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Senior Medicine EBM Report
September 22, 2008

**Question:**
Is there a best anti-platelet therapy for secondary prevention of stoke.

75 yo man with history of HTN, DM, chronic renal failure, significant tobacco presents after two episode of change in vision the past 4 days in context of URI and is not found to have focal neurological deficits. The patient had not been on any anti-platelet therapy. He received diagnostics for both cardiac and cerebral ischemia, and placed on ASA 325 po daily. There was no evidence or cardiac involvement, and cerebral parenchyma did not show ischemia. An MRA of cerebral arteries suggest variant anatomy, including a hypo plastic right PcoA. As a TIA could not be rules out, and his ABCD score was 3 (low, 1.2% 7 day risk), antiplatelet therapy was indicated.

**EBM Framing**

*Patients:* Patients who have had cerebral ischemia *Intervention:* Combination and New class Anti-platelet therapy *Comparison:* Aspirin therapy Therapy *Outcome:* Prevention of Recurrence ischemic event

**Search Strategy**
Database: USNML/NIH PubMed , All articles, Advanced search - beta
1 Anywhere AND only :secondary prevention, antiplatelet, stroke, randomized , control
2 Limit: Clinical Trial, Age greater than 45, English, Core clinical journals
Results: 9 articles since 1993

**Core Article:**
Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke.N Engl J Med. 2008 Sep 18;359(12):1238-51.

**Selected Article:**

*General*

The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial aims to measure clinical benefit to a combination antiplatelet therapies in a 2x2 factorial experiment including 695 sites from 35 countries. The study is randomized, double blinded, intention to treat, and non-inferiority analyzed.

*Validity*

The study randomized using telephone numbers and validated through comparison of means of common medical demographics, evaluated at follow up at predetermined intervals, and analyzed with standard methods using standard statistical assumptions.

*Results:*

In the first report from the trial, there seems no superiority to Aggrenox vs Palvix in 2.5 years of follow-up , contrary to pre-test prediction based on prior data from CAPRIE and ESPRIT trials estimating ~13% reduction in relative risk. Secondary outcome of stroke, myocardial infarction, or death from vascular causes were identical in the two groups

*Generalizability:*

The inclusion criteria translates well to the general population of patients with ischemic events. The population sample is large, representing a diverse cross section including over 20,00 patients in many countries. The authors have not made an attempt to compare failures to help guide therapy recommendations in those who maybe at risk of failing. Also, this study did not include TIA that could did not reveal ischemic damage on imaging.

| Group | Criteria/Definition | | n |
|---|---|---|---|
| Population screened | Individuals who were >55 years of age and who had had an ischemic stroke | | NA |
| Inclusion Criteria | Patients of either sex may be included who are at least 55 years of age and who have had an ischemic stroke within<br>90 days of entry into the study; include also patients of ages<br>50–54 years and/or 90–120 days after the qualifying stroke<br>provided that the patient has at least two of the following additional risk factors:<br>– Diabetes mellitus<br>– Hypertension (systolic BP ≥140 or diastolic BP ≥90)<br>– Smoker at time of qualifying stroke<br>– Obesity (BMI >30) | – Previous vascular disease (stroke, MI or peripheral arterial disease prior to qualifying stroke)<br>– End-organ damage (retinopathy, LVH or microalbuminuria)<br>– Hyperlipidemia<br>Stroke is defined as a new focal neurological deficit of vascular origin lasting more than 24 h, or where there is evidence of a new brain infarct upon brain imaging; brain imaging must rule out hemorrhagic stroke, but it does not need to confirm the presence of a brain infarct if clinical symptomatology is sufficient to diagnose stroke | |
| Exclusion Criteria | Patients with the following conditions are excluded<br>2 Patients unable to give informed consent<br>3 Patients presenting with a primary hemorrhagic stroke (intracerebral hemorrhage or subarachnoid hemorrhage); hemorrhagic stroke must be ruled out with brain imaging<br>4 Patients who are unable to take by mouth all required study<br>medication<br>5 Known brain tumor<br>6 Prestroke history of dementia requiring institutional care<br>7 A modified Rankin scale score >4 at baseline<br>8 The patient is unlikely to be released from hospital following the qualifying stroke, or the presence of a severe<br>disability after the qualifying stroke likely to lead to the patient being bedridden or demented, or a nonvascular disease or condition which makes it unlikely that the patient will survive to the end of the trial<br>9 Patients whose qualifying stroke had been induced by a<br>surgical or cardiovascular procedure such as carotid endarterectomy, angiogram or cardiac surgery<br>10 Patients with known hypersensitivity to DP, clopidogrel,<br>ASA or telmisartan<br>11 Uncontrolled hypertension which equals or exceeds either<br>a sitting systolic BP greater than 180 mm Hg, or a sitting diastolic BP greater than 110 mm Hg (all hypertensive patients are treated appropriately, and 'goal' BPs are much lower than 180/110)<br>12 Seated systolic BP ^120 mm Hg for patients who are still<br>hospitalized following the qualifying stroke<br>13 Patients currently being treated with an ARB (angiotensin<br>II receptor blocker) who are unable or unwilling to discontinue treatment with this type of drug<br>14 Patients with required or planned continued treatment with antithrombotics or anticoagulants including heparin or warfarin, or nonstudy platelet inhibitors | 15 Known severe renal insufficiency defined as renal artery stenosis or creatinine clearance <0.6 ml/s or serum creatinine >265 μmol/l (>3.0 mg/dl)<br>16 Known severe hepatic dysfunction as defined by the follow-<br>ing laboratory parameters:<br>SGPT (ALT) or SGOT (AST) >4<br>times upper limit of normal, or total bilirubin >20 μmol/l<br>17 Hyperkalemia, defined as potassium >5.5 mmol/l<br>18 Uncorrected volume depletion or sodium depletion; patients must be properly hydrated<br>19 Known current active peptic ulcer disease<br>20 Patients with the syndrome of asthma, rhinitis and nasal polyps (all three present)<br>21 Known severe coronary artery disease including unstable angina pectoris or an MI within the previous 3 months<br>22 Patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration<br>23 Known presence of or history of a hemostatic disorder or systemic bleeding<br>24 History of thrombocytopenia (i.e. less than 100 × 109 /l for<br>platelets) or neutropenia (1.2 × 109<br>/l for neutrophils)<br>25 Women who are breast-feeding, pregnant or of childbearing potential who do not use a medically acceptable form of contraception (surgical sterilization, birth control pills, an implantable contraceptive device, birth control injections or an IUD)<br>26 Patients who have been exposed to an investigational drug<br>or device within the last 30 days, or are currently participating in such a trial<br>27 Patients scheduled for major surgery, carotid endarterectomy or carotid angioplasty should not enter the study; such patients may enter the trial 4 weeks after such procedures, if they still meet all other entry criteria | Not reported |
| Treatment Group A | ASA + DP (25 mg/200 mg b.i.d.) | | 10,181 |
| Treatment Group B | clopidogrel (75 mg q.d.) | | 10,151 |

