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Long Term Dual Antiplatelet Therapy for Secondary Prevention of Coronary Artery Disease

A. Study Purpose and Rationale

Rationale: While dual antiplatelet therapy with aspirin and a second agent is recommended for 12 months for secondary prevention after an acute coronary syndrome (ACS), there is no data for whether long-term dual antiplatelet therapy is beneficial and protective. Given the burden of cardiovascular disease (CVD) in the United States and indeed globally, reducing secondary complications of coronary artery disease (CAD) could greatly improve the functionality and quality of life for those who have had ischemic events. Additionally, by preventing strokes and myocardial infarctions (MI), better therapy and better secondary prevention could greatly reduce the cost of care associated with cardiovascular (CV) and cerebrovascular complications.

Background: Cardiovascular disease is the leading cause of death worldwide, with more than 900,000 deaths in the United States alone. Although mortality from heart disease has been declining in the United States, rates of ischemic heart disease have been rising internationally [1]. There are approximately 7, 900,000 episodes of myocardial infarction (MI) and 9,800,000 episodes of angina pectoris annually in the US, and those who have episodes of acute coronary syndrome (ACS) then have a higher risk of subsequent coronary events and death. Aggressive antiplatelet therapy is needed for effective secondary prevention after a cardiac event.

Aspirin is considered by many to be the reference antiplatelet drug, and indeed, per the American College of Chest Physician (ACCP) guidelines, has a Class 1 A recommendation for indefinite use in patients with ACS [2]. It has been shown in a number of studies to have a net benefit in the secondary prevention of cardiovascular disease after MI, occlusive stroke, transient ischemic attack (TIA), stable angina and coronary artery bypass graft (CABG) procedures [3].

While the benefits of aspirin in secondary prevention of cardiovascular disease cannot be refuted, antiplatelet therapy with aspirin as the sole agent has limited efficacy because there is inhibition of only of one of several important pathways that lead to thrombus formation. Indeed the American College of Cardiology (ACC)/American Heart Association (AHA) clinical practice guidelines recommend 12 months of dual antiplatelet therapy for patients with ACS regardless of treatment strategy whether that is medical management, percutaneous coronary intervention (PCI) or bypass surgery [4].

Several effective antiplatelet agents are currently being used. Clopidogrel is an thienopyridine adenosine diphosphate (ADP) receptor antagonist whose efficacy was established in the CURE trial which showed that patients who received aspirin with clopidogrel had better outcomes than those given aspirin with placebo at an average followup of nine months (9.3% incidence in the combination group of the primary endpoint, a composite of CV death, MI and stroke, vs. 11.4% in the aspirin only group; $p<0.001$) [5]. Although there was no significant difference in the rates of life-threatening bleeding or hemorrhagic strokes, there was a significant increase in the rate of major bleeding (3.7% vs. 2.7%; $p = 0.001$) [6].

Prasugrel is another thienopyridine ADP receptor antagonist that in a recent study, the TRITON-TIMI 38 trial, was been found superior to clopidogrel in reducing the rate of the primary endpoint (again, the composite of CV death, MI, and strokes) with a comparable rate of significant bleeding at 15 months [7]. Ticagrelor, an antiplatelet agent of the cyclopentyltriazolopyrimindine class, was also shown in the PLATO trial to be more efficacious than clopidogrel in reducing the primary endpoint point (CV death,

MI and strokes) at 12 months [9.8% vs. 11.7%; p <0.001] with no significant differences in the rates of major bleeding [11.6% vs. 11.2%; p= 0.43] [8].

While the efficacy of dual antiplatelet therapy with these agents has been well-established in the short term period (between 9 and 15 months) after a coronary event, it is yet unclear if dual antiplatelet therapy is efficacious in reducing adverse events in the long-term period. While several practitioners do prescribe a second antiplatelet agent for longer than 12 months, it is important to consider that doing so also confers an increased risk of bleeding.

To address this issue, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial evaluated the effects of dual antiplatelet therapy with clopidogrel vs. aspirin alone for 28 months [9]. However, this trial was a primary prevention study rather than a secondary prevention study as it enrolled subjects with clinically evident cardiovascular disease or with multiple risk factors rather than those who had had a coronary event. There was no significant benefit associated with dual antiplatelet therapy in this trial. However, when a subgroup analysis was done in patients with a prior history of a MI, stroke or symptomatic PAD, it was shown that the primary endpoint (composite of CV death, MI and stroke) occurred at a significantly lower rate in the dual antiplatelet agent group as compared to the aspirin alone group [7.3% vs. 8.8%; p=0.01] with no significant difference in the rate of severe bleeding [1.7% vs 1.5%; p=0.5] but significant increase in moderate bleeding [2.0% vs. 1.3%; p = 0.004].

