Randomized trial of Apixaban vs dose adjusted Warfarin in reducing rate of cognitive function decline, silent cerebral infarcts and cerebral microbleeds in non-valvular atrial fibrillation patients with CHA2DS2-VaSc score ≥2.

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Protocol Number: 7.0

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

Mayo Clinic investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this clinical trial have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Randomized trial of Apixaban vs dose adjusted Warfarin in reducing rate of cognitive function decline, silent cerebral infarcts and cerebral microbleeds in non-valvular atrial fibrillation (NVAF) patients with CHA2DS2-VaSc score ≥2.
Study Description:	This study is a randomized clinical trial of patients with AF, whose CHA2DS2-VaSc score ≥2, it will compare Apixaban vs dose adjusted warfarin on the rate of cognitive function decline, silent cerebral infarction and cerebral microbleed. Our hypothesis is that, anticoagulation with Apixaban reduces the rate of decline in cognitive function, when compared to Warfarin and that Apixaban reduces cognitive decline by reducing the rate of new cerebral infarction and cerebral microbleeds detected by cerebral MRI compared to warfarin.
Objectives:	Primary Objective: Assess the difference in decline in cognitive function using standardized neurocognitive assessment in AF patients treated with Apixaban vs Warfarin. Secondary Objectives: Assess the difference in incident mild cognitive impairment or dementia in NVAF patients treated with Apixaban vs Warfarin. Assess the difference in development of new silent cerebral infarcts and cerebral microbleeds on brain magnetic resonance imaging (MRI) in NVAF treated with Apixaban vs Warfarin.
Endpoints:	Primary Endpoint: The individual cognitive domain and global cognitive function score in NVAF patients treated with Apixaban vs Warfarin Secondary Endpoints: (1) New mild cognitive impairment or dementia; (2) new cerebral infarcts on brain MRI and (3) new cerebral microbleeds on brain MRI in NVAF treated with Apixaban vs Warfarin.
Study Population:	Patients (male and female over the age of 60 years) diagnosed with NVAF over the age of 60 years with a CHA2DS2-VASc score ≥2, who have never been treated with Apixaban , or prior treatment with Apixaban <1 month.
Phase:	3
Description of Sites/Facilities Enrolling Participants:	Mayo Clinic, Rochester
Description of Study Intervention:	**Apixaban** 5 mg twice daily unless patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to

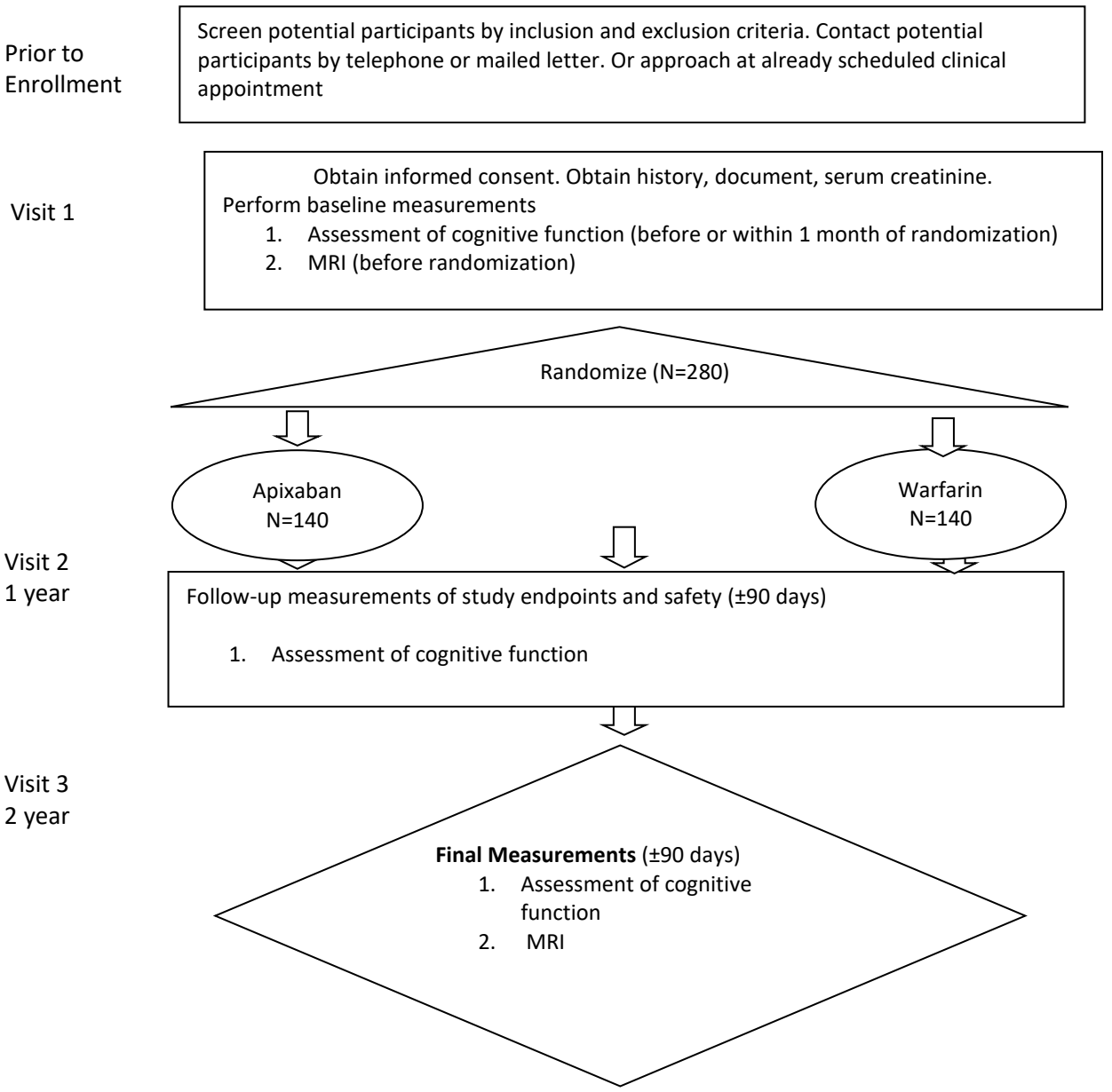
2.5 mg twice daily.

Warfarin
Dose adjusted to maintain INR between 2 – 3. Dose adjustment will be performed using a standardized nomogram at an anti-coagulation clinic or by treating physician.

Study Duration: 36 months

Participant Duration: 24 months

1.2 SCHEMA


Prior to Enrollment
Screen potential participants by inclusion and exclusion criteria. Contact potential participants by telephone or mailed letter. Or approach at already scheduled clinical appointment
Visit 1
Obtain informed consent. Obtain history, document, serum creatinine.
Perform baseline measurements
1. Assessment of cognitive function (before or within 1 month of randomization)
2. MRI (before randomization)
Randomize (N=280)
Apixaban N=140
Warfarin N=140
Visit 2 1 year
Follow-up measurements of study endpoints and safety (±90 days)
1. Assessment of cognitive function
Visit 3 2 year
Final Measurements (±90 days)
1. Assessment of cognitive function
2. MRI

2 INTRODUCTION

2.1 STUDY RATIONALE

The Problem

There is a vast growing body of evidence linking atrial fibrillation (AF) with an increased risk for cognitive impairment (from mild to severe dementia) independent of clinical stroke history [1-3]. Further, it is described that AF can lead to development of dementia at an earlier age and a more rapid decline in cognitive function [4]. Both AF and cognitive impairment have profound effects and burdens on health care systems through increasing cost and complexity of medical care associated with these diagnoses [5, 6]. It is crucial therefore to identify ways to reduce the global burden of cognitive impairment observed in patients with AF.

