Oral Anticoagulation in Elderly Patients with Atrial Fibrillation with moderate fall risk: Evaluation of bleeding complications

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A. Study Purpose and Rationale

Atrial fibrillation is a major cause of ischemic strokes in the Unites States of America. The American Heart Association estimates that the direct cost of strokes in the US in 2004 will be $33 billion dollars. The risk of atrial fibrillation and stroke increases with advancing age. In clinical practice, physicians tend NOT to anticoagulate elderly patients with atrial fibrillation citing that these individuals are at high risk for falling and oral anticoagulation will increase their chances of developing significant intracranial hemorrhage. However, there is no published data to support this notion. The current ACC/AHA/ECC Guidelines for the management of patients with atrial fibrillation (Fuster et al, 2001) does not address fall risk and the risk of oral anticoagulation in the elderly population with atrial fibrillation.

In order to guide physicians on how to manage the elderly, this proposal will address the risk/benefit of oral anticoagulation in the elderly with moderate risk of falling as determined by a simple well established test, the Timed "Get Up and Go" test.

a. Background

Several large American epidemiological studies (notably the Framingham Heart Study and Cardiovascular Health Study) have clearly demonstrated that the incidence of non-valvular atrial fibrillation in the United States increases with advancing age. The estimated number of Americans with atrial fibrillation in 2004 that are 65 years or order is approximately 1.7 million. The over 65 years old group represents about 70% of all Americans with atrial fibrillation. The median age is about 75 years old and the median age of onset is between 68 years to 72 years old depending on the epidemiological study. The overall number of men and women with AF is about equal, but approx. 60% of AF patients over 75 years are female, likely due to the longer life expectancy of women. With better health care, the average life expectancy of Americans is increasing and the geriatric population with atrial fibrillation will certainly increase.

The most dreaded complication of atrial fibrillation is thromboembolic stroke. The physical, mental and emotional consequences are devastating to the patient as well as their family. On a societal level, the economical burden of stroke is among the largest in American health care. A total of $55 billion dollars is the financial consequences of strokes, with about 66% in direct cost in health care and 34% in indirect cost, ie loss of productivity (AHA 2004). In the Framingham Heart Study, the prevalance of ischemic stroke in individuals with atrial fibrillation is highest in the elderly. A clear incraese in stroke incidence is seen in the 70 and above age group with a prevalance of 5-7% per year (Wolf et al., 1987).

Numerous large randomized clinical trials have shown that oral anticoagulation with coumadin is superior to aspirin and/or placebo in reducing the incidence of thromboembolic stroke (reviewed in Hart et al, 1999). The major risk of oral anticoagulation is the increased incidence of intracranial hemorrhage when the INR is supratherapeutic (ie INR >3). The risk/benefit ratio is optimal when the INR is maintained at 2-3. Adjusted odds ratios for ischemic stroke and intracranial bleeding relative to anticoagulation therapy intensity for atrial fibrillation patients can be found in Hylek et al. (1996). Several well-respected medical committes (Atrial Fibrillation Investigators, American College of Chest Physcians, and the Stroke Prevention in Atrial Fibrillation Study Investigators) have issued guidelines to risk stratify patients to guide clinicians in their management of patients with atrial fibrillation to prevent

ischemic strokes. The American College of Cardiology/American Heart Association/European College of Cardiology has also issued a consensus guideline to manage atrial fibrillation in regards to prevention of thromboembolic strokes (Fuster et al, 2001). One often raised contradiction to oral anticoagulation therapy is the risk of falling. Falling as defined as an unintentional loss of balance causing one to make unexpected contact with the ground. Interestingly, all the published guidelines and recommendations all agree that patients over 75 years old with atrial fibrillation should be recieving oral anticoagulation to prevent ischemic stroke. However in clinical practice, physicians tend not to anticoagulate elderly patients with atrial fibrillation citing that these individuals are at high risk for falling and oral anticoagulation will increase their chances of developing significant intracranial hemorrhage. To date, there is no published data to support this notion. Surprisingly, most clinicians make the determination of a patient's fall risk by their clinical judgement without the use of a standardized test.

