# Open-label prospective trial comparing the efficacy of warfarin sodium vs. LMWH (enoxaparin) for prevention of cerebrovascular events in atrial fibrillation

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**LAY ABSTRACT**

**Study purpose:** Atrial fibrillation (AF) greatly increases the risk of cerebrovascular events from blood clots. This risk is decreased by anticoagulation. The standard method of anticoagulation is warfarin therapy, and results in a significant reduction in stroke risk over placebo. Despite warfarin therapy, in high risk patients, the stroke risk is still significant, around 4% per year. Low molecular weight heparins (LMWH) has been shown to be similarly efficacy and safety to warfarin in multiple studies, and has been shown to be more effective than warfarin in preventing clotting events in certain patient populations. Use of LMWH in long term prevention has been limited due to the cost and the need to administer daily injections. However, warfarin therapy is not without its downsides, with multiple drug and food interactions, as well as the need for frequent monitoring of blood tests. Given the persistent high risk of strokes in high risk patients with AF on warfarin, we believe that a more effective means of anticoagulation may offer significant benefit by decreasing the incidence of strokes and their associated morbidity and mortality.

**Study subjects and method of recruitment:** 1900 patients total, or 950 patients in each study arm will be enrolled from participating medical clinics. Recruitment will be done by participating physicians from among their own patient panel. No minors will be recruited, and the patients must have a CHADS2 score of 3 or greater which places them at the highest risk group for thromboembolism among AF patients.

**Study procedures:** All study patients will have monthly phone interviews to assess for symptoms of stroke, as well as adverse effects of the medications. Patients will also be assessed in clinic one month after beginning the trial, and every 3 months. Patients on the warfarin sodium arm will have regular anticoagulation clinic visits and blood draws per standard protocol which may be combined with the study visits every 3 months to minimize additional visits. Blood tests measuring serum creatinine will be checked annually in the enoxaparin group to assess renal function, and fasting lipids will be checked annually in both groups to assess level of risk factor control.

**Issues:** The study medication enoxaparin is a LMWH that has been in widespread use for anticoagulation in a variety of settings. However, it is not yet approved for use in prophylactic therapy for AF. While our experience with the medication leads us to believe that enoxaparin will be equal to if not superior to the standard therapy (warfarin), there have not been other studies to confirm its efficacy in AF.

## A. Study Proposal and Rationale

Atrial fibrillation (AF) is a common arrhythmia that occurs in 2-4% of the population over 60 years old, and over 10% of the population over 80 years old[1]. Atrial fibrillation significantly [2]increases the risk of strokes over the general population, accounting for one-sixth of ischemic strokes in patient's older than 60[3]. Thromboembolic events from atrial fibrillation include not only major clinical strokes with significant deficits, but also innumerable silent infarcts and transient ischemic attacks[4]. These patients with AF who suffer ischemic strokes are found to have increased mortality and disability than patients who suffer strokes without underlying AF[5].

As a result of this devastating consequence of AF, anticoagulation is considered in most patients. Anticoagulation with warfarin and aspirin has been studied in these patients, with the benefit being counterbalanced by the increased adverse events of bleeding. The standard of care currently involves the stratification of patients into risk categories based on the CHADS2 model, with the intermediate and high risk patients benefiting most from warfarin therapy. Although warfarin significantly reduces the risk of thromboembolic events in patients with AF at highest risk, the risk is still around 4% per year, resulting in significant morbidity.

In patients with multiple medical problems on multiple medications, warfarin therapy poses specific challenges with its numerous drug interactions. In addition to these, dietary restrictions and frequent monitoring result in unpredictable levels of anticoagulation. LMWH provides predictable pharmacokinetics and few drug interactions[6] and can be easily self administered at home.

The use of LMWH in long term prophylaxis in AF is limited. Harenberg et al. conducted a small placebo control trial comparing LMWH to placebo, and found a 2.5x risk reduction in the treatment group compared to placebo, a reduction similar to what is seen in warfarin treatment studies later conducted[7]. However, this was a placebo control trial and did not compare the study medication to the current standard of care, warfarin.