The Mechanism

The relationship between AF and cognitive impairment is intricate and likely driven by two major mechanisms; cerebral infarction (both overt and subclinical) and cerebral micro-bleeds (CMBs). Anticoagulation can reduce the risk of cerebral infarction but this may be offset by the increased risk of CMBs.

The Solution

Therefore, there is a need for an anticoagulant in the treatment of AF that can not only reduce the incidence of clinical stroke but also silent cerebral infarcts with the added benefit of reducing the risk of CMBs and overt intracranial hemorrhage. By identifying an anticoagulant that can achieve these end points, there is a potential to reduce the risk of cognitive decline in patients with NVAF.

2.2 BACKGROUND

Atrial Fibrillation and Cognitive Decline/Dementia – a major association

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide, with an estimated prevalence of 33.5 million[7]. [7]. It is reported that 3.8 percent of people 60 years of age and older and 9.0 percent of those 80 years of age and older have atrial fibrillation [8]. Similarly to AF, cognitive impairment and dementia plots an increasing prevalence with age and share many risk factors such as advanced age, hypertension and diabetes [9-11]. The first proposal of an association between AF and dementia was 20 years ago when the Rotterdam Study described the existence of a positive association between AF and dementia, with a > 2-fold increased risk for dementia.[12] Since then there has been a growing body of strong and reproducible evidence linking AF with an increased risk of cognitive impairment and dementia independent of shared risk factors and stroke.[1-3] AF increases the risk of cognitive impairment by 40% in those without stroke and doubles it in patients with history of stroke.[13] AF also leads to development of dementia at an earlier age and a more rapid decline in cognitive function [4]. AF and cognitive impairment both have profound effects and burdens on health care systems through increasing cost and complexity of medical care associated with these diagnoses [5, 6]. It is therefore crucial to identify ways to reduce the global burden of cognitive impairment observed in patients with AF.

Mechanisms Underlying the Association between Atrial Fibrillation and Dementia

The mechanisms for the association between AF and cognitive decline are intricate and multifactorial. Potential mechanisms include linking atrial fibrillation and cognitive impairment/dementia include

cerebral hypoperfusion, vascular inflammation, cerebral vascular disease, thromboembolism and brain atrophy. Of particular interest and felt to play a major role is cerebral infraction, both overt and subclinical.

Cerebral infarctions occur due to systemic embolism as a consequence of AF and are associated with significant risk of dementia in the general population and in patients with AF.[14-16] While overt stroke is one of the most feared sequela of AF, subclinical cerebral ischemic lesions (as detected by magnetic resonance imaging [MRI]) have been reported in up to 90% of participants with AF. These lesions have been consistently associated with an increased rate of dementia and decline in global cognitive function.[17]

Similarly, CMBs also contribute towards the association of AF and dementia or cognitive decline. CMBs are asymptomatic cerebral hemorrhages detected by MRI that often occur in association with cerebral amyloid angiopathy. They increase the risk for intracranial hemorrhage (particular in the setting of anticoagulation for AF [18, 19] and are associated with worse cognitive outcomes. [20-22] Remarkably, in AF patients that manifest cognitive impairment, there is often a significant presence of cerebral micro bleeds detected on brain MRI In patients [14, 23-25].

Role of Anticoagulation

The central role of cerebral infractions and CMBs in the association between AF and dementia suggests that anticoagulation could be a key player in the association. It is plausible that effective anticoagulation of AF-patients could reduce the risk of cognitive impairment by reducing the risk of cerebral infarction. Anticoagulation however also increases the risk for macro- and micro- bleeds in the brain, which in turn may increase the risk of cognitive dysfunction. Hence an ideal anticoagulant should reduce the incidence of cerebral infarcts without significantly increasing the risk of cerebral hemorrhage.

Some observational studies have investigated the impact of various anticoagulation strategies for AF treatment on dementia. Warfarin, as the most common prescribed anticoagulant, was the initial focus of many studies and it was shown that warfarin could reduce the incidence of dementia in patients with AF.[26] However, it has a narrow therapeutic window and its efficacy in reducing dementia I contingent on maintaining a high time in therapeutic range; rates of incident dementia were nearly 2-fold higher in the subjects with the poorest anticoagulation maintenance compared to those with the highest anticoagulation time in therapeutic range. We also recently published further supporting evidence with the addition that supra-therapeutic INRs on warfarin increase the risk for dementia compared to therapeutic INR.[27] While sub-therapeutic INR increases risk of cerebral embolism, supra-therapeutic INR can increase cerebral microbleeds and intracranial hemorrhage. Patients with an INR>3 more than 25% of the time are 2.4 times more likely to develop dementia[28]. While supratherapeutic INR is a risk for CMB, it has also been highlighted that patients in general who are treated with vitamin K antagonists (VKA) were more likely to have CMBs[18]. Hence it is becoming increasingly clear that warfarin may not be the ideal anticoagulant to prevent the devastating complication of cognitive impairment.

Apixaban, a direct oral anticoagulant, may be alterative for anticoagulation to reduce the risk of dementia. The ARISTOTLE trial has demonstrated that Apixaban is non-inferior and infact superior to warfarin in reducing the incidence of clinical stroke in AF.[29] Compared to warfarin, Apixaban may provide more steady state of anticoagulation. Further, the incidence of intracranial hemorrhage was significantly lower in Apixaban treated patients compared to warfarin, which was a striking finding of the ARISTOTLE trial.[29] While it is clear that Apixaban can reduce the risk of stroke it also remarkably does not

seem to increase the prevalence of CMB in patients with atrial fibrillation, compared with aspirin[30]. Therefore, as suggested by a recent retrospective observational analysis [31], Apixaban could potentially be associated with a reduced risk of cognitive impairment compared to warfarin.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Immediate Risk

Physical

Physical immediate risks will be largely related to the anticoagulants that will be administered, whether that is warfarin or Apixaban. These risks are summarized below. It is notable that these drugs will be prescribed according to existing guidelines from the American Heart Association. Drug administration will be in accordance with FDA approved guidelines and drug package insert.

- *Apixaban (ELIQUIS)*
  The major risk for this drug is increased risk of bleeding which can be serious and potentially fatal. The safety of Apixaban has been evaluated in the ARISTOTLE and AVERROES studies and includes 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was >12 months for 9375 patients and >24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years). The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with Apixaban and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on Apixaban and aspirin, respectively. Further, concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and nonsteroidal anti-inflammatory drugs (NSAIDs). Additionally, hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving Apixaban. Lastly, should any discontinue Apixaban in the absence of adequate alternative anticoagulation there is an increases risk of thrombotic events. Therefore if Apixaban must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant will be considered. This is based on the FDA boxed warning that accompanies the drug that is stated as follows:
  “Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy.”

- Warfarin
  Warfarin can cause major or fatal bleeding with bleeding more likely to occur within the first month. Necrosis and/or gangrene of skin and other tissues is an uncommon but serious risk (<0.1%). In general, the risk of major internal bleeding is about 1 to 3 percent per year; patients

who have tolerated warfarin well for at least six months and are on a stable dose of warfarin usually have a risk for major internal bleeding that is closer to 1 percent per year.

Psychological, social, legal, and economic
We do not foresee any risks in this regard.

Long range Risk
Physical
As discussed above major long range risk will be largely related to the anticoagulants that will be administered, whether that is warfarin or Apixaban. Both Apixaban and warfarin will be prescribed only in patients who meet American Heart Association guidelines for treatment with an oral anticoagulant for stroke prevention in NVAF. Hence the treating physician has determined based on existing literature and guidelines that the benefit of anticoagulation in terms of stroke prevention outweighs the risk of bleeding in these patients.