Geriatricians and physical therapist have made significant advances in developing tests and scoring systems to characterize a patient's functional ability. A proven simple and rapid test to guage a patient's fall risk is the Timed "Get Up and Go" Fall Risk Assessment Test (Wall et al, 2000). The test can be administered anywhere there is a chair and 10 feet of space. The patient is seated in the chair prior to the start of the test. At the start time, the patient rise from the standard arm chair then walks to a line on the floor 10 feet in front of the chair, turns at the line, returns to chair and sits in chair again. This easy to administer test has been validated by several trials and is routinely used in geriatric assessment protocols. If a patient is able to complete the "Get Up and Go" test within 8.5 seconds, the patient is categorized as independently mobile and a minimal fall risk. Patients that have difficulty with completion and requires >30.0 seconds are almost always dependent on others for help with basic transfer (Podsaldio and Richardson, 1991).

b. Hypothesis

The risk of significant intracranial bleeding in elderly patients with atrial fibrillation on oral anticoagulation living in the community with moderate fall risk as determined by the Timed "Get Up and Go" test is at least 2% per year as compared to the risk of intracranial bleeding in the same population without anticoagulation.

B. Study Design and Statistical Analysis

The proposed study will be a prospective double blinded randomized placebo-controlled clinical trail.

The primary endpoint will be the incidence of significant intracranial hemorrhage. A significant intracranial hemorrhage event will be defined as: one that requires any neurosurgical intervention (ie burr hole evacuation, open craniotomy for clot removal, neurointerventional procedures), death (only if as a result of intracranial bleeding), hospitalization greater than 1 day (only if as a result of intracranial bleeding), decrease in functional capacity requiring nursing home placement or increase in baseline home services (only if as a result of intracranial bleeding).

Two secondary endpoints will also be analyzed: a) incidence of significant gastrointestinal/genitourinary bleeding. Significance is defined as requiring transfusions of any blood products except platelets, requiring operative or any invasive procedure (including embolization by interventional radiology, hypovolemic shock as a result of hemorrhage), b) Incidence of symptomatic ischemic stroke and transient ischemic attacks.

Primary Endpoint: To test the hypothesis that oral anticoagulation (goal INR 2-3) will increase the incidence of significant intracranial bleeding to 2% per year as opposed to the estimated 1% per year from any cause in the elderly with atrial fibrillation.

The study will be powered at 80% requiring 2600 patients in each arm. Standard T-test will be used to test if warfarin treatment significantly increases intracranial bleeding risk in elderly atrial fibrillation patients with moderate fall risk.

Secondary Endpoint: The incidence of significant gastrointestinal/genitourinary bleeding is 6%-13% in previous studies comparing oral anticoagulation to placebo (0.4%-1%). In patients with atrial fibrilation without oral anticoagulation the annual risk of ischemic stroke is 5-7% while patients on therapeutic levels of anticoagulation is (1-2%). With the numbers of patients in this study to study the primary endpoint, the secondary endpoints are powered to greater than 80%.

C. Study Procedure

All patients enrolled in the study will receive a general medical visit at the time of enrollment that will include History & Physical, Folstein Mini Mental Status Exam, Timed "Get Up and Go" Fall Assessment Test, review of medications and in addition a home environment assessment by a study staff member. Patients that meet the listed inclusion criteria and do not fulfill any of the exclusion criteria will be randomized. Both patients and physician/study staff that perform the initial assessments will be blinded to which arm the patient is randomized into. Patients will be randomized to either the Warfarin (target INR 2-3) or placebo arm. Pills (placebo and warfarin) will be identical in size, shape, consistency, weight, texture, taste, smell and color. All patients (both groups) will have blood work done every month except the first month when weekly bood draws are done (to titrate warfarin dosages). All blood samples will be processed at one central laboratory and physicians of placebo patients will receive bogus therapeutic INR values. All patients will be followed for a minimum of 1 year. Data will be collected by personal interview (during monthly blood draws) and/or telephone follow ups.

D. Study Drug

Warfarin is competitive inhibitor of the synthesis of vitamin K dependent coagulation factors by the liver. Warfarin has been approved for human use by the US Food and Drug Administration since the early 1980's. It is a widely used medication with a well established safety profile. In this study, all tablets (placebo and warfarin) will be identical in size, shape, consistency, weight, texture, taste, smell and color.

