

Update in Glycoprotein IIb/IIIa Receptor Antagonist Clopidogrel: Use in Cerebrovascular Accidents

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Abstract: Acute ischemic stroke is the most common manifestation of cerebrovascular disease, which ranks the first to make an adult become bedridden and/or out of productive life. Antiplatelet therapy has long been demonstrated to alleviate the risks of recurrent untoward events, especially in the setting of secondary prevention. In the last decade it has been proved that dual antiplatelet therapy (DAPT) appears to be more efficacious than monotherapy with aspirin.

Clopidogrel (CLP) -an irreversible inhibitor of the platelet P2Y₁₂ adenosine diphosphate receptor- is licensed in adults for the prevention of atherothrombotic events in patients suffering from MI, ischemic stroke (from 7 days to 6 months) or peripheral arterial disease. The recommended dose is 75 mg as a single daily dose, taken with or without food.

This review is designed to encompass use of the agent comprehensively and delineates a frame in which clinicians can view as a guide in their routine clinical practice.

Keywords: Clopidogrel, Cerebrovascular accidents, Treatment, Prevention.

INTRODUCTION

Cerebrovascular disease ranks the highest in disease burden and causes nearly one-tenth of all deaths globally [1]. Ischemic stroke is the widespread manifestation of cerebrovascular disease. Patients who experience an ischemic stroke or transient ischemic attack (TIA) are at increased risk of recurrent stroke. The risk of recurrence after cardioembolic stroke and TIA is at its peak just following the event and declines over weeks [2].

Antiplatelet therapy has been shown to reduce the risk of numerous vascular events, especially in the setting of secondary prevention. The International Stroke Trial pointed out that acetylsalicylic acid/aspirin (ASA) helps prevention of early recurrences [3] and nowadays it is clarified that dual antiplatelet therapy (DAPT) appears to be more efficacious than monotherapy, with the choice of antiplatelets less important than the use of two agents rather than one [4].

TRANSIENT ISCHEMIC ATTACK

A TIA is caused by temporary disruption of blood circulation in a brain region. It is accompanied by a rapid-onset but short-lived decline (<24 hours, usually <1 hour) in neurological abilities. It is associated with stroke-like symptoms. By definition, it is described as a stroke, should the neurological deficit lasts more than 24 hours.

Notes on Epidemiology

The British Heart Foundation (BHF) reported that almost 100,000 people has their first brain attack of stroke each year in England [5]. Its incidence is boosted with advancing age. The risk of recurrent stroke is highest in the first 6 months after the event [6]. One in every three strokes are recurrent events [7]. Between 46,000 and 65,000 people experience a TIA every year and prevalence of TIA is estimated to be around 510,000 [5].

In patients enrolled in clinical trials after a TIA, the annual risk of important vascular events (death from all vascular causes, non-fatal stroke or non-fatal MI) is reported as around 9% per year [8].

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Clopidogrel (CLP)

CLP is licensed in adults for the prevention of atherothrombotic events in patients suffering from MI, ischemic stroke (from 7 days to 6 months) or peripheral arterial disease. The recommended dose is 75 mg as a single daily dose, taken with or without food.

CLP is an irreversible inhibitor of the platelet P2Y₁₂ adenosine diphosphate receptor. Inhibition of this receptor prevents the downstream activation of the glycoprotein IIb/IIIa receptor complex which leads to reduced platelet aggregation. CLP is an inactive prodrug that requires enzymatic bioactivation via CYP2C19 and CYP3A4. Regular use of clopidogrel (75 mg daily) can produce 40%–50% inhibition of ADP-induced platelet aggregation.

CLP is not licensed for secondary prevention of occlusive vascular events in patients who have experienced a TIA, although in clinical practice it may be prescribed for these patients.

Drug Interactions

The agent depends on CYP2C19 for metabolism for activation. Based on literature data, patients with genetically reduced *CYP2C19* function experience higher cardiovascular event rates after MI than do patients with normal enzymatic function.

There is evidence that two PPIs (omeprazole and esomeprazole) reduce the effectiveness of CLP in preventing the recurrence of adverse cardiac events; current advice is that concomitant use of these with CLP should be discouraged. Administration of agents that inhibit CYP2C19 metabolism such that –prazoles should be avoided.

Agents that slow down bowel motility can delay absorption (e.g., opioid agents) and are recommended to be avoided.

Use CLP with caution in combination with any other anticoagulant or antiplatelet drug or in patients with bleeding diathesis.