- *Apixaban (ELIQUIS)*
  Risks discussed above in immediate risk.

- Warfarin
  Risks discussed above in immediate risk.

Economic
During the trial the patient will receive Apixaban (if randomized to the Apixaban arm) drug therapy free of charge. Warfarin and its monitoring will not be paid for by the study since it is considered the standard of care. The cost of medical care or other costs related to any adverse events will not be covered by the study. Following completion of an individual's participation in the trial (due to end of follow-up, or withdrawal from the study), the cost of all medications and related monitoring will be borne by the patient and/or their insurance – these costs will not be covered by the study.

Psychological, social, and legal
The psychological risk of the study include possible minor discomfort or anxiety in the setting of neuropsychologic testing or during brain MR imaging.

2.3.2 KNOWN POTENTIAL BENEFITS

Immediate potential benefits

Physical
Physical immediate benefits will largely be related to the reduction in thromboembolism risk whether that is warfarin or Apixaban. All patients in the trial would quality or warrant anticoagulation to reduce their risk according to established guidelines.

- *Apixaban (ELIQUIS)*
  The major benefit of this drug is the reduction in risk of thromboembolism. The ARISTOTLE trial showed a significant reduction in stroke or systemic embolization when compared to warfarin (1.27 % vs 1.60%/year, respectively; Hazard ratio, 0.79, P-value=0.01). Further treatment with

Apixaban in this trial resulted in a significantly lower rate of all-cause death (p = 0.046) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. The AVERROES trial showed a greater benefit compared to aspirin (1.62 % vs 3.63%/year, respectively; hazard ratio 0.45, P-value< 0.0001) in patients thought not to be candidates for warfarin therapy.

- Warfarin
  In five prospective, randomized, controlled clinical trials involving 3711 patients with non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke. The risk reduction ranged from 60% to 86% in all except one trial (CAFA: 45%), which was stopped early due to published positive results from two of these trials.

Psychological
Early data related to DAOCs show DOACs have an improved psychological impact compared with warfarin in elderly patients.[32] Apixaban, DOAC, has stable and predictable clinical pharmacology and does not require laboratory monitoring. Apixaban also does not interfere with food and has fewer interactions with other drugs compared to warfarin. Therefore it is foreseeable the physiological benefit this could provide, especially when compared to warfarin.

Social, and legal
We do not foresee any benefit in this regard.

Long range potential benefits
Physical
As discussed above major long benefit will be a reduction in thromboembolism, whether that is warfarin or Apixaban.

- *Apixaban (ELIQUIS)*
  Benefits discussed above in immediate risk.

- Warfarin
  Benefits discussed above in immediate risk.

Psychological
Benefits discussed above in immediate risk.

Social, and legal
We do not foresee any benefit in this regard.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Include an assessment of known potential risks and benefits, addressing each of the following:

- *Rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the study design*
- *Justification as to why the risks of participation in the study outweigh the value of the information to be gained*

In our trial, patients will have a CHA2DS2-VASc score ≥2 and considered by the treating physician for anticoagulation to reduce the risk of stroke in the setting of NVAF as per American Heart Association guideline. In other words, patients with this score and NVAF in general practice would be offered anticoagulation. Therefore, although patients are being exposed to a drug which could cause some adverse and rarely fatal reactions – this exposure would not be out of the realm of ordinary evidenced based clinical practice. That said, risks in particular with bleeding will be minimized by ensuring monitoring of the patients (eg. INR for warfarin, creatinine for Apixaban) and education regarding these risks.

Education will be provided to patients regarding signs of obvious bleeding, management of diet, and *how to manage* medications during travel using educational brochures.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the change in global cognitive function using standardized neurocognitive assessment in patients with atrial fibrillation over the age of 60 years with CHA2DS2-VASc score ≥2 treated with Apixaban versus warfarin	The individual cognitive domain and global cognitive function score using a battery of standardized neurocognitive function tests (presented below in detail). ○ All enrolled subjects will undergo assessment of cognitive function at (1) before or within 1 month of randomization (2) 1 year and (3) 2 years.	Cognitive function scores are chosen as the primary end point due to their sensitivity to detect changes in cognitive function within a short span of time. While dementia is also an important end point, it is increasingly recognized that milder degrees of cognitive dysfunction are more prevalent and may have an important impact on a person's quality of life and morbidity. Early recognition of cognitive decline can lead to earlier intervention to either treat or prevent progression. Hence the primary end point of decline in cognitive function in one or more domains will be a clinically relevant and a patient centered outcome. Additionally, AF may have a greater impact on non-memory cognitive domains such as executive function, thus predisposing to non-amnestic dementia. Hence we will test individual cognitive domains to

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		increase the sensitivity of the tests.
Secondary		
To assess the development of mild cognitive impairment or dementia	Clinical dementia rating scale <u>Dementia</u> Subjects with a CDR 1 will be classified as demented if they meet DSM-V criteria for 'major neurocognitive disorder' as follows: 1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on: a. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and b. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing. 2. The cognitive deficits interfere with independence in everyday activities. 3. The cognitive deficits do not occur exclusively in the context of delirium and are not better explained by another mental disorder. For subjects with CDR 0.5, a committee of the examining	The development of dementia or mild cognitive impairment are important end points with clinical relevance to the patient.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	neuropsychologist and physician will critically examine the available tests to determine whether the DSM-V criteria for dementia or MCI are met. <u>Mild cognitive impairment</u> The criteria for diagnosis of MCI are: cognitive concern expressed by a physician, informant, participant or nurse; cognitive impairment in 1 or more domains; normal functional activities and not demented. Subjects with MCI can have a CDR of 0 or 0.5; however, the final diagnosis of MCI will not be based exclusively on the CDR but rather on all available data. A committee of the examining neuropsychologist and physician will critically examine the available tests to determine whether the criteria for MCI are met.	
Tertiary end points		
MRI detected new cerebral ischemic lesions and cerebral microbleeds (CMBs)	Brain MRI will be performed at baseline and 2 years to assess the presence of new cerebral ischemic lesions on DTI imaging and new cerebral microbleeds on SWAN sequences.	The presence of cerebral infarcts, even clinically silent ones, have been associated with higher future risk of dementia. Similarly, CMBs are associated with dementia and future risk for intracerebral hemorrhage.

4 STUDY DESIGN

4.1 OVERALL DESIGN AND SCIENTIFIC RATIONALE FOR STUDY DESIGN

Our *<u>primary hypothesis</u>* is that in patients with atrial fibrillation, anticoagulation with Apixaban reduces the rate of decline in cognitive function, when compared to Warfarin. We also hypothesize that Apixaban reduces cognitive decline by reducing the rate of new cerebral infarction and cerebral microbleeds detected by cerebral MRI compared to warfarin.

This is a phase 3, open-label, single site, randomized control trial comparing neuropsychological and neuroimaging outcomes in AF patients randomized to Apixaban vs Warfarin. Patients over the age of 60 y with ECG documentation of NVAF in patient records and CHA_2DS_2VaSC score ≥2, eligible for oral

anticoagulation will be randomized to Apixaban or dose adjusted warfarin (target INR 2 – 3) for a period of 2 years. Randomization will be stratified by decade of age, and gender. All patients will undergo neuropsychometric testing at baseline, 1 and 2 years and brain MRI at baseline and 2 years. Study personnel performing and interpreting the neuropsychometric tests and brain MRI will be blinded to treatment allocation.

