

The Effect of Clopidogrel and Aspirin Alone or in Combination with Warfarin on the Incidence of Cerebral Emboli in the Presence of Left Ventricular Thrombus after an Acute Myocardial Infarction.

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A. Study Purpose And Rationale

The primary objective of this study is to compare the incidence of cerebral embolization in 12 months in patients after acute myocardial infarction (AMI) who develop a left ventricular thrombus (LVT) who are then randomized to receive 2 different antithrombotic regimens: clopidogrel and aspirin alone or in combination with warfarin (with a target INR of 1.5-2.5) for 6 months and then both groups will receive aspirin alone for 6 months. Given the substantial bleeding risk with these 2 therapies, this study will also compare the incidence of life threatening bleeds over the 12 months.

In the setting of a LVT after an AMI, anticoagulation for at least 3-6 months with warfarin is recommended given the risk of systemic embolization. The intensity and duration of warfarin have not been well studied or specified and the use of warfarin is associated with a considerable bleeding risk (1). Recently the standard practice after an AMI has changed and includes coronary stenting and the use of antiplatelet agents, aspirin and clopidogrel, which also carry a risk of bleeding. Evidence suggests that the effect of antiplatelet agents on LVT systemic embolization may not be significantly higher than that with the addition of warfarin and should be studied given the substantial risk of bleeding associated with the use of all 3 antithrombotic agents (2,3,4,6).

B. Study Design And Statistical Analysis

This will be a randomized, double blinded study, placebo controlled trial. All patients that are eligible for the study will be randomized to receive or not receive warfarin in addition to clopidogrel and aspirin. Primary outcome will be cerebral embolic event defined by symptomatic neurologic event, diagnosed by clinical evidence, and confirmed by CT or MRI of the brain as an ischemic event.

Secondary outcome will be life threatening bleed defined as a fatal bleeding event, intracranial hemorrhage (defined by symptomatic neurologic event, diagnosed by clinical evidence, and confirmed by brain CT or MRI as a hemorrhagic event), a drop in the hemoglobin of ≥ 5 g/dl, or a bleed requiring either surgical intervention, inotropic agents, or a transfusion of ≥ 4 units packed red blood cells.

Data will also be gathered on LVT characteristics by 2-D echocardiography at the beginning and at the end of the study, LV ejection fraction as determined by echo at the beginning of the study, all reported bleeding, nonfatal myocardial infarction, and death from a cardiovascular event.

The study is being designed to determine at least a 1% absolute risk reduction with the addition of warfarin on cerebral embolic events in the setting of an LVT after an AMI. The embolic event incidence on warfarin, clopidogrel, and aspirin was estimated by using previous data collected on warfarin alone and was assumed to 0.5%. It was determined from literature and discussions with experts in the field that for a risk-benefit analysis of the addition of warfarin, an embolic event rate of 1.5-2% or less would be considered allowable if the risk of bleeding decreased (9). Therefore, the embolic event rate of clopidogrel and aspirin alone was assumed to 1.5%. Chi square analysis determined the sample size for a power of 0.8 and an alpha of 0.05 is 1748 people in each group. This number will allow a sufficient sample size to determine a minimum absolute increase in life threatening bleeding risk of 2% with the addition of warfarin, using the CURE trial data that states that life threatening bleeds in patients on clopidogrel and aspirin was 2.2%.

Given the large sample size, this study will need to be multicenter. There are factors such as LVT echo characteristics of mobility and shape and patient age that increases the risk of embolization, but no stratified randomization will need to be conducted given the large sample size. All data will analyzed by an intention to treat analysis.

C. Study Procedure

After patients have been randomized to one of the two antithrombotic regimens they will followed clinically. INR will be followed and adjusted as per individual clinical centers (see below in Study Drugs). The patient will have one follow-up in a clinical setting 6 weeks after randomization and then at the end of the study, 12 months after randomization, where the patient will also have a follow up echocardiogram. The ideal average follow-up time for each patient will be 9 months.

Given the large number of subjects required for this study, the study duration will depend on how many trial centers will be recruiting subjects. Estimating 20 patients with LVT per year per clinical trial center and estimated 100 clinical centers will need to be involved for a duration of 2-3 years.

D. Study Drugs

Aspirin, clopidogrel, and warfarin have been well studied and are approved drugs. They are all antithrombotic agents and have all showed evidence in preventing thromboembolic events, however no trial has been done to show statistical difference when used in various combinations. All drugs will be taken once a day, by mouth. Aspirin will be dosed at 325mg a day. After the loading dose of 300mg of clopidogrel the daily dose will be 75mg. Warfarin will be dosed to keep the INR at range of 1.5-2.5, as monitored and adjusted at each clinical site. Allowing warfarin to be adjusted by each clinical center verse a standard protocol will allow extrapolation of data to everyday medical care.

E. Medical Device

not applicable

F. Study Questionnaires

Questionnaire is still being developed. There will be an initial assessment to determine if the patient is eligible. Follow-up questionnaires will address thromboembolic and bleeding complications subjectively and give any information that will allow the investigators to collect objective data.

G. Study Subjects

Inclusion criteria

- Patients presenting with an acute myocardial infarction who received a coronary stent and started on clopidogrel and aspirin with 24 hours of presentation to the hospital.
- All patients who have evidence by 2-D transthoracic echocardiography of an LVT within 3 days of the AMI.

Exclusion Criteria

- Other indications for warfarin or clopidogrel therapy
- Contraindications for anticoagulation
- Known bleeding disorder
- Indication to be on warfarin other than LVT (ie-atrial fibrillation, DVT, mechanical valve)
- A previous known LVT

- A documented previous stroke
- Life expectancy of less than 12 months.

H. Recruitment Of Subjects

Multicenter; all patients that present to a participating medical center with the previously defined inclusion criteria will be recruited.

I. Confidentiality Of Subjects

coded patient information

J. Potential Conflict If Interest

Not applicable

K. Location Of The Study

Multicenter.

L. Potential Risks

This study is designed to study the risk and benefits of the 2 treatment arms. Both arms have a risk of having a cerebral emboli; unclear which arm will have more or if it will be significantly different.. Both arms will have a risk of bleeding; unclear which arm will have more bleeding or if it will significantly different.

M. Potential Benefits

However both arms should decrease the baseline untreated risk of cerebral emboli

N. Alternative Therapy

As discussed above

O. Compensation To Subjects

Not applicable

P. Costs To Subjects

Not applicable

Q. Minors As Research Subjects

Not applicable

R. Radiation Or Radioactive Substances

Not applicable

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