

Pharmaceutical Selection of Antiplatelet Therapy in Cerebrovascular Disease

The following criteria are based on current literature and expert opinion from clinicians. It is expected that significant, new information will be forthcoming in this important drug class. Thus, the following recommendations are dynamic and will be revised as new clinical data becomes available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care.

A paucity of data exists in some areas of secondary stroke prevention. Management of hypertension, hyperlipidemia, smoking cessation and diabetic control have all been shown to lower the risk of an initial cerebrovascular event. However, more study is needed to define the degree of benefit these factors contribute for secondary stroke prevention. Given the significant risk reduction associated with these factors in primary prevention, it should be insured these same issues are addressed in secondary stroke prevention.

Patients should be evaluated for the presence of carotid artery stenosis. Patients with internal carotid artery stenosis of more than 70% are candidates for carotid endarterectomy. Patients with symptomatic carotid artery stenosis after surgical intervention should receive antiplatelet therapy. Adjusted dose warfarin should be employed in patients with atrial fibrillation and symptomatic ischemic events.

1. Choice of antiplatelet agent

Refer to Table

- The British Antiplatelet Trialists showed an odds reduction for combined endpoints of myocardial infarct, stroke and vascular death to be 23 % with all antiplatelet agents.
- In patients at high risk for stroke, the results from CAPRIE and ESPS2 show a NNT of 111 and 24 for clopidogrel and aspirin/extended release dipyridamole, respectively.
- The subset of patients with symptomatic peripheral vascular disease experienced the most benefit from clopidogrel therapy in the CAPRIE trial.
- The results of ESPS2 showed an advantage for aspirin/extended release dipyridamole over aspirin alone. However, the benefits in risk reduction for the outcome of stroke or death were not significant as the confidence interval included zero. This range includes the possibility of no benefit from the combination product.
- There is insufficient clinical data to support the superiority of combination therapy with clopidogrel and aspirin in secondary stroke prevention.

2. Dosage and Administration

- Clopidogrel dosage is 75 mg daily.
- Aspirin dosage is 81-325 mg daily, in patients experiencing GI upset dose may be decreased to no lower than 81 mg daily. Aspirin doses should be individualized, using the lowest dose to achieve effect (no cerebral ischemia symptoms).
- The combination of aspirin 25 mg-extended release dipyridamole 200mg is given twice daily.

3. Warnings/Adverse Events

- The development of thrombocytopenic purpura with clopidogrel therapy has been reported. The background rate is thought to be about four cases per million person-years.
- If a patient is to undergo elective surgery and an antiplatelet effect is not desired, therapy with irreversible antiplatelet agents (aspirin and clopidogrel) should be discontinued 7 days prior to surgery. Since dipyridamole is a reversible antiplatelet agent- the immediate release product could be given until 24 hrs prior to surgery.
- The use of these agents would be contraindicated in active pathological bleeding or most intracranial hemorrhage.
- In CAPRIE, clopidogrel was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin.
- In ESPS2, aspirin-extended release dipyridamole was associated with a rate of bleeding at any site of 8.7%, placebo 4.5%, aspirin alone 8.2% and extended release dipyridamole alone 4.7%.

4. Monitoring Parameters

- Patients should be monitored for development of bleeding.
- The effect of hepatic failure on the use of these agents is unknown.
- Aspirin use should be avoided in patients with creatinine clearances of <10 ml/min.

Cost Comparison of Antiplatelet agents

Agent	FSS price/tablet	Tablets/day	Cost/day
Aspirin 325 mg	\$0.007	1	\$0.007
Aspirin 81 mg	\$0.004	1	\$0.004
Clopidogrel 75 mg	\$2.03	1	\$2.03
ASA/dipyridamole 25mg/200mg	\$0.80	2	\$1.60

References:

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2. Zusman RM, Chesbero JH, Comerota A, et al. Antiplatelet Therapy in the prevention of ischemic vascular events: Literature review and evidence based guidelines for drug selection. Clin Cardiol 1999;22:559-573.
3. Sixth ACCP Consensus Conference on Antithrombotic therapy. Chest 2001;119:300s-320s.
4. ESPS Group. European Stroke Prevention Study. Stroke 1990;21:1122-1130.
5. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet 1996;348:1329-1339.

VHA Pharmacy Benefits Management (PBM)-Medical Advisory Panel (MAP) and Neurology Advisory Group

Condition	Preferred agent	Dose	Alternative	Dose
Atrial fibrillation	Warfarin ^a	Dose adjusted to maintain INR 2.0-3.0 (target INR 2.5)	Aspirin ^b	
Primary prevention	Aspirin	81-325mg	Clopidogrel ^c	75 mg PO QD
Secondary prevention	Aspirin	81-325mg	Clopidogrel ^d Aspirin/extended release dipyridamole ^e	75mg PO QD 25mg/200mg PO BID

^a In patients with atrial fibrillation, warfarin is recommended for all patients over the age of 75 (unless a specific contraindication exists), and in patients of any age with a prior embolic event or with known risk factors for stroke. Patients with lone atrial fibrillation may differ in therapy. Those under 65 years require no mandatory therapy but aspirin is optional. For those patients age 66-75 years, aspirin is recommended and warfarin is optional.

^b Patients who experience recurrent symptoms of cerebral ischemia on appropriate warfarin therapy, consideration should be given to adding aspirin 80 mg daily.

^c Patients with aspirin allergy, recent history of active gastrointestinal bleeding or other contraindications to aspirin therapy.

^d Those with a contraindication to aspirin therapy

^e Patients who experience recurrent cerebral ischemia. Alternatively, Aspirin/extended release dipyridamole may be used as first-line therapy in selected high-risk patients.