Specific objectives

Primary objective: To assess the decline in cognitive function using standardized neurocognitive assessment in patients with atrial fibrillation over the age of 60 years with CHA2DS2-VASc score ≥2 treated with Apixaban versus warfarin

Our hypothesis is that Apixaban is associated with reduction in decline of cognitive function scores when compared to dose adjusted warfarin with goal INR of 2 – 3. We will test this hypothesis by randomizing patients with AF over the age of 60 years and CHA2DS2-VASc score ≥2 to anticoagulation with Apixaban vs Warfarin. The primary endpoint of this study is the longitudinal change in cognitive function scores over a follow-up of 2 years in individual cognitive domains (executive, language, memory and visuospatial) and global cognitive function. The development of mild cognitive impairment or dementia will also be assessed as a secondary end point. By the end of this study it is our expectation that the risk of cognitive impairment in AF patients taking Apixaban compared to Warfarin will be well defined and such results will provide a novel measure to reduce the burden of cognitive impairment in AF.

Rationale: Cognitive function scores are chosen as the primary end point due to their sensitivity to detect changes in cognitive function within a short span of time. While dementia is also an important end point, it is increasingly recognized that milder degrees of cognitive dysfunction are more prevalent and may have an important impact on a person's quality of life and morbidity. Early recognition of cognitive decline can lead to earlier intervention to either treat or prevent progression. Hence the primary end point of decline in cognitive function in one or more domains will be a clinically relevant and a patient centered outcome.

Secondary objective: To determine the incidence of new cerebral infarct and new cerebral microbleeds using cerebral MRI in AF patients treated with Apixaban vs warfarin.

The secondary objective is to evaluate the impact of Apixaban on subclinical emboli and CMBs detected by brain MRI compared to Warfarin. Our hypothesis is that Apixaban is associated with fewer new subclinical emboli and CMBs, compared to warfarin. This has important clinical implications as reduction in these has significant potential to reduce the risk of cognitive impairment.

Rationale: There is growing evidence of the important relationship between subclinical emboli and cerebral microbleeds (CMBs) and the development of cognitive impairment. These MRI findings can be viewed as 'bio-markers' of risk of future cognitive decline.

4.2 JUSTIFICATION FOR DOSE

Drug dosing will be in compliance with FDA approved recommendations. There will be NO off-label use of drugs.

Apixaban

5 mg twice daily unless patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily.

Further dose adjustment will be performed in special circumstances as per FDA approved Apixaban drug label as follows:

For patients qualifying for Apixaban 5 mg twice daily, the dose of Apixaban will be decreased by 50% when co-administered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin).

Warfarin

Dose adjusted to maintain INR between 2 – 3. Dose adjustment performed using a standardized nomogram at an anti-coagulation clinic will be encouraged but not required. Interval of INR testing will be determined by the treating physician.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Patients diagnosed with atrial fibrillation based on electrocardiographic documentation
2. Male or female greater than or equal to the age of 60 years,
3. Have a CHA2DS2-VASc score ≥2
4. Have never been treated with Apixaban, or prior treatment with Apixaban <1 month.

5. Provision of signed and dated informed consent form
6. Stated willingness to comply with all study procedures and availability for the duration of the study
7. Ability to take oral medication and be willing to adhere to the study intervention regimen

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who are not a candidate for oral anticoagulation as assessed by a treating physician including the presence of active bleeding.
2. Prior treatment with Apixaban for >1 month. (Prior exposure to warfarin or novel direct oral anticoagulants other than Apixaban is not an exclusion criterion).
3. Known hypersensitivity to warfarin or Apixaban.
4. CHA2DS2-VASc score <2

5. Valvular AF defined as history of rheumatic valve disease, moderate or greater mitral stenosis, and presence of a mechanical cardiac valve.
6. Need for dual anti-platelet therapy with aspirin and another agent such as a thienopyridine.
7. Aspirin monotherapy with doses > 100 mg if the patient is unable to reduce the dose to <100 mg.
8. Severe renal insufficiency (serum creatinine level of >2.5 mg/dl or calculated creatinine clearance of <25 ml/minute) or dialysis.
9. Prior severe bleeding including intracranial hemorrhage and GI bleed requiring transfusion.
10. Recent stroke (within 7 d)
11. Known diagnosis of dementia or dementia diagnosed at first evaluation.
12. Presence of MRI non-compatible implanted devices including cardiac implantable electronic devices. Patients with MRI conditioned cardiac implantable electronic devices will also be excluded. This is done in light of concerns regarding patient safety in MRI scanner.
13. Inability to undergo MRI due to claustrophobia.
14. Current or expected systemic treatment with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban
15. Current or expected systemic treatment with strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) in patients who would qualify for Apixaban dose of 2.5 mg BID.
16. Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
17. Co-morbid condition(s) that could limit the subject's ability to participate in the trial or to comply with follow-up requirements, or that could impact the scientific integrity of the trial.
18. Prisoners or subjects who are involuntarily incarcerated. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
19. Severe comorbid condition with life expectancy ≤1 y
20. Active alcohol or drug abuse or psychosocial reasons that make study participation impractical.

5.3 LIFESTYLE CONSIDERATIONS

Warfarin arm:

- Consumption of consistent quantities of vitamin K containing food from day to day will assist in the maintenance of your INR in the therapeutic range. (Patients will be provided a copy of the Mayo Clinic booklet on dietary regulation in warfarin treated patients as a guide.)

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. An example of a screen failure is someone who is diagnosed with newly recognized dementia or intracerebral hemorrhage following the administration of the baseline neurocognitive assessment and brain MRI. Information on screen failures will be collected for purposes of reporting as follows: demography, eligibility criteria, reason for screen failure and any serious adverse event.

Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

1. This is a single center study that will be conducted at the Mayo Clinic, Rochester, MN. Target study sample is total of 280 patients. Assuming a screen failure rate of 20%, target accrual is 350 participants. Accrual will be completed in 1 year. The last patient will complete follow-up 2 years later.
2. In order to enrich the study for the population at risk of the primary end point, at least 50% of the enrollees will be >70 y of age.
3. Participants will be identified using two strategies: (1) Individuals with AF living in the 8 counties of Southeast Minnesota (Dodge, Fillmore, Goodhue, Houston, Olmsted, Mower, Wabasha and Winona counties) will be screened for eligibility. Such patients will be identified using the record linkage system of the Rochester Epidemiology Project and Mayo Clinic, Rochester clinical records. Potential participants with AF diagnosed in Olmsted county have already been identified through prior work the investigators have done. (2) Individuals seen in the inpatient and outpatient clinics at Mayo Clinic, Rochester, MN with a diagnosis of AF will also be screened for eligibility. Such patients will be identified by the treating physician, using screening of their medical records and through the Mayo ECG laboratory which flags patients with new identification of AF.
4. Potential participants will be approached using one or more of the following: (1) direct patient contact in the clinic or hospital, (2) through letters and (3) phone calls.
5. The ECG documentation of AF will be confirmed using review of the medical records. Eligibility for the study will be determined first using medical records and confirmed by direct interview of the patient prior to enrollment.
6. Participants will be compensated for their participation in the study as follows: (1) each participant will be given $15 at the time of each neurocognitive assessment and (2) a Mayo parking voucher at the time of each MRI assessment. The compensation is intended to encourage patients to continue study related tests by providing partial compensation for travel expenses.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Study intervention

Participants will be randomly assigned 1:1 to one of 2 treatment arms. Randomization will be stratif

ied by decade of age and gender. Drug administration will be according to the FDA approved labeling.

Treatment arm 1 (Apixaban arm) will receive Apixaban 5 mg twice daily unless patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily.