Another recent study, which pooled the results of 2 randomized controlled trials, looked at 2700 patients with drug eluting stents who received dual antiplatelet therapy with clopidogrel plus aspirin versus aspirin plus placebo for a median of 19.2 months [10]. Interestingly, this study found that the primary endpoint (MI or CV death) occurred in in 1.8% of those receiving dual therapy but in only 1.2% of those getting aspirin monotherapy (HR 1.65; 95% CI, 0.8 to 3.36, p = 0.17). Unfortunately, the study had lower event rates than expected, and thus had insufficient statistical power to firmly make any conclusions about the safety and efficacy of using clopidogrel for longer than 12 months after PCI.

It is thus unclear if there is benefit in using long-term dual antiplatelet therapy in those with an acute coronary event such as NSTEMI or STEMI to reduce the risk of adverse CV and cerebrovascular events. The studies that have been done to date have either not studied secondary prevention post a cardiac event or have been underpowered and therefore, unable to make any significant recommendations.

B. Study Design and Statistical Analysis

Goals: The aim of this study will be to determine if there is a benefit with regards to reducing secondary CV and cerebrovascular events with long-term dual antiplatelet agent use in those with acute coronary syndromes, specifically NSTEMIs and STEMIs.

Hypothesis: We hypothesize that there will be a reduction in primary endpoints with long-term dual antiplatelet therapy with no significant increase in life-threatening bleeding or hemorrhagic strokes, but possibly a significant increase in major bleeding.

Study Overview: This is a prospective, randomized, placebo-controlled, double masked interventional, multi-center study during which we will assess the long term benefits or lack thereof of dual antiplatelet therapy in patients with coronary artery disease after a coronary thrombotic event. The primary objective is to compare the effectiveness of 12 months versus 36 months of dual antiplatelet therapy to protect patients from major adverse CV or cerebrovascular events. The primary safety objective is to compare the risk of bleeding events in the two groups.

Population: Study subjects with coronary artery disease and ischemia secondary to occlusive or stenotic lesions in either native arteries or coronary artery bypass grafts who present with either a non-ST elevation myocardial infarction or an ST elevation myocardial infarction are eligible for study enrollment. All subjects, regardless of whether or not they undergo stent placement, will receive 12 months of aspirin along with an Food and Drug Administration (FDA) approved antiplatelet agent. These can include clopidogrel, prasugrel and ticagrelor as well as other FDA-approved antiplatelet agents. Choice of the antiplatelet agent and dose will made by the prescribing physician per their discretion and according to the local standard of practice. Subjects will be enrolled into the trial prior to the hospital discharge of their admission for NSTEMI/STEMI.

Inclusion/Exclusion Criteria at time of study: To enroll in the study, subjects must be greater than 18 years of age, must have had an acute coronary event (either an NSTEMI or a STEMI) and must be able to provide consent.

Subjects will be excluded if they are on concurrent anticoagulant therapy such as warfarin or dabigatran, or will be having planned surgery requiring discontinuation of the antiplatelet agent within 30 days after enrollment. They will also be unable to participate in the study if they have an allergy to one of the drugs being used or if they are unable to give consent. Pregnant women will also be excluded from the trial as the safety and efficacy of the newer antiplatelet agents have not yet been fully established in pregnancy.

Study Design: Subjects will be recruited during their initial hospitalization for NSTEMI or STEMI sometime before discharge from the hospital. All subjects will receive aspirin plus a second antiplatelet agent for 12 months. Each subject's primary physician or cardiologist will be responsible for choosing an appropriate antiplatelet agent as well as the dosage. At the end of 12 months, those subjects who meet criteria (listed below), will be randomized in a 1:1 fashion to either the aspirin plus antiplatelet arm or the aspirin plus placebo arm for an additional 24 months, for a total of 36 months.

Randomization: Randomization will be done at 12 months after the acute coronary event (NSTEMI or STEMI) in patients as long as they meet the following criteria:

- They must be event-free from death, myocardial infarction (MI), stroke, repeat coronary vascularization, stent thrombosis or thrombolysis in myocardial infarction (TIMI) defined moderate or severe bleeding events.
- They must demonstrate that they can be compliant with the dual antiplatelet therapy (that is no interruptions in therapy greater than 2 weeks).

Those subjects that meet these two criteria will be randomized (1:1) at the end of 12 months to either aspirin plus placebo or aspirin plus the antiplatelet agent they had already been on for the prior 12 months. Patients will be stratified by whether or not they underwent stent placement, by clinical site, and by the antiplatelet agent utilized to ensure equivalent numbers in both treatment groups. Randomization will be performed by a computer generated algorithm at a central site.