The agent inhibits the platelet for around 10 days, which is a lifespan of these structures. A return of full function occurs by 5 days. For this reason, CLP is to be withheld for 5 days before surgical procedures. In these situations, it is imperative to consult with the primary prescriber for the CLP [9].

Clinical use and Efficacy of CLP

FDA has issued an approval of CLP for the treatment of acute coronary syndromes: unstable angina pectoris (USAP), non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI) [10-12].

The MATCH [13], CHARISMA [14], and SPS3 [15] studies pointed out that DAPT was associated with increased bleeding compared with single antiplatelet therapy without a marked decline in ischemic events. Of note, in these studies, DAPT was not immediately ordered after the ischemic event. The CHANCE study gave information that early use of DAPT (in the first 24 hours) decreased the risk for future events compared with single antiplatelet therapy plus ASA [16]. The trial in 2013 shows that the combination of ASA with CLP is superior to ASA in patients with subtle or minor stroke (NIHSS \leq 3) or TIA (ABCD₂ \geq 4). The post hoc analysis of the CHANCE trial showed that risk of hemorrhage boosts following the 10th day [17]. The POINT study in 2018 confirmed the effect and safety of aggressive antiplatelet therapy in minor stroke within the first 12 h [18].

CLP is approved to be used in these situations:

- Use during a percutaneous coronary intervention (PCI) for ACS and other -stable- coronary disease states.
- Primary prevention of thromboembolism resulting from thrombi in atrial fibrillation
- Known carotid artery stenosis with relevant symptoms.
- Secondary prevention in post-coronary artery bypass grafting.
- Peripheral artery percutaneous angioplasty in peripheral artery bypass grafting.

Acute Treatment Strategy

Start ASA (162 to 325 mg/daily) alone for low-risk TIA, defined by an ABCD² score below 4.

- For high-risk TIA, defined as an ABCD² score of \geq 4, employ DAPT using ASA (160 to 325 mg loading dose, followed by 100 mg /day) plus CLP to 600 mg loading dose, followed by 75 mg/day) for three weeks.

For patients with ischemic stroke and no clue of intracranial/gastrointestinal bleeding, antiplatelet therapy should be commenced immediately.

- ASA monotherapy for those with moderate or higher stroke severity, defined by an NIHSS score >3 points.

- DAPT using ASA (160 to 325 mg loading dose, followed by 50 to 100 mg /day) plus CLP (300 mg loading dose, followed by 75 mg/day) for patients with minor stroke, known as the patients with NIHSS score ≤3 points.

Dosing Regimens

For CLP are summarized below:

- Medical treatment of UA/NSTEMI: Administer a 300 mg to 600 mg loading dose followed by 75 mg daily, in conjunction with ASA, ideally for up to 12 months.
- STEMI patients receiving fibrinolytics: If the patient is 75 years old or younger, then give a 300 mg loading dose followed by 75 mg daily for at least 14 days and up to 1 year. If the patient is older than 75 years of age, then do not give the loading dose.
- PCI during ACS/non-ACS setting: Administer a 600 mg loading dose as early as possible prior to PCI, followed by 75 mg per day. CLP should be administered with aspirin for at least 12 months post-ACS. The duration can vary with the type, location of the stent, and the hemorrhage risk.
- Peripheral artery percutaneous angioplasty or peripheral artery bypass grafting: 75 mg daily.
- Primary prevention of thromboembolism in atrial fibrillation: 75 mg daily.
- Symptomatic carotid stenosis: 75 mg daily.
- Secondary prevention coronary artery bypass graft surgery: 75 mg daily.

There is no adjustment required for renal or hepatic failure.

Toyoda *et al.* conducted a study to clarify whether DAPT combined with cilostazol is safe and appropriate for long-term use via an intention-to-treat analysis [19]. The combination of cilostazol with ASA or CLP had a reduced incidence of ischemic stroke recurrence and a similar risk of life-threatening bleeding compared with treatment with ASA or CLP alone in patients at high risk for recurrent ischemic event.

Likewise, in a recent meta-analysis Niu *et al.* demonstrated that cilostazol was significantly more effective than ASA and CLP alone in the longterm prevention of serious vascular events in patients with prior non-cardioembolic ischaemic stroke or transient ischaemic attack [20]. Cilostazol was associated with a significantly lower bleeding risk than low-dose ASA (75–162 mg daily) and ASA (50 mg daily) plus dipyridamole (400 mg daily). Low-dose ASA was as effective as higher daily doses.