For patients receiving a non-Apixaban anticoagulant at the time of enrollment, the following procedure will be followed to convert them to Apixaban:

Conversion from warfarin to apixaban: Discontinue warfarin and initiate apixaban when INR is <2

Conversion from other non-warfarin anticoagulants (oral or parenteral) to apixaban: Discontinue the other non-warfarin anticoagulant and begin taking apixaban at the usual time of the next scheduled dose of the other non-warfarin anticoagulant.

Treatment arm 2 (Warfarin arm) will receive dose adjusted warfarin to maintain INR between 2 – 3. Dose adjustment performed using a standardized nomogram at an anti-coagulation clinic will be encouraged but not required. Interval of INR testing will be determined by the treating physician.

For patients receiving a non-Apixaban oral anticoagulant at the time of enrollment, the following procedure will be followed to convert them to Warfarin: The anticoagulant will be continued until the INR is ≥2.

For patients receiving a parenteral anticoagulant at the time of enrollment to the warfarin arm, the treating physician will determine the need for 'bridging' anticoagulation until the INR is therapeutic.

6.1.2 DOSING AND ADMINISTRATION

Apixaban

5 mg twice daily unless patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily. Oral administration.

For patients qualifying for Apixaban 5 mg twice daily, the dose of Apixaban will be decreased by 50% when co-administered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin).

Need for dose adjustment will be performed at the 1 year mark or sooner if the patient's age, weight or creatinine warrant this.

Warfarin

Dose adjusted to maintain INR between 2 – 3. Dose adjustment performed using a standardized nomogram at an anti-coagulation clinic will be encouraged but not required. Interval of INR testing will be determined by the treating physician. Oral administration.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Apixaban arm: The drug will be provided by and paid for by BMS / Pfizer. The drug will be provided to Mayo Clinic. It will be distributed to patients once every 6 months via mail by the Mayo Clinic Pharmacy. Apixaban will *be* stored at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) per the drug labeling.

Warfarin arm: Warfarin will be prescribed by the treating physician. INR monitoring and dose adjustment will also be performed by the treating physician / assigned anticoagulation clinic. Warfarin will not be provided or paid for by the study.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Study participants will be randomized 1:1 to either Apixaban or dose adjusted Warfarin. Placebo pills will not be administered. Participants, the principal investigator and study coordinator will not be blinded to treatment assignment. Study personnel administering and interpreting the MRI images and cognitive function assessment will be blinded to treatment assignment. Randomization codes will be generated at the time of enrollment and each individual's cognitive function tests and MRI scan identified by this code. Blinding of participants in this study will require the use of placebo and INR testing in both groups, which will be burdensome to the patient and will not affect the outcomes of cognitive function or MRI findings.

Unblinding of personnel to treatment assignment will be performed only when there is a serious adverse event such as intra-cranial hemorrhage.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Medication information will be collected at each neurocognitive assessment visit. A list of medications will be extracted from the most recent available medical records and confirmed in person with the patient. This will be performed by the study coordinator.

6.4.1 RESCUE MEDICINE

The study site will not supply rescue medication that will be obtained locally.
The following rescue medications / treatments may be used in the setting of hemorrhagic adverse events at the discretion of the treating physician.

Apixaban: Discontinue therapy with active pathological hemorrhage and promptly evaluate for bleeding source.
A specific antidote for Apixaban is not available, and there is no established way to reverse bleeding in patients taking Apixaban. The pharmacodynamic effect of Apixaban can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. A preclinical study evaluated the impact of different clotting factors in reversing actions of apixaban. A high concentration of apixaban (200 ng/mL) was added to blood from healthy donors *in vitro* and blood-clotting response was evaluated when prothrombin complex concentrates (PCCs; product not specified), activated prothrombin complex concentrates (aPCCs), and recombinant factor VII (rFVIIa) were added. PCC and aPCC seemed to be more efficient in restoring generation of thrombin, while rFVIIa was the quickest to produce a compact blood clot and most effective in studies with blood circulating through a damaged blood vessel. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration. The use of activated oral charcoal

may be considered if ingestion occurred within 2 to 6 hours of presentation. Hemodialysis does not appear to have a substantial impact on apixaban exposure. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

Warfarin: If bleeding occurs, check INR and discontinue use. Depending on the severity of the bleeding intravenous fresh frozen plasma and oral or intravenous Vitamin K can be used to reverse the anticoagulant effect of warfarin.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study intervention (anticoagulant use) does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). Events that may trigger include:

1. Major bleeding event. The anticoagulant will be discontinued and future management of anticoagulant will be decided by the treating physician. The patient will not be re-challenged with anticoagulant as part of the study protocol.
2. Ischemic Stroke / TIA. Management of anticoagulant in the first month following an ischemic stroke / TIA will be determined by the treating physician. Following this, a decision regarding whether to continue study intervention will be made in consultation with the treating physician and the patient. Whether the anticoagulant was being used in a therapeutic fashion at the time of event will be part of this discussion.
3. Hemorrhagic stroke. The study intervention will be discontinued and future anticoagulation decision will be made by the treating physician.
4. Participants will be strongly encouraged by the study staff to remain on treatment assigned through randomization and to comply with the study protocol and follow-up. However, participants or their physician may voluntarily discontinue study intervention or change OAC treatment at any time. Study staff will make every effort to discourage this.

Participants who change OAC treatment during follow-up will be withdrawn from the study. A CRF will collect details of the reason for discontinuation of study intervention. Endpoints will be assessed at the time of withdrawal from the study including MRI and cognitive function. The MRI of the head and / or cognitive assessment will be performed at the time of withdrawal from the study if it is greater than 6 months since their last assessment of MRI and / or cognitive function. If a patient withdraws within 6 months of the last assessment, repeat testing will not be performed and the last assessment will be used for the analysis. Participants who withdraw from the study will be followed for 30 days after withdrawal for adverse events. A primary intention to treat analysis will be performed at the end of the study. Participants who withdraw or change OAC treatment will be censored at the time of withdrawal.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a visit within a 6 month time frame and is unable to be contacted by the study site staff.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The study coordinator will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- If a participant is reachable but is unable to come in person for the study visit, a telephone interview will be conducted with the participant and an informant to assess the secondary end point of dementia / MCI.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Screening assessment
Screening for eligible participants will be performed using the Mayo medical records by a study coordinator. Only patients who have previously given consent to the use of their medical records for research purposes will be screened. ECG, Holter, telemetry recordings will be reviewed to confirm the diagnogsis of AF. Charts will be reviewed to assess eligibility for the study including past medical history, current medications, laboratory tests and calculation of the CHA2DS2-VaSC score. The creatinine will be checked if a measurement within 3 months of enrollment is not available.

Potential participants will be contacted in person or through a letter or on the phone. Interested persons will be interviewed on the phone to confirm eligibility and will have a blood test for creatinine if needed. Once enrolled, subjects will be randomized to one of the study arms and will start study drug.

Baseline assessment of brain MRI will be performed prior to initiation of study drug. Baseline assessment of cognitive function will be performed prior to or within 1 month of enrollment. Subsequent assessments will be performed at 1 and 2 year follow-up or within a 3 month time frame of this date.

Measurement of primary endpoint: The individual cognitive domain and global cognitive function score

All enrolled subjects will undergo assessment of cognitive function at (1) enrollment, (2) 1 year and (3) 2 years.

AF may have a greater impact on non-memory cognitive domains such as executive function, thus predisposing to non-amnestic dementia. Hence we will test individual cognitive domains to increase the sensitivity of the tests.

The following standardized tests will be administered at each visit by a trained neuropsychometrist.