The majority of studies involving low molecular weight heparin (LMWH) in atrial fibrillation have involved using LMWH requiring anticoagulation peri-procedures such as cardioversion or surgery. In these studies, LMWH has been compared to unfractionated heparin (a mainstay of in-hospital anticoagulation) with similar efficacy and safety profiles[8] in short term use. A landmark trial from 2003 by Lee et al., compared LMWH to warfarin and found superior for prevention of recurrent venous thromboembolism in cancer patients[9]. This randomized study in almost 700 patients found a 48% reduction in thromboembolic events in the LMWH group compared to the warfarin group over the study period without significant difference in adverse events. Previous studies had failed to show a difference between warfarin and enoxaparin for venous thromboembolism prevention when studying patients with and without cancer. However, those studies were smaller and may not have been powered to detect the difference[10,11]. Whether the benefit lies only in cancer patients or can be generalized to other conditions requiring anticoagulation is unknown. It has been proposed that the hypercoagulable state in induced by cancers may partially account for the benefit seen. Interestingly, a hypercoagulable state has been hypothesized in patients with AF as well. Both thrombotic and fibinolytic pathways appear to be increased in patients with AF[12,13,14], suggesting that the increased risk of thromboembolism does not come only from mechanical stasis of the heart chamber.

Based on the existing data, we feel that it is reasonable to hypothesize that LMWH (enoxaparin) is not only non-inferior to warfarin, but could offer a significant benefit to high risk patients with AF in offering a similar reduction in thromboembolic events as found by Lee et al.

**B. Study Design and Statistical Analysis**

We propose an interventional trial designed as a multi-centered, open-labeled, randomized control study. Patients will be recruited from participating medical centers and cardiology practices. Inclusion criteria will be based on patients with on anticoagulation, or to be started on anticoagulation for atrial fibrillation who are in the high risk group for stroke, defined as having a CHADS2 score equal to or greater than 3.

Table 1[15]

| Clinical parameter | Points |
|---|---|
| **C**ongestive heart failure (any history) | 1 |
| **H**ypertension (prior history) | 1 |
| **A**ge ≥75 | 1 |
| **D**iabetes mellitus | 1 |
| **S**econdary prevention in patients with a prior ischemic stroke or a transient ischemic attack; most experts also include patients with a systemic embolic event | 2 |

Approval from the FDA will be obtained for this new use of enoxaparin. Informed consent will be obtained from all subjects. Subjects will be randomized to receive standard treatment (Warfarin sodium), and the study drug, enoxaparin. Warfarin sodium will be administered according to the standard practice at that institution. Enoxaparin will be dosed at 0.5mg/kg in single subcutaneous injections daily.

Our primary endpoint will be clinical signs of a cerebrovascular event (stroke or transient ischemic attack), with secondary endpoints of mortality and adverse events.

We estimate an event rate of 4% per year in the warfarin group, for a 12% event rate over the study period of 3 years. Patients and caregivers of patients in the enoxaparin arm will receive instruction as to the administration of enoxaparin. We will enroll 1900 patients total, or 950 patients in each arm, which is calculated based on the rate of strokes in this patient population with atrial fibrillation found in the literature[16,17] in order to detect a 25% reduction in stroke risk over the 3 year period based on the chi-squared calculation.

We propose an open-label design, as we believe a double-blind design would not be logistically feasible or safe in patients with AF who likely have many other serious conditions and are taking multiple drugs, potentially increasing the risk of drug interactions. We will attempt to minimize the bias that could be introduced in having an open-label design by having outcomes and events evaluated by a central committee whose members are unaware of the patient's treatment assignments. As the proposed study medication varies from the standard of

care, an independent board will also be evaluating the safety data and adverse events to assure the safety of our study subjects.

Data will be analyzed comparing rates of stroke between the 2 arms. Relative risk calculations of the primary and secondary endpoints will be done. Data will be measured on an intention to treat basis.