CLP is not to be prescribed in patients who have had known allergy/ anaphylaxis to CLP or have active bleeding associated with the agent.

Some patients can have genetic polymorphisms to the CYP enzymes. Genetic testing may be considered in high risk patients prior to commencement of therapy (for example, patients with increased risk of stent thrombosis).

Cost Effectiveness

In 2005, Karnon *et al.* performed a cost utility analysis based on clinical data from CAPRIE from UK, focusing on the incremental cost effectiveness of CLP versus ASA in this population [21]. They found that a couple of years' therapy with CLP is considered a cost effective strategy in patients at risk of secondary occlusive events.

Safety Issues

CLP use may be accompanied by bleeding complications. Bleeding is the widespread adverse effect of the agent. Risk factors for bleeding include age older than 75 years, recent bleeding event, low body weight, or anticoagulant use.

Pregnancy

CLP has a risk factor B classification which can be translated as negligible or no risk. There are a number of well-written case reports in the literature regarding use of CLP during pregnancy [22, 23]. Although there is limited data on this specific situation, authors commented that CLP use in pregnancy has not been shown to convey important toxicity to either the mother or the neonate. Furthermore, Yilmaz *et al.* have stressed that a seven-week pregnant woman diagnosed with acute myocardial infarction was treated accordingly and was discharged home with a beta blocker, clopidogrel and ASA [24].

On the other hand, there should be well-designed studies to clarify secretion of CLP into the breast milk. Experts recommend to stop nursing or to cease the treatment in breastfeeding.

Reversal of Bleeding

There is no specific reversing 'antidote' for CLP. Hemostasis can be restored via platelet administration in severe, life-threatening hemorrhage [25].

While the drug is useful for the treatment of ischemic heart disease, its use must be monitored. Because the drug has the potential to cause bleeding, the patient's hemoglobin and other blood counts must be regularly monitored [9]. Although platelet transfusion was recommended by some authors, PATCH trial in 2016 showed a higher three-month death rate in platelet transfused patients [26]. The trial probed reversal of acute spontaneous primary intracranial hemorrhage in adult patients taking antiplatelet therapy at 60 hospitals in western Europe (Netherlands, UK, and France). The researchers concluded that platelet transfusion cannot be advocated for this scenario in clinical practice.

In patients with traumatic intracranial hemorrhage while on therapy with CLP, Canadian scientists in Orlando Regional Medical Center recommended clinicians to take following actions [27]:

- Obtain initial platelet function assay for ASA and CLP
- Reversal with combination of platelet transfusion and Desmopressin injection (dDAVP) 0.3 mcg/kg IV

Some reports suggested the patients with untoward platelet inhibition be administered methylprednisolone to relieve symptoms and prevent severe bleeding.

Rash

In cases of remarkable hypersensitivity resulting in rash, the patient can be given steroids without disrupting therapy. The patient can also be switched to an alternative agent such that ticagrelor.

KEY LITERATURE FINDINGS

In a prospective, randomized, open-label, blinded-endpoint trial on those with TIA and ischemic stroke TARDIS investigators compared intensive antiplatelet

therapy (combined aspirin 75 mg, CLP 75 mg, and dipyridamole 200 mg twice daily) or guideline-based therapy (comprising either CLP alone or combined aspirin and dipyridamole) [28]. The authors reported that intensive antiplatelet therapy did not diminish the incidence and severity of recurrent stroke or TIA, but significantly increased the bleeding risk. Triple antiplatelet therapy should not be used in routine clinical practice.

Greenhalgh *et al.* conducted a research to assess the clinical effectiveness and cost-effectiveness of CLP and modified-release dipyridamole (MRD) alone or with aspirin compared with ASA (and each other where appropriate) in the prevention of occlusive vascular events in patients with a history of MI, ischaemic stroke/TIA or established peripheral arterial disease [29]. They concluded that the most cost-effective treatment for patients with ischemic stroke/TIA is CLP followed by MRD + ASA followed by ASA; for patients with MI, ASA followed by CLP; and for patients with established peripheral arterial disease or multivascular disease, CLP followed by ASA.

Davis *et al.* reviewed the safety and efficacy of DAPT with ASA and CLP in the setting of secondary stroke prevention in 2015 [30]. They have noted that DAPT (*i.e.*, ASA combined with CLP) is effective only for those with minor neurological deficits or TIA when commenced in the first 24 hours of the ischemic event and maintained for three weeks. They also concluded that currently available evidence did not support routine use of ASA with CLP for the secondary prevention of ischemic stroke or TIA in the long run.

