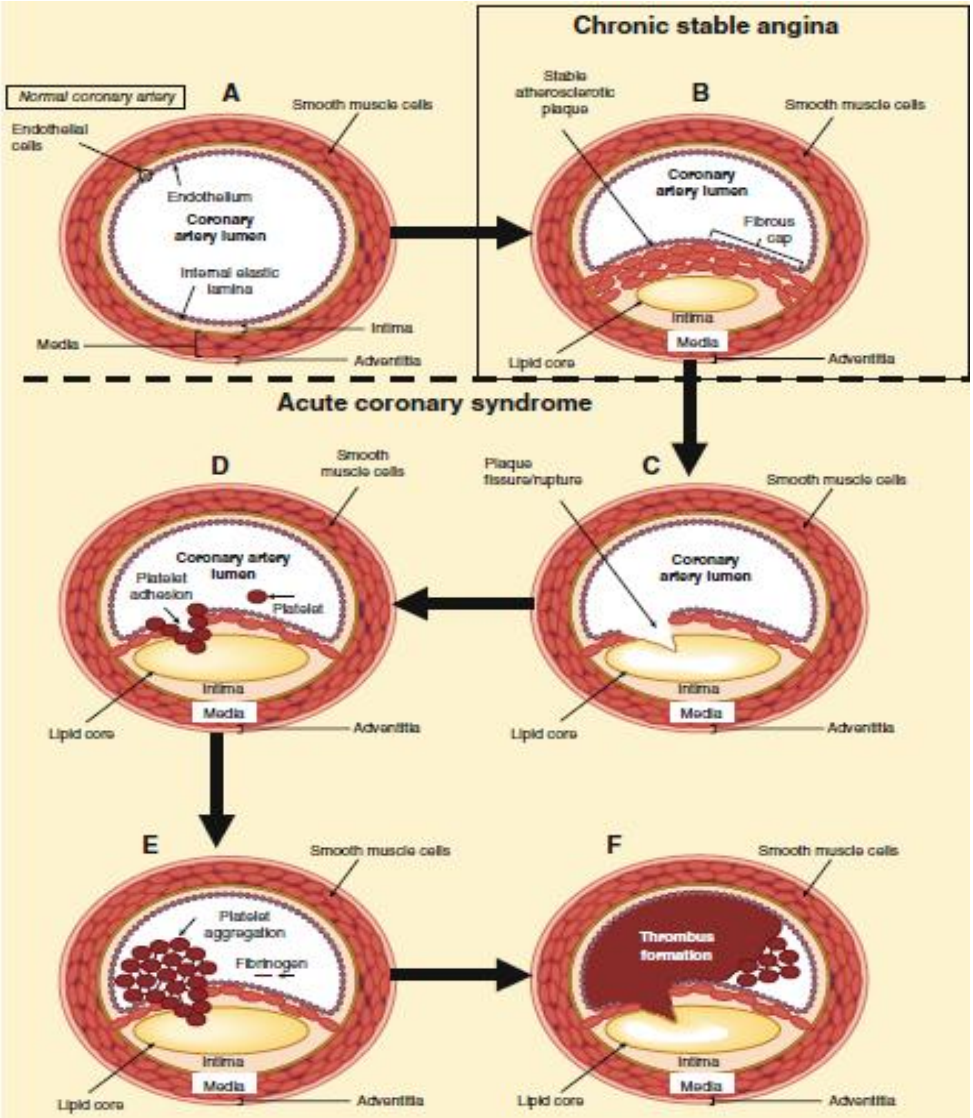

Figure 2: Pathophysiology of chronic stable angina vs. acute coronary syndrome. Panel A illustrates a normal coronary artery. Panel B illustrates stable atherosclerotic plaque in coronary artery. The lipid core is relatively small and the fibrous cap is consists of some smooth muscle cell layers. Panel C illustrates unstable atherosclerotic plaque with bigger lipid core and thinner fibrous cap with only a layer of smooth muscle cell that cracks or ruptures. Panel D illustrates platelet adhesion as a response to ruptured plaque. As platelet activation happens, platelet aggregation as fibrinogen binds to thrombocyte to form a net occlusion in the coronary lumen (Figure E). In this step, the patient may suffers from acute coronary syndrome. If the endogenous anticoagulant protein fail to stop this process, platelet aggregation will continues and fibrinogen turns into fibrin that leads to occlusive thrombus formation (Panel F).