E. Study Devices

No medical devices will be used in this study.

F. Study Questionnaire

No questionnaire will be used in this study.

G. Study Subjects

Inclusion Criteria: Enrolled patients will be: 75 years of age or older: Have new onset atrial fibrillation, chronic atrial fibrillation, or a history of persistent or paroxymal atrial fibrillation; Complete the Timed "Get Up and Go" Fall Risk Assessment Test within 30 seconds but not under 8.5 seconds - use of walking device permitted (ie cane, walker, crutch); Living independently - visiting nurse services and home health aide (no more than 10 hours per week) services permitted; Perform >24 on the Folstein Mini Mental Status Examination.

Exclusion Criteria: Patients ineligible for the study include: Requiring oral anticoagulation for diagnosis other than atrial fibrillation; Absolute contraindications to warfarin therapy (-surgical procedure within 3 months -intracranial procedure within 6 months -history of CVA (any etiology) -uncontrolled hypertension -history of GI/GU hemorrhage requiring transfusion -history of warfarin induced skin necrosis; hypercoagulable state including (active cancer, untreated cancer, coagulopathy); Residents of nursing homes; Recieve more than 10 hours a week of home health aide services; Completion of Timed

"Get Up and Go" under 8.5 sec or over 30 sec; Perform <24 on the Folstein Mini Mental Status Examination.

H. Recruitment

Patients will be recruited from senior centers, natural occuring retirement communities (NORC), clinics (general medicine and cardiology). Advertisements will also be posted in community bulletin boards at senior centers, houses of worship and senior-oriented periodicals.

I. Confidentiality

Each pateint enrolled will be assigned a random number from a pre-generated master list. The master list will be generated before the start of the study and will be stored at an independent facility not affiliated with the study. All blood samples will only be identified by the patient's assigned code and all blood work reports also by the assigned code. The principal investigator will not be able to assess the master list until the conclusion of the study period.

J. Potential Conflict of Interest

None.

K. Location of Study

To recruit the required number of patients, the study will be conducted out of 80 university affliated teaching instituition in the United States. The lead institution will be Columbia University Medical Center in New York City, New York. All blood work will be process by a single commercial laboratory (Quest Diagnostics, NJ).

L. Potential Risks

The potential risks include: exposing the placebo group to an annual 5-7% risk of ischemic stroke; a significantly greater than 2% incidence of intracranial hemorrhage in the warfarin group. To address the former risk, several published studies have strongly suggested that the elderly patient population with atrial fibrillation are grossly undertreated with oral anticoagulation (less than 40% treated) (Gurwitz et al, 1997; Deplanque et al, 1999; Perez et al, 1999; Humphries et al, 2001; Lau et al, 2004). One study conducted in Pennsylvania reported that only about 20% of elderly atrial fibrillation patients are receiving oral anticoagulation (Perez et al, 1999). In light of these studies, the current proposal in not treating less potential patients than what is done in current clinical practice. The proposal actually would be treating a larger proportion (50% of the study population) than the general practice.

An analysis at 6 months will compare the number of adverse events among all patients enrolled to calculate the incidence of adverse bleeding events. If the incidence is greater than 3%, the study will be halted, unblinded and data analysis to evaluate if the treated group has had more adverse events.

M. Potential Benefits

No evidence based studies have addressed the risk/benefit ratio of oral anticoagulation in elderly patients with atrial fibrillation with moderate risk of falling. Physicians tend not to anticoagulate this population with a 5-7% yearly risk of ischemic stroke fearing bleeding complications from falling.

This study will evaluate the utility of a rapid simple well-established Fall Risk Assessment test (Timed "Get Up and Go" test) in determining the risk of oral anticoagulation in this population. A

successful trial will provide clinicians the first validated fall risk assessment tool to guide anticoagulation therapy in a growing population.

N. Alternative Therapies

No equivalent alternative therapies at this time.

O. Compensation to Subjects

No compensation will be offered.

P. Cost to Subjects

Patients will not incur any cost for any clinical services and tests related to the study.

Q. Minors as Research Subjects

No minors will be used as research subjects. Patients will be limited to >75 years old.

R. Radiation or Radioactive Substances

No radiation or radioactive materials will be used in this study.

S. References

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