Aspirin and Extended-Release Dipyridamole Versus Ticagrelor, a new ADP-receptor antagonist, for Prevention of Recurrent Stroke

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Study Purpose and Rationale

Stroke is the third leading cause of death in the United States. 795,000 strokes occur annually, 80% of which are ischemic and 23% of which are recurrent in nature.[1] Not only do strokes result in significant morbidity and mortality, but will account for up to $2.2 trillion in health care expenditures by 2050 according to recent estimates.[2] As such, numerous trials have examined strategies for secondary stroke prevention. In particular, there has been a significant focus on antiplatelet agents including aspirin, dipyridamole, and clopidogrel.

Aspirin (ASA), a COX-1 > COX-2 inhibitor, is an efficacious antiplatelet agent via its inhibition of thromboxane synthase and thromboxane (TxA_2) formation. ASA has been shown to reduce recurrent stroke by up to 23% when compared to placebo at doses ranging from 50mg to 325mg without differences in efficacy.[3] Further studies have shown that this effect is magnified when placed in combination with extended release dipyridamole (ER-DP), an adenosine deaminase and phosphodiesterase inhibitor. The mechanism of action of dipyridamole is more complex, but ultimately involves upregulation of intracellular cyclic adenosine monophosphate (cAMP), inhibiting platelet activity. In combination, these two medications result in relative risk reductions of 20% - 23% compared to aspirin alone and 37% in comparison to placebo.[4] Although both of the aforementioned treatments have been noted to increase bleeding risks amongst patients, the combination of ASA-ER DP does not increase bleeding significantly versus that of ASA alone.

Clopidogrel, a $P2Y_{12}$ ADP receptor inhibitor has also been evaluated in the use of secondary stroke prevention. Pathophysiologically, blockade of the ADP receptor ultimately results in increased intracellular cAMP and platelet inhibition. In comparison to ASA, clopidogrel showed a relative risk reduction of 8.7% of recurrent MI, stroke or vascular death in patients with previously diagnosed stroke, MI, or PAD.[5] Notably, the subgroup analysis of patients only with prior strokes did not have any significant improvement secondary to clopidogrel use. In combination with ASA, clopidogrel showed no benefit over clopidogrel alone in preventing stroke, MI, vascular death, or rehospitalization for acute ischemia in patients with recent TIA or ischemic stroke.[6] It did however lead to an increase in bleeding rates. More recent studies in secondary stroke prevention were unable to show non-inferiority of clopidogrel relative to ASA-ER DP, although similar recurrent stroke rates were noted.[7]

Ticagrelor (Brilinta®) is also a $P2Y_{12}$ ADP receptor inhibitor, however has multiple advantages in comparison to clopidogrel. This includes reversibility, reduced functional variability on platelets amongst patients, and quicker onset of action.[8] One might suspect that this would translate into improved clinical outcomes, and indeed has already shown benefits in preventing MI, stroke, and death from vascular causes in patients with acute coronary syndrome (ACS) as compared to clopidogrel.[9] Unsurprisingly, its increased efficacy has also resulted in a small, although significant increase in bleeding risk in this same population.

No guidelines currently exist on which specific antiplatelet therapy to initiate for secondary stroke prevention. Given its recent success in ACS as an antiplatelet agent, we believe ticagrelor can be an excellent option for secondary stroke prevention. In the context of similar reduction in recurrent stroke between ASA-ER DP and clopidogrel, and ticagrelor's superiority to clopidogrel in the PLATO study, we hypothesize ticagrelor will be superior to ASA ER-DP in the prevention of recurrent ischemic stroke.

Study Design and Statistical Analysis
This study will be a multi-center, randomized controlled, double-blinded study, aimed to test the hypothesis that ticagrelor (Brilinta®) will be more efficacious than ASA-ER DP in prevention of recurrent strokes in those patients with recent ischemic strokes.