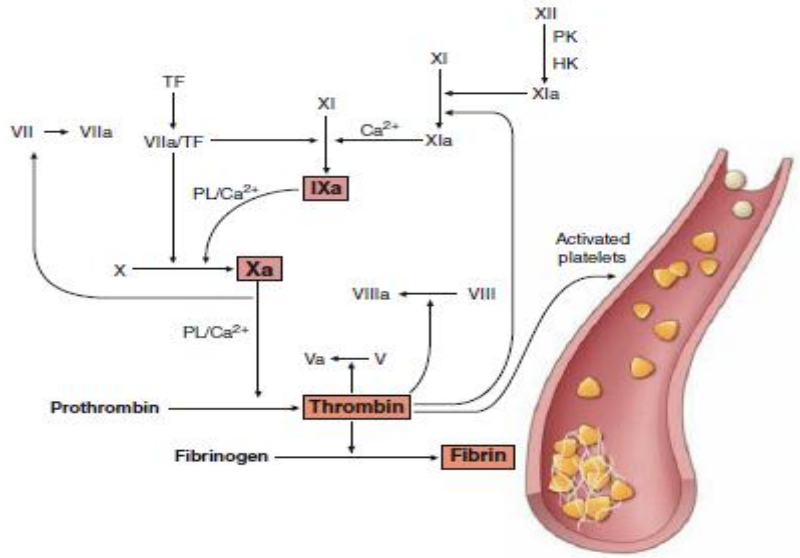

Figure 3: Summary of coagulation cascade. The specific coagulation factor ("A" shows an active form) is responsible to convert plasma soluble fibrinogen into unsoluble fibrin. This process happens through some reactions where active enzymatic products turn into active protein that downstream to active serine protease. On the other hand, thrombin activation stimulates the thrombocyte (HK, high molecule weight kininogen; PK, prekallikrein; TF, tissue factor).[9]

After initiation event, secondary event happens in the cellular level, contributes to the cell death. This cellular process might happen in the same way. Amino acid stimulation, such as glutamate, accumulates in the cell causing intracellular calcium accumulation. This event leads to inflammation and oxygen free radical formation in the cell death pathway. Usually there is ischaemic core that contains contaminated brain cell and surrounded by an area called ischaemic penumbra. In ischaemic penumbra, the cell can be saved, but highly depends on the time. Without an adequate perfusion restoration, the cell deaths continue in the wider brain area causing neurological deficit.

The pathophysiology of haemorrhagic stroke is not learned as deep as ischaemic stroke; but it is more complex. Most of this processes are related to the presence of blood in brain tissue and surrounding space that causing compression. The hematoma formation continues to grow and develop after the initial bleeding, and related to poor outcomes. The oedema and injured brain tissue is caused by inflammation from thrombin and the other blood products. This event leads to increased intracranial pressure (ICP) and herniation.[10,11]

IV. Clopidogrel for Stroke

The key event in platelet activation and aggregation increases in cytoplasmic calcium. It changes the configuration of inactive GPIIb/IIIa receptor (▭) in the plasma membrane into high affinity receptor for fibrinogen (⬭), forms a cross-link between platelet and aggregation. Thrombin, TXA2 and 5HT activate phospholipase C, resulting inositol-1,4,5-triphosphate (insP3) that stimulates calcium release from the endoplasmic reticulum. ADP inhibits the adenylate cyclase and the decreased cyclic adenosine monophosphate (cAMP) also increases cytoplasmic calcium. All antiplatelet drugs inhibit calcium dependent pathway through this platelet activation pathway.

Clopidogrel is thienopyridine deviation that reduce platelet aggregation by inhibiting ADP effect on thrombocyte, irreversibly. Clopidogrel has a synergic effect with aspirin (acetylsalicylic acid, ASA). Clopidogrel is also used when the aspirin is contraindicated. Clopidogrel is slightly more effective than ASA and similar with the combination of extended-release (ER) dipyridamole and aspirin.[12,13] The usual dose of clopidogrel, 75 mg once a day, has a lower diarrhoea and neutropenia rate compared to ticlopidine, and doesn't need any laboratory monitoring. Clopidogrel can be used as a monotherapy for secondary stroke prevention. This is an initial option of secondary ischaemic stroke prevention and considered as the first line therapy for the patients with peripheral artery disease or allergy to the aspirin.