**C. Study Procedure**

The management of patients randomized to the control arm receiving warfarin therapy will be very similar to standard management on long-term anticoagulation. They will attend regular warfarin clinics as dictated by standard procedure during which time blood tests will be done to assess level of anticoagulation, with a minimum of 1 clinic visit per month if they are on a stable therapeutic dose.

Subjects randomized to the enoxaparin arm will be given the standard prophylactic dose of 40mg SC daily. Subjects on enoxaparin and their caregivers will receive special instruction on the proper administration of the medication to minimize risk of infection. Serum creatinine will be measured yearly, and treatment may be discontinued for worsened renal function meeting the exclusion criteria. No routine monitoring of factor X will be conducted, and participating physicians are discouraged from monitoring levels except in patients who develop significant renal insufficiency (not meeting exclusion criteria) during the course of the study.

Lipid profiles will be checked annually for all patients to assess degree of risk factor control in both groups.

Patients who have a thromboembolic event will be removed from the study and treated at the discretion of their primary physician. Patients will be contacted by phone monthly, with a standardized assessment of signs and symptoms of stroke, bleeding events, or adverse reactions. All patients are also to be seen in clinic 1 month, 3 months, and every 3 months after that for a visit including history taking, physical examination, assessment of compliance and adverse events, and blood drawing at aforementioned time periods. Patients are instructed to report to clinical care immediately if they have any bleeding or symptoms of stroke.

Each patient will be followed for the 3 year study period, death, or withdrawal of consent.

**D. Study Drugs [18]**

***Enoxaparin (Lovenox)*** is a low molecular weight heparin FDA Approved for the following indications:

- Deep vein thrombosis prophylaxis in patients with abdominal, hip or knee replacement surgery or severely restricted mobility during acute illness.
- Inpatient treatment of acute DVT with or without pulmonary embolism
- Outpatient treatment for acute DVT without pulmonary embolism
- Prophylaxis of ischemic complications of unstable angina and non-Q-wave MI
- Treatment of acute ST-segment elevation MI managed medically or with subsequent percutaneous coronary intervention.

Common Adverse effects include:

- Bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, nausea

Serious but rare effects include:

- Heart failure, skin necrosis, anaphylactoid reaction, spinal hematoma, pulmonary edema.

Contraindications include:

- Active major bleeding
- Thrombocytopenia with positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium
- Hypersensitivity to enoxaparin sodium
- Hypersensitivity to heparin or pork products

While it is not approved for stroke prevention in atrial fibrillation, it has been used in prevention of other thromboembolic events such as pulmonary embolism, and has been used successfully in bridging therapy for peri-procedural anticoagulation in AF. The dosage used in this study is the standard dosage used for prophylaxis of thromboembolic events.

***Warfarin sodium (Warfarin)*** is FDA approved for:

- Prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
- Prophylaxis and/or treatment of venous thrombosis and pulmonary embolism
- Reducing risk of death, recurrent myocardial infarction and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

Common Adverse effects include:

- Hemorrhage

Serious but rare effects include:

- Skin necrosis, hypersensitivity, cholesterol microembolization, elevated liver enzymes, tracheobroncheal calcification.

Contraindications include:

- Any situation in which hazard of hemorrhage might be greater than potential benefits of anticoagulation: Pregnancy, hemorrhagic tendencies or blood dyscrasias, recent or upcoming surgery, active ulceration associated with bleeding, inadequate laboratory facilities, unsupervised senility, malignant hypertension, known hypersensitivity to warfarin or components, spinal procedures.

Warfarin sodium is the standard of care in anticoagulation for stroke prevention in atrial fibrillation. Dosage of warfarin sodium will be determined based on standard practices, and titrated as needed based on standard warfarin management. Precautions must be taken with warfarin sodium because of the extensive drug and food interactions that may affect a patient's level of anticoagulation.

**E. Study Questionnaires**

Patients will complete a general health questionnaire about preexisting medical conditions and risk factors at the beginning of the study. Questionnaires gauging the patient's tolerance with and satisfaction with their assigned form of anticoagulation will be used at each 3 month visit to assess the tolerability and feasibility of both methods of anticoagulation.