Patients will be randomized into two trial groups – one that receives standard low dose aspirin (25mg) in combination with extended-release dipyridamole (200mg) twice daily and the other which will receive ticagrelor (90mg) twice daily. The latter dose being chosen as it was demonstrated to have superior efficacy to standard clopidogrel dosing of 75mg daily in preventing stroke, MI, and death from cardiovascular causes in patients with acute coronary syndrome.[10]

Eligible and consenting patients will be randomly assigned through a central telephone randomization system to receive one of the two aforementioned treatments. Patients will be monitored at 1 week after randomization and then at 1, 3, and 6 months and every 6 months thereafter for a total of 2.5 years duration. If they cannot make scheduled clinic visits, an attempt to speak with them via phone will be made.

The primary outcome will be recurrent stroke of any type. Secondary outcomes include a composite of myocardial infarction, recurrent stroke or death from vascular causes, as well as a composite of recurrent stroke of any type plus major hemorrhagic event. Other secondary outcomes are myocardial infarction, death from vascular causes[11], all-cause mortality, and new or worsening heart failure. Recurrent ischemic strokes will be classified utilizing the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[12,13] Three months after stroke recurrence, disability will be assessed according to the modified Rankin scale (scored from 0 to 6 with increasing scores indicating greater disability).[14]

Bleeding events will be evaluated as major safety outcomes. Major life threatening bleeding will be defined as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells. Other, non-life threatening major bleeding includes bleeding that leads to clinically significant disability (e.g., intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the hemoglobin level of at least 3.0 g per deciliter but less than 5.0 g per deciliter or requiring transfusion of 2 to 3 units of red cells. Minor bleeding is any bleeding requiring medical intervention but not meeting the criteria for major bleeding.

Prior studies, including that of the PRoFESS trial, suggest that recurrent stroke in patients with prior ischemic stroke occur in 9.0% of patients followed over a 2.5 year period taking ASA-ER DP (25mg-200mg) twice daily. Utilizing a chi-square statistical model between the two groups and assuming a 16% relative risk reduction with ticagrelor, 11,000 patients will be recruited to satisfy an 80% power for this study with a two-tailed type I error rate of $\alpha = 0.05$. This aforementioned analysis will be done in an intention to treat fashion. It should be noted that utilizing this same statistical criteria, a relative increase or decrease of major bleeding by 27% of ticagrelor as compared to ASA-ER DP can also be detected.

Study Procedure
As previously mentioned, patients will be followed over 2.5 years with follow-up 1 week after randomization, and then at 1, 3, and 6 months and every 6 months thereafter. No procedures will otherwise be performed.

Study Drugs

- Aspirin/Extended-release dipyridamole (25mg-200mg PO BID) – FDA approved drug for secondary stroke prevention. Shown in prior studies to result in significant reductions in recurrent stroke when compared to aspirin alone or placebo as previously mentioned.[15] Used in this particular study as the standard of care at its typical dosing. Utilizing data from the PRoFESS trial, we expect major bleeding at an approximately 4.1% rate, and total bleeding (major and minor) at an approximately 5.3% rate.[16] Other side effects include headache (5.9%), nausea/vomiting (3.1%), dizziness (1.3%), and diarrhea (1.0%).

- Ticagrelor (90mg PO BID) – FDA approved drug for treatment in acute coronary syndrome. A $P2Y_{12}$ ADP receptor inhibitor that has shown improved efficacy over clopidogrel in outcomes in acute coronary syndrome patients. Used here at dosages studied in the PLATO trial. Known side effects include bleeding (approximately 4.5% major bleeding), as well as dyspnea (10% - 13%), headache (6.5%), and bradycardia (4.0%).

Medical Device
N/A

Study Questionnaires
N/A

Study Subjects

- *Inclusion Criteria*
    - Recent ischemic stroke (< 90 days prior to randomization) – defined as symptoms of stroke persisting for >24 hours or symptoms of a shorter duration but with evidence of recent infarction on computed tomography scan or magnetic resonance imaging
    - Clinical and neurologic stability prior to randomization
    - Age $\geq$ 50