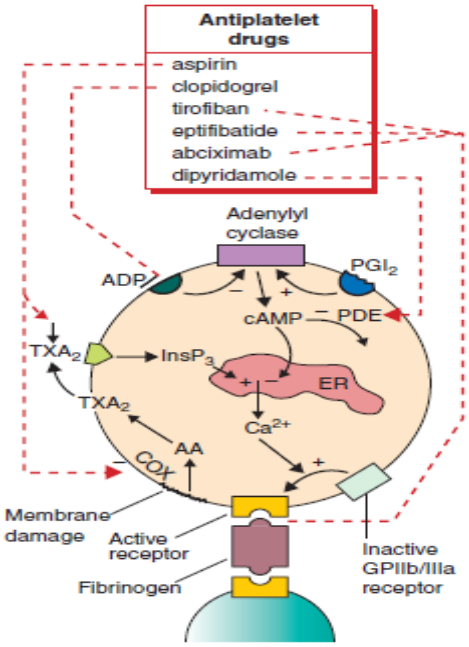

Figure 4. Mechanism action of clopidogrel as an antiplatelet.

Clopidogrel specifically disrupts ADP receptor binding with Gi/adenylyl cyclase (P2YAC ADP receptor). Clopidogrel eliminates P2YAC receptor by inhibit ADP effect mediated with receptor in prostaglandin E1 stimulation, which depends on cAMP and VASP without altering epinephrine, thrombin, and thromboxane signalling. VASP phosphorylation is highly correlated with the inhibition of platelet and fibrinogen receptor (glycoprotein IIb/IIIa) activation. So, the inhibition of platelet ADP P2YAC receptor and its intracellular signalling, including decreased VASP phosphorylation, is the mechanism action of clopidogrel.

It is expected that clopidogrel is activated by hepatic cytochrome P450 3A (CYP3A) to form an active metabolite.[14,15] Clopidogrel active metabolite inhibits adenosine diphosphate (ADP)-induced thrombocyte aggregation by irreversibly binding to platelet P2Y12 receptor.[16] Consistently, coadministration of CYP3A inducer or inhibitor responsively modulates in vivo.[17,18] There is a report of subject with defect CYP2C19 alel (CYP2C19 * 2) responded poorly compared with normal CYP2C19 alel.[19,20] Then, an in vitro study showed that beside CYP3A, CYP2C19 was involved in clopidogrel activation.[21,22]

The efficacy of clopidogrel as an antiplatelet for atherorhrombotic disruption in Indonesia was reported by CAPRIE study.[23] In this study, more than 19.000 patients with the history of myocardial infarct (MI), stroke, or peripheral artery disease (PAD), were treated by clopidogrel 75 mg/day or aspirin 325 mg/day to compare their efficacy to lower MI, stroke, and cardiovascular death. In the final analysis, clopidogrel was slightly (8% reduced risk relative [RRR]) more effective than aspirin (p = 0,043) and had the same bad impact. There was no relationship with blood discrasias (neutropenia). Usually used with congener, ticlodipine, and widely used for atherosclerosis patients.

In MATCH study, clopidogrel combined with aspirin 75 mg per day was not more effective compared with clopidogrel alone in preventing stroke.[24] But, in patients with acute coronary syndrome or patients underwent percutaneous coronary intervention, this combination was significantly more effective than aspirin alone in reducing MI, stroke, or cardiovascular death.[25,26] When clopidogrel was combined with aspirin, the bleeding risk that threatened life increased from 1,3% to 2,6%. This combination only recommended for ischaemic stroke patients with recent history of MI or the other coronary event. And this combination only used ultra low dose aspirin to minimize its bleeding risk.[27]

Clopidogrel has an unique antiplatelet aggregation effect because it contains platelet aggregation adenosine diphosphate (ADP) pathway inhibitor and inhibits the stimulation of thrombocyte aggregation.[23,28] This effect alters thrombocyte membrane and disrupts membrane-fibrogenic interaction that blocks platelet glycoprotein IIb/IIIa receptor. An interval of 3 until 7 days before achieving maximum antiplatelet effect is recommended. The toleration of clopidogrel 75 mg/day is as good as medium dose (325 mg/day) aspirin with lower GI bleeding.