Testing of four major cognitive function domains

1. Executive function - Trail Making Test B and Digit Symbol Substitution Test
2. Language - Boston Naming Test and Category Fluency
3. Memory - Logical Memory-II (delayed recall), Visual Reproduction-II (delayed recall) and Auditory Verbal Learning Test (delayed recall)
4. Visuospatial - Picture Completion and Block Design

Questionnaires to rule out competing diagnoses:

1. The Beck Depression Inventory
2. The Beck Anxiety Inventory

An informant, identified by the subject as someone with whom they have contact at least once every week, will be interviewed in person or by telephone to complete the following:

1. Clinical dementia rating scale (CDR)
2. Functional assessment questionnaire

For patients lost to clinic follow-up, assessment of cognitive state will be performed using the following questionnaires administered over the telephone:

Telephone interview of cognitive status (TICS-M) (administered to subject)

2. Clinical dementia rating scale (administered to informant)
3. Functional assessment questionnaire (administered to informant)

Adjustment of Neurocognitive function scores using normative data and derivation of 'Global cognitive function score'

The raw scores on each neuropsychological test will be transformed into age- and education-adjusted scores using Mayo's Older American Normative Studies normative data. The adjusted scores within each of the 4 domains will be added to obtain the domain specific score. Since different numbers of tests are used within each domain (i.e., 2 tests for the executive, language, and visuospatial domains versus 3 tests for memory), the domain scores will also scaled for the number of tests to allow comparisons

across domains. The global cognitive function score will then be derived using an average of the 4 domain specific scores.

The performance of a person in a particular domain and their global performance will then be measured by comparing the person's score with the score in normal person that has been previously established to derive a 'z-score'. These comparisons rely on extensive previous normative work we have performed in assessing the cognitive abilities of the population from which the sample will be derived.[33, 34] The tests and definitions provided here have been previously described in detail by our group.[34] The tests will parallel those used by the NIH funded Mayo Clinic Study of Aging, a large ongoing community based study of cognitive function in Olmsted County, MN.

The 'z-score' in individual cognitive domains and the global cognitive function score will be plotted at each time point for the two treatment groups to assess temporal changes.

Measurement of secondary endpoint: Mild cognitive impairment or dementia

The CDR score (range 0–3) will be assessed in addition to the results of the neuropsychological testing. A team of Neurologist and Neuropsychometrist will assign a diagnosis of normal cognition or mild cognitive impairment or dementia to each subject at each time point. This team will be blinded to treatment assignments. Each assessment of an individual patient will be assessed independent of prior assessments. The definitions used are as follows:

Dementia

Subjects with a CDR 1 will be classified as demented if they meet DSM-V criteria for 'major neurocognitive disorder' as follows:

1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on:
    a. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
    b. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing.
2. The cognitive deficits interfere with independence in everyday activities.
3. The cognitive deficits do not occur exclusively in the context of delirium and are not better explained by another mental disorder.

For subjects with CDR 0.5, a committee of the examining neuropsychologist and physician will critically examine the available tests to determine whether the DSM-V criteria for dementia or MCI are met.

Mild cognitive impairment

The criteria for diagnosis of MCI are: cognitive concern expressed by a physician, informant, participant or nurse; cognitive impairment in 1 or more domains; normal functional activities and not demented. Subjects with MCI can have a CDR of 0 or 0.5; however, the final diagnosis of MCI will not be based exclusively on the CDR but rather on all available data. A committee of the examining neuropsychologist and physician will critically examine the available tests to determine whether the criteria for MCI are met.

Normal Cognition

Subjects judged to have no cognitive impairment based on the criteria above and received a CDR of 0, will be considered as cognitively normal.

Brain MRI imaging to assess burden of cerebral infarcts and cerebral microbleeds

MR Imaging of brain

Cerebral MRI will be performed *without* gadolinium contrast using a 3 Tesla scanner at enrollment and at 2 years. If a subject is withdrawn or withdraws prior to the completion of follow-up, an attempt to obtain MRI prior to withdrawal will be made. The following imaging sequences will be performed per standard protocols at our institution: (1) sagittal T1-weighted, (2) axial T2-weighted fast spin echo (FSE), (3) axial T2-weighted fluid-attenuated inversion recovery (FLAIR), (4) axial gradient echo (GRE), (5) axial diffusion tensor-tracer imaging (DTI), (7) 3-dimensional magnetization prepared rapid gradient-echo (MPRAGE) sequence and (8) Axial SWAN (T2 Star Weighted Angiography).

The MRI will be read by a board certified Radiologist who is blinded to treatment assignment.

A new cerebral infarct will be defined as an unequivocal focus of hyperintensity to gray matter on DTI images. GRE and MPRAGE sequences will be used to quantitate the cerebral microbleeds. Cerebral volume analysis will be performed for total cerebral and hippocampal volume using standardized software. The number, size and location of new cerebral infarcts (cortical vs. subcortical and specific anatomic location of infarct) and cerebral microbleeds (lobar vs subhemispheric and specific anatomic location of infarct) will be determined and documented in a CRF.

Interview by study coordinator

Interview of the subject by study coordinator at 1- and 2- year follow-up to assess (1) new medical conditions, (2) adverse events, (3) continued eligibility for the study, (4) medication compliance and (5) review of co-administered medications.

Other assessments

Patients will undergo the following tests at enrollment:

(1) serum creatinine to determine eligibility for the study and Apixaban dosing

8.2 SAFETY AND OTHER ASSESSMENTS

1. Assessment for adverse events will be performed on an ongoing basis and at each patient visit.
2. At each study visit, the participant will be interviewed by the study coordinator to assess for adverse events. The medical records will be reviewed on an ongoing basis to identify occurrence of adverse events and hospitalizations.
3. Occurrence of medical events and addition of drugs that may affect continued eligibility for the study will be assessed at each visit. The age, creatinine and patient weight will be assessed at each patient visit to assess appropriateness of drug dosing.
4. The brain MRI will be screened for adverse events such as identification of asymptomatic intracranial bleeding after each assessment.

Definitions for a selection of important adverse events:

Major bleeding
Major bleeding is defined as acute or subacute clinically overt bleeding with one or more of the following criteria: (1) Fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome (2) Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more over a 24 hr period, or (3) leading to transfusion of two or more units of whole blood or packed red cells.

Clinically Relevant nonmajor Bleed
A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission for bleeding, or
- A physician guided medical or surgical treatment for bleeding, or
- A change in antithrombotic therapy (including interruption or discontinuation of study drug).

Minor Bleeding
All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant nonmajor bleeding will be classified as minor bleeding.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, adverse events of special interest, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.3.2.1 EVENTS OF SPECIAL INTEREST

In this study, the following adverse events are to be reported to BMS as serious events, regardless of whether these reports are classified as serious or unexpected:

Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

8.3.2.2 PREGNANCY

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

8.3.2.3 OVERDOSE

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The intensity of the adverse event will be determined by a physician on the data monitoring and safety board as:

- Mild (Grade 1): Event detected, but without any interference with activity
- Moderate (Grade 2): Some interference with activities of daily living
- Severe (Grade 3): Severe interference with activities of daily living
- Very Severe (Grade 4): Resulting in severe disability despite medical therapy

All SAEs will be grade 3 or 4 at minimum.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The data monitoring and safety board physician will also classify the relationship of the AE to the study drug as follows:

- Certain: There is sufficient medical data supporting causality of the AE to the study drug. The AE resolves or improves with withdrawal of the study drug and, when possible, recurs with reintroduction of study drug
- Probable: There is sufficient medical data supporting causality of the AE to the study drug. The AE resolves or improves with withdrawal of the study drug. Reintroduction of the study drug is not required
- Possible: There is sufficient medical data supporting causality of the AE to the study drug. The resolution or improvement of the AE with study drug withdrawal is unclear or did not occur.
- Unlikely: There is insufficient medical data supporting the causality of the AE to the study drug, but a temporal relationship to study drug exposure is present.
- No relationship: There is no temporal relationship between study drug exposure and the AE.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 NON-SERIOUS ADVERSE EVENT REPORTING

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment. Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Nonserious Adverse events will be reported to the Data Safety and Monitoring Board every 3 months.

Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Following the subject's written consent to participate in the study, all SAEs, whether or not related to the BMS product under study, must be collected, including those thought to be associated with protocol-specified procedures. SAEs must be recorded on FDA MedWatch 3500A Form and reported to BMS (or designee) within 24 hours/1 business day to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness. Although overdose and cancer are not always serious by regulatory definition, these events should be recorded on a form and reported to BMS within 24 hours/1 business day.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:
SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 1-609-818-3804

If only limited information is initially available, follow-up reports may be required.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to the BMS product under study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be recorded on a Pregnancy Surveillance Form and reported to BMS (or designee) within **24 hours/1 business day** by confirmed fax or reported via electronic mail to Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. The original BMS forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

8.3.7 NONSERIOUS ADVERSE EVENT REPORTING

The collection of non-serious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

8.3.8 SAE RECONCILIATION

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be done every three months and once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

8.3.9 LABORATORY TEST ABNORMALITIES

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

8.3.10 OTHER SAFETY CONSIDERATIONS

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8.3.11 REPORTING EVENTS TO PARTICIPANTS

Study participants will be informed of any adverse events or incidental findings through a letter or phone call. In the case of a serious adverse event, the participant will be informed through a phone call within 48 hours of the occurrence. If patient is not reachable, attempts will be made to reach the alternative contact person and the primary treating physician, whose contact information will be sought from the subject at enrollment. The participant will be encouraged to seek care with the primary

treating physician to treat SAEs and to assess any incidental findings, such as findings on brain imaging that require further assessment.

Interpretation of the brain MRI will be performed by a board certified clinical Radiologist and a report generated in the patient's clinical record. This report will be shared with the participant through a letter. This report is however different from the more detailed analysis of the sequences that will be performed by the study Radiologist in a blinded fashion. The results of the cognitive function testing will be shared with individual participants only in the event of diagnosis of dementia, which is expected to have an impact on the overall management of the subject. The aggregate results of the study will be shared with all the participants once published in a peer review journal.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An UPIRTSO: An Unanticipated Problem Involving Risk to Subjects or Others is defined as any problem or event which, in the opinion of the Investigator, meets all three of the following criteria:
1. Serious: Serious problems or events that result in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or places subjects or others at a greater risk of harm than was previously known or recognized. Note that actual harm need not have occurred for there to be a change in the risk/benefit ratio.

2. Unanticipated: A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence and is:

Not already described as a potential risk in the approved informed consent
Not already described as a potential risk in the approved protocol
Not listed in the Investigator's Brochure
Not part of an underlying disease
Occurred at an increased frequency or at an increased severity than expected

3. Related: A problem or event is "related" if it is possibly related to the research procedures.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The Investigator must report a UPIRTSO to the IRB, using the IRB electronic Reportable Event form, within five working days of becoming aware of the problem or event. The report will include a detailed description of the event, incident, experience, or outcome.

All reportable events submitted to the IRB and meeting the UPIRTSO criteria will be sent to an IRB Chairperson for review. If the IRB Chairperson considers the event is a UPIRTSO, a convened IRB reviews it and determines whether it is a UPIRTSO or not. The investigator is notified in writing and the review, determination, and investigator communication is documented in the IRB electronic system.

A UPIRTSO, as determined by the convened IRB, is reported to the Mayo Clinic Institutional Official and other relevant Federal agencies, when required, within 30 days from the date of IRB determination. The investigator is notified in writing of this action.

The investigator will submit a modification application to the IRB if the problem or event requires revision of the protocol and/or consent document.

If the convened IRB confirms the UPIRTSO, the investigator reports the IRB's determination to the research project sponsor.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems occurring in individual subjects will be reported to the subject using the methods described for AEs and SAEs noted above.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint:

Treatment with Apixaban is associated with reduced rate of decline in global cognitive function score compared to treatment with Warfarin in AF patients ≥ 60 years of age and CHA2DS2-VaSC score ≥2.

Measurement of primary endpoint: The individual cognitive domain and global cognitive function score

All enrolled subjects will undergo assessment of cognitive function at (1) enrollment, (2) 1 year and (3) 2 years.

AF may have a greater impact on non-memory cognitive domains such as executive function, thus predisposing to non-amnestic dementia. Hence we will test individual cognitive domains to increase the sensitivity of the tests.

The following standardized tests will be administered at each visit by a trained neuropsychometrist.

<u>Testing of four major cognitive function domains</u>

5. Executive function - Trail Making Test B and Digit Symbol Substitution Test
6. Language - Boston Naming Test and Category Fluency
7. Memory - Logical Memory-II (delayed recall), Visual Reproduction-II (delayed recall) and Auditory Verbal Learning Test (delayed recall)
8. Visuospatial - Picture Completion and Block Design

Questionnaires to rule out competing diagnoses:

1. The Beck Depression Inventory
2. The Beck Anxiety Inventory

An informant, identified by the subject as someone with whom they have contact at least once every week, will be interviewed in person or by telephone to complete the following:

1. Clinical dementia rating scale (CDR)
2. Functional assessment questionnaire

For patients lost to clinic follow-up, assessment of cognitive state will be performed using the following questionnaires administered over the telephone:

Telephone interview of cognitive status (TICS-M) (administered to subject)

2. Clinical dementia rating scale (administered to informant)
3. Functional assessment questionnaire (administered to informant)

Patients who no longer present for in person neurocognitive assessment will be censored from the analysis of the primary endpoint of neurocognitive function scores. The telephone interview will be used to classify as MCI / dementia and the data will be used for this secondary endpoint only.

Adjustment of Neurocognitive function scores using normative data and derivation of 'Global cognitive function score'

The raw scores on each neuropsychological test will be transformed into age- and education-adjusted scores using Mayo's Older American Normative Studies normative data. The adjusted scores within each of the 4 domains will be added to obtain the domain specific score. Since different numbers of tests are used within each domain (i.e., 2 tests for the executive, language, and visuospatial domains versus 3 tests for memory), the domain scores will also scaled for the number of tests to allow comparisons across domains. The global cognitive function score will then be derived using an average of the 4 domain specific scores.

The performance of a person in a particular domain and their global performance will then be measured by comparing the person's score with the score in normal person that has been previously established to derive a 'z-score'. These comparisons rely on extensive previous normative work we have performed in assessing the cognitive abilities of the population from which the sample will be derived.[33, 34] The tests and definitions provided here have been previously described in detail by our group.[34] The tests will parallel those used by the NIH funded Mayo Clinic Study of Aging, a large ongoing community based study of cognitive function in Olmsted County, MN.

The 'z-score' in individual cognitive domains and the global cognitive function score will be plotted at each time point for the two treatment groups to assess temporal changes.

- Secondary Efficacy Endpoints:

Treatment with Apixaban is associated with lower rate of development of new dementia or mild cognitive impairment compared to treatment with warfarin.

Measurement of secondary endpoint: Mild cognitive impairment or dementia

The CDR score (range 0–3) will be assessed in addition to the results of the neuropsychological testing. A team of Neurologist and Neuropsychometrist will assign a diagnosis of normal cognition or mild cognitive impairment or dementia to each subject at each time point. This team will be blinded to treatment assignments. Each assessment of an individual patient will be assessed independent of prior assessments. The definitions used are as follows:

Dementia

Subjects with a CDR 1 will be classified as demented if they meet DSM-V criteria for 'major neurocognitive disorder' as follows:

1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on:
    a. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
    b. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing.
2. The cognitive deficits interfere with independence in everyday activities.
3. The cognitive deficits do not occur exclusively in the context of delirium and are not better explained by another mental disorder.