- *Exclusion Criteria*
    - Primary hemorrhagic stroke or patients whose stroke was induced secondary to surgical or cardiovascular procedure (e.g. carotid endarterectomy)
    - Uncontrolled hypertension which equals or exceeds either 180mmHg systolic or 110mmHg diastolic
    - Known brain tumor
    - Active peptic ulcer disease
    - Known history of a hemostatic disorder or systemic bleeding
    - Patients with thrombocytopenia (platelets < 100×10^9/L)
    - Known severe coronary artery disease including unstable angina or MI within the past 3 months
    - Patients with required or planned treatments with antithrombotics, anticoagulants (e.g. heparin, warfarin) or non-study platelet inhibitors
    - Known severe renal insufficiency defined as renal artery stenosis, creatinine clearance <0.6mL/s, or serum creatinine > 3.0mg/dL
    - Known severe hepatic impairment as defined by the following: ALT or AST > 4 times the upper limit of normal, or total bilirubin > 20μmol/L

- Inability to comply with the study procedure (e.g. cannot give informed consent, baseline dementia, cannot take medications orally, deemed by the investigator to be unable to follow-up appointments or unreliable) or seemingly unlikely to survive until the trial is completed (e.g. severe disability after the stroke leading to the patient remaining bedridden or demented).
- Hypersensitivity or intolerance to either of the study medications
- Patients enrolled in another investigational trial or who have been taking an investigational drug or device 30 days prior to randomization
- Patients scheduled for a major surgery, carotid endarterectomy or carotid angioplasty
- Women who are breastfeeding, pregnant or of childbearing potential in the absence of a medically acceptable form of contraception (e.g. surgical sterilization, birth control pills, IUD)

Recruitment of Subjects
Subjects will be recruited while in the hospital after a confirmed ischemic stroke has occurred or in the outpatient clinical setting as long as they adhere to the above inclusion and exclusion criteria. Prior to enrollment, all subjects will need to sign a consent form.

Confidentiality of Study Data
As previously mentioned, the study will be carried out in a double-blinded fashion. Treatment assignment will be done through a central telephone randomization system. Each patient will receive a unique code number to this end.

Potential Conflict of Interest
None of the current investigators have any existing conflicts of interest.

Location of the Study
The main clinical site of recruitment and follow-up will occur at the New York Presbyterian-Columbia University Medical Center. Since this will be a multi-center study, other clinical sites will obtain IRB approval from their respective institutions and conduct follow-up at those locations.

Potential Risks
Potential risks include that of life threatening and non-life threatening major bleeding, in addition to clinically significant minor bleeding. These risks are approximated above. Further, multiple side effects of both ASA-ER DP and ticagrelor exist which have been outlined individually. It is possible that patients will derive no benefit from ticagrelor, however, be exposed to its side effects. This is not an expected outcome.

Potential Benefits
Potentially patients will benefit from decreased recurrent stroke risk with minimal to no increase in bleeding risk by utilizing ticagrelor as an antiplatelet agent instead of ASA-ER DP. However, this is not assured, and the patients may or may not benefit as a result of their participation in this study.

Alternative Therapies
Ticagrelor is not an approved therapy for recurrent stroke prevention at this time. Alternative therapies include ASA-ER DP, clopidogrel or ASA alone. The choice of therapy is usually a decision made between the physician and patient, however, studies seem to show relative benefit of ASA-ER DP over the other treatments mentioned.

Compensation to Subjects
Subjects will receive no direct compensation in return for participating in this trial. They will, however, be seen by a trained and licensed physician at their scheduled clinic appointments.

Costs to Subjects
Subjects will incur no costs as a result of participating in this study.

Minors as Research Subjects
N/A

Radiation or Radioactive Substances
N/A

References

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[6] Diener HC, Bogousslavsky J, Brass LM et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. *Lancet* 2004; 364:331-7.

[7] Sacco RL, Diener HC, Yusuf S, et al. Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke. *N Eng J Med* 2008. 359: 1238-51.

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[10] *Ibid.*

[11] Vascular events include: stroke, myocardial infarction, pulmonary embolism, deep venous thrombosis, peripheral arterial occlusion, TIA, cerebral venous thrombosis, or retinal vascular accidents NOT confirmed as retinal artery occlusion.

[12] Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter trial: TOAST: Trial of Org 10172 in Acute Stroke Treatments. *Stroke* 1993; 24: 35-41.

[13] The TOAST classification system subdivides acute ischemic strokes into the following categories: (1) large artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, (5) stroke of undetermined etiology.

[14] van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; 19:604-7.

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