**F. Study Subjects**

All patients with documented atrial fibrillation and a CHADS2 score greater or equal to 3 currently on or are to be started on anticoagulation for atrial fibrillation will be included.

Exclusion criteria will include patients who are not candidates for anticoagulation, or have a CHADS2 score less than 3, or other indications for therapeutic anticoagulation such as prosthetic valves, malignant disease, or other known hypercoagulable state. Patients with contraindications to either study medication would also be excluded, including patients with a serum creatinine greater than three times the upper limit of normal, or patients who are pregnant. Patients with a weight greater than 200kg will also be excluded, as the pharmacokinetics and efficacy of enoxaparin becomes more unpredictable with extremely obese patients.

**G. Recruitment of Subjects**

Patients will be recruited by study investigators at medical centers and medical clinics participating in the study from the patient panels of participating physicians.

**H. Confidentiality of Study Data**

All participants will be coded by a random number system in order to ensure confidentiality. Data will be stored in a secure location, only accessible to the study investigators.

**I. Potential Conflicts of Interest**

The enoxaparin used as the study medication will be provided by the manufacturer. However, the primary endpoints and adverse events will be objective data points, and all data will be evaluated by a central committee without ties to the manufacturer, and without knowledge of each subject's treatment assignment. An external safety board will also evaluate the study arms for problems related to patient safety while participating in the study. Because of possible bias introduced due to the open label design, patient characteristics and risk factors will be stratified at the beginning and end of the study to determine if there were differences in care rendered between the 2 groups. i.e. differences in blood pressure or lipid control.

**J. Location of the Study**

This study will take place in the clinical offices of the participating investigators and clinics. In patients recruited in the hospital, the study may be initiated while the patient is

hospitalized, with subsequent follow-ups to be completed with their primary physician. If subjects endorse signs or symptoms suggestive of stroke, they will be asked to return to their local emergency department for further evaluation and treatment.

**K. Potential Risks**

The primary risk to the subject is that Enoxaparin may not be as effective in reducing stroke as Warfarin sodium. Although Enoxaparin has been shown to be as effective or more effective in reducing the risk of thromboembolic events in other settings, its use in atrial fibrillation has been limited. However, evidence in the efficacy of enoxaparin in bridging therapy for atrial fibrillation is reassuring as to enoxaparin's efficacy in preventing strokes in atrial fibrillation. Other risks involve possible bruising or infection at the injection site. Proper hygienic practices will be taught to the patients beginning therapy with Enoxaparin to minimize the risk of infection. In both arms, there is a risk of bleeding events. However, the literature has shown that the risk of bleeding has been shown to be roughly equivalent with the two agents.

**L. Potential Benefits**

The study subjects may or may not benefit from participating in this study. If Enoxaparin is shown to be superior to Warfarin sodium, the subjects who take Enoxaparin may have a significant decrease in strokes. This may translate into improved quality of life and fewer hospitalizations. The shorter half-life of Enoxaparin may also offer the additional benefit of increased flexibility timing peri-procedure in these patients.

**M. Alternative Therapies**

The standard of care for stroke prevention in intermediate and high risk patients with atrial fibrillation involves anticoagulation with warfarin sodium in conjunction with rate or rhythm control. The alternative would be to choose not to enroll in this study for randomization and instead engage in standard therapy under the guidance of the patient's primary physician. In patients who the risk of adverse events such as bleeding is thought to be great, the alternative therapy could involve no anticoagulation or aspirin therapy under the guidance of the subject's principle physician.

Other, non-medical, therapies such as cardioversion or ablation may be attempted to cure the patient of atrial fibrillation. The risks and benefits of those procedures should be addressed with the patient's primary physician.

**N. Compensation to Subjects**

Subjects on both arms will be reimbursed for any travel expenses related to follow-up visits. Warfarin will be provided by the study. Enoxaparin will be provided to study patients free of charge by Sanofi Aventis.

**O. Cost to Subjects**

The subjects will not incur additional costs as a result of participating in this study.

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