Niu *et al.* conducted a network meta-analysis which depicted that ASA plus CLP, two regimens of ASA plus dipyridamole, low (75–162 mg daily) and high (500–1500 mg daily) doses of ASA, CLP, ticlopidine and cilostazol, were significantly effective compared with placebo in preventing stroke [20] (Figure).

CONCLUSION

Use of CLP, ASA and other antiplatelet agents should be tailored individually and are not to be viewed a standard approach. Patients' needs, characteristics and drug properties should be taken into account in decision making process. After all, adding CLP to conventional treatment with ASA appears to be more efficacious in preventing recurrent stroke in general population.

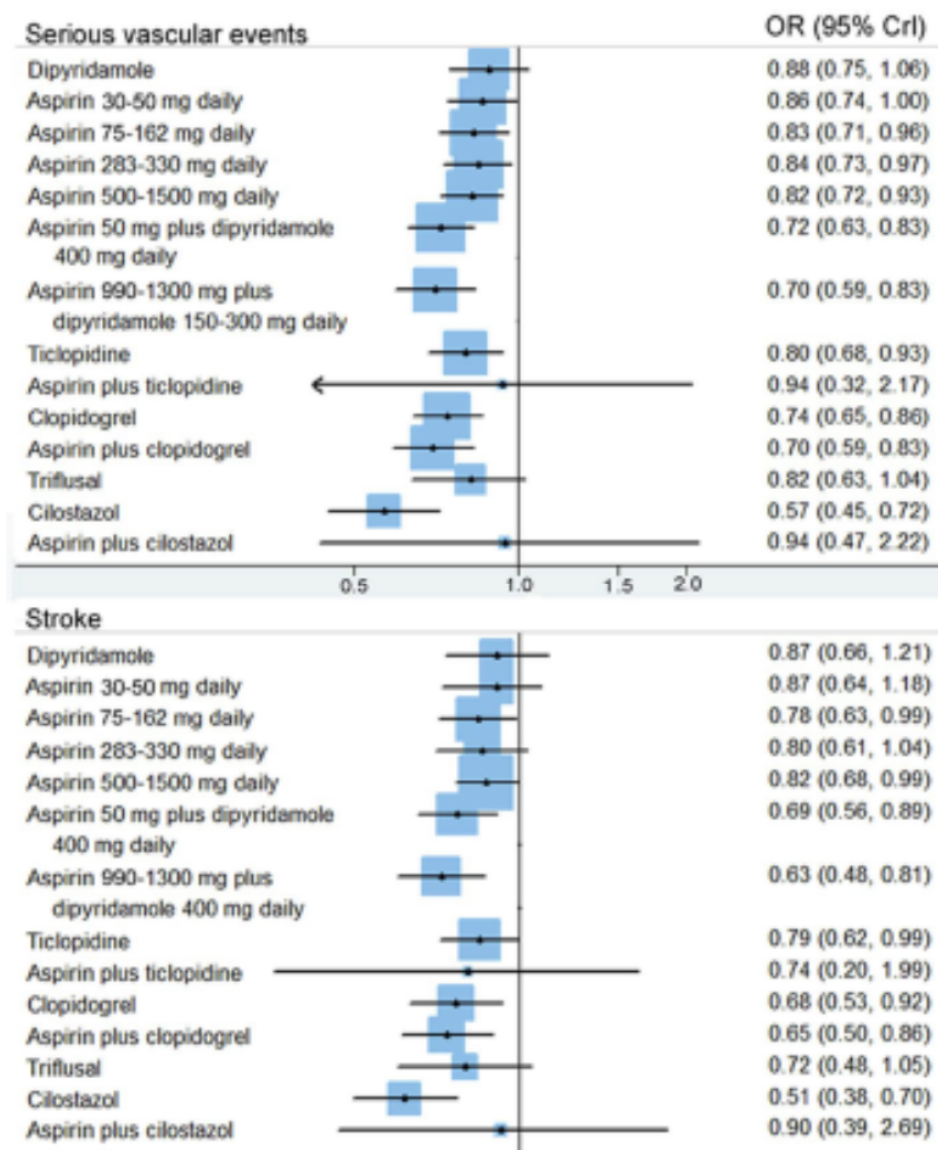


Figure: Findings of the network meta-analyses for various antiplatelet treatment modalities. Squares represent the magnitude of the estimates. Horizontal lines demonstrates estimated ORs and relevant 95% confidence intervals [20] (Adapted from Niu, *et al.* 2016).

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