Clopidogrel is related with higher risk of diarrhoea and rash, compared with aspirin 325 mg/day (5,3% to 6%, respectively).[27] There is no excessive neutropenia in patients treated with clopidogrel, and extent thrombotic purpura. Clopidogrel is thienopyridine prodrug and needed a biotransformation by liver to form its active metabolite. The evidence showed that cytochrome P450 3A4 (CYP3A4) was an enzyme that responsile for clopidogrel conversion. The antiplatelet effect of clopidogrel is reduced in patients receiving CYP3A4 enzyme inhibitor agents.[29]

Pharmacology. Clopidogrel is an antiplatelet agent that prevents thrombocyte aggregation by directly inhibits ADP binding to the receptor, and inhibits the activation of glycoprotein IIb/IIIa. This effect is irreversible.

Adult dose per oral to reduce stroke, MI, or vascular death: 75 mg once a day. Initial dose 300 mg in the first day is usually used to shorten the intervention onset.

Formulation dose. Tablet 75 mg.

Pharmacokinetics. Clopidogrel is rapidly absorbed; its bioavaibility is approximately 50%; 98% binds to plasma protein. The main compound doesn't have activity thrombocyte inhibitor and extensively underwent hepatic metabolism into carboxylate acid derivation (the main metabolite) and other unknown active metabolite. The half life of carboxylate acid metabolite is 8 hours.

Adverse reaction. The most common adverse events are diarrhoea (4,5%), rash (4,2%), GI bleeding (2%) and GI ulcer (0,7%). The serious adverse event is rarely happened, including intracranial haemorrhage (0,4%) and severe neutropenia (0,04%). Clopidogrel is related to thrombotic thrombocytopenia purpura.[30] This drug is contraindicated in active bleeding patients such as peptic ulcer or intracranial haemorrhage. Precaution in patients with

increased bleeding risk due to trauma, surgery, or the other condition. Clopidogrel must be stopped 7 days before the surgery if antiplatelet effect isn't expected.

Drug interaction. Precaution in patients receiving anticoagulant drugs or drugs that inhibit thrombocyte function such as NSAID.

Notes. Reduced overall risk of clopidogrel is 8,7% higher than aspirin in CAPRIE study of patients that have the risk of ischaemic event.[23]

Table 1: Pharmacotherapy Recommendations for Ischemic Stroke.

	Primary Agents	Alternatives
Acute Treatment	tPA 0.9 mg/kg IV[6,17] (maximum 90 kg) over 1 hour in selected patients within 3 hours of onset. ASA 160–325 mg daily[6,17] started within 48 hours of onset	tPA (various doses) intraarterially up to 6 hours after onset in selected patients
Secondary Prevention		
Noncardioembolic	Aspirin 50–325 mg daily[6] Clopidogrel 75 mg daily[6] Asprin 25 mg + extended-release dipyridamole 200 mg twice daily[6]	Ticlopidine 250 mg twice daily[6]
Cardioembolic (esp. atrial fibrillation)	Warfarin (INR = 2.5)[6]	
All	ACE inhibitor + diuretic or ARB[45] blood pressure lowering[33,34] Statin[39]	

Table 2: Monitoring in Stroke Patients.

	Treatment	Parameter(s)	Frequency	Comments
Ischemic stroke	tPA	BP, neurologic function, bleeding	Every 15 min × 1 h; every 0.5 h × 6 h; every 1 h × 17 h; every shift after	
	Aspirin	Bleeding	Daily	
	Clopidogrel	Bleeding	Daily	
	ERDP/ASA	Headache, bleeding	Daily	
	Ticlopidine	CBC, bleeding, diarrhea	CBC every 2 weeks × 3 months; other, daily	
	Warfarin	Bleeding, INR, Hb/Hct	INR daily × 3 days; weekly until stable; monthly	
Hemorrhagic stroke		BP, neurologic function, ICP	Every 2 h in ICU	Many patients require intervention with short-acting agents to reduce BP to <180 mm Hg systolic
	Nimodipine (for SAH)	BP, neurologic function, fluid status	Every 2 h in ICU	
All		Temperature, CBC	Temp. every 8 h; CBC daily	For infectious complications such as UTI or pneumonia
		Pain (calf or chest)	Every 8 h	For DVT, MI, acute headache
		Electrolytes and ECG	Up to daily	For fluid and electrolyte imbalances, cardiac rhythm abnormalities
	Heparins for DVT prophylaxis	Bleeding, platelets	Bleeding daily, platelets if suspected thrombocytopenia	