For subjects with CDR 0.5, a committee of the examining neuropsychologist and physician will critically examine the available tests to determine whether the DSM-V criteria for dementia or MCI are met.

Mild cognitive impairment

The criteria for diagnosis of MCI are: cognitive concern expressed by a physician, informant, participant or nurse; cognitive impairment in 1 or more domains; normal functional activities and not demented. Subjects with MCI can have a CDR of 0 or 0.5; however, the final diagnosis of MCI will not be based exclusively on the CDR but rather on all available data. A committee of the examining neuropsychologist and physician will critically examine the available tests to determine whether the criteria for MCI are met.

Normal Cognition

Subjects judged to have no cognitive impairment based on the criteria above and received a CDR of 0, will be considered as cognitively normal.

Treatment with Apixaban is associated with lower incidence of new cerebral infarction and cerebral microbleeds noted on brain MRI imaging.

Measurement of secondary endpoint: This will be performed using brain MRI as noted above.

9.2 SAMPLE SIZE DETERMINATION

Sample size calculation is based on the primary endpoint, the rate of decline in the global cognitive function score. The sample size calculations are based on data from the Mayo Clinic Study of Aging which has enrolled community dwelling individuals to perform the same battery of neurocognitive tests proposed in this study. We investigated the rate of decline in the global cognitive function score in (1) patients with and without AF and (2) in AF patients on warfarin vs. not on warfarin. The Mayo Clinic Study of Aging (MCSA) has identified a significant decline in the individual and global cognitive function scores in patients with AF compared to those without AF. In addition, the rate of decline was similar in AF patients treated with warfarin and those not treated with warfarin. The observed rate of decline in global cognitive score in AF patients on warfarin was -0.12 / year (SD 0.16). A reduction in the rate of decline in the global cognition function score of 0.05/year with Apixaban compared to Warfarin was considered clinically relevant. We used R to calculate power as a single sided test of superiority of Apixaban over Warfarin. A sample size of 140 in each arm is required to achieve >80% power to detect

the difference stated assuming an alpha error of 0.05. Assuming a screen failure rate of 20%, a total of 175 will be accrued in each arm.

Enrollment will be age and gender stratified with goal of enrolling >50% patients over the age of 70 years in whom the risk of cognitive decline is greater. Recruitment of the required number of subjects will be feasible given the high volume of AF patients in the local community and those seeking care for AF at the Mayo Clinic. For example, 5000 individuals developed incident (new onset) AF in Olmsted county alone after the year 2000. The rate of prevalent AF is higher in this population. The other 7 counties from which participants will be recruited have similar population demographics and prevalence of AF. We anticipate that we will be able to recruit the required number of subjects in the first year of the study.

9.3 POPULATIONS FOR ANALYSES

The following datasets will be used for analysis:

1. Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)
2. Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model.
3. Pre-specified subgroup analyses – (1) Gender, (2) decade of age, (3) pattern of AF, (4) warfarin naïve vs prior warfarin exposure, (5) Time in therapeutic range on warfarin divided by the median.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Continuous and categorical variables will be summarized as mean (standard deviation, SD) and number (%) respectively. Differences between the two treatment arms at baseline will be examined using t-tests for continuous variables and chi-square tests for categorical variables.

The baseline variables include age, sex, education, cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia), past medical history (including stroke, TIA, heart failure, peripheral arterial disease, MI, coronary artery disease, liver disease, renal disease, malignancy), duration of AF, pattern of AF (paroxysmal, persistent), prior h/o anticoagulation (duration and type of drug used), prior treatment of AF (antiarrhythmic drug, ablation procedure), and current medications. This data will be reviewed and updated at each visit. The INR values during the study will be collected for patients on warfarin and the time in therapeutic range calculated using the Rosendaal method of interpolation.

Longitudinal changes in each cognitive domain (language, attention, memory, visual spatial and global) will be analyzed using multiple adjusted linear mixed effects models comparing Apixaban vs warfarin. These models will be adjusted for baseline variables that differ between the groups. These results will be presented as beta estimates for baseline differences in cognitive function score by treatment status, change with time and the effect of treatment on the change in scores over time.

For the secondary end point of dementia/MCI, the mid-point between the most recent visit with a cognitively normal diagnosis and the first visit with a diagnosis of MCI or dementia will be considered the date of onset. Participants who are lost to follow-up or die during follow-up will be censored at the

date of last follow-up. Cox proportional hazards model will be used to assess the secondary end points of MCI/dementia, cerebral infarction and cerebral microbleeds. Adjustment for baseline factors noted above will be performed in the multivariable model.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The study coordinator / investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the investigators and, IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the investigators and their staff. This confidentiality is extended to cover all testing and clinical information. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research

activities will be conducted in as private a setting as possible. The study participant's contact information will be securely stored at each clinical site for internal use during the study. Electronic study data will be stored in secure servers and all paper documents will be filed in locked cabinets. These data will be accessible only to the investigators and study personnel. Each participant's data will be coded using a unique identification number and the codes placed in a secure server. Data will be de-identified before sharing with any party outside of the study investigators and study personnel. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the IRB.

10.1.4 FUTURE USE OF STORED DATA

Data collected for this study will be analyzed and stored at the Mayo Clinic, Rochester. After the study is completed, the de-identified, archived data may be made available for use by other researchers within the institution after obtaining IRB approval.

10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of one Cardiologist, one Neurologist and a biostatistician outside of the research team. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety data on each arm of the study. The DSMB will provide its input to the investigator and sponsor.

10.1.6 DATA HANDLING AND RECORD KEEPING

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Hardcopies of the study visit worksheets including cognitive function battery and baseline clinical characteristics will be the source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. Electronic data on clinical characteristics will be stored in RedCap and data on neurocognitive testing will be stored in SDMS. Brain MRI images and their interpretation will be served in electronic form in a secure server. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

10.1.6.2 STUDY RECORDS RETENTION

10.1.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the participant, the investigator, or the study staff. It is the responsibility of the investigator to identify and report deviations. The timing of investigator reporting of protocol violation/deviations to the IRB, using the IRB electronic Reportable Event form, is dependent on the severity of the protocol violation/deviation. Major protocol violations/deviations that affect the rights and welfare of subjects and others, increase risks to subjects and others, decrease potential benefits, compromise the integrity or validity of the research; or represent willful or knowing misconduct must be reported by the investigator within five working days of becoming aware of the

violation/deviation. Minor non-compliance should be summarized and submitted to the IRB at the time of continuing review.

Examples of problems or events which may meet the definition of Major Protocol Violations/Deviations (non-compliance):
• Enrolling subjects who did not meet inclusion/exclusion criteria on a greater-than-minimal risk study
• Performing study procedures not approved by the IRB
• Performing study procedures before obtaining informed consent
• Failure to obtain and/or document informed consent
• Use of an unapproved consent document
• Changing the protocol without prior IRB approval except when necessary to eliminate immediate harm to a subject
• Breach of confidentiality (i.e. any occurrence of unapproved PHI disclosure)
• Receipt of incorrect treatment or dose by a subject
• Loss or destruction of samples or data
• Over-enrollment of subjects on a greater than minimal risk study
• Unauthorized (i.e. not IRB approved) persons participating in the conduct of a research study

10.1.8 PUBLICATION AND DATA SHARING POLICY

Protocol Amendment History

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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