Study end points: The primary endpoint will be a composite of CV death, MI and stroke. Secondary endpoints will include death from any cause, CV death, stent thrombosis, need for repeat revascularization, MI and stroke. The primary safety endpoint will be a major bleed per the previously published TIMI criteria (defined as an intracranial hemorrhage or a greater than or equal to 5 g/dl decrease in the hemoglobin concentration or a greater than or equal to 15% absolute decrease in hematocrit.) [6]

Masking: The subject, the physician, and all study staff and investigators except the pharmacists dispensing the medication at each of the sites will be masked. Each of the antiplatelet agents will have its own matching placebo pill of a similar size, color, consistency, smell and taste.

Follow-up
All subjects who are randomized will be followed for a total of 36 months after their acute coronary event (either an NSTEMI or a STEMI). Data will be collected during the initial hospital visit and then subsequently at 6, 12 (around time of randomization), 18, 24, 30 and 36 months. At the time of enrollment, baseline characteristics, type of coronary event, whether or not the subject underwent a stent placement, the type of stent and other medical comorbidities will be recorded. At subsequent clinic visits, adverse clinical events or bleeding will be ascertained as well as compliance with the antiplatelet regimen and other concomitant medications being used. Subjects will receive therapy with the additional antiplatelet agent or placebo for a total of 36 months.

Statistical Analysis: The assumed primary end point rates for the two treatment groups are extrapolated from published data. In powering the study for the primary endpoint, the following are the treatment effect size assumptions used based on published data.

	Dual Antiplatelet Therapy	ASA alone
Primary Endpoints:	7.0%	8.5%
Effect Size:	1.5%	

With 1: 1 randomization, using the chi-square test for 80% power and significant $p < 0.05$, the number needed in each group is 5, 216. Thus, there will need to be a total of at least 10,500 subjects for randomization. Assuming that 20% of patients initially enrolled at time 0 will not be eligible for randomization at 12 months post acute coronary event (NSTEMI or STEMI) due to dropout or due to the criteria mentioned above, the number to be enrolled at time of cardiac event is 14,000.

After results are collected, each of the endpoints will be assessed with Kaplan Meier curves. A covariate analysis will be performed on baseline characteristics to ensure homogeneity between the two groups.

C. Study Procedures
No procedures will be performed as a part of the study. Patients who present to the hospital with an NSTEMI or a STEMI routinely undergo cardiac catheterizations to diagnose and determine the extent of their coronary artery disease. We will be enrolling these patients into our study after their catheterization has been performed. However, patients will not be undergoing any additional procedures as a part of this study.

D. Study Drugs
All patients in the study will receive aspirin (81mg to 325 mg) PO daily with the dosage determined by their primary physician or cardiologist. For the first 12 months, all patients will receive a Food and Drug Administration (FDA)-approved second antiplatelet agent. This can include clopidogrel, prasgurel, ticagrelor, or another FDA-approved antiplatelet agent. Choice of the antiplatelet agent and dose will made by the prescribing physician per their discretion and according to the local standard of practice. After 12 months, the patients will be randomized (1:1) into continued dual antiplatelet therapy (with whichever antiplatelet agent they had already been on) or aspirin with placebo treatment groups.

Of note, all antiplatelet drugs have an increased risk of bleeding; however, the absolute risk of bleeding with dual therapy as compared to monotherapy is well below 5%.

E. Medical Devices
Not applicable.

F. Study Questionnaires
Not applicable

G. Study Subjects
Please see above.

H. Recruitment
Subjects will be recruited in the hospital prior to discharge during the admission for their NSTEMI/STEMI.

I. Confidentiality of Study Data
Patient data will be maintained confidentially at all times per HIPAA standards on locked computers. No personnel that are not directly involved with the study will be able to access information pertaining to the study about the subjects. Only pharmacists at each of the individual sites will be aware of treatment group assignment.

J. Potential Conflict of Interest
None of the investigators have any proprietary interest in any of the drugs to be used in the study nor do they stand to benefit financially in any way from the results of the investigation.

K. Location of the study
This will be a multi-center study with the main clinical site being NYP-CUMC. Other clinical sites will obtain IRB consent from their respective institutions.

L. Potential Risks
Potential risks from conducting this study to the control group may be an increased risk of thrombotic events. Potential risks to the dual antiplatelet group may be an increased risk of bleeding events. The exact numbers cannot be determined until the conclusion of the study.

N. Alternative Therapies
An alternative therapy to participating in the trial would be not participating in the trial and continuing on whichever regimen the subject's primary care physician or cardiologist asked them to be on.

O. Compensation to Subjects
No direct compensation to the subjects will be provided.

P. Costs to the Subjects
Information will be collected at routine visits, thus there should not be any additional transportation or co-payment costs for the subjects.

Q. Minors
No minors will be allowed to participate in this study

R. Radiation
Not applicable

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