REFERENCES

1. Chisholm-burns, Marie A., Schwinghammer, Terry L., Wells, Barbara G., Malone, Patrick M., Kolesar, Jill M., DiPiro, J., 2016. Pharmacotherapy Principles and Practice, Fourth Edition. McGraw Hill Professional.
2. Dowling, T.C., Comstock, T.J., 2005, Quantification of Renal Function dalam Dipiro, J.T., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.J. dan Posey, L.M., Pharmacotherapy A Pathophysiologic Approach, Sixth Edition, The McGraw-Hill Companies, USA.
3. Tomlinson, Stephen., Heagerty, Anthony M., Weetman, Anthony AP., Malik, Rayaz., 2008, Mechanism of Diseases, Second Edition, Cambridge University Press, UK.
4. Goldstein LB, Bushnell CD, Adam R, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2011; 42: 517–584.
5. Grysiewicz RA, Thomas D, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: Incidence, prevalence, mortality and risk factors. Neurol Clin, 2008; 26: 871–895.
6. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke, 2009; 40: 2276–2293.
7. Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: Time window for prevention is very short. Neurology, 2005; 64: 817–820.
8. Sacco RL, Kasner SE, Broderick JP, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology an Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2013; 44: 2064–2089.

9. Freedman JE, Loscalzo J. Arteri dan trombosis vena Dalam: Longo DL, Fauci AS, Kasper DL, dkk., Eds. Harrison Prinsip Pengobatan Internal, 18 ed. New York, NY: McGraw-Hill, 2012; 985.
10. Connelly ES, Rabinstein AA, Carhuapoma JR; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, and Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke, 2012; 43: 1711–1737.
11. Testai FD, Aiyagari V. Acute hemorrhagic stroke pathophysiology and medical interventions: blood pressure control, management of anticoagulant-associated brain hemorrhage and general management principles. Neurol Clin, 2008; 26: 963–985
12. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. Lancet, 1996; 348: 1329–1339.
13. Sacco RL, Deiner HC, Yusuf S, et al; PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med, 2008; 359: 1238–1251.
14. Pereillo, J.M. et al. Structure and stereochemistry of the active metabolite of clopidogrel. Drug Metab. Dispos, 2002; 30: 1288–1295.
15. Savi, P. et al. Identification and biological activity of the active metabolite of clopidogrel. Thromb. Haemost, 2000; 84: 891–896.
16. Savi, P., Labouret, C., Delesque, N., Guette, F., Lupker, J. & Herbert, J.M. P2y(12), a new platelet ADP receptor, target of clopidogrel. Biochem. Biophys. Res. Commun, 2001; 283: 379–383.
17. Lau, W.C. et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. Circulation, 2004; 109: 166–171.
18. Suh, J.W. et al. Increased risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel. CMAJ, 2006; 174: 1715–1722.
19. Hulot, J.S. et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood, 2006; 108: 2244–2247
20. Fontana, P., Hulot, J.S., De Moerloose, P. & Gaussem, P. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. J. Thromb. Haemost, 2007; 5: 2153–2155.

21. Giusti, B. et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10+12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. Pharmacogenet. Genomics, 2007; 17: 1057–1064.
22. Kurihara, A., Hagihara, K., Kazui, M., Ozeki, T., Farid, N.A. & Ikeda, T. In vitro metabolism of antiplatelet agent clopidogrel: cytochrome P450 isoforms responsbile for two oxidation steps involved in the active metabolite formation. Drug Metab. Rev, 2005; 37: 99.
23. CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet, 1995; 348: 1329–1339.
24. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomized, doubleblind, placebo-controlled trial. Lancet, 2004; 364: 331–337.
25. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med, 2001; 54: 1022–1028.
26. Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized, controlled trial. JAMA, 2002; 288: 2411–2420.
27. Peters RJG, Mehta SR, Fox KAA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: Observations from the clopidogrel in unstable angina to prevent recurrent events (CURE) study. Circulation, 2003; 108: 1682–1687.
28. Albers GW, Amerenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest, 2004; 126(3 suppl): 483S–512S.
29. Lau WC, Waskell LA, Watkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: Anewdrug-drug interaction. Circulation 2003; 107: 32–37.
30. Bennet CL et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Me,* 2000; 342: 1773–7.