**Primary Outcomes**
Stroke (nonfatal or fatal): Ischemic OR Hemorrhagic OR Of uncertain cause

**Secondary Outcomes**
Vascular events or CHF: Stroke (nonfatal or fatal) OR MI (nonfatal or fatal) OR Vascular death OR New or worsening CHF
New Onset Diabetes

| | | | |
|---|---|---|---|
| Randomized | Yes | All patients accounted for at end? | Yes |
| Intention to treat | Yes | Blinding | yes |
| Equal treatment of groups? | Yes | Did randomization work? | yes |

**Are the results of the trial important? Do they apply to the patient?**
*The patient did not meet definition of inclusion as no documented ischemia was found. It is up to the practitioner to extend result to a possible TIA.

| | Aggrenox | Plavix | Hazard Ratio for ASA+DP |
|---|---|---|---|
| Primary outcome: recurrent stroke ( total) | 916 | 898 | 1.01 (0.92-1.11):95% |
| Secondary outcome: composite of vascular events (stroke, MI, or death from vascular causes) ( total) | 1333 | 1333 | 0.99 (0.92–1.07):95% |

**Discussion**
- The evidence from this trial does not directly pertain to the case at hand. The patient may have had a TIA, though there was no radiographic evidence to confirm the suspicion. It is up to the practitioner and patient to weigh the risk of beginning anti-platelet therapy
- The trial selected highlights our inability to predict outcomes based on historic results. The article helps call into question our understanding of the efficacy of antiplatelet regimens. Prior to the experiment , we expected a significant advantage to Aggrenox, around 13 % based on data from previous trials showing superiority to Aggrenox and Plavix to aspirin. The ProFESS data suggest this information did not translate in into head-to-head significant difference.
- Those physicians not doubting the ESPRIT conclusion ( instead opting the 23% reduction is real and best EBM practice to include the patient in our discussion), will likely continue to prescribe this more costly Aggrenox regimen. Though, careful review of all anti-platelet trials must be made to assert clear superiority of treatment
- As Aggrenox and Plavix appear equivocal, we cannot conclude one treatment is preferred outside of already established contraindication for each medication. Therefore, the economics of the daily cost of therapy is appropriate.

**Recommendation for the Case**
The patient, not having any contraindications, would benefit from Aggrenox antiplatelet therapy, though there appears no difference in all-cause mortality and morbidity versus Plavix. Given in incongruent results of PRoFESS, ESPRIT , and CAPRIE, there is reason to suspect all three therapies may have similar efficacy and non-significant differences in risks. A skeptical conclusion requires further investigation into study design, and possible further study of antiplatelet therapy.